Evidence-Based Medicine

Do the kidney protective benefits of SGLT 2 inhibitors in non diabetes patients with chronic kidney disease or heart failure disease

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指導藥師：陳新中 藥師

112.03.30

臨床情境

陳小姐，81歲女性，eGFR：35 ml/min/1.73m2，UPCR(Urine Protein / Creatinine Ratio) 1100 mg/g，Grade 3b 的慢性腎臟病(CKD)病患，BP：150~160mm/hg，過去病史有高血壓，高血脂，及正常收縮分率心臟衰竭(HFpEF Class III)，無糖尿病及無腎臟移植病史，目前相關用藥有使用Amlodipine 5mg QD, Pentoxifylline 100mg QD , Carvedilol 25mg #0.5 tab BID，Sacubitril+Valsartan(Entresto®)200mg #0.5tab BID 。

陳小姐女兒為護理師，打電話詢問藥師：醫生告訴我媽媽，目前處於CKD Grade 3 b，屬於pre ESRD階段，目前首要目標就是減緩腎惡化，避免進入至末期腎臟病，及降低其他相關心血管風險。最近國外有越多文獻分析SGLT-2 inhibitor此機轉用藥，除了在原本糖尿病族群有此方面好處外，甚至也可推廣至無糖尿病的心衰竭族群或慢性腎臟病族群。

請問藥師:對我媽媽而言，適合使用SGLT-2 inhibitor來減緩腎惡化或進入末期腎疾病?若比現在藥物相比需多負擔多少額外成本，及其效益考量呢？

目錄

01

Asking

根據臨床問題 形成PICO

P

陳小姐，81歲女性，eGFR：35 ml/min/1.73m2，UPCR(Urine Protein / Creatinine Ratio) 1100 mg/g，**Grade 3b 的慢性腎臟病(CKD)病患**，BP：150~160mm/hg，過去病史有高血壓，高血脂，及**正常收縮分率心臟衰竭(HFpEF Class III)**，**無糖尿病**及無腎臟移植病史，目前相關用藥有使用Amlodipine 5mg QD, Pentoxifylline 100mg QD , Carvedilol 25mg #0.5 tab BID , Sacubitril+Valsartan(Entresto®)200mg #0.5tab BID 。

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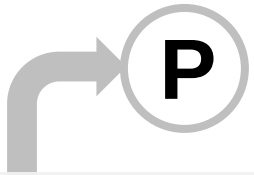
I

O

根據臨床問題 形成PICO



Keywords			
P	Chronic kidney disease Heart failure No diabetes	I	Sodium-Glucose Transporter 2 Inhibitors
C	Standard care	O	Kidney disease outcome，End stage renal disease

Type of Question:

✓ Intervention ☐ Harm ☐ Diagnosis ☐ Prognosis ☐ Etiology

適當的文獻類型

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or *n*-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non -randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

背景知識

Chronic kidney disease

Definition Abnormalities of kidney structure or function, present for >3 months

Criteria for CKD (either of the following present > 3months)	
1. Decreased	GFR < 60ml/min per 1.73 m^2 , (GFR categories G3a-G5)
2. Markers of kidney damage (one or more)	• Albuminuria (AER ≥>30mg/24h;ACR ≥30 mg/g (≥3 mg/mmol)) • Urine sediment abnormalities • Electrolyte and other abnormalities due to tubular disorders • Abnormalities detected by histology • Structural abnormalities detected by imaging • History of kidney transplantation

ACR：Albumin-to-creatinine ratio; AER：Albumin excretion rate; GFR：glomerular filtration rate

KDOQI and KDIGO 2012 guidelines

背景知識

Chronic kidney disease

Staging

GFR stages

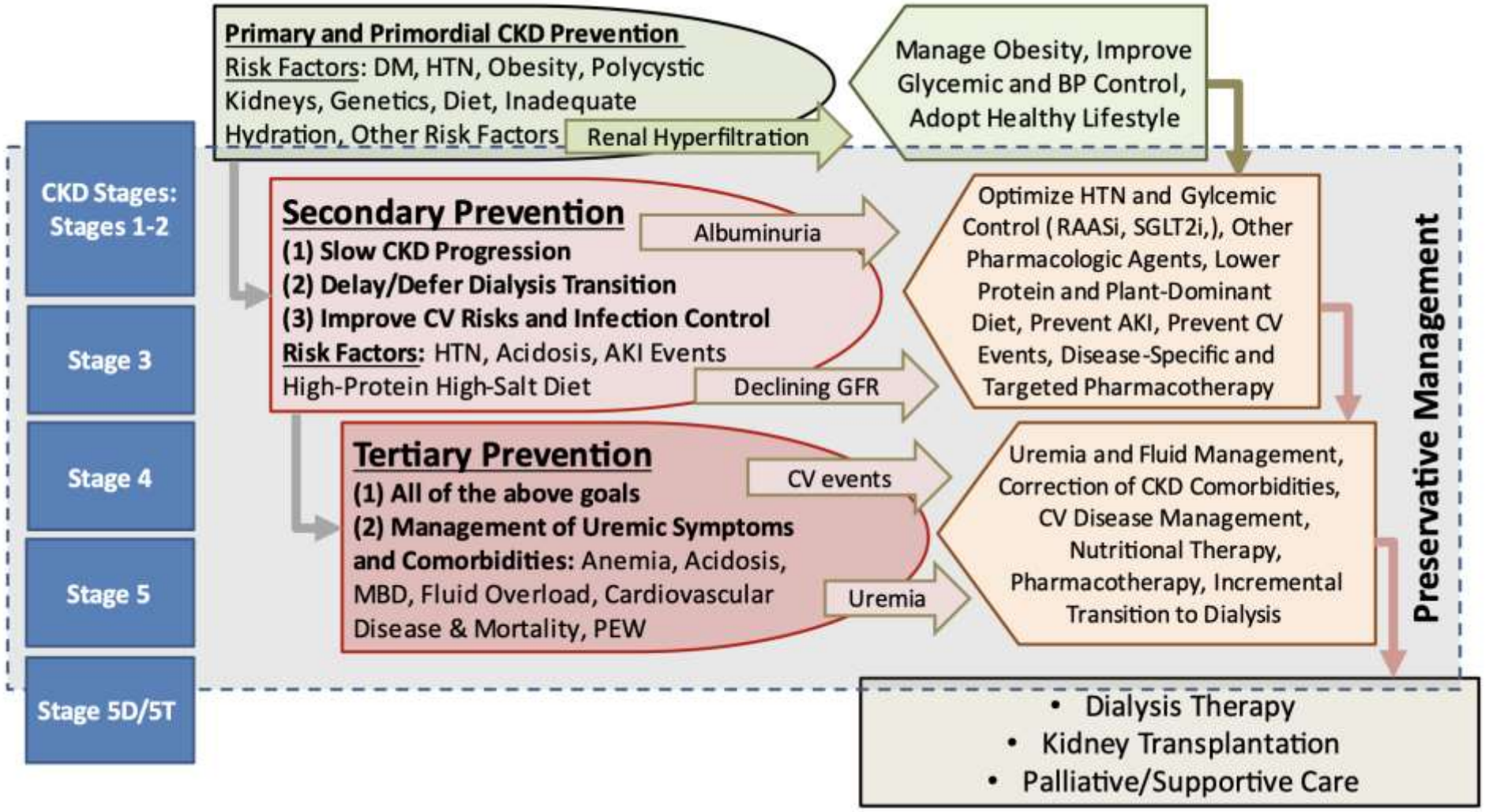
Albuminuria stages

GFR categories (mL/min/1.73 m²) description and range				Persistent albuminuria categories description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90	1 if CKD	1	2
	G2	Mildly decreased	60-89	1 if CKD	1	2
	G3a	Mildly to moderately decreased	45-59	1	2	3
	G3b	Moderately to severely decreased	30-44	2	3	3
	G4	Severely decreased	15-29	3	3	4+
	G5	Kidney failure	<15	4+	4+	4+

