

社團法人臺灣臨床藥學會 保腎護心小學堂

# ~大糖腎事~

## 血糖用藥保腎機轉之探討

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高醫附設醫院 藥學部





# 簡報大綱

I

Diabetes Management in CKD

II

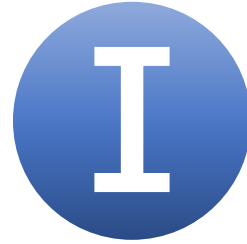
Mechanisms of Renal Protection of SGLT-2 Inhibitors

III

Mechanisms of Renal Protection of GLP1 RA

IV

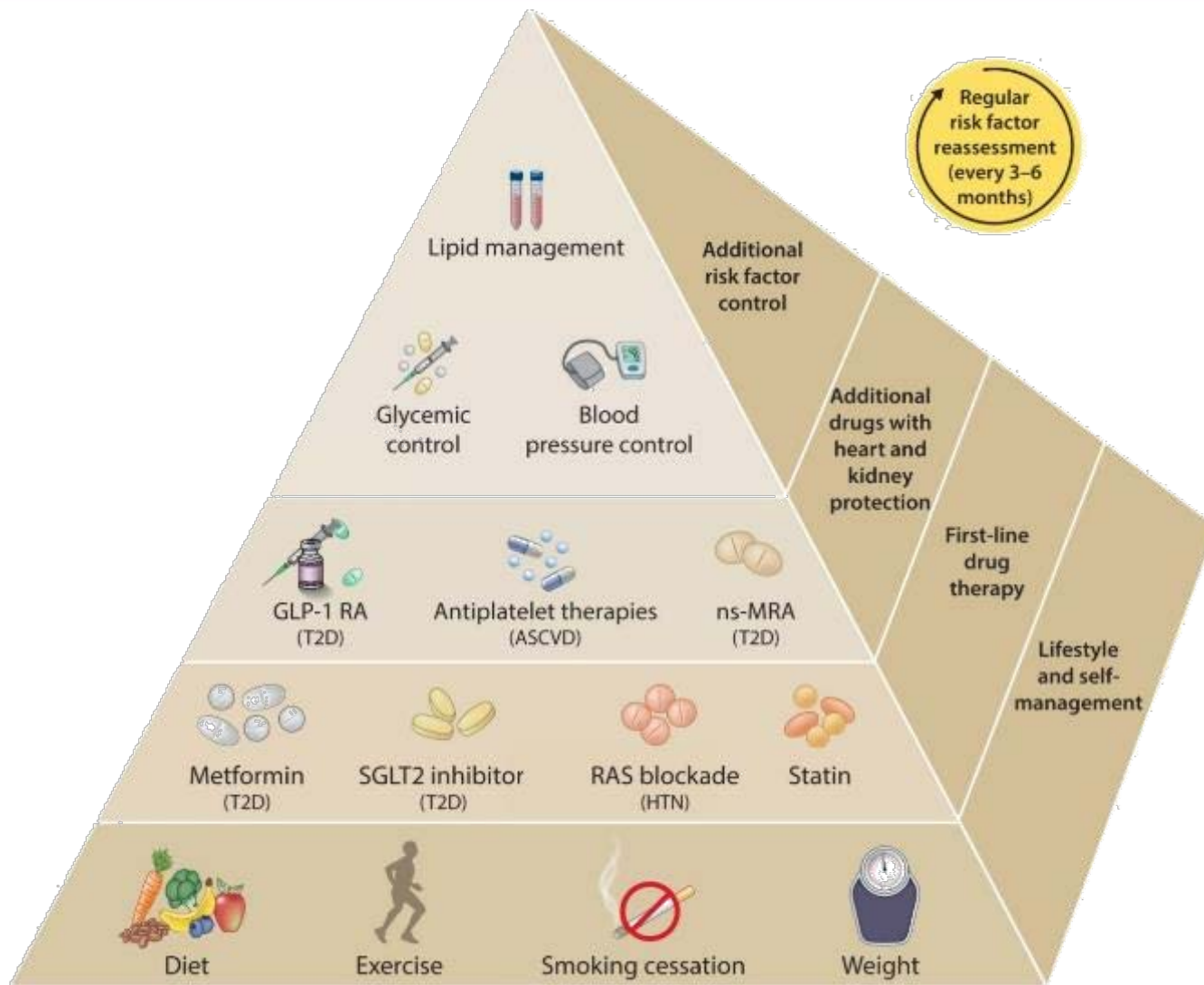
Conclusion



# Diabetes Management in CKD



# COMPREHENSIVE CARE IN PATIENTS WITH DIABETES AND CKD

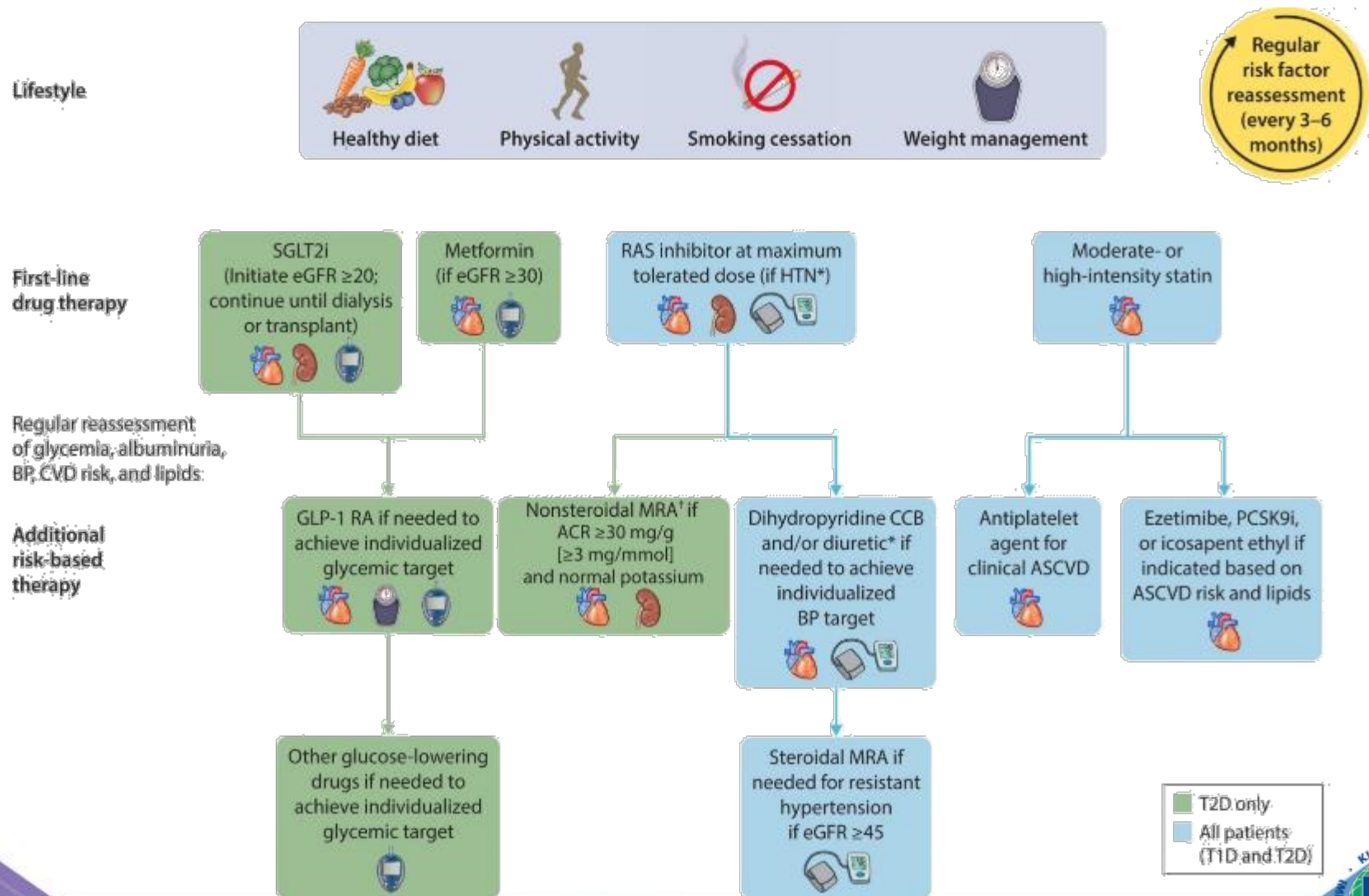


Diabetes with CKD

KMUH

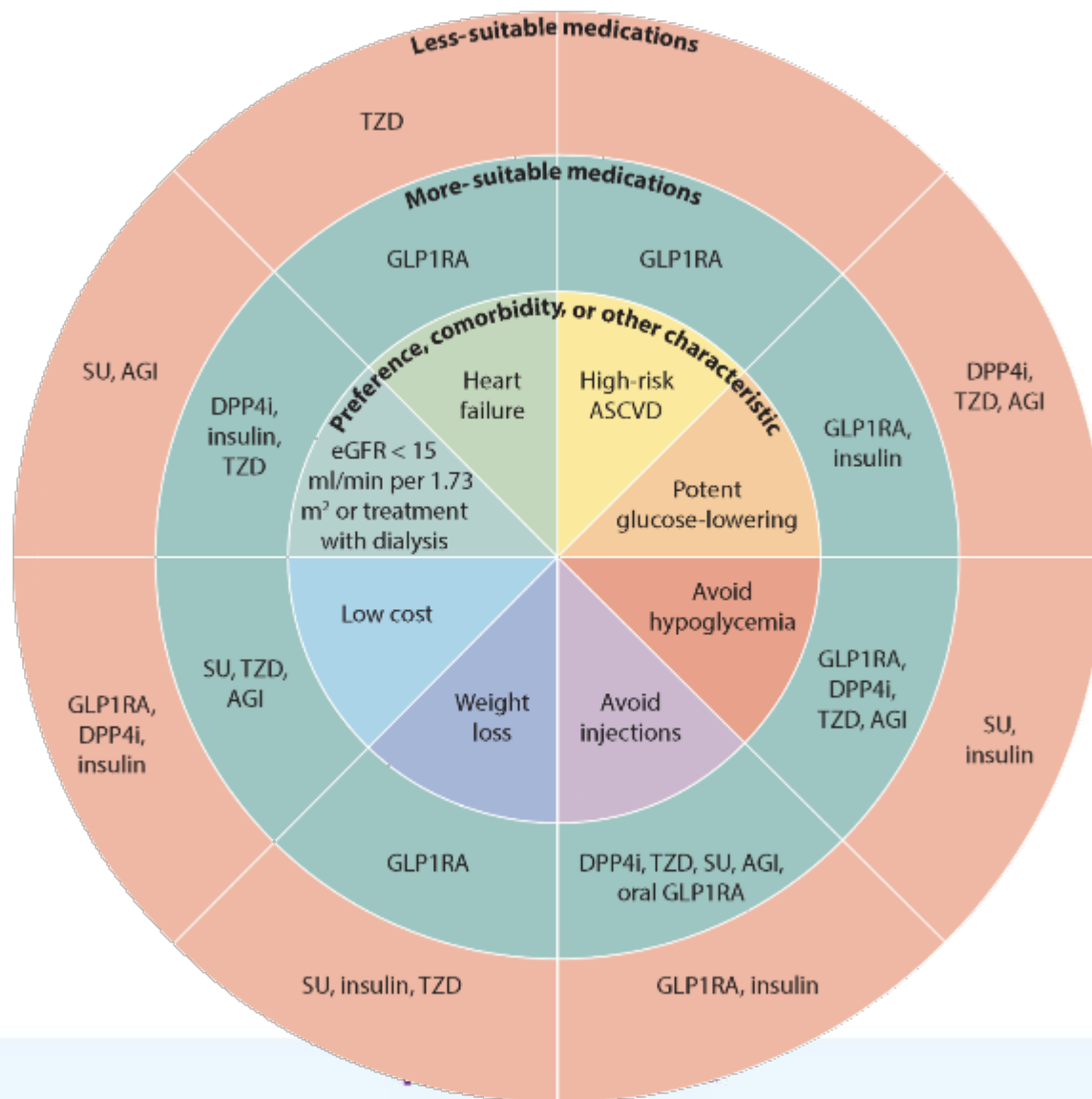
Kaohsiung Medical University  
Chung-Ho Memorial Hospital

# Holistic approach for improving outcomes in patients with diabetes and chronic kidney disease





# Patient factors influencing the selection of glucose-lowering drugs other than SGLT2i and metformin in type 2 diabetes (T2D) and chronic kidney disease (CKD)





# Considerations for selecting glucose-lowering agents in patients with T2D and CKD

	Progression of CKD	ASCVD	Heart failure	Glucose-lowering efficacy	Hypoglycemia risk	Weight effects	Cost
<b>Metformin</b>	Neutral	Potential benefit	Potential benefit	High	Low	Neutral	Low
<b>SGLT2 inhibitors</b>	Benefit <sup>a</sup>	Benefit <sup>c</sup>	Benefit	Intermediate	Low	Loss	High
