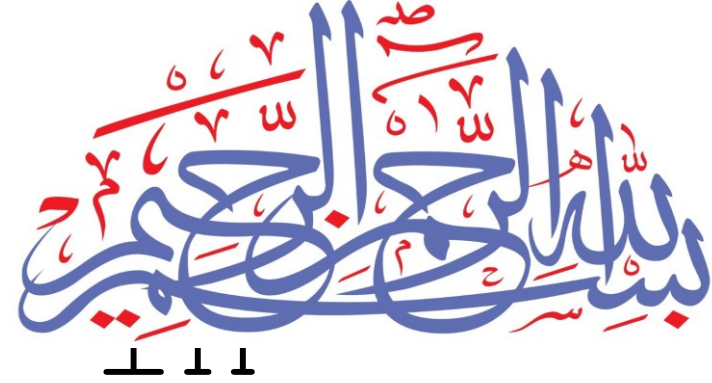
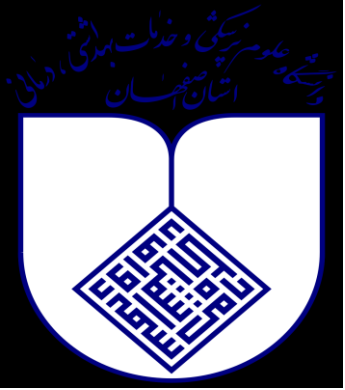


