Újdonságok a glomeruláris betegségekkel kapcsolatban

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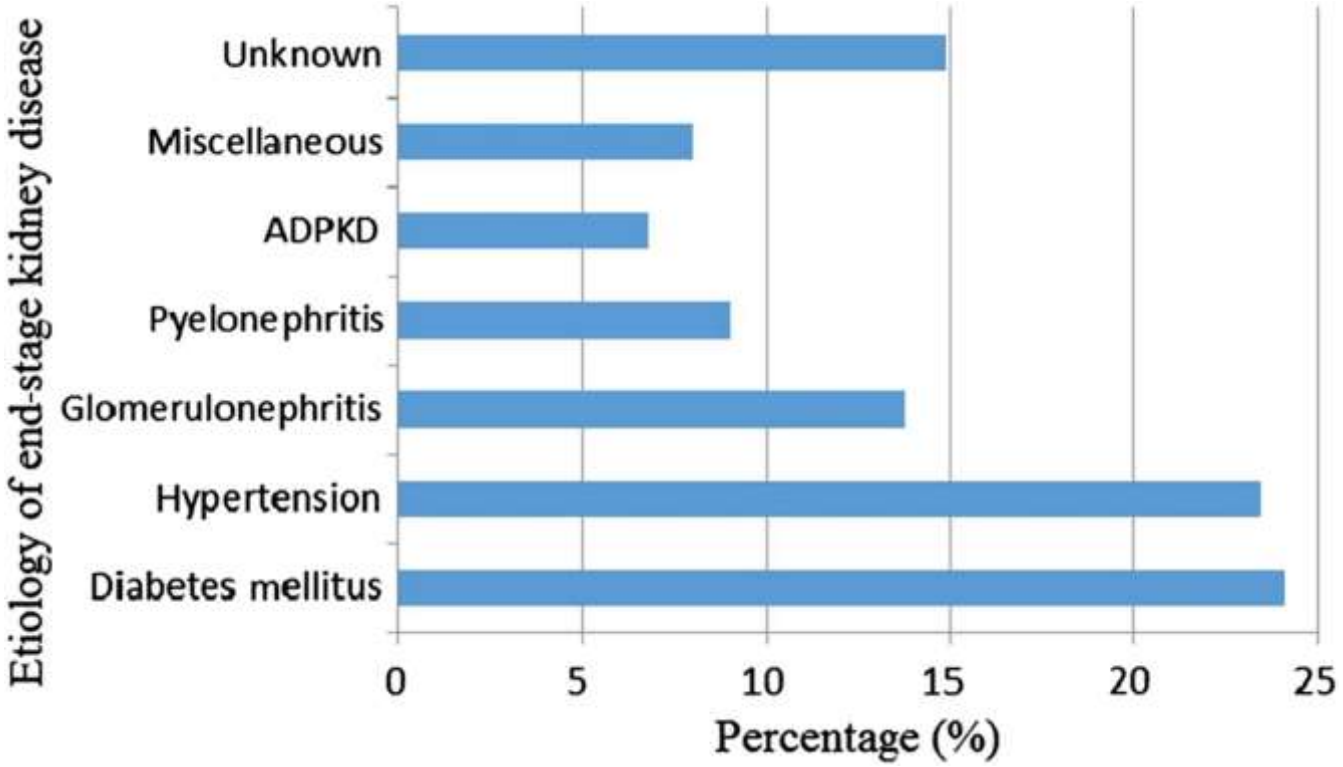
Pécs

ELŐADÁS VÁZLAT

- Primer glomerulonephritisekről
- Általános vesevédő kezelés
- Mikor van szükség nephrologusra? - mikor tudunk segíteni
- Hipertónia kezelése krónikus vesebetegségekben – RAAS gátlás

ESRD prevalenciája (%) Kelet- és Közép Európában



Kidney International 2019 96, 287-290DOI: (10.1016/j.kint.2019.02.040)

Table 1 | Common features of the major glomerular diseases (GDs) in adults for inclusion in Standardized Outcomes in Nephrology—Glomerular Disease (SONG-GD)

Renal-limited GDs	Clinical features	Clinical course	Treatment	Renal outcome	Risk of transplant loss
IgA nephropathy	Hematuria/ proteinuria; nephritic syndrome; rarely nephrotic	Benign; relapsing–remitting; progressive	Supportive; immunosuppression	Highly variable; CKD and ESKD common	Low

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Minimal change disease	Nephrotic syndrome	Relapsing–remitting	Supportive; immunosuppression	ESKD rare	Not applicable
Focal segmental glomerulosclerosis	Proteinuria; nephrotic syndrome	Progressive	Supportive; immunosuppression	Variable depending on treatment response; often progresses to ESKD	Variable

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Focal segmental glomerulosclerosis	Proteinuria; nephrotic syndrome	Progressive	Supportive; immunosuppression	Variable depending on treatment response; often progresses to ESKD	Variable
Complement-mediated glomerulopathy[a]	Hematuria/ proteinuria; rarely nephrotic	Relapsing–remitting, progressive	Supportive; complement blockade or immunosuppression; plasmapheresis	Variable; risk of CKD and ESKD	Variable
Idiopathic immune complex–mediated membranoproliferative glomerulonephritis	Hematuria/ proteinuria; nephritic-nephrotic syndrome	Relapsing–remitting, progressive	Supportive; treat underlying cause; immunosuppression	CKD common; ESKD	Moderate