<b>GLP-1 receptor agonists</b>	Benefit <sup>b</sup>	Benefit <sup>c</sup>	Potential benefit	High	Low	Loss	High
<b>DPP-4 inhibitors</b>	Neutral	Neutral	Potential risk <sup>c</sup> (saxagliptin)	Intermediate	Low	Neutral	High
<b>Insulin</b>	Neutral	Neutral	Neutral	Highest	High	Gain	High (analogues)
							Low (human)
<b>Sulfonylureas</b>	Neutral	Neutral	Neutral	High	High	Gain	Low
<b>Thiazolidinediones</b>	Neutral	Potential benefit (pioglitazone)	Increased risk	High	Low	Gain	Low
<b>α-Glucosidase inhibitors</b>	Neutral	Neutral	Neutral	Intermediate	Low	Neutral	Low

Neutral

Potential benefit or intermediate glucose-lowering efficacy

Benefit (organ protection, high efficacy, low hypoglycemia risk, weight loss, or low cost)

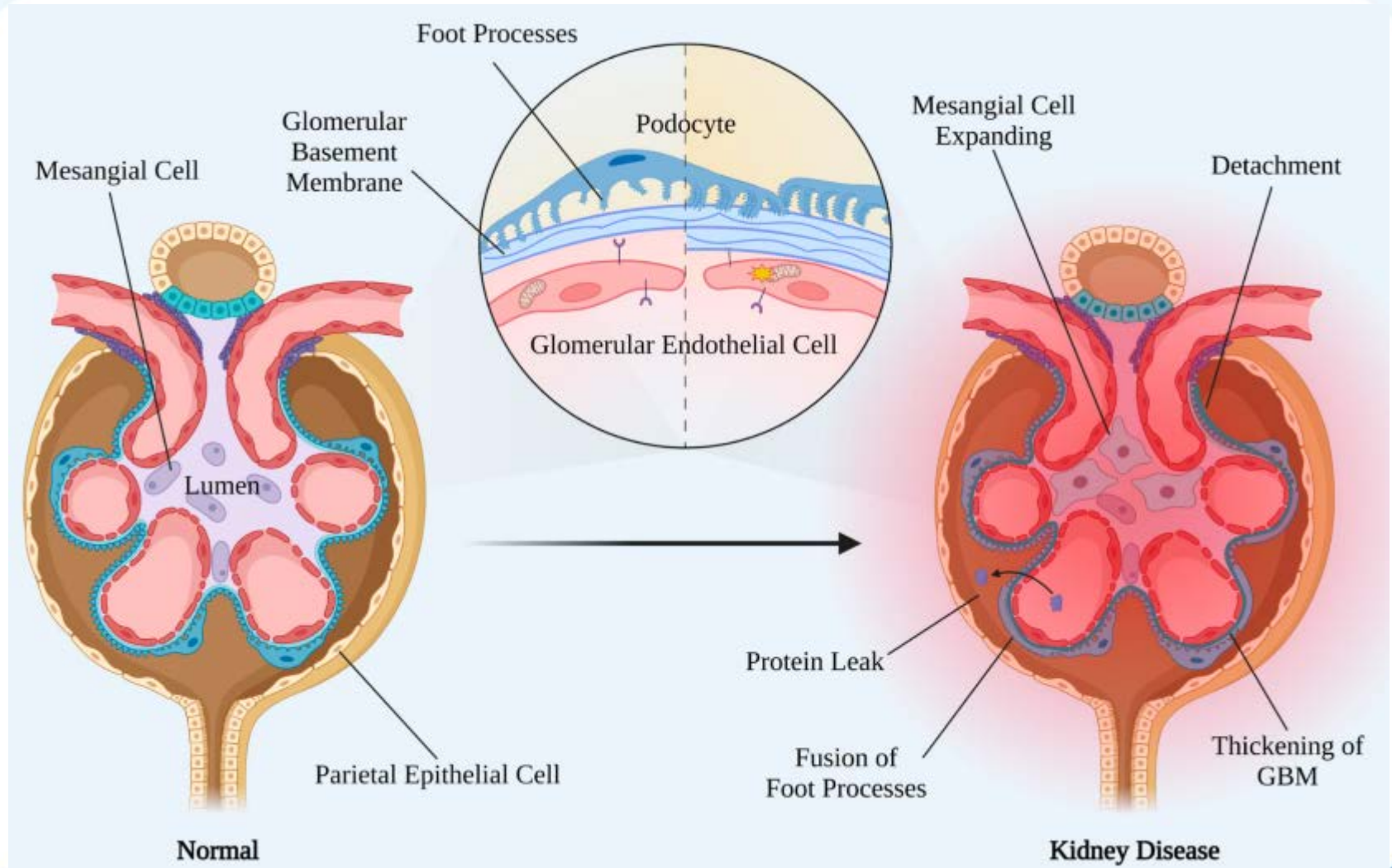
Potential risk or high cost to patient

Increased risk for adverse effects

<sup>a</sup>Benefit supported by primary and secondary outcome data. <sup>b</sup>Benefit supported by secondary outcome data. <sup>c</sup>Benefit or risk is agent specific.  
atherosclerotic cardiovascular disease; CKD, chronic kidney disease; DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1; SGLT2, sodium glucose cotransporter 2.