KDOQI and KDIGO 2012 guidelines

背景知識

Risk factors and treatment goal



Lancet chronic kidney disease 2021; 398: 786–802

背景知識

Pharmacotherapy

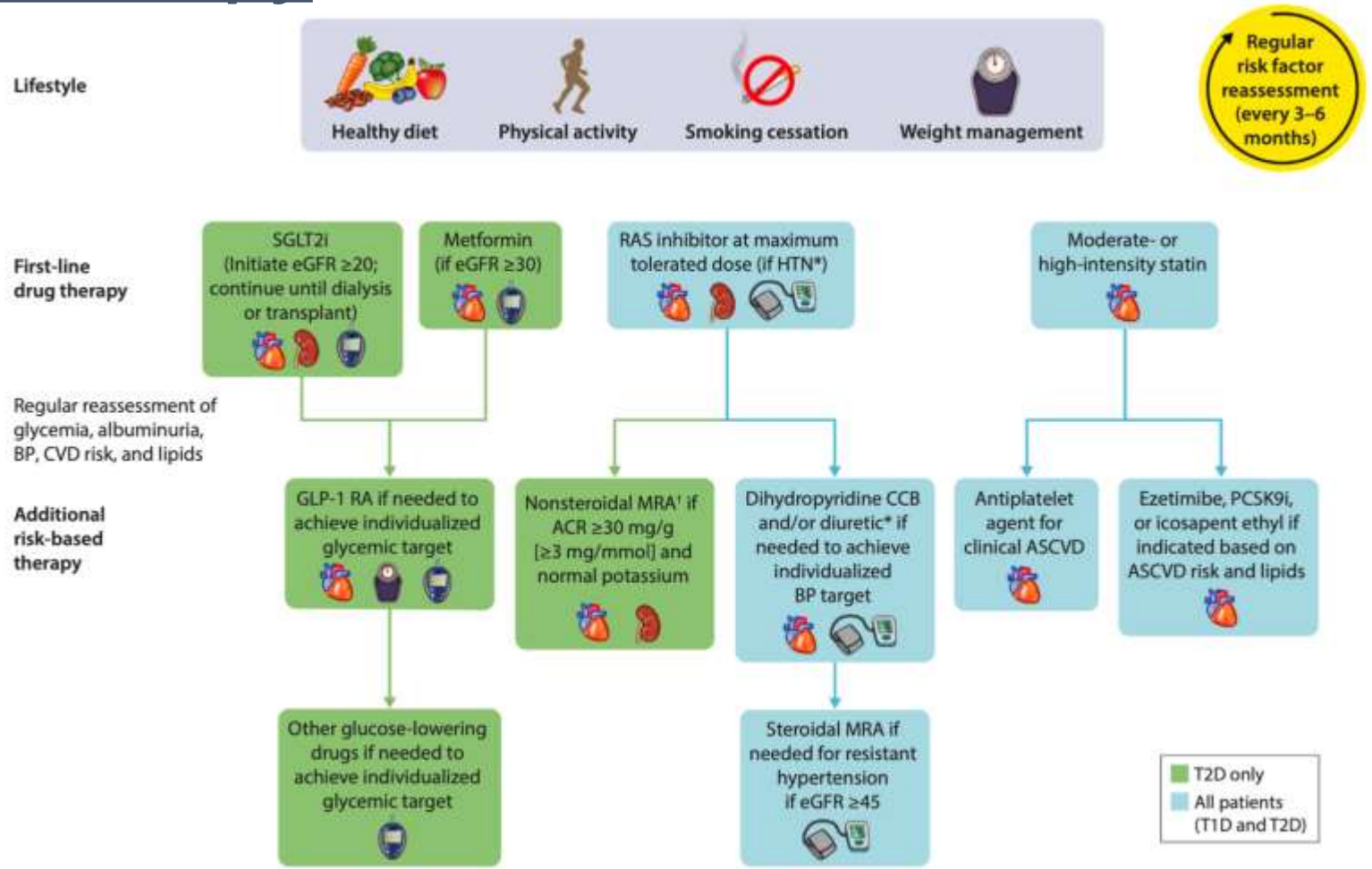


Figure 3 | Holistic approach for improving outcomes in patients with diabetes and chronic kidney disease. *Angiotensin-converting

KDIGO 2022 guideline for Diabetes in CKD

背景知識

Pharmacotherapy

SGLT2 inhibitors

Recommendation 1.3.1: We recommend treating patients with type 2 diabetes (T2D), CKD, and an eGFR ≥20 ml/min per 1.73 m^2 with an SGLT2i (1A).

Practice Point 1.3.1: The recommendation for SGLT2i is for kidney and cardiovascular protection and SGLT2i have been shown to have safety and benefit in CKD patients, even for those without T2D. Thus, if patients are already being treated with other glucose-lowering agents, an SGLT2i can be added to the current treatment regimen.

Practice Point 1.3.2: The choice of an SGLT2i should prioritize agents with documented kidney or cardiovascular benefits and take eGFR into account.

Practice Point 1.3.3: It is reasonable to withhold SGLT2i during times of prolonged fasting, surgery, or critical medical illness (when patients may be at greater risk for ketosis).

Practice Point 1.3.4: If a patient is at risk for hypovolemia, consider decreasing thiazide or loop diuretic dosages before commencement of SGLT2i treatment, advise patients about symptoms of volume depletion and low blood pressure, and follow up on volume status after drug initiation.

Practice Point 1.3.5: A reversible decrease in the eGFR with commencement of SGLT2i treatment may occur and is generally not an indication to discontinue therapy.

Practice Point 1.3.6: Once an SGLT2i is initiated, it is reasonable to continue an SGLT2i even if the eGFR falls below 20 ml/min per 1.73 m^2, unless it is not tolerated or kidney replacement therapy is initiated.

Practice Point 1.3.7: SGLT2i have not been adequately studied in kidney transplant recipients, who may benefit from SGLT2i treatment, but are immunosuppressed and potentially at increased risk for infections; therefore, the recommendation to use SGLT2i does not apply to kidney transplant recipients (see Recommendation 1.3.1).

KDIGO 2022 guideline for Diabetes in CKD

背景知識

Pharmacotherapy

Sodium glucose transporter 2 inhibitors

Mechanism

Inhibit sodium and glucose reabsorption in the proximal tubule, leading to increased sodium and chloride delivery to the macula densa. This results in vasoconstriction in the afferent arteriolar secondary to adenosine-mediated myogenic activation which leads to a reduction in the intra-glomerular pressure and glomerular filtration rate

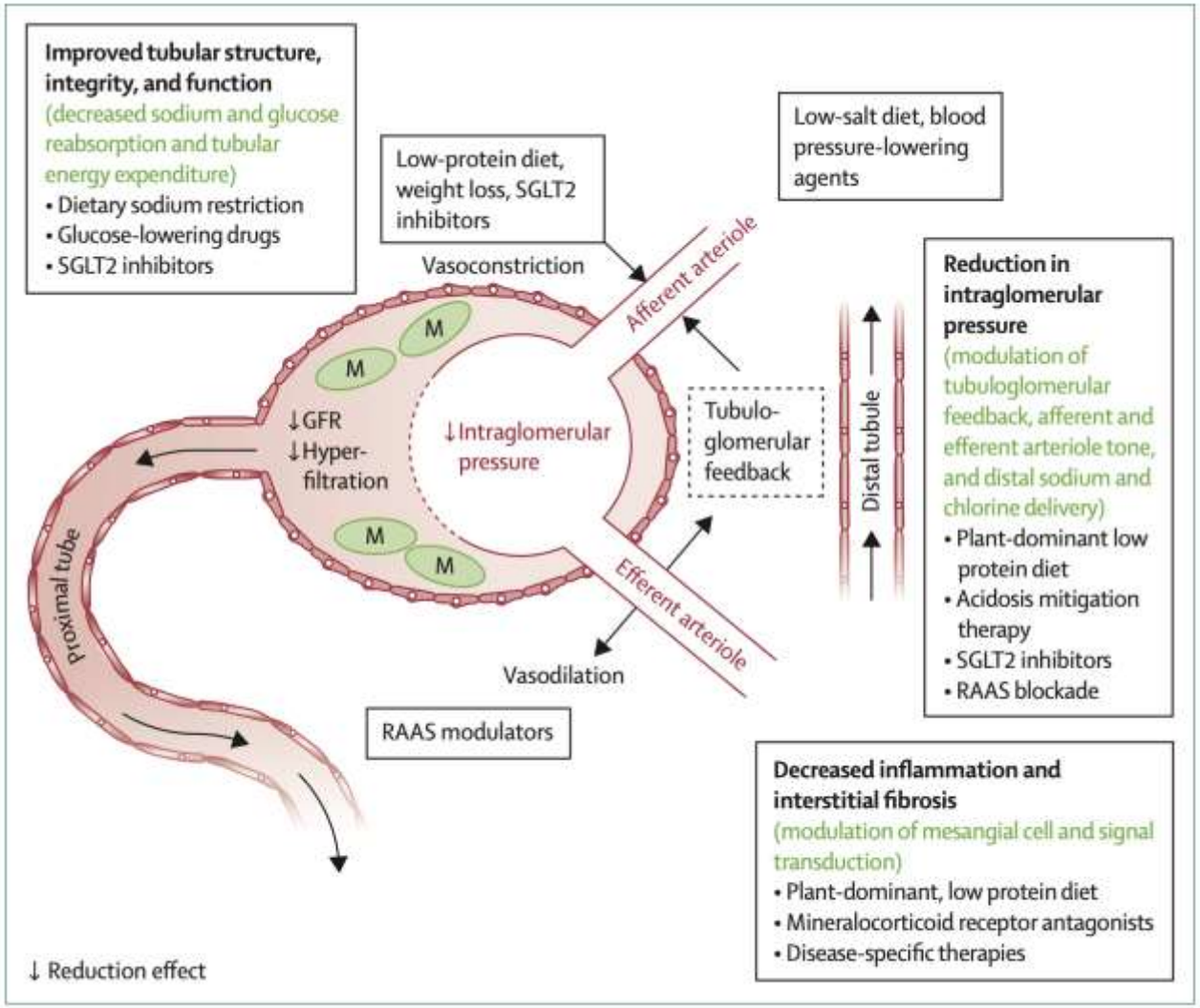


Figure 2: **Effects of dietary protein and sodium intake and pharmacological therapies on afferent and efferent arteriolar tone, intraglomerular pressure, and glomerular structures and functions**

Lancet chronic kidney disease 2021; 398: 786–802

02

Acquiring

搜索策略-關鍵字

	Keywords	Mesh/Emtree term
P	(Chronic Kidney Disease) or (Heart failure) Non diabetes	Chronic kidney disease Renal Insufficiency, Chronic Heart failure Heart failure
I	Sodium-Glucose Transporter 2 Inhibitors	Sodium-Glucose Transporter 2 Inhibitors
C	Standard care	-
O	Kidney outcomes ,Renal outcomes	

搜尋策略	針對**P,I,C** 輸入適當關鍵字以及同義詞運用布林邏輯Filter，再設立Outcome	
限定搜尋範圍	• **Systematic review, Meta analysis**	• 時間：1~2 年

搜索策略-Pubmed

Search	Actions	Details	Query	Results	Time
#8	···	›	Search: **(((renal insufficiency chronic[MeSH Terms]) OR (Heart Failure[MeSH Terms])) AND (Sodium-Glucose Transporter 2 Inhibitors[MeSH Terms])) AND ((kidney outcome) OR (renal outcome))** Filters: **Full text, Meta-Analysis, Systematic Review, in the last 1 year**	19	01:29:18
#7	···	›	Search: **(((renal insufficiency chronic[MeSH Terms]) OR (Heart Failure[MeSH Terms])) AND (Sodium-Glucose Transporter 2 Inhibitors[MeSH Terms])) AND ((kidney outcome) OR (renal outcome))** Filters: **Full text, Meta-Analysis, Randomized Controlled Trial, Systematic Review, in the last 1 year**	42	01:29:01
#6	···	›	Search: **(kidney outcome) OR (renal outcome)** Filters: **Full text, Meta-Analysis, Randomized Controlled Trial, Systematic Review, in the last 1 year**	1,656	01:28:25
#5	···	›	Search: **((renal insufficiency chronic[MeSH Terms]) OR (Heart Failure[MeSH Terms])) AND (Sodium-Glucose Transporter 2 Inhibitors[MeSH Terms])** Filters: **Full text, Meta-Analysis, Randomized Controlled Trial, Systematic Review, in the last 1 year**	86	01:27:51
#4	···	›	Search: **Sodium-Glucose Transporter 2 Inhibitors[MeSH Terms]** Filters: **Full text, Meta-Analysis, Randomized Controlled Trial, Systematic Review, in the last 1 year**	195	01:27:21
#3	···	›	Search: **(renal insufficiency chronic[MeSH Terms]) OR (Heart Failure[MeSH Terms])** Filters: **Full text, Meta-Analysis, Randomized Controlled Trial, Systematic Review, in the last 1 year**	1,106	01:26:35
#2	···	›	Search: **Heart Failure[MeSH Terms]** Filters: **Full text, Meta-Analysis, Randomized Controlled Trial, Systematic Review, in the last 1 year**	710	01:25:53
#1	···	›	Search: **renal insufficiency chronic[MeSH Terms]** Filters: **Full text, Meta-Analysis, Randomized Controlled Trial, Systematic Review, in the last 1 year**	426	01:24:48

