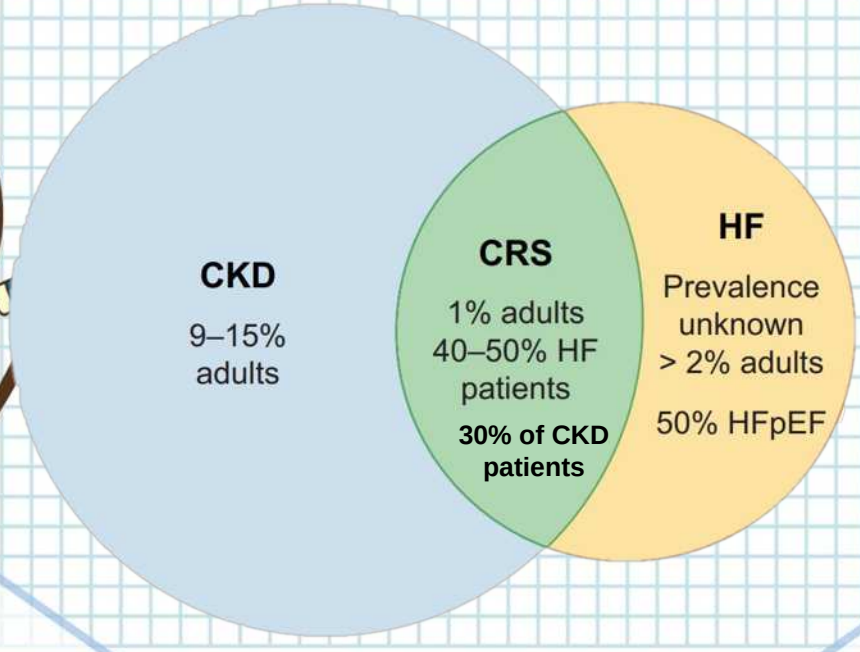
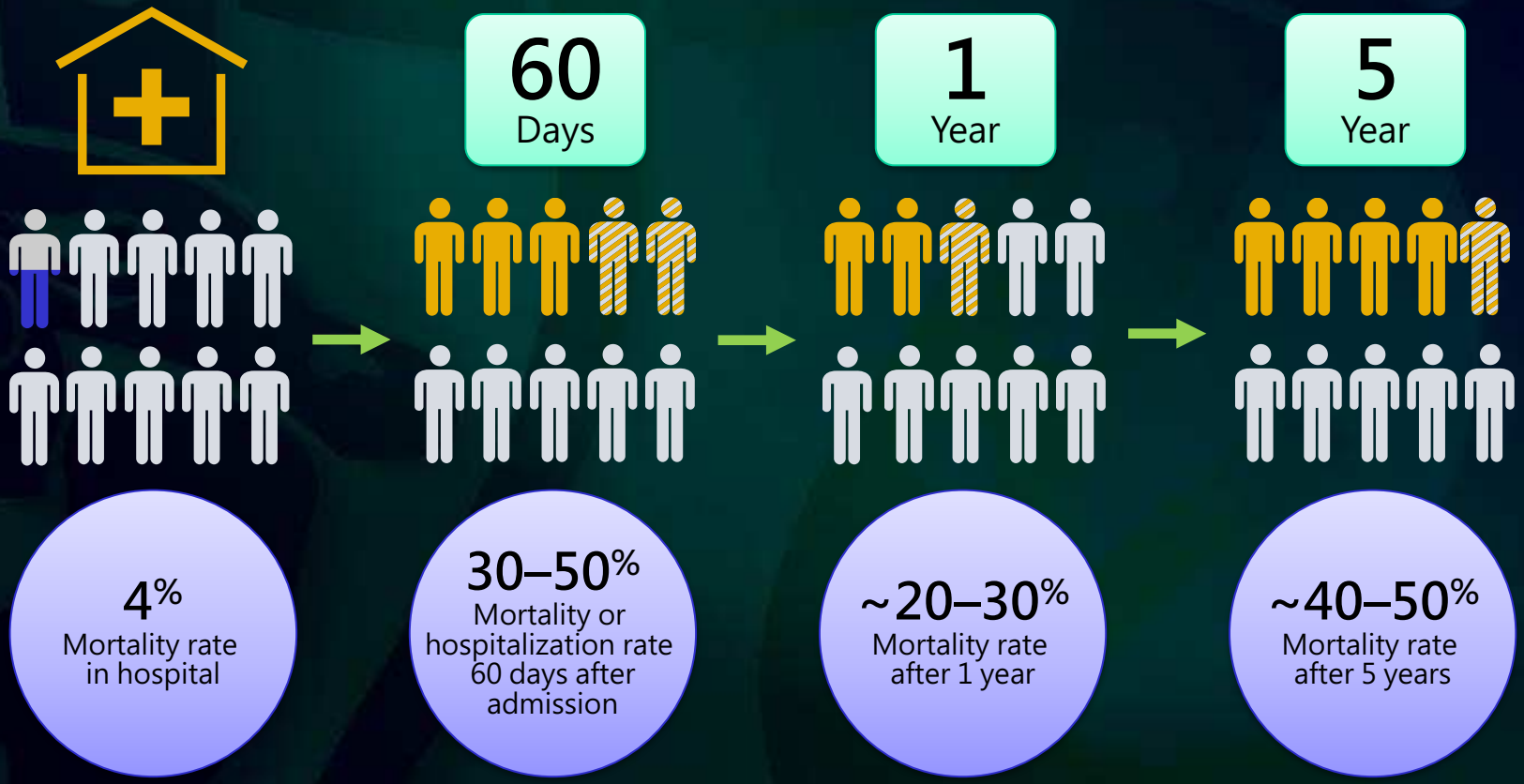
Care of C-K-D Patients

嘉義慈濟診所
大林慈濟腎臟科主任
5月22日
蔡任弼

心腎症候群

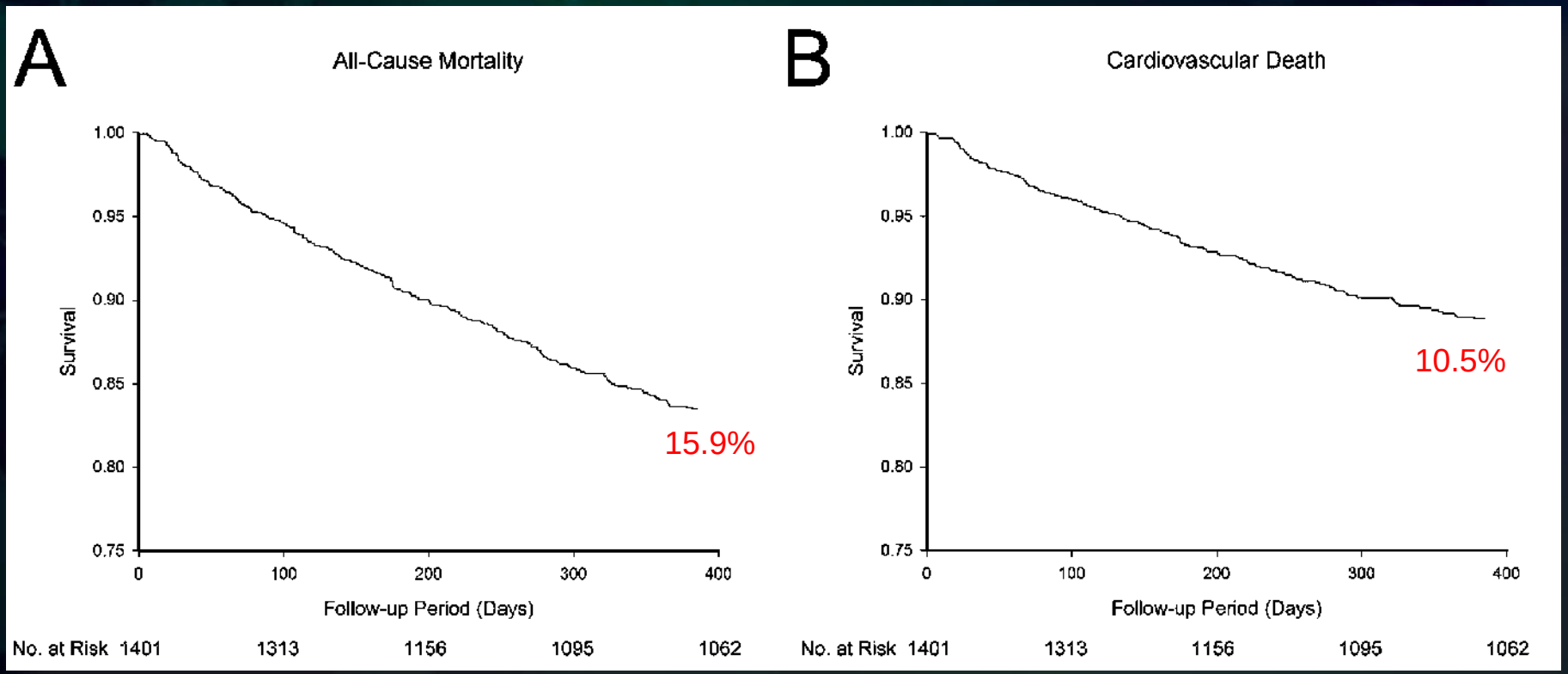

CKD
9–15%
adults
CRS
1% adults
40–50% HF
patients
30% of CKD
patients
HF
Prevalence
unknown
> 2% adults
50% HFpEF

HFrEF與經常入院和較高死亡率相關



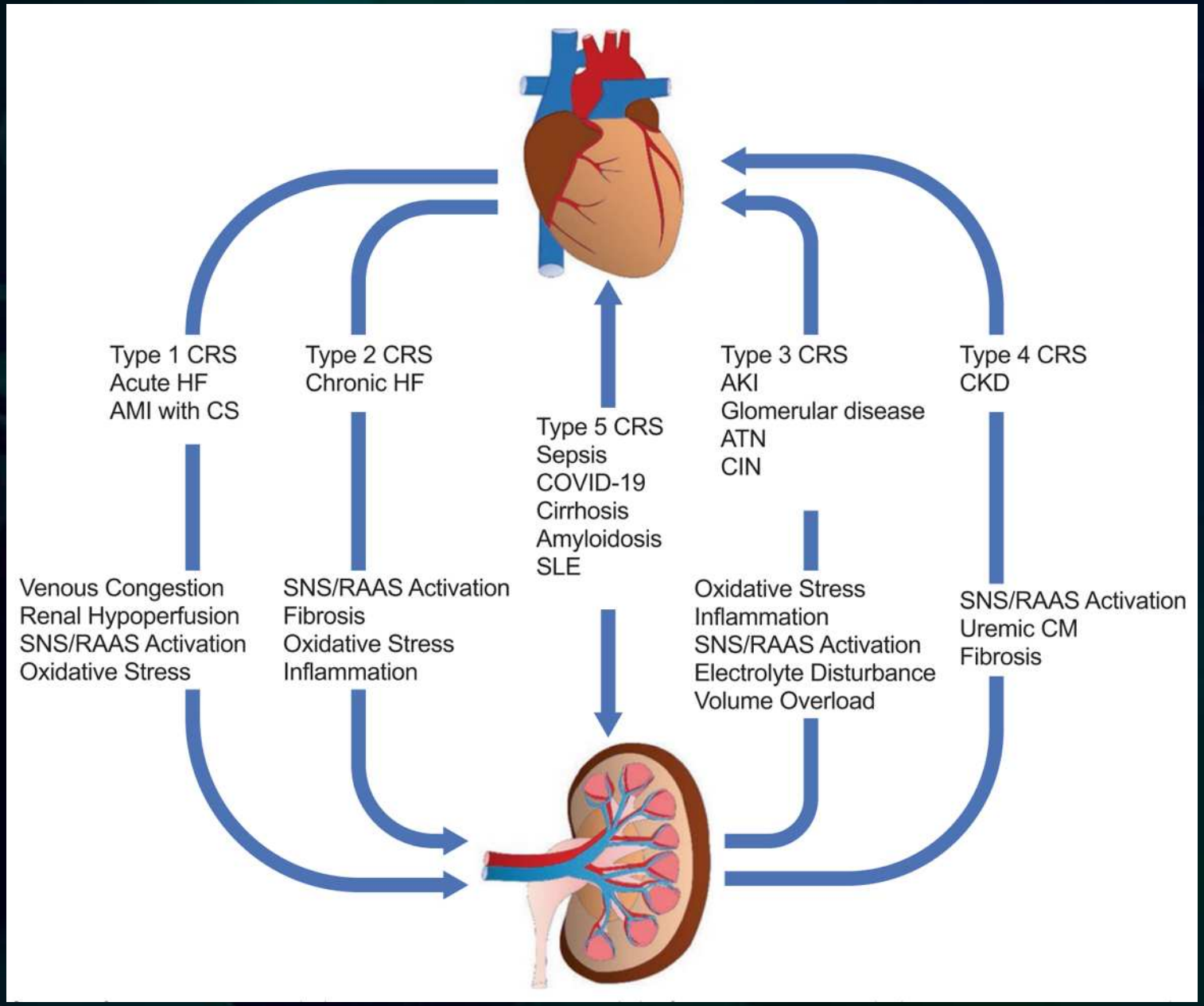
~50% of heart failure deaths occur suddenly

One-year result of TSOC HF registry



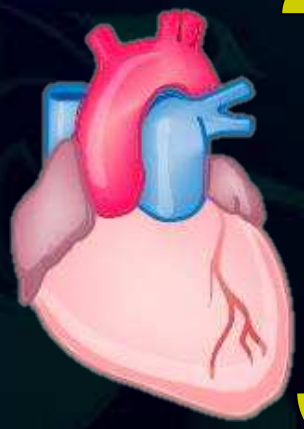
1-yr Re-hospitalization rates for HF: 38.5%
At 1-yr, only 46.4% free from death, hospitalization for HF, LVAD or Tx

HY Chang et al. Acta Cardiol Sin 2017;33:127-138

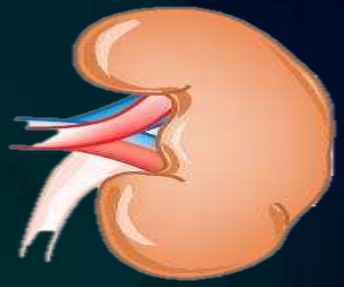

Type 1 CRS
Acute HF
AMI with CS
Type 2 CRS
Chronic HF
Type 5 CRS
Sepsis
COVID-19
Cirrhosis
Amyloidosis
SLE
Type 3 CRS
AKI
Glomerular disease
ATN
CIN
Type 4 CRS
CKD
Venous Congestion
Renal Hypoperfusion
SNS/RAAS Activation
Oxidative Stress
SNS/RAAS Activation
Fibrosis
Oxidative Stress
Inflammation
Oxidative Stress
Inflammation
SNS/RAAS Activation
Electrolyte Disturbance
Volume Overload
SNS/RAAS Activation
Uremic CM
Fibrosis

Arterial Underfilling

Decreased CO
Decreased Effective circulating volume
Decreased RBF, RPF
Activating of RAAS, SNS
Inflammatory pathways

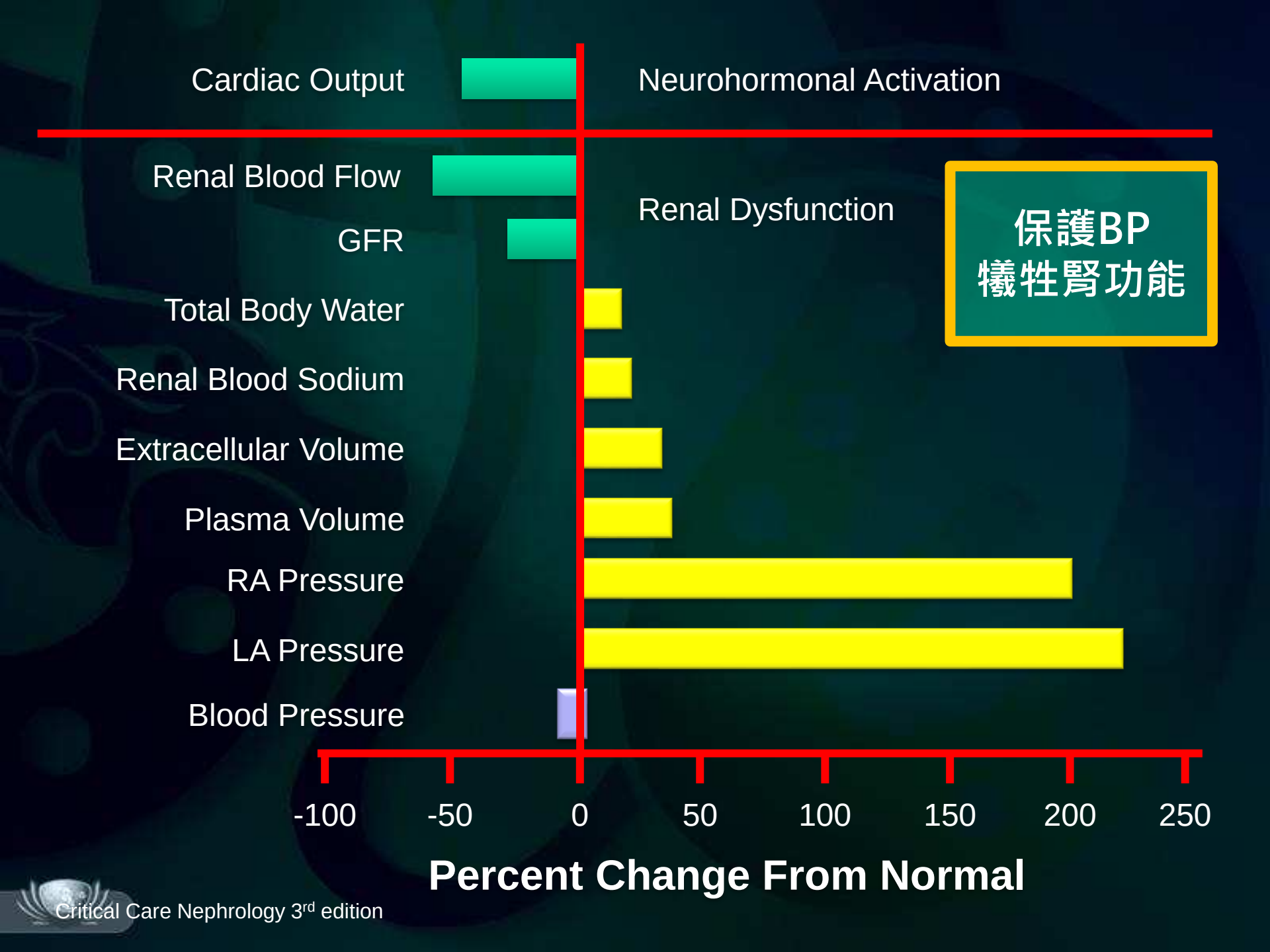


Decreased GFR
Na and H_2O retention
Increased edema, preload
Increased Afterload



Venous Congestion

Venous congestion, HTN, Raised IAP
Decreased AV perfusion gradient
Kidney interstitial edema
Activation of RAAS, SNS
Inflammatory pathways


Cardiac Output
Neurohormonal Activation
Renal Blood Flow
GFR
Renal Dysfunction
保護BP
犧牲腎功能
Total Body Water
Renal Blood Sodium
Extracellular Volume
Plasma Volume
RA Pressure
LA Pressure
Blood Pressure
-100
-50
0
50
100
150
200
250
Percent Change From Normal

Diagnosis of CRS in HFpEF

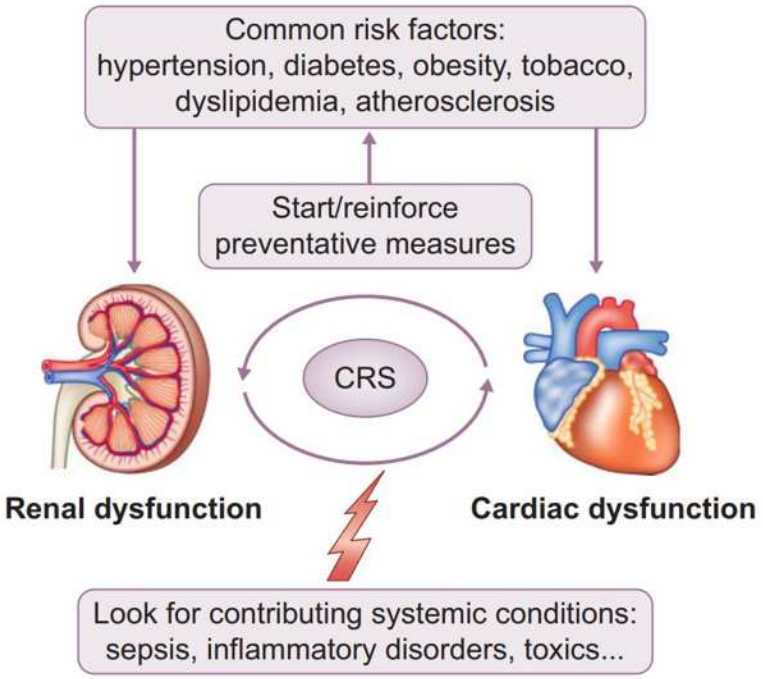
Renal assessment

Renal function:
- Serum creatinine and eGFR
- Consider cystatin C
- Urine sample: urinary sodium, proteinuria, hematuria
- Blood gas assessment

Structural:
- Renal Doppler ultrasound

Classify:
- RIFLE (acute)/KDIGO (chronic)

Seek nephrology advice:
- Systemic disease, significant proteinuria, need for RRT



Cardiac assessment

Echocardiogram (LVEF ≥ 50%):
- LA size > 34 ml/m² (SR)
  > 40 ml/m² (AF)
- TR velocity > 2.8 m/s
- E/e′ > 9

Peptides:
- NTproBNP > 220 pg/ml (SR)
  > 660 pg/ml (AF)
- Consider CA-125

Scores:
- HFA-PEFF and H2F-PEEF

Seek cardiology advice:
- Revascularization, valvulopathies, arrhythmias, pericardial effusion...

