PATHOGENESIS OF DIABETIC KIDNEY DISEASE

1. **Genetic and Environmental Factors**

- Only 30% to 40% of patients with type 1 or type 2 diabetes will ultimately develop nephropathy.
- The frequency is only 17% if there is a first-degree relative with diabetes but without nephropathy

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PATHOGENESIS OF DIABETIC KIDNEY DISEASE

2. **Hemodynamic Changes**

- *Hyperfiltration is commo*n and so Increased GFR involves glucose-dependent effects causing afferent arteriolar dilation, mediated by a range of vasoactive mediators, including (IGF-1), (TGF-β1), vascular endothelial growth factor (VEGF), nitric oxide (NO), prostaglandins, and glucagon.
- Shear stress increases glucose transport into mesangial cells by upregulation of specific glucose transporters and trigger autocrine and paracrine release of cytokines and growth factors in the glomerulus.

PATHOGENESIS OF DIABETIC KIDNEY DISEASE

- Hyperfiltration increases the colloid osmotic pressure in postglomerular capillaries, facilitating reabsorption of sodium in the proximal tubule.
- Angiotensin II also appears to have a role, causing hypertrophic proximal tubular growth and increased sodium reabsorption.
- Specific inhibition of the sodium-glucose cotransporter 2 (SGLT2) in proximal tubular cells is associated with reduced progression of diabetic kidney disease.

PATHOGENESIS OF DIABETIC KIDNEY DISEASE

3. **Renal Hypertrophy and Mesangial Matrix Expansion**

- Renal growth occurs early after the onset of diabetes.
- Mesangial cells proliferation and hypertrophy
- Tubular epithelial cells proliferation and hypertrophy.
- Hyperglycemia causes hypertrophy by stimulating growth factors in the kidney, including IGF-1, epidermal growth factor (EGF), platelet-derived growth factor (PDGF), VEGF, TGF-β, and Ang II and thrombospondin, a potent activator of latent TGF-β.
- inhibition of VEGF prevented glomerular hypertrophy in models of DKD and reduced albuminuria.

PATHOGENESIS OF DIABETIC KIDNEY DISEASE

4. **Inflammation and Diabetic Kidney Disease**

- Glomerular and interstitial infiltration by monocytes/macrophages and activated T lymphocytes are observed both in human and experimental DKD.
- Chemokines and their receptors, in particular monocyte chemotactic protein-1 (MCP-1/CCL2), RANTES/CCL5, IL-6, and TNF receptors, as well as adhesion molecules (e.g., ICAM-1), seem to contribute to this.

PATHOGENESIS OF DIABETIC KIDNEY DISEASE

5. **Mechanisms Underlying Proteinuria**

- Accumulation of type IV collagen and net reduction in negatively charged heparin sulfate proteoglycan in GBM.
- The expression of one permeability-controlling protein, nephrin, is abnormally low in DN.
- Apoptosis of podocytes is triggered by various factors, including Ang II and TGF-β.
- Adiponectin levels are low in patients with type 2 diabetes, which may contribute to development of albuminuria.

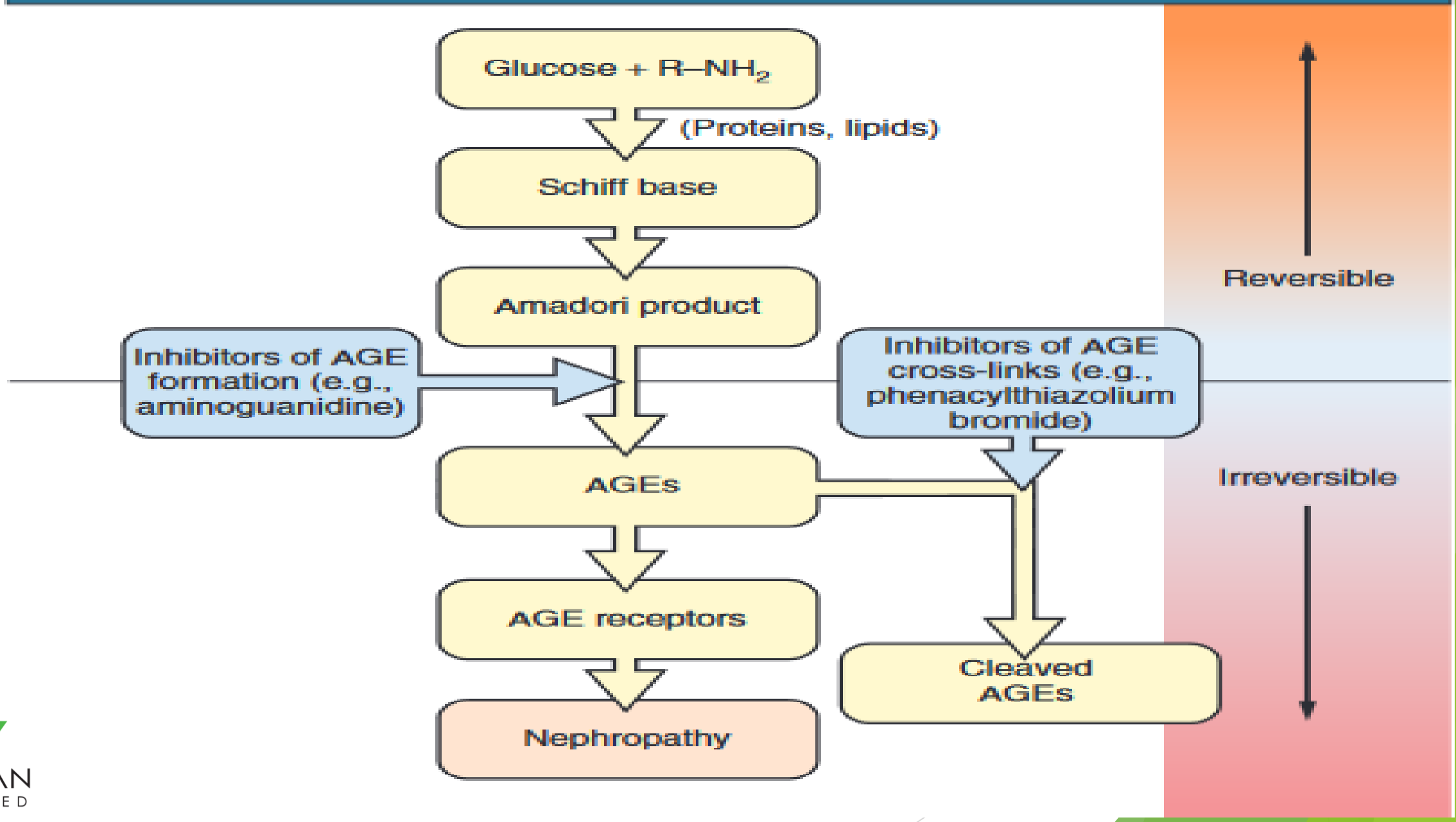
Hyperglycemia and Diabetic Kidney Disease

