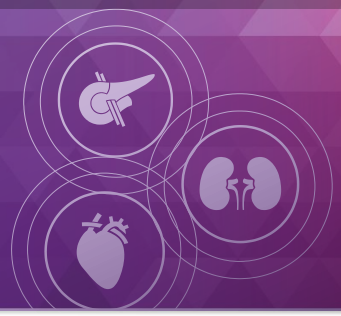
SGLT2i 於糖尿病及心腎風險管理中的角色

廖國盟 醫師

臺北市立聯合醫院忠孝院區



處方藥物請參考衛生福利部核准仿單說明

0

Outline

- 台灣糖尿病腎心共病情況
- SGLT-2i 在 DKD 治療的角色
- SGLT-2i 在 HF 治療的角色

1

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IDF 估計 2017 年台灣糖尿病人口為 218 萬

Diabetes cases (18-99 years)	2,183,905
Diabetes (18-99 years) national prevalence (%)	11.3
Diabetes age-adjusted (18-99 years) comparative prevalence (%)	8.9
Undiagnosed diabetes cases (18-99 years)	934,711
One in X adults has diabetes	9

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照顧市民健康．守護弱勢族群

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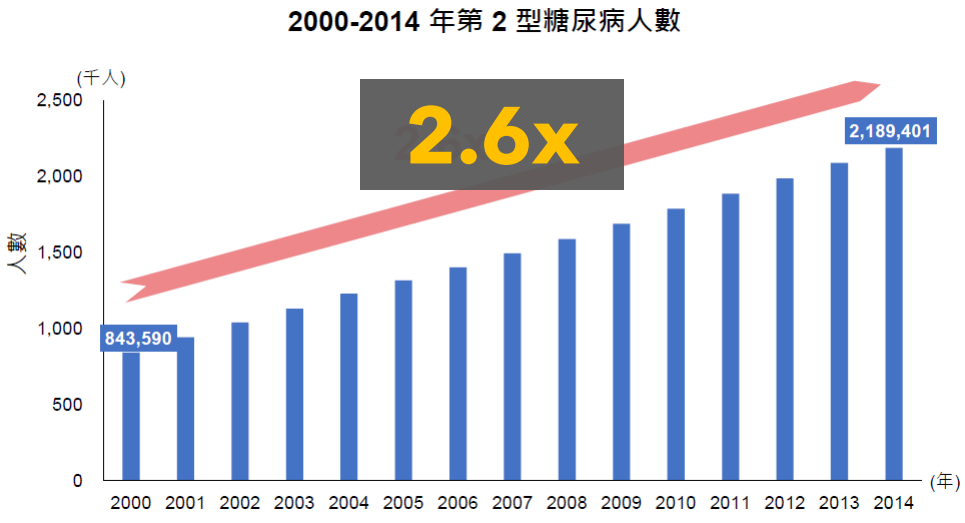
2.6-fold increase in prevalence of diabetes in Taiwan from 2000 to 2014



臺灣糖尿病年鑑2019。第二型糖尿病。

3

T2DM patients:
Under-estimated risks lurking beneath the surface

High blood glucose

CLINICAL

RISKS

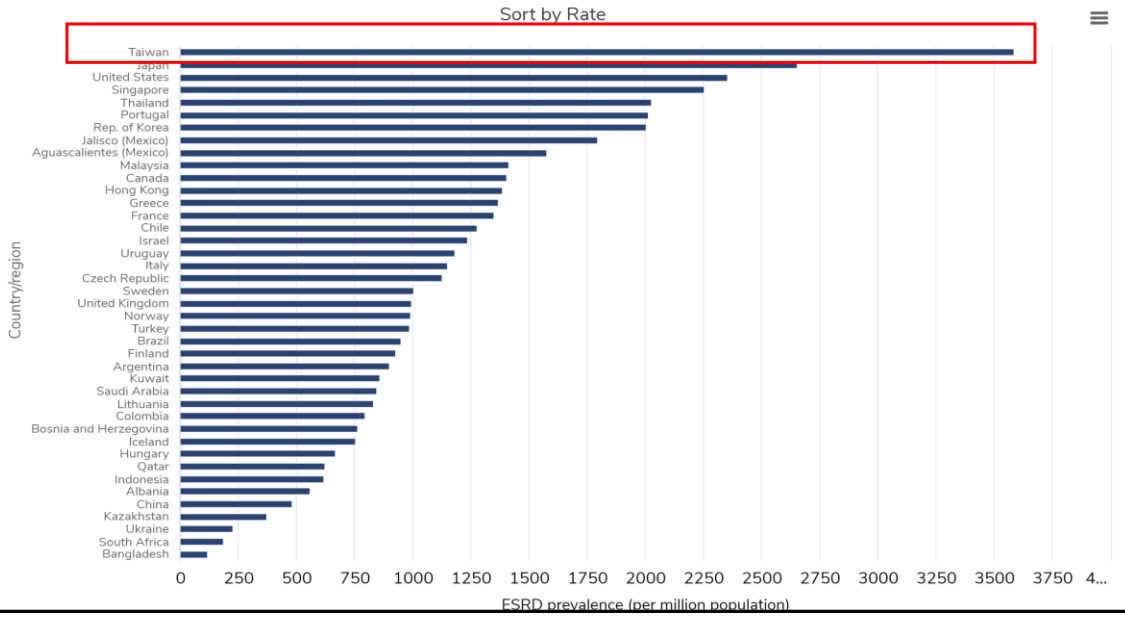
Cardiorenal complications

4

4

Figure 11.9 Prevalence of treated ESRD, by country or region, 2018

Sort by Rate | Sort by Country/region name | Sort by Continent and Country/region name



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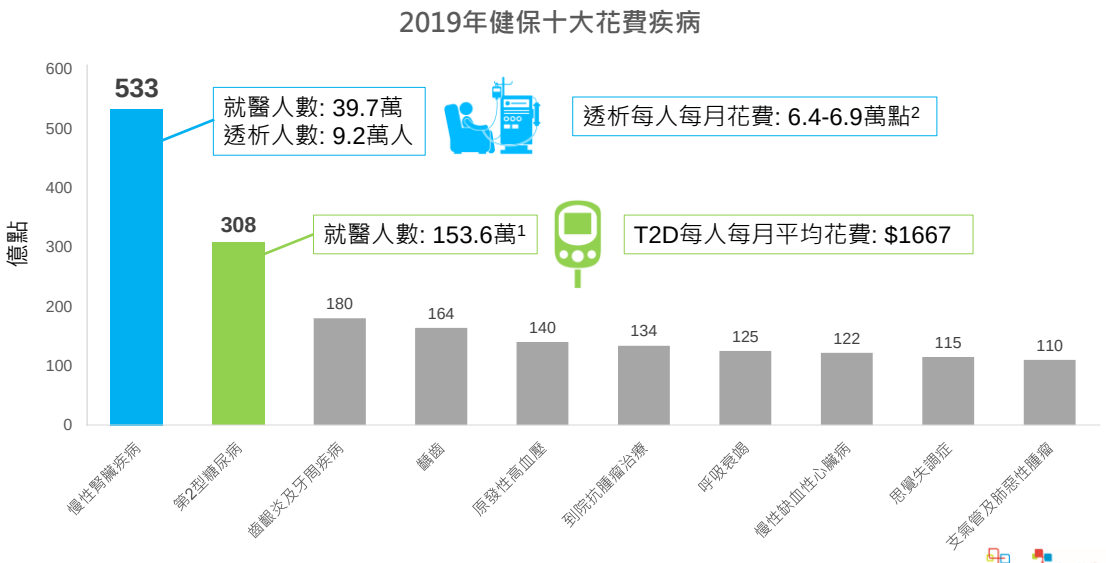
健保支出10大疾病 - 慢性腎病居首 洗腎佔大部分花費



1. https://ctee.com.tw/lohas/health/299440.html 2. 2019 Annual Report on Kidney Disease in Taiwan (p.147)

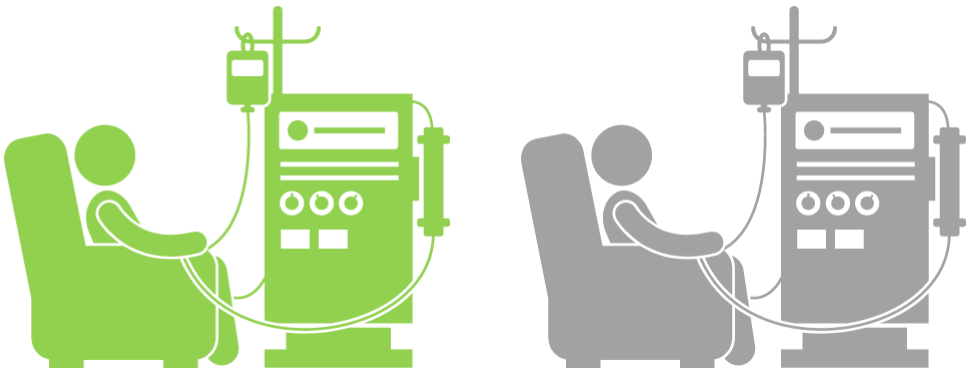
6

forxiga (dapagliflozin) xigduo XR Extended-Release Tablets (dapagliflozin/metformin HCl) QTERN (saxagliptin/dapagliflozin)

6

台灣每2位透析病患有1位患有糖尿病

51.2% dialysis patients have diabetes
45.4% new dialysis patients' principal diagnosis is diabetes



2019 Annual Report on Kidney Disease in Taiwan https://www.tsn.org.tw/UI/L/L002.aspx

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forxiga (dapagliflozin) xigduo XR Extended-Release Tablets (dapagliflozin/metformin HCl) QTERN (saxagliptin/dapagliflozin)

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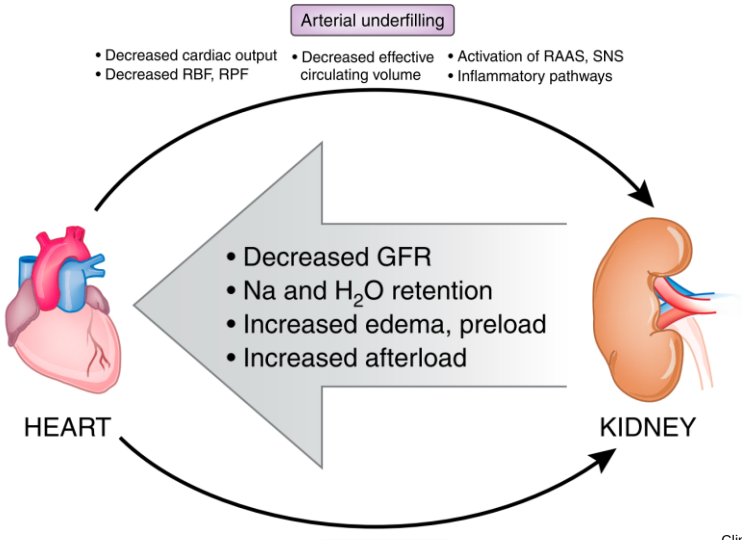
心腎症候群: 腎功能不好連帶影響心臟



Clin J Am Soc Nephrol. 2013 Oct;8(10):1808-15.

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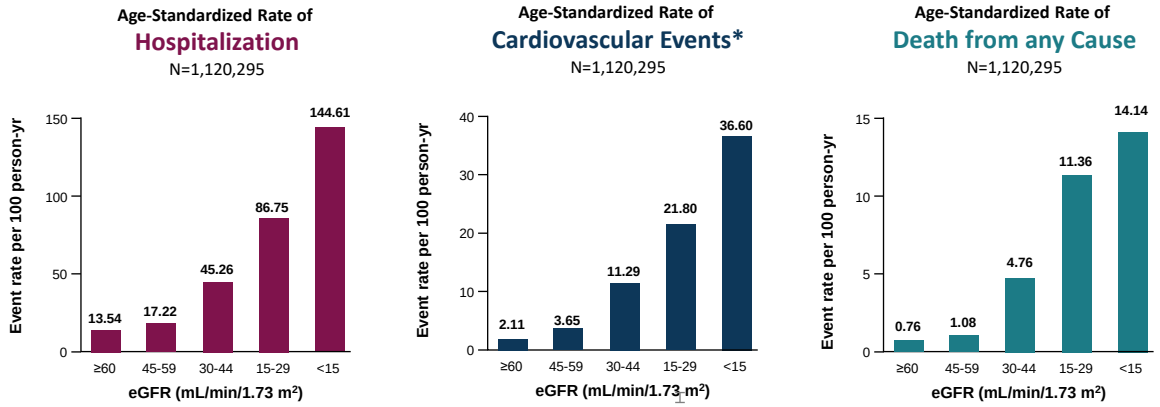
The Risk of Morbidity and Mortality Rises Sharply as CKD Progresses



*Cardiovascular event was defined as hospitalization for coronary heart disease, heart failure, ischemic stroke, and peripheral arterial disease.

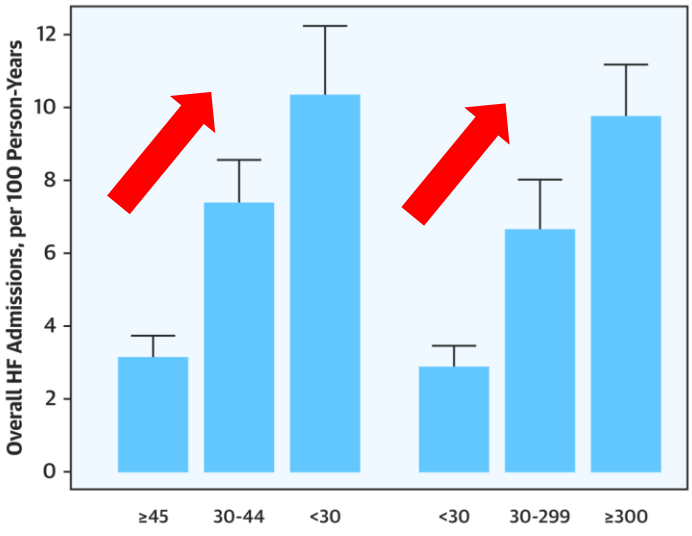
CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate.

9

Go A, et al. *N Engl J Med.* 2004;351:1296-1305.

9

腎功能越差，心衰竭住院風險越高



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J Am Coll Cardiol. 2019 Jun 4;73(21):2691-2700.