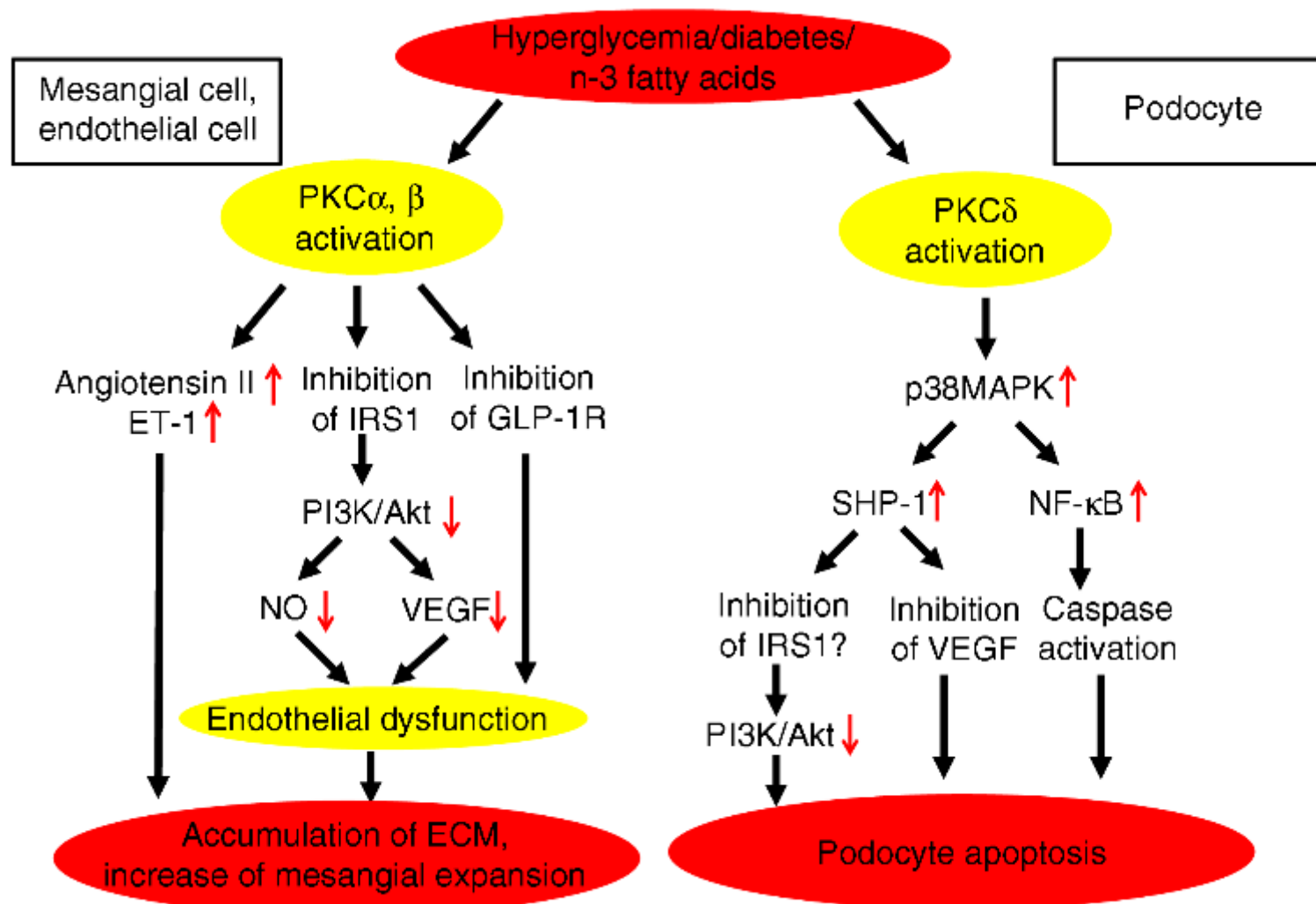


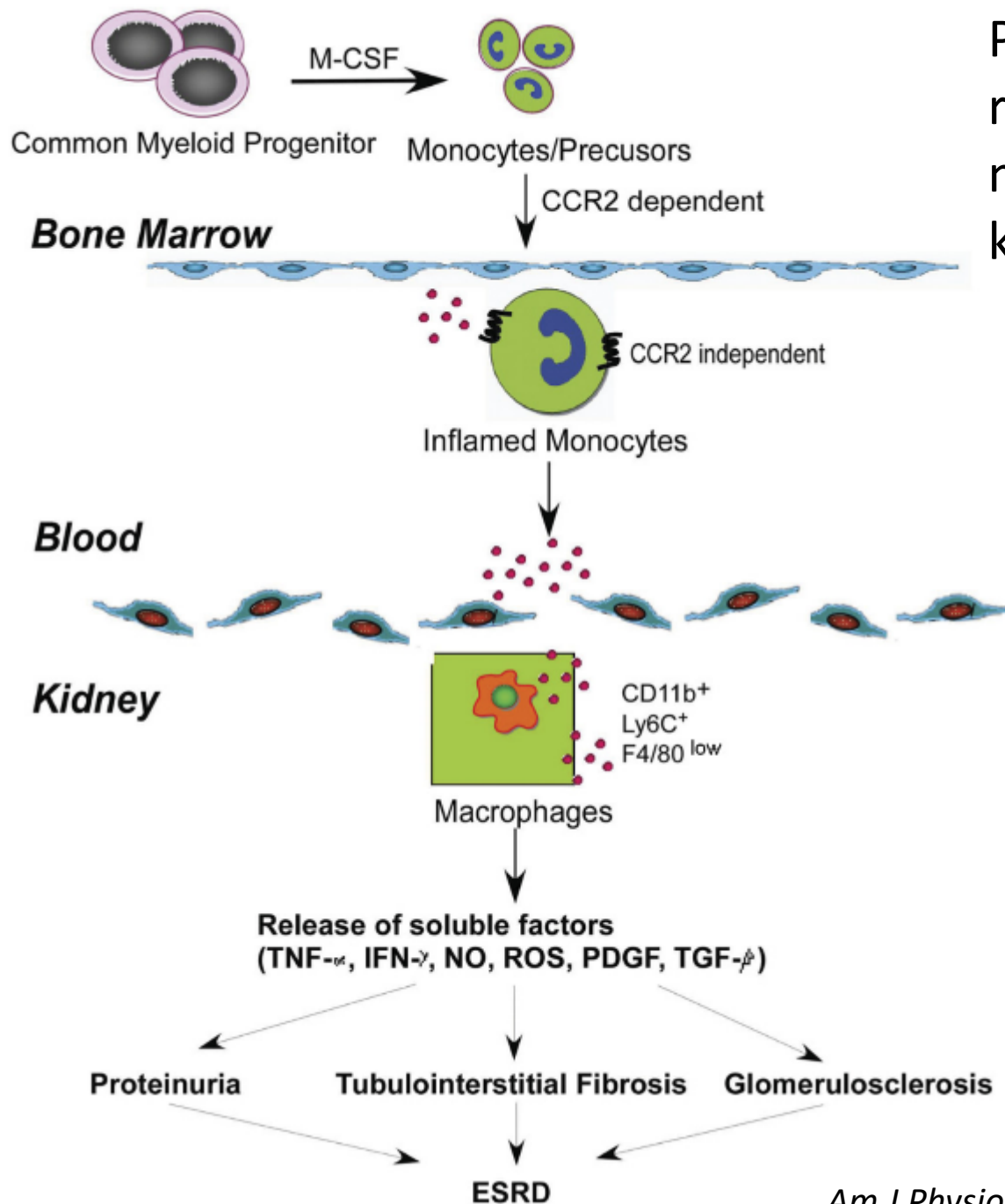
# Features of normal and DKD glomerular filtration barriers





# Potential protective factors and biological targets of PKC activation leading to DN





Proposed scheme for the role of CCR2 in monocyte/macrophage induced kidney injury in diabetes.