- remarkable reduction in progression of microvascular complications, specifically retinopathy, in patients with type 1 diabetes with tight glycemic control.
- Euglycemia that followed isolated pancreatic transplantation was associated with regression of diabetic glomerulosclerosis after 10 years.
- HbA1clevel of 6.5% was associated with a long-term reduction in ESRD

Hyperglycemia induced pathways

1. Protein kinase C pathway
2. Advanced glycation end products pathway
3. Polyol pathway
4. Hexosamine pathway
5. Adenosine monophosphate kinase
6. Kallikrein-kinin pathway
7. Activation of innate immunity

Formation of Advanced Glycation End-Products



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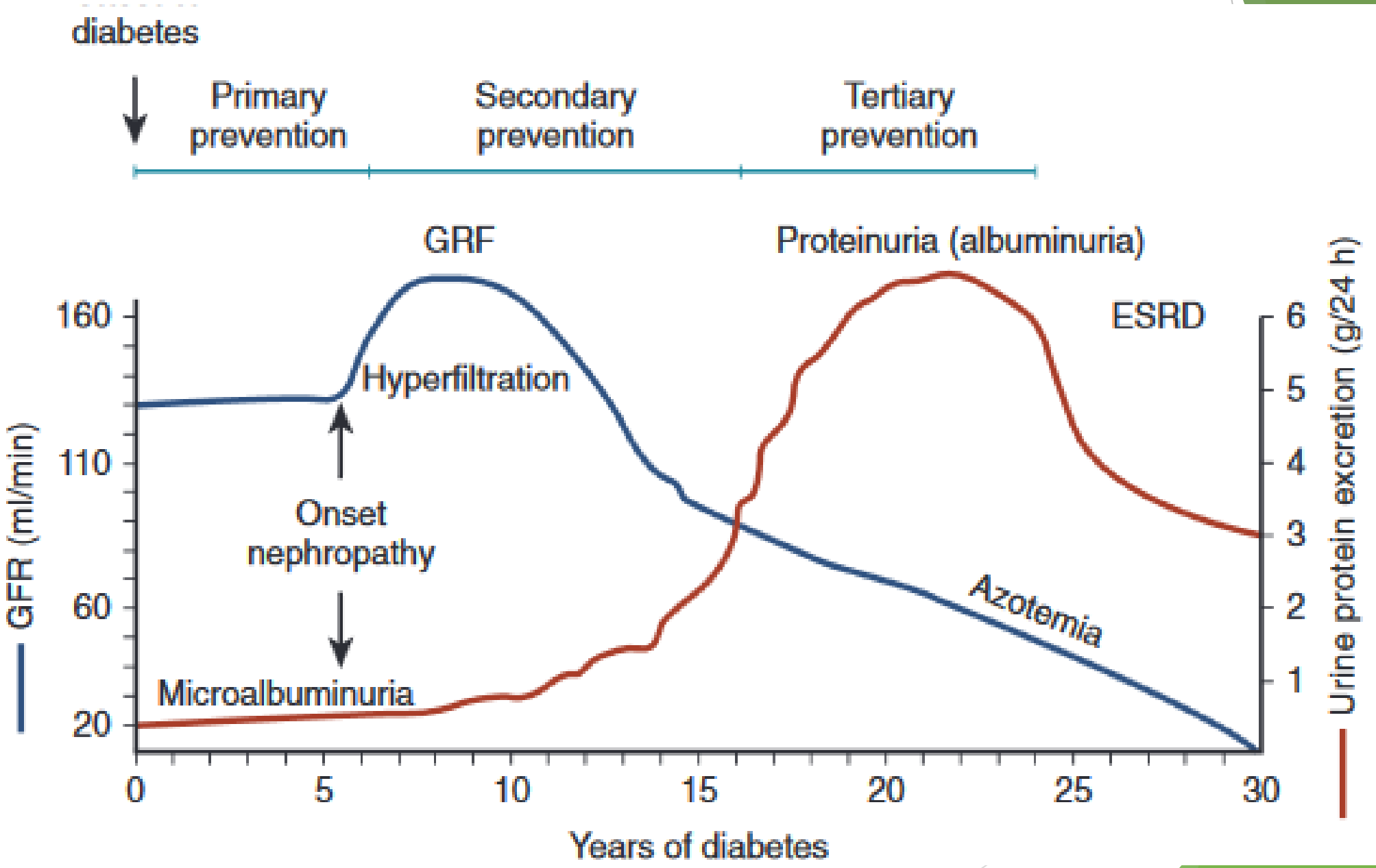
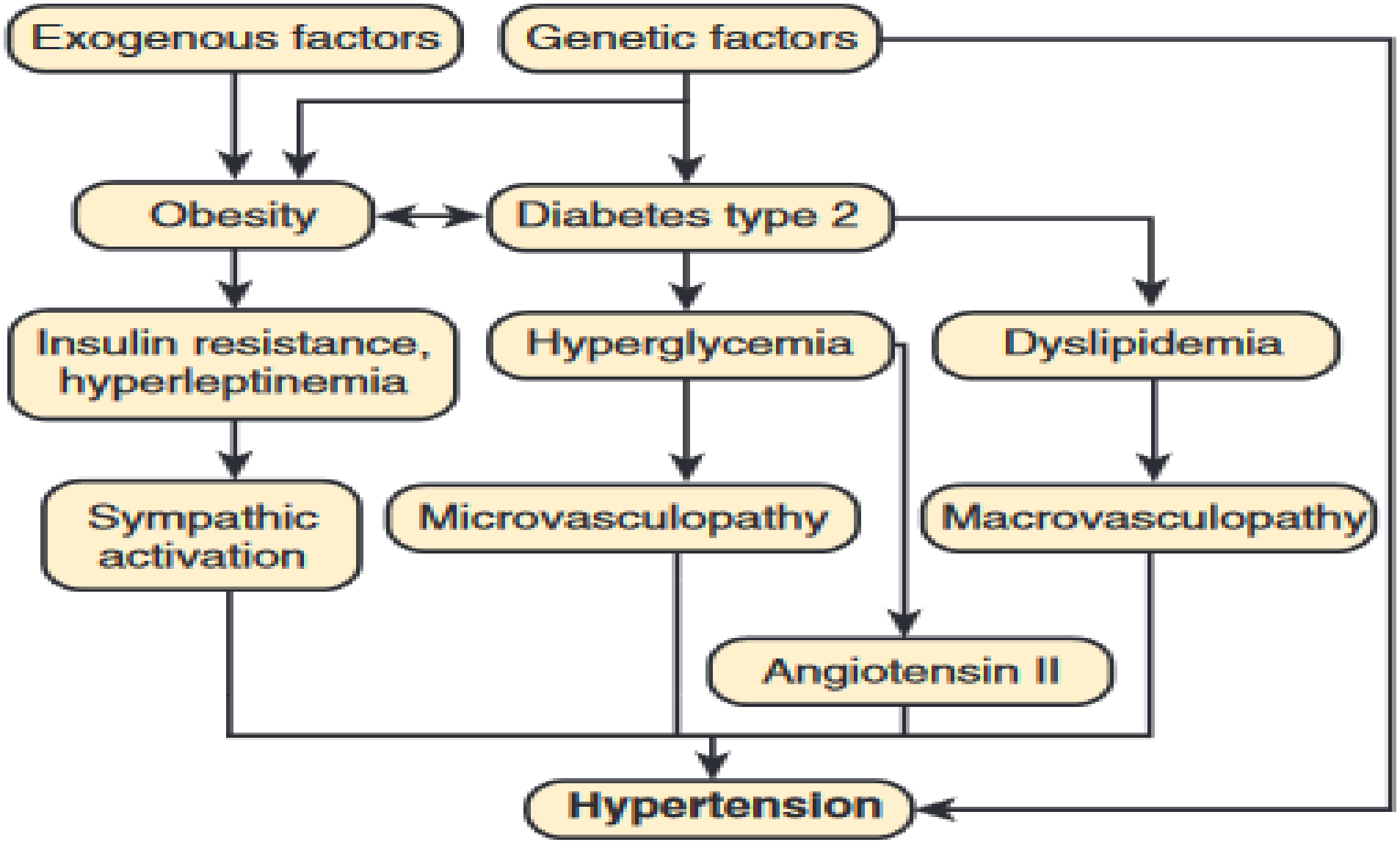
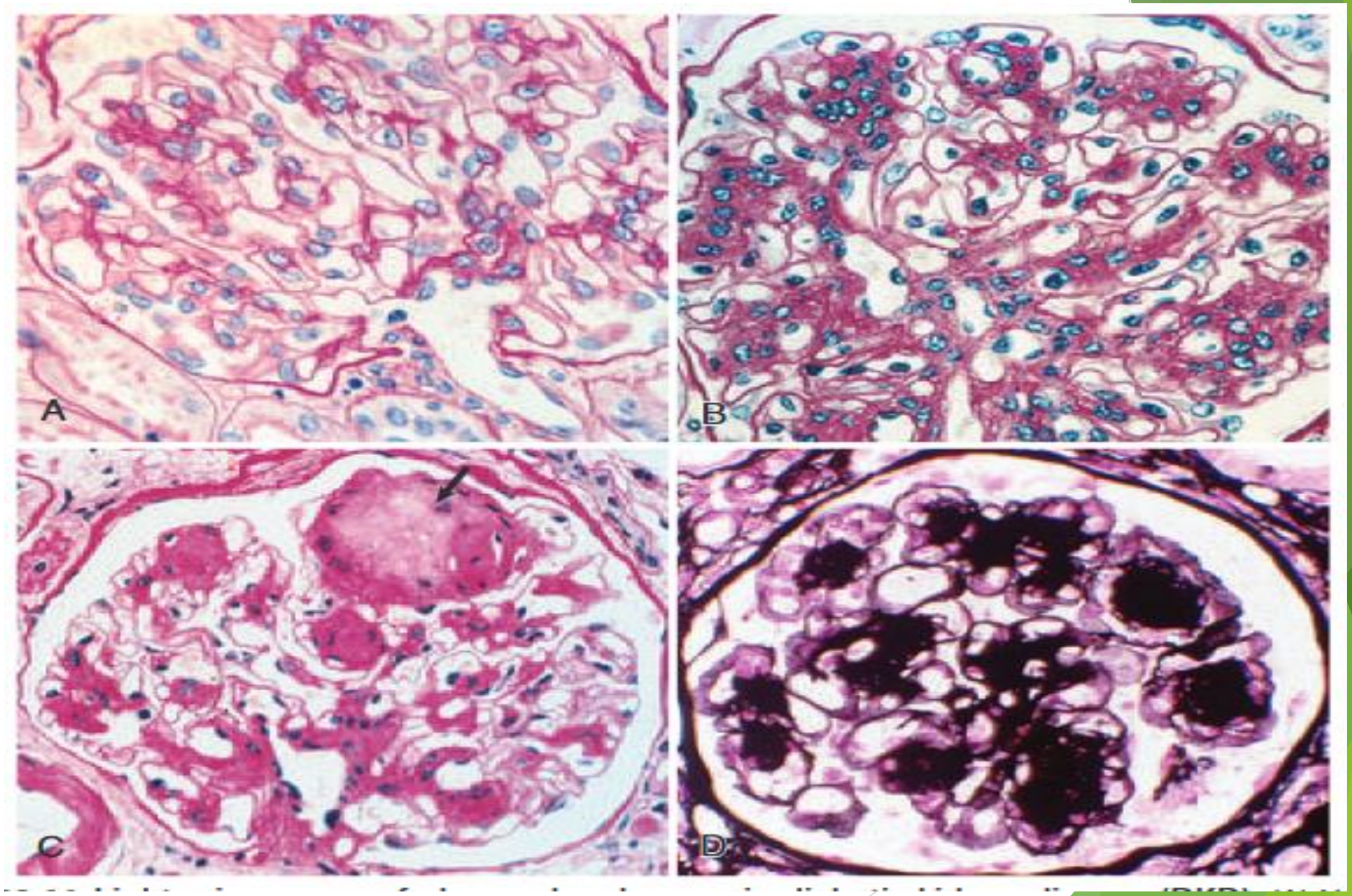