TW-19382_FOR_30/03/2022

forxiga (dapagliflozin) xigduo XR Extended-Release Tablets (dapagliflozin/metformin HCl) QTERN (saxagliptin/dapagliflozin)

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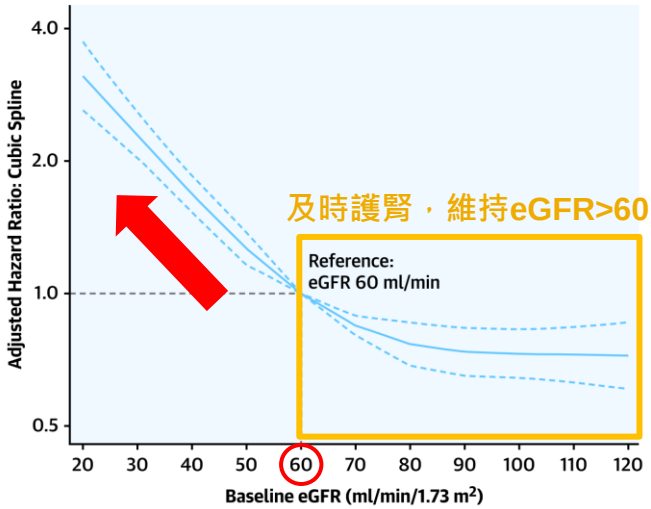
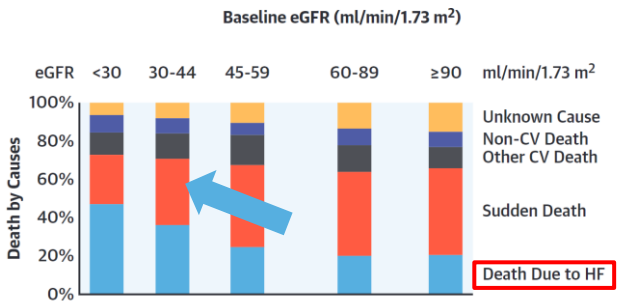
心衰竭患者的腎功能越差，死亡風險越高

All-cause mortality in patients with HF by eGFR



Death by cause in patients with HF by eGFR



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Analysis of 16,740 individual patients with left ventricular ejection fraction <50% from 10 double-blind, placebo-controlled trials

J Am Coll Cardiol. 2019 Dec, 74 (23) 2893–2904.

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forxiga (dapagliflozin) xigduo XR Extended-Release Tablets (dapagliflozin/metformin HCl) QTERN (saxagliptin/dapagliflozin)

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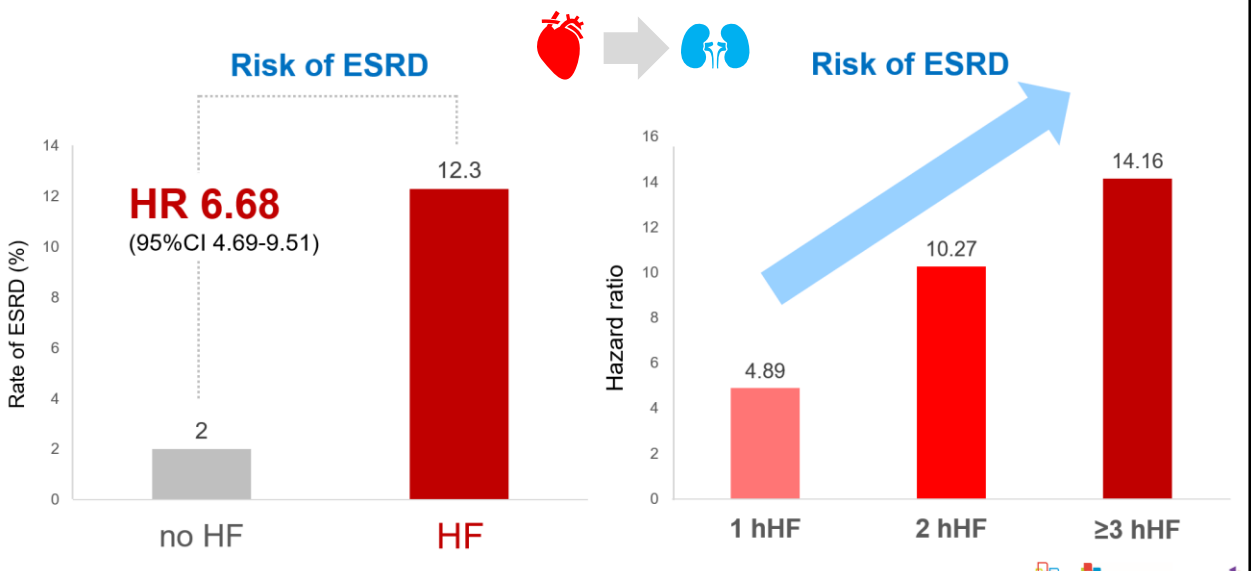
HF會大幅增加罹患ESRD的風險，HF住院次數越多風險越高



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hHF: heart failure hospitalizations

J Am Soc Nephrol. 2015 Mar;26(3):715-22.

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Outline

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- SGLT-2i 在 HF 治療的角色

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2021 ADA standard of care

Consider independently of baseline A1c, individualized A1C target, or metformin use*

+ASCVD/Indicators of High Risk

- Established ASCVD
- Indicators of high ASCVD risk (age ≥55 years with coronary carotid, or lower-extremity artery stenosis >50%, or LVH)

EITHER/OR

- GLP-1 RA with proven CVD benefit
- SGLT2i with proven CVD benefit

+HF

Particularly HFrEF (LVEF <45%)

SGLT2i with proven benefit in this population

+CKD

DKD and Albuminuria

PERFERABLY SGLT2i with primary evidence of reducing CKD progression

OR SGLT2i with evidence of reducing CKD progression in CVOT

OR GLP-1 RA with CVD proven benefit if SGLT2i not tolerated or contraindicated

American Diabetes Association.

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Anti-diabetic agents CV and renal outcome trials

DPP-4 inhibitors	GLP-1 agonists		SGLT-2 inhibitors
SAVOR (n=16,492)	ELIXA (n=6,068)	HARMONY (n=9,463)	EMPA-REG (n=7,020)
EXAMINE (n=5,380)	LEADER (n=9,340)	REWIND (n=9,901)	CANVAS (n=10,142)
TECOS (n=14,671)	SUSTAIN-6 (n=3,297)	PIONEER-6 (n=3,176)	DECLARE (n=17,160)
CARMELINA (n=6,980)	EXSCEL (n=14,752)		CREDENCE (n=4,401)

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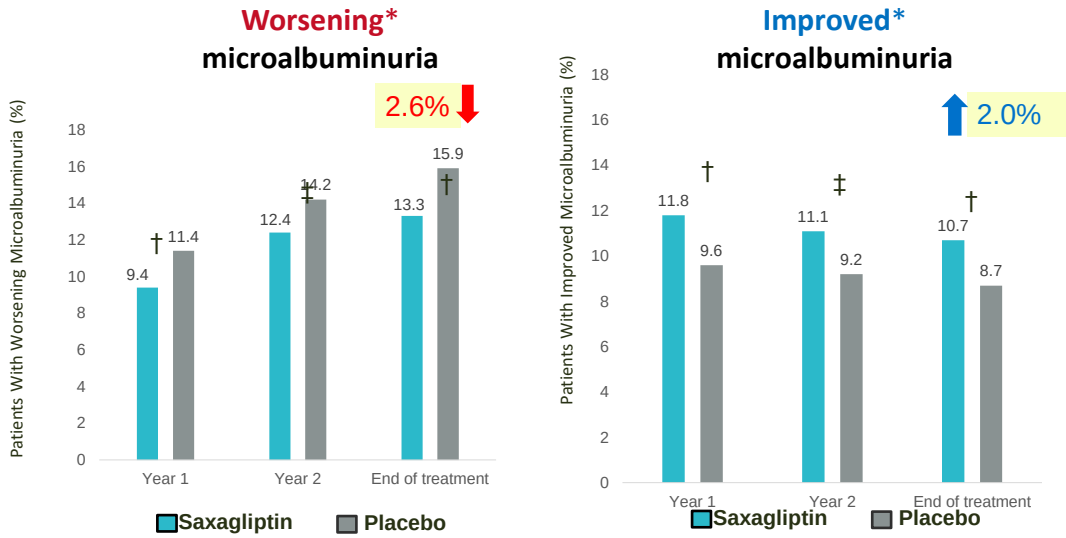
Saxagliptin significantly decrease albuminuria compare with PBO

SAVOR



*Treatment difference in the number and proportion of patients with albumin/creatinine ratios that worsened, did not change, or improved is defined as a shift from baseline category (<3.4, ≥3.4 to ≤33.9, or >33.9 mg/mmol).
†P<0.001 vs placebo; ‡P = 0.0058 vs placebo.

Scirica BM, Bhatt DL, Braunwald E, et al.… Raz I. *NEJM* 2013; 369:1317-1326

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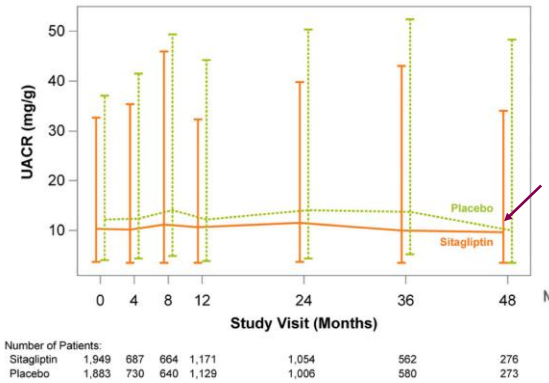
DPP4i did not demonstrate evidence of renoprotection except reduced albuminuria progression

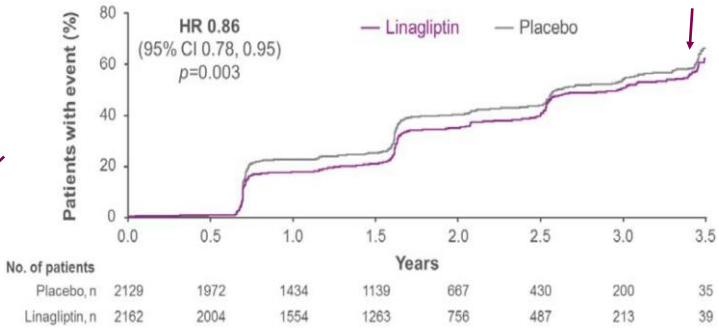
TECOS[1]

UACR over 4 years



CARMELINA[2]

Time to First Occurrence of Albuminuria Progression



The Secondary kidney outcome* HR:
1.04 (0.89-1.22), P=0.06

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*First sustained end-stage renal disease; Death due to renal failure; Sustained decrease of 40% in eGFR from baseline

1.Diabetes Care. 2017 Jan;40(1):69-76; 2. Diabetes Care 2016;39:2304 – 2310; 3.JAMA. 2019;321(1):69-79

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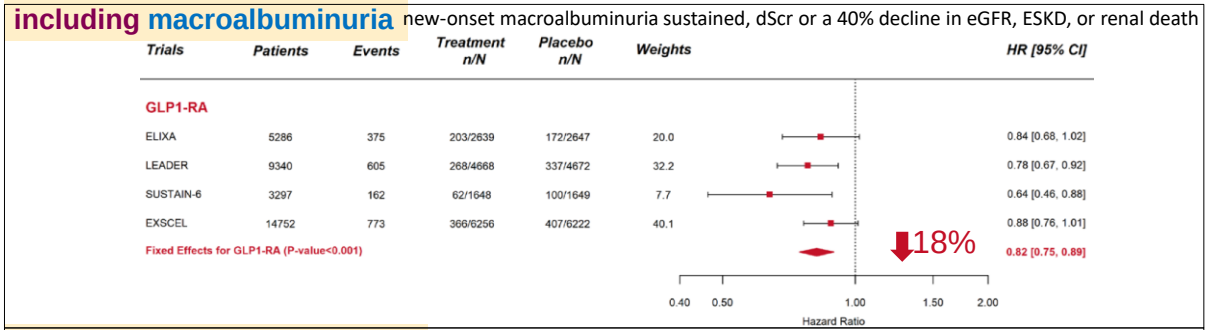
Meta-Analysis of GLP1-RA on kidney outcome

including macroalbuminuria new-onset macroalbuminuria sustained, dScr or a 40% decline in eGFR, ESKD, or renal death



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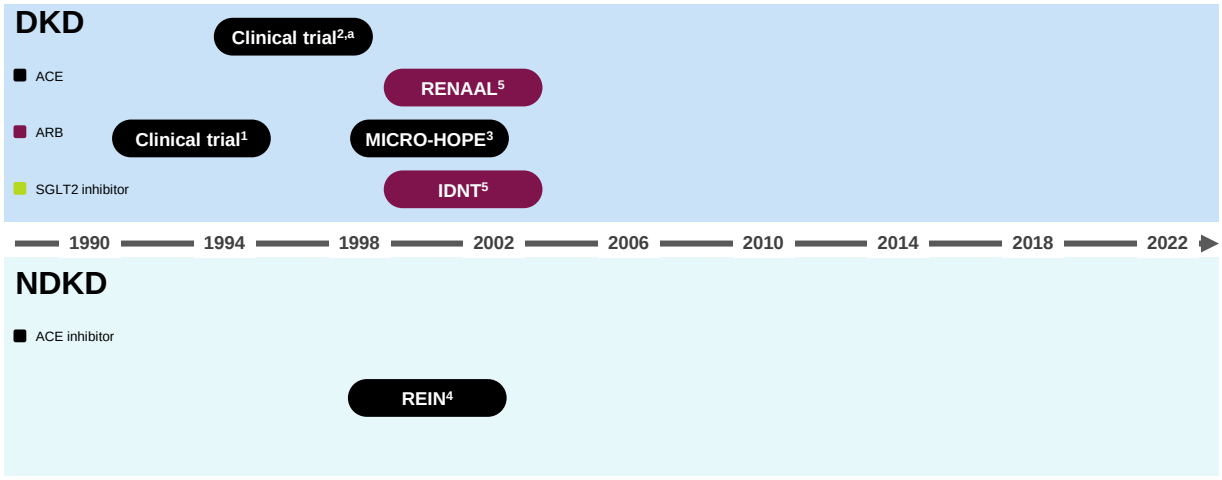
Over the past 20 years, the number of successful trials with approved indication in CKD has been sparse



ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CKD, chronic kidney disease; NDKD, non-diabetic kidney disease; SGLT2i, sodium–glucose co-transporter 2 inhibitor