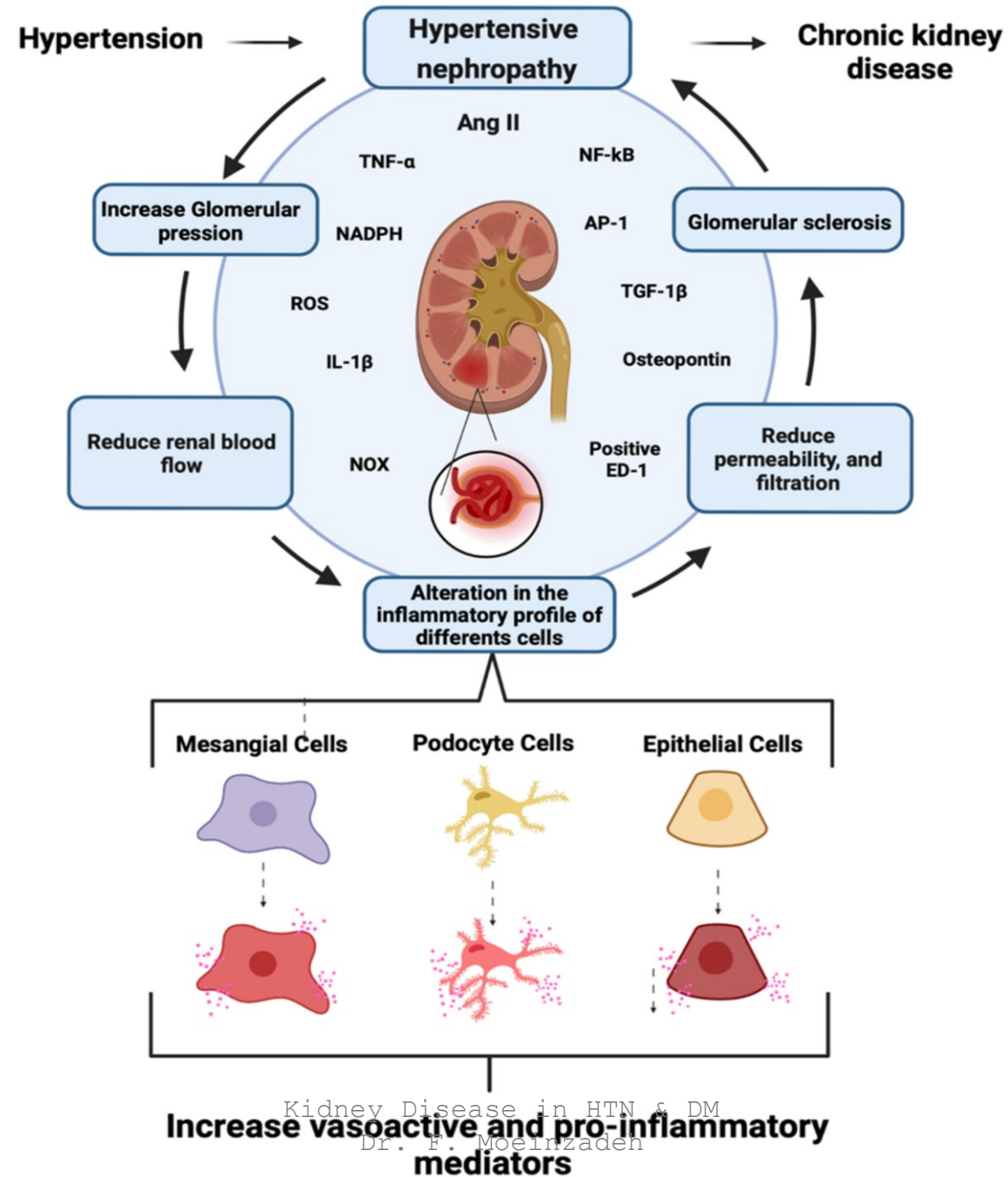


Kidney disorders Diabetes mellitus & Hypertension

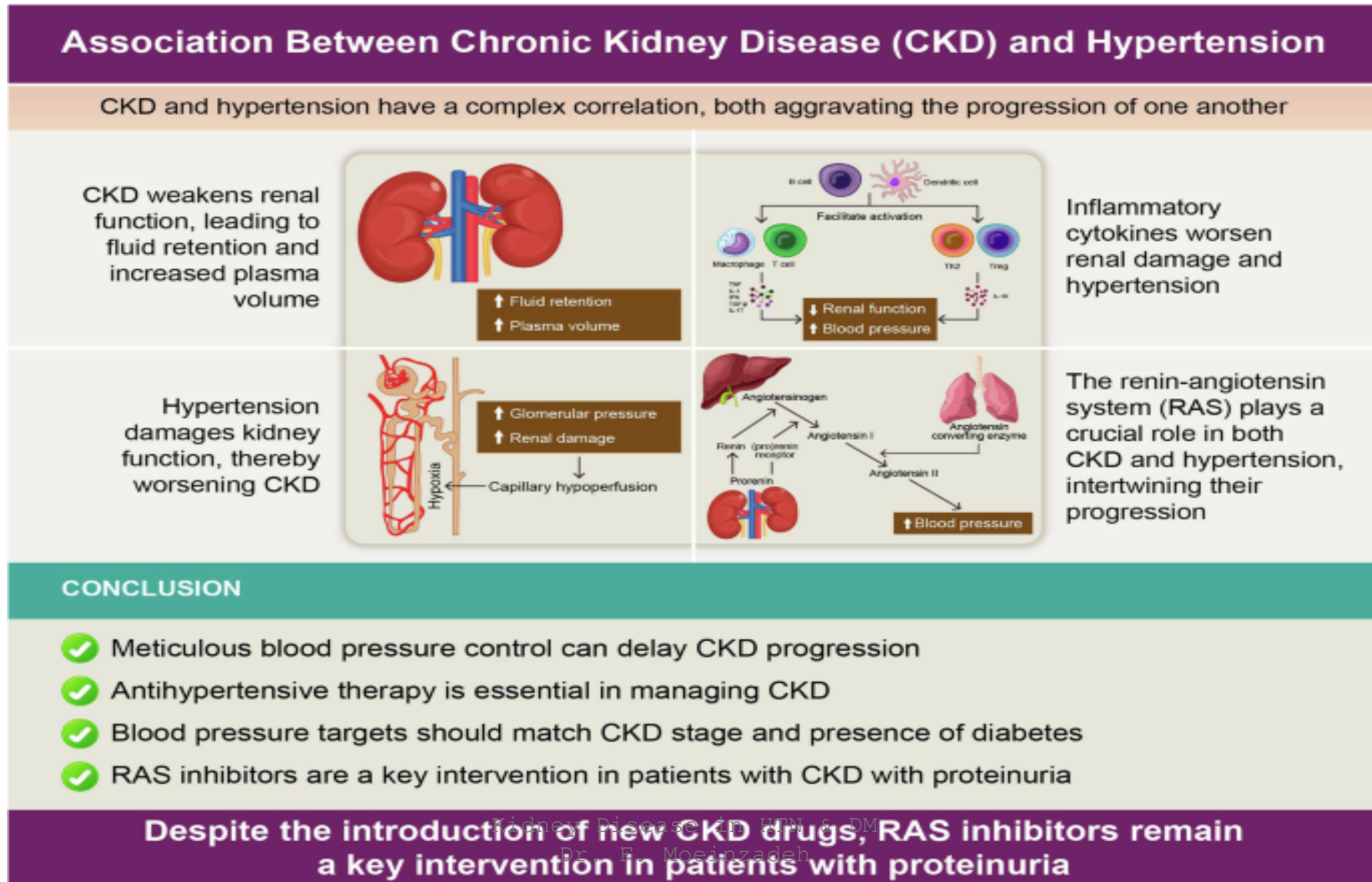
Dr. Firouzeh Moeinzadeh

Associate professor of Nephrology

Isfahan University of Medical Sciences



Hypertension & Kidney diseases



Non-Pharmacological Treatment

- reducing dietary sodium intake to a target of <50 mmol/day (~ 3 g/day of salt) decreased systolic BP by a further ~ 10 mmHg
- restriction to a target <100 mmol/day (~ 6 g/day of salt) has also demonstrated a reduction in proteinuria by $\sim 25\%$

Non-Pharmacological Treatment

- Weight loss is effective in reducing BP and proteinuria and may slow CKD progression
- In overweight patients (body mass index [BMI] >27 kg/m²) with CKD and proteinuria (>1 g/24 h), a mean weight loss of $\sim 4\%$ can reduce proteinuria by $\sim 30\%$

Use of Risk-Based Thresholds for Initiation of BP Treatment in Adults

BP Level-Only

Does the patient have an average BP $\geq 140/90$ mm Hg?

YES

Initiate antihypertensive medications to lower BP and reduce CVD risk for primary or secondary prevention of CVD

1

NO

Risk-Based Thresholds for Initiation of BP Treatment for Adults*

Does the patient have existing clinical CVD (CHD, stroke, HF)?

YES

Initiate antihypertensive medications to lower BP and reduce CVD risk if average SBP ≥ 130 mm Hg or DBP ≥ 80 mm Hg for secondary prevention of CVD

1

NO

Does the patient have diabetes or CKD, or is the patient at increased short-term risk of CVD (10-year PREVENT-CVD risk $\geq 7.5\%^{\dagger}$)?