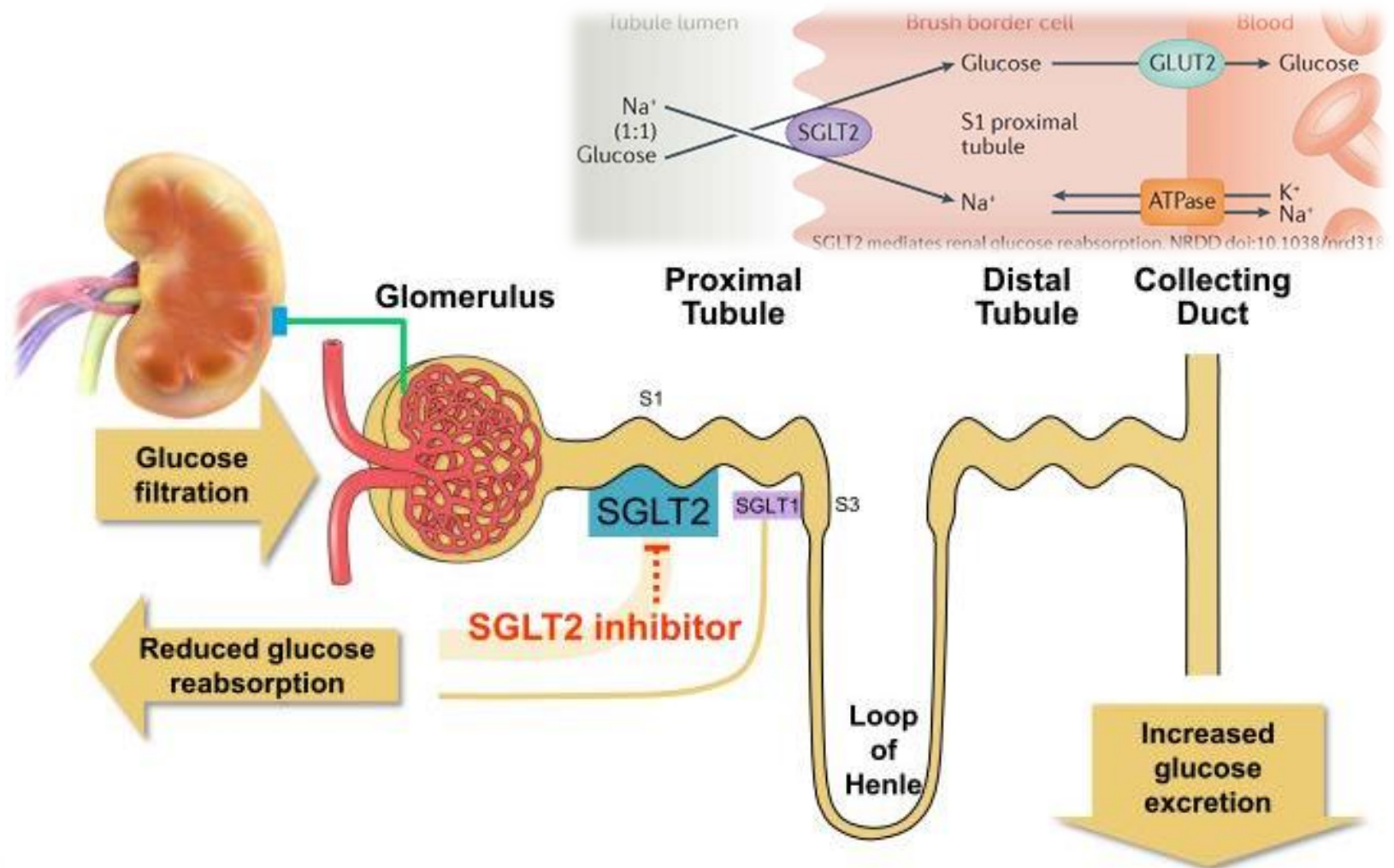
## II

# Mechanisms of renal protection of SGLT-2i

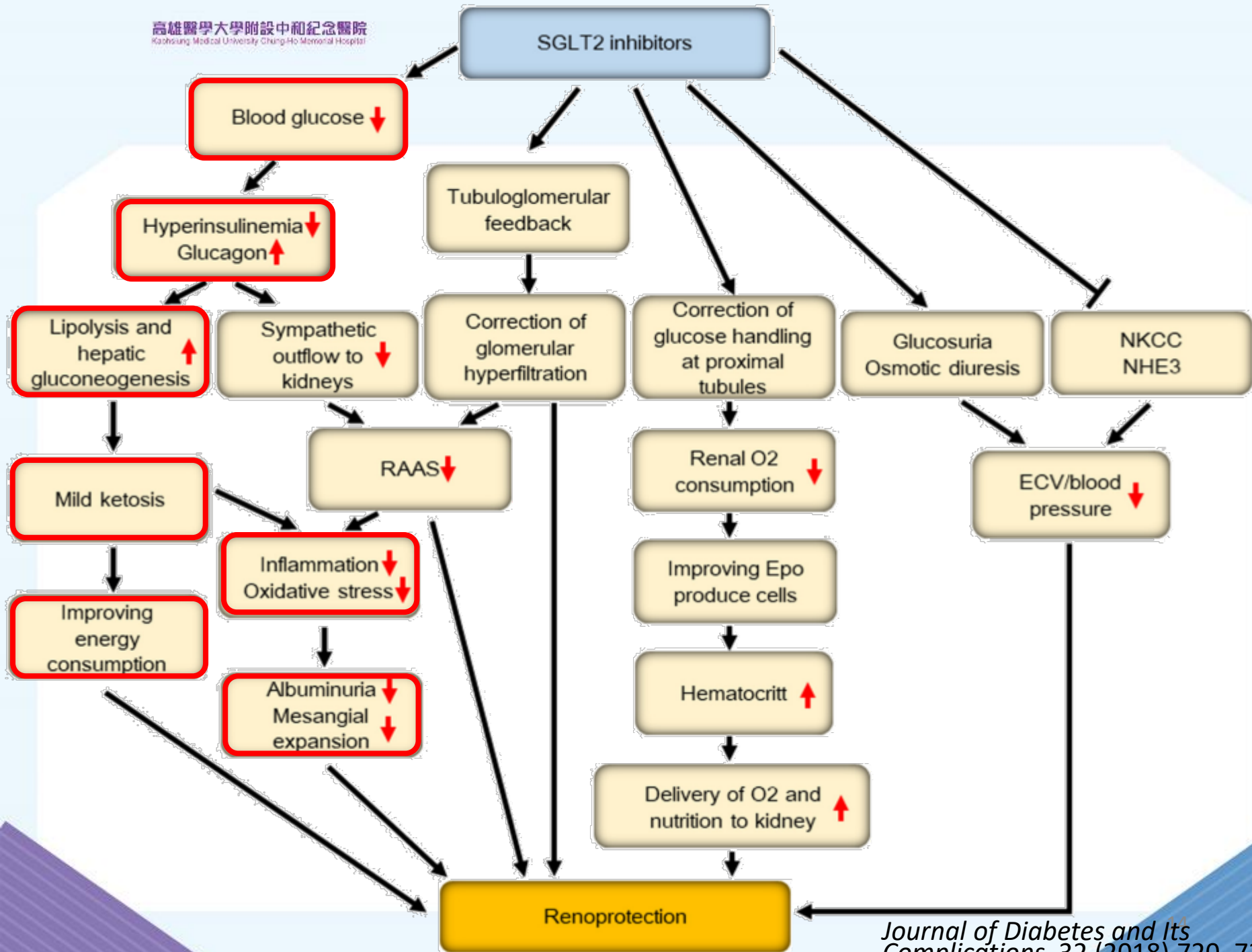
# Kidney Trials

	CREDESCENCE	DAPA-CKD	EMPA-KIDNEY
<b>Drug</b>	Canagliflozin 100 mg once daily	Dapagliflozin 10 mg once daily	Empagliflozin 10 mg once daily
<b>Total of participants</b>	4401	4304	6609
<b>% with CVD</b>	50	37.4	27
<b>eGFR criteria for enrollment (ml/min per 1.73 m<sup>2</sup>)</b>	30–90	25–75	≥20–<45 or ≥45–<90
<b>Mean eGFR at enrollment (ml/min per 1.73 m<sup>2</sup>)</b>	56	43	37.5
<b>% with eGFR &lt;60</b>	59	88	No information [<45: 5185 (78%); ≥45: 1424 (22%)]
<b>ACR</b>	Criteria: ACR >300–5000 mg/g [>30–500 mg/mmol] Median ACR 927 mg/g [92.7 mg/mmol]	ACR 200–5000 mg/g [20–500 mg/mmol] ACR Median DAPA: 965 mg/g [96.5 mg/mmol]; Placebo: 934 mg/g [93.4 mg/mmol]	eGFR ≥45–<90: ACR ≥200 mg/g [≥20 mg/mmol] (or PCR ≥300 mg/g [≥30 mg/mmol]) No ACR criteria for eGFR ≥40–<45 Median ACR 412 mg/g [41.2 mg/mmol]
<b>Follow-up (yr)</b>	2.6	2.4	Expected ≥3
<b>Kidney outcome results</b>	Primary kidney: HR: 0.70; 95% CI: 0.59–0.82	Primary outcome: HR: 0.61; 95% CI: 0.51–0.72	[Trial stopped early due to positive results]

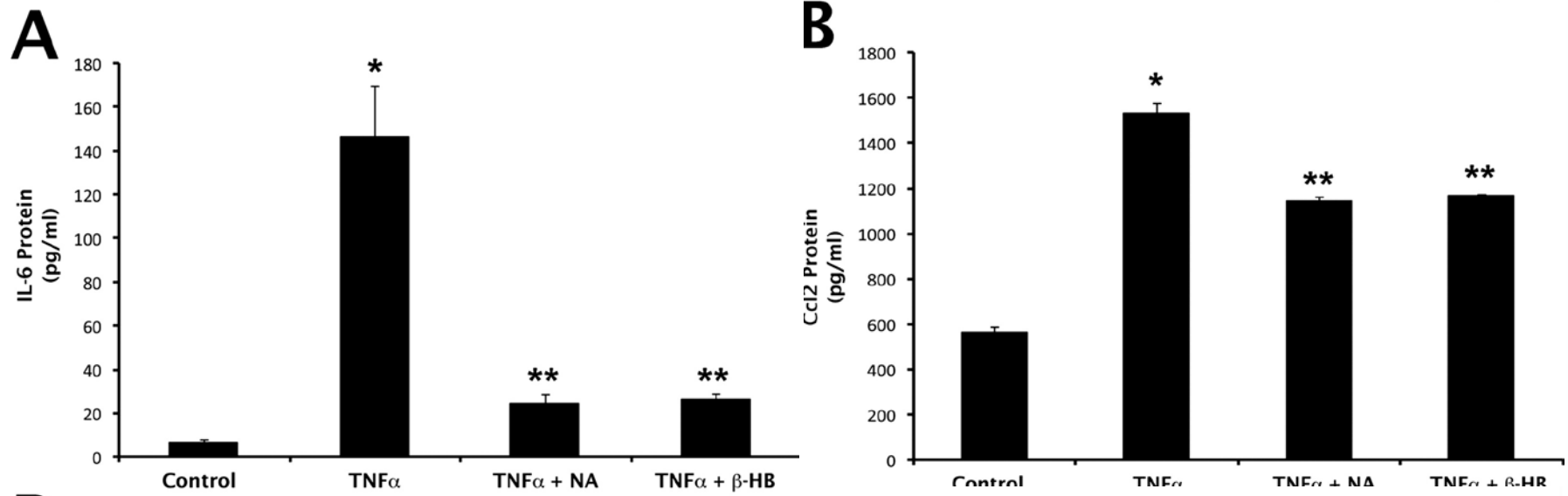
# SGLT-2i block SGLT-2 and reduce glucose and $\text{Na}^+$ reabsorption