1. Lewis EJ, et al. *N Engl J Med* 1993;329:1456–1462; 2. Agardh CD, et al. *J Hum Hypertens* 1996;10:185–192; 3. HOPE Study Investigators. *Lancet* 2000;355:253–259; 4. The GISEN Group. *Lancet* 1997;349:1857–1863; 5. Chan GC, et al. *Nephrol Dial Transplant*. 2016;31:359-368; 6. Perkovic V, et al. *N Engl J Med* 2019;380:2295–2306

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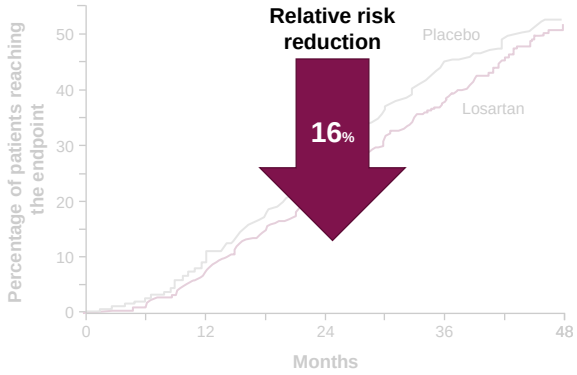
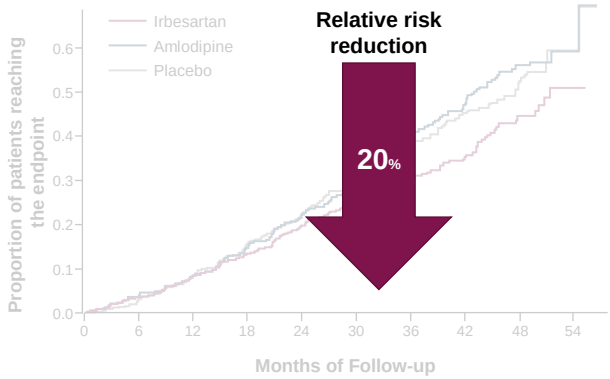
RENAAL and IDNT: losartan and irbesartan significantly reduced the risk of progressing to hard renal endpoints in DKD populations

RENAAL: risk of progressing to ESRD, doubling of serum creatinine, or death with Losartan compared with placebo in patients with DKD[1]



IDNT: risk of progressing to ESRD, doubling of serum creatinine, or death with Irbesartan, compared with amlodipine and placebo in patients with DKD[2]



CKD, chronic kidney disease; DKD, diabetic kidney disease; ESRD, end-stage renal disease; NDKD, non-DKD

1. Brenner B, et al. *N Engl J Med* 2001;345(12):861–869; 2. Lewis EJ, et al. *N Eng J Med*. 2001;345(12):851-860

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However, neither RENAAL nor IDNT showed risk reduction in all-cause mortality

RENAAL[1]

TABLE 3. INCIDENCE OF THE PRIMARY COMPOSITE END POINT AND ITS COMPONENTS.*

END POINT	LOSARTAN GROUP (N=751)		PLACEBO GROUP (N=762)		P VALUE	RISK REDUCTION
	no. (%)	no./100 patient-yr	no. (%)	no./100 patient-yr		% (95% CI)
Primary composite end point†	327 (43.5)	15.9	359 (47.1)	18.1	0.02	16 (2 to 28)
Doubling of serum creatinine concentration	162 (21.6)	7.9	198 (26.0)	10.0	0.006	25 (8 to 39)
End-stage renal disease	147 (19.6)	6.8	194 (25.5)	9.1	0.002	28 (11 to 42)
Death	158 (21.0)	6.8	155 (20.3)	6.6	0.88	−2 (−27 to 19)
End-stage renal disease or death	255 (34.0)	11.7	300 (39.4)	14.1	0.01	20 (5 to 32)
Doubling of serum creatinine concentration and end-stage renal disease	226 (30.1)	11.0	263 (34.5)	13.2	0.01	21 (5 to 34)

IDNT[2]

TABLE 2. OUTCOMES ACCORDING TO STUDY GROUP.*

VARIABLE	IRBESARTAN GROUP (N=579)	AMLODIPINE GROUP (N=567)	PLACEBO GROUP (N=569)	ALL PATIENTS (N=1715)
Primary composite outcome — no. (%)	189 (32.6)	233 (41.1)	222 (39.0)	644 (37.6)
Doubling of serum creatinine concentration	98 (16.9)	144 (25.4)	135 (23.7)	377 (22.0)
End-stage renal disease	82 (14.2)	104 (18.3)	101 (17.8)	287 (16.7)
Death from any cause	87 (15.0)	83 (14.6)	93 (16.3)	263 (15.3)
Secondary composite outcome — no. (%)	138 (23.8)	128 (22.6)	144 (25.3)	410 (23.9)
Never received study medication — no. (%)†	2 (0.3)	8 (1.4)	6 (1.1)	16 (0.9)
Lost to follow-up — no. (%)‡	5 (0.9)	2 (0.4)	4 (0.7)	11 (0.6)
Completed study without primary	385 (66.5)	332 (58.6)	343 (60.3)	1060 (61.8)
days§				932

Did not reduce all-cause mortality

1. Brenner B, et al. *N Engl J Med* 2001;345(12):861–869; 2. Lewis EJ, et al. *N Eng J Med*. 2001;345(12):851-860

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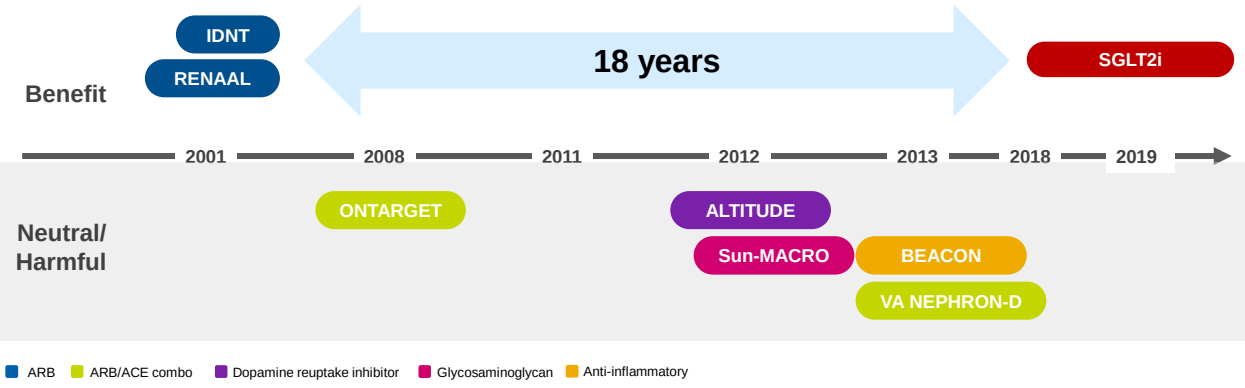
隔上一個能減少糖尿病患腎臟硬終點*的藥物已18年

FOR TODAY. FOR TOMORROW.



***Renal endpoint: doubling of serum creatinine, ESKD, or death**

ONTARGET, BEACON demonstrated increased risk of events.

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

Chan GC, et al. *Nephrol Dial Transplant.* 2016;31:359-368.

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forxiga (dapagliflozin) xigduo XR Extended-Release Tablets (dapagliflozin/metformin HCl) QTERN (saxagliptin/dapagliflozin)

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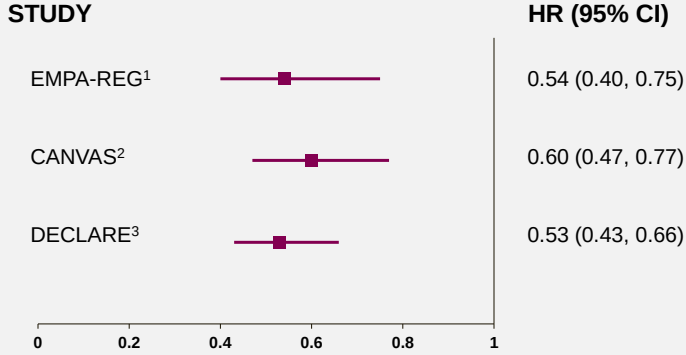
SGLT-2i have consistently shown a reduction in renal outcomes

Impact of SGLT2 inhibitor on composite renal outcomes[1-3]



Renal Endpoints:[1-3]

- **EMPA-REG OUTCOME**: Doubling of serum creatinine level accompanied by eGFR of ≤45 ml/min/1.73 m^2, initiation of renal-replacement therapy, or death from renal disease
- **CANVAS:** 40% reduction in eGFR, renal-replacement therapy, or renal death
- **DECLARE[a]:** Confirmed sustained ≥40% decrease in eGFR to eGFR <60 mL/min/1.73 m^2 and/or ESRD and/or renal death

AstraZeneca does not recommend the use of dapagliflozin for indications other than T2D

eGFR,estimated glomerular filtration rate; ESR, end stage renal disease; HR, hazard ratio

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1. Wanner, C. N Engl J Med. 2016;375:323-334. . 2. Neal B, et al. N Engl J Med. 2017;377:644-657 3. Wiviott SD et al. Online ahead of print. N Engl J Med. 2018; 4. Raz et al. Diabetes Obes Metab. 2018;20:1102-1110; 5. Zinman B. Cardiovasc Diabetol. 2014.

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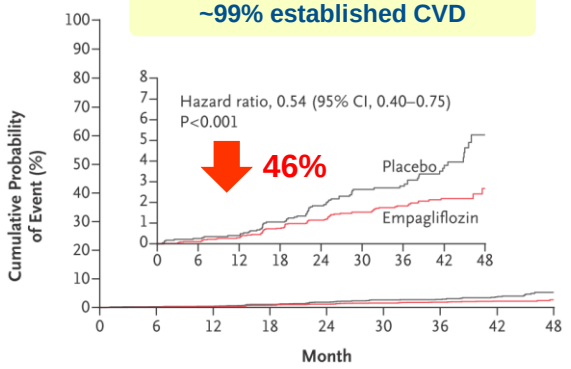
Renal Composite Outcome in CV outcome trial of SGLT2i

EMPA-REG (Empagliflozin)†

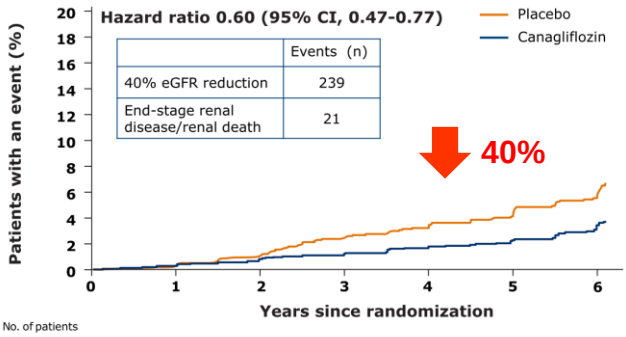
~99% established CVD



No. at Risk									
Empagliflozin	4645	4500	4377	4241	3729	2715	2280	1496	360
Placebo	2323	2229	2146	2047	1771	1289	1079	680	144

CANVAS (Canagliflozin)‡

~66% established CVD



No. of patients								
Placebo	4347	4227	3029	1274	1229	1173	819	
Canagliflozin	5795	5664	4454	2654	2576	2495	1781	

†Doubling of the serum creatinine level, the initiation of renal-replacement therapy, or death from renal disease.
‡40% reduction in eGFR, requirement for renal-replacement therapy, or death from renal causes

1. Wanner C et al. N Engl J Med. 2016 Jul 28;375(4):323-34. 2. Bruce Neal et al. N Engl J Med. 2017 Jun 12. doi: 10.1056/NEJMoa1611925.

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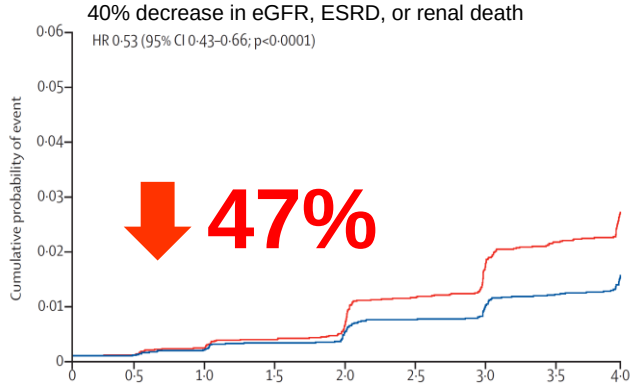
In T2D patients with relatively good baseline renal function dapagliflozin slowed renal disease progression in the DECLARE trial

The patients in the DECLARE[1,2] trial had better baseline renal function than the EMPA-REG OUTCOME[3,4] or CANVAS[5] trials[a]

	DECLARE	CANVAS	EMPA-REG
eGFR, mean (mL/min/ 1.73m²)	**85.2**	76.5	74[b]
Micro-/macro-albumin-uria (%)	**30.9[c]**	30.2	39.6

Renal composite endpoint:
40% decrease in eGFR, ESRD, or renal death



Number at risk									
Placebo group	8578	8504	8415	8321	8193	8056	7925	7403	5382
Dapagliflozin group	8582	8523	8422	8338	8242	8127	8004	7522	5464

[a] eGFR Calculations: DECLARE CKD; EPI CANVAS MDRD; EMPA-REG MDRD; [b] Based on a pre-final version of the database (N=7034). [c] UACR was not measured at baseline for all patients, so N values are smaller for UACR group than for the overall population (N=16,843). [d]Cardiorenal composite endpoint defined as sustained confirmed eGFR decrease ≥ 40% to eGFR < 60 ml/min/1.73m2 using CKD-EPI equation and/or ESRD (dialysis ≥ 90 days or kidney transplantation, sustained confirmed eGFR < 15 ml/min/1.73m²) and/or renal or CV death (pre-specified renal secondary outcome). CKD = chronic kidney disease; CV = cardiovascular; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease;

1. Raz I, et al. *Diabetes Obes Metab* 2018;20:1102–1110; 2. Wiviott SD et al. *N Engl J Med*. 2019;380:347-357 3. Zinman B, et al. *N Engl J Med* 2015;373:2117–2128; 4. Zinman B, et al. Supplementary appendix. *N Engl J Med* 2015;373:2117–2128; 5. Neal B, et al. *N Engl J Med* 2017;377:644–657; 6. Wiviott SD et al. *N Engl J Med*. 2019;380:347-357.