YES

Initiate antihypertensive medications to lower BP and reduce CVD risk if average SBP ≥ 130 mm Hg or DBP ≥ 80 mm Hg for primary prevention of CVD

1

NO

Initiate antihypertensive medications to lower BP if average SBP ≥ 130 mm Hg or DBP ≥ 80 mm Hg after 3-6 months of lifestyle intervention

1

LEGEND

COR 1

COR 2a

COR 2b

COR 3-No Benefit

COR 3-Harm

(Class of Recommendation)



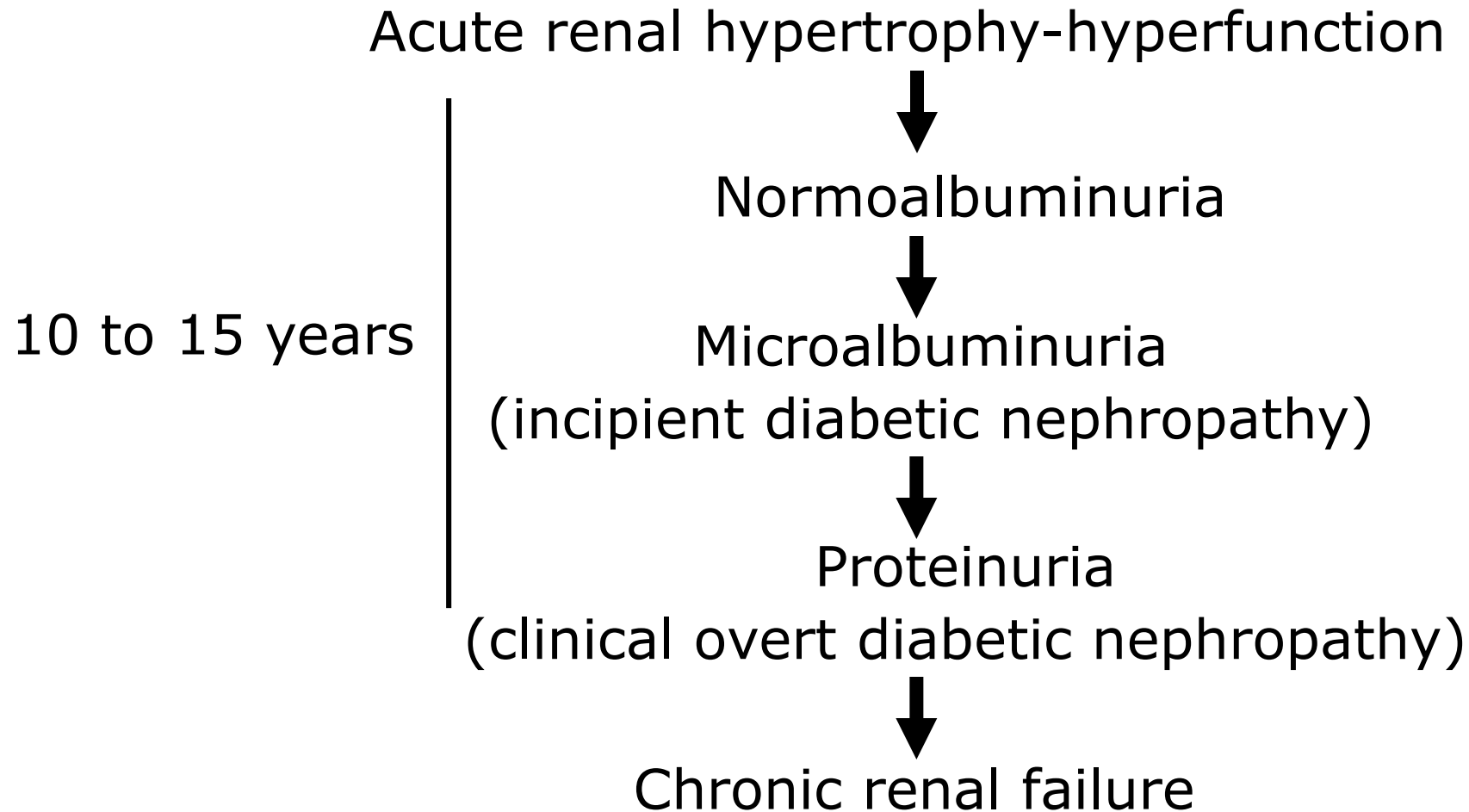
Definition of diabetic kidney disease.

- Approximately 20% to 40% of patients with type 1 or type 2 diabetes mellitus develop diabetic kidney disease
 - Persistent albuminuria (> 300 mg/24 h, or > 300 mg/g creatinine) confirmed in at least 2 of 3 samples
 - A relentless decline in glomerular filtration rate (GFR)

Risk factors

- Poor glycaemic control
- Hyperlipidaemia
- Hypertension
- Genetic predisposition
- Ethnicity
- Long disease duration
- Smoking

Natural history of diabetic nephropathy



Clinical course

- The first clinical sign is moderately increased urine albumin excretion (microalbuminuria: 30–300 mg/24 h, or 30–300 mg/g creatinine; albuminuria grade A2).
- Untreated microalbuminuria will gradually worsen, reaching clinical proteinuria or severely increased albuminuria (albuminuria grade A3) over 5 to 15 years.
- GFR then begins to decline, and without treatment, end-stage renal failure is likely to result in 5 to 7 years

Diagnosis and Detection of Microalbuminuria

- Microalbuminuria: elevation in albumin excretion in 2 of 3 spot urine samples that persists over a three- to six-month period.
- In this period, microalbuminuria should be positive in 2 or more than 2 tests .
- Urinary albumin excretion may be elevated independent of kidney disease by factors such as severe exercise within 24 hours, severe UTI, menstruation, fever, heart failure, and marked hyperglycemia.