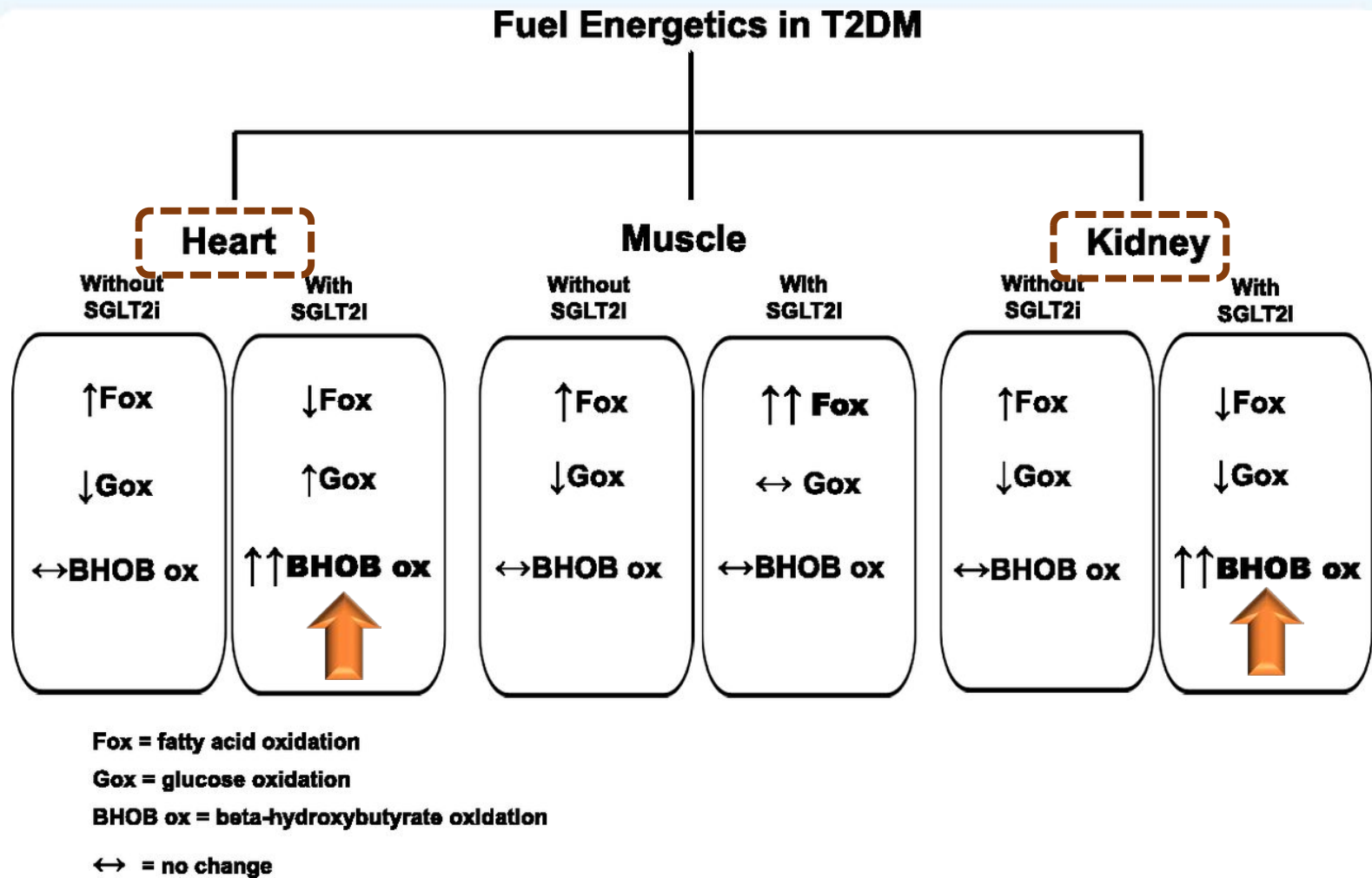


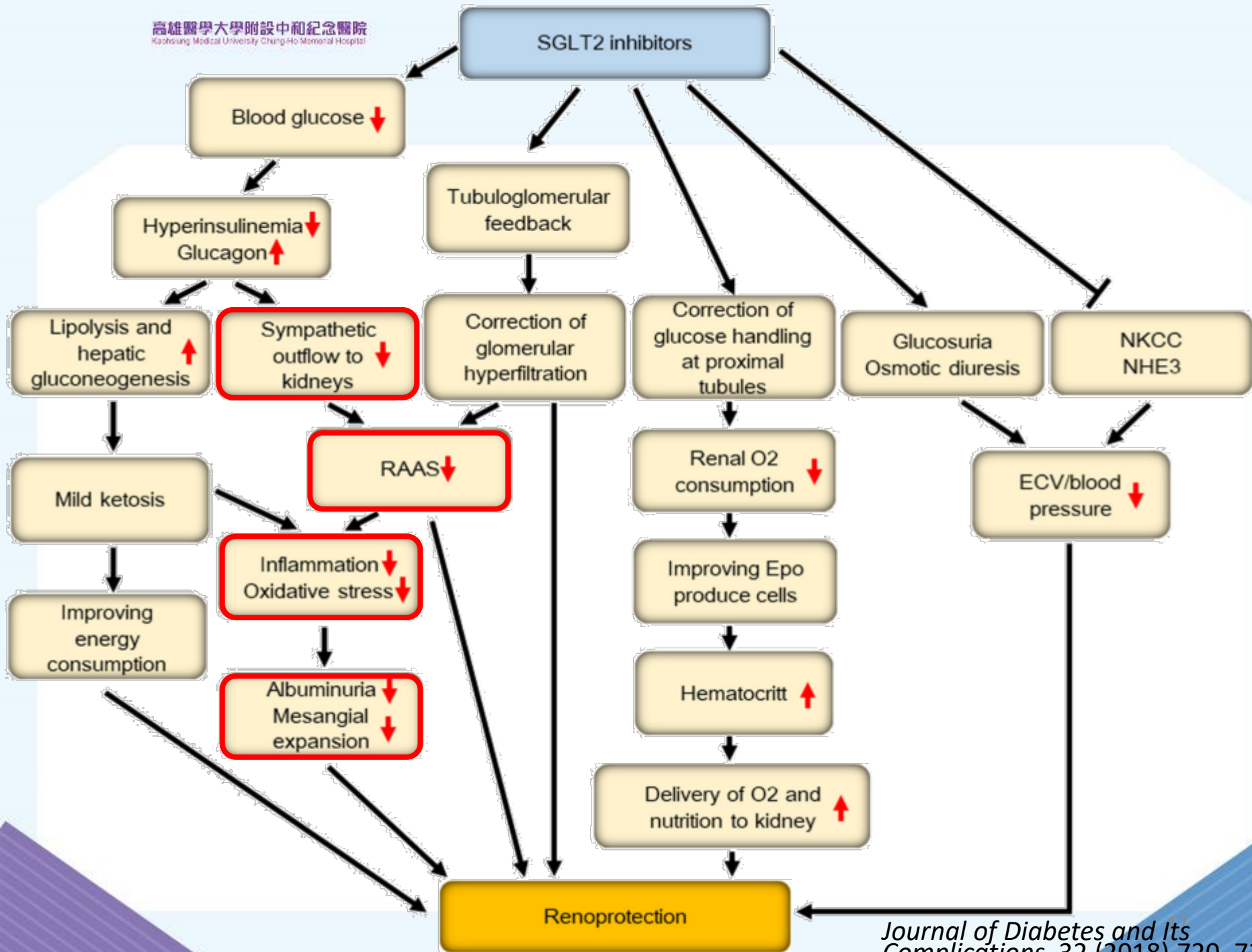


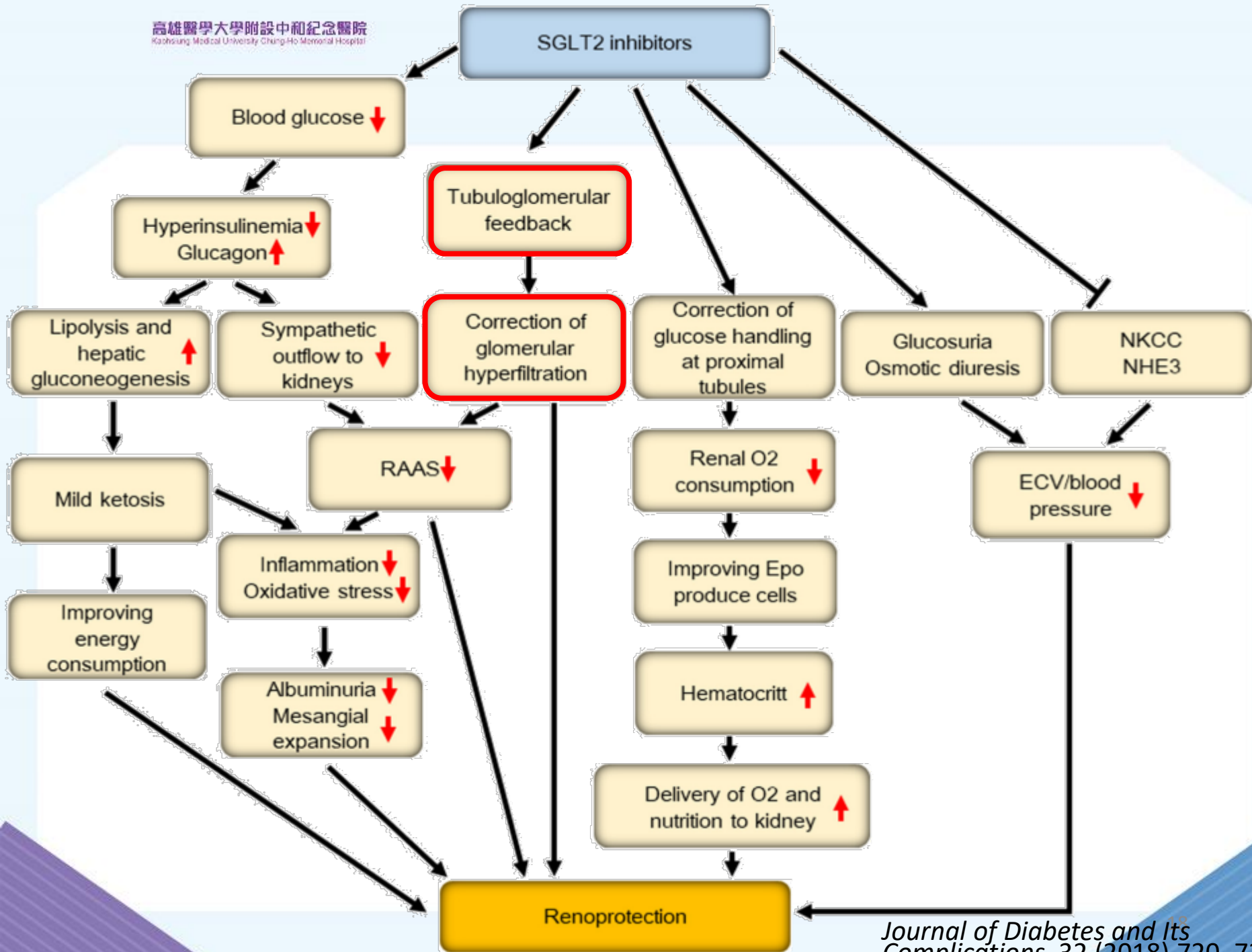


From: GPR109A as an Anti-Inflammatory Receptor in Retinal Pigment Epithelial Cells and Its Relevance to Diabetic Retinopathy Invest. Ophthalmol. Vis. Sci.. 2012;53(4):2208-2217. doi:10.1167/iovs.11-8447



