蛋白尿
- 評估與處置

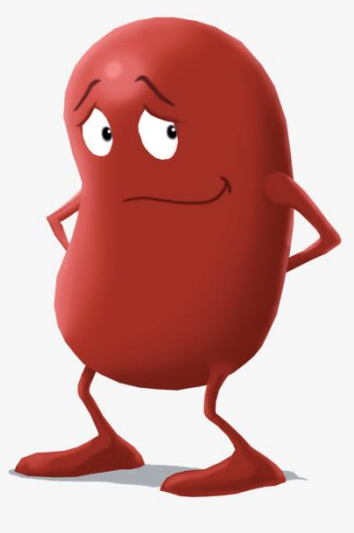
2022/08/25

Nephro 裘亮德

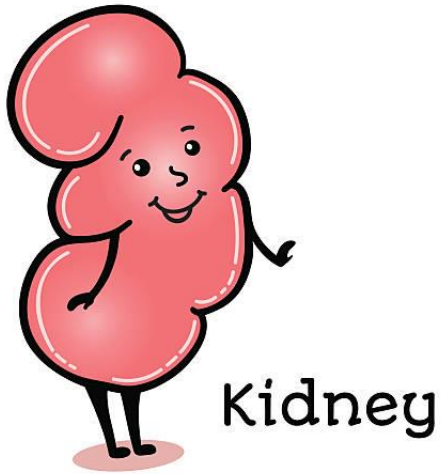
大綱

蛋白尿之:

- 1. 分類/成因
- 2. 定義
- 3. 評估
- 4. 處置



1. 分類/成因



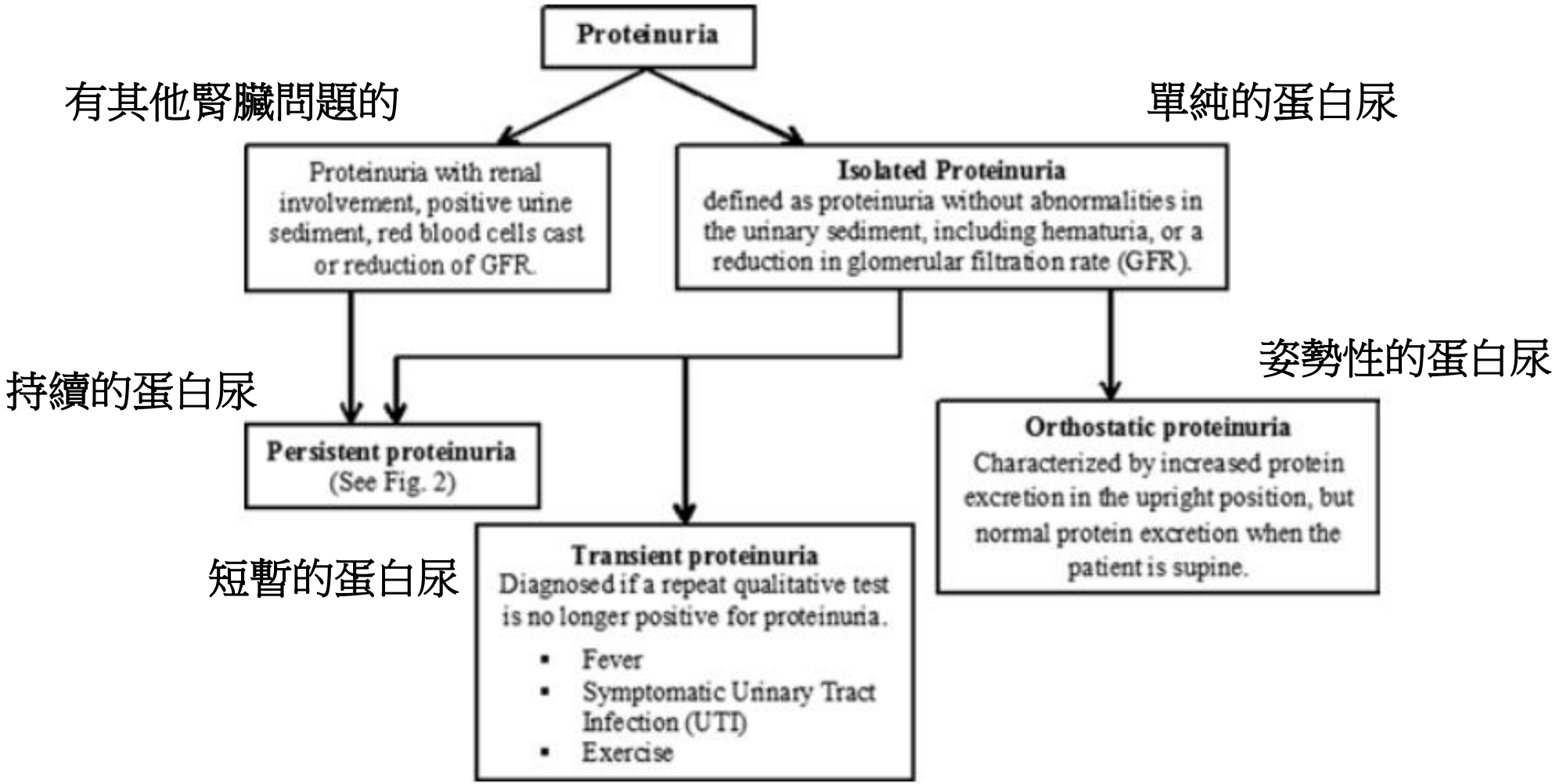


Fig. 1 - Classification of proteinuria. GFR = glomerular filtration rate.

Proteinuria and Albuminuria at Point of Care
Article in Nephrology Point of Care · February 2016
DOI: 10.5301/pocj.5000194