diabetes
Primary prevention
Secondary prevention
Tertiary prevention
GRF
Proteinuria (albuminuria)
ESRD
Hyperfiltration
Onset nephropathy
Microalbuminuria
Azotemia
GFR (ml/min)
160
110
60
20
Urine protein excretion (g/24 h)
6
5
4
3
2
1
0
5
10
15
20
25
30
Years of diabetes

Potential Mechanisms Leading to Hypertension in Type 2 Diabetics




A
B
C
D

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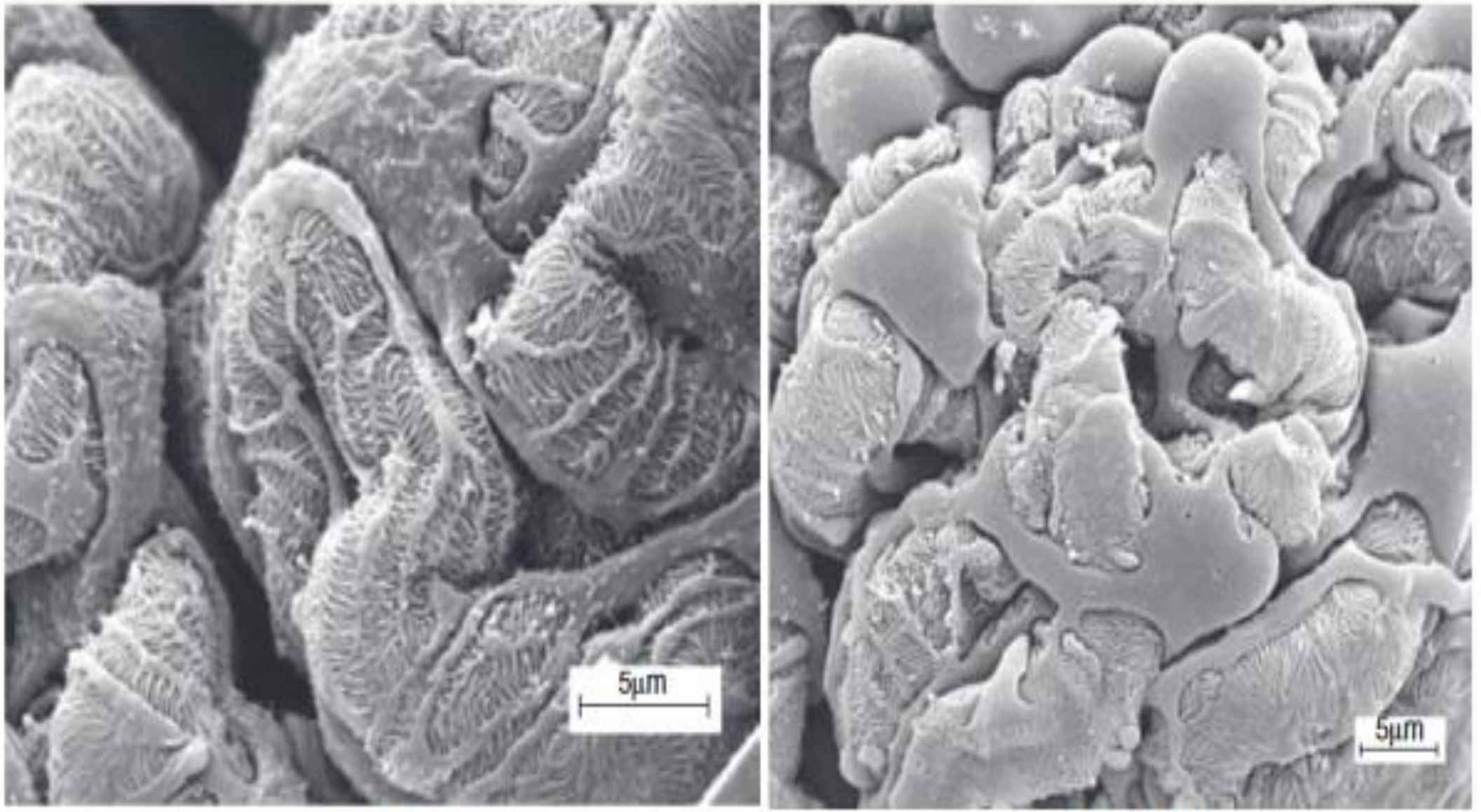
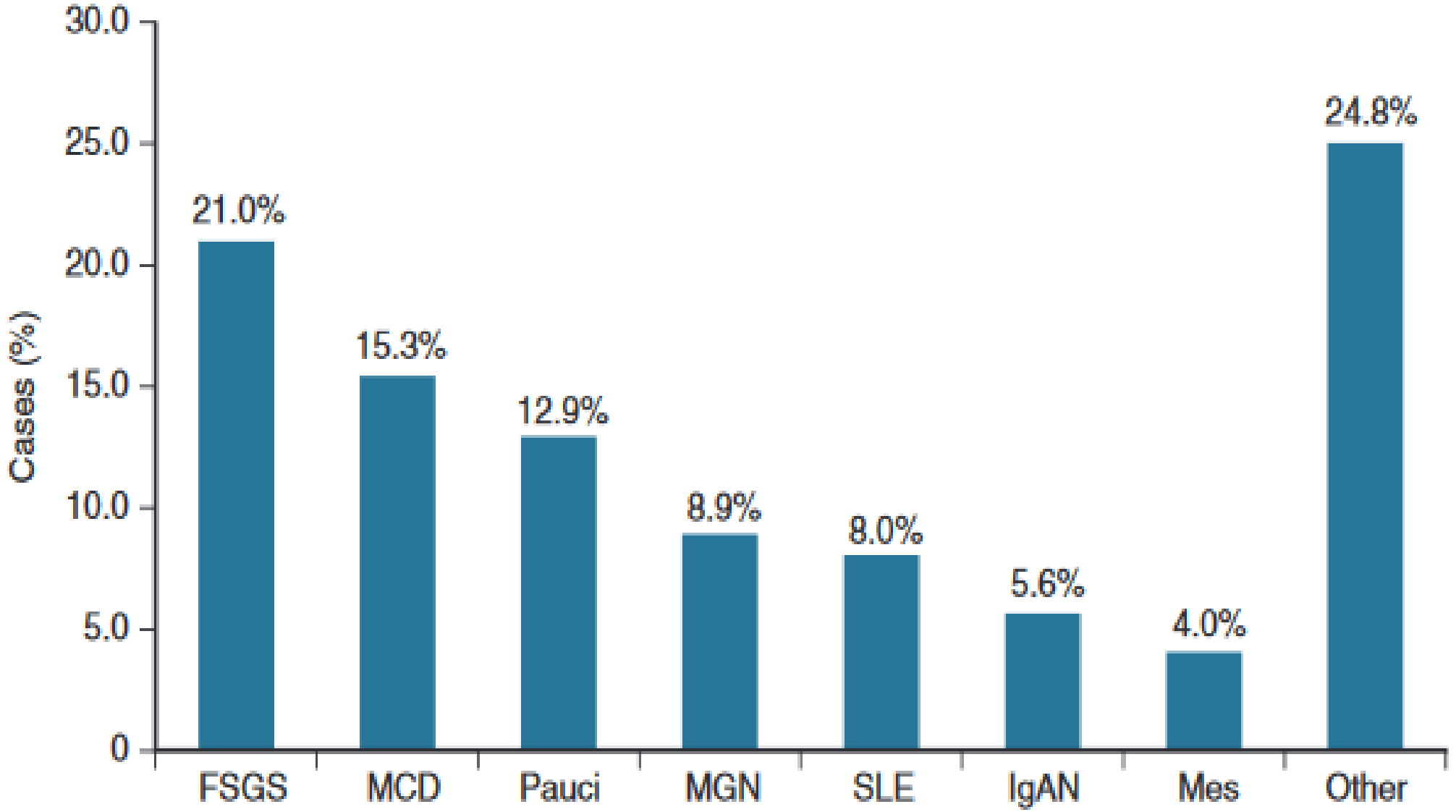