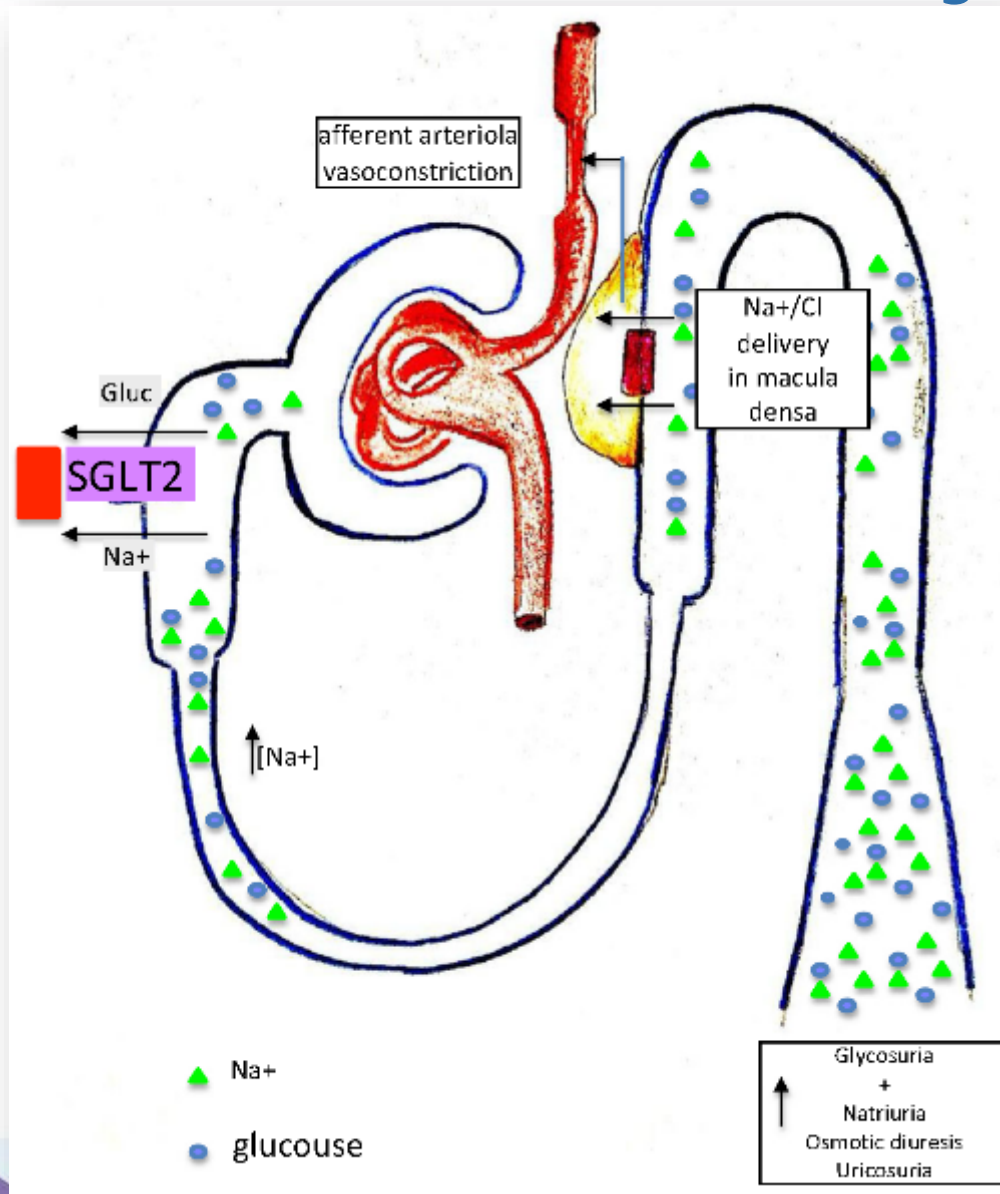




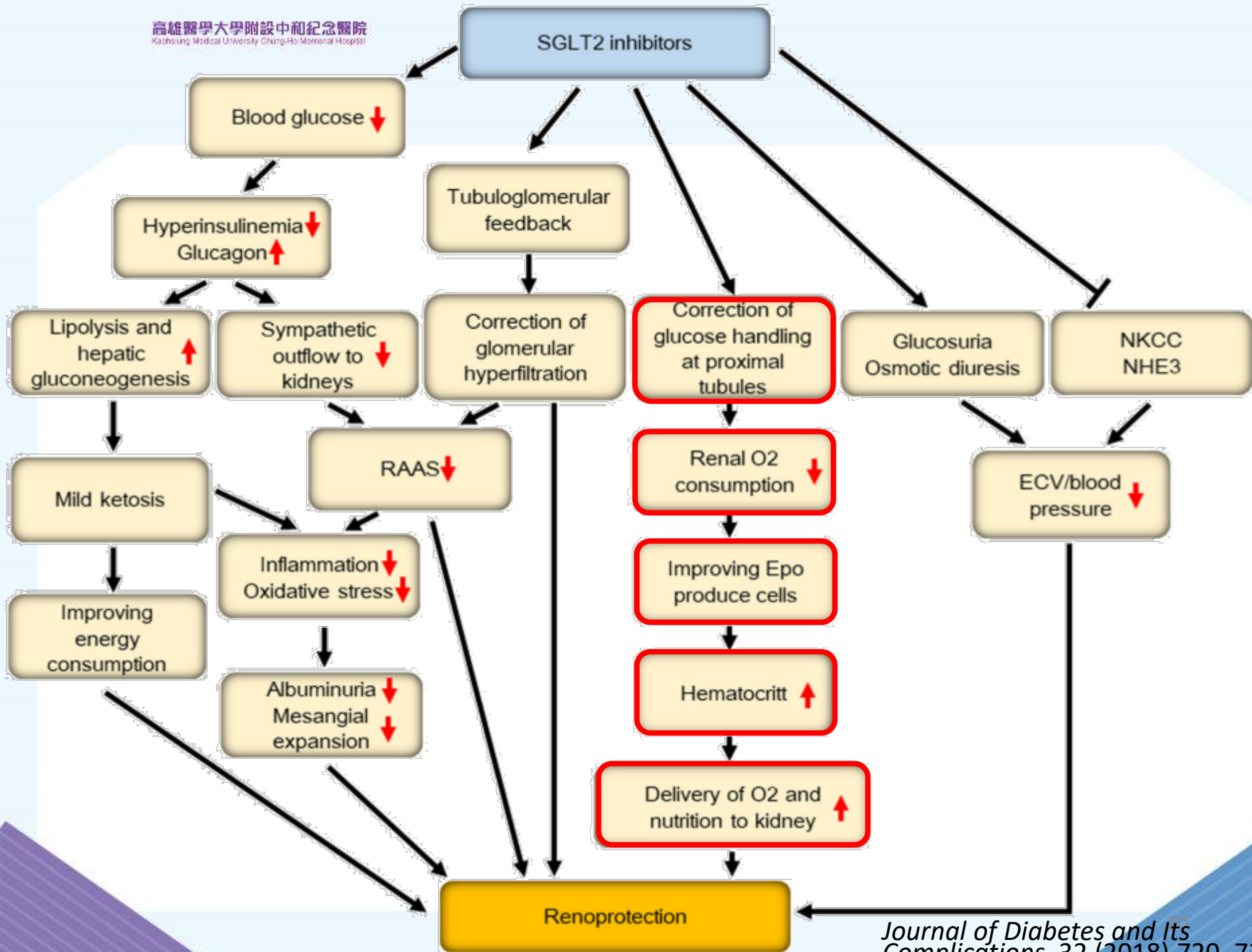




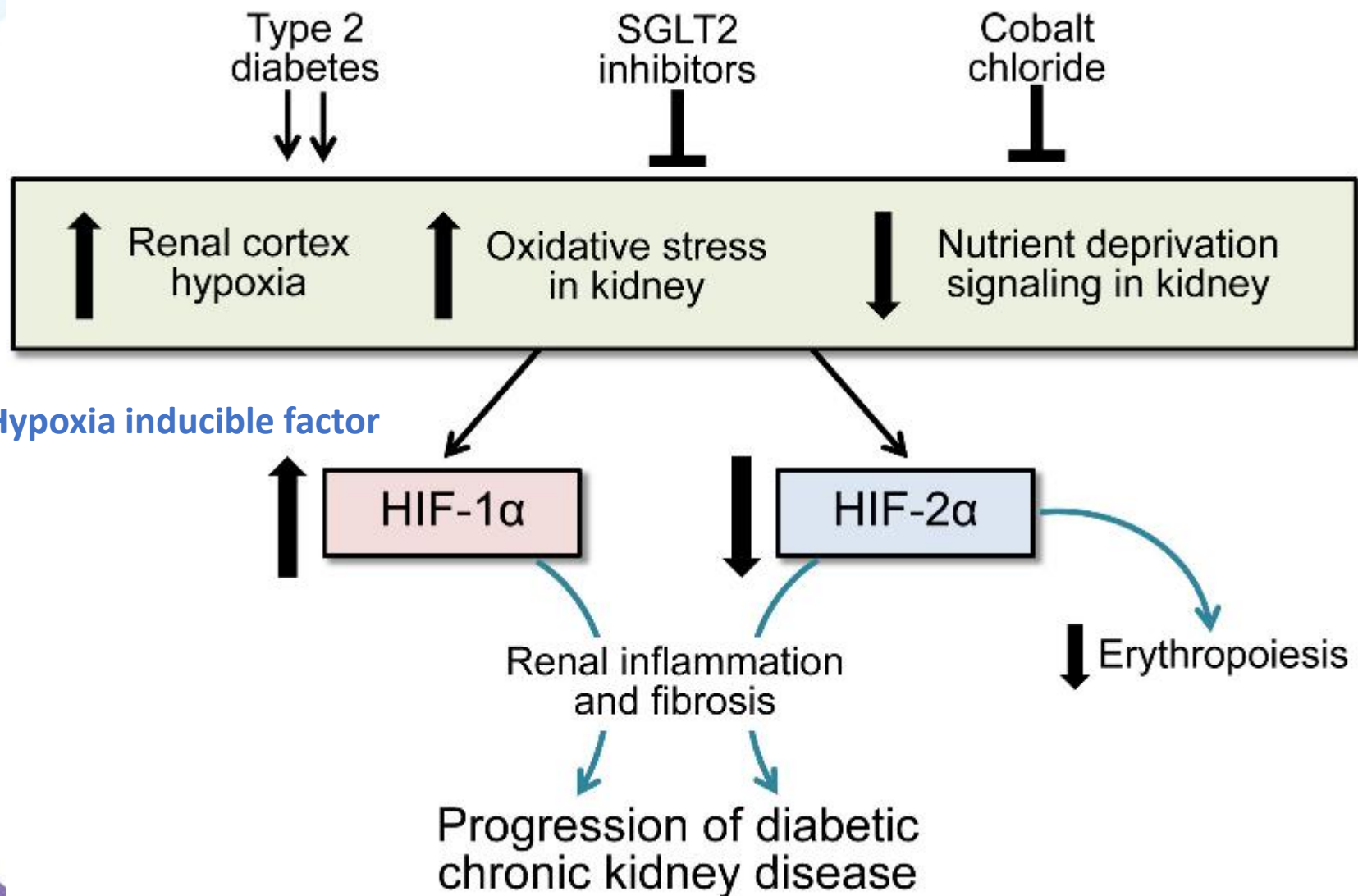
# Effects of SGLT2 inhibition on the kidney and direct and indirect renal benefits obtained through SGLT2 inhibition