病態性的蛋白尿

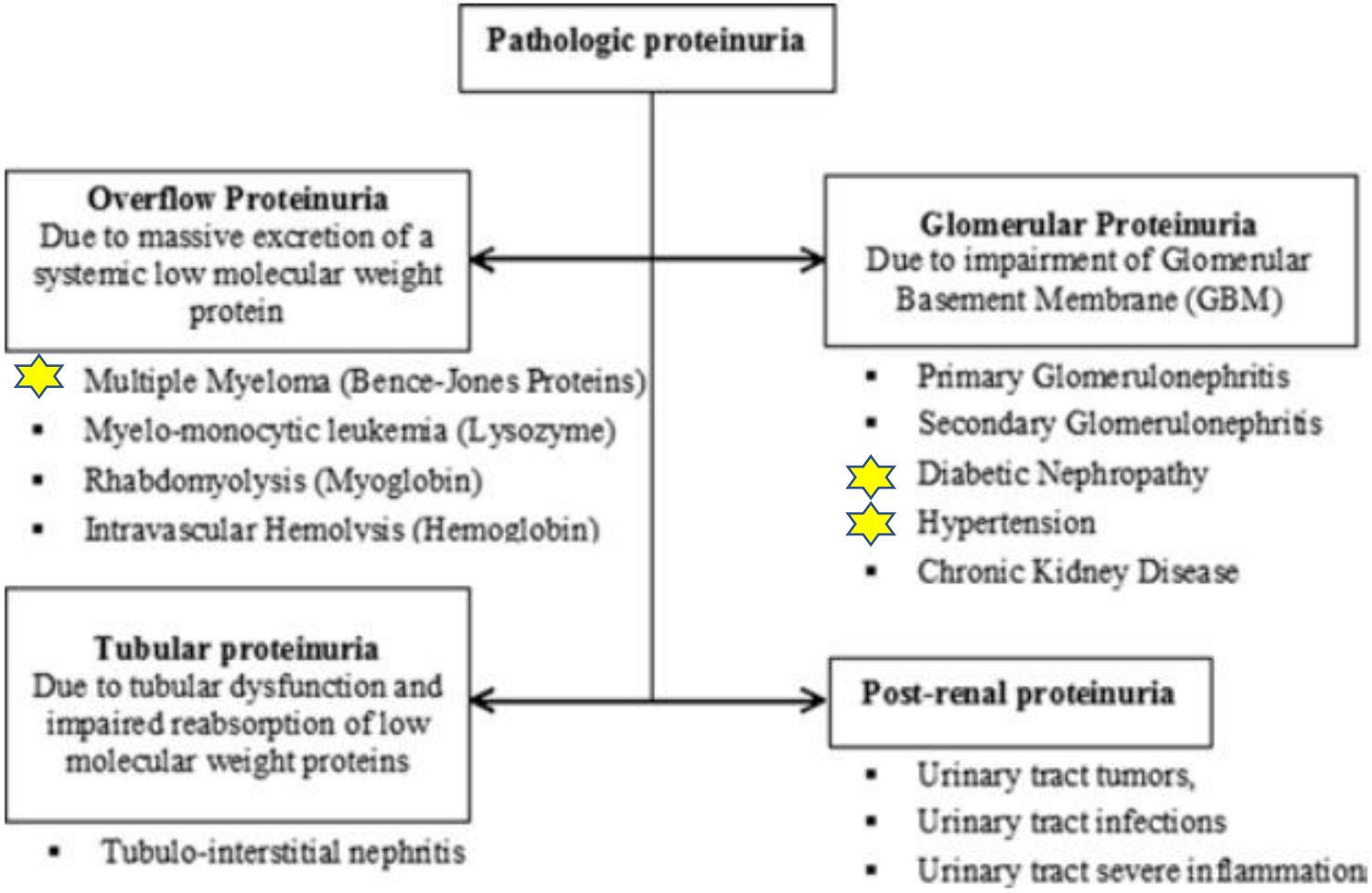


Fig. 2 - Classification of pathological proteinuria, based on different pathophysiological mechanisms, with some typical etiologies.

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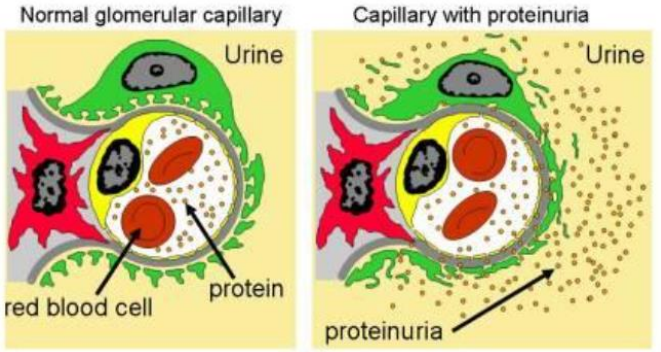
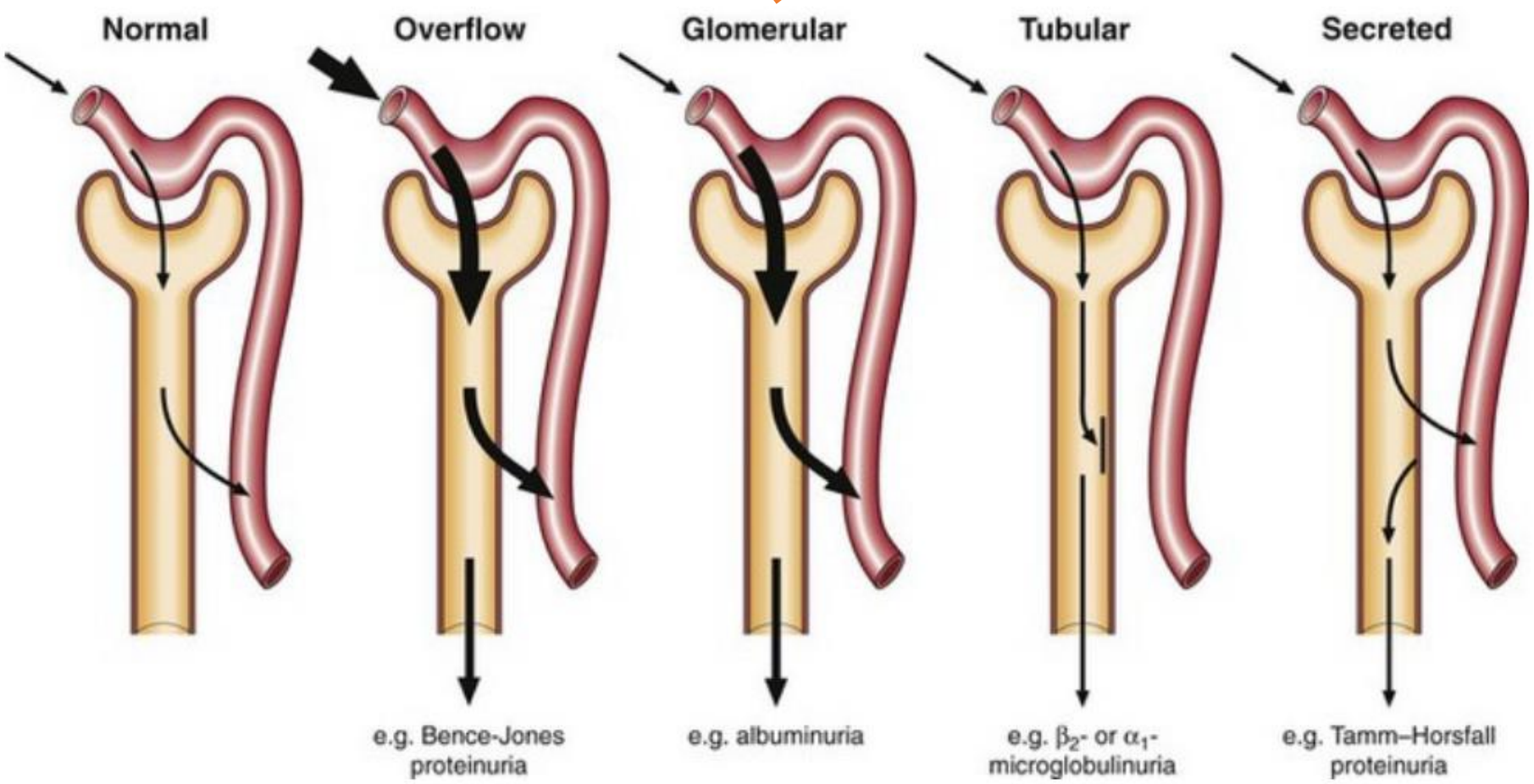
Mechanism of proteinuria



