In The Name of God

RAS blockers in diabetic nephropathy

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SUBJECT

- Role of the renin angiotensin system in diabetic nephropathy
- ACE inh v/s ARB
- Dual Therapy
- Treatment in normal BP and microalbuminuria
- Primary prevention
- Hyporeninemic Hypoaldostronism Syndrom
- ACE polymorphism and diabetic nephropathy

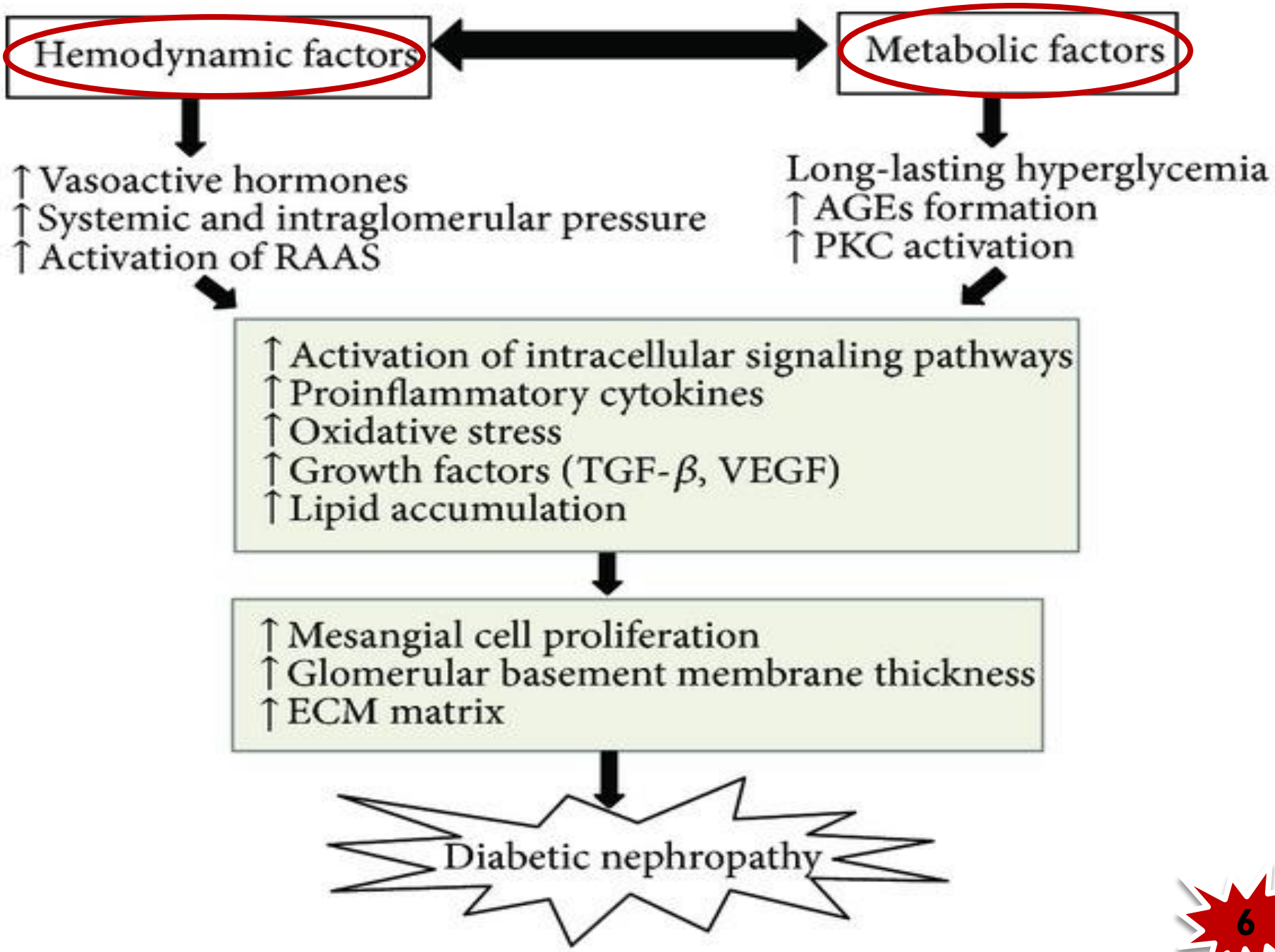
Hyperglycemic Injury

cellular elements of the kidney that are targets for hyperglycemic injury:

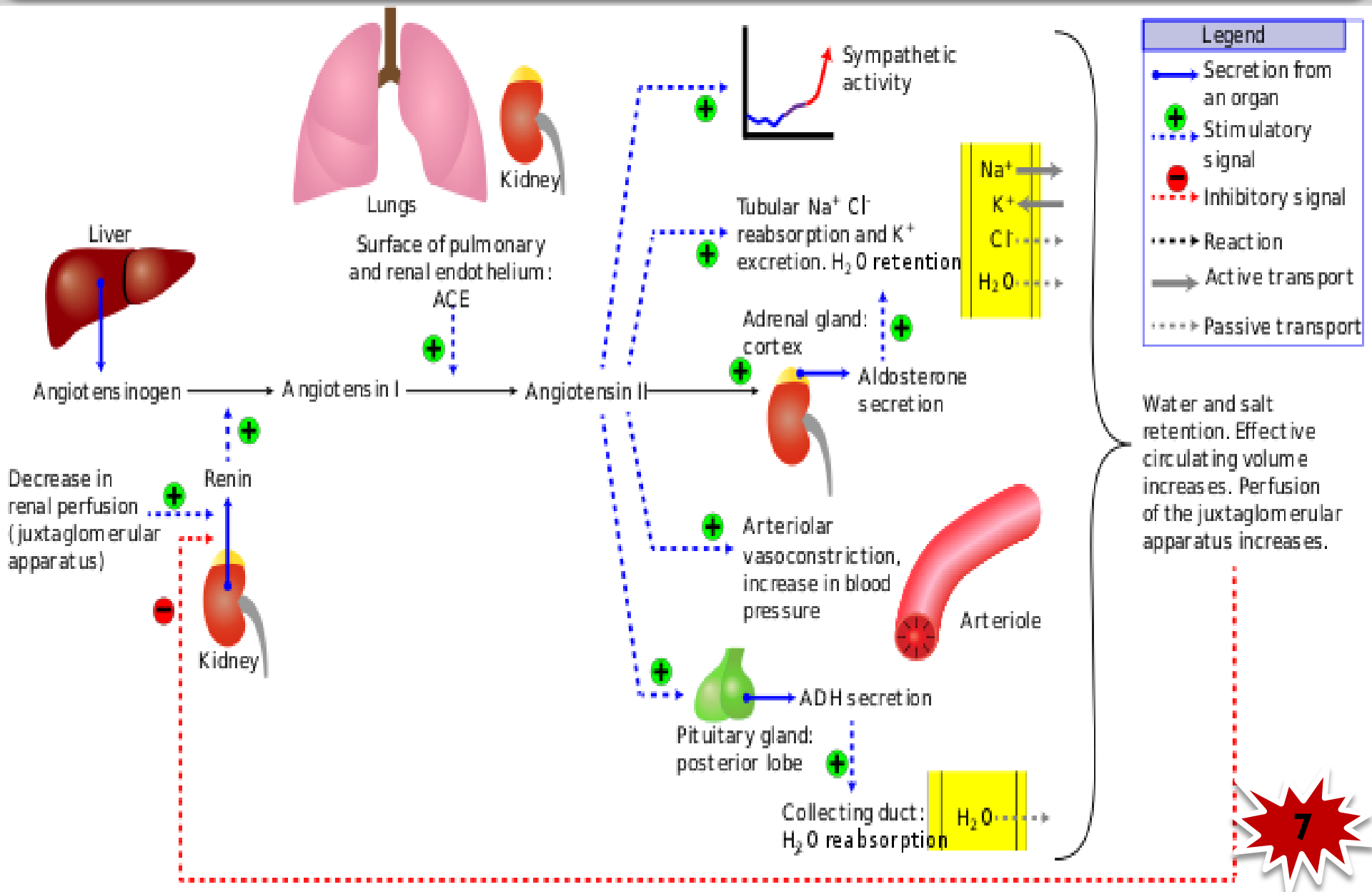
- **Glomerular endothelial**
- **Mesangial cells**
- **Podocytes**
- **Tubular epithelial**