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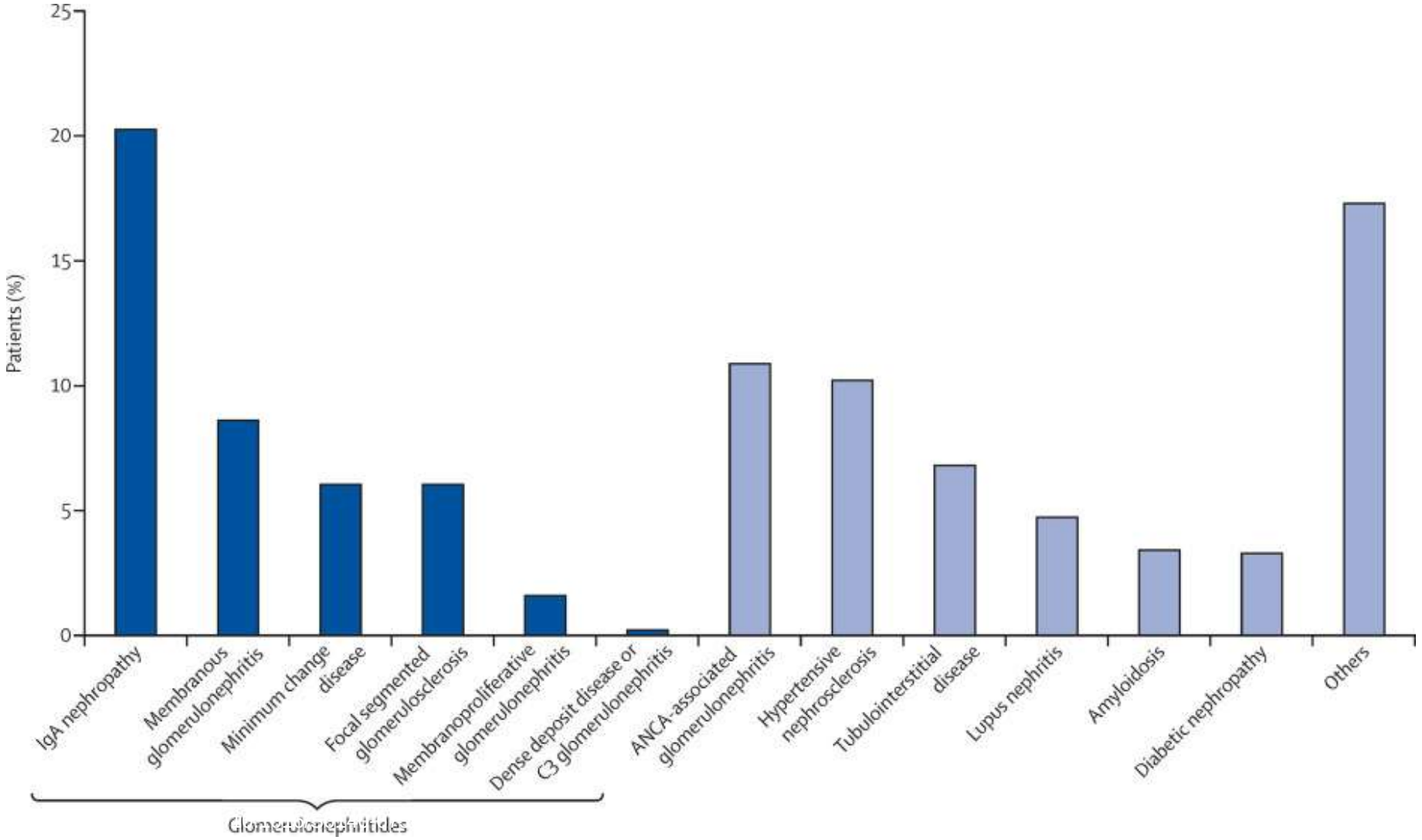
	Clinical features	Clinical course	Treatment	Renal outcome	Risk of transplant loss
GDs with systemic involvement					
Anti-neutrophil cytoplasmic antibody-associated vasculitis	Hematuria/ proteinuria; nephritic syndrome; respiratory symptoms; multi-system involvement	Rapidly progressive; relapsing–remitting	Supportive; immunosuppression; plasmapheresis	High risk of CKD and ESKD	Low
Lupus nephritis	Hematuria/ proteinuria; nephritic syndrome; nephrotic syndrome; multi-system involvement	Relapsing–remitting	Supportive; immunosuppression	Variable; significant risk of CKD and ESKD	Rare
IgA vasculitis (Henoch-Schoenlein purpura)	Hematuria/ proteinuria; nephritic syndrome; rarely nephrotic	Benign; relapsing–remitting; progressive	Supportive; immunosuppression	Highly variable; risk of ESKD	Low
Anti-glomerular basement membrane disease	Nephritic syndrome; pulmonary hemorrhage	Rapidly progressive; low relapse rate	Plasmapheresis; immunosuppression	Highly variable; risk of ESKD	Rare

CKD, chronic kidney disease; ESKD, end-stage kidney disease.
[a]GD arising from dysregulation and activation of the solid phase of the alternative complement pathway, including those with a membranoproliferative pattern on histology. Postinfectious glomerulonephritis that does not have alternative complement pathway

Kidney biopsy diagnoses in 2243 adult patients undergoing native kidney biopsy between 1990 and 2013 (Aachen, Germany)



Floege Lancet 2016

Nephrosis syndoma hátterében előforduló szövettani kórképek

	Gyerek	Fiatal felnőtt	Középkorú és idős
Minimal change	78	23	21
FSGS	8	19	13
Membranosus GN	2	24	37
Membranoprolif.	6	13	4
Amyloid	0	5	13
Egyéb	6	14	12

Membranosus glomerulonephritis

- **Dg:** FM ezüst festéssel megvastagodott glomeruláris kapilláris fal
- IF: granularis IgG és C3 EM: subepithelialis depositumok

Klinikai kép: felnőtt korban, idősekben

nephrosis sy (25%-ban nincs!)