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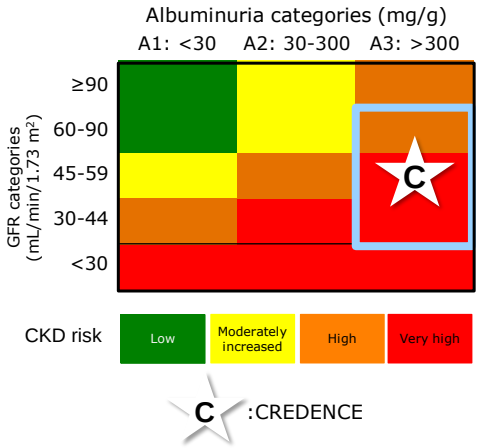
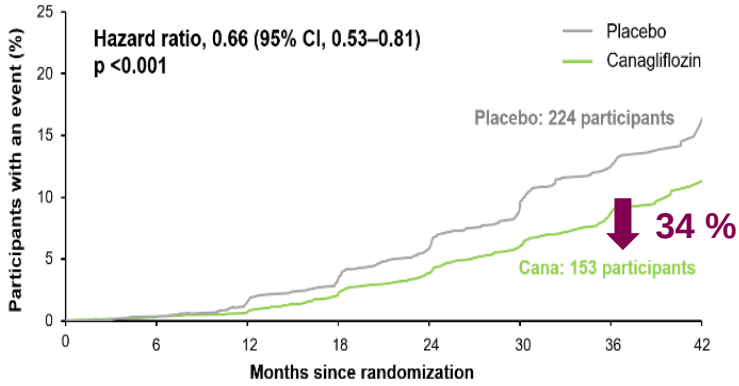
Patient populations and renal outcome in CREDENCE study

CREDENCE
eGFR > 60: 40%
Micro: 11·3%;
macro 88%



Renal-specific composite outcome:
end-stage kidney disease, doubling of serum creatinine level, or renal death



26 N Engl J Med. 2019 Apr 14. doi: 10.1056/NEJMoa1811744

26

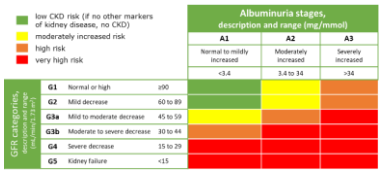
The Renal Stages Populations in SGLT2i CVOTs and renal OTs are quite different

DECLARE (T2DM + CVD risk/History)
eGFR# > 60: 93%
Micro:23.4%; Macro:6.8%

CANVAS (T2DM+CVD risk/history)
eGFR# > 60: 81%
Micro:22.6%; Macro:7.6%

EMPA-REG (T2DM+CVD History)
eGFR# > 60: 74%
Micro:29%; Macro:11%

CREDENCE (T2DM+DKD)
eGFR# > 60: 40%
Micro:11·3%; Macro:88%



Adapted from Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. Kidney Int Suppl 2013;3:1

27
#mL/min/1.73m²

Curr Diab Rep. 2011;11(4):323 – 9.

27

SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis

Brendon L Neuen, Tamara Young, Hiddo J L Heerspink, Bruce Neal, Vlado Perkovic, Laurent Billot, Kenneth W Mahaffey, David M Charytan, David C Wheeler, Clare Arnott, Severine Bompoint, Adeera Levin, Meg J Jardine

Lancet Diabetes Endocrinol
2019; 7: 845–54

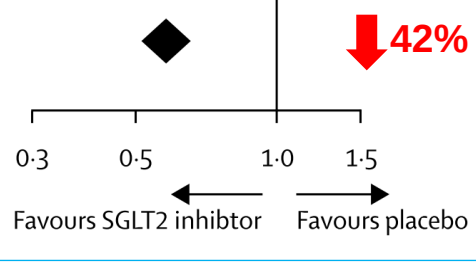
28

統合分析顯示SGLT-2i減少42%腎臟事件

Substantial loss of kidney function, ESKD, or death due to kidney disease

CREDENCE	377	4401	0·66 (0·53–0·81)
DECLARE–TIMI 58	365	17160	0·53 (0·43–0·66)
CANVAS Program	73	10142	0·53 (0·33–0·84)
EMPA–REG OUTCOME	152	6968	0·54 (0·40–0·75)
Overall			**0·58 (0·51–0·66; p<0·0001)**

I^2=0·0%; $p_{heterogeneity}$=0·49



RENAAL: ↓**16%** (Losartan), IDNT ↓**20%** (Irbesartan)

THE LANCET
Diabetes & Endocrinology
Lancet Diabetes Endocrinol. 2019 Nov;7(11):845-854.

29

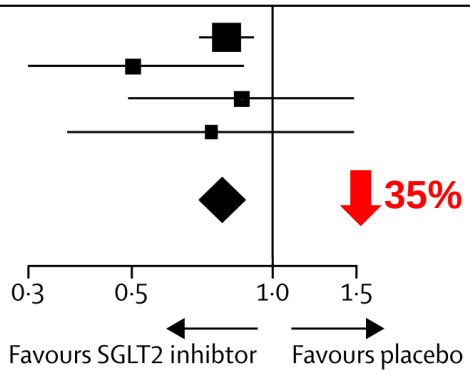
29

統合分析顯示SGLT-2i減少35%ESKD

ESKD

	Events	Patients	RR (95% CI)
CREDENCE	281	4401	0·68 (0·54–0·86)
DECLARE–TIMI 58	25	17160	0·31 (0·13–0·79)
CANVAS Program	18	10142	0·77 (0·30–1·97)
EMPA–REG OUTCOME	11	7020	0·60 (0·18–1·98)
Overall			0·65 (0·53–0·81; p<0·0001)

I^2=0·0%; $p_{heterogeneity}$=0·41



THE LANCET
Diabetes & Endocrinology
Lancet Diabetes Endocrinol. 2019 Nov;7(11):845-854.

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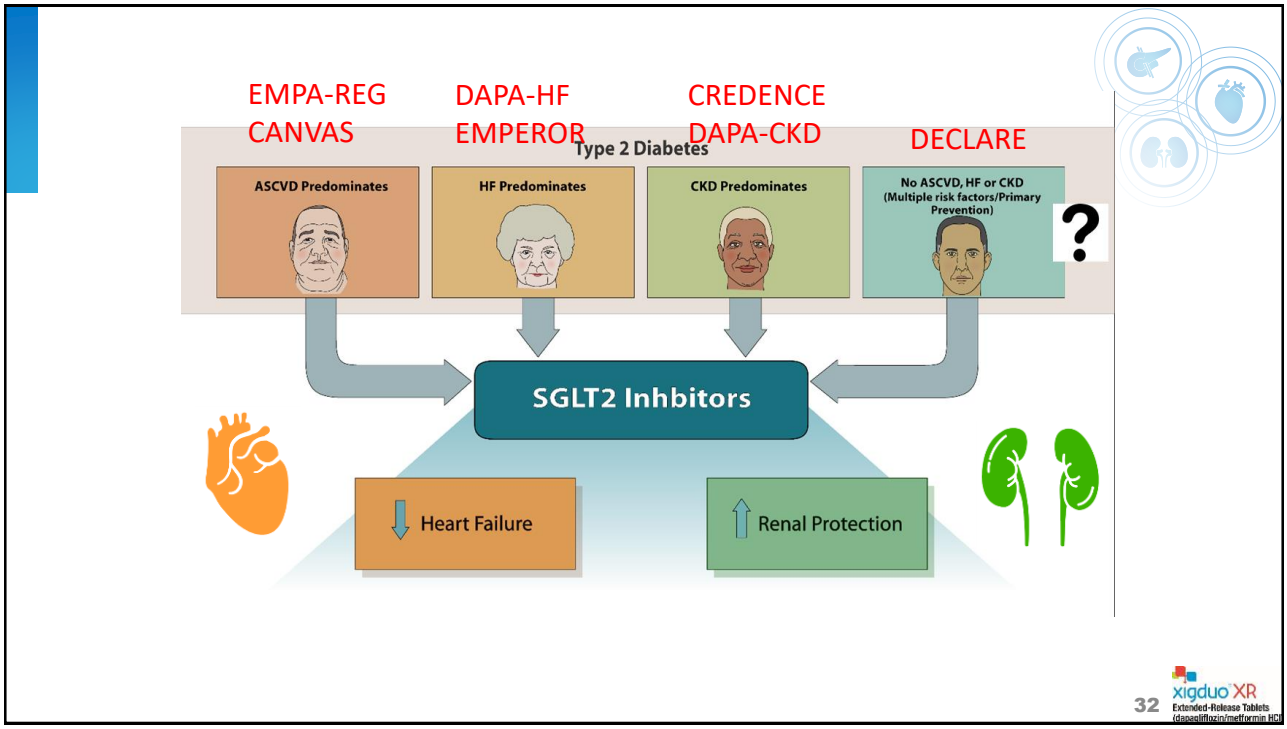
30

Question

1. 我們應該多早將SGLT-2i 納入治療策略, 以保護CKD?
2. High risk group primary prevention for CKD, DECLARE 提供的證據足夠嗎?

31

31



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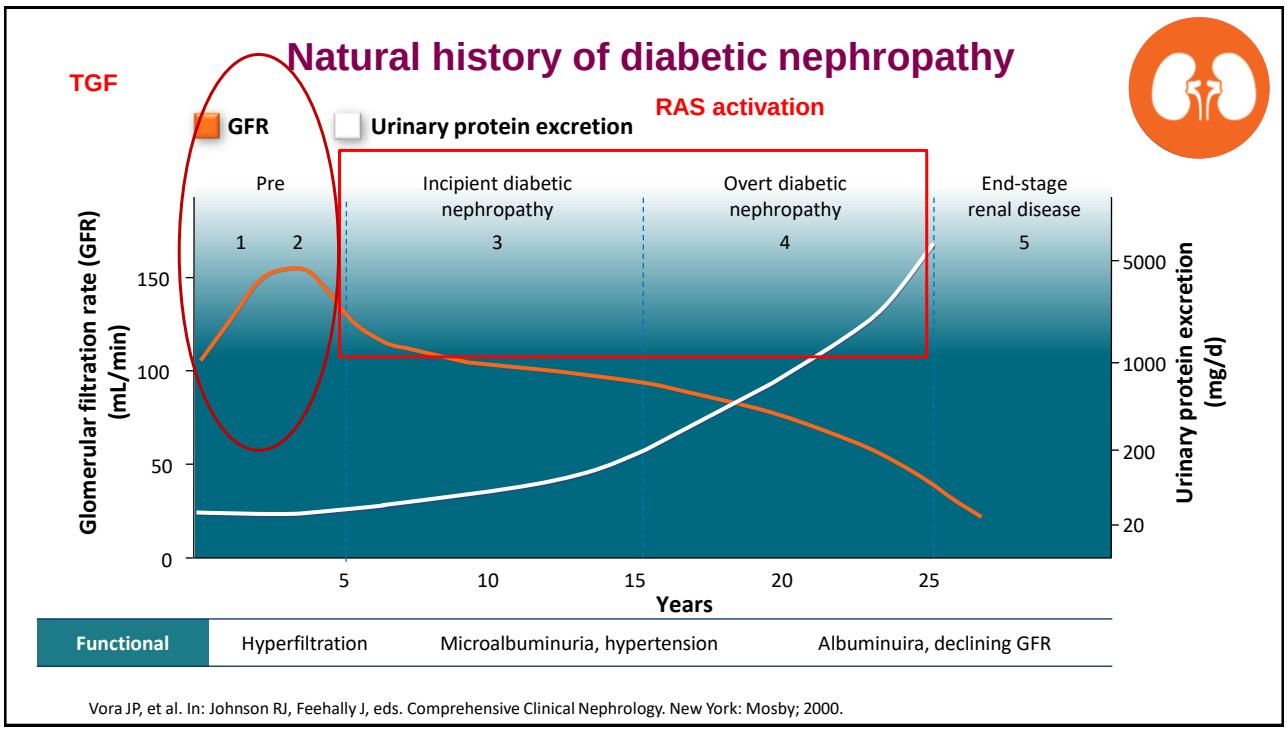
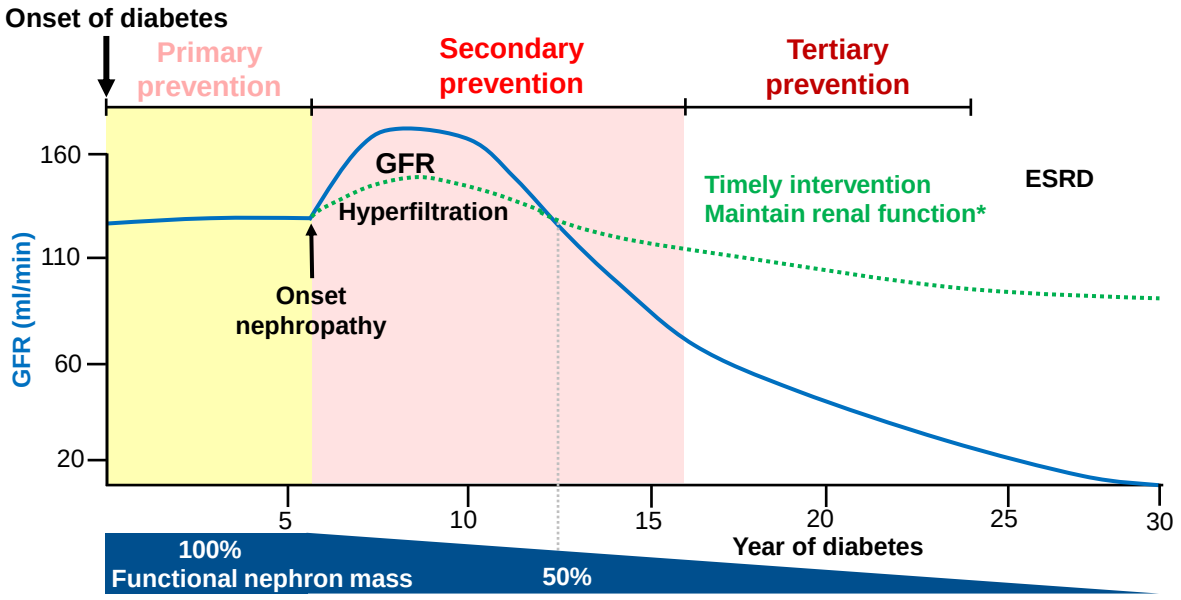


Vora JP, et al. In: Johnson RJ, Feehally J, eds. Comprehensive Clinical Nephrology. New York: Mosby; 2000.