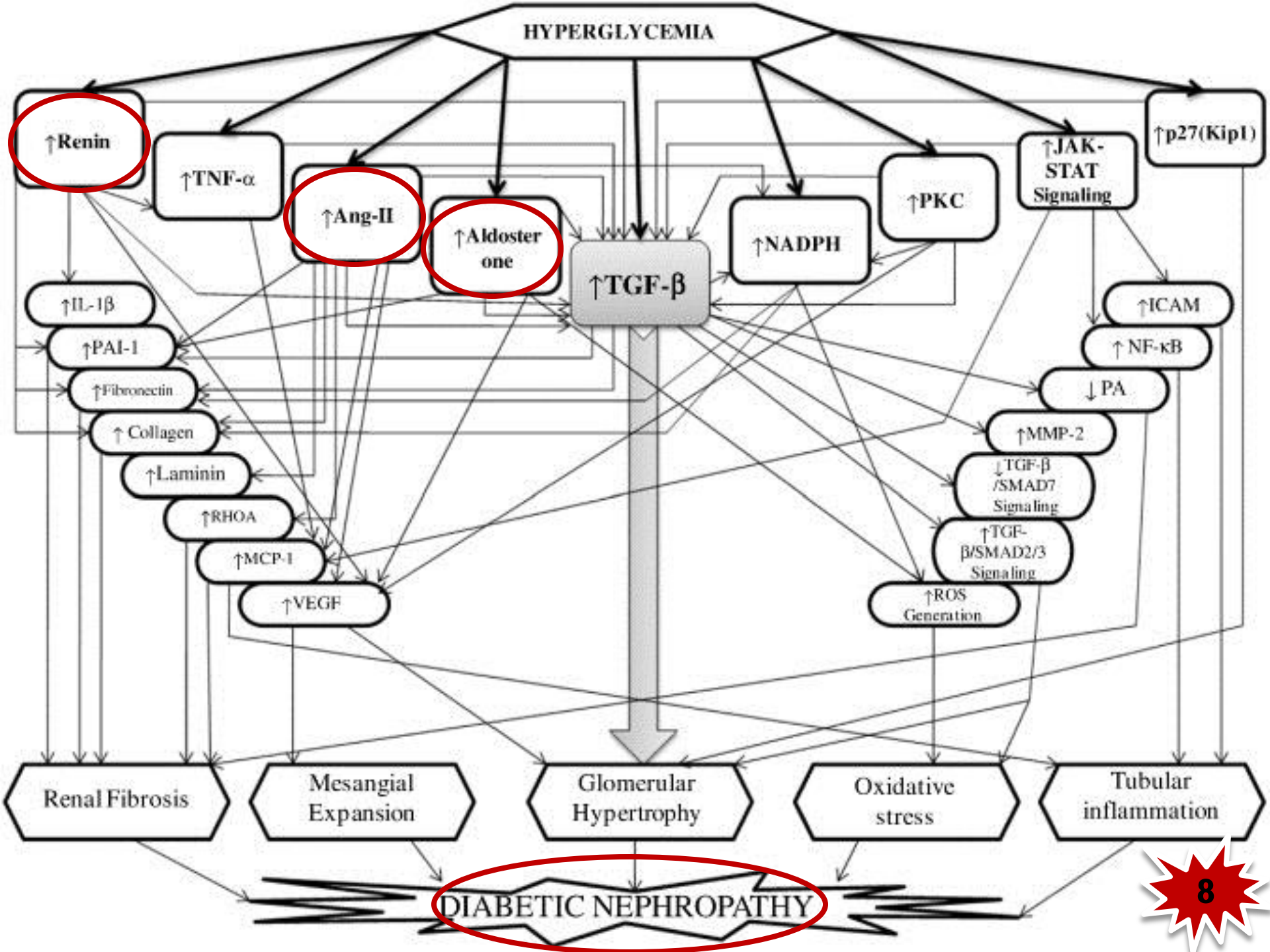
Pathological Changes

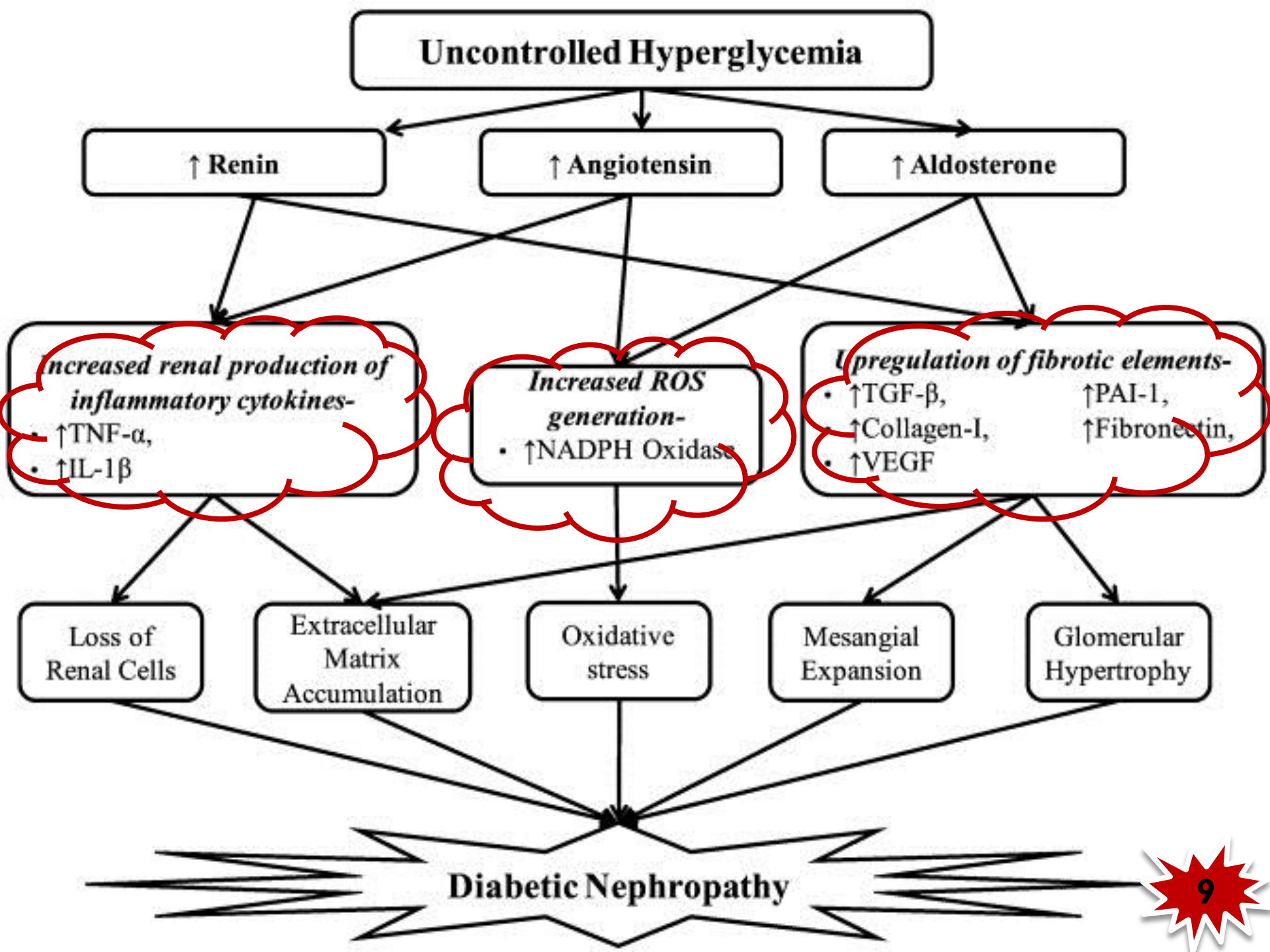
- Glomerulosclerosis
- Thickening of the glomerular basement membrane
- Glomerular hypertrophy
- Mesangial cell expansion
- Podocyte loss
- Renal-cell hypertrophy
- Tubulointerstitial fibrosis


Hemodynamic factors
Metabolic factors
↑ Vasoactive hormones
↑ Systemic and intraglomerular pressure
↑ Activation of RAAS
Long-lasting hyperglycemia
↑ AGEs formation
↑ PKC activation
↑ Activation of intracellular signaling pathways
↑ Proinflammatory cytokines
↑ Oxidative stress
↑ Growth factors (TGF-β, VEGF)
↑ Lipid accumulation
↑ Mesangial cell proliferation
↑ Glomerular basement membrane thickness
↑ ECM matrix
Diabetic nephropathy

Renin angiotensin –aldosterone system




HYPERGLYCEMIA
↑Renin
↑TNF-α
↑Ang-II
↑Aldosterone
↑TGF-β
↑NADPH
↑PKC
↑JAK-STAT Signaling
↑p27(Kip1)