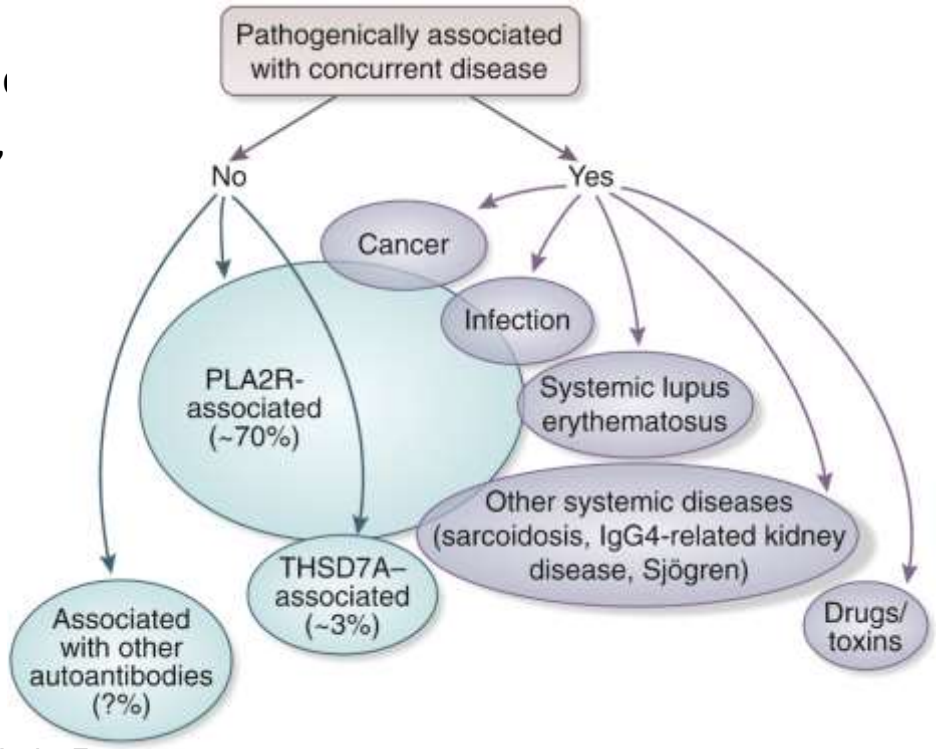
HT: 20-40%

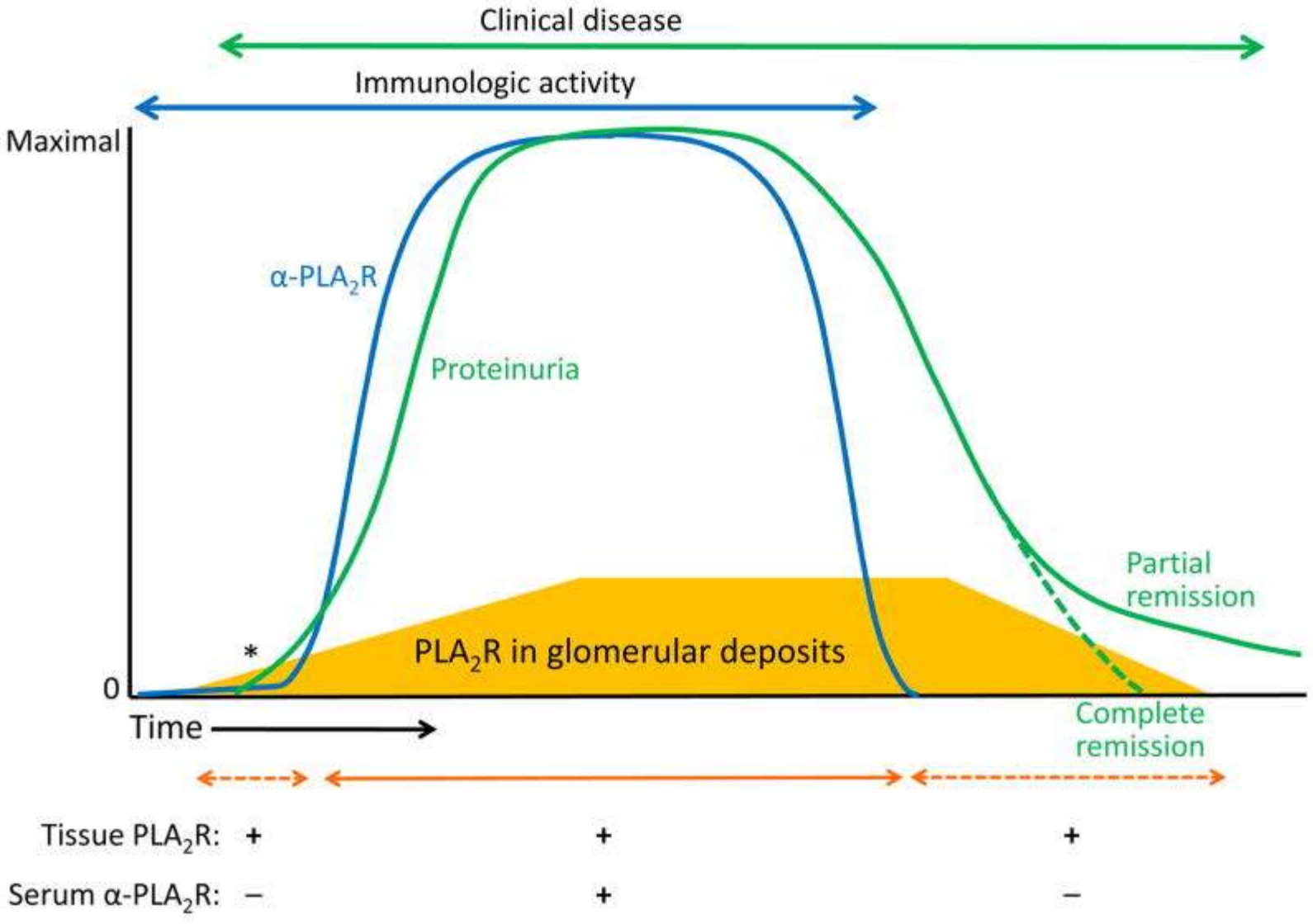
vesevéna thrombózis: 20-30%

Prognózis: jó, spontán remisszió is gyakori (kb 30%)

Membranosus glomerulonephritis etiológiája

- **Primer (75%)**
  - Foszfolipaz A2 receptor ellenes AT – *PLA2R* (podocytákon, subepitheliális IC-ben)
  - Thrombospondin type 1 domain containing 7A ell. AT *THSD7A*
- **Secunder (25%)**
  - Immunbetegségek (SLE, RA)
  - Vírus fertőzések (Hepatitis B, C,)
  - Tumorok (tüdő, prostata, hematológiai,
  - Gyógyszer indukálta (arany, penicilamin,





10.1053/j.ajkd.2016.01.030

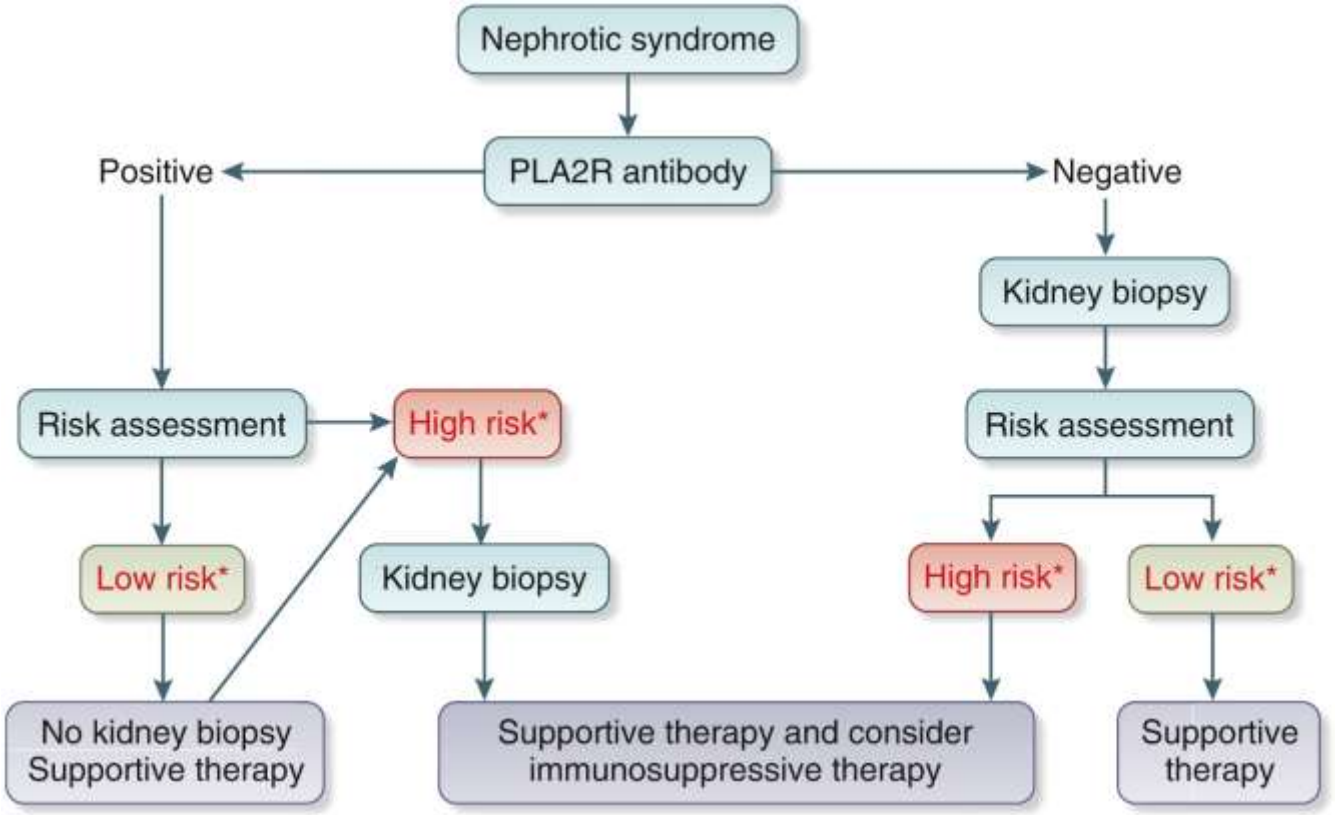
Vesebiopszia: diagnózis, terápia, prognózis vs. non-invazív diagnosztika