Article type limitation

P+I+O

Outcome

P+I

Intervention

Population

搜索策略-關鍵字

使用Embase PICO search
Emtree及free text
同時使用Syn語法

Embase

Population e.g. diabetes

chronic kidney failure /exp | 13 synonyms :all | OR

heart failure /exp | 21 synonyms :all

Intervention e.g. insulin

sodium glucose cotransporter 2 inhibitor /exp | 9 synonyms :all

Comparison e.g. placebo

Outcome e.g. risk

kidney outcomes :all | OR | renal outcomes :all

Study design e.g. randomized controlled trial

systematic review /exp | 2 synonyms :all | OR

meta analysis /exp | 4 synonyms :all

Show 44 results

搜索策略-Cochrane

Cochrane Library

Advanced Search

Search | Search manager | Medical terms (MeSH) | PICO search

Save this search | View/Share saved searches | ? Search help

Print search history

#1	MeSH descriptor: [Renal Insufficiency, Chronic] this term only	MeSH		3452
#2	MeSH descriptor: [Heart Failure] this term only	MeSH		12103
#3	#1 or #2	Limits		15433
#4	Sodium glucose co-transporter 2 inhibitors	Limits		400
#5	kidney outcomes or renal outcomes	Limits		17411
#6	#3 and #4 and #5	Limits		23
#7	#6	Limits		5

with Cochrane Library publication date in The last year, in Trials

Population

Intervention

Outcome

P+I+O

Article type limitation

搜索結果

			
Screening Process			
Number	5	19	44
Title review			
Not target our PICO	5	16	41
SR or MA	0	3	3

搜索結果

年份	文章名稱
202211	Articles Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials The Nuffield Department of Population Health Renal Studies Group* and the SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium*

Lancet 2022; 400: 1788–801

比較搜索結果-選出最佳文獻

S	Systematic Review and Meta-analysis	
P	Chronic Kidney Disease or heart failure	
I	Sodium-Glucose Transporter 2 Inhibitors	
C	Standard care	
O	Kidney outcomes or Renal outcomes	

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202211	Articles Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials The Nuffield Department of Population Health Renal Studies Group* and the SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium*

選擇原因	• 符合PICO • 收納Trial篇數最多

Lancet 2022; 400: 1788–801

03

Appraising

CASP
Critical Appraisal Skills Programme

Section A

Are the results of the review valid?

Section B

What are the results?

Section C

Will the results help locally?

CASP
Critical Appraisal Skills Programme

Section A

Are the results of the review valid?

Section B

What are the results?

Section C

Will the results help locally?

1.Did the review address a clearly focused question?

Summary

Background Large trials have shown that sodium glucose co-transporter-2 (SGLT2) inhibitors reduce the risk of adverse kidney and cardiovascular outcomes in patients with heart failure or chronic kidney disease, or with type 2 diabetes and high risk of atherosclerotic cardiovascular disease. None of the trials recruiting patients with and without diabetes were designed to assess outcomes separately in patients without diabetes.

Methods We did a systematic review and meta-analysis of SGLT2 inhibitor trials. We searched the MEDLINE and Embase databases for trials published from database inception to Sept 5, 2022. SGLT2 inhibitor trials that were double-blind, placebo-controlled, performed in adults (age ≥18 years), large (≥500 participants per group), and at least 6 months in duration were included. Summary-level data used for analysis were extracted from published reports or provided by trial investigators, and inverse-variance-weighted meta-analyses were conducted to estimate treatment effects. The main efficacy outcomes were kidney disease progression (standardised to a definition of a sustained ≥50% decrease in estimated glomerular filtration rate [eGFR] from randomisation, a sustained low eGFR, end-stage kidney disease, or death from kidney failure), acute kidney injury, and a composite of cardiovascular death or hospitalisation for heart failure. Other outcomes were death from cardiovascular and non-cardiovascular disease considered separately, and the main safety outcomes were ketoacidosis and lower limb amputation. This study is registered with PROSPERO, CRD42022351618.

P

I

C

O

Primary outcome	**Kidney disease progression** (decline in eGFR , end stage kidney disease or death from kidney failure)

Yes ✓

Can't tell

No

2.Did the authors look for the right type of papers?

The inclusion criteria for this study included those of the previous meta-analysis, with an additional requirement (pre-specified in the PROSPERO-registered protocol) that studies should have a duration of greater than 6 months.

The final inclusion criteria were as follows:

- Parallel-group randomised controlled trial in adults
- Randomisation of ≥1000 participants to an SGLT2 inhibitor (including combined SGLT1/2 inhibitors) versus placebo (required ≥500 participants in each group)
- Duration ≥6 months (additional inclusion criterion for updated systematic review)
- Reporting any of the pre-specified main efficacy outcomes and any of the pre-specified safety outcomes

Trials were classified according to their primary inclusion criteria into three populations: type 2 diabetes at high risk of cardiovascular disease, stable heart failure (i.e. not in receipt of intravenous diuretic therapy), and CKD.

Prespecified efficacy outcome

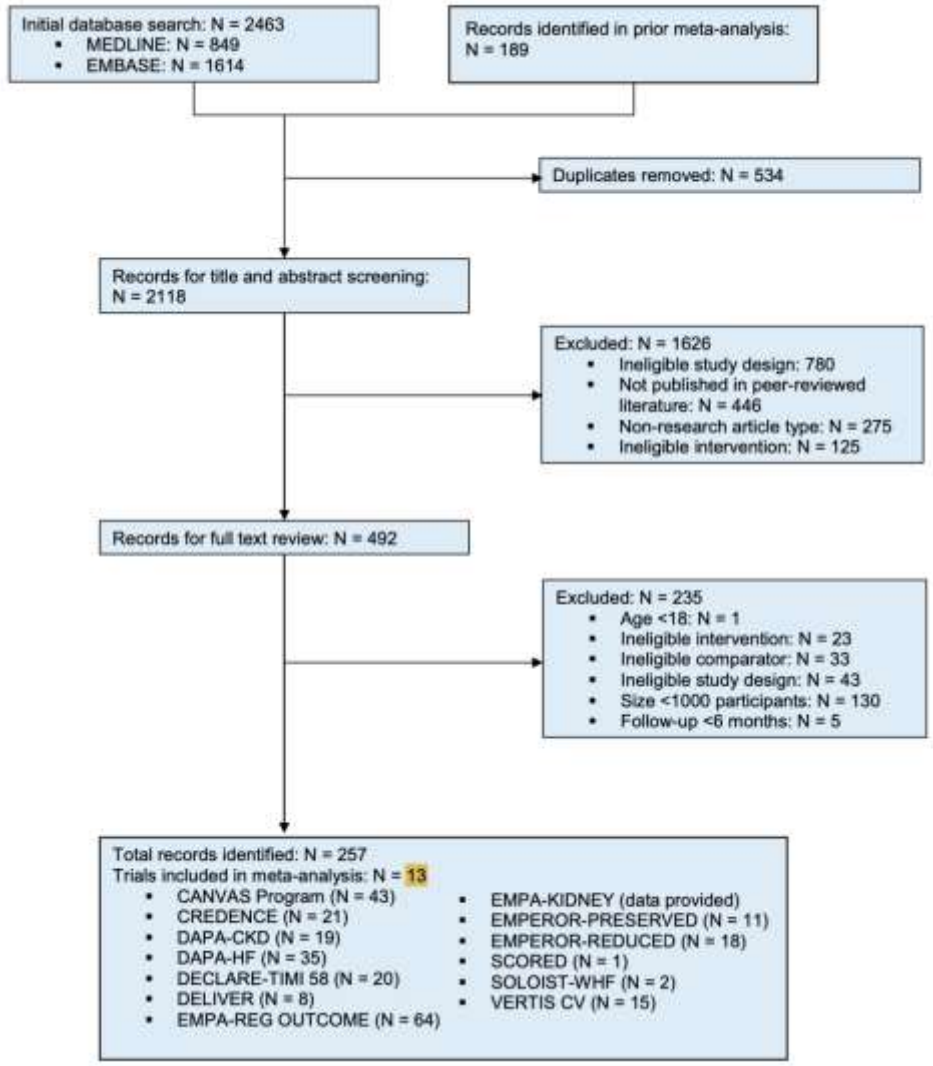
- Decline in eGFR , end stage kidney disease or death from kidney failure)
- Acute kidney disease
- Hospitalization for heart failure or cardiovascular death

Yes ☑
Can't tell ☐
No ☐

3 . Do you think all the important, relevant studies were included?

信度 V Validity　重要性 I Importance　可應用性 P Applicability

Webfigure 1: Study selection



Assessment	
Study Type	Randomized controlled trials
Database	MEDLINE, EMBASE,
Language	No language restriction was applied
Date of Publication	Data inception to Sep 5,2022

Prespecified efficacy outcome

- Decline in eGFR , end stage kidney disease or death from kidney failure) · Acute kidney disease
- Hospitalization for heart failure or cardiovascular death

Yes ☑
Can't tell ☐
No ☐

4. Did the review’ s authors do enough to assess quality of the included studies?

信度 V Validity　重要性 I Importance　可應用性 P Applicability

Methods

Search strategy and selection criteria

MEDLINE and Embase databases via Ovid to cover the period from database inception to Sept 5, 2022. Further details and search terms are listed in the appendix (pp 3–7). Trials were eligible if they assessed SGLT2 inhibitors (including combined SGLT1/2 inhibitors) and if they were double-blind and placebo-controlled (excluding crossover trials), performed in adults (age ≥18 years), large (defined as ≥500 participants in each arm, thereby minimising any potential for publication bias to distort findings), at least 6 months in duration, and reported any of the prespecified efficacy or safety outcomes. Titles and abstracts were initially screened for relevance and duplicates by one author (AJR). The EMPA-KIDNEY trial baseline report[12] was available while the final report[13] was unpublished at the time of the search. Subsequent screening of full texts and risk of bias assessments (with version 2 of the Cochrane Risk-of-Bias tool[16]) were completed independently by two authors (KJM, AJR) with conflicts resolved by consensus discussion.