Clinical Kidney Journal, 2022, vol. 15, no. 10, 1807–1815

CHF 治療目標

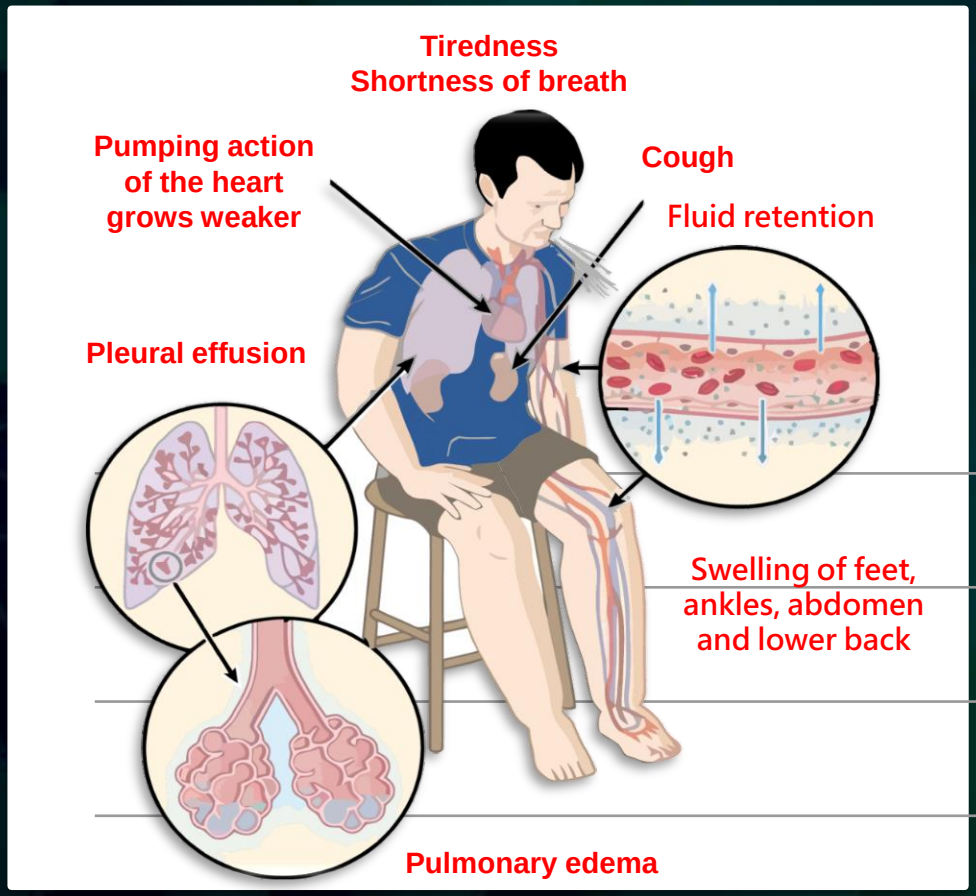
何者重要?

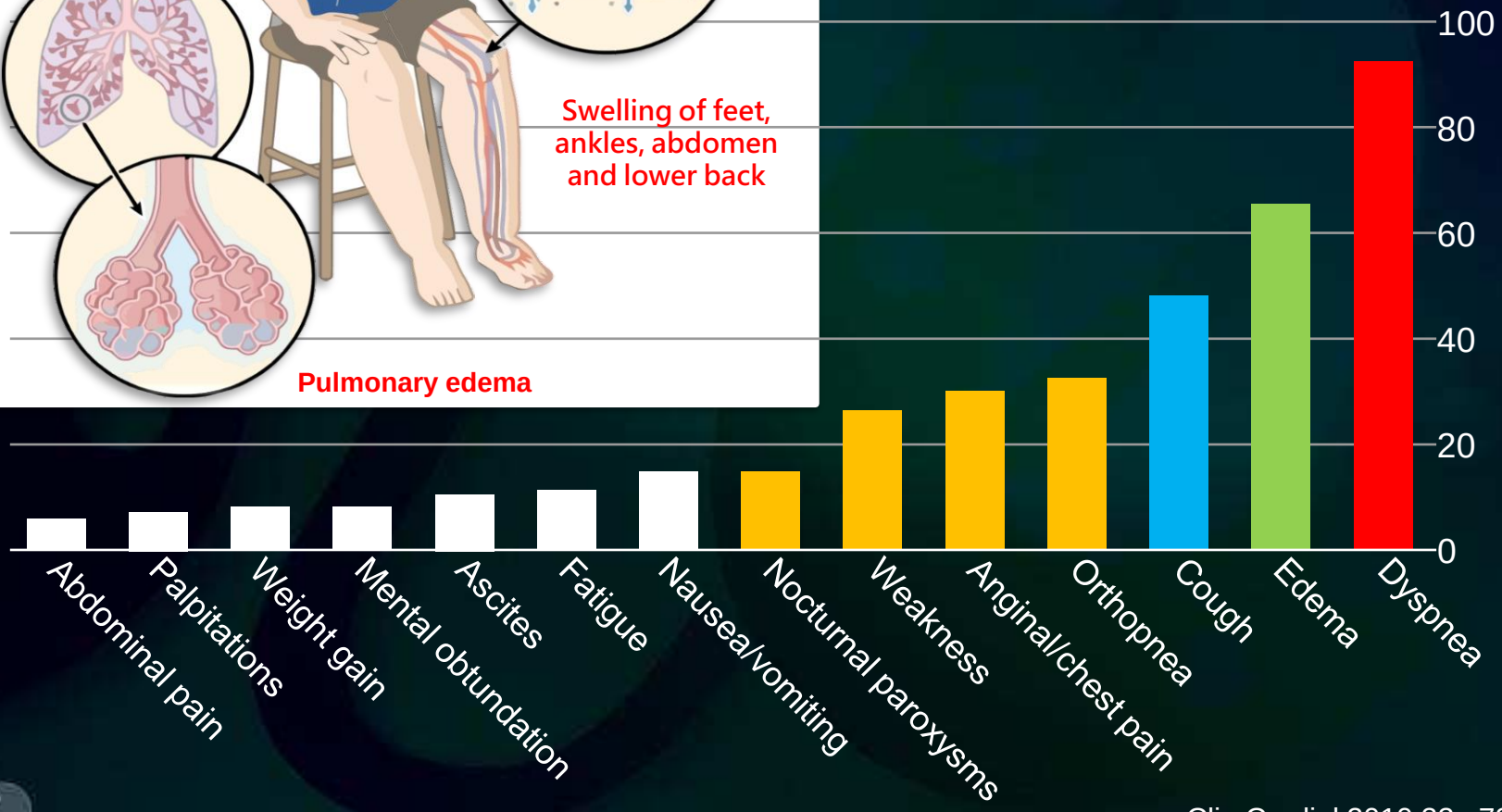
急性/慢性

Decongestion?

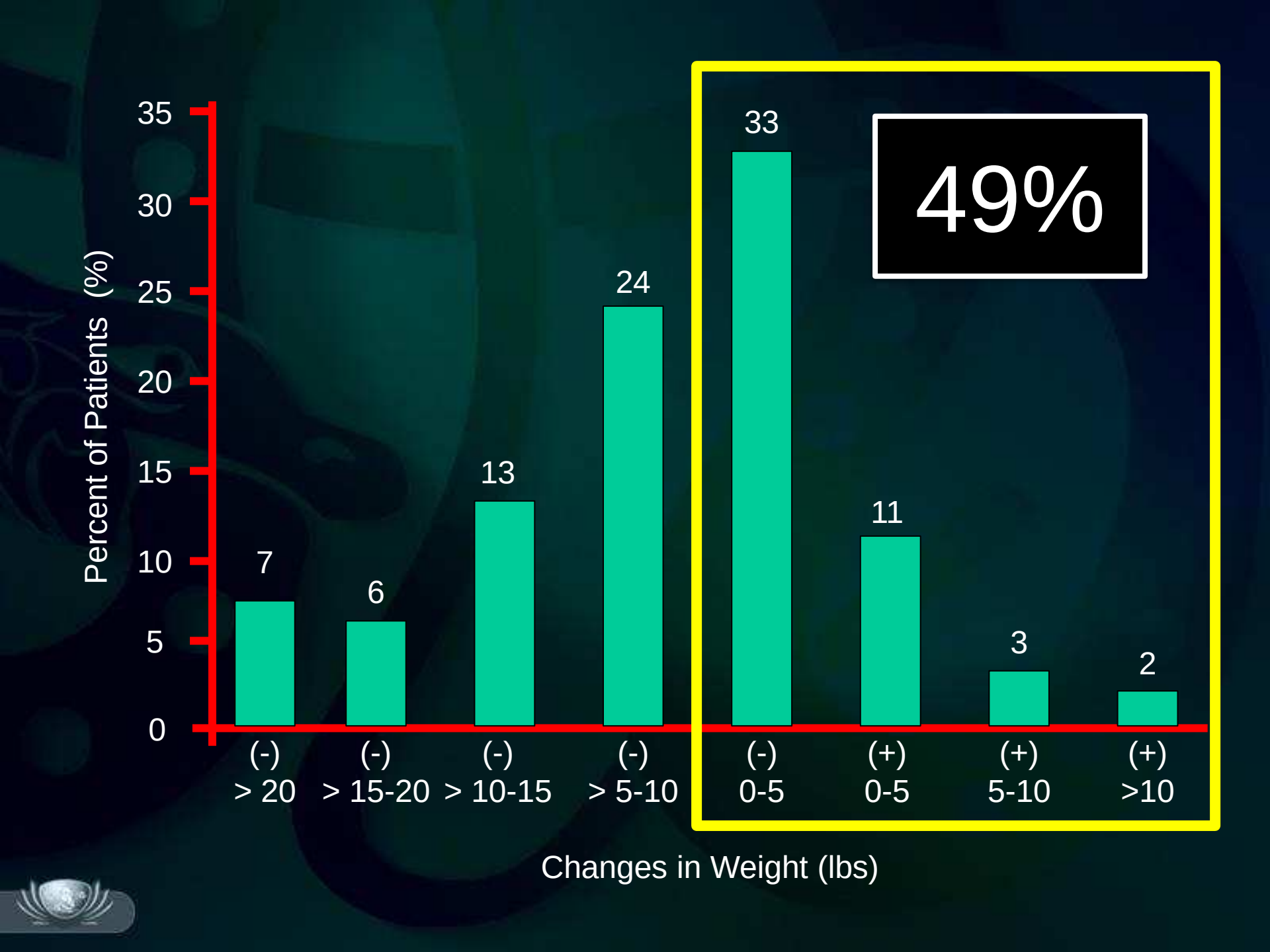
保護腎功能?

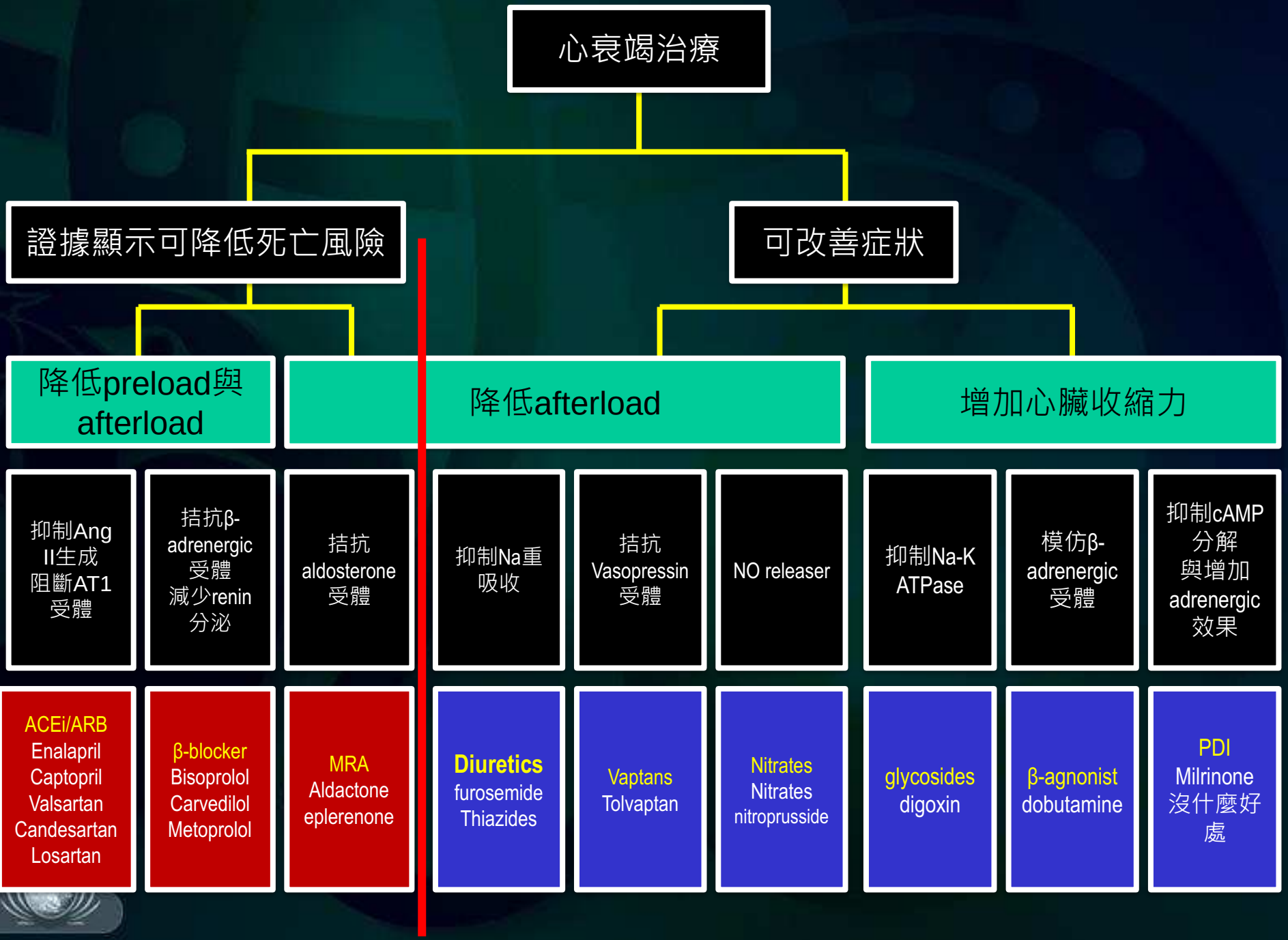
心衰竭
常見症狀

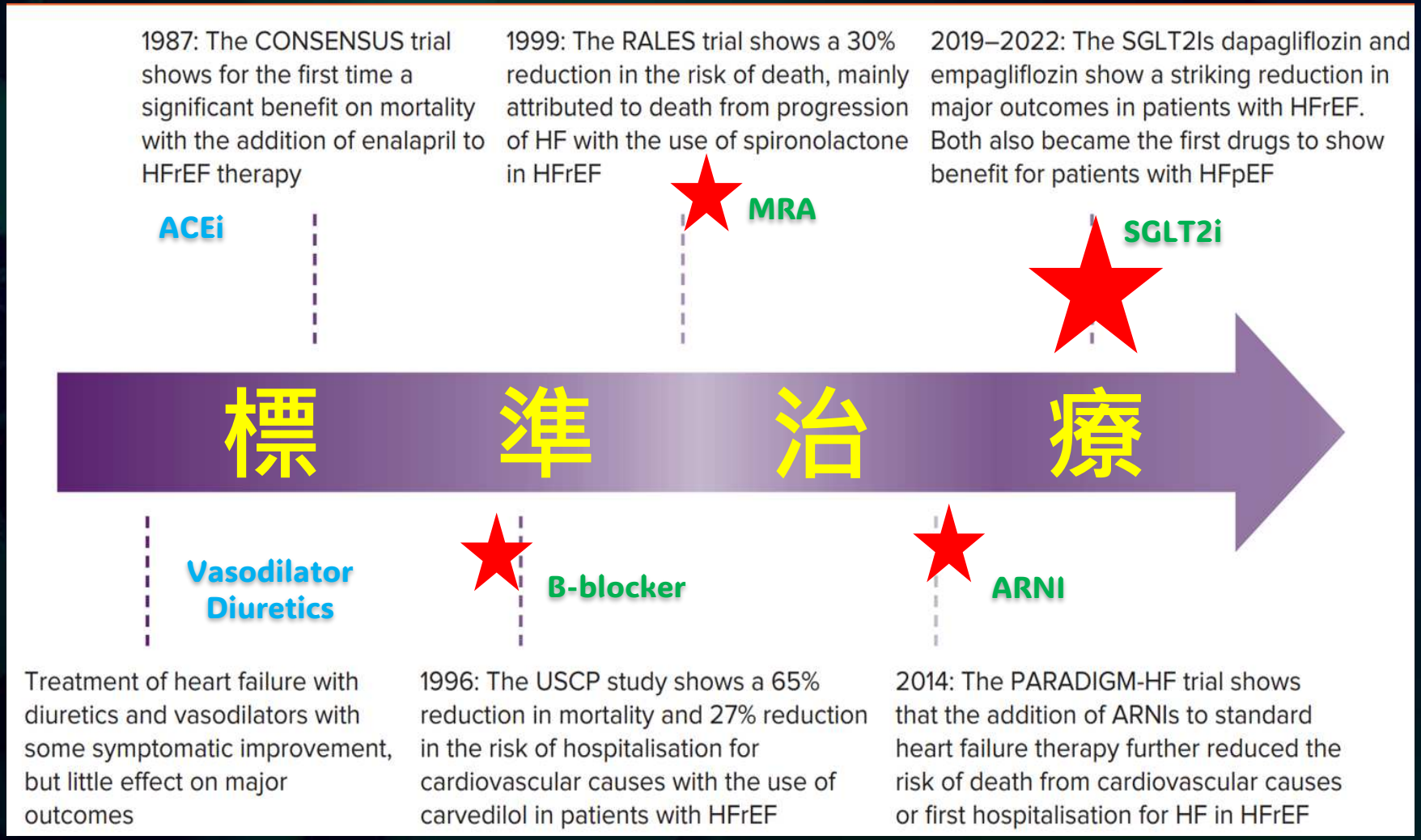




Clin Cardiol 2010;33:e73–80


49%
Percent of Patients (%)
35
30
25
20
15
10
5
0
7
6
13
24
33
11
3
2
(-) > 20
(-) > 15-20
(-) > 10-15
(-) > 5-10
(-) 0-5
(+) 0-5
(+) 5-10
(+) >10
Changes in Weight (lbs)