Diagnosis and Detection of Microalbuminuria

- 24-hour urine collection: the initial gold standard
- Screening can be more simply achieved by a timed urine collection or measurement of the urine albumin concentration on an early morning
- **Complete collection is often difficult, and so this method is usually restricted to those with established diabetic kidney disease**

Urine albumin-to-creatinine ratio.....

- An untimed urinary sample
- The preferred screening strategy for microalbuminuria in all diabetics.
- It is simple to perform and inexpensive, and repeat values can be easily obtained to ascertain that microalbuminuria, if present, is persistent.

	24h albumin excretion rate	Spot urinary microalbumin	Alb/ Cr ratio
Microalbuminuria	30–299 mg/24h	30–299 mg/L	30–299 mg/g
Macroalbuminuria	□ 300 mg/24h	□ 300 mg/L	□ 300 mg/g

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

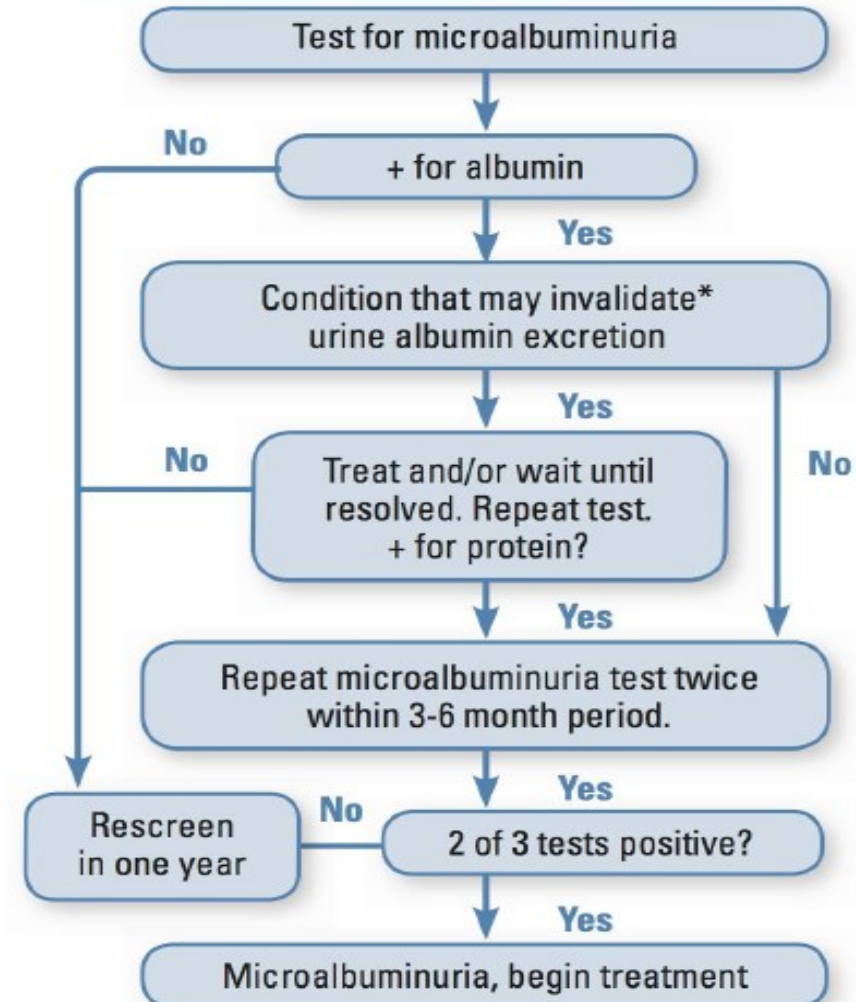
Screening for microalbuminuria in

When?

Begin screening:

- In type 1 diabetes – 5 years after diagnosis, then annually
- In type 2 diabetes – at diagnosis, then annually

How?



Natural history of microalbuminuria in diabetes mellitus.....

- The development of significant albuminuria before 5 years' or after 25 years' duration of T1DM decreases the likelihood of diabetic nephropathy.
- The onset of T2DM is generally unknown, one cannot as reliably use the natural history timeline to assist in diagnosis

Diabetic Nephropathy AND Diabetic Retinopathy

- **95% of patients with T1DM** and DN also have DR, so the **absence of retinopathy may imply a diagnosis other than DN**
- **T2DM:** DR is concordant with DN in only about **60% to 65% of cases;** thus, its absence does not generate a high negative predictive value for the

Treatment of Diabetic Nephropathy

- Cardiovascular risk reduction
- Glycemic control
- BP control
- Inhibition of the RAS

Reduction in protein intake

- Strong evidence indicates that high dietary protein intake increases risk of diabetic Nephropathy & its progression to ESRD.
- Lower intake of proteins has a lower incidence of albuminuria.
- It reduces Hyperfiltration & intraglomerular pressure.
- **ADA** recommends 0.8 gr/kg in **diabetic nephropathy**.