33

理想的糖尿病腎病變介入：及時降低高過濾狀態，維持eGFR

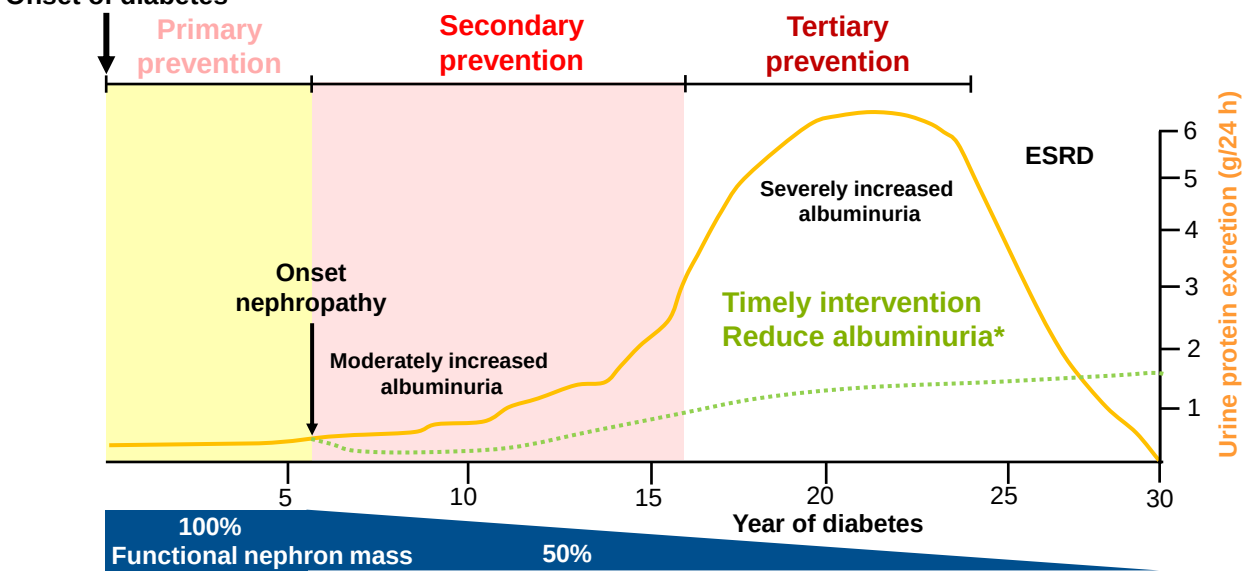


34

GFR: glomerular filtration rate, ESRD: end-stage renal disease. *Dot line in green is an assumed hypothesis.
1. Curr Diab Rep. 2015 Jul;15(7):44. 2. J Am Soc Nephrol. 2017 Apr;28(4):1023-1039.

34

理想的糖尿病腎病變介入：及時減少蛋白尿，降低蛋白尿惡化風險

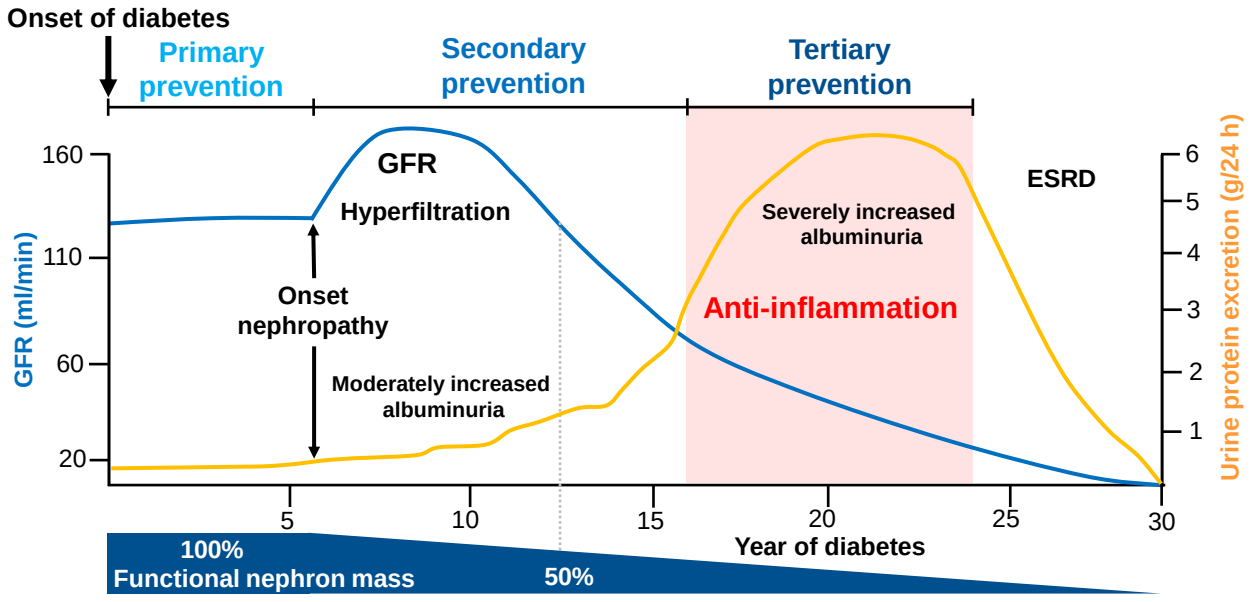


35

GFR: glomerular filtration rate, ESRD: end-stage renal disease. *Dot line in green is an assumed hypothesis.
1. Curr Diab Rep. 2015 Jul;15(7):44. 2. J Am Soc Nephrol. 2017 Apr;28(4):1023-1039.

35

糖尿病腎病變末期介入：抗發炎

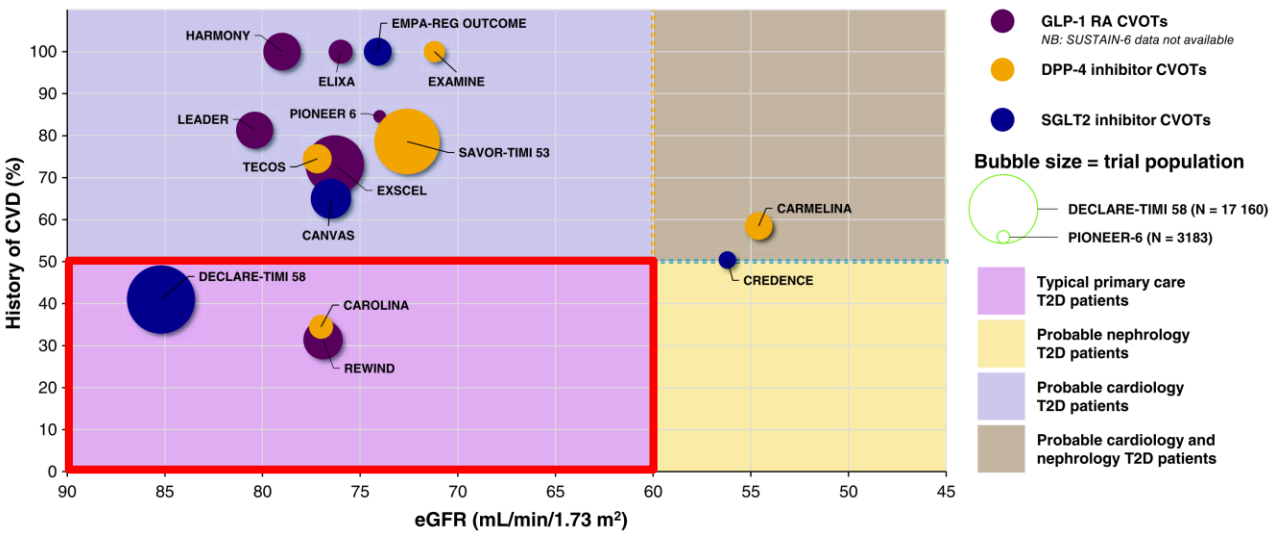


36

GFR: glomerular filtration rate, ESRD: end-stage renal disease. *Dot line in green is an assumed hypothesis.
1. Curr Diab Rep. 2015 Jul;15(7):44. 2. J Am Soc Nephrol. 2017 Apr;28(4):1023-1039.

36

DECLARE在CVOT中收納最多primary care的糖尿病患



37

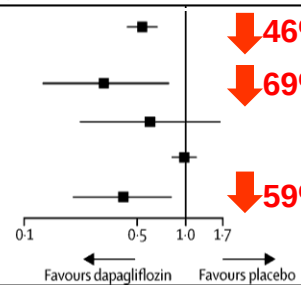
Diabetes Obes Metab. 2020 Sep;22(9):1481-1495.

37

The individual components of renal outcome in DECLARE

eGFR ↓ ≥40% to eGFR <60 mL/min per 1.73m² | **End-stage renal disease** | **Renal death** | **↓ 47%**

	Dapagliflozin group n/N (%)	Dapagliflozin group Kaplan-Meier event rate (4 years)	Placebo group n/N (%)	Placebo group Kaplan-Meier event rate (4 years)	Hazard ratio (95% CI)	p value
eGFR ↓ ≥40% to eGFR <60 mL/min per 1.73m²	120/8582 (1·4%)	1·4%	221/8578 (2·6%)	2·5%	↓46% 0·54 (0·43–0·67)	<0·0001
End-stage renal disease	6/8582 (0·1%)	0·1%	19/8578 (0·2%)	0·2%	↓69% 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
Cardiovascular death	245/8582 (2·9%)	2·7%	249/8578 (2·9%)	2·7%	0·98 (0·82–1·17)	0·83
End-stage renal disease or renal death	11/8582 (0·1%)	0·1%	27/8578 (0·3%)	0·3%	↓59% 0·41 (0·20–0·82)	0·012



American Diabetes Association. 79TH SCIENTIFIC SESSIONS SAN FRANCISCO, CA • JUNE 7 - 11, 2019

Lancet Diabetes Endocrinol. 2019 Aug; 7(8): 606-617.

38

eGFR好、無/微蛋白尿、未有CVD/CVD糖尿病患使用 FORXIGA皆一致有較低腎臟惡化事件風險

	Dapagliflozin group n/N (%)	Dapagliflozin group Kaplan-Meier event rate (4 years)	Placebo group n/N (%)	Placebo group Kaplan-Meier event rate (4 years)	Hazard ratio (95% CI)	p value	$p_{interaction}$
Medical history							
Established cardiovascular disease	65/3474 (1·9%)	1·9%	118/3500 (3·4%)	3·2%	0·55 (0·41–0·75)	0·0001	0·72
Multiple cardiovascular risk factors	62/5108 (1·2%)	1·2%	120/5078 (2·4%)	2·3%	0·51 (0·37–0·69)	<0·0001	
History of hypertension	122/7769 (1·6%)	1·6%	222/7658 (2·9%)	2·7%	0·54 (0·43–0·67)	<0·0001	0·41
No history of hypertension	5/813 (0·6%)	0·5%	16/920 (1·7%)	1·8%	0·36 (0·13–0·98)	0·046	
Laboratory measurements							
eGFR ≥90 mL/min per 1·73m²	41/4137 (1·0%)	1·0%	79/4025 (2·0%)	2·0%	0·50 (0·34–0·73)	0·0003	0·87
eGFR 60 to <90 mL/min per 1·73m²	65/3838 (1·7%)	1·6%	121/3894 (3·1%)	2·8%	0·54 (0·40–0·73)	<0·0001	
eGFR <60 mL/min per 1·73m²	21/606 (3·5%)	3·8%	38/659 (5·8%)	5·8%	0·60 (0·35–1·02)	0·059	
UACR <30 mg/g	50/5819 (0·9%)	0·9%	95/5825 (1·6%)	1·5%	0·52 (0·37–0·74)	0·0002	0·30
UACR 30–300 mg/g	39/2017 (1·9%)	2·0%	66/2013 (3·3%)	3·3%	0·59 (0·39–0·87)	0·0082	
UACR >300 mg/g	31/594 (5·2%)	4·8%	75/575 (13·0%)	12·8%	0·38 (0·25–0·58)	<0·0001	

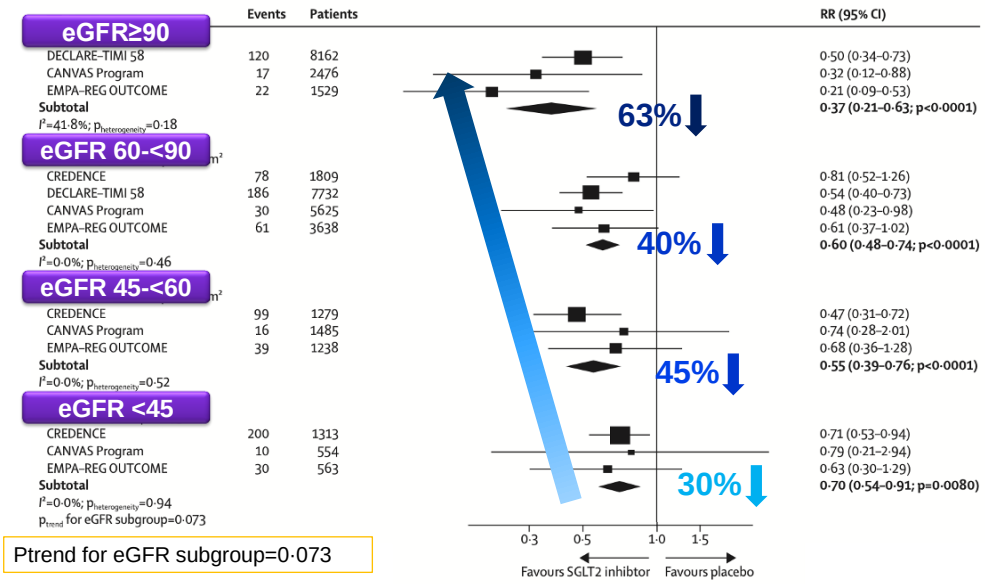
39 Prespecified exploratory endpoint: decrease eGFR ≥40% to <60 mL/min/1.73 m2, ESRD or Renal Death; UACR = urine albumin-creatinine ratio. Lancet Diabetes Endocrinol. 2019 Aug;7(8):606-617. AstraZeneca does not recommend the use of dapagliflozin for indications other than T2DM

forxiga (dapagliflozin) xigduo XR Extended-Release Tablets (dapagliflozin/metformin HCl) QTERN (saxagliptin/dapagliflozin)

39

SGLT-2i 統合分析：越早使用，腎臟惡化風險降低越多

Composite of substantial loss of kidney function, ESKD, or death due to kidney diseasestratified by the eGFR levels