↑IL-1β
↑PAI-1
↑Fibronectin
↑ Collagen
↑Laminin
↑RHOA
↑MCP-1
↑VEGF
↑ICAM
↑ NF-κB
↓ PA
↑MMP-2
↓TGF-β /SMAD7 Signaling
↑TGF-β/SMAD2/3 Signaling
↑ROS Generation
Renal Fibrosis
Mesangial Expansion
Glomerular Hypertrophy
Oxidative stress
Tubular inflammation
DIABETIC NEPHROPATHY


Uncontrolled Hyperglycemia
↑ Renin
↑ Angiotensin
↑ Aldosterone
Increased renal production of inflammatory cytokines-
• ↑TNF-α,
• ↑IL-1β
Increased ROS generation-
• ↑NADPH Oxidase
Upregulation of fibrotic elements-
• ↑TGF-β, ↑PAI-1,
• ↑Collagen-I, ↑Fibronectin,
• ↑VEGF
Loss of Renal Cells
Extracellular Matrix Accumulation
Oxidative stress
Mesangial Expansion
Glomerular Hypertrophy
Diabetic Nephropathy

ACEin

Inhibits ACE activity by blocking the conversion from AngI to AngII

inhibits BK degradation. Bradykinin, via its B2 receptors, stimulates NO, cGMP, prostaglandin E2, and prostacyclin.