Smoking cessation

- In both type 1 & 2 -It affects **renal Hemodynamics**, increases **Catecholamines** production.
- Patients With DM I & II who smoke have a greater risk of **Urine albuminuria, and progression to ESRD is about twice** as rapid than non-smokers.

Lipid lowering therapy

- **Hypercholesterolaemia** in **progressive glomerular injury**
- Reduction in cholesterol: reduce the rate of decline of GFR
- Reduction of AER in normotensive ,microalbuminuric type 2 diabetic patients has also observed on **statin** therapy.

RAS blockers

- RAS blockade using various drugs, including ACE inhibitors, ARBs, direct renin inhibitors, and mineralocorticoid antagonists.
- RAS inhibition has proved to be the single most effective therapy for slowing the progression of diabetic nephropathy

RAS blockers

- Efficacy of ACEIs independent of BP control in slowing the progression of diabetic nephropathy in patients with T1DM and overt proteinuria.
- Although RAS blockade with more than 1 agent may be effective in reducing proteinuria, **the adverse-event profile** (hyperkalemia, acute kidney injury, and increased cardiovascular events) and no benefit in preventing end-stage kidney disease preclude its general use for the treatment of diabetic nephropathy.

When I use ACEIs/ARBs in diabetic nephropathy?.....

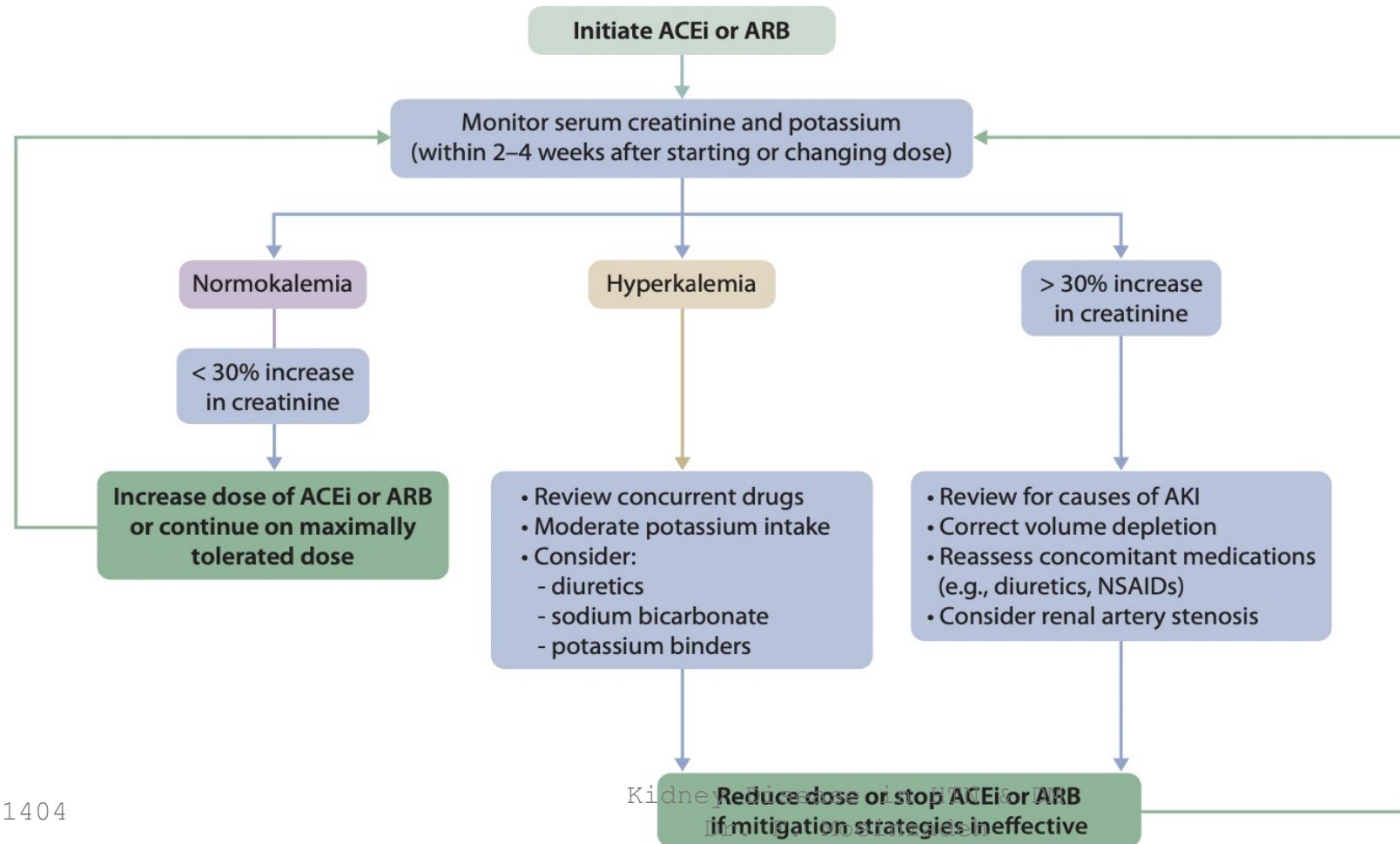
- **There is no evidence that ACE inhibitors or ARBs are effective for the primary prevention of microalbuminuria in patients with type 1 diabetes who are normoalbuminuric and normotensive.**
- These patients should be screened yearly for microalbuminuria after five years and **angiotensin inhibition initiated if persistent microalbuminuria is documented**

When I use ACEIs/ARBs in diabetic nephropathy?