Normal Rat

Diabetic Rat

Pathologic Diagnoses Other Than Diabetic Nephropathy

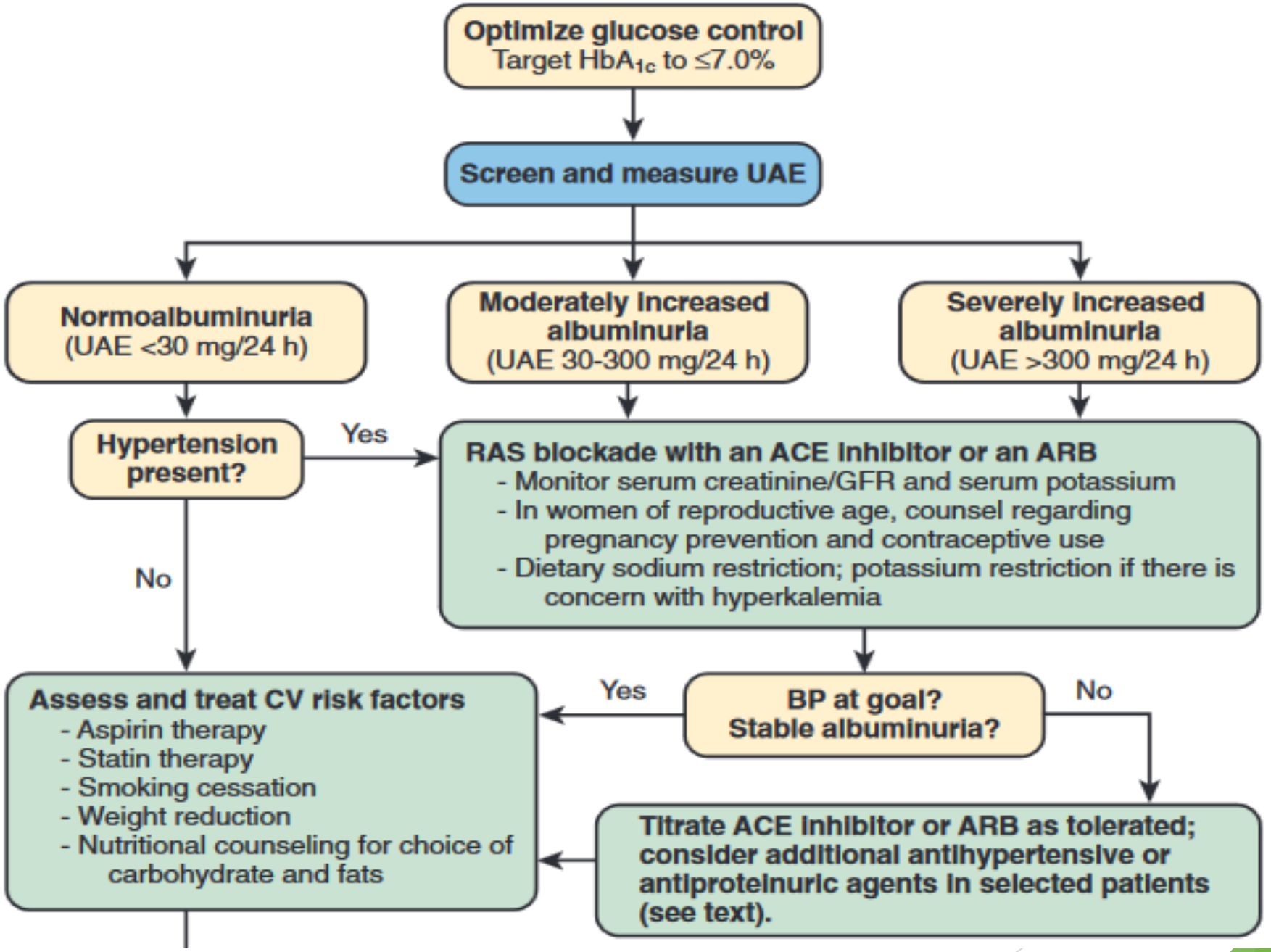


Approach to the Diabetic Patient With Impaired Renal Function

- Assess the cause of CKD (acute vs. chronic renal impairment; DKD vs. alternative causes of renal damage).
- Assess the magnitude of proteinuria and the rate of progression.
- Search for evidence of the typical extrarenal microvascular and macrovascular complications of diabetes.

Treatment Targets

- Stable GFR
- Stable albuminuria or normoalbuminuria
- Blood pressure to <140/90 mm Hg (<130/80 mm Hg if patient has severely increased albuminuria or is at high risk of stroke)
- HbA1c to ≤7.0% - BMI ≤25 kg/m2


Optimize glucose control
Target HbA1c to ≤7.0%
Screen and measure UAE
Normoalbuminuria
(UAE <30 mg/24 h)
Moderately increased albuminuria
(UAE 30-300 mg/24 h)
Severely increased albuminuria
(UAE >300 mg/24 h)
Hypertension present?
Yes
No
RAS blockade with an ACE inhibitor or an ARB
- Monitor serum creatinine/GFR and serum potassium
- In women of reproductive age, counsel regarding pregnancy prevention and contraceptive use
- Dietary sodium restriction; potassium restriction if there is concern with hyperkalemia
BP at goal? Stable albuminuria?
Yes
No
Assess and treat CV risk factors
- Aspirin therapy
- Statin therapy
- Smoking cessation
- Weight reduction
- Nutritional counseling for choice of carbohydrate and fats
Titrate ACE inhibitor or ARB as tolerated; consider additional antihypertensive or antiproteinuric agents in selected patients (see text).

Antihyperglycemic Therapeutic Options

- Sodium glucose cotransporter-2 (SGLT2) inhibitors
- Dipeptidyl peptidase-4 inhibitors (DPP4i)
- Glucagon-like peptide-1 (GLP-1) analogues
- This drugs have expanded the options to control glycemia and BP in patients with type 2 diabetes and improve CV and/or renal outcomes.

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SGLT2 Inhibitors

- Empagliflozin, dapagliflozin, and canagliflozin, are now widely approved antihyperglycemic therapies with a glycosuric mechanism.
- SGLT2 inhibitors induce osmotic diuresis and have natriuretic effects contributing to plasma volume contraction.
- They decrease systolic and diastolic BP by 4 to 6/1 to 2 mm Hg, respectively.
- They also decrease weight.