Histology:
light, immunofluorescence,
and electron microscopy

Molecular pathology:
omics

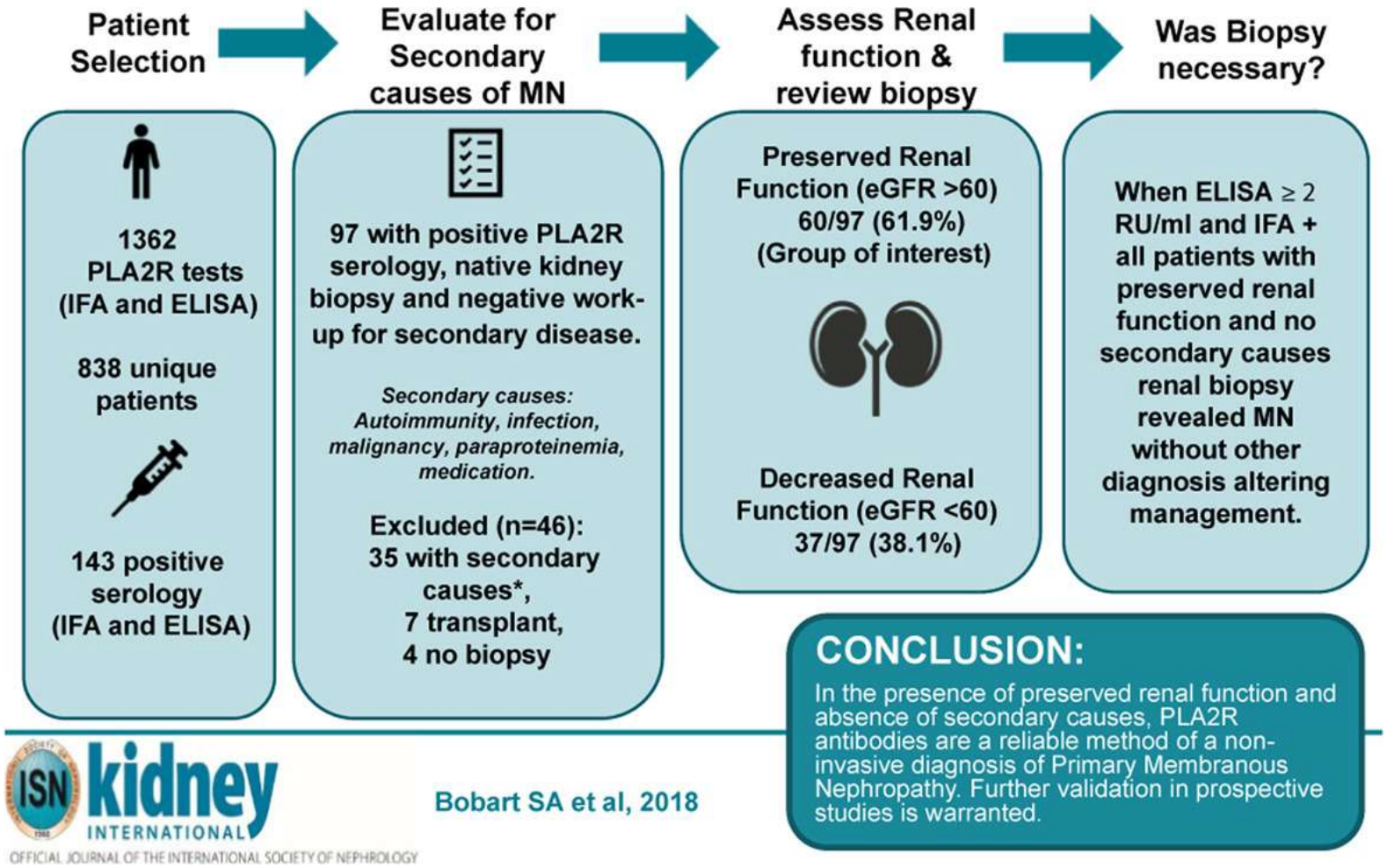
Kidney International 2019 95, 265-267DOI: (10.1016/j.kint.2018.11.016)

Membranosus nephropathia diagnosztikai algoritmusa



Kidney International 2019 95, 268-280DOI: (10.1016/j.kint.2018.10.018)

Non-Invasive Diagnosis of Primary Membranous Nephropathy using Phospholipase A2 Receptor Antibodies



ISN kidney INTERNATIONAL
OFFICIAL JOURNAL OF THE INTERNATIONAL SOCIETY OF NEPHROLOGY

Bobart SA et al, 2018

Kidney International 2019 95, 429-438DOI: (10.1016/j.kint.2018.10.021)

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- Hipertónia kezelése vesebetegségekben – RAAS gátlás

Általános vesevédő kezelés glomeruláris betegségekben

- **A szintű ajánlások**
  - Célvérnyomás 120-129 Hgmm
  - ACEI vagy ARB feltitrálása a célvérnyomás illetve PU < 1 g/nap –ig
  - Kerüljük a dihidropiridin CCB-t, ha csak nem szükséges
  - Mérsékelten fehérjeszegény diéta (0,8 g/l)

Floege Lancet 2016

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- **B szintű ajánlások**
  - Sómegszorítás és/vagy diuretikus kezelés
  - Kontrollált folyadék bevitel
  - Non-dihidropiridin CCB
  - A metabolikus szindróma elemeinek kezelése
  - Aldoszteron-antagonista kezelés (vesefunkcióhoz adaptálva – KÁLIUM!)
  - Béta-blokkoló
  - Dohányzás elhagyása
  - Allopurinol (ellentmondásos)
  - Metabolikus acidózis korrekciója

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  - Allopurinol (ellentmondásos)
  - Metabolikus acidózis korrekciója
- **Egyéb lehetőségek**
  - NSAID-ok kerülése (max. hetente 1-2x)
  - D vitamin hiány korrekciója
  - Hyperphosphataemia és hyperparathyroidismus kezelése
  - Súlyos hypokalaemia kerülése

Floege Lancet 2016

Cost-effectiveness of lipid lowering with statins and ezetimibe in chronic kidney disease