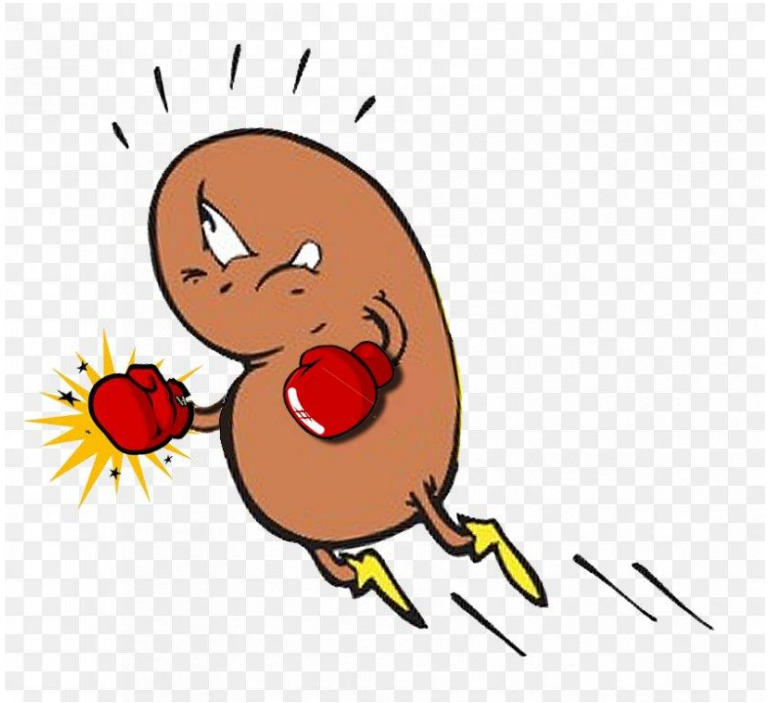


Brenner & Rector's The Kidney, 10th ed. Ch. 31

Classification and characterization of proteinuria types

Classification of proteinuria	Clinical setting	Typical level of proteinuria in adults	Predominant protein type
Transient proteinuria	Fever, heavy exercise, vasopressor infusion, albumin infusion	<1 g/day	Albumin
Persistent proteinuria – orthostatic proteinuria	Uncommon over age 30 years, may occur in 2 to 5% of adolescents	<1 to 2 g/day	Albumin
Persistent proteinuria – overflow proteinuria	Myeloma (monoclonal light chains), hemolysis (hemoglobinuria), rhabdomyolysis (myoglobinuria)	Variable, could be nephrotic range	Nonalbumin
Persistent proteinuria – glomerular proteinuria	Primary glomerular diseases, secondary glomerular diseases, diabetic nephropathy, hypertensive nephrosclerosis	Variable, often nephrotic range	Albumin
Persistent proteinuria – tubulointerstitial proteinuria	Heavy metal intoxications, autoimmune or allergic interstitial inflammation, medication-induced interstitial injury	<3 g/day	Nonalbumin
Post-renal proteinuria	Urinary tract infections, nephrolithiasis, genitourinary tumor	<1 g/day	Nonalbumin

2. 定義



Foamy urine/ proteinuria

- **小便有無泡沫無法斷定一定有或沒有蛋白尿**
  - 尿中**含氮廢物**和**礦物質**上升時(改變了尿液的表面張力活性)易有泡泡
  - 晨尿 → **整晚尿液濃縮** + **尿液沖激到馬桶**(ex: 男生)易有泡泡
  - 正常生理形成的尿液泡沫一般會在數秒~數分鐘內消失
  - 真正的蛋白尿小便特徵 = **表面漂浮著一層細小的泡沫** + **久久不消失**
  - 真正的蛋白尿需經由客觀的評估 = **尿液分析**
- **正常的尿中有沒有蛋白？多少算正常？**
  - 正常的尿蛋白組成
    - **Tamm-Horsfall protein** (Loop of Henle上皮細胞分泌的Mucoprotein)
    - Albumin (~20%) (65,000 Daltons)
    - 少量Immnuoglobulin light chain & ß2-microglobulin
  - 正常尿蛋白量
    - **Total protein < 150mg/24hr & albumin < 30mg/24hr**

Reference: 基層醫學雜誌 第二十一卷 第六期 蛋白尿與微量白蛋白尿 (2003)

蛋白尿與腎絲球疾病的評估與處置

microalbuminuria macroalbuminuri

Table 7 | Relationship among categories for albuminuria and proteinuria

Measure	Categories		
	Normal to mildly increased (A1)	Moderately increased (A2)	Severely increased (A3)
AER (mg/24 hours)	<30	30–300	>300
PER (mg/24 hours)	<150	150–500	>500
ACR			
(mg/mmol)	<3	3–30	>30
(mg/g)	<30	30–300	>300
PCR			
(mg/mmol)	<15	15–50	>50
(mg/g)	<150	150–500	>500
Protein reagent strip	Negative to trace	Trace to +	+ or greater

Abbreviations: ACR, albumin-to-creatinine ratio; AER, albumin excretion rate; PCR, protein-to-creatinine ratio; PER, protein excretion rate.
Albuminuria and proteinuria can be measured using excretion rates in timed urine collections, ratio of concentrations to creatinine concentration in spot urine samples, and using reagent strips in spot urine samples. Relationships among measurement methods within a category are not exact. For example, the relationships between AER and ACR and between PER and PCR are based on the assumption that average creatinine excretion rate is approximately 1.0 g/d or 10 mmol/d. The conversions are rounded for pragmatic reasons. (For an exact conversion from mg/g of creatinine to mg/mmol of creatinine, multiply by 0.113.) Creatinine excretion varies with age, sex, race and diet; therefore the relationship among these categories is approximate only. ACR <10 mg/g (<1 mg/mmol) is considered normal; ACR 10–30 mg/g (1-3 mg/mmol) is considered "high normal." ACR >2200 mg/g (>220 mg/mmol) is considered "nephrotic range." The relationship between urine reagent strip results and other measures depends on urine concentration.

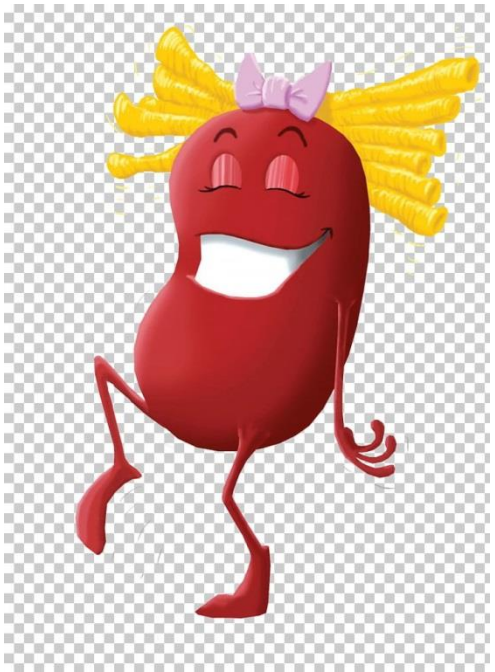
KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease

尿蛋白的檢驗

- **Urinalysis (dipstick, 半定量法)**
  - **1+ 30mg/dL, 2+ 100mg/dL,3+ 300mg/dL, 4+ 1~2g/dL**
    - Se 32~46%, Sp 97~100%
  - **只能測Albumin; 需一天尿蛋白>300~500mg/d才會(+)**
    - 30mg/dL = 30mg/100ml x 1000~1500 ml(假設一天尿量) = 300~450mg
  - 一旦持續Positive就已經是Macroalbuminuria(>300mg/day)
    - **無法早期偵測Diabetic kidney disease的Microalbuminuria (30~300mg/d)**
      - 在Microalbuminuria時開始用ACEI/ARB有機會改善DKD/延緩腎功能惡化
  - False positive
    - Sp. gravity >1.020 (太濃) or Urine Ph >7 or pyuria/hematuria
    - 24hr內用過含碘顯影劑
  - False negative
    - Sp. gravity <1.005 (太稀) or Urine Ph 太低(ex: <5.0)

Reference: 基層醫學雜誌 第二十一卷 第六期　蛋白尿與微量白蛋白尿 (2003)

3. 評估



Urine analysis + 鏡檢

UPCR/UACR

Renal function
BP
Cause…

AMERICAN FAMILY PHYSICIAN

Proteinuria in Adults: A Diagnostic Approach

尿液鏡檢

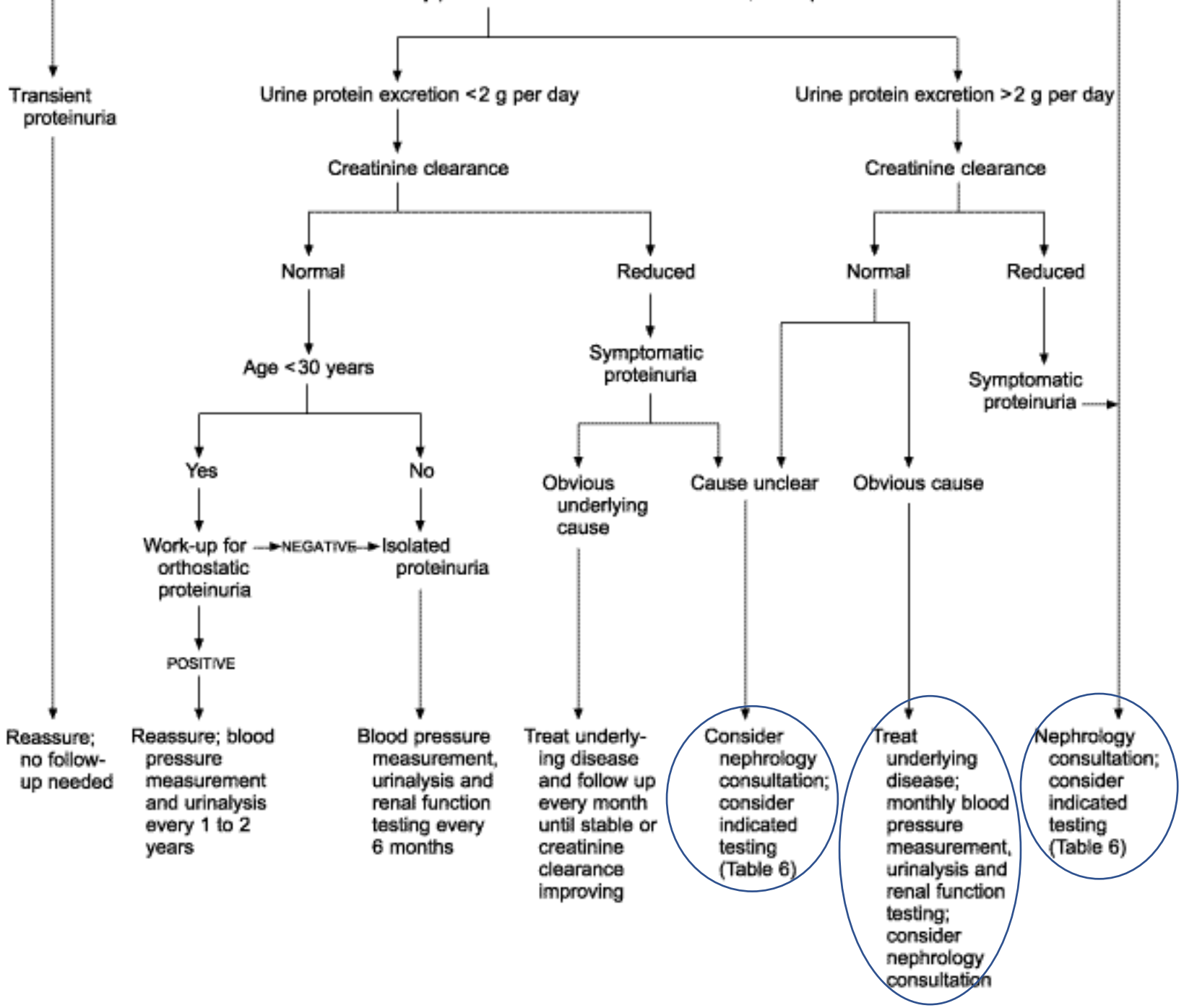
Microscopic finding	*Pathologic process*
Fatty casts, free fat or oval fat bodies	Nephrotic range proteinuria (> 3.5 g per 24 hours)
Leukocytes, leukocyte casts with bacteria	Urinary tract infection
Leukocytes, leukocyte casts without bacteria	Renal interstitial disease
Normal-shaped erythrocytes	Suggestive of lower urinary tract lesion
Dysmorphic erythrocytes	Suggestive of upper urinary tract lesion
Erythrocyte casts	Glomerular disease
Waxy, granular or cellular casts	Advanced chronic renal disease
Eosinophiluria*	Suggestive of drug-induced acute interstitial nephritis
Hyaline casts	No renal disease; present with dehydration and with diuretic therapy

**—A Wright stain of the urine specimen is necessary to detect eosinophiluria.*

Adapted from Larson TS. Evaluation of proteinuria. Mayo Clin Proc 1994;69: 1154–8.

AMERICAN FAMILY PHYSICIAN®

Proteinuria in Adults: A Diagnostic Approach



AMERICAN FAMILY PHYSICIAN

Proteinuria in Adults: A Diagnostic Approach

- Nephrology consultation
- treat underlying dz
- f/u

Prognosis of CKD by GFR and albuminuria category

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

GFR categories (ml/min/ 1.73 m^2) 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			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.