- SGLT2 inhibition is associated with an acute, dose-dependent reduction in eGFR by approximately 5 ml/min/1.73 m2 and approxi-mately 30% to 40% reduction in albuminuria.

- Glycosuric effects are attenuated in patients with CKD (eGFR <60 ml/min/1.73 m2) but BP, eGFR, and albuminuria lowering effects are preserved.
- Proximal tubular natriuresis activates renal tubuloglomerular feedback through increased macula densa sodium and chloride delivery, leading to afferent vasomodulation.

Daily Dosing for Oral Hypoglycemic Agents

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Class	Drug	CKD1 and 2	CKD3	CKD4	CKD5	Dialysis
Biguanide	Metformin	No adjustment	850-1500 mg	500 mg	Awaiting further data	Awaiting further data
Sulfonylureas:						
First generation	Tolazamide	Avoid	Avoid	Avoid	Avoid	Avoid
	Tolbutamide	250 mg daily-tid	250 mg daily-tid	250 mg daily-tid	Avoid	Avoid
Second generation	Gliclazide	Low dose and titrate every 1-4 wk	Low dose and titrate every 1-4 wk	Low dose and titrate every 1-4 wk	Low dose and titrate every 1-4 wk	Low dose and titrate every 1-4 wk
	Glipizide	No adjustment	No adjustment	No adjustment	No adjustment	No adjustment
	Glimeprimide	Reduce to 1 mg	Reduce to 1 mg	Reduce to 1 mg	Avoid	Avoid
α-Glucosidase inhibitors	Acarbose	No adjustment	No adjustment	Lowest dose <50 mg	Lowest dose <50 mg	Lowest dose <50 mg
Meglitinides	Repaglinide	No adjustment	No adjustment	No adjustment	Limited experience	Limited experience
	Nateglinide	No adjustment	No adjustment	No adjustment	Start at 60 mg	Avoid
Gliptins (DPP-4 inhibitors)	Linagliptin	No adjustment	No adjustment	No adjustment	No adjustment	No adjustment
	Sitagliptin	No adjustment	Reduce to 50 mg	Reduce to 25 mg	25 mg	25 mg
	Saxagliptin	No adjustment	Reduce to 2.5 mg	2.5 mg	2.5 mg	2.5 mg
Thiazolidinediones	Pioglitazone	No adjustment	No adjustment	No adjustment	No adjustment	No adjustment
Amylin analogue	Pramlintide	No adjustment	No adjustment	No adjustment	Dose reduction, awaiting further data	Awaiting further data
Incretin mimetics (GLP-1 analogues)	Exenatide	No adjustment	Reduce to 5 mcg	Avoid	Avoid	Avoid
	Liraglutide	Limited experience	Limited experience	Limited experience	Limited experience	Limited experience
SGLT-2 inhibitors	Canagliflozin	Reduced efficacy	Careful monitoring	Careful monitoring	Avoid	Avoid
	Empagliflozin/ Dapagliflozin	Limited experience	Limited experience	Limited experience	Limited experience	