Ptrend for eGFR subgroup=0·073

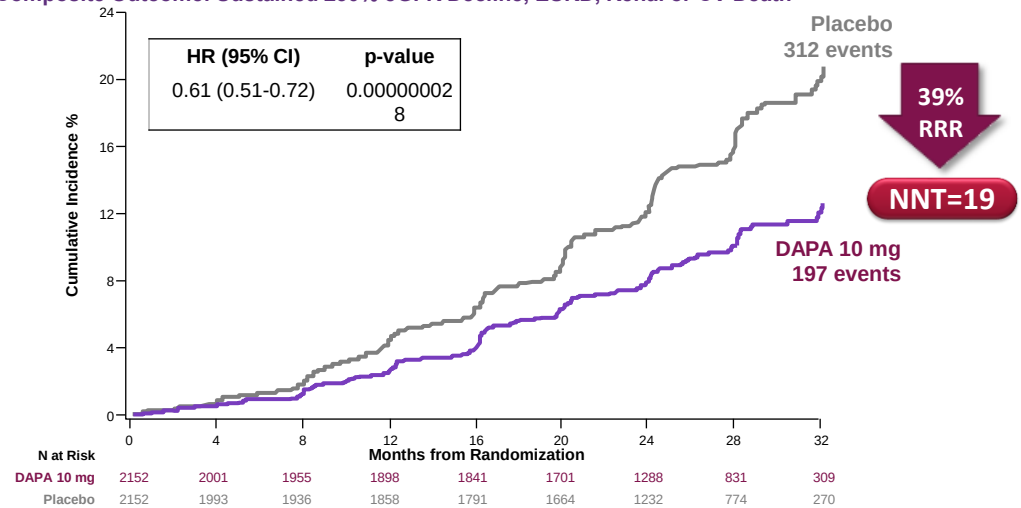
THE LANCET

40 Brendon L Neuen et al. Lancet Diabetes Endocrinol . 2019 Nov;7(11):845-854.

40

DAPA-CKD 試驗：FORXIGA相較於安慰劑組降低39%腎臟惡化事件

Primary Composite Outcome: Sustained ≥50% eGFR Decline, ESKD, Renal or CV Death[a]



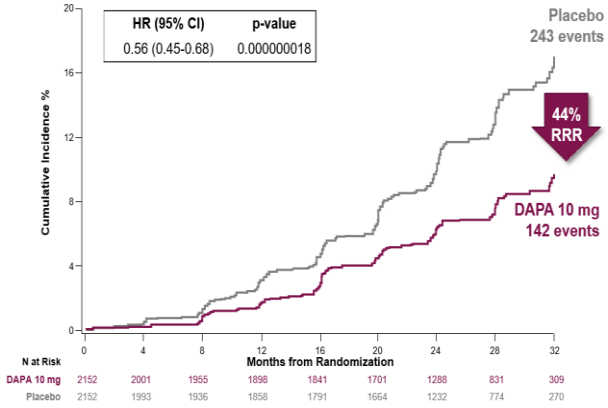
41

41

Dapagliflozin significantly reduced both secondary and exploratory renal composite outcomes (chronic dialysis, kidney transplantation or renal death)

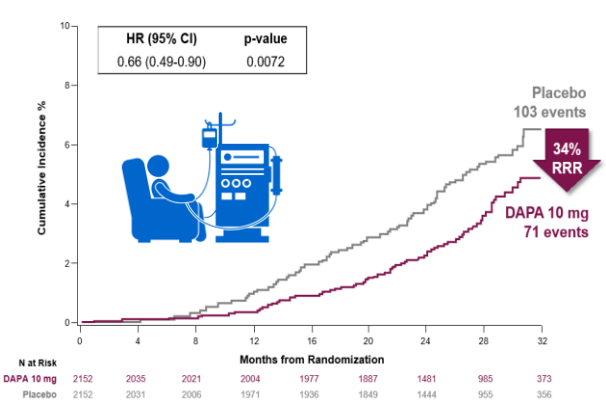
Secondary

Sustained ≥50% eGFR Decline, ESKD, or Renal Death[a]



Exploratory

Chronic Dialysis, Kidney Transplantation, or Renal Death



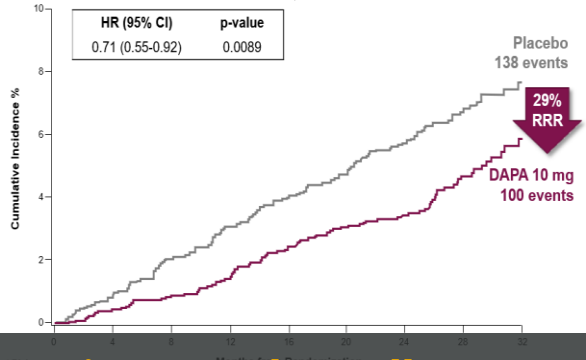
- [a]ESKD defined as the need for maintenance dialysis (peritoneal or hemodialysis) for at least 28 days and renal transplantation or sustained eGFR <15mL/min/1.73m^2 for at least 28 days. Renal death was defined as death due to ESKD when dialysis treatment was deliberately withheld for any reason.[2] DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HR = hazard ratio; RRR = relative risk reduction.
- 1. Heerspink HJL. Presented at: ESC Congress – The Digital Experience; August 29 - September 1, 2020. 2. Heerspink HJL et al. *Nephrol Dial Transplant*. 2020;35:274–282.

42

Dapagliflozin significantly reduced CV Death/hHF and all-cause mortality

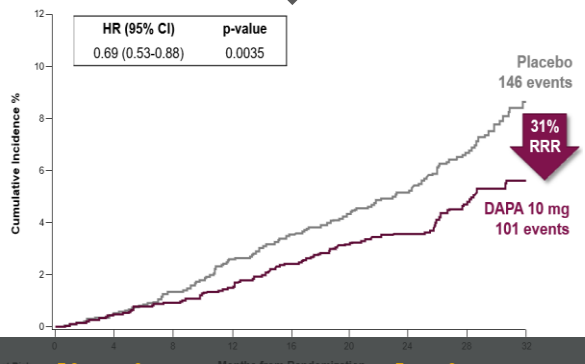
Secondary

CV Death or Hospitalization for Heart Failure



Secondary

All-Cause Mortality



First to reduce all-cause mortality in CKD population

- [a]ESKD defined as the need for maintenance dialysis (peritoneal or hemodialysis) for at least 28 days and renal transplantation or sustained eGFR <15mL/min/1.73m^2 for at least 28 days. Renal death was defined as death due to ESKD when dialysis treatment was deliberately withheld for any reason.[2] DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HR = hazard ratio; RRR = relative risk reduction.
- 1. Heerspink HJL. Presented at: ESC Congress – The Digital Experience; August 29 - September 1, 2020. 2. Heerspink HJL et al. *Nephrol Dial Transplant*. 2020;35:274–282.

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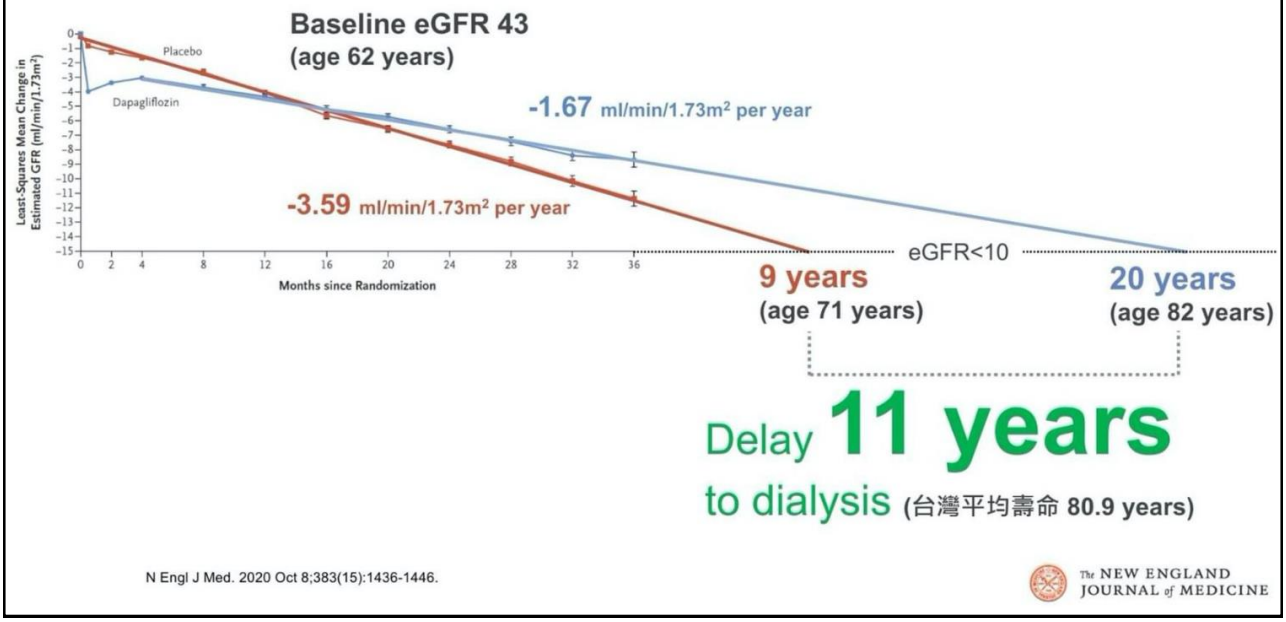
DAPACKD

Change from Baseline in eGFR

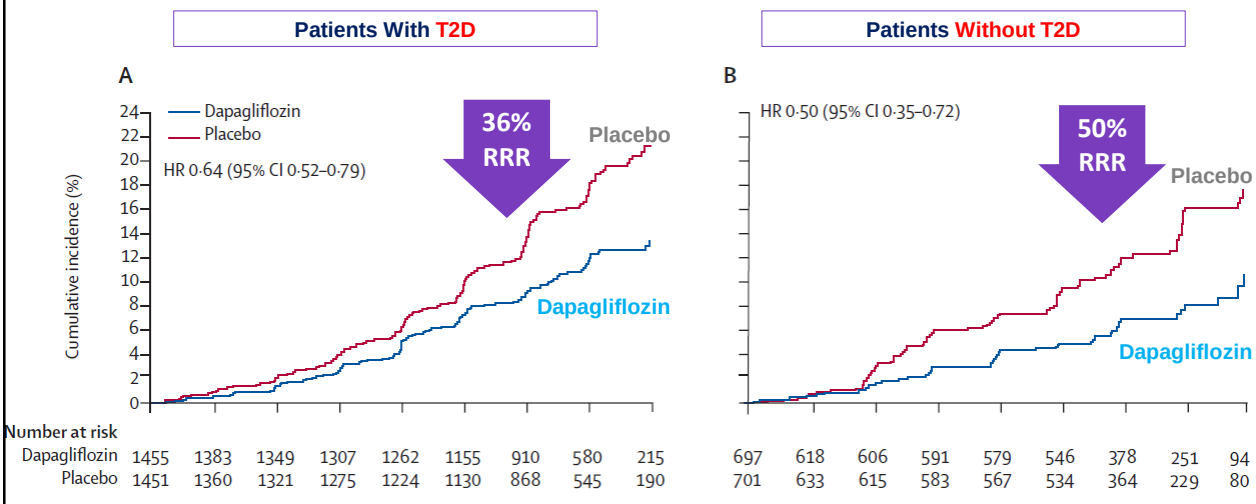


N Engl J Med. 2020 Oct 8;383(15):1436-1446.

The NEW ENGLAND JOURNAL of MEDICINE

44

DAPA-CKD 次分析:
不論有無糖尿病，FORXIGA皆能降低腎臟惡化事件風險

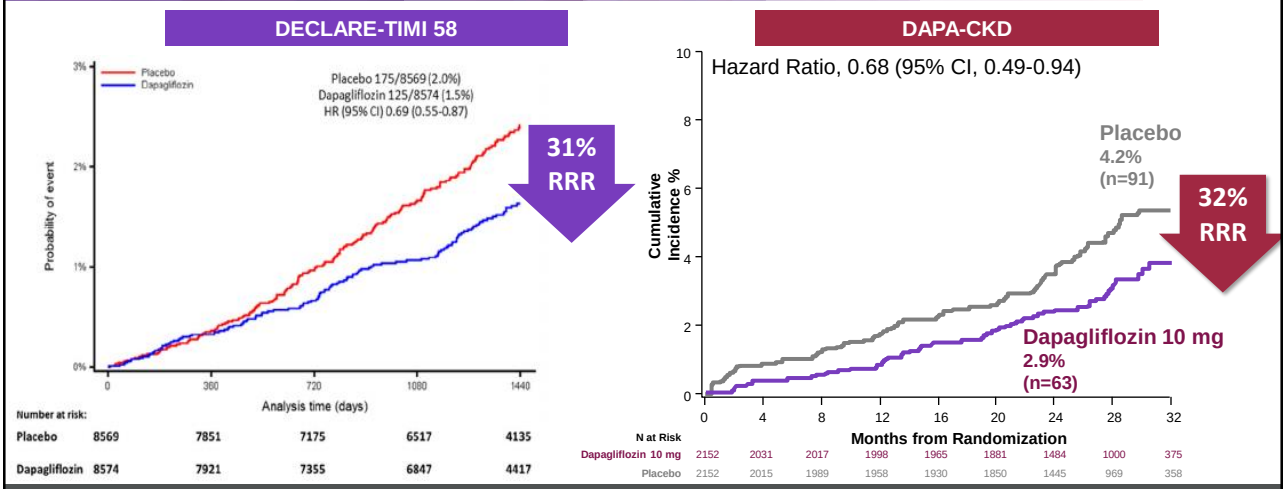


ESKD = end stage kidney disease; eGFR = estimated glomerular filtration rate; T2D = type 2 diabetes

45 Wheeler DC, et al. Lancet Diabetes Endocrinol. 2021 Jan;9(1):22-31.

45

DECLARE-TIMI 58 & DAPA-CKD觀察到FORXIGA不增加AKI發生率



Significantly fewer AKI events in dapa group vs placebo

AKI = acute kidney injury; CI = confidence interval
Cahn A, et al. Diabetes, obesity & metabolism. 2020.
Heerspink HJL et al. Presented at: ERA-EDTA Congress; June 5-8, 2021; Virtual.