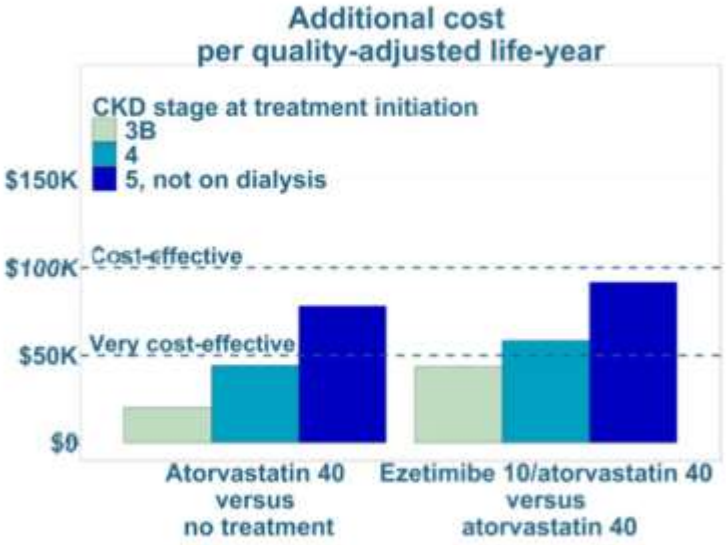
Study population

6,235 SHARP participants with moderate-to-advanced non-dialysis-dependent CKD[1]

Risk reductions with statin-based treatments from CTT meta-analysis[2]

SHARP CKD-CVD lifetime model[3]

US (2019$):
Atorvastatin 40mg $0.10/day
Ezetimibe 10mg $0.20/day



[1]Baigent et al, Lancet 2011; [2]CTT Collaboration, Lancet Diabetes Endocrinol 2016; [3]Schlackow et al, Heart 2017

CONCLUSION:

In non-dialysis-dependent CKD, low-cost statin plus ezetimibe treatment is cost-effective. The most cost-effective regimen is with the highest safe statin dose. Results are similar in the UK.

ISN kidney INTERNATIONAL
OFFICIAL JOURNAL OF THE INTERNATIONAL SOCIETY OF NEPHROLOGY

Schlackow et al, 2019

Kidney International 2019 96, 170-179DOI: (10.1016/j.kint.2019.01.028)

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Mikor utaljuk betegünket nephrológushoz? (1B)

A nephrológiai beutalás javallatai a kombinált bGFR-fehérjevizelés táblázat alapján

				Normális ACR <3 vagy TPCR <15	Mérsékelt ACR 3-30 vagy TPCR 15-45	Jelentős ACR >30 vagy TPCR 45-350
GFR stádium ml/perc/ 1.73m^2	G1	Normál vagy magas	>90	125/45é - 100/80é	követés ?	beutalás
	G2	Enyhén csökkent	60-89		követés ? ?	beutalás
	G3a	Mérsékelten csökkent	45-59	követés	követés ?	beutalás
	G3b	Középsúlyosan csökkent	30-44	követés 220/45é – 175/80é	követés	beutalás
	G4	Súlyosan csökkent	15-29	beutalás	beutalás	beutalás
	G5	Végstádiumú veseelégtelenség	<15	beutalás	beutalás	beutalás

Mikor utaljuk betegünket nephrologushoz? (1B)

- AKI vagy feltételezett gyors GFR csökkenés
- GFR < 30 ml/min/1,73m2 (CKD IV-V)

KDIGO 2012

Mikor utaljuk betegünket nephrologushoz? (1B)

- AKI vagy feltételezett gyors GFR csökkenés
- GFR < 30 ml/min/1,73m2 (CKD IV-V)
- Szignifikáns albuminuria (>300 mg/nap) vagy proteinuria (>500 mg/nap)
- CKD progresszió esetén
- Renális anémia gyanúja

KDIGO 2012

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- CKD progresszió esetén
- Renális anémia gyanúja
- Hematuria, vvt cylinduria
- Rezisztens HT és CKD együttes fennállása
- Perzisztáló hyperkalaemia
- Öröklődő vesebetegség

KDIGO 2012

Milyen vizsgálatok segíthetnek?

- Hasi UH

vese méret, felszín echogenitás

- Korábbi vesefunkciós illetve vizelet eredmények?

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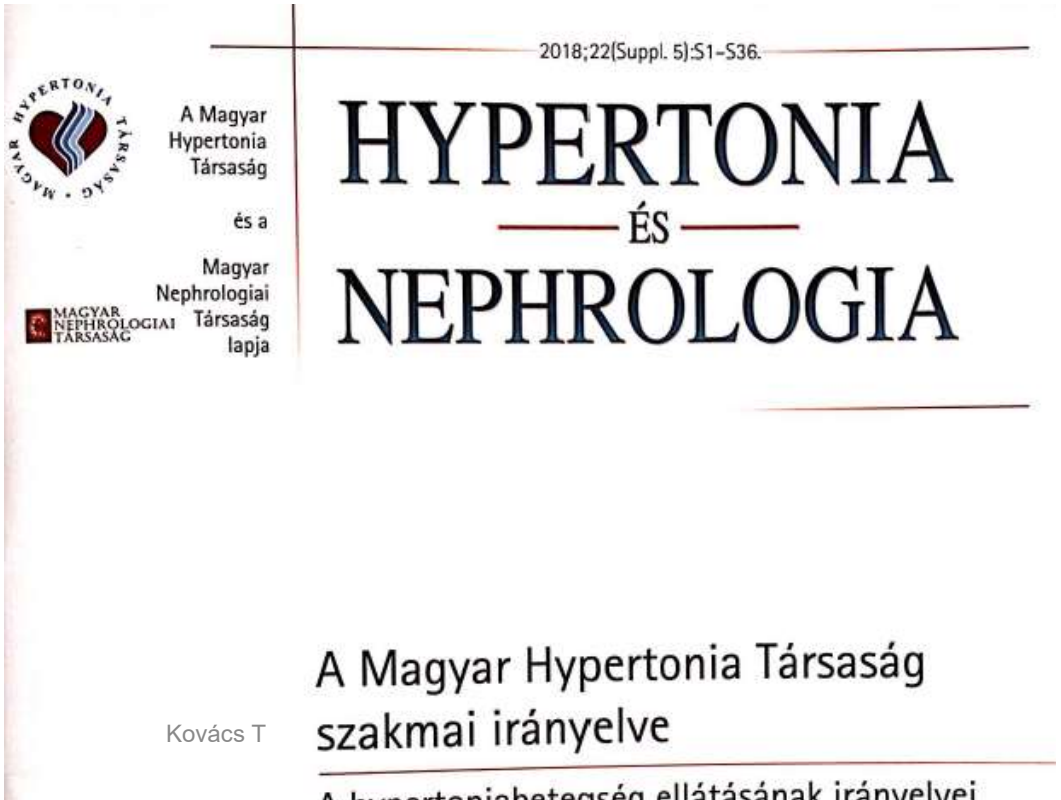
ESC European Society of Cardiology