1. Biguanides: Metformin is an insulin sensitizer that decreases hepatic glucose production, increases insulin sensitivity and insulin-mediated utilization of glucose in peripheral tissues while decreasing glucose intestinal absorption.
2. Sulfonylureas are a class of insulin secretagogues that stimulate pancreatic insulin secretion and close K-ATP channels on β-cell plasma membranes

3. Thiazolidinediones (pioglitazone) are peroxisome proliferator-activated receptor (PPAR) modulators, which work to increase insulin sensitivity.

Their use is limited by causing weight gain and fluid retention through transcriptional upregulation of tubular amiloride-sensitive sodium channels.

4. Meglinitides are primarily metabolized in the liver and act as insulin secretagogues similar to sulfonylureas.

5. Incretin Mimetics: Glucagon-Like Peptide-1 Analogues:

- GLP-1 analogues promote glucose-mediated insulin secretion by pan-creatic β-cells in response to food entering the gut and suppress glucagon secretion.
- The GLP-1 analogues help stimulate weight loss by appetite suppression, both centrally and by affecting gastric motility.

Gliptins: Dipeptidyl Peptidase-4 Inhibitors

6. The gliptin class inhibits the effect of DPP-4, a cellular membrane protein expressed in a variety of tissues that function to rapidly degrade endogenous incretin hormones (e.g., GLP-1).

7. α-Glucosidase Inhibitors:

α-Glucosidase is an intestinal enzyme needed to digest carbohydrates.

Inhibition of this enzyme maintains the integrity of complex carbohydrates, thereby allowing less glucose absorption, and thus should be taken at the start of meals.

Amylin analogues

8. Amylin analogues regulate glucose levels according to food intake and control gastric emptying and postprandial glucagon secretion.

They increase satiety and thus reduce food intake.

SGLT-2 Inhibitors

9. Sodium glucose cotransporter protein subtype-2 (SGLT-2) in the renal proximal convoluted tubule is blocked by SGLT-2 inhibitors, thereby increasing renal excretion of glucose.

- Empagliflozin was seen to reduce the risk for CV mortality, all-cause mortality, and hospitalization for congestive heart failure with favorable effects on weight, systolic blood pressure (BP), and serum uric acid.
- SGLT2 inhibition is associated with an acute, dose-dependent reduction in eGFR by approximately 5 ml/min/1.73 m2 and approximately 30% to 40% reduction in albuminuria.
- Glycosuric effects are attenuated in patients with CKD (eGFR <60 ml/min/1.73 m2) but BP, eGFR, and albuminuria lowering effects are preserved.

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SGLT-2 Inhibitors

- With regard to long-term clinical outcomes, the Empagliflozin Cardiovascular Outcome Event (EMPA-REG OUTCOME) trial, using empagliflozin 10 or 25 mg/day in patients with type 2 diabetes and established CVD reported a 14% reduction in the primary composite outcome of CV death, nonfatal myocardial infarction, nonfatal stroke, and more than 30% reductions in CV mortality, overall mortality, and heart failure hospitalizations

Zinman B, Wanner C, Lachin JM, et al.