心衰竭治療
證據顯示可降低死亡風險
可改善症狀
降低preload與afterload
降低afterload
增加心臟收縮力
抑制Ang II生成阻斷AT1受體
拮抗β-adrenergic受體減少renin分泌
拮抗aldosterone受體
抑制Na重吸收
拮抗Vasopressin受體
NO releaser
抑制Na-K ATPase
模仿β-adrenergic受體
抑制cAMP分解與增加adrenergic效果
ACEi/ARB
Enalapril
Captopril
Valsartan
Candesartan
Losartan
β-blocker
Bisoprolol
Carvedilol
Metoprolol
MRA
Aldactone
eplerenone
Diuretics
furosemide
Thiazides
Vaptans
Tolvaptan
Nitrates
Nitrates
nitroprusside
glycosides
digoxin
β-agnonist
dobutamine
PDI
Milrinone
沒什麼好處



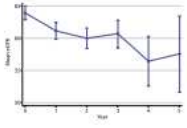
Foundational therapy with the combination of four medications is established as the standard of care for heart failure, with major improvements in outcomes and quality of life

Cardiac Failure Review 2024;10:e03

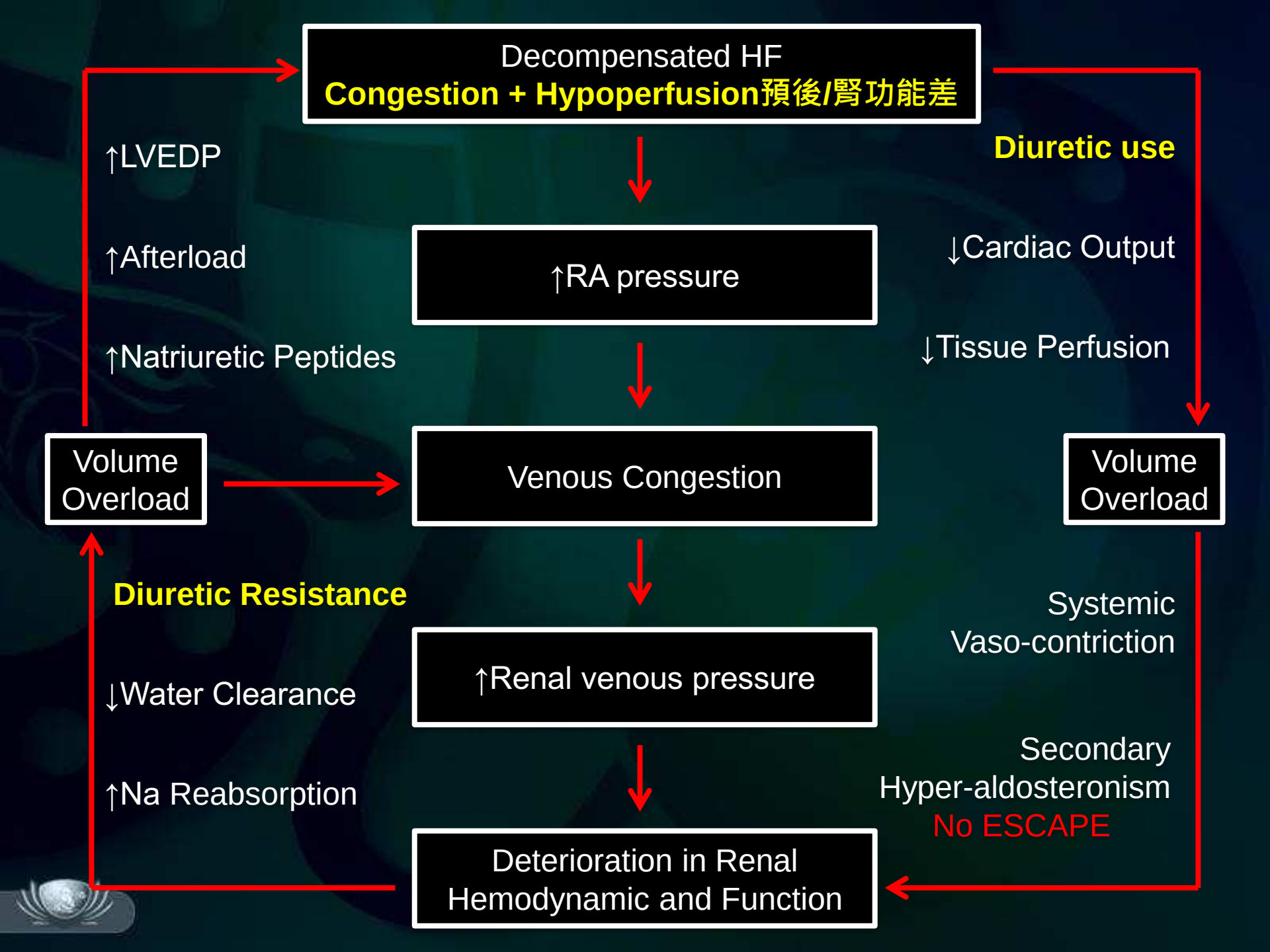
Baseline characteristics[a]

SGLT2i trial in HF	DAPA-HF		EMPEROR-Reduced		DELIVER		EMPEROR-Preserved	
Treatment group	Dapagliflozin (N = 2373)	Placebo (N = 2371)	Empagliflozin (N = 1863)	Placebo (N = 1867)	Dapagliflozin (N = 3131)	Placebo (N = 3132)	Empagliflozin (N = 2997)	Placebo (N = 2991)
LVEF, %	31.2 ± 6.7	30.9 ± 6.9	27.7 ± 6.0	27.2 ± 6.1	54.0 ± 8.6	54.3 ± 8.9	54.3 ± 8.8	54.3 ± 8.8
LVEF category, N (%)	Not stated	Not stated	≤ 30, 1337 (71.8)	≤ 30, 1392 (74.6)	≤ 49%, 1067 (34.1) 50–59%, 1133 (36.2) ≥ 60%, 931 (29.7)	≤ 49%, 1049 (33.5) 50–59%, 1123 (35.9) ≥ 60%, 960 (30.7	> 40% to < 50%, 955 (33.2) ≥ 50% to < 60%, 1028 (34.3) ≥ 60%, 974 (32.5)	> 40% to < 50% 988 (33.0) ≥ 50% to < 60% 1030 (34.4) ≥ 60%, 973 (32.
eGFR, mL/min/1.73 m²	66.0 ± 19.6	65.5 ± 19.3	61.8 ± 21.7	62.2 ± 21.5	61 ± 19	61 ± 19	60.6 ± 19.8	60.6 ± 19.9
eGFR < 60 mL/min/1.73 m², N/total (%)	962/2372 (40.6)	964/2371 (40.7)	893/1862 (48.0)	906/1866 (48.6)	1516/3131 (48.4)	1554/3132 (49.6)	1504/2997 (50.2)	1484/2989 (49.6)

Outcomes[b]

SGLT2i trial in HF	DAPA-HF	EMPEROR-Reduced	DELIVER	EMPEROR-Preserved
Primary endpoint (composite including HHF) 	↓ 26% HR: 0.74 95% CI 0.65–0.85; p < 0.001	↓ 25% HR: 0.75 95% CI 0.65–0.86; p < 0.001	↓ 18% HR: 0.82 95% CI 0.73–0.92; p < 0.001	↓ 21% HR: 0.79 95% CI 0.69–0.90; p < 0.001 (Attenuated effect on HHF at EF > 60%)
Kidney endpoint (eGFR rate of decline) 	↓ (Days 14–720) +1.76 difference (mL/min/1.73 m² per year) Dapagliflozin –1.09 (95% CI–1.40 to –0.77) vs placebo–2.85 (95% CI –3.17 to –2.53) mL/min/1.73 m² per year; p < 0.001	↓ +1.73 difference (mL/min/1.73 m² per year) 95% CI 1.10–2.37; p < 0.001	↓ (Months 1–36) +1.4 difference (mL/min/1.73 m² per year) 95% CI 1.0–1.8; p < 0.001	↓ +1.36 difference (mL/min/1.73 m² per year) 95% CI 1.06–1.66; p < 0.001
Kidney endpoint (composite including worsening kidney function) 	No effect	↓ 50% HR: 0.50 95% CI 0.32–0.77	No prespecified composite kidney endpoint	↓ 22% [c] HR: 0.78 95% CI 0.54–1.13; p = 0.02 (Attenuated effect at higher EFs)


臨床使用
利尿劑
Diuretic Resistance
SGLT2i ?


Decompensated HF
Congestion + Hypoperfusion預後/腎功能差
↑LVEDP
↑Afterload
↑Natriuretic Peptides
Diuretic use
↓Cardiac Output
↓Tissue Perfusion
↑RA pressure
Volume Overload
Venous Congestion
Volume Overload
Diuretic Resistance
↓Water Clearance
↑Na Reabsorption
↑Renal venous pressure
Systemic Vaso-contriction
Secondary Hyper-aldosteronism
No ESCAPE
Deterioration in Renal Hemodynamic and Function

Group	Drugs	Site of action	Mechanism (inhibition)	Relative natriuretic potency (%)
Osmotic diuretics	Mannitol	PT and LOH	Water and solute	Dose dependent (>10)
Carbonic anhydrase inhibitor	Acetazolamide	PT	Carbonic anhydrase	1-3
Loop	**Furosemide Bumetanide**	**LOH (TA)**	**Na/K/2Cl co-transporter**	**20-25**
Distal tubule	Hydrochlorothiazide Indapamide	Early DCT	Na/Cl co-transporter	5
K+ sparing	Amiloride apirololactone	CCD	ENaC MR receptor	1-3

改善症狀

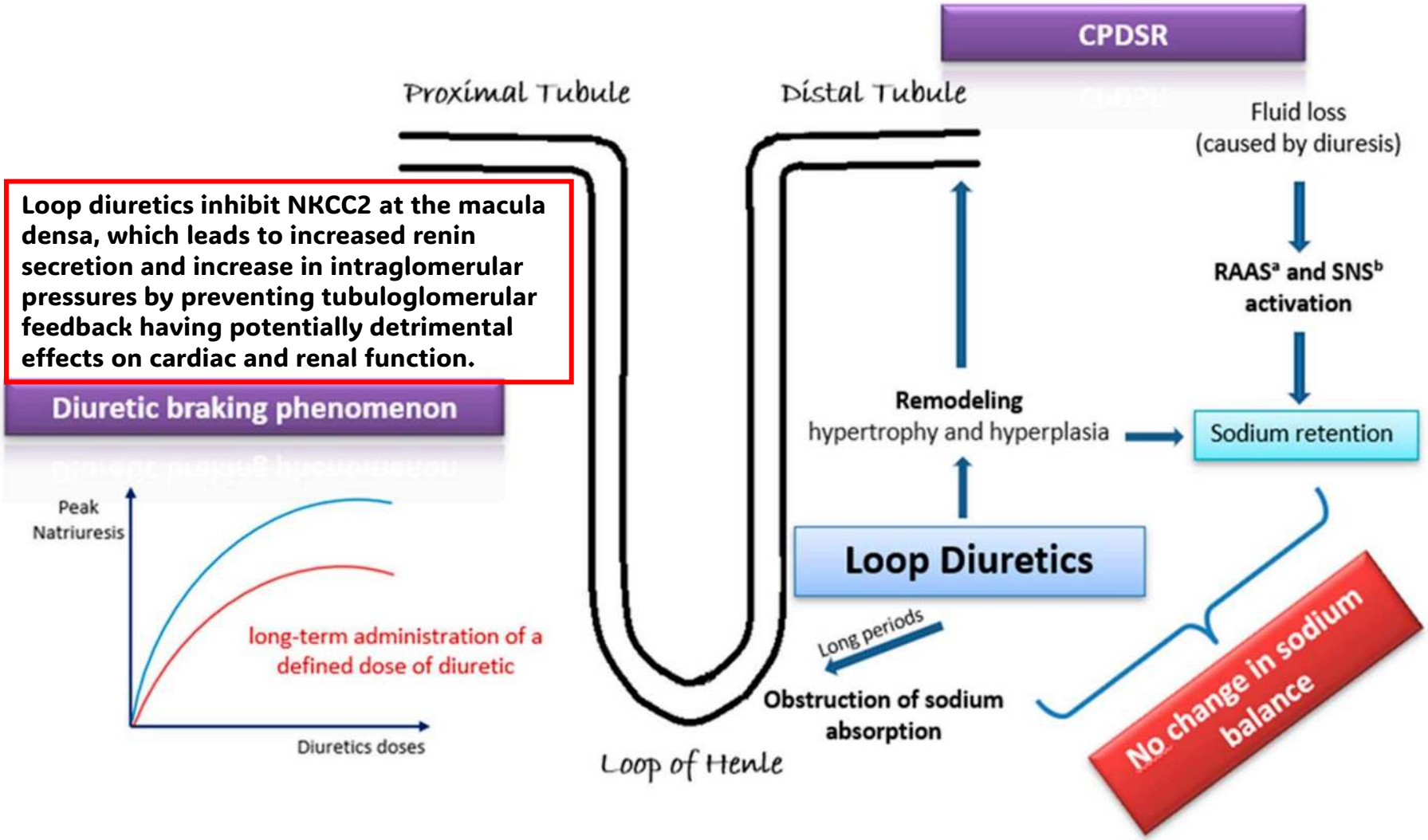
European Society of Cardiology認為需要加倍使用利劑時機尿為

1. **使用利尿劑2小時,spot urine Na ＜ 50 mmol/L**
2. **使用利尿劑後6小時內尿量＜100 ml/hr**

Mechanism of Diuretic Resistance in Heart Failure at nephron level

- Compensatory Post-Diuretic Sodium Reabsorption (CPDSR)

- Braking phenomenon



Int. J. Mol. Sci. 2024, 25, 3122

如何處理CHF & Diuretic resistance

確認水腫

(排除藥物如CCB之副作用)