Summary of relative risks from categorical meta-analysis
(dipstick included)
(−, ±, +, ⩾++)

All-cause mortality

	ACR <10	ACR 10–29	ACR 30–299	ACR ⩾300
eGFR > 105	1.1	1.5	2.2	5.0
eGFR 90–105	Ref	1.4	1.5	3.1
eGFR 75–90	1.0	1.3	1.7	2.3
eGFR 60–75	1.0	1.4	1.8	2.7
eGFR 45–60	1.3	1.7	2.2	3.6
eGFR 30–45	1.9	2.3	3.3	4.9
eGFR 15–30	5.3	3.6	4.7	6.6

Cardiovascular mortality

	ACR <10	ACR 10–29	ACR 30–299	ACR ⩾300
eGFR > 105	0.9	1.3	2.3	2.1
eGFR 90–105	Ref	1.5	1.7	3.7
eGFR 75–90	1.0	1.3	1.6	3.7
eGFR 60–75	1.1	1.4	2.0	4.1
eGFR 45–60	1.5	2.2	2.8	4.3
eGFR 30–45	2.2	2.7	3.4	5.2
eGFR 15–30	14	7.9	4.8	8.1

Kidney failure (ESRD)

	ACR <10	ACR 10–29	ACR 30–299	ACR ⩾300
eGFR > 105	Ref	Ref	7.8	18
eGFR 90–105	Ref	Ref	11	20
eGFR 75–90	Ref	Ref	3.8	48
eGFR 60–75	Ref	Ref	7.4	67
eGFR 45–60	5.2	22	40	147
eGFR 30–45	56	74	294	763
eGFR 15–30	433	1044	1056	2286

Acute kidney injury (AKI)

	ACR <10	ACR 10–29	ACR 30–299	ACR ⩾300
eGFR > 105	Ref	Ref	2.7	8.4
eGFR 90–105	Ref	Ref	2.4	5.8
eGFR 75–90	Ref	Ref	2.5	4.1
eGFR 60–75	Ref	Ref	3.3	6.4
eGFR 45–60	2.2	4.9	6.4	5.9
eGFR 30–45	7.3	10	12	20
eGFR 15–30	17	17	21	29

Progressive CKD

	ACR <10	ACR 10–29	ACR 30–299	ACR ⩾300
eGFR > 105	Ref	Ref	0.4	3.0
eGFR 90–105	Ref	Ref	0.9	3.3
eGFR 75–90	Ref	Ref	1.9	5.0
eGFR 60–75	Ref	Ref	3.2	8.1
eGFR 45–60	3.1	4.0	9.4	57
eGFR 30–45	3.0	19	15	22
eGFR 15–30	4.0	12	21	7.7

4. 處置 (以糖尿病腎病變為主)

DKD 之診斷：臨床上 UACR≥30 mg/g 或 eGFR ＜ 60 mL/min/1.73m^2) 且無其他原發性腎臟疾病通常就可以診斷為 DKD。

表二．糖尿病腎臟疾病人之定期監測和處置

eGFR ($mL/min/1.73\ m^2$)	建議處置
All patients	每年測量 UACR, serum creatinine, potassium
45-60	如果懷疑為非糖尿病引起之腎臟病，轉介至腎臟專科醫師 考慮調整藥物劑量 每 6 個月測 eGFR 至少一年測量 electrolytes, bicarbonate, hemoglobin, calcium, phosphorus 和 para-thyroid hormone 確認 vitamin D sufficiency Hepatitis B virus 疫苗注射 考慮 Bone mineral density (BMD) 測定 營養師指導
30-44	每 3 個月測 eGFR 每 3-6 個月測量 electrolytes, bicarbonate, calcium, phosphorus, parathyroid hormone, hemoglobin, albumin 藥物劑量調整
< 30	轉介腎臟專科

第 **1-3 期**糖尿病腎臟疾病的病人，建議轉介至腎臟專科醫師的 時機如下：

(1) 合併有快速腎損傷時（GFR 每年下降＞ 5 ml/min/1.73m2 ）。
(2) 白蛋白尿（ACR ≧ 300 mg/g）或蛋白尿（PCR ≧ 500 mg/ g）。
(3) 無法解釋的持續性血尿（RBC ＞ 20/HPF）或尿檢發現紅血 球及其他圓柱體。
(4) 合併難以控制的高血壓（服用四種或四種以上的降血壓 藥）。
(5) 持續的血鉀異常。
(6) 遺傳性腎病變。

2019台灣糖尿病腎臟疾病臨床照護指引
2019 Taiwan Clinical Practice Guideline for Diabetic Kidney Disease

2. 糖尿病腎臟疾病

臨床建議	證據等級	臨床建議強度	華人資料
DKD 篩檢： 1. 對象：得病 5 年（含）以上之第 1 型糖尿病人及所有新診斷第 2 型糖尿病人和糖尿病孕婦。 2. 方法：檢測尿液中白蛋白和肌酸酐的比值（urine albumin to creatinine ratio, UACR）與檢驗血清肌酸酐值 (serum creatinine)，並換算成 eGFR。	中	強烈建議	
積極控制血糖可減少或延緩腎病變的發生。	高 ==	強烈建議	
針對大部分糖尿病腎病變病人，血糖控制的目標為糖化血色素在 7.0% 以下。	中	中等建議	
積極治療高血壓可減少或延緩腎病變的發生和惡化。	高	強烈建議	
血壓目標：無白蛋白尿的病人，維持在 140/90 mmHg 以下；有白蛋白尿病人，維持在 130/80 mmHg 以下。	中	中等建議	
尿液白蛋白 / 肌酸酐比值 ≧ 300 mg/g，eGFR<60 mL/min/1.73 m^2 之高血壓者，建議優先使用血管張力素轉換酶抑制劑 (ACEI) 或血管張力素受體拮抗劑 (ARB) ＊。	高	強烈建議	
血壓正常，且尿液白蛋白 / 肌酸酐比值介於 30-299 mg/g 的糖尿病人，可考慮使用血管張力素轉換酶抑制劑 (ACEI) 或血管張力素受體拮抗劑 (ARB) ＊。	低	中等建議	

＊非懷孕者

飲食建議

臨床建議	證據等級	臨床建議強度	華人資料
DKD 病人熱量攝取應與一般人相當，建議 25-35 大卡 / 公斤 / 天，並可依個人活動程度進行調整。	中	中等建議	115
DKD 病人體重及腰圍超過 10% 至 15% 以上，發展成 CKD 風險提高，建議維持理想體重。	中	中等建議	3
建議 DKD 病人之飲食蛋白質攝取量為 0.8 公克 / 公斤 / 天。低蛋白飲食 (<0.8 克 / 公斤 / 天) 是否可延緩糖尿病人腎臟功能惡化仍無明確定論。	中	中等建議	無
DKD 病人未有具體的醣類熱量比例之建議，可依照臨床狀況調整，但精緻糖應該限制在總熱量 10% 以下。	中	中等建議	無
建議含醣食物以全穀類，水果和蔬菜為主。DKD 後期，若發生血磷及血鉀過高，需適當限制高鉀高磷食物份量，並進行低磷和低鉀的飲食衛教。	中	中等建議	無
建議 DKD 病人鈉的攝取量為每天小於 1.5-2.3 公克 (3.75-5.75 g 鹽)，對血壓控制有益，且可能有助於降低蛋白尿風險 。	高	強烈建議	無

KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease

Daily Protein Intake

Protein intake

3.1.13: We suggest lowering protein intake to 0.8 g/kg/day in adults with diabetes (*2C*) or without diabetes (*2B*) and GFR <30 ml/min/ 1.73 m^2 (GFR categories G4-G5), with appropriate education.