N Engl J Med. 2015;373:2117–2128

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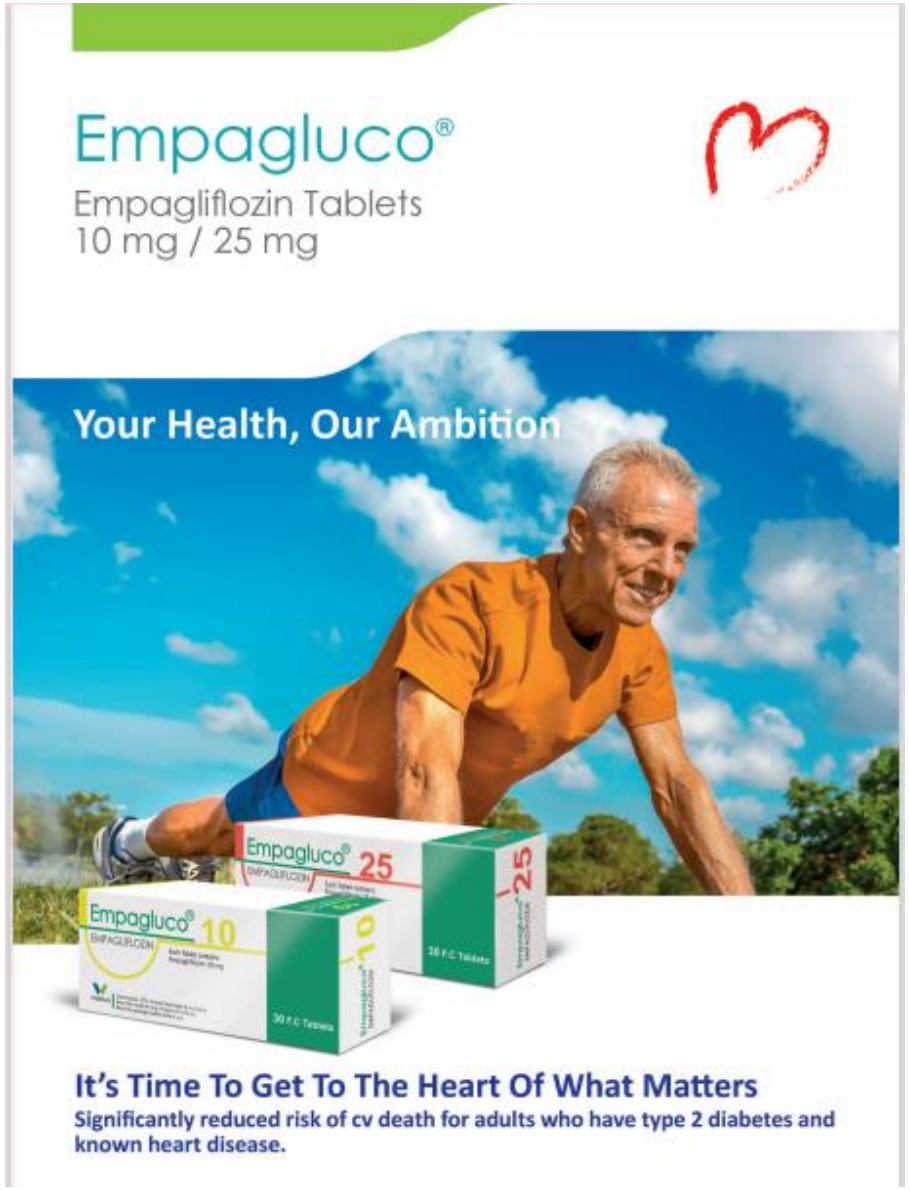
- Some guidelines now recommend that SGLT2 inhibitors with proven CV benefit be prioritized in patients with type 2 diabetes with insufficient glycemic control and who have atherosclerotic CVD.
- EMPA-REG OUTCOME study reported a 39% reduction in incident or worsening nephropathy that included doubling of serum creatinine (relative risk reduction, 44%) and renal-replacement therapy (relative risk reduction, 55%) in the empagliflozin group.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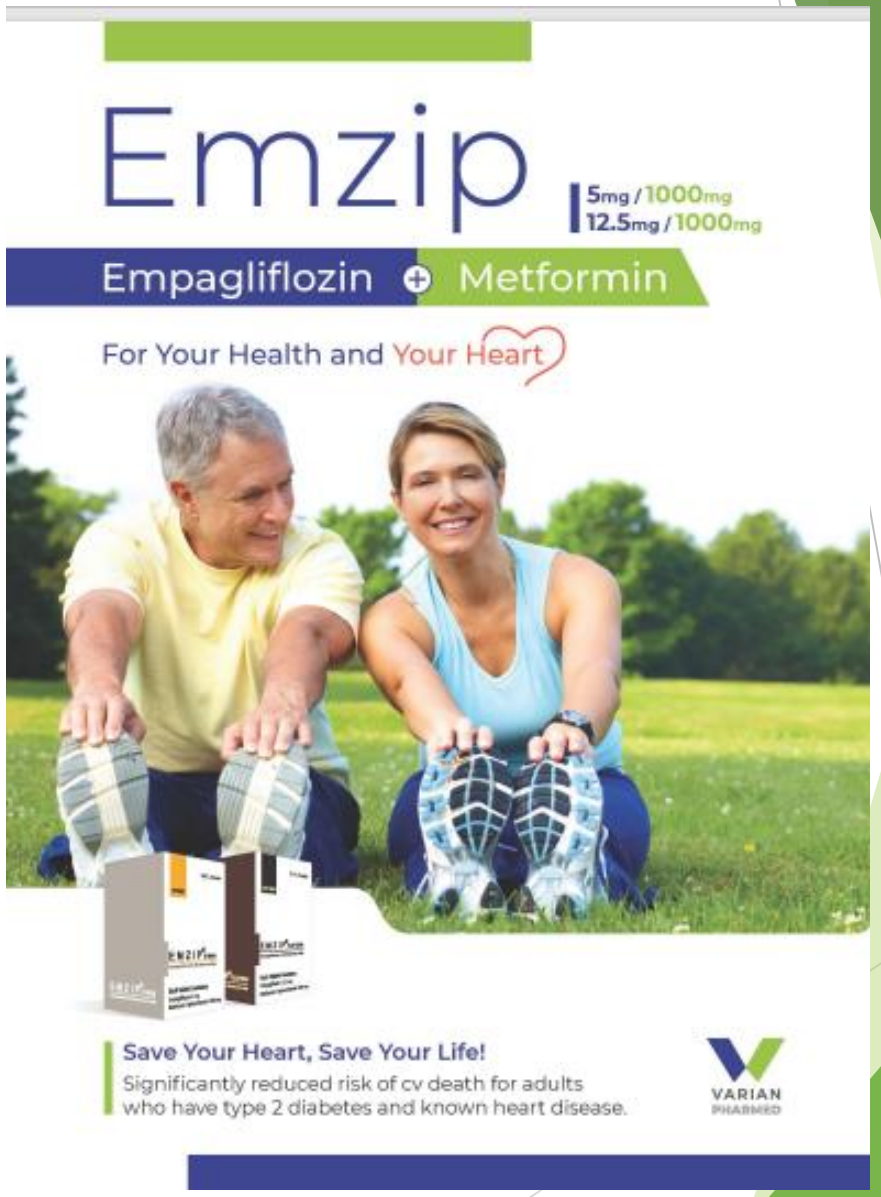
It's Time To Get To The Heart Of What Matters
Significantly reduced risk of cv death for adults who have type 2 diabetes and known heart disease.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For Your Health and Your Heart
Save Your Heart, Save Your Life!
Significantly reduced risk of cv death for adults who have type 2 diabetes and known heart disease.
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Thank you