Therefore, ACEi therapy not only inhibits AngII production but also increases the production of the vasodilatory factors.

Inhibits the ACE mediated **degradation** of Ang 1–7 augmenting the renoprotective effects of **Ang** 1–7.

ACE inhibitors

The pleiotropic effects of ACEi include:

- anti-inflammatory
- Antioxidant
- Antithrombotic
- Anti profibrinolytic activities
- ACEi is also important in significantly improving arterial compliance through cytoprotection of vascular endothelium

ARB

Some of the beneficial effects of using ARB are thought to be due to selective inhibition of AT1 and the concomitant **renoprotective stimulation of AT_2 receptors**

ARB

It has been proposed that ARBs might have a greater potential in preventing renal interstitial fibrosis compared to ACEi mediated by AT_2 receptor.

ACE inh v/s ARB

Are angiotensin-converting enzyme (ACE) inhibitors or angiotensin-II receptor blockers (ARBs) better for all-cause mortality reduction and renal protection in patients with diabetic kidney disease?

ACE inh v/s ARB

There were too few trials comparing ACE inhibitors with ARBs to draw clear conclusions

In patients with diabetes, recent meta-analyses provided controversial results for the efficacy of RAS blockers.

A meta-analysis indicated that RAS blockers were not superior to other antihypertensive drugs at reducing the risk of renal endpoints in people with diabetes

However, other meta-analyses showed that compared to other blood pressure-lowering strategy, RAS blockers were the most effective strategies against renal diseases in adults with diabetes

The inconsistent results causes from these meta-analyses:

- The selections of diabetic patients (eg. complicating with chronic kidney diseases, albuminuria or hypertension)
- time of follow-up (eg. RCTs less than six months),
- controls (placebo or other antihypertensive drugs)
- outcomes (eg. changes of UACR, or incidence of ESRD)

multi-center RCTs with large sample size such as DIABHYCAR, RENAAL and IDNT and DETAIL exhibited discordant results

DIABHYCAR study

Determination in the Noninsulin-Dependent Diabetes, Hypertension, Microalbuminuria, Proteinuria, Cardiovascular Events, and Ramipril (DIABHYCAR) Study (4912 patients with type 2 diabetes aged >50 years who use oral antidiabetic drugs and have persistent microalbuminuria or proteinuria) with follow up for 3 to 6 (median 4) years indicated that an ACE inhibitor (Low dose (1.25 mg) ramipril once daily) has no effect on ESRD or doubling of serum creatinine

RENAAL study

Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan investigation (1,513 patients were enrolled from **250 centers** in 28 countries in Asia, Europe, Central America, South America, and North America)suggested an ARB (50–100 mg once daily losartan) conferred significant renal benefits such as reduction of ESRD incidence.

IDNT study

- The Irbesartan Diabetic Nephropathy Trial (300 mg daily irbesartan or 10 mg daily **amlodipine** slow the progression of nephropathy in 1715 hypertensive patient with type 2 diabetes, independent of effects on systemic blood pressure (BP)lowering)Showed a trend of renal protection effect for ARB .

- This protection is **independent** of the reduction in blood pressure it causes.

DETAIL STUDY

Both groups (**enalapril vs telmisartan**) had similar 5-year GFR decline, annual changes in the GFR, blood pressure, serum creatinine, urinary albumin excretion, ESRD, cardiovascular events, and mortality.