Webtable 4: Risk of bias assessments

Study ID	Intervention	Comparator	Randomisation process	Deviations from the intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result
DECLARE-TIMI 58	Dapagliflozin	Placebo	+	+	+	+	+
CANVAS Program	Canagliflozin	Placebo	+	+	+	+	+
VERTIS CV	Ertugliflozin	Placebo	+	+	+	+	+
EMPA-REG OUTCOME	Empagliflozin	Placebo	+	+	+	+	+
DAPA-HF	Dapagliflozin	Placebo	+	+	+	+	+
DELIVER	Dapagliflozin	Placebo	+	+	+	+	+
EMPEROR-REDUCED	Empagliflozin	Placebo	+	+	+	+	+
EMPEROR-PRESERVED	Empagliflozin	Placebo	+	+	+	+	+
CREDENCE	Canagliflozin	Placebo	+	+	+	+	+
SOLOIST-WHF	Sotagliflozin	Placebo	+	+	+	+	+
SCORED	Sotagliflozin	Placebo	+	+	+	+	+
DAPA-CKD	Dapagliflozin	Placebo	+	+	+	+	+
EMPA-KIDNEY	Empagliflozin	Placebo	+	+	+	+	+

Risk of bias of included trials as assessed using Version 2 of the Cochrane Risk-of-Bias tool for randomised trials (ROB2).

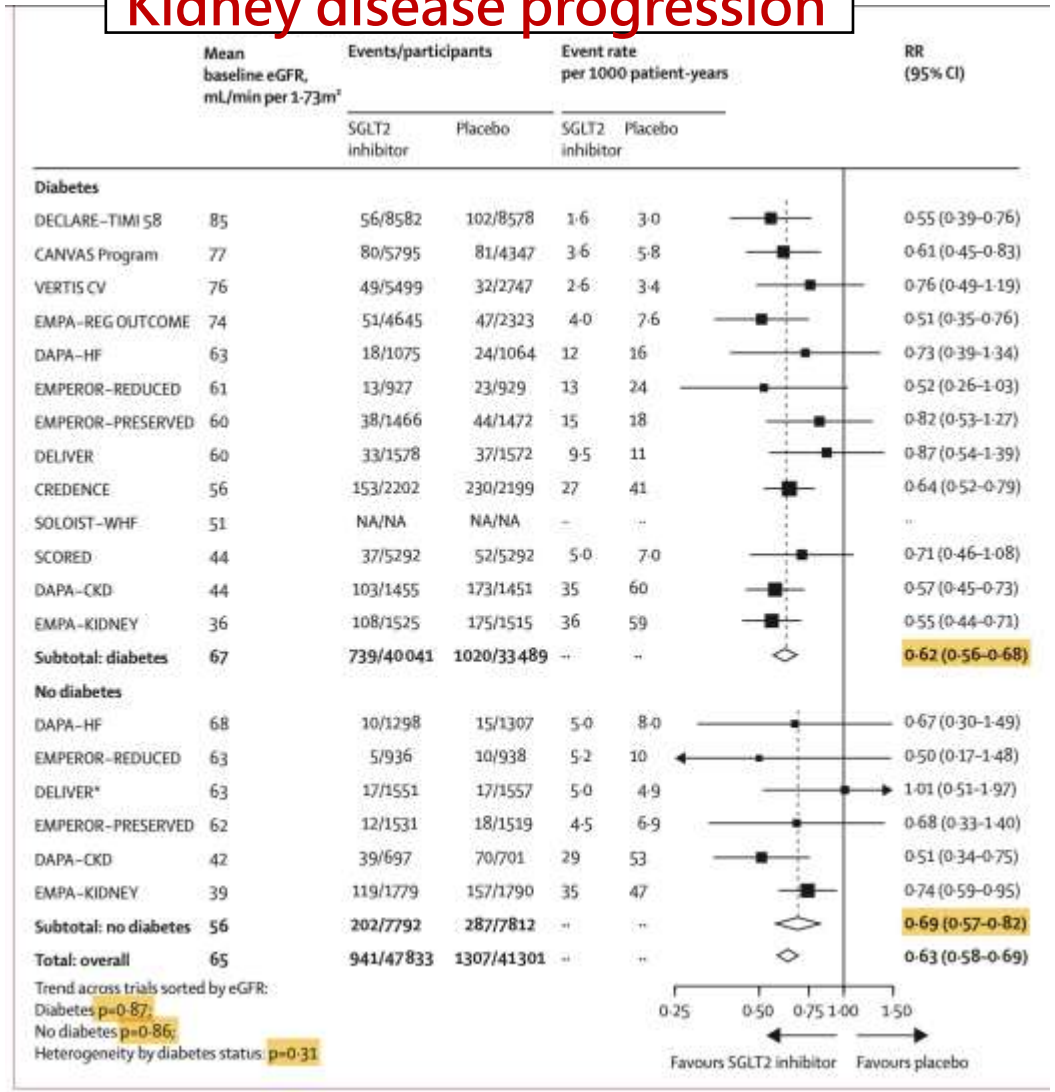
Key:

\+ **Low risk of bias**

Yes ✓
Can’t tell
No

5 . If the results of the review have been combined, was it reasonable to do so?

Kidney disease progression



	Mean baseline eGFR, mL/min per 1·73m²	Events/participants: SGLT2 inhibitor	Events/participants: Placebo	Event rate per 1000 patient-years: SGLT2 inhibitor	Event rate per 1000 patient-years: Placebo	RR (95% CI)
Diabetes						
DECLARE–TIMI 58	85	56/8582	102/8578	1·6	3·0	0·55 (0·39–0·76)
CANVAS Program	77	80/5795	81/4347	3·6	5·8	0·61 (0·45–0·83)
VERTIS CV	76	49/5499	32/2747	2·6	3·4	0·76 (0·49–1·19)
EMPA–REG OUTCOME	74	51/4645	47/2323	4·0	7·6	0·51 (0·35–0·76)
DAPA–HF	63	18/1075	24/1064	12	16	0·73 (0·39–1·34)
EMPEROR–REDUCED	61	13/927	23/929	13	24	0·52 (0·26–1·03)
EMPEROR–PRESERVED	60	38/1466	44/1472	15	18	0·82 (0·53–1·27)
DELIVER	60	33/1578	37/1572	9·5	11	0·87 (0·54–1·39)
CREDENCE	56	153/2202	230/2199	27	41	0·64 (0·52–0·79)
SOLOIST–WHF	51	NA/NA	NA/NA	..	..	..
SCORED	44	37/5292	52/5292	5·0	7·0	0·71 (0·46–1·08)
DAPA–CKD	44	103/1455	173/1451	35	60	0·57 (0·45–0·73)
EMPA–KIDNEY	36	108/1525	175/1515	36	59	0·55 (0·44–0·71)
Subtotal: diabetes	**67**	**739/40041**	**1020/33489**	..	..	**0·62 (0·56–0·68)**
No diabetes						
DAPA–HF	68	10/1298	15/1307	5·0	8·0	0·67 (0·30–1·49)
EMPEROR–REDUCED	63	5/936	10/938	5·2	10	0·50 (0·17–1·48)
DELIVER*	63	17/1551	17/1557	5·0	4·9	1·01 (0·51–1·97)
EMPEROR–PRESERVED	62	12/1531	18/1519	4·5	6·9	0·68 (0·33–1·40)
DAPA–CKD	42	39/697	70/701	29	53	0·51 (0·34–0·75)
EMPA–KIDNEY	39	119/1779	157/1790	35	47	0·74 (0·59–0·95)
Subtotal: no diabetes	**56**	**202/7792**	**287/7812**	..	..	**0·69 (0·57–0·82)**
Total: overall	**65**	**941/47833**	**1307/41301**	..	..	**0·63 (0·58–0·69)**

Trend across trials sorted by eGFR:
Diabetes p=0·87;
No diabetes p=0·86;
Heterogeneity by diabetes status p=0·31

Figure 1: Effect of sodium glucose co-transporter-2 inhibition on kidney disease outcomes by diabetes status

信度 V Validity　重要性 I Importance　可應用性 P Applicability

Heterogeneity
• Analyses were done separately in patients with diabetes and without diabetes。
• Fixed effect model   • **Inverse-variance–weighted averages** of log RRs
• **Standard χ2** tests for heterogeneity were used to assess whether treatment effects differed between those with and without diabetes at recruitment

Yes	
Can’t tell	
No	

5 . If the results of the review have been combined, was it reasonable to do so?

Trial	Components & definitions used in this meta-analysis					Definitions originally applied by individual trials
	Sustained ≥50% eGFR decline	Kidney replacement therapy	Sustained eGFR <15 (or <10)	Renal death	Definition of sustained	
DECLARE-TIMI 58	✓	✓	✓	✓	As confirmed by two tests at the central laboratory ≥4 weeks apart	Sustained ≥40% eGFR decline to <60 mL/min/1.73 m² or ESKD (defined as dialysis ≥90 days, kidney transplantation, or sustained eGFR <15 mL/min/1.73 m²) or renal death
CANVAS Program	✓	✓	✓	✓	Two consecutive measurements ≥30 days apart unless identified on the last available measurement	Sustained 50% eGFR decline or ESKD (defined as maintenance dialysis ≥30 days, kidney transplantation, sustained eGFR <15 mL/min/1.73 m²) or renal death
VERTIS CV	✓	✓	✓	✓	Subsequent value that also met the cut-off criterion >30 days later	Pre-specified secondary: Doubling of serum creatinine, dialysis*/kidney transplantation or renal death Pre-specified exploratory: Sustained ≥40% decline in eGFR, chronic* dialysis/kidney transplantation or renal death
EMPA-REG OUTCOME	✓	✓	✓	✓	Sustained for ≥28 days according to central laboratory assessment	Pre-specified: Sustained ≥40% eGFR decline or ESKD (defined as "sustained continuous"* dialysis/ kidney transplantation or sustained eGFR <15 mL/min/1.73 m²) or *hospitalisation for heart failure or cardiac* or renal *death*. Post-hoc: Sustained ≥40%; (also published for ≥30%, ≥50% and ≥57%) eGFR decline or RRT initiation or renal death.
DAPA-HF	✓	✓	✓	✓	Defined as lasting ≥28 days	Sustained ≥50% eGFR decline, ESKD (defined as chronic* dialysis, kidney transplantation or sustained eGFR <15 mL/min/1.73 m²) or renal death
EMPEROR-REDUCED	✓	✓	✓	✓	Sustained for ≥30 days according to central laboratory assessment or if the last measurement meets criteria and death occurred within 60 days	Sustained ≥40% eGFR decline or ESKD (defined as chronic* dialysis/ kidney transplantation or sustained eGFR <15 for patients with baseline eGFR ≥30, or sustained eGFR <10 for patients with baseline eGFR <30 mL/min/1.73 m²)
EMPEROR-PRESERVED	✓	✓	✓	✓	Sustained for ≥30 days according to central laboratory assessment or if the last measurement meets criteria and death occurred within 60 days	Sustained ≥40% eGFR decline or ESKD (defined as chronic* dialysis/ kidney transplantation or sustained eGFR <15 for patients with baseline eGFR≥30 or sustained eGFR<10 for patients with baseline eGFR<30 mL/min/1.73 m²)
DELIVER	✓	✓	✓	✓	Measured at two consecutive scheduled study follow-up visits (≥1 month apart), or at last available visit	Sustained ≥50% eGFR decline, ESKD (defined from adverse event reports), sustained eGFR <15 mL/min/1.73 m², or renal death
SOLOIST-WHF	Not available					
CREDENCE	✓	✓	✓	✓	Sustained for ≥30 days according to central laboratory assessment	Primary: Sustained doubling of serum creatinine, ESKD (defined as maintenance dialysis ≥30 days, kidney transplantation or sustained eGFR <15 mL/min/1.73 m²) or renal or *cardiovascular death* Secondary: Sustained doubling of serum creatinine, ESKD or renal death
SCORED	✓	✓	✓	X	Sustained for ≥30 days	Sustained ≥50% eGFR decline, long-term* dialysis, kidney transplantation or sustained eGFR <15 mL/min/1.73 m²
DAPA-CKD	✓	✓	✓	✓	Two consecutive central laboratory eGFR values ≥28 days apart	Sustained ≥50% eGFR decline, ESKD (defined as maintenance dialysis ≥28 days, kidney transplantation or sustained eGFR <15 mL/min/1.73 m²) or renal death
EMPA-KIDNEY	✓	✓	✓	✓	(a) measured at two consecutive scheduled study follow-up visits; or (b) last available measurement	Sustained ≥40% eGFR decline, ESKD (defined as maintenance dialysis ≥90 days or kidney transplantation), sustained eGFR <10 mL/min/1.73m² or renal death