46

46

Dapagliflozin Addresses the Burden of CKD Across the Disease Spectrum in T2D to Prevent Onset, Slow Progression and Improve Outcomes of Patients

DECLARE TIMI-58

Dapagliflozin has demonstrated significant reductions in the risk of new or worsening nephropathy in patients with T2D and predominantly preserved renal function[1–3]

DAPACKD

Dapagliflozin significantly reduced the risk of kidney disease progression, ESKD and risk of death in patients with CKD with and without T2D[4]

PREVENTION		TREATMENT
	Patient population	
17,160	**N**	4304
100	**Patients with T2D (%)**	68
13	**Median UACR (mg/g)**	949
85	**Mean eGFR (mL/min/1.73m²)**	43
	Outcomes	
47% RRR[a] (HR, 0.53 [95% CI, 0.43-0.66])	**Renal progression**	**44% RRR[b]** (HR, 0.56 [95% CI, 0.45-0.68])
17% RRR (HR, 0.83 [95% CI, 0.73-0.95])	**CV death or hHF**	**29% RRR** (HR, 0.71 [95% CI, 0.55-0.92])
NS (HR, 0.93 [95% CI, 0.82-1.04])	**All-cause mortality**	**31% RRR** (HR, 0.69 [95% CI, 0.53-0.88])

For reactive use only. This slide includes information for the purpose of scientific medical exchange only. AstraZeneca has no intention to promote its drugs outside of it approved indications.
See slide notes for footnotes, abbreviations, and references.

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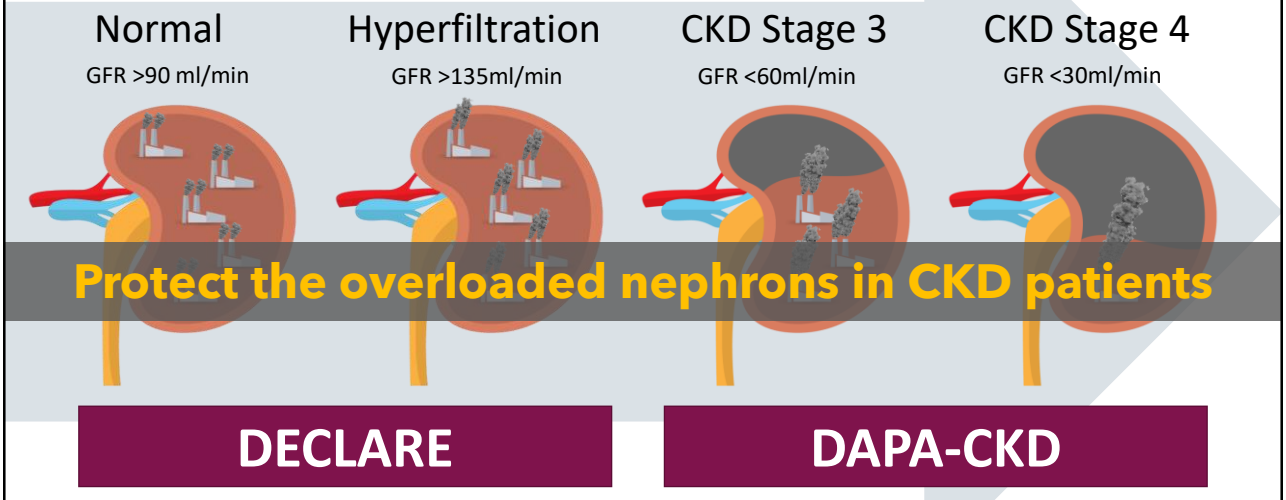
Glomerular hyperfiltration is the main culprits in CKD progression



DECLARE | **DAPA-CKD**

- Kanzaki G, et al. *Hypertension Res* 2015;38:633–641

Courtesy M. Eynatten

48

福適佳 膜衣錠 5 毫克、10 毫克
Forxiga Film-coated Tablets 5 mg, 10 mg

本藥須由醫師處方使用
5 毫克 衛部藥輸字第 026475 號
10 毫克 衛部藥輸字第 026476 號

1 適應症

1.1 第二型糖尿病

- 血糖控制：配合飲食和運動，以改善第二型糖尿病成人病人的血糖控制。
- 預防心血管事件：用於具第二型糖尿病且已有心血管疾病(CVD)或多重心血管風險因子的成人病人時，可降低心衰竭住院的風險。
- 預防腎臟病：降低慢性腎臟病(CKD)新發生或惡化的風險。

1.2 心衰竭

用於心衰竭(NYHA 分類第二至四級) 且心室射出分率降低(≤ 40%)的成人病人時，可降低心血管死亡和心衰竭住院的風險。

1.3 慢性腎臟病

用於治療有惡化風險之慢性腎臟病的成人病人時，可降低持續性腎絲球過濾率(eGFR)下降、末期腎病(ESKD)、心衰竭住院和心血管死亡的風險。

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Outline

- 台灣糖尿病腎心共病情況
- SGLT-2i 在 DKD 治療的角色
- SGLT-2i 在 HF 治療的角色

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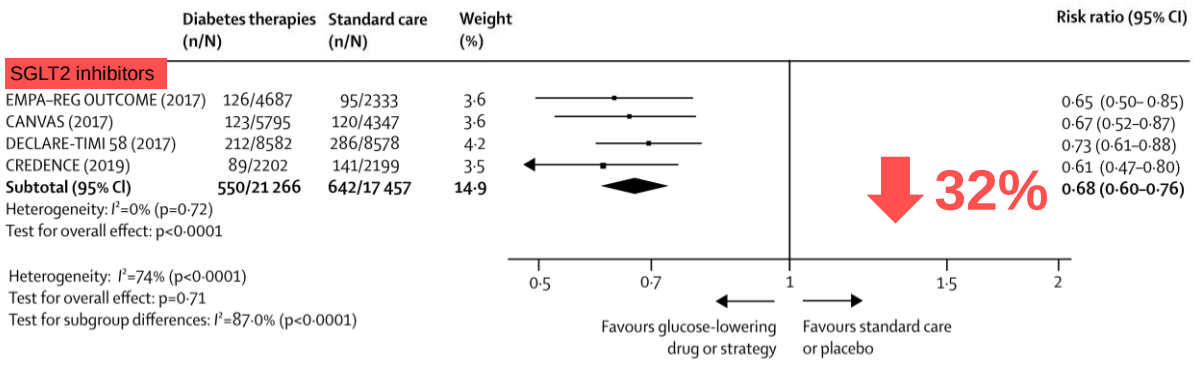
SGLT2i 能夠降低心衰竭住院風險



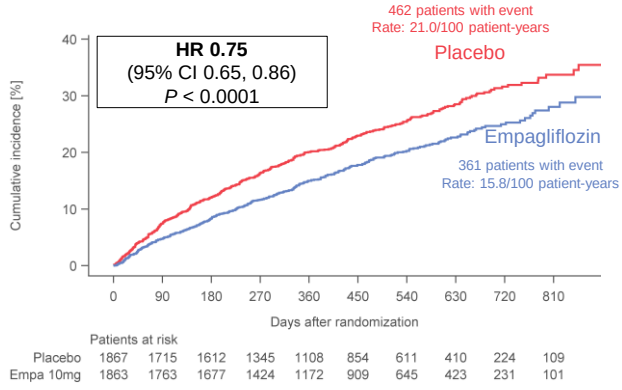
51

Lancet Diabetes Endocrinol. 2020 May;8(5):418-435. doi: 10.1016/S2213-8587(20)30038-3.

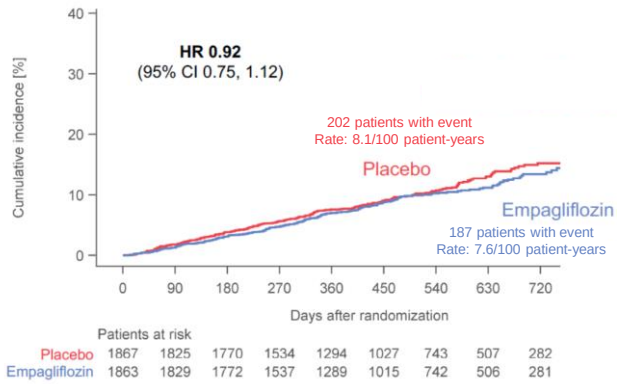
51

EMPEROR-Reduced: Primary endpoint

CV death or Hospitalization for Heart Failure



CV Death



N Engl J Med. 2020 Oct 8;383(15):1413-1424. Supplementary Appendx

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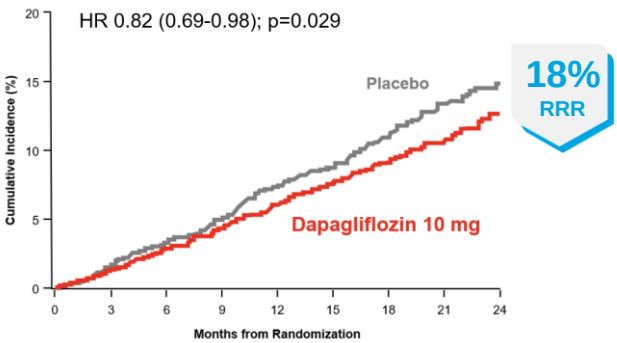
FORXIGA 唯一 SGLT-2i針對HFrEF

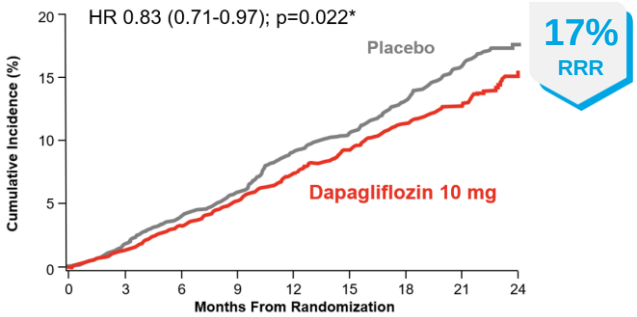
顯著減少心血管死亡、總死亡

DAPAHF

CV Death



All-cause Mortality



*nominal P value N Engl J Med. 2019 Nov 21;381(21):1995-2008.

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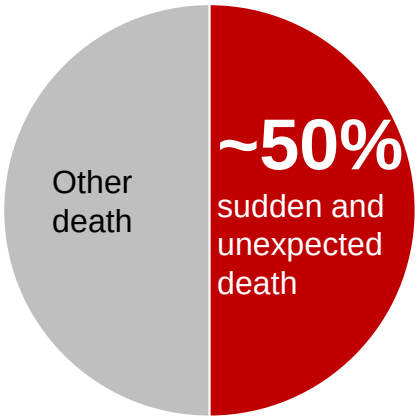
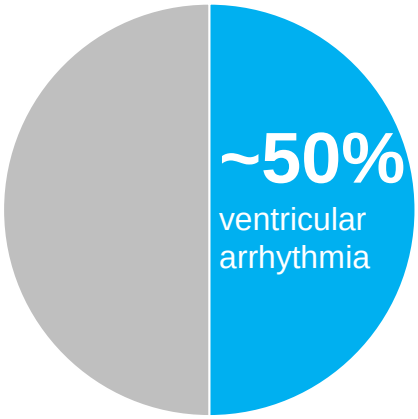
猝死及心室心律不整是心衰竭的重要死因

Ventricular arrhythmias are common and are one of the key causes of death in HFrEF

Death in patients with HF



~50% of the premature death are sudden and attributable to VT or VF in patients with HF



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VT: ventricular tachycardia, VF: ventricular fibrillation

1. Circ Res. 2004 Oct 15;95(8):754-63. 2. Pacing Clin Electrophysiol. 2001 May;24(5):871-88.

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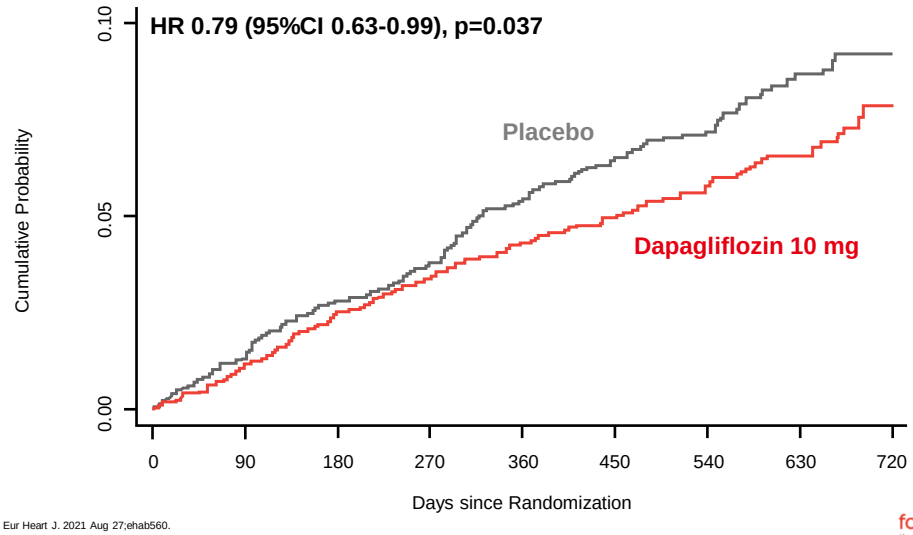
FORXIGA治療HFrEF 觀察到心室性心律不整、心臟驟停或猝死風險較低

DAPA-HF

Serious Ventricular Arrhythmia/Resuscitated Cardiac Arrest / Sudden Death



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Eur Heart J. 2021 Aug 27;ehab560.