Kidney & Blood Pressure Research

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Original Paper

Effects of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers on All-Cause Mortality and Renal Outcomes in Patients with Diabetes and Albuminuria: a Systematic Review and Meta-Analysis

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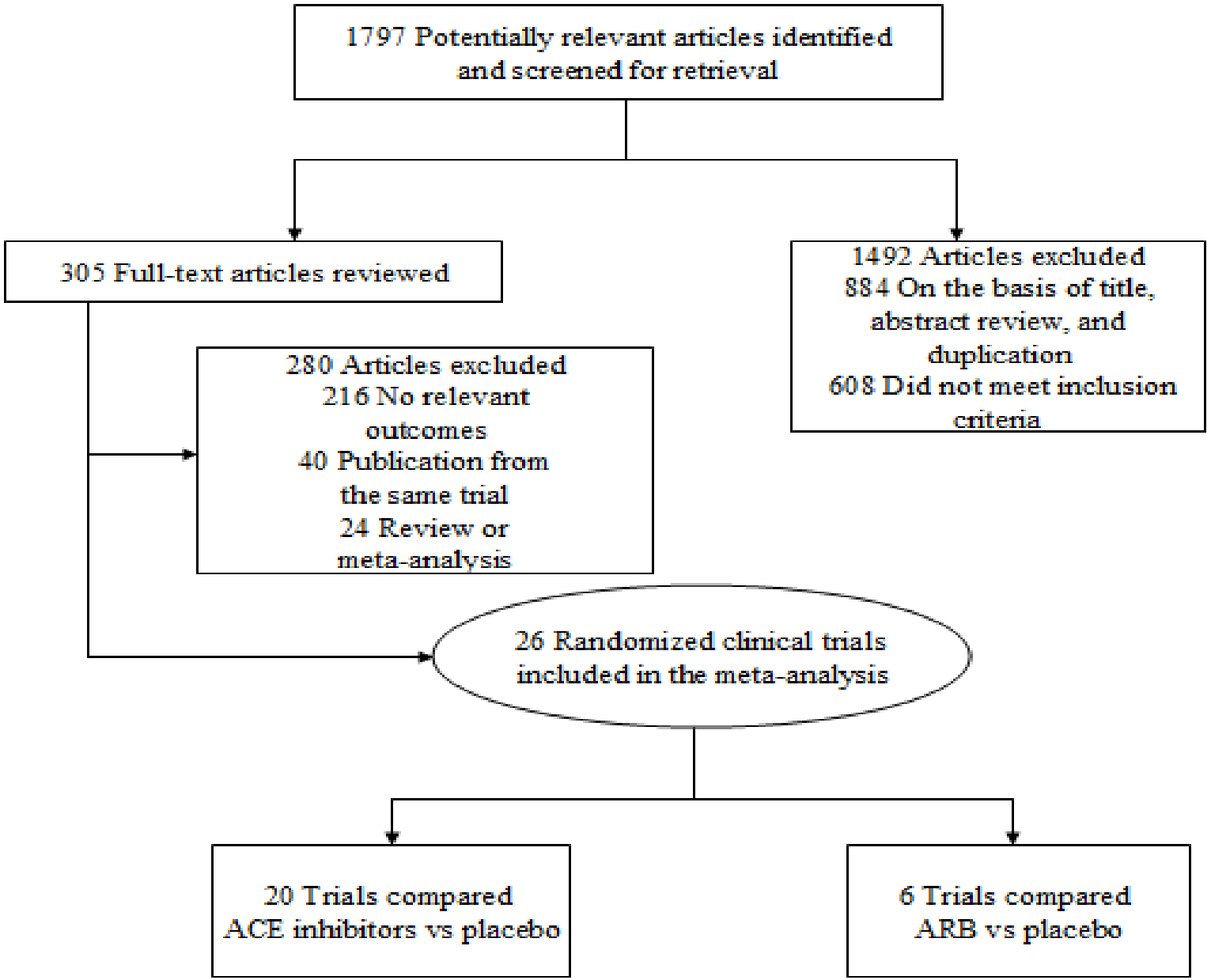
- In this meta-analysis, electronic data sources (Medline, the Cochrane Collaboration, and EMBASE) were searched. Randomized controlled trials (RCTs) comparing ACE inhibitors **or** ARB with **placebo** in subjects with diabetes and albuminuria (defined as urinary albumin-to-creatinine ratio, **UACR≥30**mg/g Cr) were included.

- Eventually comprising 10378 participants with diabetes and albuminuria were followed for a mean of 2.3 years


1797 Potentially relevant articles identified and screened for retrieval
305 Full-text articles reviewed
1492 Articles excluded
884 On the basis of title, abstract review, and duplication
608 Did not meet inclusion criteria
280 Articles excluded
216 No relevant outcomes
40 Publication from the same trial
24 Review or meta-analysis
26 Randomized clinical trials included in the meta-analysis
20 Trials compared ACE inhibitors vs placebo
6 Trials compared ARB vs placebo

➢Compared to placebo, treatment with ACE inhibitors or ARBs did not reduce all-cause mortality or CV.