停用NSAID

確認利尿劑效果

**利尿劑最佳效果產生在初始劑量

**DOUBLE DOSE

初始劑量有達到效果後,可以使用相同劑量BID/TID

**若是Lasix無效,可以試burinex

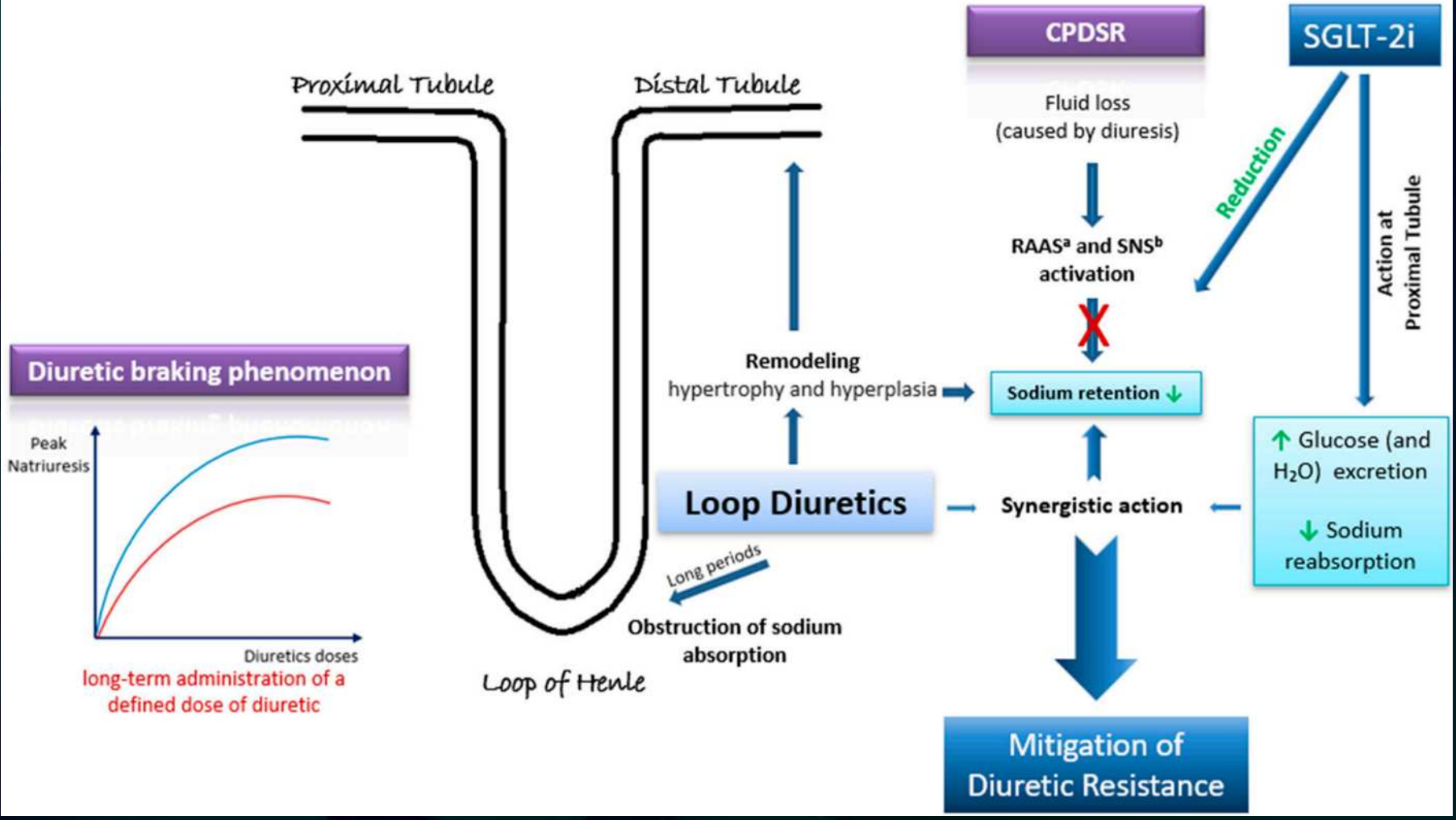
若無法達到預期效果,可以加上其它種類利尿劑

或是用infusion

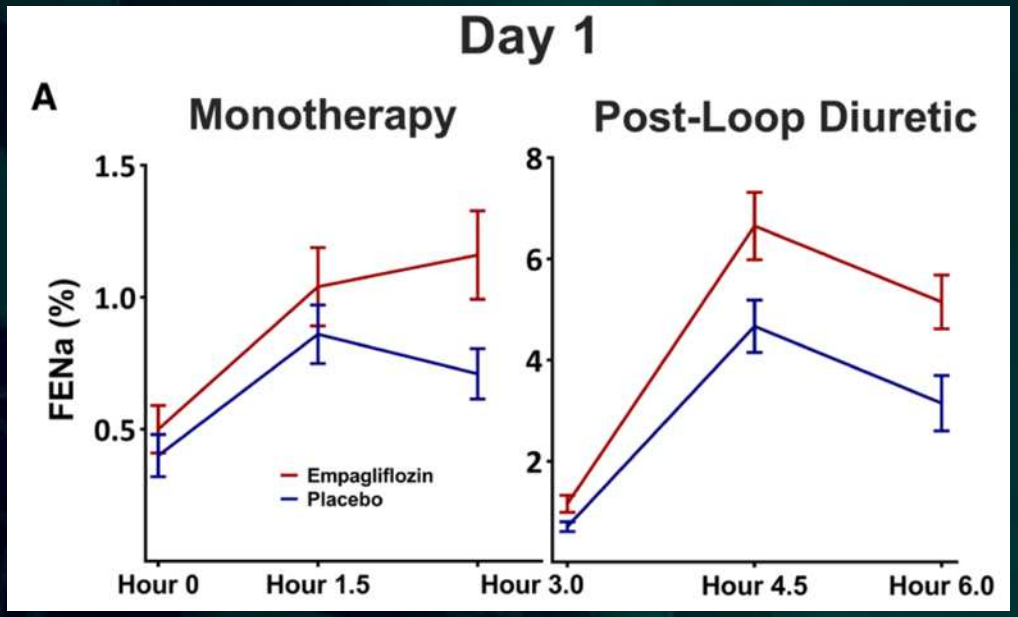
若是效果仍不佳

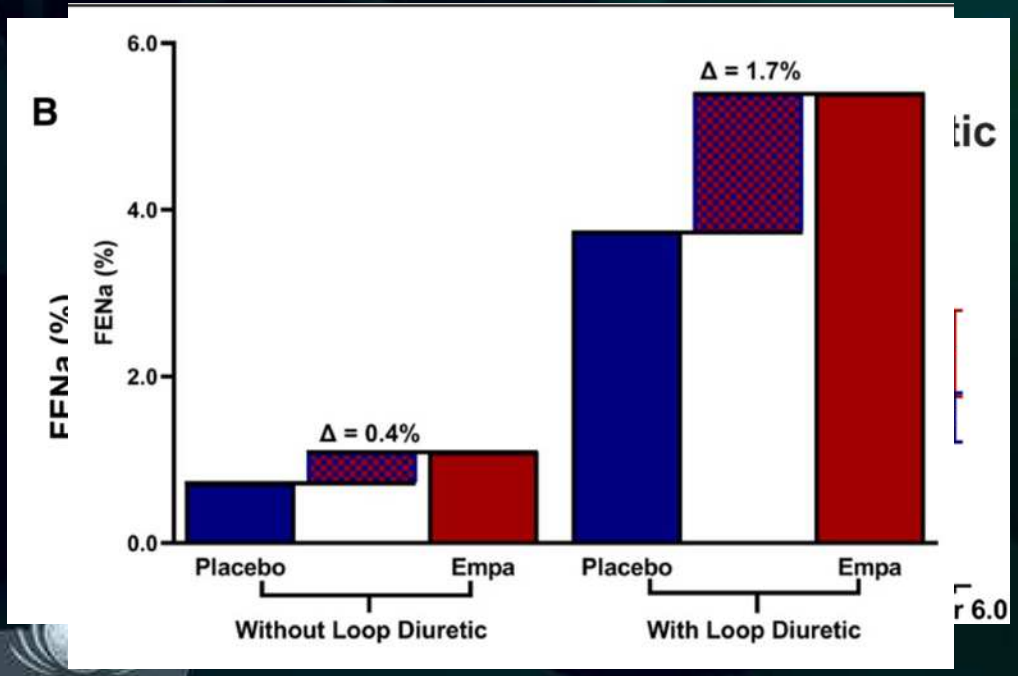
考慮透析(UF)

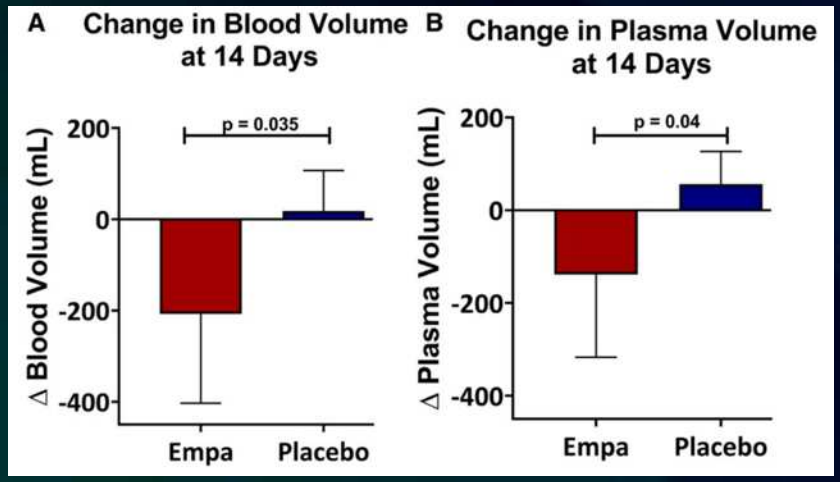
Mechanism of mitigation of Diuretic Resistance by SGLT-2i[c]

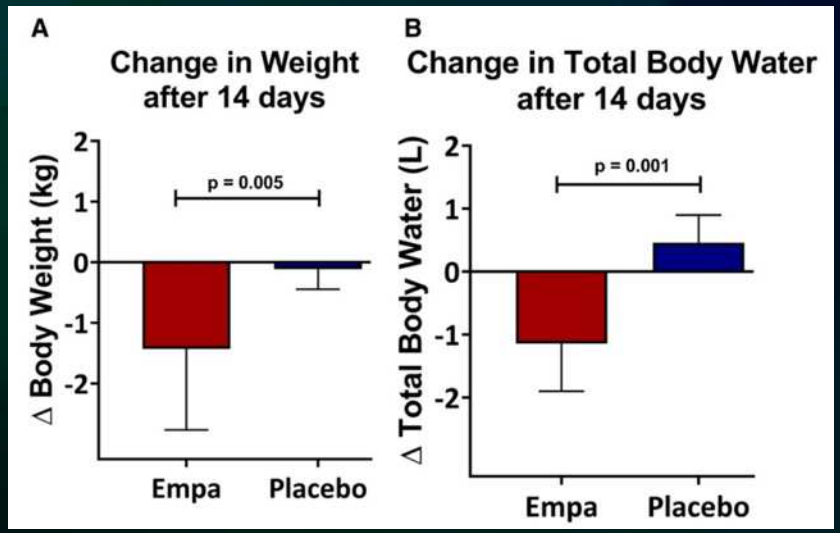


Type 2 DM & HF



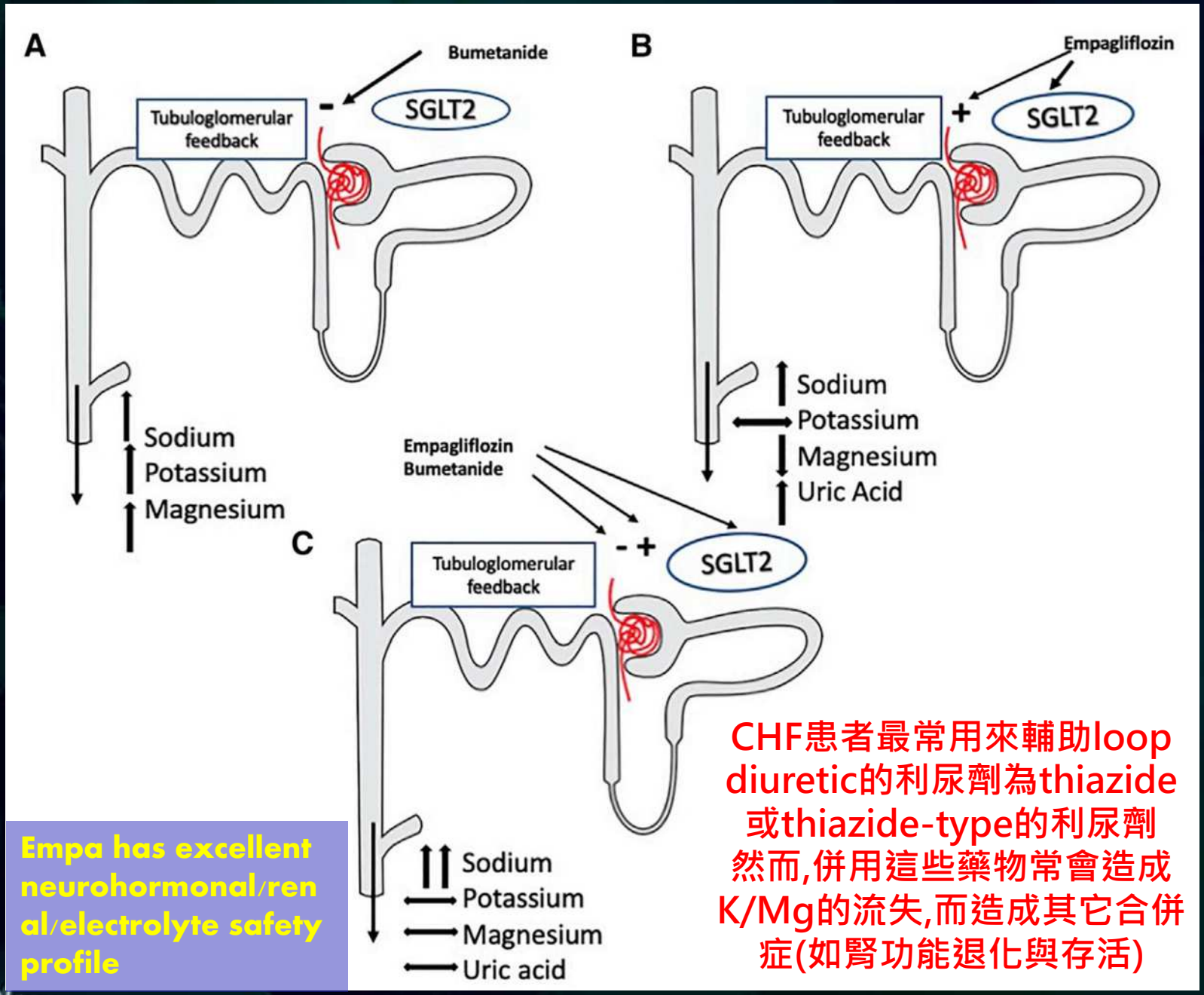






- **Empa functions as a loop diuretic adjuvant with a clinically significant effect on natriuresis**

Circulation. 2020;142:1028–1039



Empa has excellent neurohormonal/renal/electrolyte safety profile

CHF患者最常用來輔助loop diuretic的利尿劑為thiazide或thiazide-type的利尿劑 然而,併用這些藥物常會造成K/Mg的流失,而造成其它合併症(如腎功能退化與存活)

Cell Metabolism 32, July 7, 2020

Table 1. Key studies investigating the impact of SGLT-2 inhibitors on the attenuation of diuretic resistance in patients with HF.

Study ID	Type of Study	Population (Main Characteristics)	SGLT2 Inhibitor vs. Comparator	Follow-Up	Main Outcomes
Biegus et al., 2023 [52]	Prespecified secondary analysis of the multicenter, double-blind RCT (EMPULSE trial)	530 patients hospitalized due to symptoms and signs of ADHF requiring iv loop diuretics after initial stabilization	Empagliflozin 10 mg/day vs. placebo as add-on therapy for 3 months. Randomization 1:1.	90 days	✓ Empagliflozin was associated with significantly greater reductions in body weight compared to the control group at day 15 (adjusted MD = −1.97 kg, 95% CI: [−2.86 to −1.08], $p < 0.0001$), at day 30 (MD = −1.74 kg, 95% CI: [−2.73 to −0.74], $p = 0.0007$), and after 3 months (MD = −1.53 kg, 95% CI: [−2.75 to −0.31], $p = 0.0137$). ✓ Empagliflozin was not associated with the administration of greater doses of loop diuretics compared to the control group at day 15 (adjusted MD = 6.7 mg of iv furosemide (or equivalent), 95% CI: [−1.0 to 14.4], $p = 0.0862$), at day 30 (MD = 5.3 mg of iv furosemide (or equivalent), 95% CI: [−1.6 to 12.3], $p = 0.1295$), and after 3 months. (MD = 3.1 mg of iv furosemide (or equivalent), 95% CI: [−3.4 to 9.6], $p = 0.3488$) ✓ Treatment with empagliflozin was associated with greater congestion score reductions compared to controls at day 15 (adjusted MD = −0.34, 95% CI: [−0.60 to −0.09], $p < 0.01$) and after 3 months (MD = −0.23, 95% CI: [−0.47 to 0.02], $p = 0.067$).
Packer et al., 2021 b [50]	Multicenter, double-blind, RCT (EMPEROR-Reduced trial)	3730 patients with HFrEF (39.6% in "volume overload" and 57% "euvolemic").	Empagliflozin 10 mg/day vs. placebo as an add-on to conventional therapy. Randomization 1:1.	720 days	✓ Patients with "volume overload" were at a higher risk of increase in the sustained dose of loop diuretics when treated with a placebo vs. empagliflozin (HR: 1.22; 95% CI: [1.00–1.48]; $p = 0.047$). ✓ Empagliflozin administration was associated with a lower probability of the up-titration of loop diuretics (HR = 0.68, 95% CI: [0.55–0.85] in patients with recent volume overload and HR = 0.67, 95% CI: [0.55–0.82] in euvolemic patients. ✓ Patients in the empagliflozin arm experienced a moderate decrease in NT-proBNP levels after 4 weeks and a more significant one at week 52, regardless of volume status ($p = 0.38$ and $p = 0.67$, respectively). ✓ Patients receiving empagliflozin had a higher probability of improvement in the NYHA functional class after 4 weeks and experienced an amelioration in the KCCQ score after 12 weeks of treatment irrespective of their volume status. ✓ A statistically significant decline in body weight (mean 1 kg) and an increase in hematocrit were observed in the group receiving empagliflozin regardless of volume status. ✓ The eGFR decreased at a slower rate in patients receiving empagliflozin regardless of "volume overload".
Packer et al., 2021 a [57]	Multicenter, double-blind, RCT (EMPEROR-Preserved trial)	5988 patients with HF and EF > 40%	Empagliflozin 10 mg/day vs. placebo as an add-on to conventional therapy. Randomization 1:1.	26 months	✓ The outpatient up-titration of furosemide was observed less frequently in the SGLT2 inhibitor arm compared to the control group (HR = 0.76, 95% CI: [0.67–0.86]; $p < 0.0001$). ✓ Treatment with empagliflozin was associated with a 20% to 50% greater likelihood of experiencing a better NYHA functional class after a period of 3 months.

SGLT2i reduce the risk of severe hyperkalemia in patients with T2D through a variety of risk factors without increasing the risk of hypokalemia.

Cardiovascular and Renal Effects of SGLT2 Initiation in Acute Heart Failure

A meta-analysis of Randomized Controlled Trials

Design

Population: Acute Heart Failure

Intervention: SGLT2i + Conventional diuretic therapy

Control: Conventional diuretic therapy alone

2,824 patients from 9 RCTs were included

Results

Addition of SGLT2i to conventional diuretic therapy:

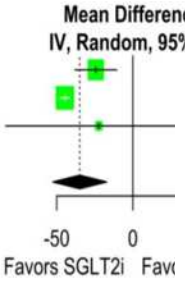
All-cause death *(OR 0.75; 95% CI 0.56-0.99)*
Readmissions for HF *(OR 0.54; 95% CI 0.44-0.66)*
CV death or readmissions for HF *(HR 0.71; 95% CI 0.60-0.84)*

Increased diuresis *(MD 0.45 liters; 95% CI 0.03-0.87)*
Reduced doses of loop diuretics *(MD -34.90 mg furosemide equivalent; 95% CI [-52.58;-17.21])*

A) Mean daily dose of loop diuretics in mg furosemide equivalent

Author	SGLT2i	Control	MD	IC 95%	Weight
Charaya 2022	50	52	-24.360	[-38.099; -10.621]	40.3%
Ibrahim 2020	50	50	-44.710	[-47.651; -41.769]	52.5%
Thiele 2022	10	9	-22.400	[-83.548; 38.748]	7.2%
Total (95% CI)	**110**	**111**	**-34.896**	**[-52.583; -17.210]**	**100.0%**

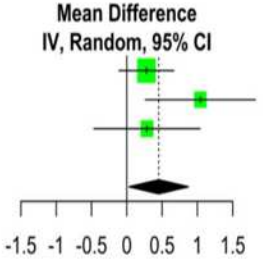
Heterogeneity: $Tau^2 = 152.9368$; $Chi^2 = 8.53$, df = 2 (P = 0.01); $I^2 = 77\%$
Test for overall effect: Z = -3.87 (P = 0.0001)



B) Mean daily urinary output in liters

Author	SGLT2i	Control	MD	IC 95%	Weight
EMPAG-HF 2022*	30	29	0.278	[-0.111; 0.667]	53.7%
EMPA-RESPONSE-AHF 2020§	30	28	1.042	[0.262; 1.822]	22.5%
Thiele 2022*	10	9	0.286	[-0.466; 1.038]	23.8%
Total (95% CI)	**70**	**66**	**0.452**	**[0.031; 0.874]**	**100.0%**

Heterogeneity: $Tau^2 = 0.0469$; $Chi^2 = 3.07$, df = 2 (P = 0.22); $I^2 = 35\%$
Test for overall effect: Z = 2.10 (P = 0.0355)



Clinical Research in Cardiology, 2023

慢性腎臟病

SCREEN OR NOT

Why
- High prevalence (14%) but LOW awareness (9%)
- CKD indicates higher mortality and morbidity

Who
- 全面篩檢的可能性? Annually ! Cost-effectiveness !