AstraZeneca does not recommend the use of dapagliflozin for indications other than T2D, HFrEF or CKD

forxiga (dapagliflozin) xigduo XR Extended-Release Tablets (dapagliflozin/metformin HCl) QTERN (saxagliptin/dapagliflozin)

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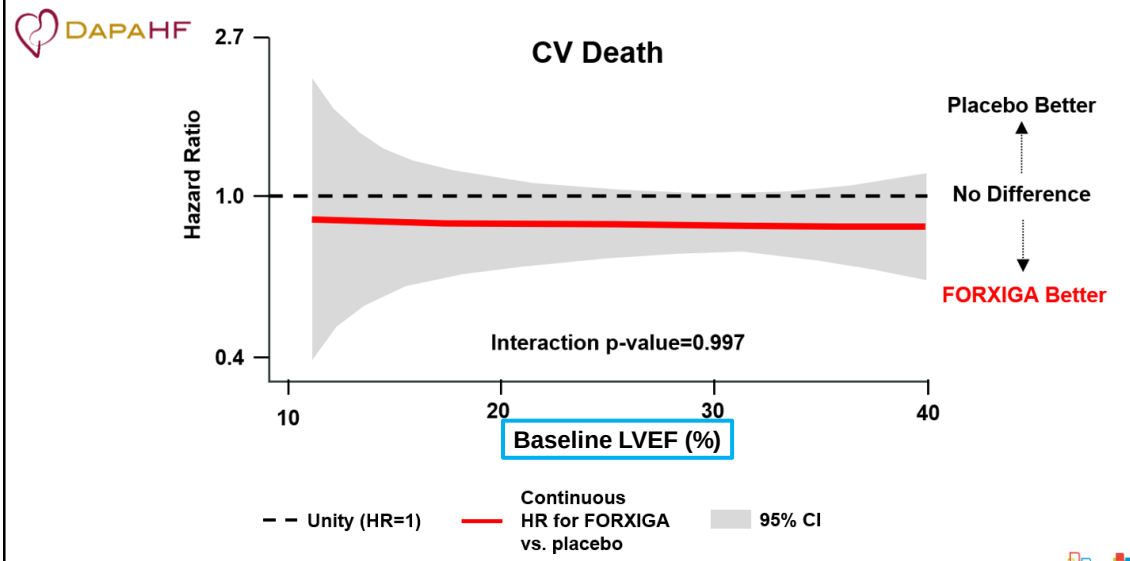
FORXIGA減少HFrEF心血管死亡 無差別LVEF



56 Eur J Heart Fail. 2020 Jul;22(7):1247-1258.

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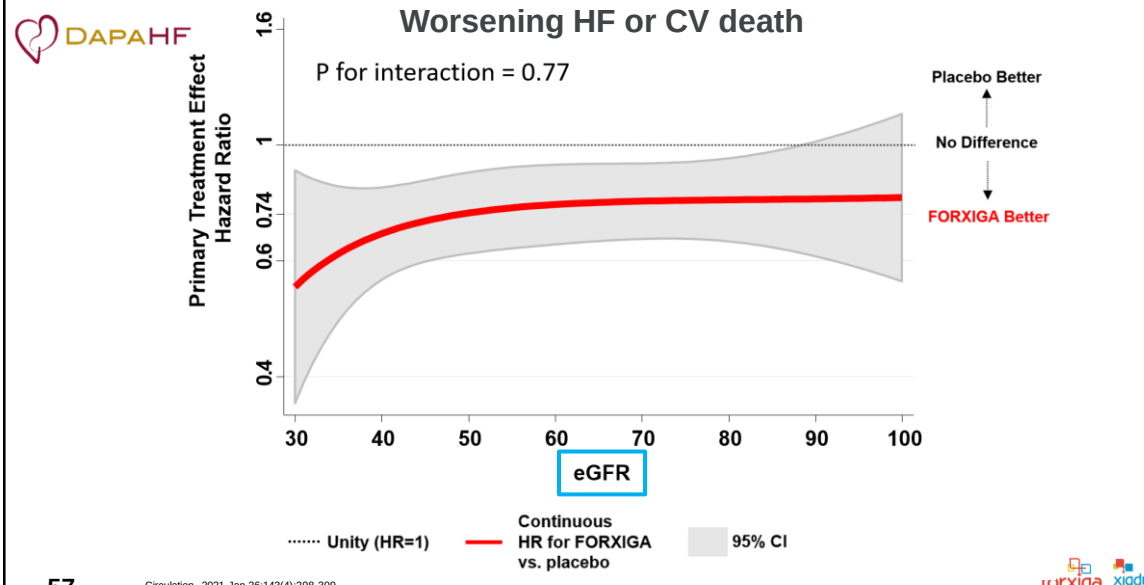
FORXIGA治療HFrEF療效 無差別eGFR高低



57 Circulation. 2021 Jan 26;143(4):298-309.

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2021 ESC HFA consensus: SGLT-2i適用HFrEF全部11種情境

Total 11 Scenarios

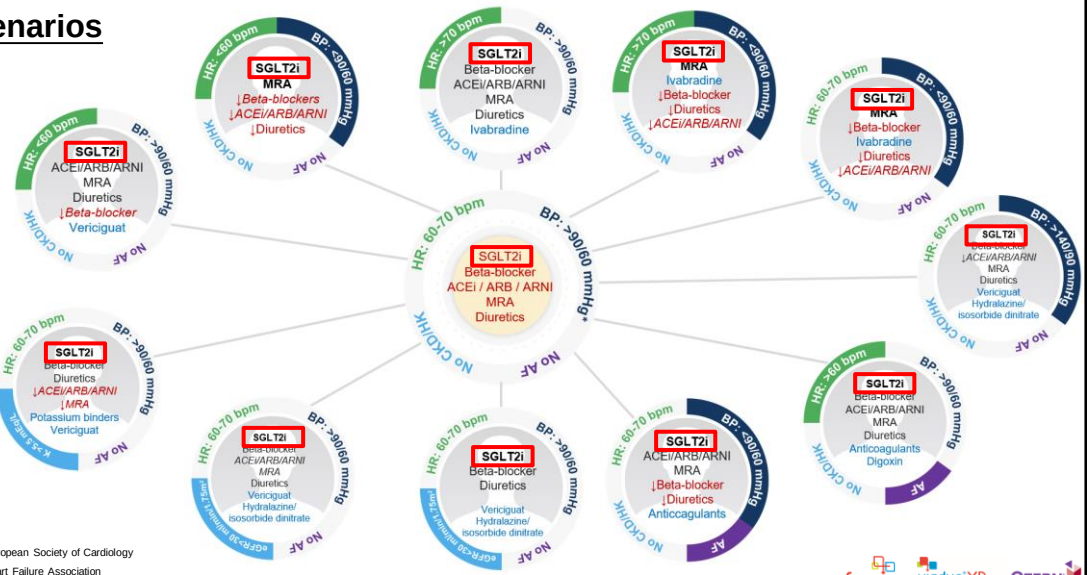
SGLT-2i: 11

RAASi: 6

BB: 6

MRA: 9

Diuretics: 7



ESC: European Society of Cardiology

HFA: Heart Failure Association

Eur J Heart Fail. 2021 Jun;23(6):872-881. *In patients with predominant chronic coronary syndrome, BP threshold is 120/80 mmHg.

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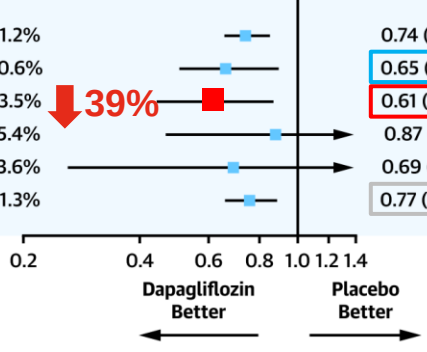
FORXIGA治療HFrEF東亞族群效果佳

DAPAHF

	Dapagliflozin	Placebo	Effect Estimate (95% CI)	Interaction *P* Value
Primary Composite Outcome				
All trial patients (n = 4,744)	16.3%	21.2%	0.74 (0.65, 0.85)	
Patients enrolled in Asia (n = 1,096)	14.2%	20.6%	0.65 (0.49, 0.87)	
East Asia (n = 721)	15.4%	23.5%	0.61 (0.43, 0.86)	0.32
South Asia (n = 237)	13.3%	15.4%	0.87 (0.45, 1.72)	
South-East Asia (n = 138)	9.7%	13.6%	0.69 (0.26, 1.85)	
Patients not enrolled in Asia (n = 3,648)	16.9%	21.3%	0.77 (0.66, 0.89)	



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JACC: Asia. Mar 29, 2022. Epublished DOI: 10.1016/j.jacasi.2022.02.004

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FORXIGA顯著減少HFrEF死亡、一天一次不需調整劑量，可同時治療CKD、T2D的優質治療選擇

In Heart Failure (HFrEF)	FORXIGA (dapagliflozin)	Empagliflozin	Sacubitril/ Valsartan	ACEI/ ARB	Beta Blockers	MRA
Composite endpoint of CV death or hospitalization for HF	✓	✓	✓	✓	✓	✓
CV death alone in RCT	✓	✗	✓	✓	✓	✓
Single dose/No titration	✓ 10 mg	✓ 10 mg	✗	✗	Depends#	✗
Once daily dose	✓	✓	✗	Depends#	✗	✓
Beyond Heart Failure#	**FORXIGA (dapagliflozin)**	**Empagliflozin**	**Sacubitril/ Valsartan**	**ACEI/ ARB**	**Beta Blockers**	**MRA**
Chronic kidney disease	✓	✗	✗	✓	✗	✗
Type 2 diabetes	✓	✓	✗	✗	✗	✗

#Depends on the specific agent in the class 1. FRORXIGA仿單: 核准治療第二型糖尿病、心衰竭、慢性腎臟病 2. Empagliflozin 10 mg仿單: 核准治療第二型糖尿病、心臟衰竭 3. Sacubitril/valsartan仿單: 核准治療慢性心臟衰竭 4. Enalapril仿單: 核准治療高血壓、充血性心臟衰竭 5. Ramipril仿單: 核准治療高血壓、心肌梗塞後的心衰竭、降低因心血管疾病導致之心肌梗塞、中風及死亡的危險 6. Lisinopril仿單: 核准治療高血壓、充血性心衰竭、急性心肌梗塞 7. Candesartan仿單: 核准治療本態性高血壓、左心室射出分率≤40%之心臟衰竭 8. Valsartan仿單: 核准治療高血壓、心衰竭、心肌梗塞後左心室功能異常 9. Bisoprolol仿單: 核准治療狹心症、高血壓、穩定型慢性中度至重度心衰竭 10. Carvedilol仿單: 核准治療高血壓、嬰血性心臟衰竭 11. Spironolactone仿單: 核准治療利尿、高血壓、原發性醛類酮過多症 12. Eplerenone 50 mg仿單: 核准治療心肌梗塞後之心衰竭、NYHA第II級(慢性)心衰竭、高血壓

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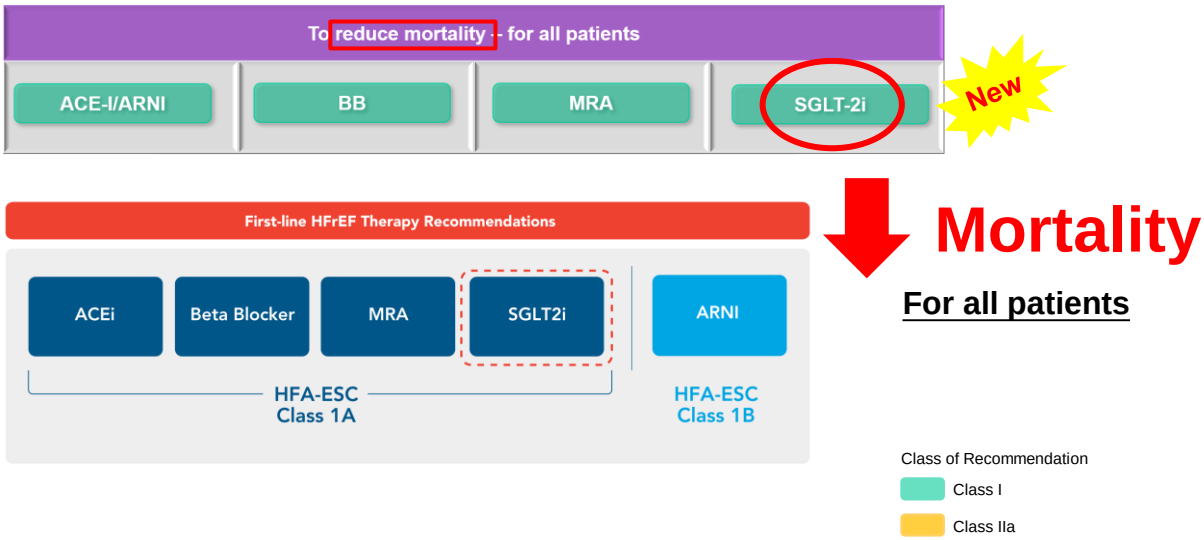
2021 ESC HF治療指引 class IA建議：SGLT-2i為一線用藥，為HFrEF患者降低死亡



Eur Heart J. 2021 Aug 27;ehab368.

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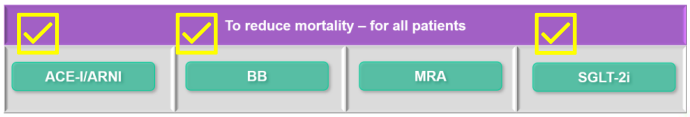
ESC HF指引建議一線降死亡藥物
FORXIGA心衰竭健保給付5/1生效

FORXIGA心衰竭健保給付流程 (自111年5月1日生效)

慢性收縮性心衰竭患者
NYHA II-IV
LVEF ≤40%
(初次使用需檢附一年內指定檢查之LVEF數值結果)

- ACEI or ARB ＋ β-blocker 最大耐受劑量 → ≥ 4周 → FORXIGA 10 mg
- ACEI or ARB & 因禁忌症而無法使用β-blocker → ≥ 4周 → FORXIGA 10 mg

2021 ESC HF治療指引 class IA建議：
SGLT-2i為一線用藥，為HFrEF患者降低死亡



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1. https://www.nhi.gov.tw/BBS_Detail.aspx?n=73CEDFC921268679&sms=D6D5367550F18590&s=3CFD97064180A136
2. Eur Heart J. 2021 Aug 27;ehab368.

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FORXIGA心衰竭健保給付規定 (自111年5月1日生效)

心衰竭功能分級(NYHA)	☐ 二級 ☐ 三級 ☐ 四級
左心室射出率(LVEF)	☐≤ 40% ※初次使用者須檢附一年內(擇一即可) ○ 心臟超音波 ○ 心導管左心室造影 ○ 核醫 ○ 電腦斷層 ○ 磁振造影 ○ 其他標準心臟功能檢查的左心室射出分率數值
傳統用藥	需符合以下2點： ☐ ACEI 或 ARB穩定劑量治療已達4 週(含)以上 ☐ 及 β-阻斷劑最大可耐受劑量已達4 週(含)以上 或β-阻斷劑有禁忌症而無法使用，仍有心衰竭症狀者。

63 https://www.nhi.gov.tw/BBS_Detail.aspx?n=73CEDFC921268679&sms=D6D5367550F18590&s=3CFD97064180A136

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Thank you and QA

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