➢For **renal outcomes**

ARBs significantly reduced the risk of ESRD by 23% (odds ratio 0.77, 95%CI 0.65-0.92), while ACE inhibitors were not associated with a decreased risk of ESRD (0.69, 0.43-1.10)with *P<0.0001*

Uptodate Recommendation

- It now seems clear in **type 1** diabetes that angiotensin-converting enzyme (**ACE inhibitors**), as part of a therapeutic regimen to achieve blood pressure goals, both lower protein excretion and slow the rate of disease progression in patients with **moderately** increased albuminuria and in those with **severely** increased albuminuria .

- A similar effect is seen in type 2 diabetes with ARBs or ACE inhibitors

Dual Therapy therapy

Combination therapy with an ACE inhibitor and an ARB was associated with an **increased risk of adverse events** among patients with diabetic nephropathy.

Treatment in normal BP and microalbuminuria

Guidelines from National Institute for Health and Care Excellence **(NICE) 2014** and Kidney Disease Outcomes Quality Initiative **(KDOQI) 2012** **recommended** the use of an ACE inhibitors **or** a ARB in patients with diabetes and albuminuria, even for subjects with **microalbuminuria** (UACR 30–299 mg/g Cr) and normal blood pressure

However, the use of RAS blockers in diabetic patients with microalbuminuria or normal blood pressure was not recommended by American Diabetes Association **(ADA) 2017** guideline.

Primary prevention for diabetic nephropathy

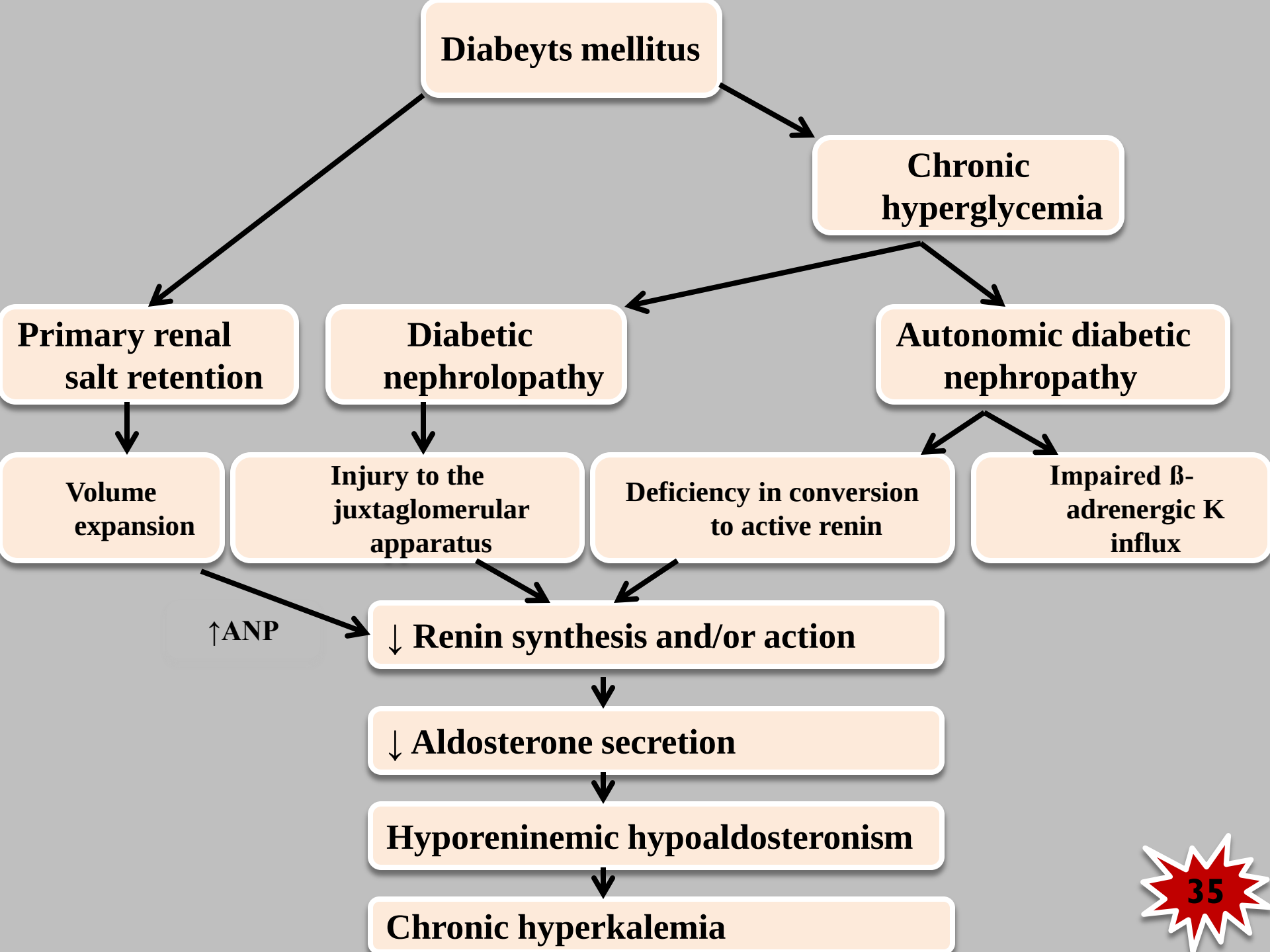
In type 2 diabetes patients with **normoalbuminuria** there is evidence that ACE inhibitors are effective in preventing microalbuminuria only in those patients with hypertension.