European Heart Journal (2018) **00**, 1–98
doi:10.1093/eurheartj/ehy339

2018 ESC/ESH Guidelines for the management of arterial hypertension

The Task Force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH)



Kovács T

Hipertónia kezelése CKD-ban 2018

Therapeutic strategies for treatment of hypertension in CKD

Recommendations	Class[a]	Level[b]
In patients with diabetic or non-diabetic CKD, it is recommended that an office BP of ≥140/90 mmHg be treated with lifestyle advice and BP-lowering medication.[9,203,485]	I	A
In patients with diabetic or non-diabetic CKD: • It is recommended to lower SBP to a range of 130–139 mmHg.[9,487,489]	I	A
• Individualized treatment should be considered according to its tolerability and impact on renal function and electrolytes.	IIa	C
RAS blockers are more effective at reducing albuminuria than other antihypertensive agents, and are recommended as part of the treatment strategy in hypertensive patients in the presence of microalbuminuria or proteinuria.[487,489]	I	A
A combination of a RAS blocker with a CCB or a diuretic[c] is recommended as initial therapy.[175]	I	A
A combination of two RAS blockers is not recommended.[298]	III	A

©ESC/ESH 2018

Rendelői vérnyomás célértékek az új ajánlásban a komorbid állapotok függvényében

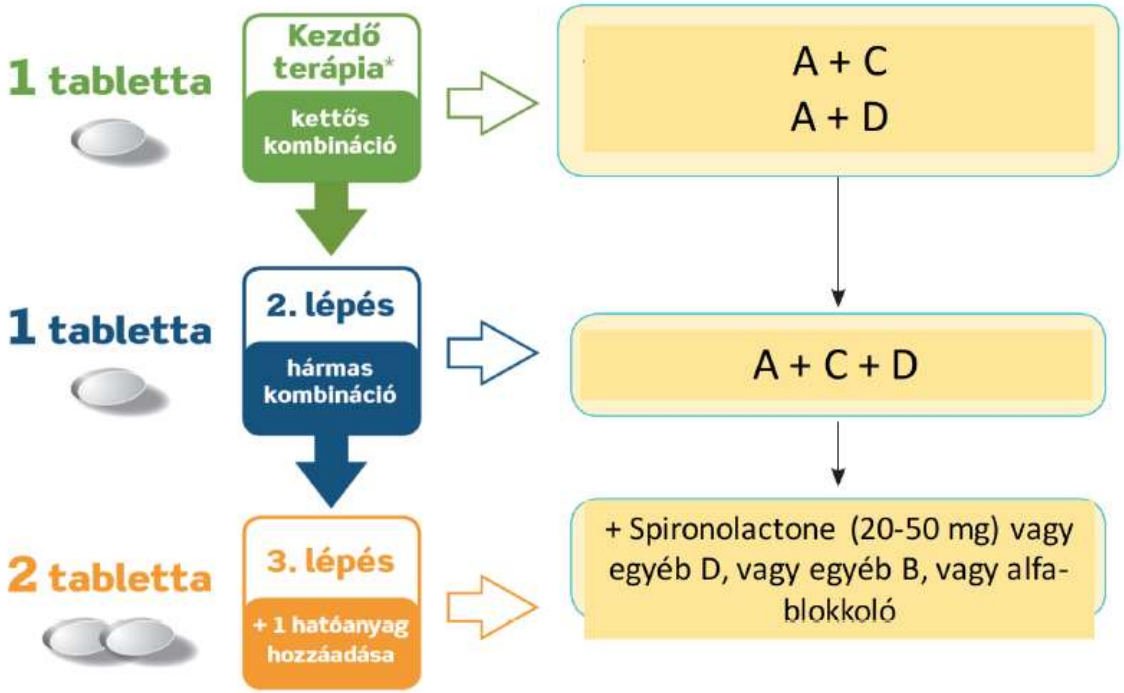
14. táblázat. *Célértéktartományok hypertonia kezelésekor*

Életkori csoportok	Rendelői szisztolés vérnyomáscélérték tartományai (Hgmm)							Diasztolés vérnyomáscélérték tartományai (Hgmm)
	Nem komplikált HT	HT+DM	HT+CAD	HT+ stroke/TIA[1]	HT+ PAD	HT+CKD+ PU[2]	HT+ CKD[3]	
18–65 éves	120–129	120–129	120–129	120–129	120–129	120–129	130–139	70–79
> 65 év	130–139	130–139	130–139	130–139	130–139	130–139	130–139	70–79

HT = hypertonia; DM = diabetes mellitus; CAD = coronariabetegség; TIA = átmeneti ischaemiás attak; PAD = perifériás verőérbetegség; CKD = krónikus vesebetegség; PU = proteinuria

[1]Megelőző stroke/TIA esetében és nem közvetlenül stroke után.
[2]Proteinuria ≥ 30 mg/nap.
[3]Proteinuria < 30 mg/nap.

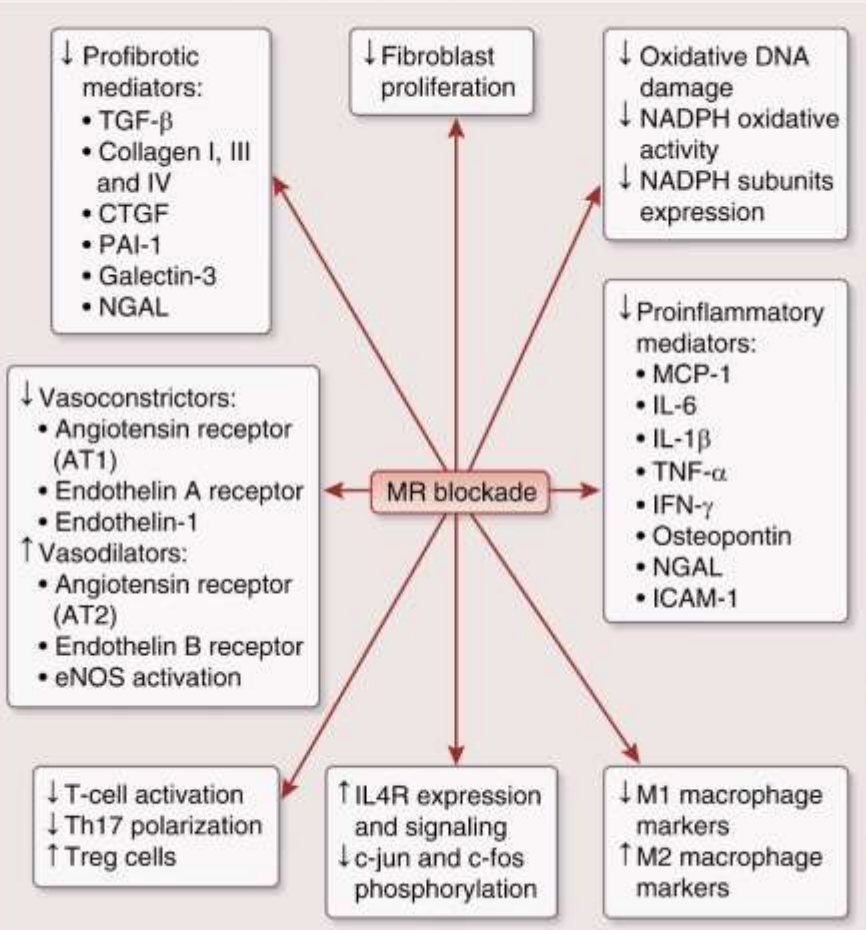
VI-7. ábra. Vérnyomáscsökkentő stratégia krónikus vesebetegséggel szövődött hypertonia esetében