- Studies in normoalbuminuric normotensive patients with type 2 diabetes are fewer but also show no benefit.
- For **normoalbuminuric** patients with type 2 diabetes and **hypertension**, or pre-existing CVD, use of ACE-Is with or without diuretics reduces the absolute risk of developing microalbuminuria by 2-4% over 4-5 years.

- *We suggest using an ACE-I or an ARB in normotensive patients with diabetes and albuminuria levels >30 mg/g who are at high risk of DKD or its progression. (2C)*

Monitoring of serum Cr and K during ACEi or ARB treatment—dose adjustment and monitoring of side effects.



Other considerations

- Most sympathetic blockers and dihydropyridine CCB do not have significant antiproteinuric action despite effective blood pressure reduction, unlike nondihydropyridine CCB.
- Only **diltiazem** and **verapamil** appear to be as consistently **effective** as an **ACE** inhibitor or **ARB** in lowering protein excretion in diabetic patients

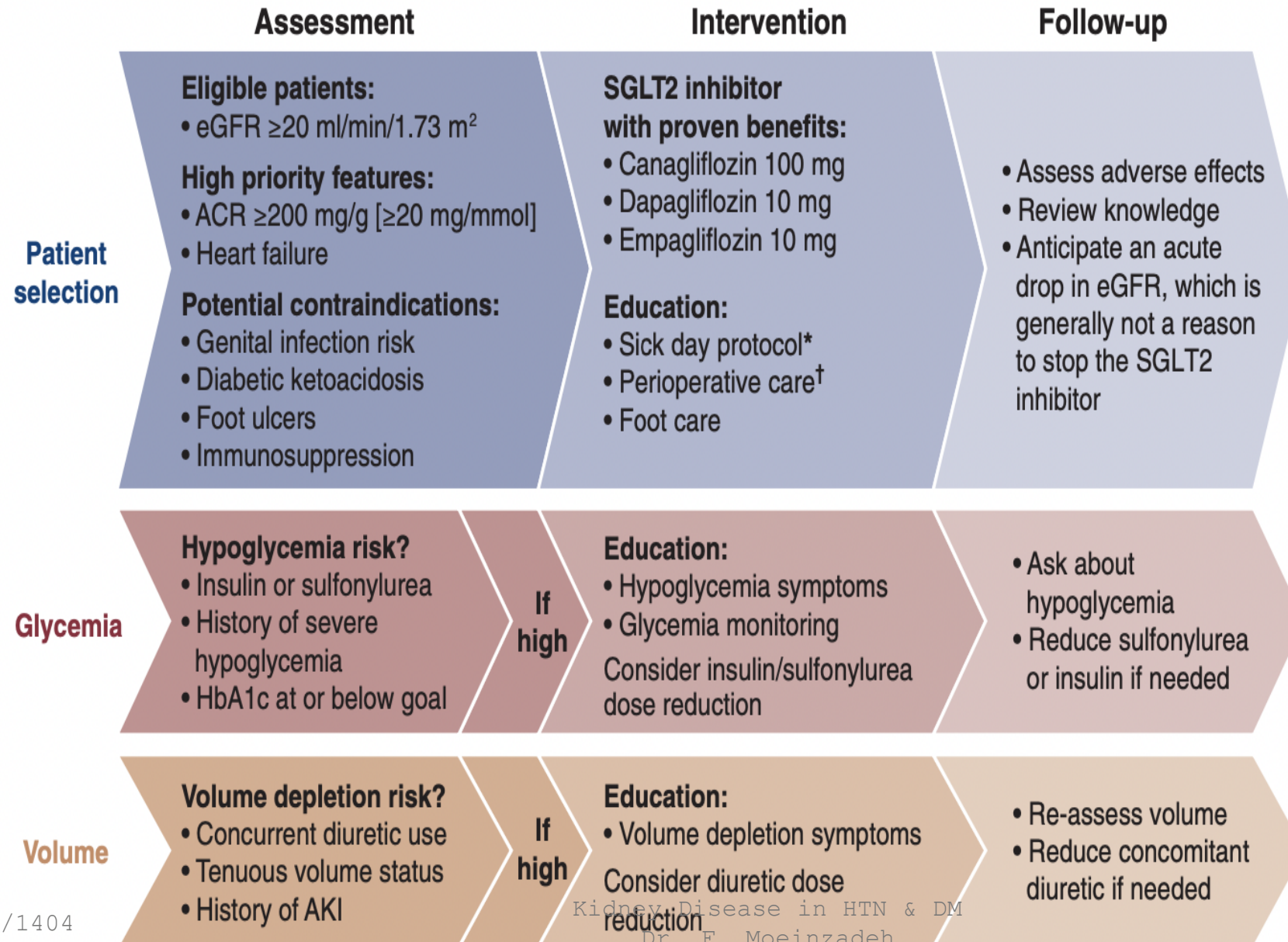
Other considerations

- Aldosterone antagonists appear to reduce proteinuria when used alone, and to have an **additive** effect on proteinuria when used in combination with an **ACE inhibitor** or an **ARB** in both type 1 and type 2 diabetes.

Sodium glucose transporter 2 inhibitors

- SGLT2 inhibitors have also been suggested to have **favorable renal effects** in addition to lowering of glucose.
- They **lower blood pressure, albuminuria and body weight**.
- **Hyperfiltration** was ameliorated with **empagliflozin** in type 1 diabetes and may be very important for the potential renoprotective effect of this class of agents .