信度 Validity　重要性 Importance　可應用性 Applicability

Kidney disease progression

- Decline in eGFR ,
- End stage kidney disease
- Death from kidney failure)

Yes ✓
Can't tell
No

CASP
Critical Appraisal Skills Programme

Section A

Are the results of the review valid?

Section B

What are the results?

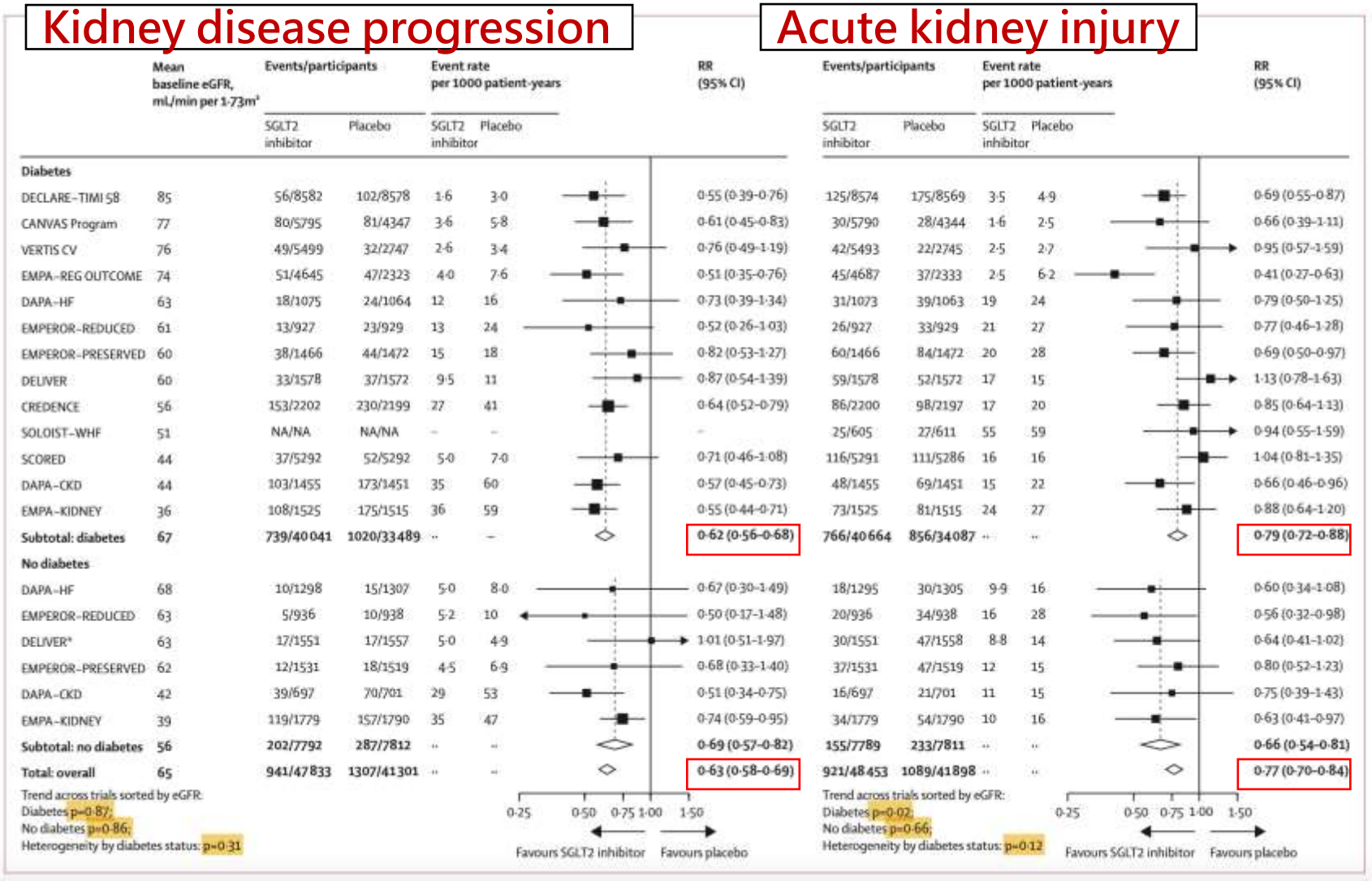
Section C

Will the results help locally?

6. What are the overall results of the review?
7. How precise are the results?

信度 V Validity　重要性 I Importance　可應用性 P Applicability

Kidney disease progression



	Mean baseline eGFR, mL/min per 1·73m²	Events/participants: SGLT2 inhibitor	Events/participants: Placebo	Event rate per 1000 patient-years: SGLT2 inhibitor	Event rate per 1000 patient-years: Placebo	RR (95% CI)
Diabetes						
DECLARE-TIMI 58	85	56/8582	102/8578	1·6	3·0	0·55 (0·39–0·76)
CANVAS Program	77	80/5795	81/4347	3·6	5·8	0·61 (0·45–0·83)
VERTIS CV	76	49/5499	32/2747	2·6	3·4	0·76 (0·49–1·19)
EMPA-REG OUTCOME	74	51/4645	47/2323	4·0	7·6	0·51 (0·35–0·76)
DAPA-HF	63	18/1075	24/1064	12	16	0·73 (0·39–1·34)
EMPEROR-REDUCED	61	13/927	23/929	13	24	0·52 (0·26–1·03)
EMPEROR-PRESERVED	60	38/1466	44/1472	15	18	0·82 (0·53–1·27)
DELIVER	60	33/1578	37/1572	9·5	11	0·87 (0·54–1·39)
CREDENCE	56	153/2202	230/2199	27	41	0·64 (0·52–0·79)
SOLOIST-WHF	51	NA/NA	NA/NA	..	..	..
SCORED	44	37/5292	52/5292	5·0	7·0	0·71 (0·46–1·08)
DAPA-CKD	44	103/1455	173/1451	35	60	0·57 (0·45–0·73)
EMPA-KIDNEY	36	108/1525	175/1515	36	59	0·55 (0·44–0·71)
Subtotal: diabetes	**67**	**739/40 041**	**1020/33 489**	..	..	**0·62 (0·56–0·68)**
No diabetes						
DAPA-HF	68	10/1298	15/1307	5·0	8·0	0·67 (0·30–1·49)
EMPEROR-REDUCED	63	5/936	10/938	5·2	10	0·50 (0·17–1·48)
DELIVER*	63	17/1551	17/1557	5·0	4·9	1·01 (0·51–1·97)
EMPEROR-PRESERVED	62	12/1531	18/1519	4·5	6·9	0·68 (0·33–1·40)
DAPA-CKD	42	39/697	70/701	29	53	0·51 (0·34–0·75)
EMPA-KIDNEY	39	119/1779	157/1790	35	47	0·74 (0·59–0·95)
Subtotal: no diabetes	**56**	**202/7792**	**287/7812**	..	..	**0·69 (0·57–0·82)**
Total: overall	**65**	**941/47 833**	**1307/41 301**	..	..	**0·63 (0·58–0·69)**

Trend across trials sorted by eGFR:
Diabetes p=0·87;
No diabetes p=0·86;
Heterogeneity by diabetes status: p=0·31

0·25　0·50　0·75　1·00　1·50
Favours SGLT2 inhibitor　Favours placebo

Acute kidney injury

	Events/participants: SGLT2 inhibitor	Events/participants: Placebo	Event rate per 1000 patient-years: SGLT2 inhibitor	Event rate per 1000 patient-years: Placebo	RR (95% CI)
DECLARE-TIMI 58	125/8574	175/8569	3·5	4·9	0·69 (0·55–0·87)
CANVAS Program	30/5790	28/4344	1·6	2·5	0·66 (0·39–1·11)
VERTIS CV	42/5493	22/2745	2·5	2·7	0·95 (0·57–1·59)
EMPA-REG OUTCOME	45/4687	37/2333	2·5	6·2	0·41 (0·27–0·63)
DAPA-HF	31/1073	39/1063	19	24	0·79 (0·50–1·25)
EMPEROR-REDUCED	26/927	33/929	21	27	0·77 (0·46–1·28)
EMPEROR-PRESERVED	60/1466	84/1472	20	28	0·69 (0·50–0·97)
DELIVER	59/1578	52/1572	17	15	1·13 (0·78–1·63)
CREDENCE	86/2200	98/2197	17	20	0·85 (0·64–1·13)
SOLOIST-WHF	25/605	27/611	55	59	0·94 (0·55–1·59)
SCORED	116/5291	111/5286	16	16	1·04 (0·81–1·35)
DAPA-CKD	48/1455	69/1451	15	22	0·66 (0·46–0·96)
EMPA-KIDNEY	73/1525	81/1515	24	27	0·88 (0·64–1·20)
Subtotal: diabetes	**766/40 664**	**856/34 087**	..	..	**0·79 (0·72–0·88)**
DAPA-HF	18/1295	30/1305	9·9	16	0·60 (0·34–1·08)
EMPEROR-REDUCED	20/936	34/938	16	28	0·56 (0·32–0·98)
DELIVER*	30/1551	47/1558	8·8	14	0·64 (0·41–1·02)
EMPEROR-PRESERVED	37/1531	47/1519	12	15	0·80 (0·52–1·23)
DAPA-CKD	16/697	21/701	11	15	0·75 (0·39–1·43)
EMPA-KIDNEY	34/1779	54/1790	10	16	0·63 (0·41–0·97)
Subtotal: no diabetes	**155/7789**	**233/7811**	..	..	**0·66 (0·54–0·81)**
Total: overall	**921/48 453**	**1089/41 898**	..	..	**0·77 (0·70–0·84)**