A: ACE-gátló vagy ARB
C: kalciumantagonista
D: diureticum (sz.e. kacsdiuretikum)

Mineralocorticoid receptor (MR) antagonisták kedvező hatásai a vesében

Renal cell types	Tissue effects	Clinical settings	Clinical effects
Distal tubular cells	↓ Tubular injury	Situations with risk of IRI: • cardiac surgery • kidney transplantation • other?	IRI prevention
	↓ Fibrosis		Prevention of AKI to CKD transition
Endothelial cells SMC	↓ Glomerulosclerosis	Hypertension	Antihypertensive
	↓ Podocyte injury	Diabetes	Antiproteinuric
Podocytes Mesangial cells Fibroblasts	↓ Inflammation	Glomerulonephritis	Prevention of CV outcomes
	↓ Vasoconstriction	CKD–fibrosis	Prevention of CKD progression
Macrophages T cells	↓ Vascular injury	Kidney transplantation	Prevention of CNI toxicity
	↓ Mesangium expansion		



Kidney International 2019 96, 302-319DOI: (10.1016/j.kint.2019.02.030)

Blood pressure in chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference

OPEN

Dual inhibition of the renin-angiotensin system

Post hoc analyses from the ONgoing Telmisartan Alone and in (ONTAR-
tes Using
ns Affairs
suggested
rect renin
y benefit
GFR and
lower.[81]

Additionally, the risks of hyperkalemia, acute kidney injury, and hypotension were greater with dual regimens.[82] In 2014, the European Medicines Agency endorsed restrictions on combining different classes of RAAS inhibitors in patients with diabetic nephropathy. A more recent meta-analysis suggested that dual ACEi and ARB treatments have efficacy in preventing ESKD in adults with diabetic kidney disease, if the treatments can be implemented safely.[83] Conference participants discussed the possibility that dual RAAS regimens have long-term benefits in specific subgroups of patients, particularly those with a substantially lower degree of albuminuria while they are on dual versus monotherapy of RAAS inhibitors or when dual blockers are used in combination with potassium binders. Combining an ACEi or ARB with mineralocorticoid receptor antagonist may also confer additional protection, but the absence of informative RCTs means that we cannot currently assess the relative risks
g acute kidney injury and hyperkalemia) and benefits.

Kidney International (2019) **95,** 1027–1036; https://doi.org/10.1016/j.kint.2018.12.025

Revisiting RAAS blockade in CKD with newer potassium-binding drugs

Panagiotis I. Georgianos, Rajiv Agarwal

Kidney International Volume 93, Issue 2, Pages 325-334 (February 2018)
DOI: 10.1016/j.kint.2017.08.038

Table 2 | Major randomized, controlled trials evaluating the effect of dual RAAS blockade on renal outcomes and the associated risk of hyperkalemia

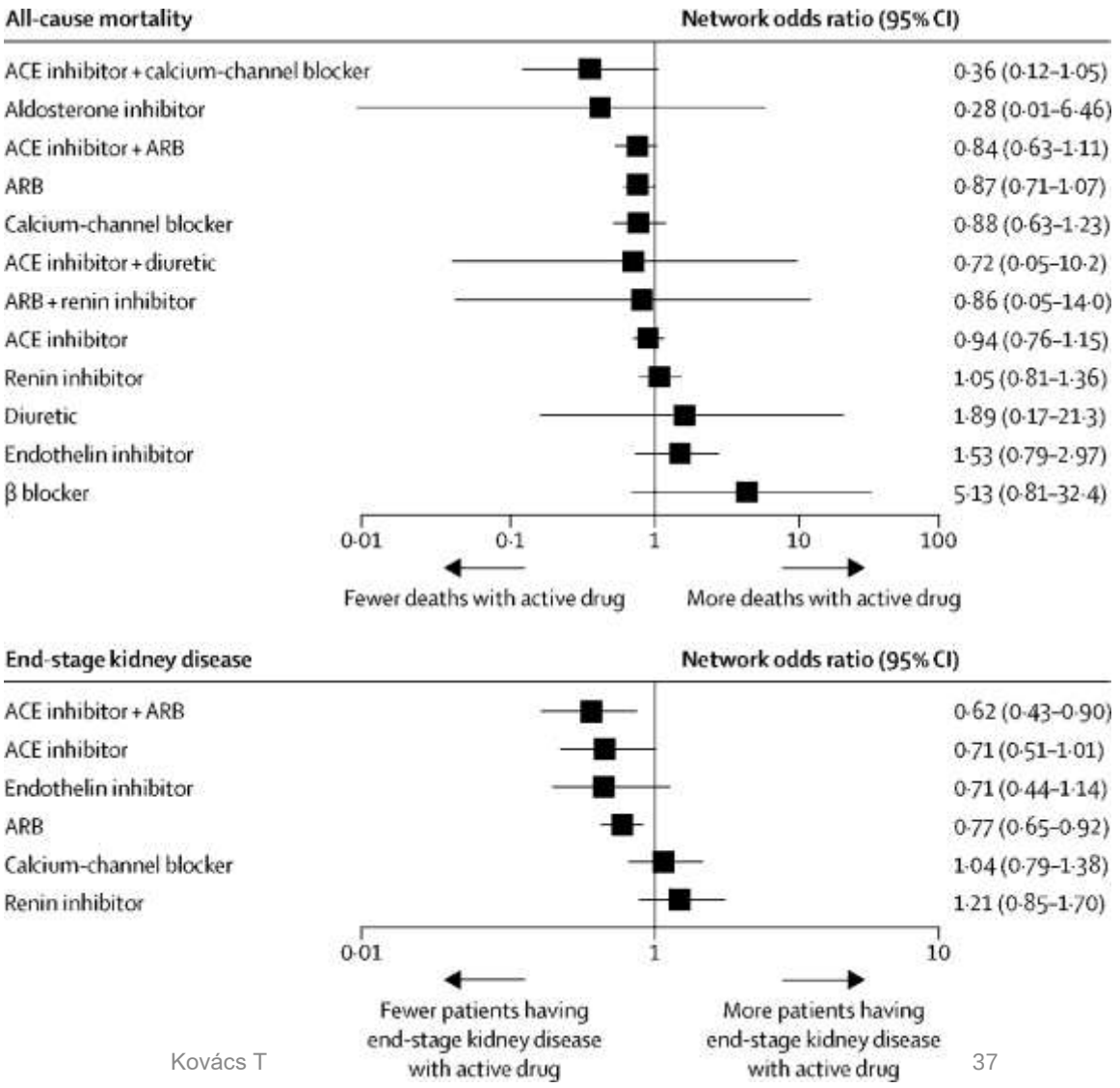
					Effect on renal outcomes		Associated hyperkalemia risk				
Study	Patient characteristics	*N*	Intervention	Follow-up, yr	DScr	ESRD	Definition	Incidence in dual RAAS group	Incidence in monotherapy	Comparison	Ref.
ONTARGET	Established CV disease or high-risk DM	26,620	Ramipril (10 mg/d) vs. telmisartan (80 mg/d) vs. their combination	4.6	↑						
ALTITUDE	Type 2 DM, CKD, CV disease or both	8651	Aliskiren (300 mg/d) vs. placebo on background therapy with ACEI or ARB	2.7	No differe						
VA-NEPHRON-D	Type DM with overt nephropathy	1448	Lisinopril (10–40 mg/d) vs. placebo on a background therapy with losartan (100 mg/d)	2.2	No differe						