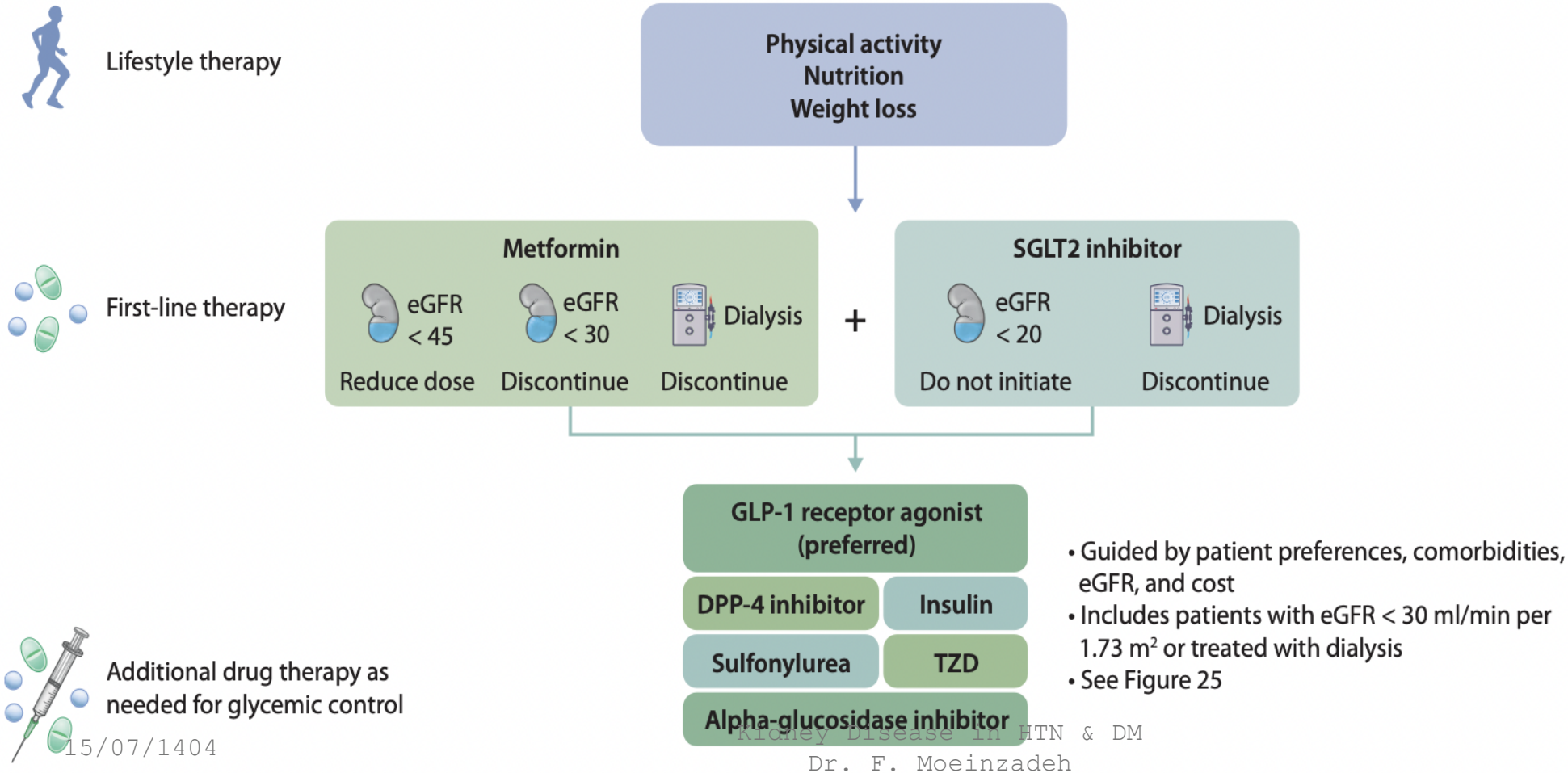
Practical provider guide to initiating SGLT2 inhibitors in patients with type 2 diabetes and CKD



SGLT2Is

- A reversible decrease in the eGFR with commencement of SGLT2i treatment may occur and is generally not an indication to discontinue therapy.
- Once an SGLT2i is initiated, it is reasonable to continue an SGLT2i even if the eGFR falls below 20 ml/min per 1.73 m², unless it is not tolerated or kidney replacement therapy is initiated.