Trend across trials sorted by eGFR:
Diabetes p=0·02;
No diabetes p=0·66;
Heterogeneity by diabetes status: p=0·12

0·25　0·50　0·75　1·00　1·50
Favours SGLT2 inhibitor　Favours placebo

Median follow up

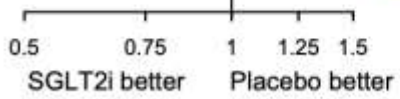
- T2D：2.4~4.2 years
- CKD：1.2~2.6 years
- HF ：0.8~2.2 years

Yes	✓
Can't tell	
No	

6. What are the overall results of the review?
7. How precise are the results?

Webfigure 2: Effect of SGLT2 inhibition on Kidney Failure, by diabetes status (CKD trials only)

	Mean baseline eGFR (mL/min/1.73m²)	Events/participants SGLT2i	Events/participants Placebo	Rate per 1000 patient years SGLT2i	Rate per 1000 patient years Placebo	Relative risk (95% CI)	Trend across trials sorted by eGFR
Diabetes							
CREDENCE	56	116/2202	165/2199	20	29	0.68 (0.54, 0.86)	
SCORED	44	NA/NA	NA/NA				p=0.48
DAPA-CKD	44	77/1455	109/1451	26	37	0.69 (0.51, 0.92)	
EMPA-KIDNEY	36	74/1525	116/1515	24	39	0.59 (0.44, 0.79)	
Subtotal: DIABETES	**47**	**267/5182**	**390/5165**			**0.66 (0.56, 0.77)**	
No diabetes							
DAPA-CKD	42	32/697	52/701	24	39	0.56 (0.36, 0.87)	p=0.19
EMPA-KIDNEY	39	83/1779	105/1790	25	31	0.80 (0.60, 1.07)	
Subtotal: NO DIABETES	**40**	**115/2476**	**157/2491**			**0.72 (0.56, 0.91)**	
TOTAL: OVERALL	**45**	**382/7658**	**547/7656**			**0.67 (0.59, 0.77)**	



Heterogeneity by diabetes status: p=0.54

Kidney failure

- Sustained eGFR <15
- Maintenance dialysis
- Kidney transplantation

6. What are the overall results of the review?
7. How precise are the results?

	Mean baseline eGFR, mL/min per 1·73m²	Events/participants		Event rate per 1000 patient-years		RR (95% CI)
		SGLT2 inhibitor	Placebo	SGLT2inhibitor	Placebo	
Diabetic kidney disease or nephropathy*						
CREDENCE	56	153/2202	230/2199	27	41	0·64 (0·52–0·79)
SCORED	44	37/5292	52/5292	5	7	0·71 (0·46–1·08)
DAPA-CKD	43	93/1271	157/1239	36	64	0·55 (0·43–0·71)
EMPA-KIDNEY	36	85/1032	133/1025	42	67	0·56 (0·43–0·74)
Subtotal	**46**	**368/9797**	**572/9755**	..	..	**0·60 (0·53–0·69)**
Ischaemic and hypertensive kidney disease						
DAPA-CKD	43	18/324	26/363	28	37	0·74 (0·40–1·36)
EMPA-KIDNEY	35	37/706	52/739	27	37	0·69 (0·45–1·05)
Subtotal	**38**	**55/1030**	**78/1102**	..	..	**0·70 (0·50–1·00)**
Glomerular disease						
DAPA-CKD	43	21/343	46/352	33	70	0·43 (0·26–0·72)
EMPA-KIDNEY	42	69/853	95/816	44	64	0·68 (0·50–0·93)
Subtotal	**42**	**90/1196**	**141/1168**	..	..	**0·60 (0·46–0·78)**
Other kidney disease or unknown						
DAPA-CKD	43	10/214	14/198	25	37	0·81 (0·35–1·83)
EMPA-KIDNEY	36	36/713	52/725	26	36	0·72 (0·47–1·10)
Subtotal	**38**	**46/927**	**66/923**	..	..	**0·74 (0·51–1·08)**
Any diagnosis						
CREDENCE	56	153/2202	230/2199	27	41	0·64 (0·52–0·79)
SCORED	44	37/5292	52/5292	5	7	0·71 (0·46–1·08)
DAPA-CKD	43	142/2152	243/2152	33	58	0·56 (0·45–0·68)
EMPA-KIDNEY	37	227/3304	332/3305	36	52	0·64 (0·54–0·76)
Total	**44**	**559/12950**	**857/12948**	..	..	**0·62 (0·56–0·69)**

Heterogeneity across groups of primary kidney disease: p=0·67
Trend across trials sorted by eGFR for any diagnosis: p=0·88

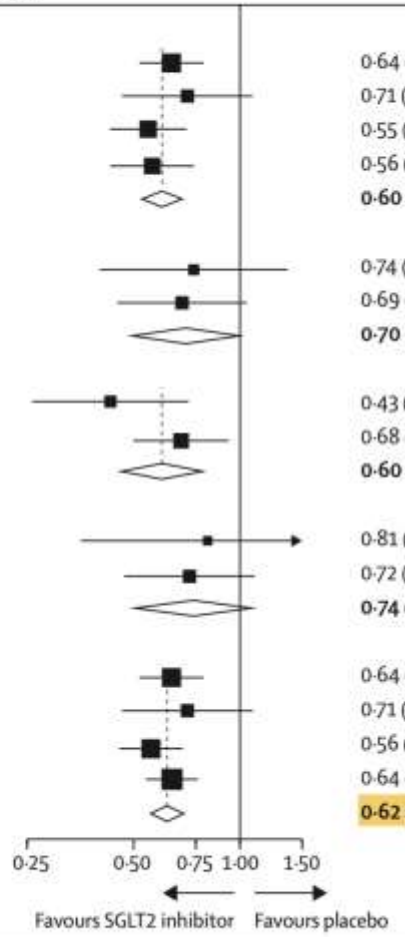


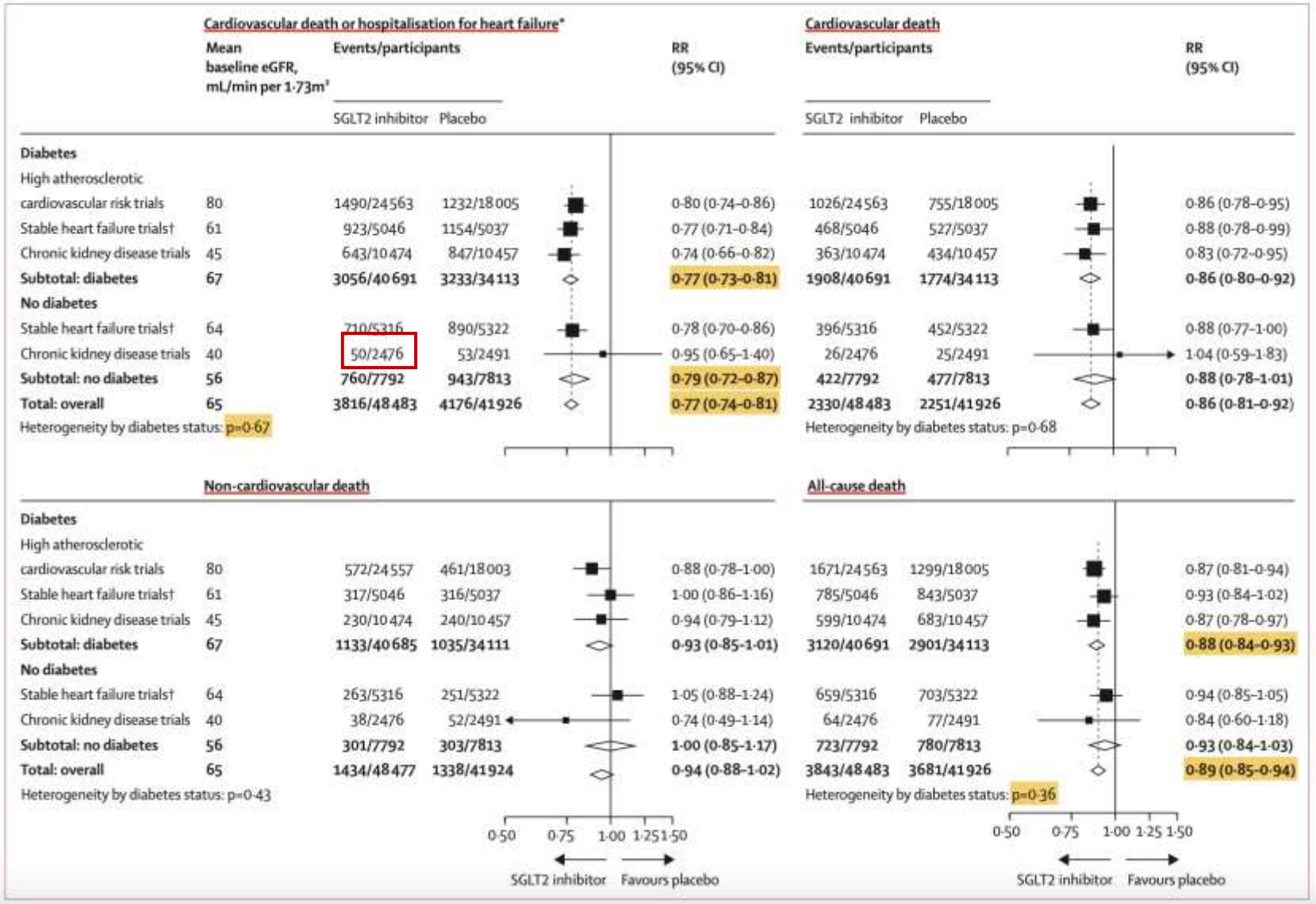
Figure 2: Effect of sodium glucose co-transporter-2 inhibition on kidney disease progression by presumed primary kidney disease (chronic kidney disease trials only)