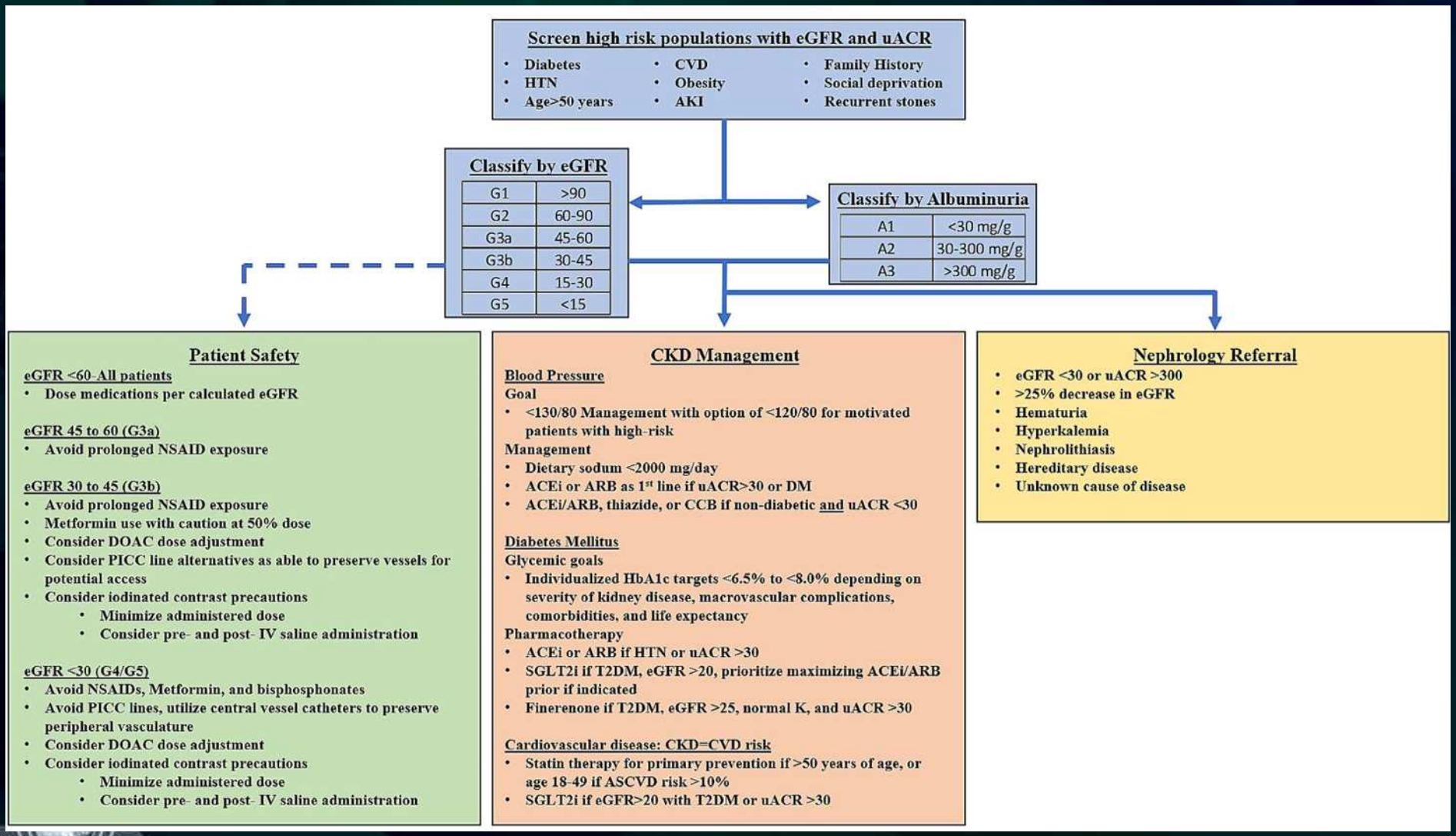
When
- CKD比率: DM 40%; > 65 y/o 33%; HTN 22%

How
- eGFR; albuminuria (CGA)
- Echo, U/A, renal biopsy

What
- 確認chronicity (AKI or CKD needed to be confirmed)
- Once confirmed, CGA should be done

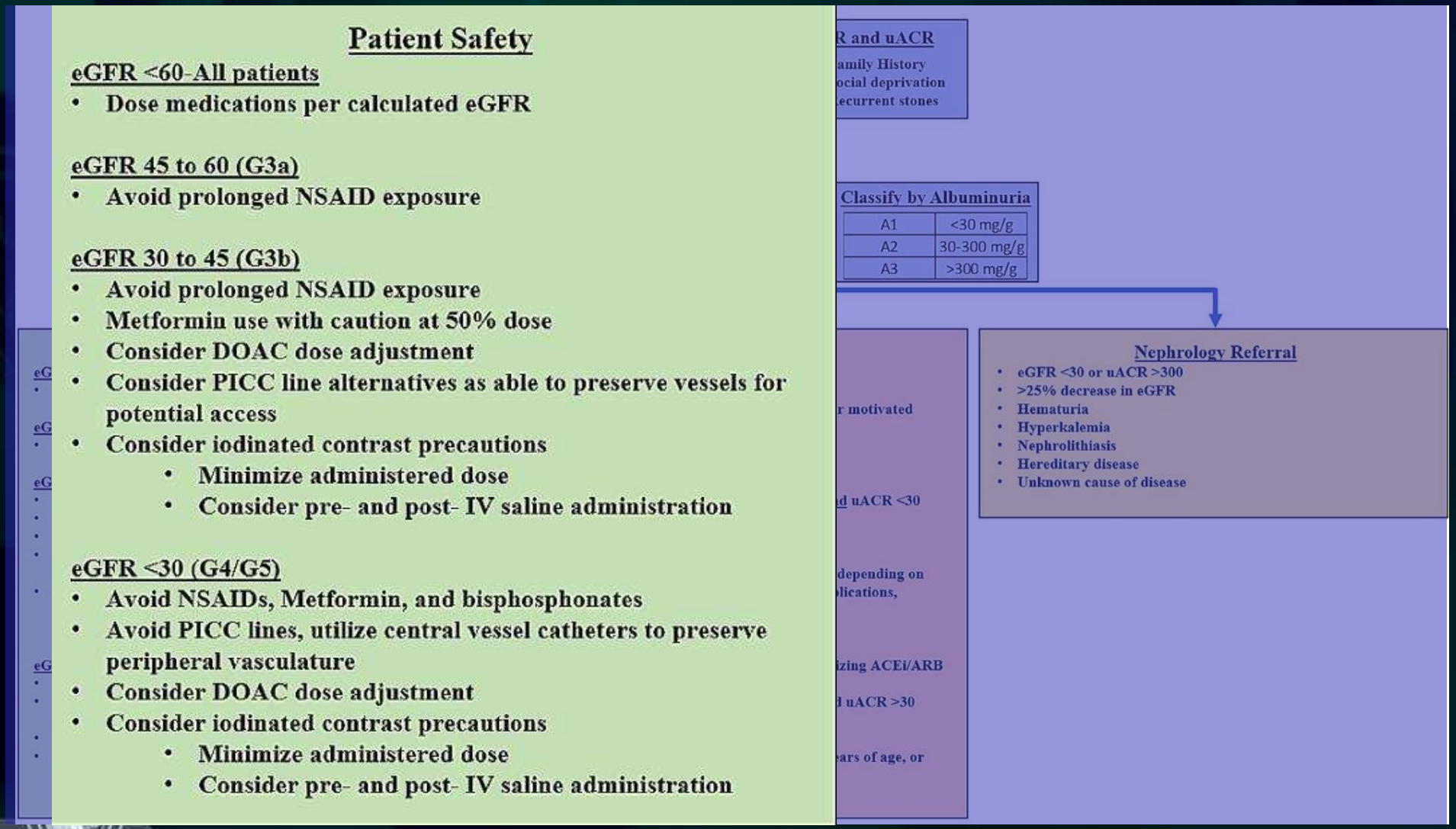
BMC Nephrology (2024) 25:34

慢性腎臟病照護



BMC Nephrology (2024) 25:34

慢性腎臟病照護



BMC Nephrology (2024) 25:34

慢性腎臟病照護

CKD Management

Blood Pressure

Goal

- <130/80 Management with option of <120/80 for motivated patients with high-risk

Management

- Dietary sodum <2000 mg/day
- ACEi or ARB as 1st line if uACR>30 or DM
- ACEi/ARB, thiazide, or CCB if non-diabetic and uACR <30

Diabetes Mellitus

Glycemic goals

- Individualized HbA1c targets <6.5% to <8.0% depending on severity of kidney disease, macrovascular complications, comorbidities, and life expectancy

Pharmacotherapy

- ACEi or ARB if HTN or uACR >30
- SGLT2i if T2DM, eGFR >20, prioritize maximizing ACEi/ARB prior if indicated
- Finerenone if T2DM, eGFR >25, normal K, and uACR >30

Cardiovascular disease: CKD=CVD risk

- Statin therapy for primary prevention if >50 years of age, or age 18-49 if ASCVD risk >10%
- SGLT2i if eGFR>20 with T2DM or uACR >30

Patient Safety

eGFR <60-All patients
- Dose medications per calculated eGFR

eGFR 45 to 60 (G3a)
- Avoid prolonged NSAID exposure

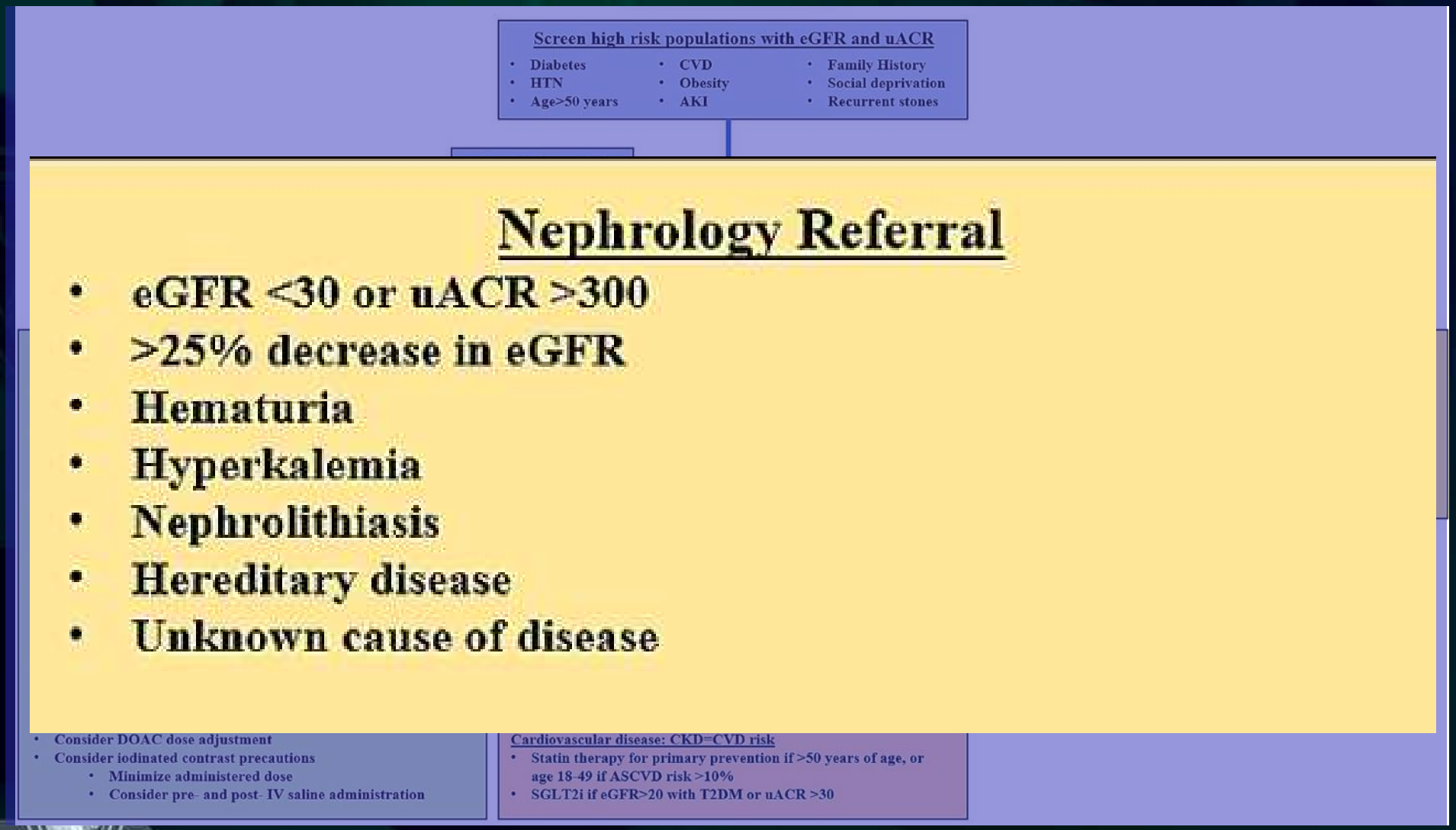
eGFR 30 to 45 (G3b)
- Avoid prolonged NSAID exposure
- Metformin use with caution at 50% dose
- Consider DOAC dose adjustment
- Consider PICC line alternatives as able to preserve ves potential access
- Consider iodinated contrast precautions
  - Minimize administered dose
  - Consider pre- and post- IV saline administrati

eGFR <30 (G4/G5)
- Avoid NSAIDs, Metformin, and bisphosphonates
- Avoid PICC lines, utilize central vessel catheters to pre peripheral vasculature
- Consider DOAC dose adjustment
- Consider iodinated contrast precautions
  - Minimize administered dose
  - Consider pre- and post- IV saline administrati