Glucose-lowering therapies in patients with T2D and CKD



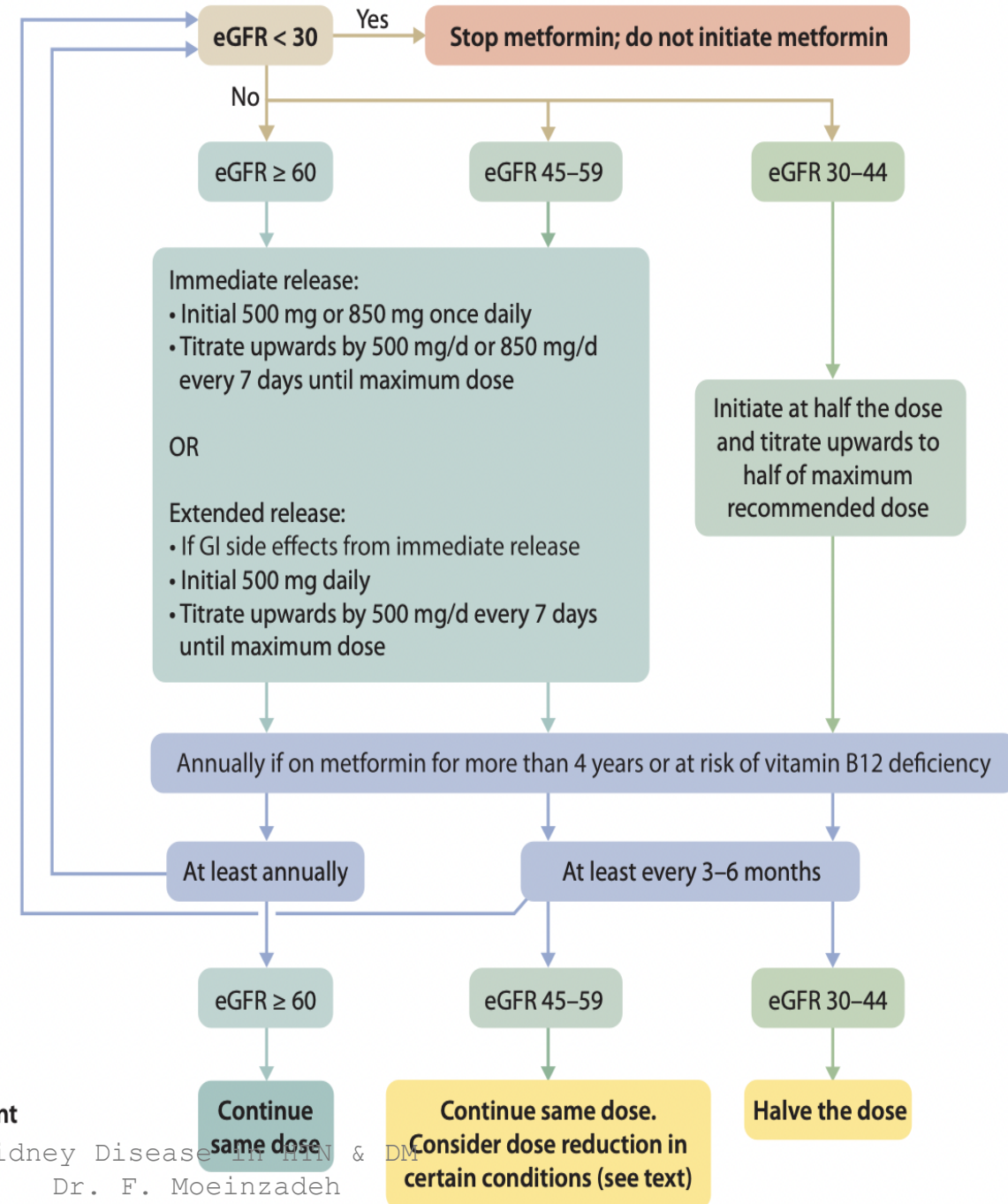
Suggested approach in dosing metformin based on the level of kidney function

Dose initiation

Monitor vitamin B12

Monitor kidney function

Subsequent dose adjustment



Dose adjustments for eGFR <45 ml/min/1.73 m²

	Stage 3b (eGFR 30–44 mL/min/1.73 m ²)	Stage 4 (eGFR 15–29 mL/min/1.73 m ²)	Stage 5 (eGFR <15 mL/min/1.73 m ²)
Metformin	Reduce dose to 1000 mg/day	Contraindicated	
Insulin	Initiate and titrate conservatively to avoid hypoglycemia		
SGLT2 inhibitors*			
Canagliflozin	Maximum 100 mg daily	Initiation not recommended; may continue 100 mg daily if tolerated for kidney and CV benefit until dialysis	
Dapagliflozin	10 mg daily [†]	Initiation not recommended with eGFR <25 mL/min/1.73 m ² ; may continue if tolerated for kidney and CV benefit until dialysis	
Empagliflozin	10 mg daily [†]	Initiation not recommended with eGFR <20 mL/min/1.73 m ² ; may continue if tolerated for kidney and CV benefit until dialysis	
Ertugliflozin	Use not recommended with eGFR <45 mL/min/1.73 m ²		
GLP-1 receptor agonists [§]			
Exenatide	Caution initiating or increasing dose; avoid once-weekly formulation	Use not recommended	
Dulaglutide	No dose adjustment required		
Liraglutide	No dose adjustment required		
Lixisenatide	No dose adjustment required	Use not recommended	
Semaglutide	No dose adjustment required		
DPP-4 inhibitors			
Alogliptin	Maximum 12.5 mg daily	Maximum 6.25 mg daily	
Linagliptin	No dose adjustment required		
Saxagliptin	Maximum 2.5 mg daily		
Sitagliptin	Maximum 50 mg daily	Maximum 25 mg once daily	
Sulfonylureas (2nd generation)			
Glimepiride	Initiate conservatively at 1 mg daily and titrate slowly to avoid hypoglycemia		
Glipizide	Initiate conservatively (e.g., 2.5 mg once daily) and titrate slowly to avoid hypoglycemia		
Glyburide	Use not recommended		
Thiazolidinediones			
Pioglitazone	No dose adjustment required		
α-Glucosidase inhibitors			
Acarbose	No dose adjustment required	Use not recommended	
Miglitol	No dose adjustment required	Use not recommended	

36

Dr. F. M.