Chronic kidney disease trial

- Analysis were separated by primary kidney diagnose

6. What are the overall results of the review?
7. How precise are the results?

信度 V Validity　重要性 I Importance　可應用性 P Applicability



Cardiovascular death or hospitalisation for heart failure*

	Mean baseline eGFR, mL/min per 1·73m²	Events/participants SGLT2 inhibitor	Events/participants Placebo	RR (95% CI)
Diabetes				
High atherosclerotic cardiovascular risk trials	80	1490/24563	1232/18005	0·80 (0·74–0·86)
Stable heart failure trials†	61	923/5046	1154/5037	0·77 (0·71–0·84)
Chronic kidney disease trials	45	643/10474	847/10457	0·74 (0·66–0·82)
Subtotal: diabetes	67	3056/40691	3233/34113	**0·77 (0·73–0·81)**
No diabetes				
Stable heart failure trials†	64	710/5316	890/5322	0·78 (0·70–0·86)
Chronic kidney disease trials	40	50/2476	53/2491	0·95 (0·65–1·40)
Subtotal: no diabetes	56	760/7792	943/7813	**0·79 (0·72–0·87)**
Total: overall	65	3816/48483	4176/41926	**0·77 (0·74–0·81)**
Heterogeneity by diabetes status: p=0·67				

Cardiovascular death

	Events/participants SGLT2 inhibitor	Events/participants Placebo	RR (95% CI)
Diabetes			
High atherosclerotic cardiovascular risk trials	1026/24563	755/18005	0·86 (0·78–0·95)
Stable heart failure trials†	468/5046	527/5037	0·88 (0·78–0·99)
Chronic kidney disease trials	363/10474	434/10457	0·83 (0·72–0·95)
Subtotal: diabetes	1908/40691	1774/34113	**0·86 (0·80–0·92)**
No diabetes			
Stable heart failure trials†	396/5316	452/5322	0·88 (0·77–1·00)
Chronic kidney disease trials	26/2476	25/2491	1·04 (0·59–1·83)
Subtotal: no diabetes	422/7792	477/7813	**0·88 (0·78–1·01)**
Total: overall	2330/48483	2251/41926	**0·86 (0·81–0·92)**
Heterogeneity by diabetes status: p=0·68			

Non-cardiovascular death

		Events/participants SGLT2 inhibitor	Events/participants Placebo	RR (95% CI)
Diabetes				
High atherosclerotic cardiovascular risk trials	80	572/24557	461/18003	0·88 (0·78–1·00)
Stable heart failure trials†	61	317/5046	316/5037	1·00 (0·86–1·16)
Chronic kidney disease trials	45	230/10474	240/10457	0·94 (0·79–1·12)
Subtotal: diabetes	67	1133/40685	1035/34111	**0·93 (0·85–1·01)**
No diabetes				
Stable heart failure trials†	64	263/5316	251/5322	1·05 (0·88–1·24)
Chronic kidney disease trials	40	38/2476	52/2491	0·74 (0·49–1·14)
Subtotal: no diabetes	56	301/7792	303/7813	**1·00 (0·85–1·17)**
Total: overall	65	1434/48477	1338/41924	**0·94 (0·88–1·02)**
Heterogeneity by diabetes status: p=0·43				

All-cause death

	Events/participants SGLT2 inhibitor	Events/participants Placebo	RR (95% CI)
Diabetes			
High atherosclerotic cardiovascular risk trials	1671/24563	1299/18005	0·87 (0·81–0·94)
Stable heart failure trials†	785/5046	843/5037	0·93 (0·84–1·02)
Chronic kidney disease trials	599/10474	683/10457	0·87 (0·78–0·97)
Subtotal: diabetes	3120/40691	2901/34113	**0·88 (0·84–0·93)**
No diabetes			
Stable heart failure trials†	659/5316	703/5322	0·94 (0·85–1·05)
Chronic kidney disease trials	64/2476	77/2491	0·84 (0·60–1·18)
Subtotal: no diabetes	723/7792	780/7813	**0·93 (0·84–1·03)**
Total: overall	3843/48483	3681/41926	**0·89 (0·85–0·94)**
Heterogeneity by diabetes status: p=0·36			

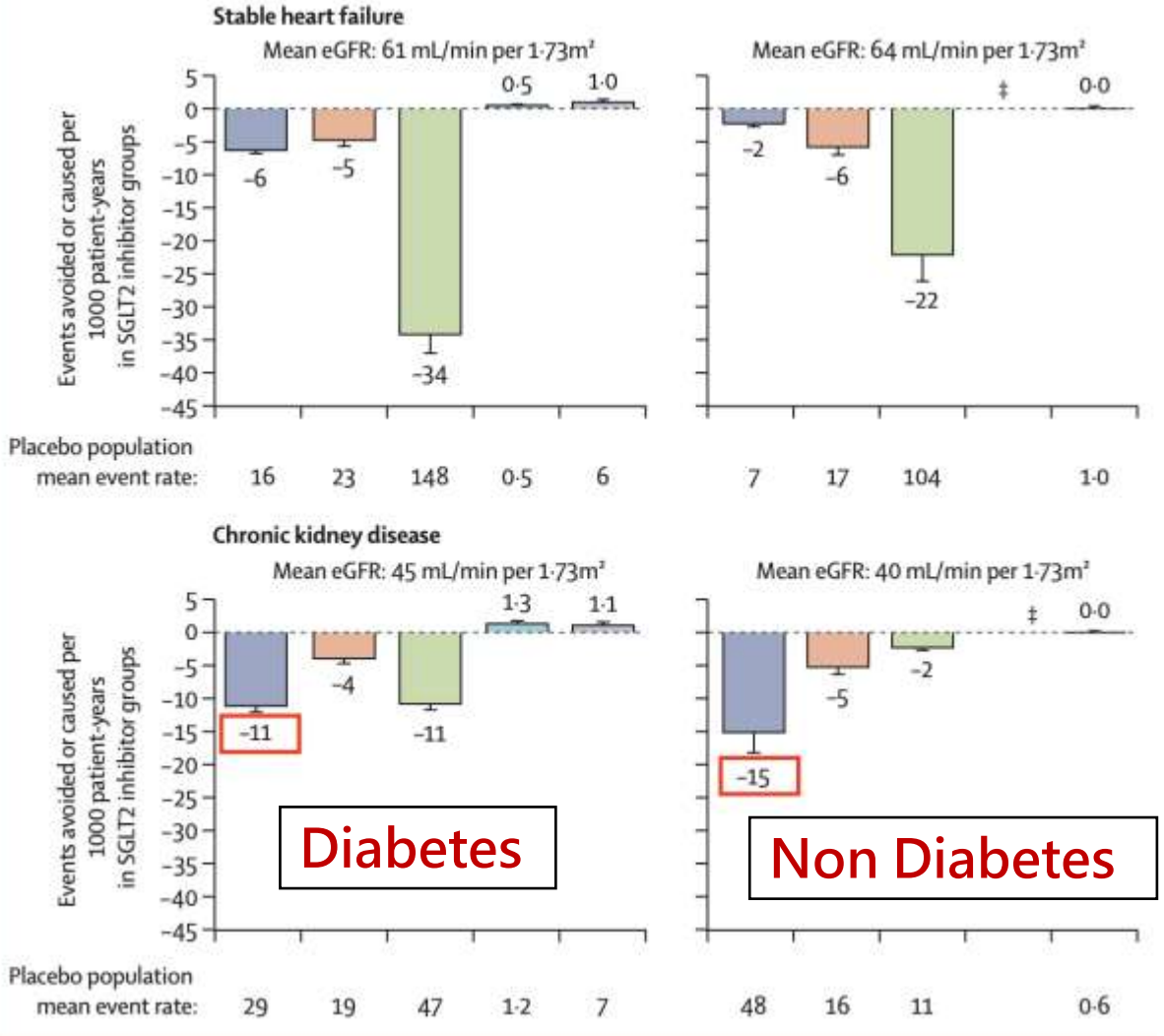
0·50　0·75　1·00　1·25　1·50

SGLT2 inhibitor　Favours placebo

6. What are the overall results of the review?
7. How precise are the results?

信度 V Validity　重要性 I Importance　可應用性 P Applicability

Absolute rates and subsequently the benefits and harms of allocation to an SGLT2 inhibitor versus placebo



6. What are the overall results of the review?
7. How precise are the results?

Safety

Ketoacidosis

Lower limb amputation

	Mean baseline eGFR, mL/min per 1·73m²	Events/ participants: SGLT2 inhibitor	Events/ participants: Placebo	RR (95% CI)	Events/ participants: SGLT2 inhibitor	Events/ participants: Placebo	RR (95% CI)
Diabetes							
High atherosclerotic cardiovascular risk trials	80	63/24549	20/17994	2·44 (1·44–4·12)	462/24544	248/17991	1·25 (1·07–1·47)
Stable heart failure trials*	61	9/5043	5/5032	1·31 (0·43–4·02)	54/5043	60/5032	0·89 (0·62–1·30)
Chronic kidney disease trials	45	46/10469	18/10448	2·40 (1·36–4·25)	160/10469	151/10448	1·05 (0·84–1·32)
Subtotal: diabetes	67	120/40666	47/34085	2·12 (1·49–3·04)	680/40661	460/34082	1·15 (1·02–1·30)
No diabetes							
Stable heart failure trials	64	0/5313	0/5318	..	7/5313	10/5318	0·73 (0·27–1·97)
Chronic kidney disease trials	40	1/2475	0/2489	..	5/2475	3/2489	1·90 (0·43–8·32)
Subtotal: no diabetes	56	1/7788	0/7807	..	12/7788	13/7807	0·98 (0·43–2·25)
Total: overall	65	..	..	..	692/48449	473/41889	1·15 (1·02–1·30)
Total: overall (excluding CANVAS)†	64	..	..	..	552/42659	426/37545	1·06 (0·93–1·21)

Heterogeneity by diabetes status: p=0·71

0·25 0·5 1 2 3 4 5

Favours SGLT2 inhibitor Favours placebo

0·25 0·5 1 2 3 4 5

Favours SGLT2 inhibitor Favours placebo

CASP
Critical Appraisal Skills Programme

Section A

Are the results of the review valid?