In these patients good metabolic control and ACE inhibitor therapy are clearly able to prevent microalbuminuria.

Remission or Regression

among patients with diabetic nephropathy due to type 1 diabetes mellitus, including some with advanced disease, remission or regression may occur with aggressive control of systemic blood pressure, particularly with ACE inhibitors

Hyporeninemic Hypoaldostronism Syndrom


Diabeyts mellitus
Chronic hyperglycemia
Primary renal salt retention
Diabetic nephrolopathy
Autonomic diabetic nephropathy
Volume expansion
Injury to the juxtaglomerular apparatus
Deficiency in conversion to active renin
Impaired ß-adrenergic K influx
↑ANP
↓ Renin synthesis and/or action
↓ Aldosterone secretion
Hyporeninemic hypoaldosteronism
Chronic hyperkalemia

Diabetic Hyporeninemic hypoaldosteronism

HH predominantly occurs in patients 50 to 70 years of age with DN and/or chronic tubulointerstitial disease who have mild to moderate kidney failure It is more frequent among women.

Inapropriate hyperkalemia present

Therefore, patients with these characteristics should be monitored.

The beneficial effects of RAS blockers in slowing the progression of diabetic nephropathy have been well documented **despite** the low systemic renin state in DKD. This phenomenon is thought to be reflecting the activated intrarenal renin system or increased intrarenal sensitivity to AngII.

ACE polymorphism and diabetic nephropathy

- In **overall populations** presence of ACE insertion/deletion (I/D) polymorphism affects the plasma level of ACE.

- ACE DD genotype is associated with highest **systemic** and **renal** ACE levels, compared with the lowest ACE activity in carriers of II genotype.

Results from published studies on the **relationship** between angiotensin-converting enzyme (*ACE) insertion/deletion (I/D) gene polymorphism* and ESRD risk in DN patients are **still conflicting**

Most studies confirmed that ACE I/D polymorphism is involved in the susceptibility to overt nephropathy with protective role of ACE II genotype against the disease in both **type 1 and 2 diabetes** mellitus.

NEPHROLOGY

Nephrology 17 (2012) 480–487

Original Article

Meta-analysis of the relationship between *ACE* I/D gene polymorphism and end-stage renal disease in patients with diabetic nephropathy

ZE-YAN YU,[1] LI-SHENG CHEN,[2] LEI-CHANG ZHANG[2] and TIAN-BIAO ZHOU[3]

[1]Postgraduate School of GuangXi Medical University, Departments of [2]Colorectal and Anal Surgery and [3]Pediatrics, The First Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi, China

- Association studies were identified from the databases of PubMed,Embase and Cochrane Library on 1 October 2011

D allele or DD homozygous is associated with the **ESRD** susceptibility in DN patients. However, more investigations are required to further this association.

- Furthermore, *ACE I/D gene polymorphism* was associated with ESRD risk in patients with DN due to diabetes mellitus **type 2**, but the association **was not found** for patients with DN due to diabetes mellitus **type-1.**

Conclusion1

- In patients with diabetes, recent meta-analyses provided controversial results for the efficacy of RAS blockers.

Recent Meta Analysis:

- ACE inhibitors and ARBs failed to reduce all-cause mortality and CV.
- Based on the renoprotective effects, ARBs may be preferred for diabetic patients with albuminuria.

Conclusion2

- Uptodate:It now seems clear in type 1 diabetes that angiotensin-converting enzyme (ACE inhibitors) and a similar effect is seen in type 2 diabetes with ARBs or ACE inhibitors

- NICE 2014 and KDOQI 2012 recommended the use of RAS blocker in patients with diabetes and albuminuria, even for subjects with microalbuminuria and normal blood pressure but ADA2017 not recommended.

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