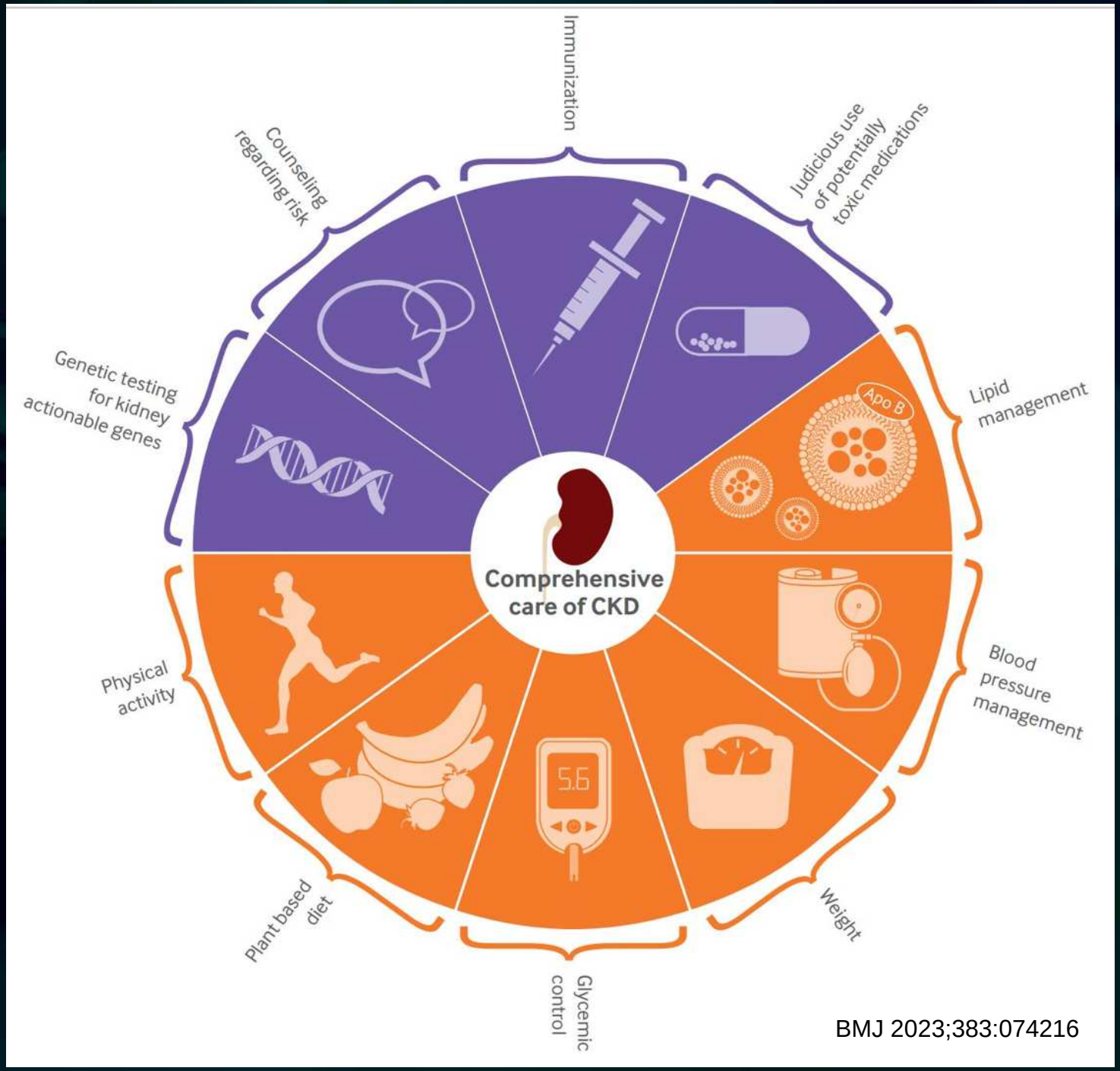
logy Referral

BMC Nephrology (2024) 25:34

慢性腎臟病照護



BMC Nephrology (2024) 25:34

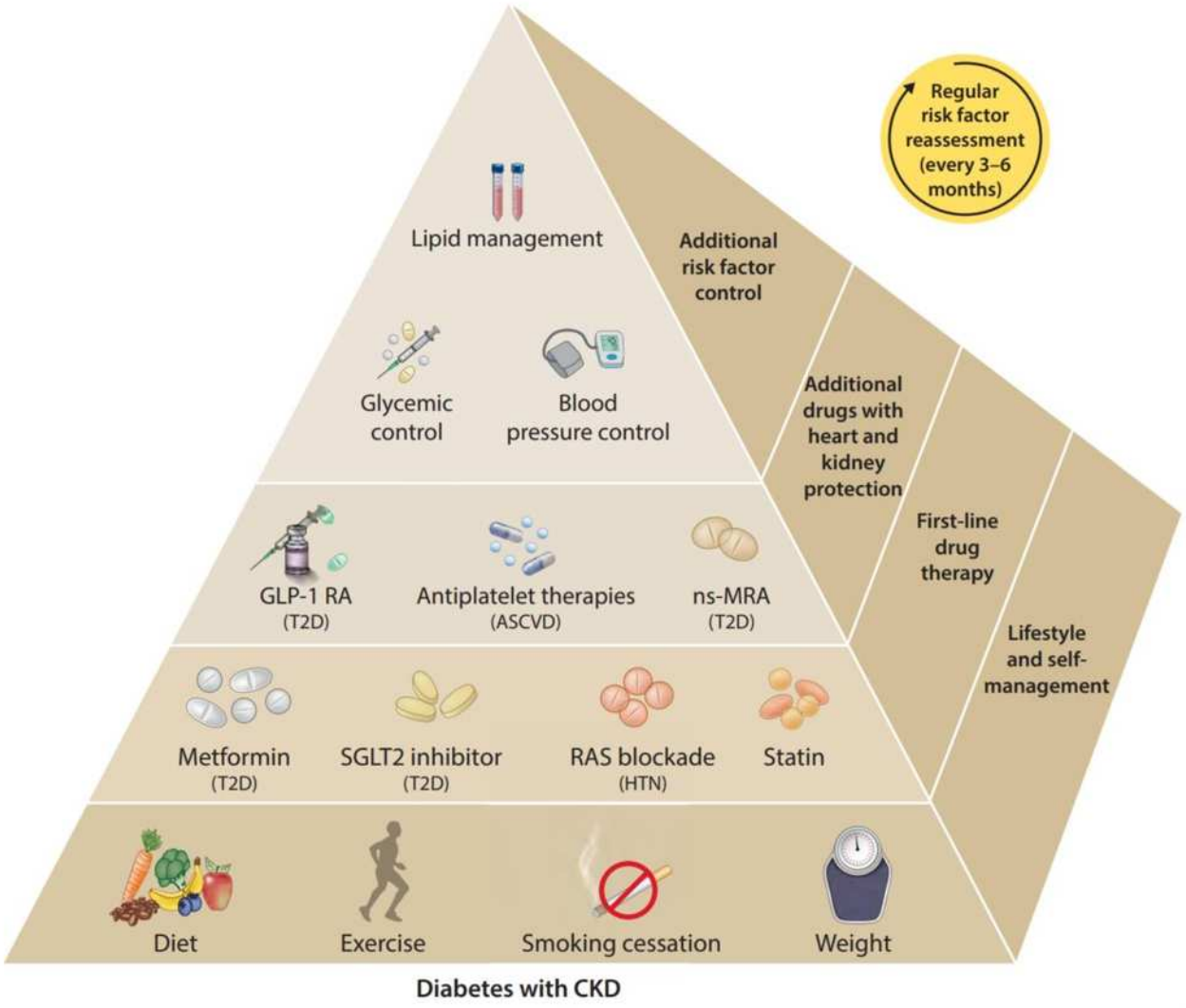


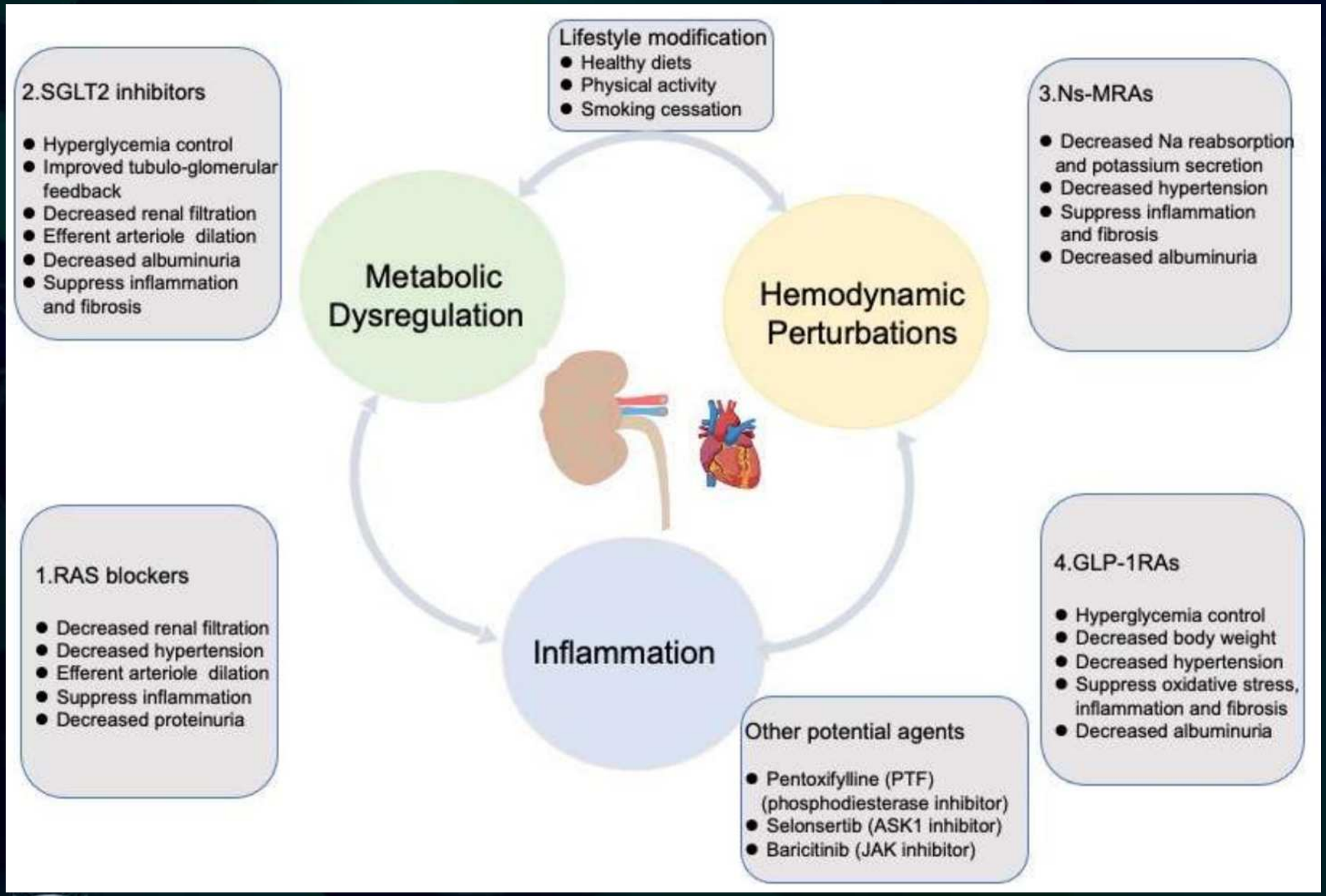
BMJ 2023;383:074216

糖尿病
&
腎病變

DKD患者的照護

Kidney-Heart

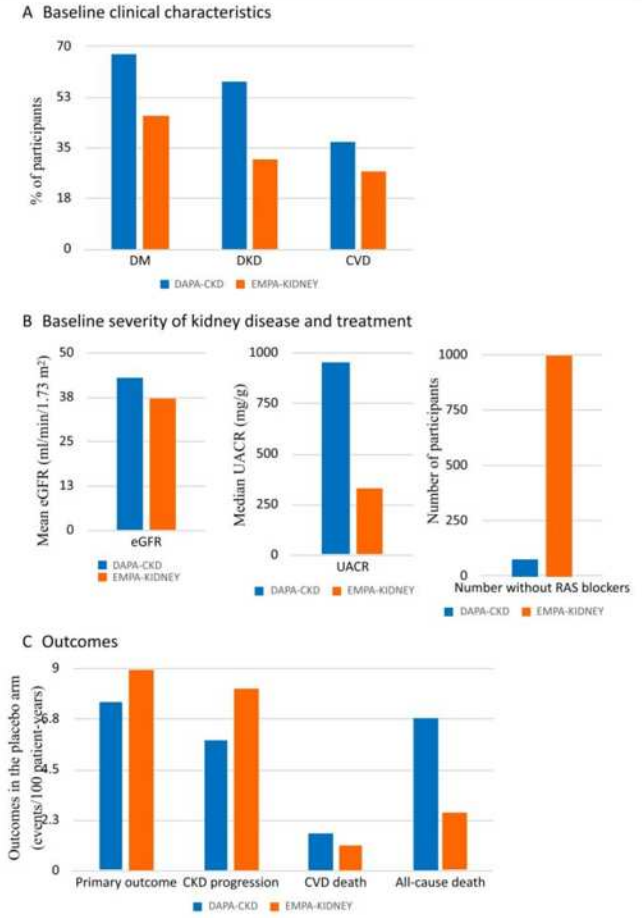




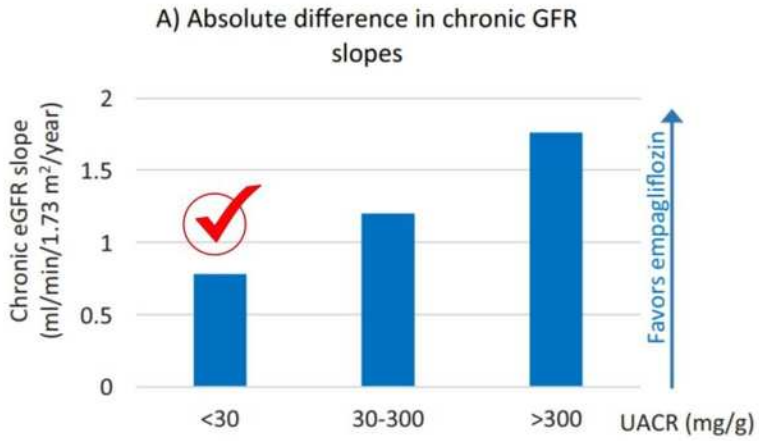
Int. J. Mol. Sci. 2024, 25, 3086

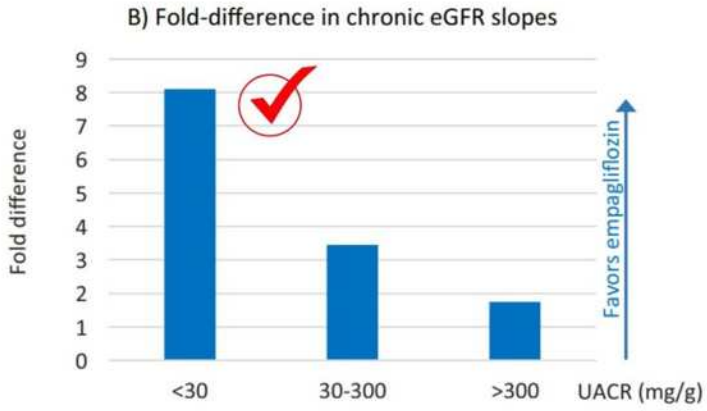
Table 1: Key inclusion and exclusion criteria, baseline characteristics and outcomes in the placebo arm in DAPA-CKD and EMPA-KIDNEY (data are from references [7] and [9], unless otherwise specified). Colored cells indicate major differences between the two trials.

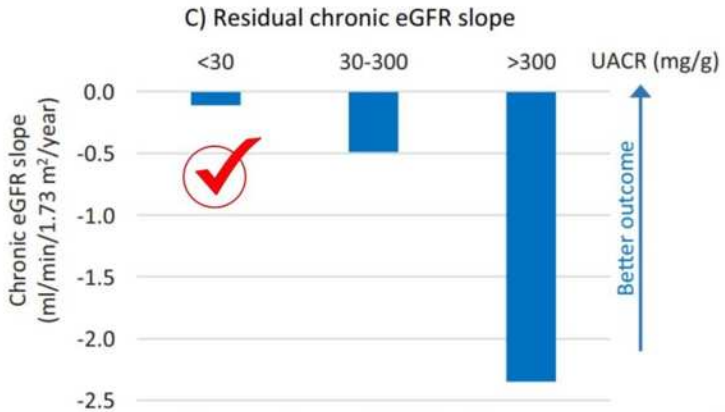
	DAPA-CKD	EMPA-KIDNEY
Key trial characteristics		254人eGFR 15-20
Trial metrics		
N	4304	6609
Median follow-up	2.4	2.0
Inclusion criteria		
eGFR (mL/min/1.73 m^2)	25 to 75	20 to <90
UACR (mg/g)	200 to 5000	≥200 if eGFR 45 to <90 No limit for eGFR <45
CVD	Atherosclerotic CVD within 12 weeks prior to enrolment	Prior atherosclerotic CVD in T2DM participants with an eGFR >60 mL/min/1.73 m^2
RAS blockade	Yes, if not contraindicated	Yes; also included participants not on RAS blockade when RAS blockade not indicated or not tolerated
Exclusion criteria		
PKD	Excluded	Excluded
Lupus nephritis, vasculitis	Excluded	Included
Kidney transplantation	Excluded	Excluded
T1DM	Excluded	Initially included (69 randomized), later excluded[a]
Baseline data		
Clinical characteristics		
Age (years)	62	64
Women (%)	33	33
Non-DM (%)	32.5	54
CVD (%)	37	27 (36 in DM, 19 in non-DM)
HF (%)	11	10 (14 in DM, 6 in non-DM)
Causes of CKD	(16)	(17)
DKD, *n* (%)	2510 (58.3)	2057 (31)
Glomerular, *n* (%)	695 (16.1)	1669 (25)
Hypertensive/renovascular, *n* (%)	687 (16.0)	1445 (22)
Tubulointerstitial, *n* (%)	53 (1.2)	468 (7)
Unknown/other, *n* (%)	214 (5.0)	630 (10)
Baseline CKD status		
KDIGO risk category very high, n (%)	2336 (54) [15]	4911(74)
eGFR (mL/min/1.73 m^2)	43 (±12)	37 (±14)
eGFR category G4, *n* (%)	624(14.5)	2280 (34.5)
UACR (mg/g)[b]	934–965	330
UACR category A1, *n* (%)	0 (0)	1332 (20)
UACR category A2, *n* (%)	444 (10) [15]	1862 (28)
UACR > 1000 mg/g (%)	48	ND
RAS blockade, *n* (%)	4174 (97)	3399 (85)



Clinical Kidney Journal, 2023, 8, 1187–1198



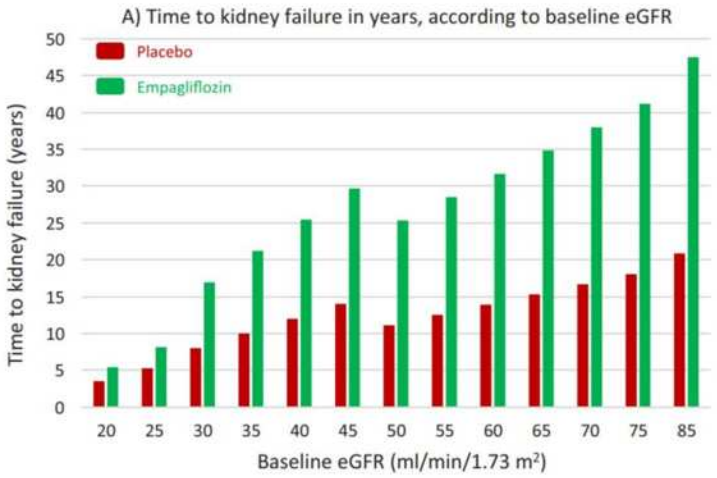


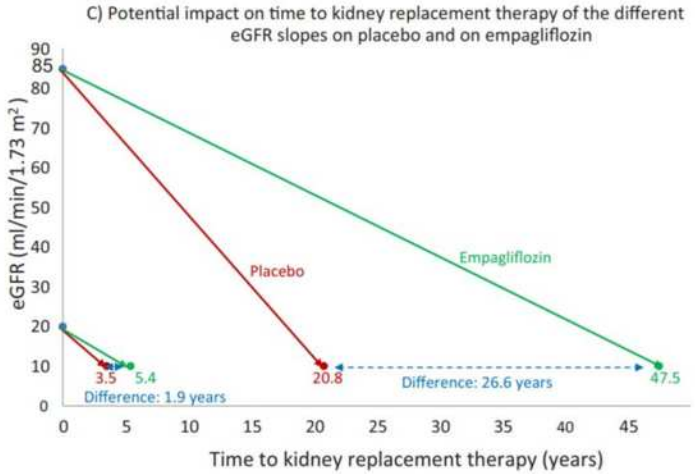


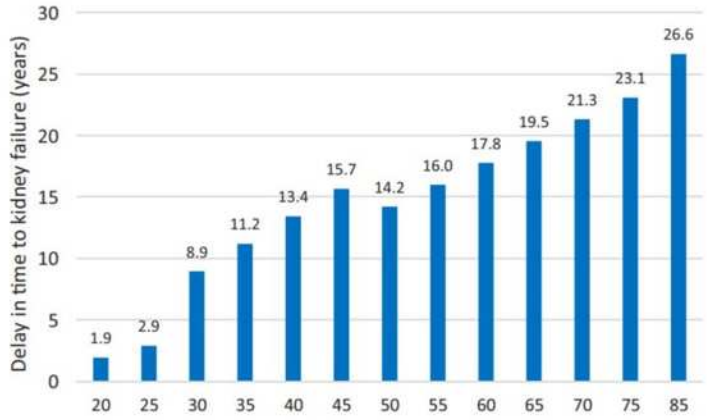
- 有蛋白尿患者,愈早使用,愈能保護腎功能
- 沒有蛋白尿患者,也應使用

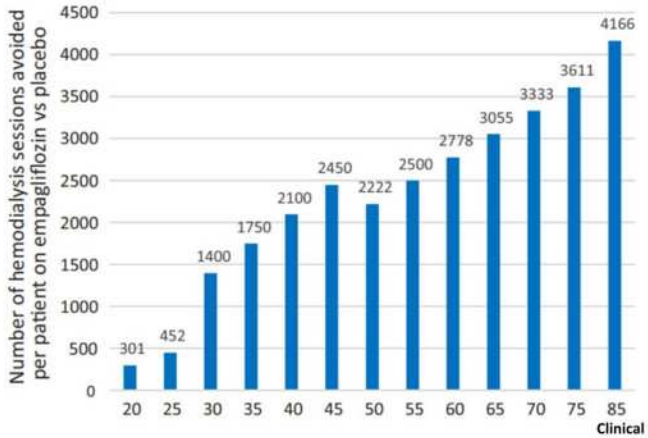
Chronic eGFR slope according to baseline UACR category in EMPA-KIDNEY