Section B

What are the results?

Section C

Will the results help locally?

8. Can the results be applied to the local population?

	Literature	Clinical Scenario	Conclusion
Target subject	Non diabetes (CKD or HF)	CKD stage 3b, HfpEF, Non diabetes	✓
Local population	Race of ethnic group：White, Black, Asian。	Taiwan	✓
Intervention	SGLT-2 inhibitors	SGLT-2 inhibitors	✓

Yes ✓

Can't tell

No

9. Were all important outcomes considered?

評估面向	

Efficacy	• **Kidney disease progression**
	  • **eGFR decline ≥ 50%**
	  • **Kidney failure (ESKD)**
	  • **Death from kidney failure**
	• Hospitalization for heart failure or cardiovascular death
	• Mortality

Safety	• Ketoacidosis • Limb amputation • Urinary tract infection

Yes ☑
Can't tell ☐
No ☐

10. Are the benefits worth the harms and costs?

考量風險與利益

療效	1. 有使用SGLT-2 inhibitors比起未治療組，**腎臟相關結果之風險降低37% (relative risk 0.63,95% CI [0.58 to 0.69]，且在CKD或HF族群，儘管有無糖尿病，均有Benefits** 2. 嚴重不良反應無顯著差異 (lower limb amputation：relative risk 1.06 95%CI [0.93 to 1.21]
副作用	仍可能產生不良事件，包含泌尿道感染，骨折，生殖器感染，體液耗損

考量成本利益

		SGLT 2 inhibitors	
直接成本	費用	**HF** • **左心室收縮功能不全，(LVEF)≦40%** • **經ACEI或ARB穩定劑量治療，及合併使用β-阻斷劑最大可耐受劑量已達4週，仍有心衰竭症狀**	**CKD：** 尚未納入健保 (Ex：Dapagliflozin) 37.5元 / 粒* QD/年 =13687.5年

Yes
Can't tell ✓
No

Conclusion

Validity	Importance	Applicability
Clear Question	Results	Local Population
Appropriate Study Type	Precision: Precise	Significance
General Inclusion		Benefits vs. Harm
Quality Assessment		
Result Combination		

Result:
SGLT2 inhibitors reduce the risk of kidney disease progression, acute kidney injury, cardiovascular death, and hospitalization for heart failure in patients with chronic kidney disease or heart failure, irrespective of diabetes status

Yes No Can't tell

Discussion-1

Does the SGLT-2 inhibitor benefit of kidney protective effect among eGFR 20-30 ml/min per 1.73m^2 patients without diabetes?

- Patients with a wide range of kidney function have been studied in the reported trials, and despite attenuation of the effects of SGLT2 inhibitors on glycosuria with lower kidney function

- We found no good evidence that the **kidney benefits were modified by the average level of kidney function studied in the trials**. Importantly, efficacy and safety data from **EMPA-KIDNEY and DAPA-CKD** combined include information on nearly **3000 patients with an eGFR of 20–30 mL/min per 1·73 m2**. A total of 489 kidney disease progression outcomes accrued in those with an eGFR less than 30 mL/min per 1·73 m2 in those two trials
- SGLT2 inhibitors also appear safe at low levels of kidney function down to an eGFR **of at least 20 mL/min per 1·73 m2 with patients without diabetes** being at particularly low risk of ketoacidosis or amputation

Discussion-1

Does SGLT-2 inhibitor have kidney protective effect among eGFR 20-30 ml/min per 1.73m^2 ?

Recommendation 1.3.1: We recommend treating patients with type 2 diabetes (T2D), CKD, and an eGFR ≥20 ml/min per 1.73 m^2 with an SGLT2i (1A).

Practice Point 1.3.1: The recommendation for SGLT2i is for kidney and cardiovascular protection and SGLT2i have been shown to have safety and benefit in CKD patients, even for those without T2D. Thus, if patients are already being treated with other glucose-lowering agents, an SGLT2i can be added to the current treatment regimen.

Practice Point 1.3.2: The choice of an SGLT2i should prioritize agents with documented kidney or cardiovascular benefits and take eGFR into account.

Practice Point 1.3.3: It is reasonable to withhold SGLT2i during times of prolonged fasting, surgery, or critical medical illness (when patients may be at greater risk for ketosis).

Practice Point 1.3.4: If a patient is at risk for hypovolemia, consider decreasing thiazide or loop diuretic dosages before commencement of SGLT2i treatment, advise patients about symptoms of volume depletion and low blood pressure, and follow up on volume status after drug initiation.

Practice Point 1.3.5: A reversible decrease in the eGFR with commencement of SGLT2i treatment may occur and is generally not an indication to discontinue therapy.

Practice Point 1.3.6: Once an SGLT2i is initiated, it is reasonable to continue an SGLT2i even if the eGFR falls below 20 ml/min per 1.73 m^2, unless it is not tolerated or kidney replacement therapy is initiated.

Practice Point 1.3.7: SGLT2i have not been adequately studied in kidney transplant recipients, who may benefit from SGLT2i treatment, but are immunosuppressed and potentially at increased risk for infections; therefore, the recommendation to use SGLT2i does not apply to kidney transplant recipients (see Recommendation 1.3.1).

KDIGO 2022 guideline for Diabetes in CKD

Discussion

Strength

- Addresses the scarcity of a single standardized kidney disease progression outcome in previous meta-analyses
- Takes into account **all of the available large-scale randomized evidence** from around 90000 people recruited into 13 relevant SGLT2 inhibitor clinical trials

Limitation

- Low numbers of cardiovascular deaths and heart failure hospitalizations in patients with **chronic kidney disease without diabetes**
- Adjudication of acute kidney injury was not performed in most trials
- Although there was no significant between-study heterogeneity for all efficacy and safety outcomes, whether the cardiorenal benefits **differ among different stages of heart failure or CKD** deserves further study.

05

Apply

FDA許可品項

	Canagliflozin 100mg CANAGLU ®	Dapagliflozin 10mg Forxiga®	Empagliflozin 10mg JARDIANCE®	Ertugliflozin 5mg Steglatro®
				
Indication	• 第二型糖尿病 • 糖尿病腎病變(巨量蛋白尿期)	• 血糖控制 • 預防心血管事件 • 心衰竭 • 慢性腎臟病	• 血糖控制：第二型糖尿病 • 預防心血管事件：用於具第二型糖尿病且已有心血管疾病的成人病人時	• 改善第二型糖尿病成人病人的血糖控制
Dose	100mg	10mg	10mg	5mg
Renal adjustment	X：eGFR <30	X：eGFR <25	X：eGFR <20	X：eGFR<45
Hemodialysis	Not dialyzable; use is contraindicated			

治療目標

History
- HTN, dyslipidemia
  HFpEF class 3
  CKD 3b proteinuria A3

Objective
BP：150~160

Lab

BUN	eGFR/CR	UPCR	Hb	Na	K
18	35/1.53	1105	10.7	140	4.6

Pharmacotherapy

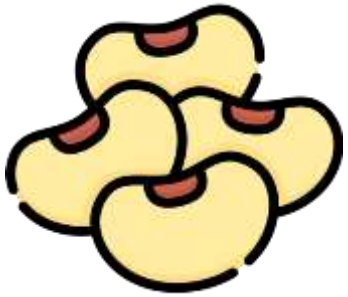
腎臟科
- Amlodipine 5mg QD
- Pentoxifylline 100mg QD
- Hi-beston

心臟內科
- Entresto 200mg #0.5tab BID
- Carvedilol 25mg #0.5 tab BID
- Rosuvastatin QD
- Amino acid 630mg QD

- **Recommendation 3.1.1**

We suggest that adults with high BP and CKD be treated with a target systolic blood pressure (SBP) of <120 mm Hg, when tolerated, using standardized office BP measurement *(2B)*.

飲食與生活調整



Plant-dominant, low protein diets (PLADO)

- **Low protein diet**：
  0.6~0.8 mg/kg/day
- **Plant dominant**：
  >50% plant based sources

Nutrient focused dietary intervention

- Low sodium, low phosphate, and low potassium

Increasing physical activity, weight reduction

Avoid protein- energy wasting!

台灣慢性腎臟病臨床診療指引

Lancet chronic kidney disease 2021; 398: 786–802

討論觀點

實證醫學

根據文獻。SGLT 2 inhibitors對於慢性腎臟疾病族群或者是心衰竭族群均可以降低腎臟疾病惡化，且不分糖尿病族群，及任何成因之腎臟疾病

利弊平衡

SGLT 2 inhibitors常見副作用為生殖器黴菌感染，尿路感染，鼻咽炎

病人的考量

是否可以使用SGLT 2 inhibitors 來減緩腎功能惡化

費用資源

目前對於慢性腎臟疾病族群或正常收縮分率之心衰竭病人，健保還未補助，若使用院內SGLT 2 inhibitors(Dapagliflozin)需一個月自費約792元

回覆問題

請問

SGLT 2 inhibitors，對我目前的疾病狀況有幫助嗎？

回覆問題

妳好

根據文獻查證，添加SGLT 2 inhibitors在妳原本的治療上，對於減緩腎功能惡化的方面可以有更好的療效，目前臨床指引也說明SGLT-2 inhibitor對於非糖尿病慢性腎臟病族群也有心腎保護療效。
不過常見的副作用會有像是泌尿道感染或者是鼻咽炎等症狀

但目前台灣健保，目前尚未給付慢性腎臟病或者是正常收縮分率心衰竭的族群，因此需自費使用。因此我們還是會陪著妳，考慮自身的情況和喜好，再決定是否要使用此治療方式！

Reference

1. David C Wheeler, Bergur V Stefa´nsson, Niels Jongs, Glenn M Chertow, et al
   Effects of dapagliflozin on major adverse kidney and cardiovascular events in patients with diabetic and non-diabetic chronic kidney disease: a prespecified analysis from the DAPA-CKD trial。 Lancet Diabetes Endocrinol 2021; 9: 22–31
2. Hiddo J.L. Heerspink, Ph.D., Bergur V. Stefánsson Dapagliflozin in Patients with Chronic Kidney Disease N Engl J Med 2020; 383:1436-1446
3. 2022 台灣慢性腎臟病臨床診療指引
4. KDOQI and KDIGO 2012 guidelines
5. Gregorio T Obrador, MD, MPH Epidemiology of chronic kidney disease, Uptodate(Accessed on December 18,2022)

Thank you for your listening~~~