3.1.14: We suggest avoiding high protein intake (>1.3 g/kg/day) in adults with CKD at risk of progression. (*2C*)

5.4 其他慢性腎疾病之用藥於糖尿病腎臟疾病之使用

臨床建議	證據等級	臨床建議強度	華人資料
吉多利錠 (Ketosteril®)	中	中	有 [273; 274]
克裏美淨細粒（Kremezin®）	中	中	有 [275]
Pentoxifylline	強	強	有 [242; 276; 277]
重碳酸鹽（Sodium bicarbonate）	中	中	無
紅血球生成素（erythropoietin）	強	強	有 [278]
維生素 D3	中	中	無

- 此藥物被廣泛使用於 **CKD 病人具有蛋白尿時**
- 在國內研臨床照護指引發現此藥物對於 CKD 病人，具有**降蛋白尿**的效果
- 至於糖尿病腎臟疾病，meta-analysis 研究發現，此藥可以降低病人之蛋白尿
- PREDIAN trial 更發現，在原本已經使用 RAAS blocker 的病人，再加上此藥物，可以更減少微白蛋白尿及減少 eGFR 的下降

KDIGO 2022 CLINICAL PRACTICE GUIDELINE FOR DIABETES MANGEMENT IN CHRONIC KIDNEY DISEASE

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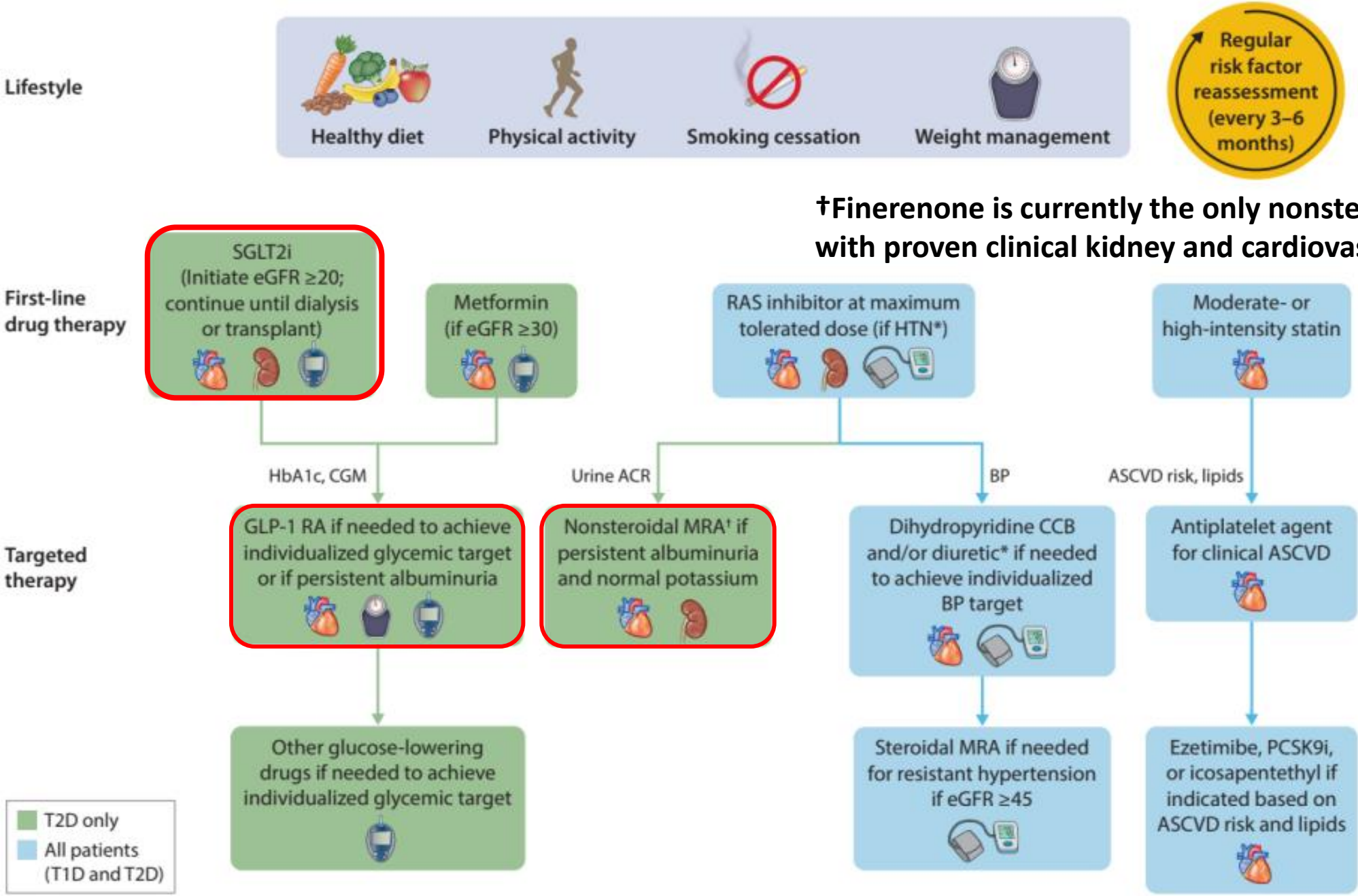
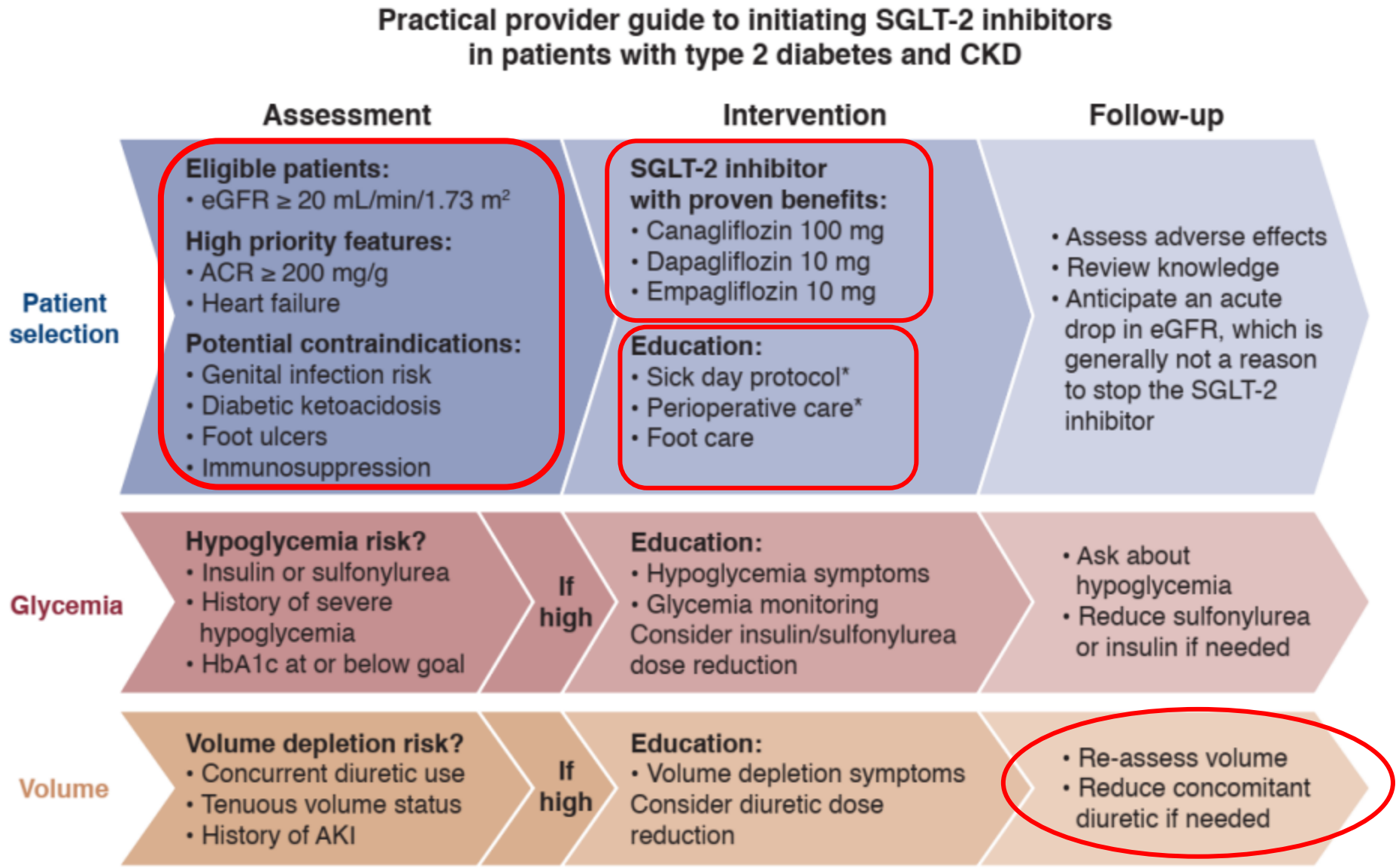
*Figure 2. Holistic approach for improving outcomes in patients with diabetes and CKD**