Clinical Kidney Journal, 2023, 8, 1187–1198





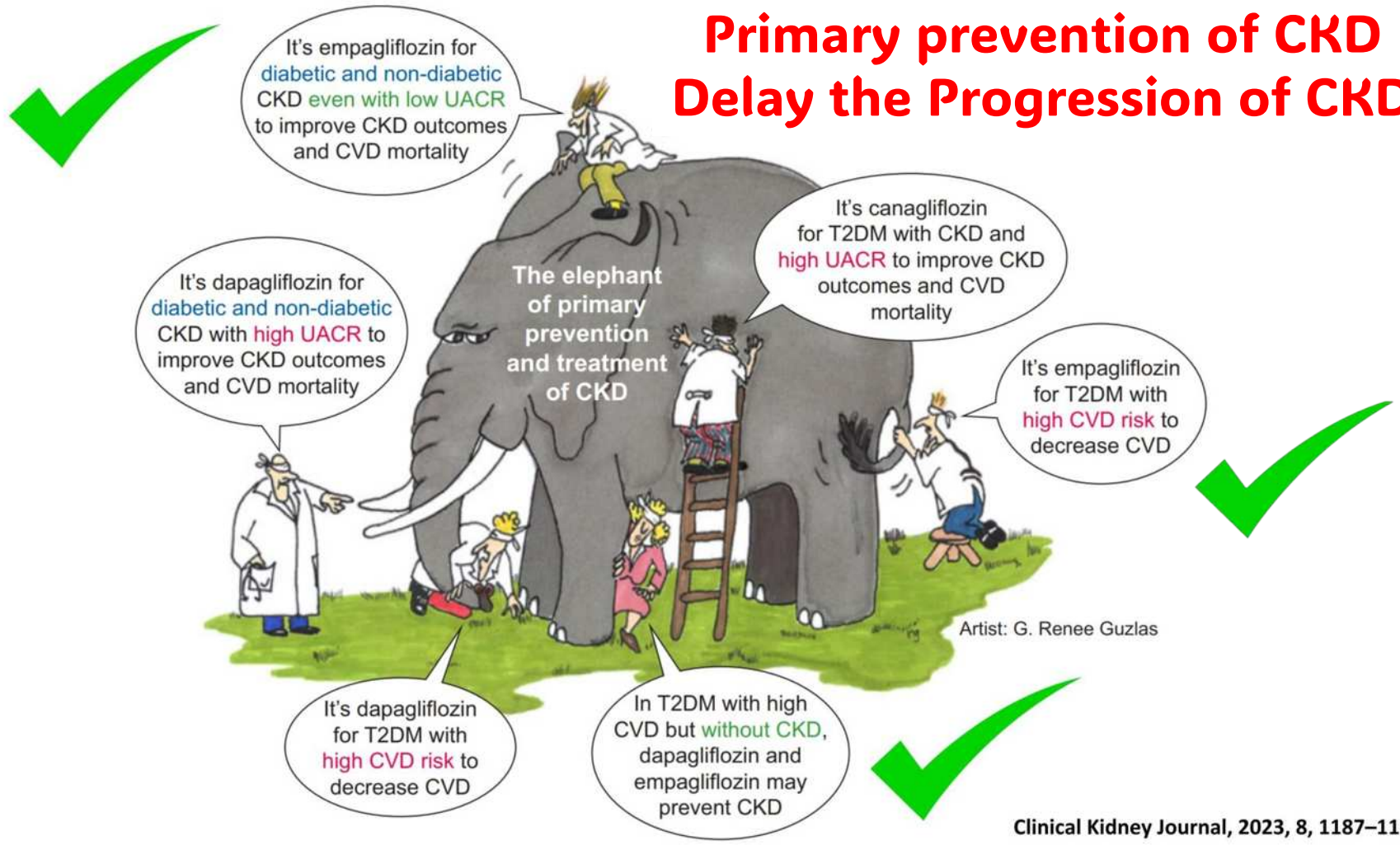




EMPA-KIDNEY

Clinical Kidney Journal, 2023, 8, 1187–1198

Primary prevention of CKD
Delay the Progression of CKD



Clinical Kidney Journal, 2023, 8, 1187–1198

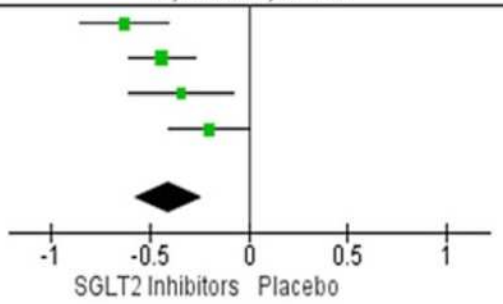

Safety
serious adverse events
hypoglycemia
hyperK
AKI
2022, Cureus 14(11): e31898.

SGLT 2 i in CKD & DM

Association of SGLT2 inhibitors on reduction of HbA1C

Study or Subgroup	SGLT2 Inhibitors Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Barnett et al, 2014 (a) [13]	-0.57	0.7981	98	0.06	0.7854	95	24.2%	-0.63 [-0.85, -0.41]
Barnett et al, 2014 (b) [13]	-0.32	0.8318	187	0.12	0.8318	187	29.2%	-0.44 [-0.61, -0.27]
Fioretto et al, 2018 [16]	-0.37	1.2169	160	-0.03	1.2207	161	20.7%	-0.34 [-0.61, -0.07]
Haneda et al, 2016 [17]	-0.11	0.4418	95	0.09	0.6686	50	25.8%	-0.20 [-0.41, 0.01]
Total (95% CI)			**540**			**493**	**100.0%**	**-0.40 [-0.58, -0.23]**

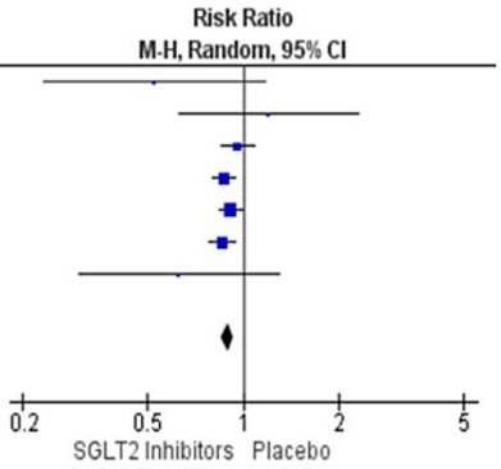
Heterogeneity: Tau² = 0.02; Chi² = 8.11, df = 3 (P = 0.04); I² = 63%
Test for overall effect: Z = 4.52 (P < 0.00001)



Comparison of serious adverse events between SGLT2i and placebo

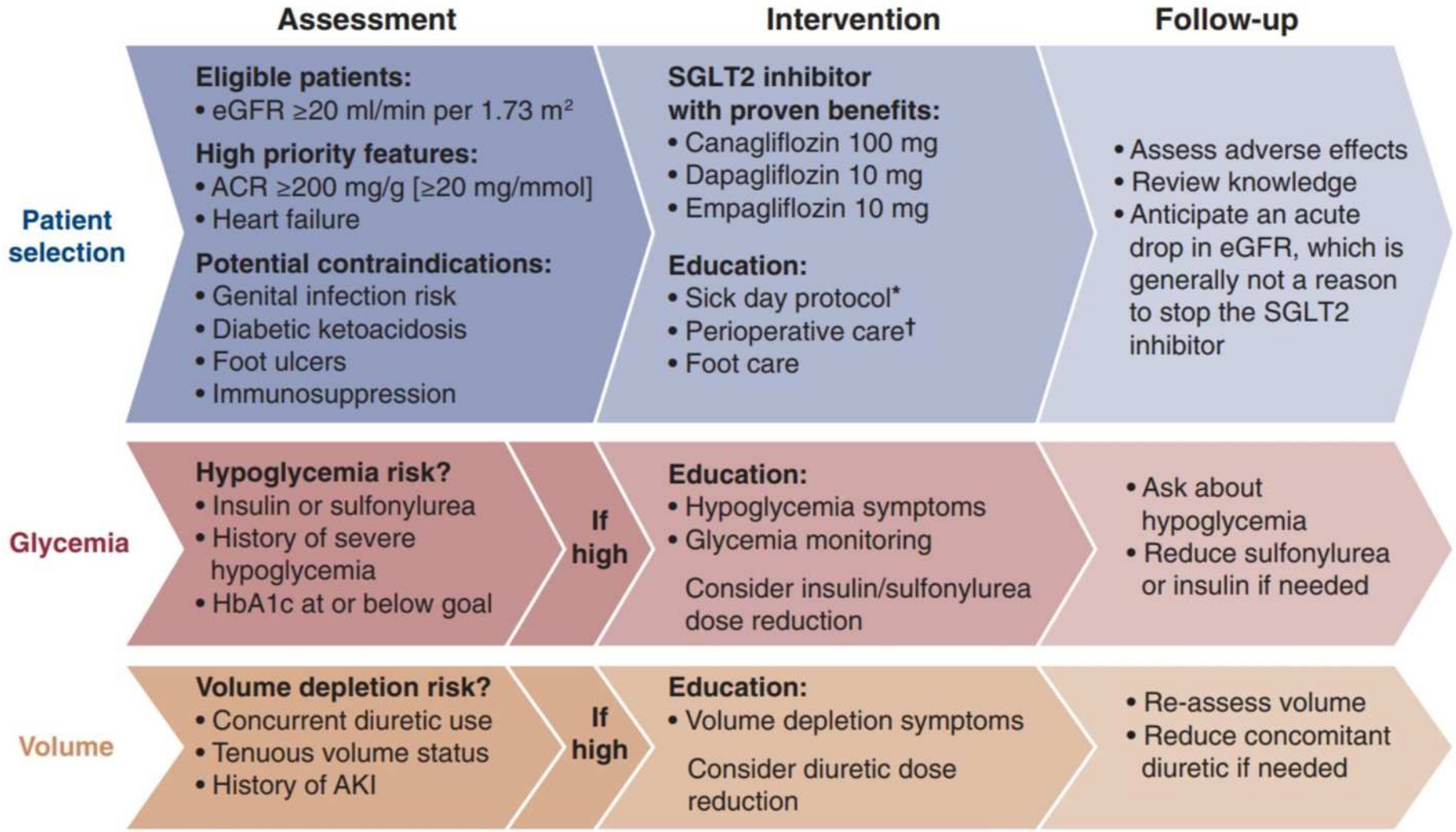
Study or Subgroup	SGLT2 Inhibitors Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Barnett et al, 2014 (a) [13]	8	97	15	95	0.3%	0.52 [0.23, 1.17]
Barnett et al, 2014 (b) [13]	18	187	15	187	0.5%	1.20 [0.62, 2.31]
Cannon et al, 2020 [15]	474	1199	250	608	15.6%	0.96 [0.85, 1.08]
Heerspink et al, 2020 [18]	633	2149	729	2149	27.6%	0.87 [0.80, 0.95]
Perkovic et al, 2019 [19]	737	2200	806	2197	32.8%	0.91 [0.84, 0.99]
Wanner et al, 2016 [20]	552	1212	321	607	22.8%	0.86 [0.78, 0.95]
Yale et al, 2013 [22]	10	90	16	90	0.4%	0.63 [0.30, 1.30]
Total (95% CI)		**7134**		**5933**	**100.0%**	**0.89 [0.85, 0.94]**
Total events	2432		2152			

Heterogeneity: Tau² = 0.00; Chi² = 6.09, df = 6 (P = 0.41); I² = 2%
Test for overall effect: Z = 4.67 (P < 0.00001)

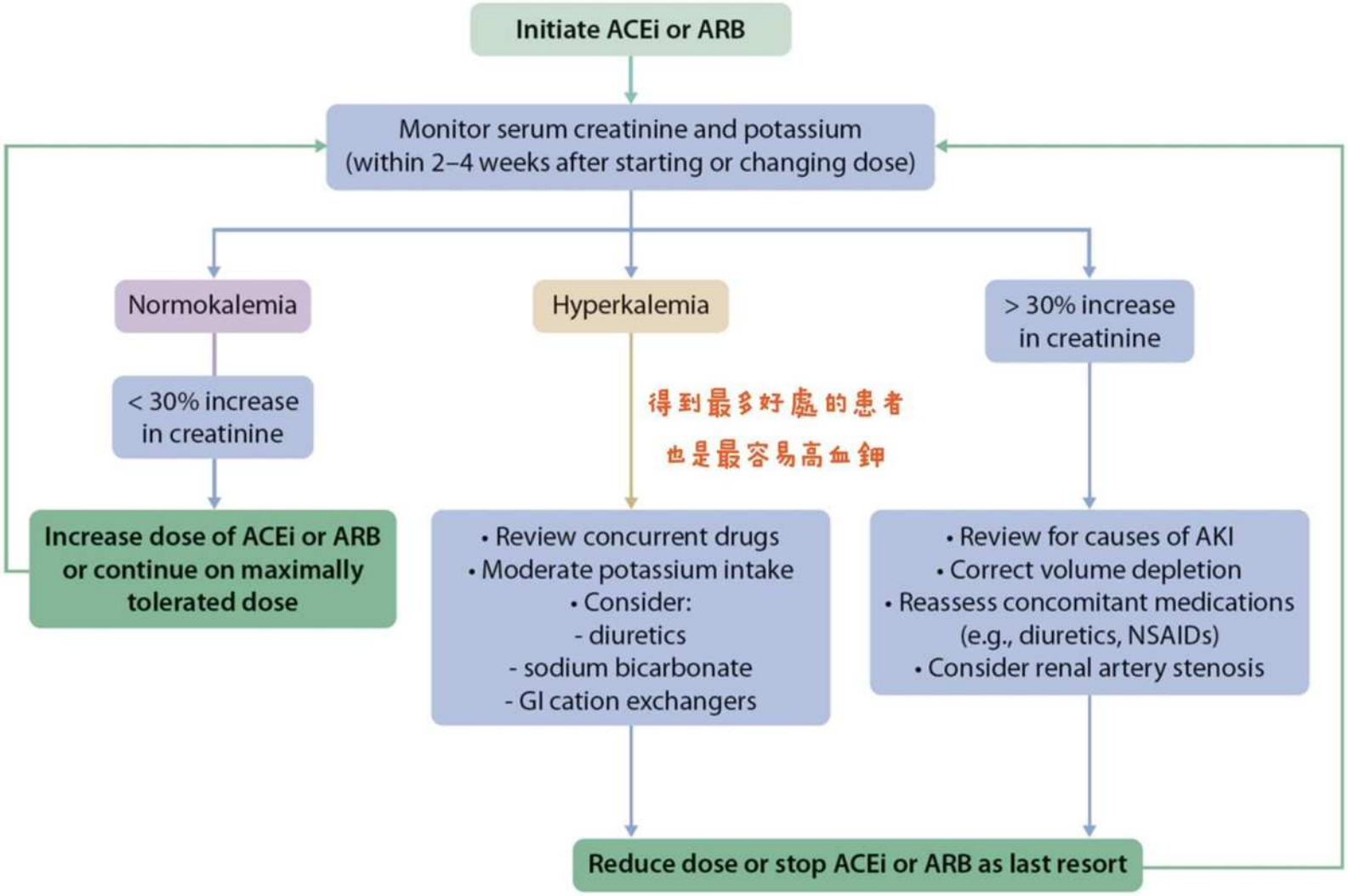


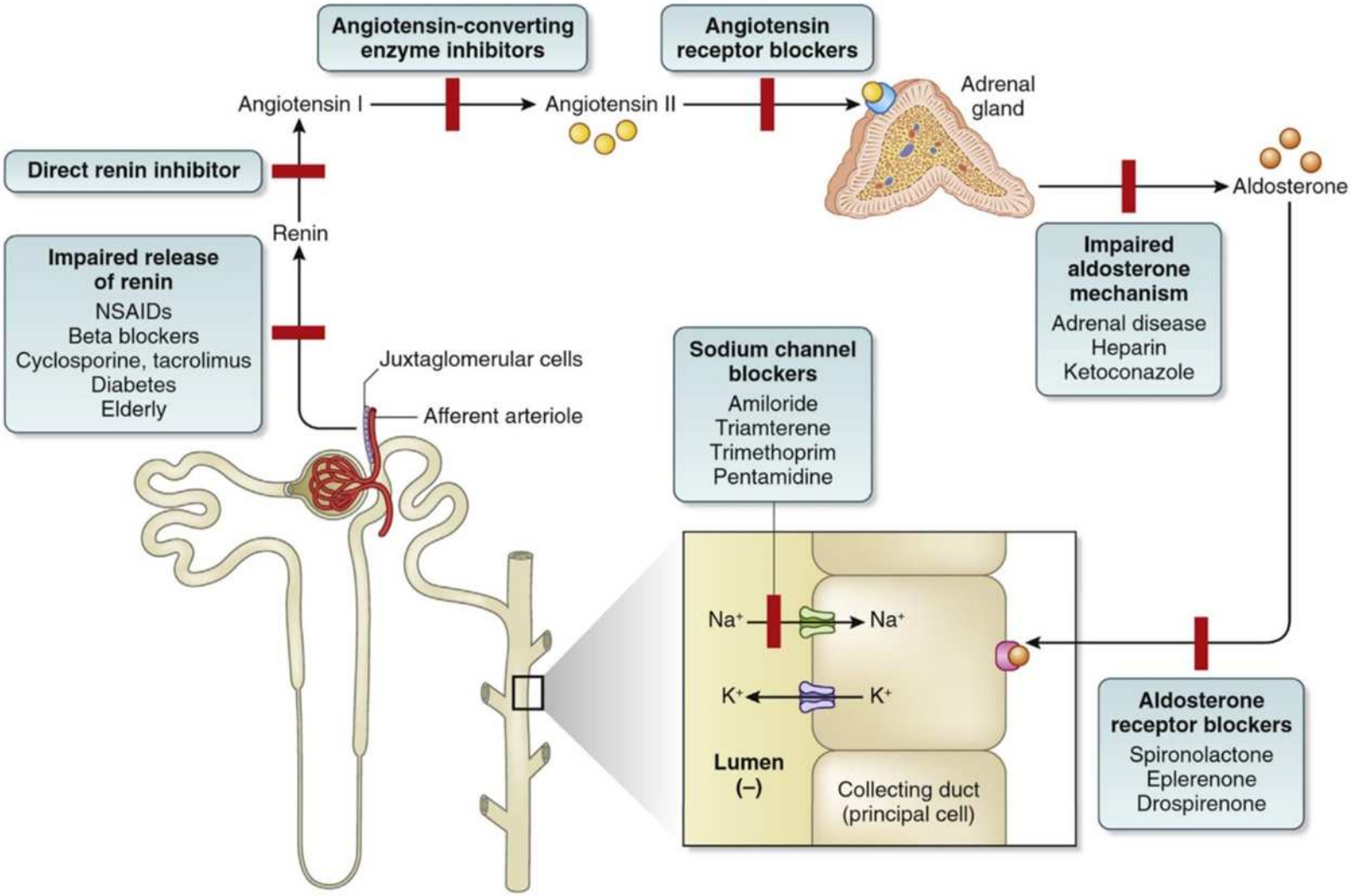
Events	Number of studies	RR	95% CI	p-value
Acute kidney injury*	3	0.81	0.67-0.98	0.031
Hypoglycemia	5	0.91	0.82-1.02	0.101
Hyperkalemia*	3	0.77	0.63-0.93	0.008

Practical provider guide to initiating SGLT2 inhibitors in patients with type 2 diabetes and CKD