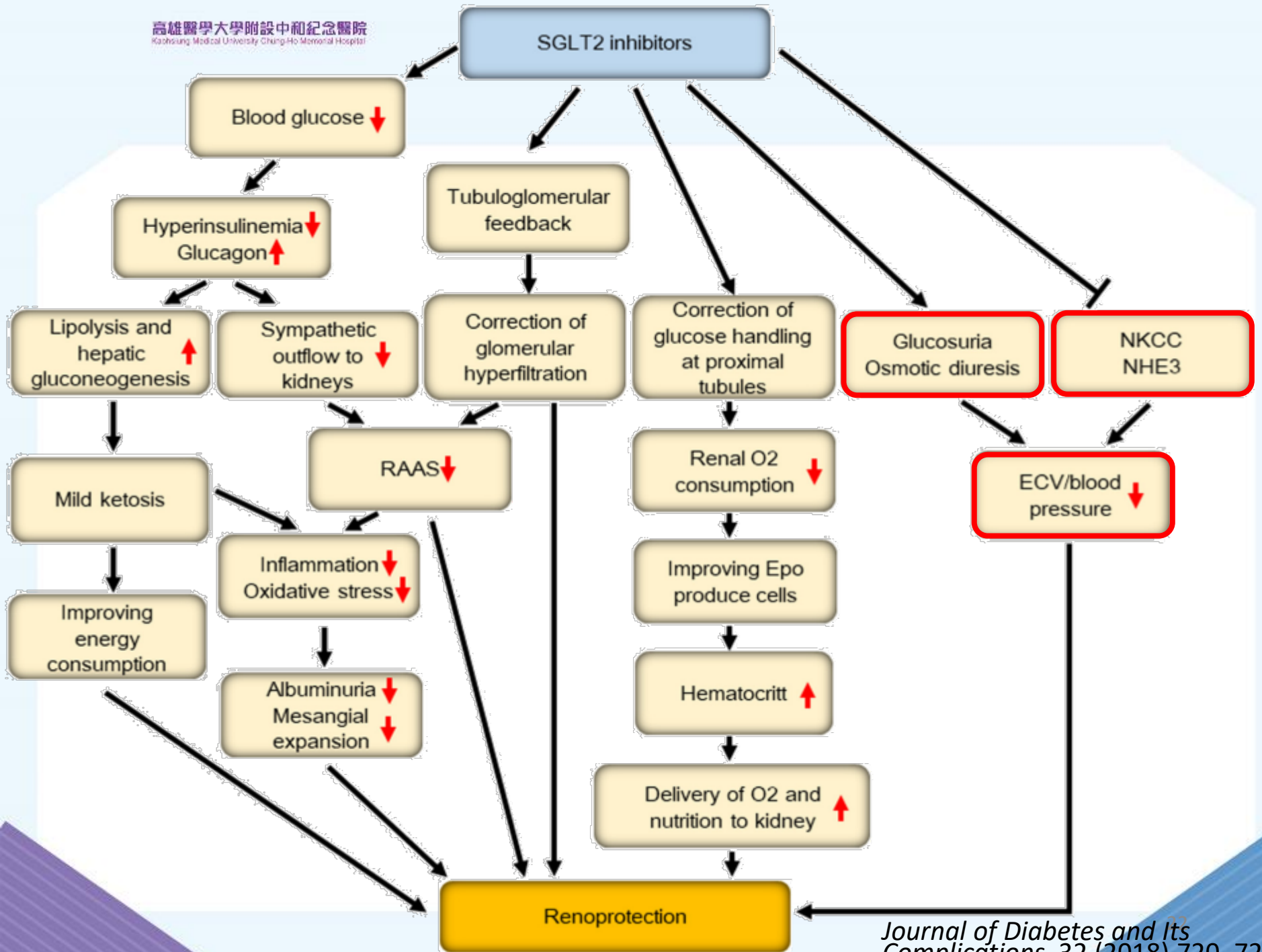


**TGF :**  
**TubuloGlomerular**  
**Feedback**

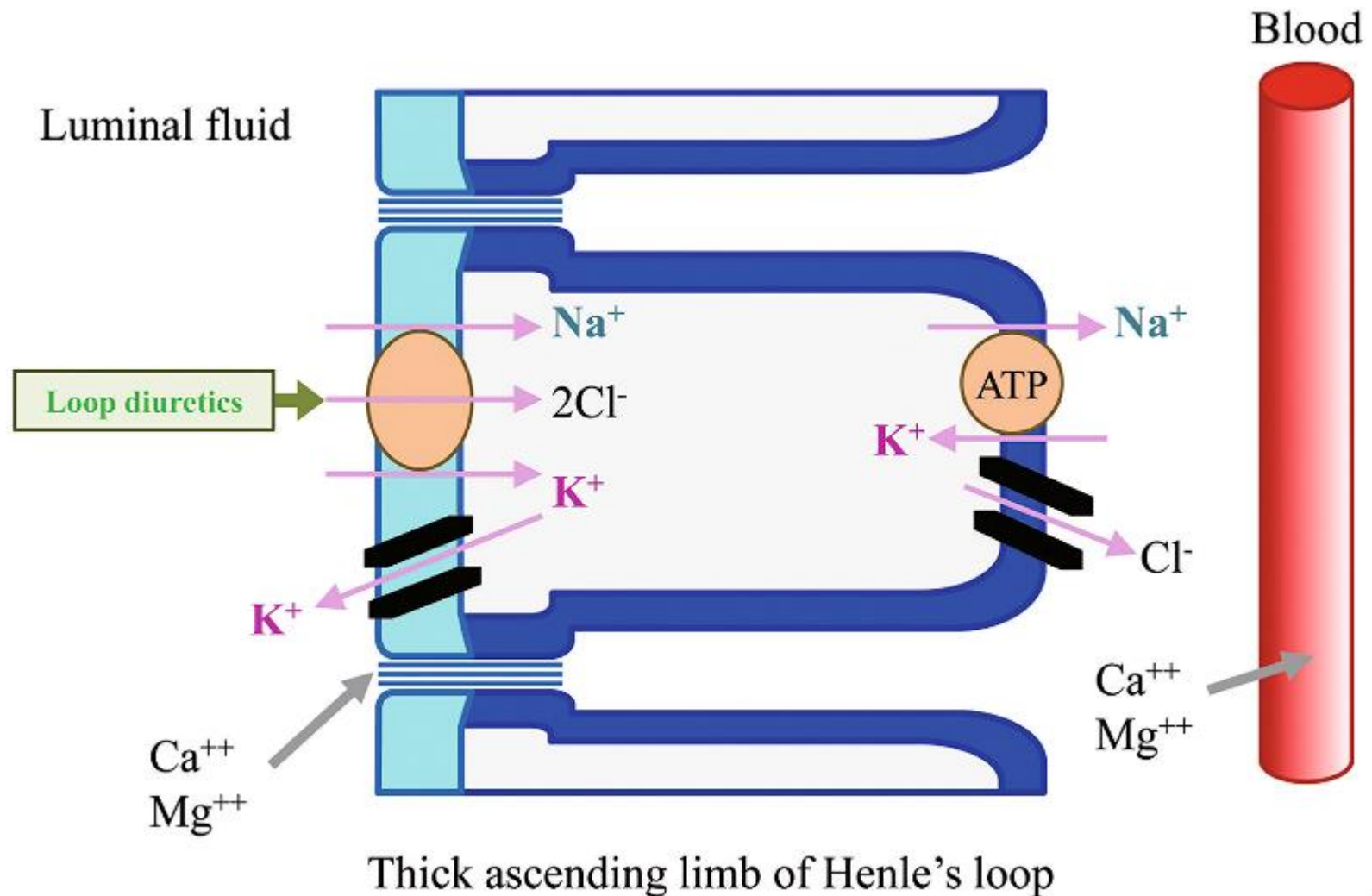


# HIFs and Hypoxia Mimetics



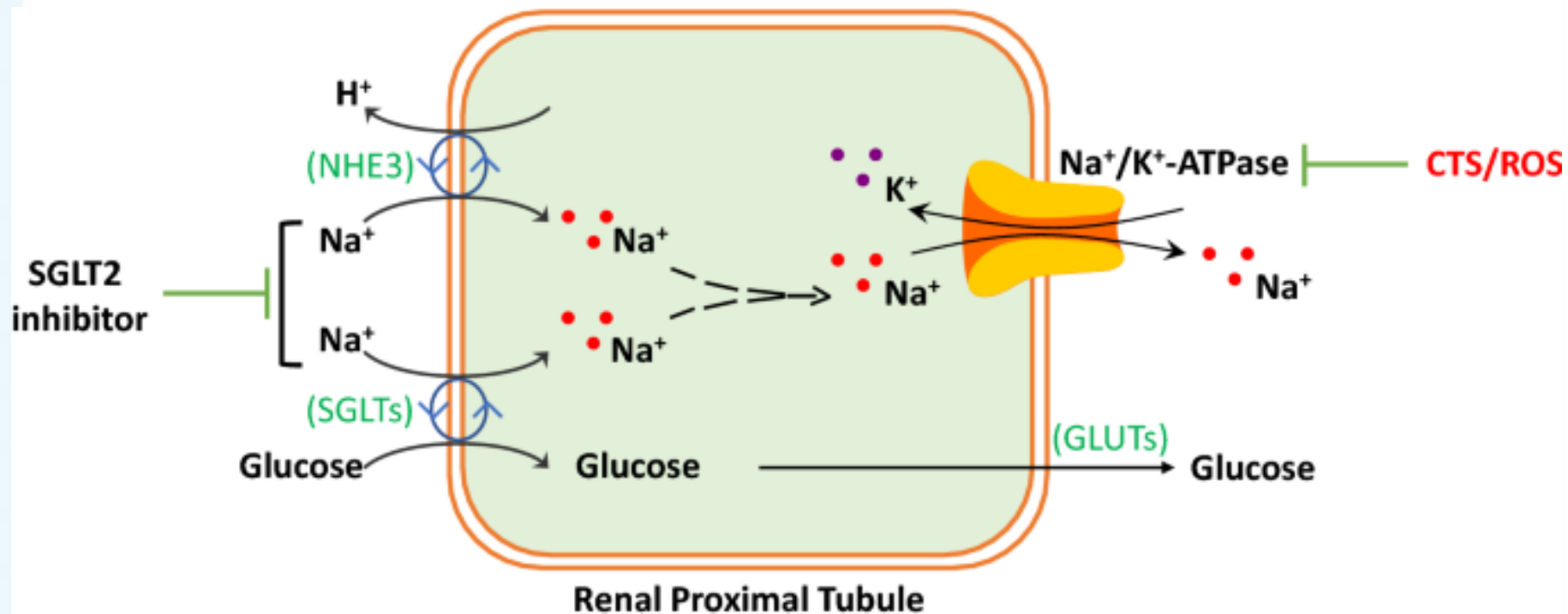


# Mechanisms of reabsorption in the loop of Henle and osmotic diuresis





# Inhibition of SGLT2 may block the Na/H exchanger **NHE3** in the proximal tubule.

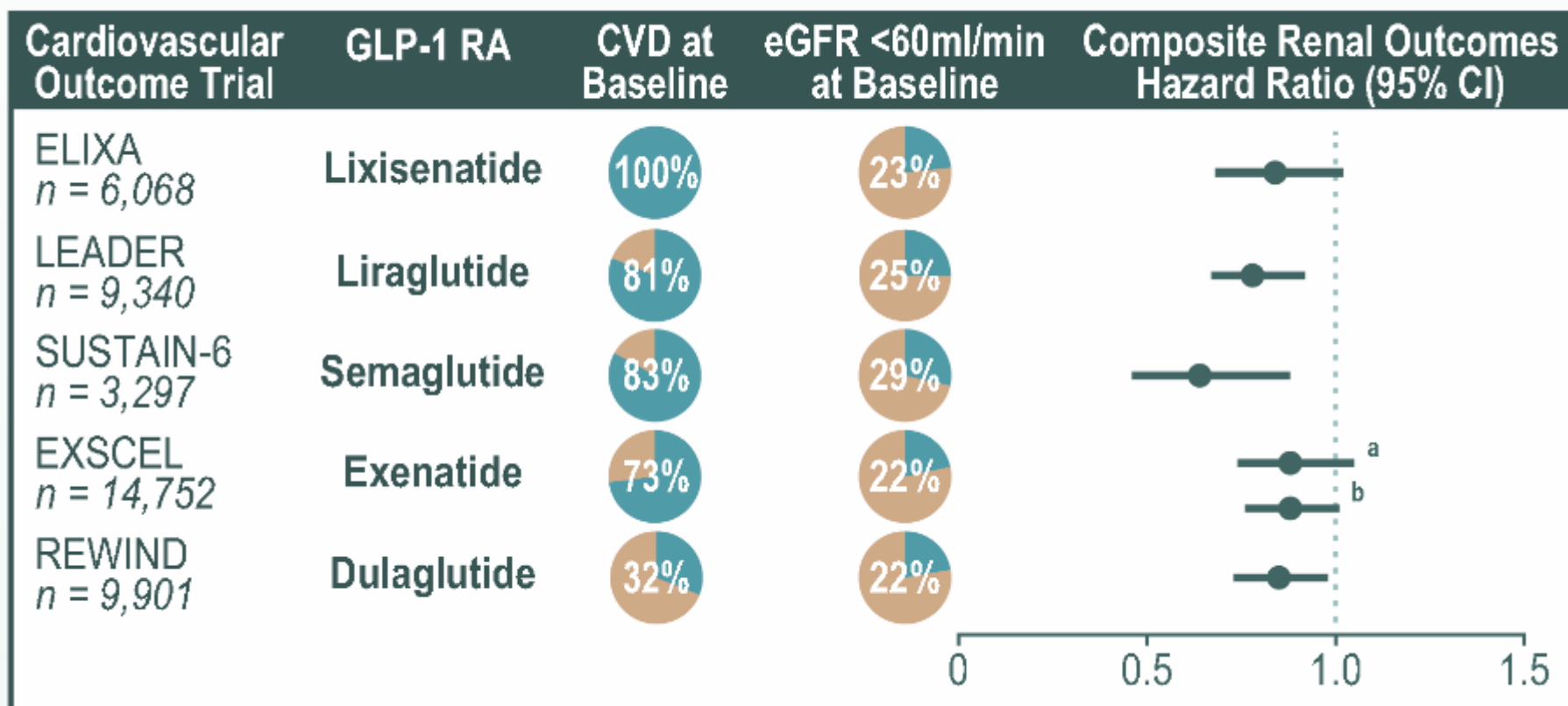




# Mechanisms of renal protection of GLP1 RA

# Renal outcome from GLP-1 RA CVOTs

## Renal outcomes from GLP-1 RA CVOTs



# Potential direct and indirect renoprotective effects of GLP-1 RAs



## Direct Effect

- Proximal tubular natriuresis simulation
- Modulation of cAMP/PKA signaling
- Inhibition of renin angiotensin system
- Decreased renal hypoxia
- Renal endothelial dependent vasodilation
- Increased tubuloglomerular feedback

# Potential direct and indirect renoprotective effects of GLP-1 RAs



## Indirect Effect

- Improved glycemic control
- Improved blood pressure control
- Weight loss
- Increase insulin sensitivity





# IV

# CONCLUSION

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An unmet need remains for new treatment strategies for preventing, arresting, treatment and reversing CKD in patients with diabetes.

Let's explore more new weapons that can protect organs by understanding the mechanism of these drugs.



高雄醫學大學附設中和紀念醫院

Kaohsiung Medical University Chung-Ho Memorial Hospital

# THANK YOU

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