†Finerenone is currently the only nonsteroidal MRA with proven clinical kidney and cardiovascular benefits.

Figure 6. Practical approach to initiating sodium-glucose transport protein 2 inhibitors (SGLT2i) in patients with T2D and CKD



Sick day protocol & Periprocedural/perioperative care

- Sick day protocol (for illness or excessive exercise or alcohol intake): temporarily withhold sodium-glucose cotransporter 2 inhibitor (SGLT2i), keep drinking and eating (if possible), check blood glucose and blood **ketone** levels more often, and seek medical help early.
- Periprocedural/perioperative care: inform patients about risk of diabetic ketoacidosis**, withhold SGLT2i the day of day-stay procedures and limit fasting to minimum required**, withhold SGLT2i **at least 2 days in advance** and the day of procedures/surgery requiring one or more days in hospital and/or bowel preparation (which may require increasing other glucose-lowering drugs during that time), measure both **blood glucose and blood ketone levels** on hospital admission (proceed with procedure/surgery if the patient is clinically well and ketones are, 1.0 mmol/l), and restart SGLT2i after procedure/surgery only when eating and drinking normally.

HbA1c, hemoglobin A1c; ACR, albumin-creatinine ratio.

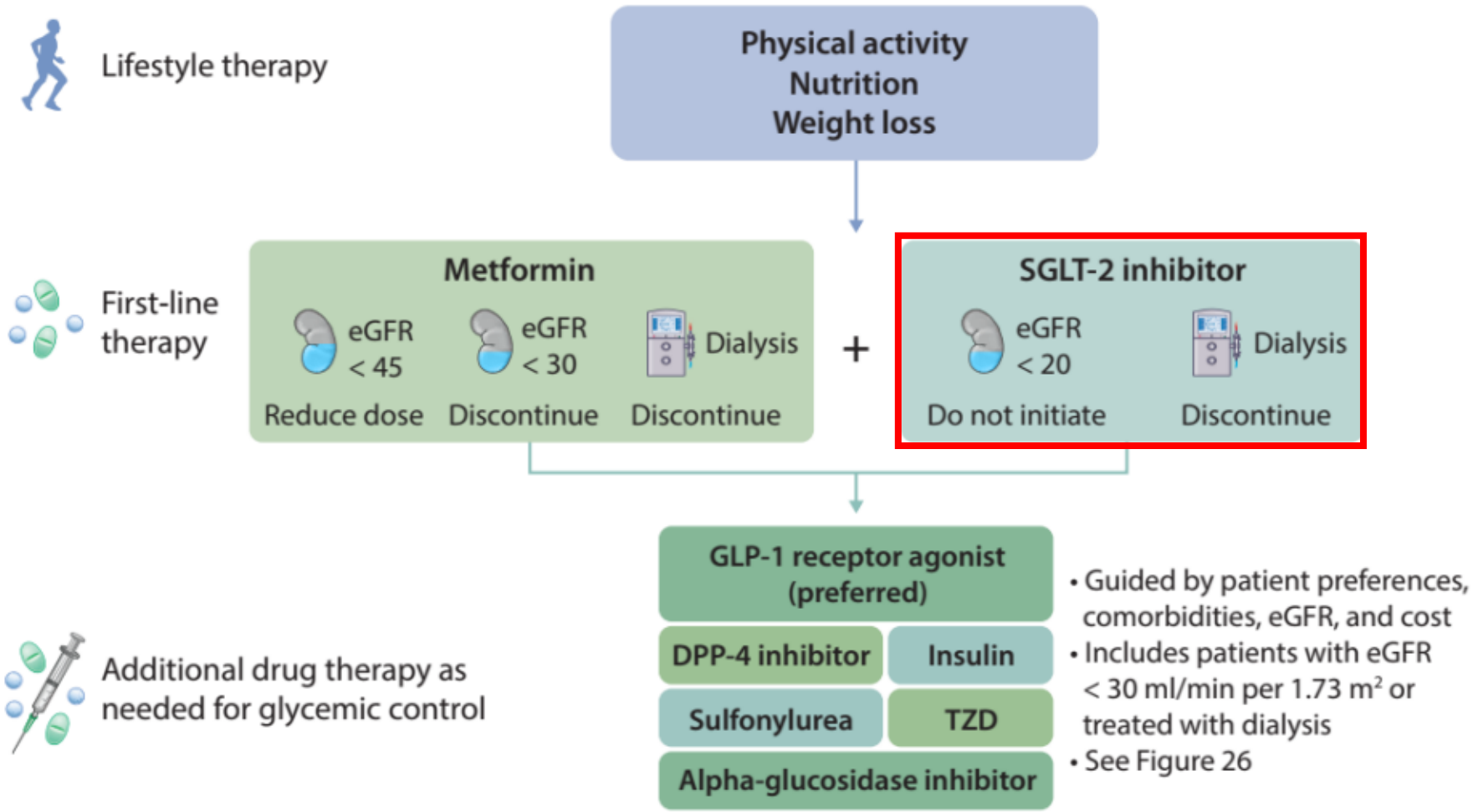
Figure 7. SGLT2i with established kidney and cardiovascular benefits and dose adjustments as approved by the US FDA (take note of country-to-country variation)