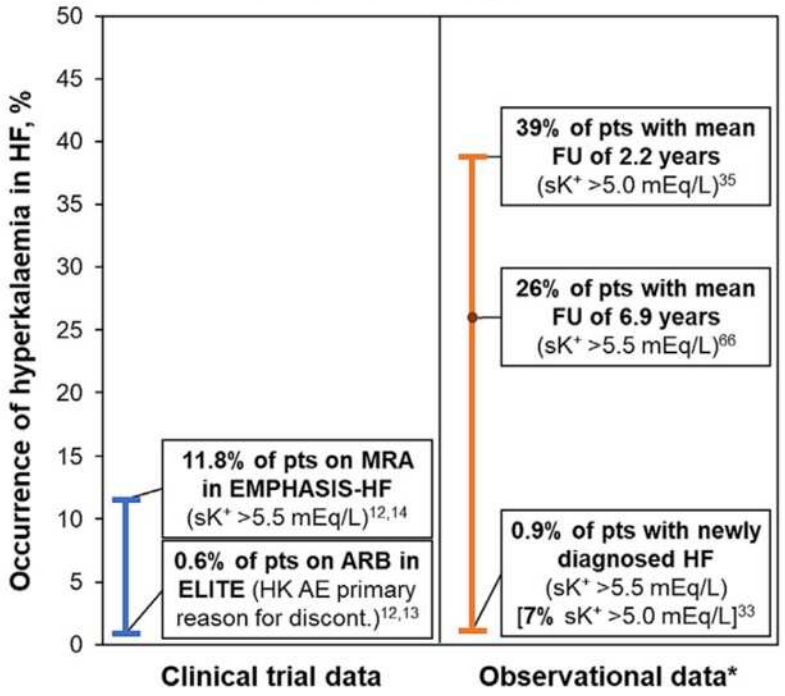


高血鉀
&
藥物

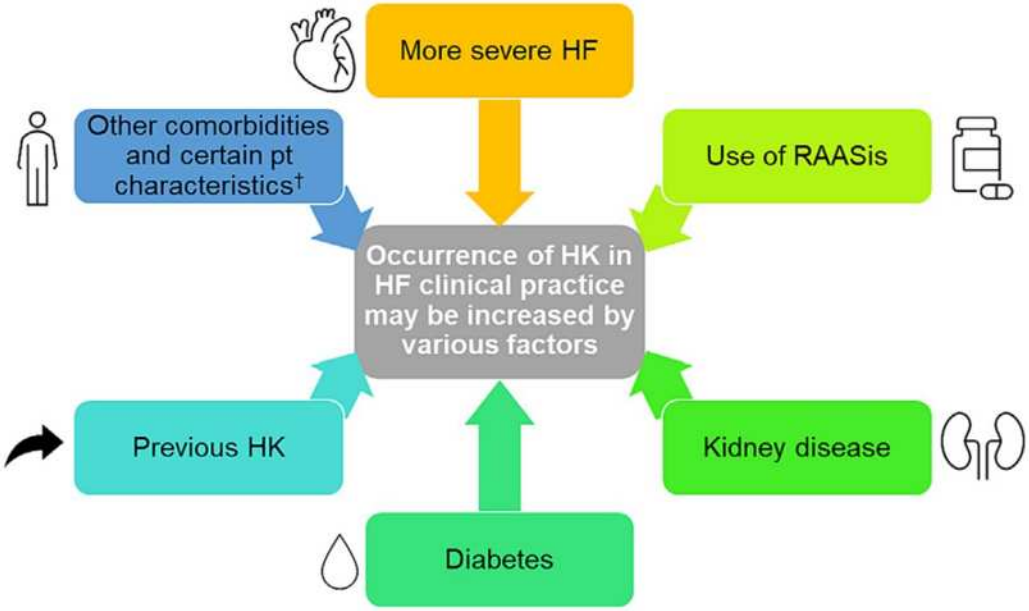

Initiate ACEi or ARB
Monitor serum creatinine and potassium (within 2–4 weeks after starting or changing dose)
Normokalemia
Hyperkalemia
> 30% increase in creatinine
< 30% increase in creatinine
得到最多好處的患者
也是最容易高血鉀
Increase dose of ACEi or ARB or continue on maximally tolerated dose
• Review concurrent drugs
• Moderate potassium intake
• Consider:
- diuretics
- sodium bicarbonate
- GI cation exchangers
• Review for causes of AKI
• Correct volume depletion
• Reassess concomitant medications (e.g., diuretics, NSAIDs)
• Consider renal artery stenosis
Reduce dose or stop ACEi or ARB as last resort


Angiotensin-converting enzyme inhibitors
Angiotensin receptor blockers
Angiotensin I
Angiotensin II
Adrenal gland
Direct renin inhibitor
Aldosterone
Renin
Impaired release of renin
NSAIDs
Beta blockers
Cyclosporine, tacrolimus
Diabetes
Elderly
Impaired aldosterone mechanism
Adrenal disease
Heparin
Ketoconazole
Juxtaglomerular cells
Afferent arteriole
Sodium channel blockers
Amiloride
Triamterene
Trimethoprim
Pentamidine
Na+
Na+
K+
K+
Lumen (–)
Collecting duct (principal cell)
Aldosterone receptor blockers
Spironolactone
Eplerenone
Drospirenone

Occurrence of hyperkalaemia varies widely in HF clinical practice



Risk factors for hyperkalaemia in patients with HF



There is a need for international prospectively designed observational studies with complete and systematic data collection to better understand hyperkalaemia occurrence, persistence, progression and monitoring, and the impact of GDMT using the four pillars of HF therapy‡ in HF clinical practice

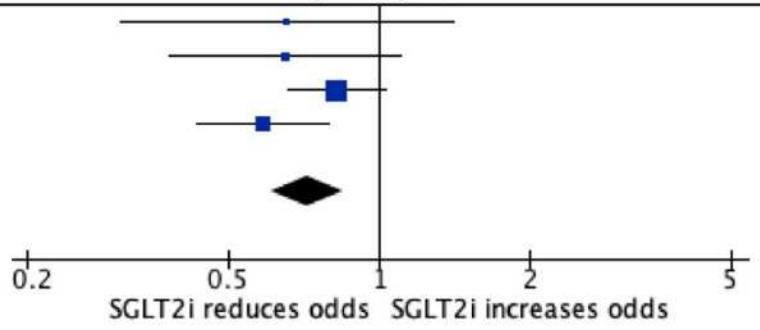
ESC Heart Failure (2024)

使用SGLT2i後鉀離子的變化

9 RCTs of DM patients; SGLT2i : Placebo = 13328 : 9462
Mean age 58.6 years; Duration : 8 days to 3.1 years

Study or Subgroup	SGLT2i Events	SGLT2i Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Kohan 2014	18	168	13	84	4.8%	0.66 [0.30, 1.41]
Neal 2017	26	5795	30	4347	10.7%	0.65 [0.38, 1.10]
Perkovic 2019	151	2200	181	2197	52.7%	0.82 [0.66, 1.03]
Wanner 2016	93	4685	78	2333	31.9%	0.59 [0.43, 0.79]
Total (95% CI)		**12848**		**8961**	**100.0%**	**0.72 [0.61, 0.85]**
Total events	288		302			

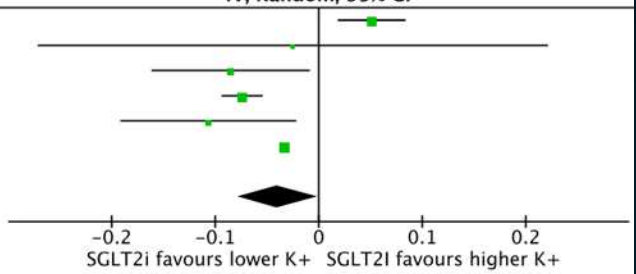
Heterogeneity: $Chi^2 = 3.28$, df = 3 (P = 0.35); $I^2 = 9\%$
Test for overall effect: Z = 3.85 (P = 0.0001)



B

Study or Subgroup	SGLT2i Mean [mmol/L]	SGLT2i SD [mmol/L]	SGLT2i Total	Placebo Mean [mmol/L]	Placebo SD [mmol/L]	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Forst 2014	0.1511	0.2517	227	0.1	0.0067	115	22.2%	0.05 [0.02, 0.08]
Heise 2013	0.075	0.2989	36	0.1	0.4	12	2.2%	-0.03 [-0.27, 0.22]
Rosenstock 2012	-0.0351	0.419	281	0.05	0.3537	139	12.9%	-0.09 [-0.16, -0.01]
Wanner 2016	0	0.4	4685	0.074	0.4023	2333	24.7%	-0.07 [-0.09, -0.05]
Wilding 2012	-0.0867	0.5401	607	0.02	0.52	193	11.5%	-0.11 [-0.19, -0.02]
Wilding 2013	0.0418	0.0161	313	0.0748	0.0074	156	26.5%	-0.03 [-0.04, -0.03]
Total (95% CI)			**6149**			**2948**	**100.0%**	**-0.04 [-0.08, -0.00]**

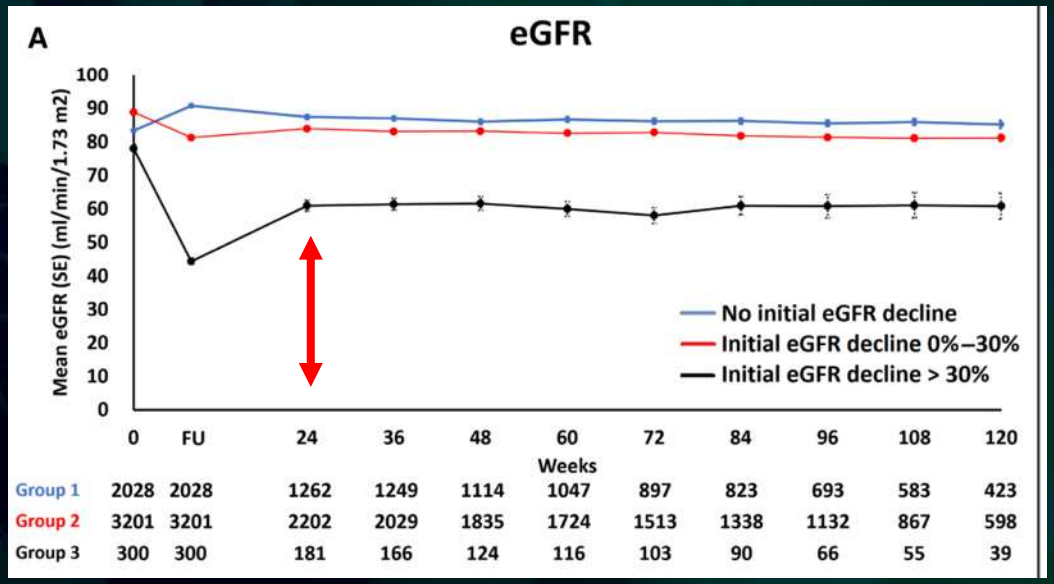
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 46.18$, df = 5 (P < 0.00001); $I^2 = 89\%$
Test for overall effect: Z = 2.02 (P = 0.04)



28% lower odds of experiencing a Hyperkalaemia-event with SGTL2i over placebo; but no effect in reducing serum potassium

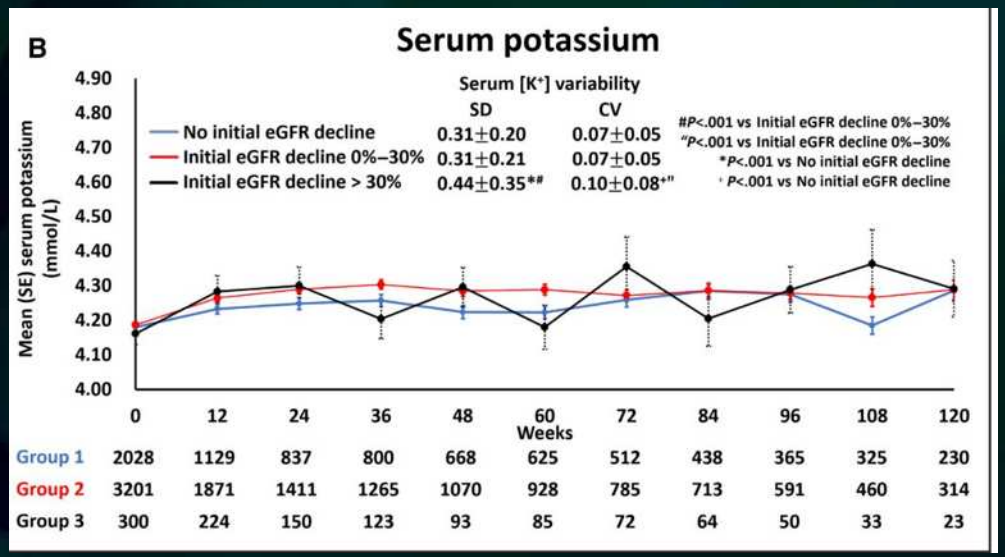
Diabetes Research and Clinical Practice 196 (2023) 110239

使用SGLT2i後的Initial eGFR decline程度是否與鉀離子異常有關

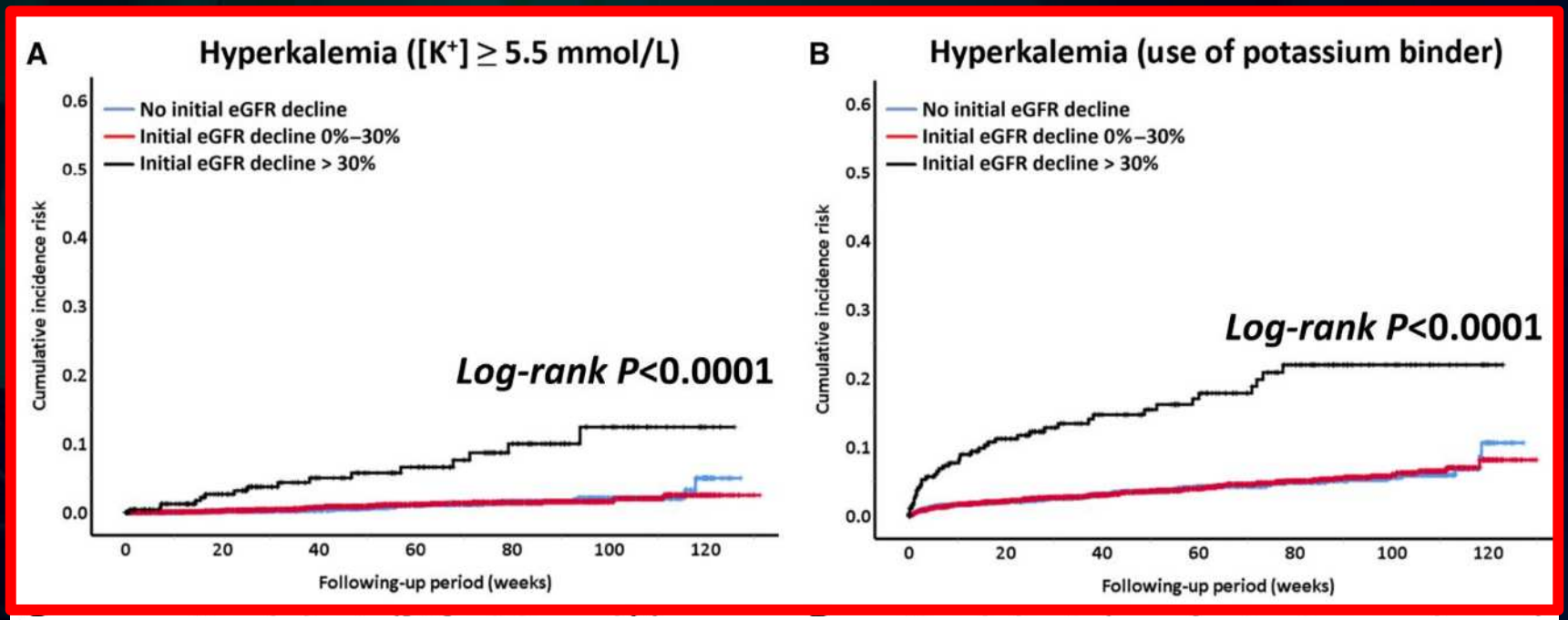


- Taiwan(長庚醫療)
- DM Patient: 5529人
- Time : 2016/01 to 2018/12
- eGFR data available after 4 to 12 weeks of SGLT2i treatment
- an initial mean (SEM) eGFR decline of −3.5 (0.2) mL/min per 1.73m2(全部)

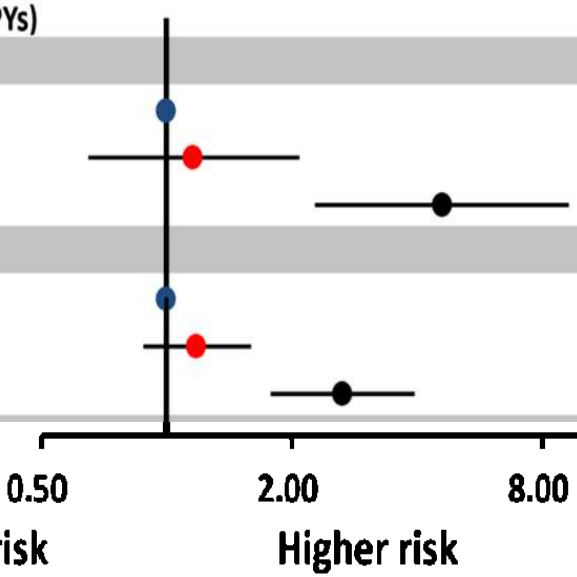
an abrupt initial decline of eGFR >30% following SGLT2i therapy may be a sign of a higher risk for increased serum potassium variability



J Am Heart Assoc. 2024;13:e033236.



	Event-Rate (per 100 PYs)	aHR*	95% CI	*P* value
Hyperkalemia ([K+] ≥ 5.5 mmol/L)				
No initial eGFR decline	0.88	1.00	Ref.	
Initial eGFR decline 0%–30%	0.86	1.16	(0.65–2.09)	<0.001
Initial eGFR decline > 30%	5.76	4.59	(2.28–9.26)	
Hyperkalemia (use of potassium binder)				
No initial eGFR decline	3.31	1.00	Ref.	
Initial eGFR decline 0%–30%	3.38	1.18	(0.88–1.59)	<0.001
Initial eGFR decline > 30%	16.01	2.65	(1.78–3.95)	



J Am Heart Assoc. 2024;13:e033236.

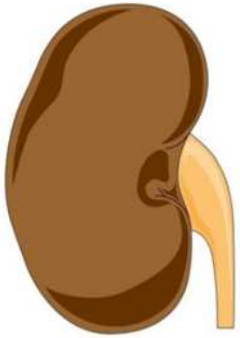
結論

Type 2 diabetes

Lifestyle modifications	Classical treatments	New treatments
-Smoking cessation.	-Glycemic control.	-SGLT2i.
-Physical activity.	-Blood pressure reduction.	-GLP-1 RAs.
-Weight loss.	-RAS blockade.	-ns-MRAs.
	-Lipid management.	-Tirzepatide (GIP and GLP-1 RA).

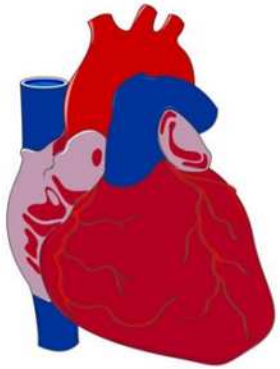
Diabetic cardiorenal syndrome

Chronic kidney disease ⇄ **Heart failure**



延緩腎功能退化
減少合併症

延緩心功能退化
減少合併症



Front. Cardiovasc. Med. 10:1185707

Take Home Message

- SGLT2i在糖心腎患者的角色(延緩退化/減少合併症)
- A-SK III (Kremezin/Ketosteril/Kerendia) in CKD care
- 心衰竭患者diuretic resistance或高血鉀時,SGLT2i在臨床上有其有益的角色
- SGLT2i的1st & 2nd prevention
- 注意eGFR/K(4-12週)的變化,副作用(感染及酮酸症)以及sick day medications (SAD MANS)

Take Home Message

- SGLT2i在糖心腎患者的角色(延緩退化/減

An Apple a Day Keeps Doctors Away

及酮酸症)以及sick day medications

(SAD MANS)

THANK YOU!