SGLT-2 inhibitor	Dose	Kidney function eligible for inclusion in pivotal randomized trials	Dosing approved by the US FDA
Dapagliflozin	10 mg daily	eGFR ≥25 ml/min per 1.73 m^2 in DAPA-CKD eGFR ≥30 ml/min per 1.73 m^2 in DAPA-HF and DECLARE	eGFR ≥25 ml/min per 1.73 m^2
Empagliflozin	10 mg daily (Can increase to 25 mg daily if needed for glucose control)	eGFR ≥30 ml/min per 1.73 m^2 in EMPA-REG eGFR ≥20 ml/min per 1.73 m^2 in EMPEROR-Reduced and EMPEROR-Preserved	eGFR ≥30 ml/min per 1.73 m^2 for T2D and ASCVD for glucose control eGFR ≥20 ml/min per 1.73m^2 for HFrEF
Canagliflozin	100 mg daily (The higher dose of 300 mg is not recommended for CKD)	eGFR ≥30 ml/min per 1.73 m^2 in CREDENCE	eGFR ≥30 ml/min per 1.73 m^2

Chapter 4: Glucose-lowering therapies in patients with type 2 diabetes (T2D) and CKD

Practice Point 4.1: Glycemic management for patients with T2D and CKD should include lifestyle therapy, first-line treatment with metformin and a SGLT2i, and additional drug therapy as needed for glycemic control (Figure 23).

Figure 23. Treatment algorithm for selecting glucose-lowering drugs for patients with T2D and CKD



GLP-1 RA

Practice Point 4.2.1: The choice of GLP-1 RA should prioritize agents with documented cardiovascular benefits.

- the priority would be to use one of the other GLP-1 RA, which have proven cardiovascular and kidney benefit (i.e**., liraglutide, semaglutide [injectable], and dulaglutide**).

Practice Point 4.2.2: To minimize gastrointestinal side effects, start with a low dose of GLP-1 RA, and titrate up slowly (Figure 29).

Practice Point 4.2.3: GLP-1 RA should not be used in combination with dipeptidyl peptidase-4 (DPP-4) inhibitors.

Practice Point 4.2.4: The risk of hypoglycemia is generally low with GLP-1 RA when used alone, but risk is increased when GLP-1 RA is used concomitantly with other medications such as sulfonylureas or insulin. The doses of sulfonylurea and/or insulin may need to be reduced.

Practice Point 4.2.5. GLP-1 RA may be preferentially used in patients with obesity, T2D, and CKD to promote intentional weight loss.

1.2 Renin-angiotensin system (RAS) blockade

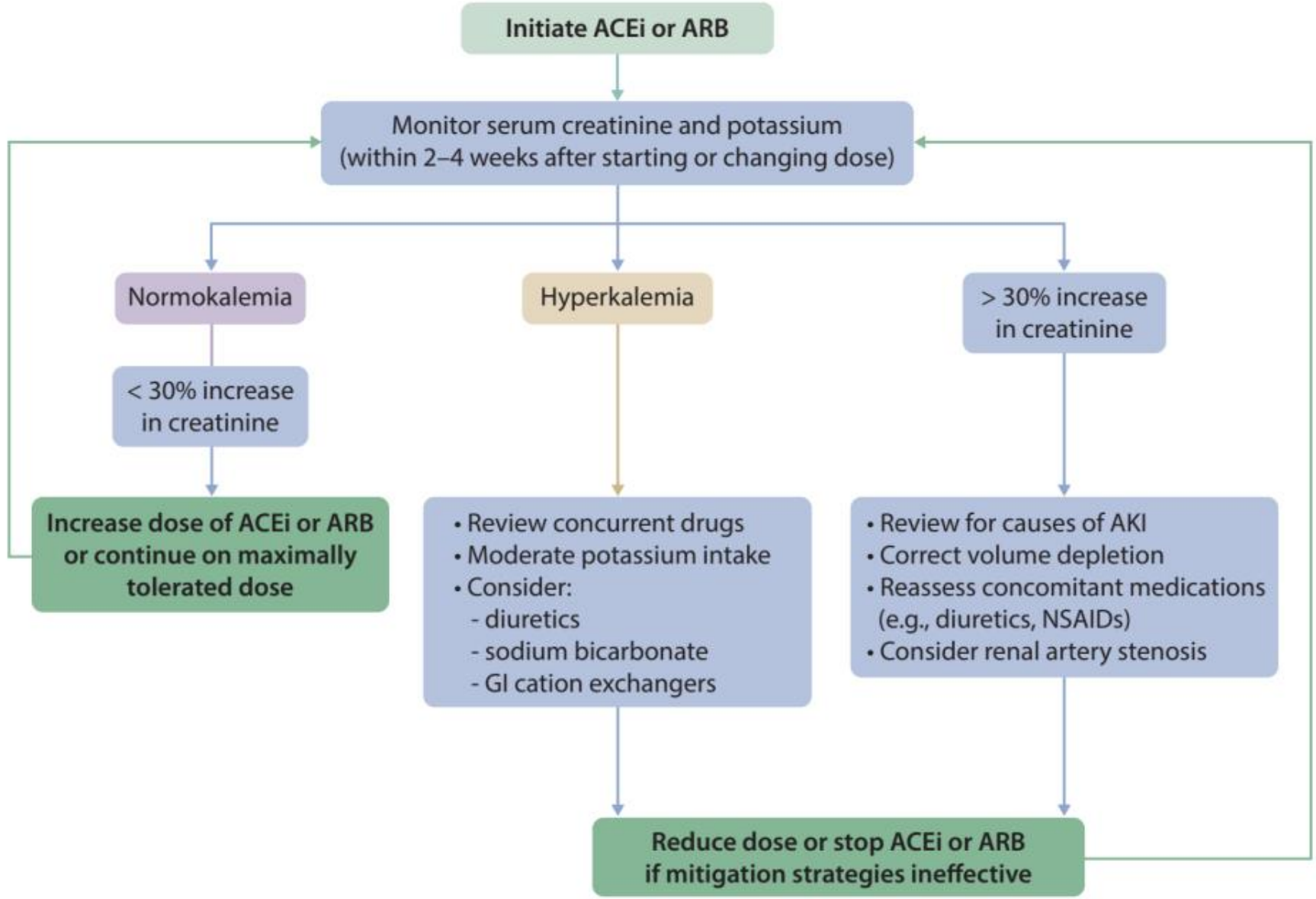
Recommendation 1.2.1: We recommend that treatment with an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin II receptor blocker (ARB) be initiated in patients with diabetes, hypertension, and albuminuria, and that these medications be titrated to the highest approved dose that is tolerated (1B).

Practice Point 1.2.1: For patients with diabetes, albuminuria, and normal blood pressure, treatment with an ACEi or ARB may be considered.

Practice Point 1.2.2: Monitor for changes in blood pressure, serum creatinine, and serum potassium within 2–4 weeks of initiation or increase in the dose of an ACEi or ARB (Figure 4).

Practice Point 1.2.3: Continue ACEi or ARB therapy unless serum creatinine rises by more than 30% within 4 weeks following initiation of treatment or an increase in dose (Figure 4).

Figure 4. Monitoring of serum creatinine and potassium during ACEi or ARB treatment – dose adjustment and monitoring of side effects



ACEi, angiotensin-converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin II receptor blocker; GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug.

Thank you~