ACEI, angiotensin-converting enzyme inhibitor; ALTITUDE, Aliskiren Trial in Type 2 Diabetes Using Cardioren
DM, diabetes mellitus; DScr, doubling of serum creatinine; ESRD, end-stage renal disease; HR, hazard ratio; O
aldosterone system; sK, serum potassium; VA-NEPHRON-D, Veterans Affairs Nephropathy in Diabetes trial.

95% CI 1.8–4.3).[8] When the VA-NEPHRON-D trial was closed, dual RAAS blockade showed a strong trend to lowering the risk of end-stage renal disease versus monotherapy (HR: 0.66; 95% CI 0.41–1.07, $P = 0.07$).[8] This trend suggests a potential emerging signal for renoprotection with combination therapy.[22]

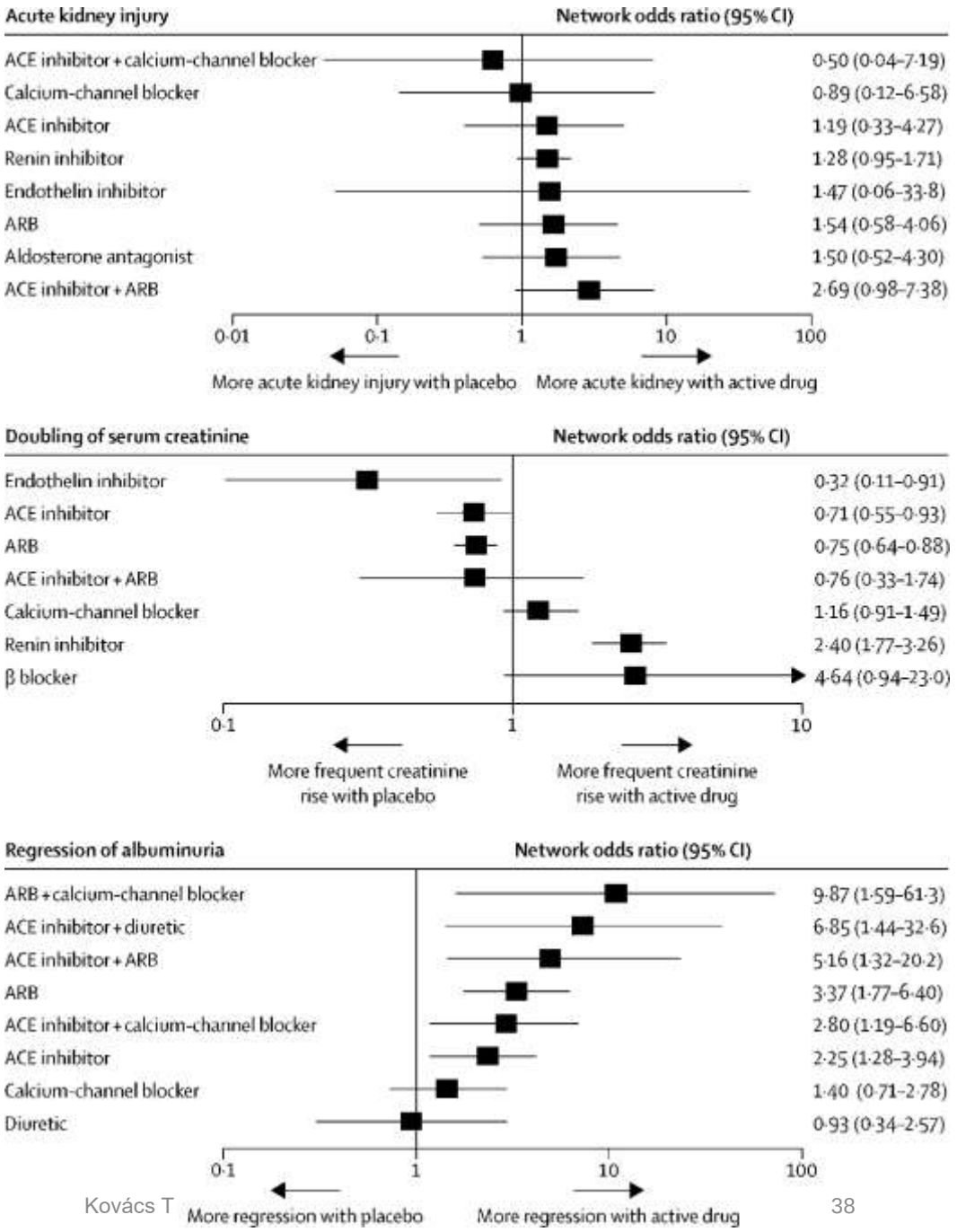
The notion that the premature termination of the VA-NEPHRON-D should not be conclusively considered as the end of dual RAAS blockade is supported by a 2015 network meta-analysis of 157 RCTs incorporating data from 43,256 participants with diabetic kidney disease.[10] This meta-analysis showed that dual RAAS blockade was associated with a 38% reduced risk of incident end-stage renal disease versus placebo (OR: 0.62; 95% CI 0.43–0.90). Combination therapy increased the risks of hyperkalemia (OR: 2.69; 95% CI 0.97–7.47) and acute kidney injury (OR: 2.69; 95% CI 0.98–7.38),[10] but the 95% CI of the ORs crossed 1.0.

Network meta-analysis of blood pressure-lowering agents compared with placebo for primary outcomes in adults with diabetes and kidney disease n=43256



Palmer Lancet 2015

Network meta-analysis of blood pressure-lowering agents compared with placebo for kidney function outcomes in adults with diabetes and kidney disease n=43256



Palmer Lancet 2015

ÖSSZEFOGLALÁS

-Primer glomerulonephritisek
  -Áttekintés
  -Non-invazív diagnosztika
-Általános vesevédő kezelés szempontjai
-Nephrologiai konzílium
-Hipertónia kezelése CKD-ban

Köszönöm a figyelmet!

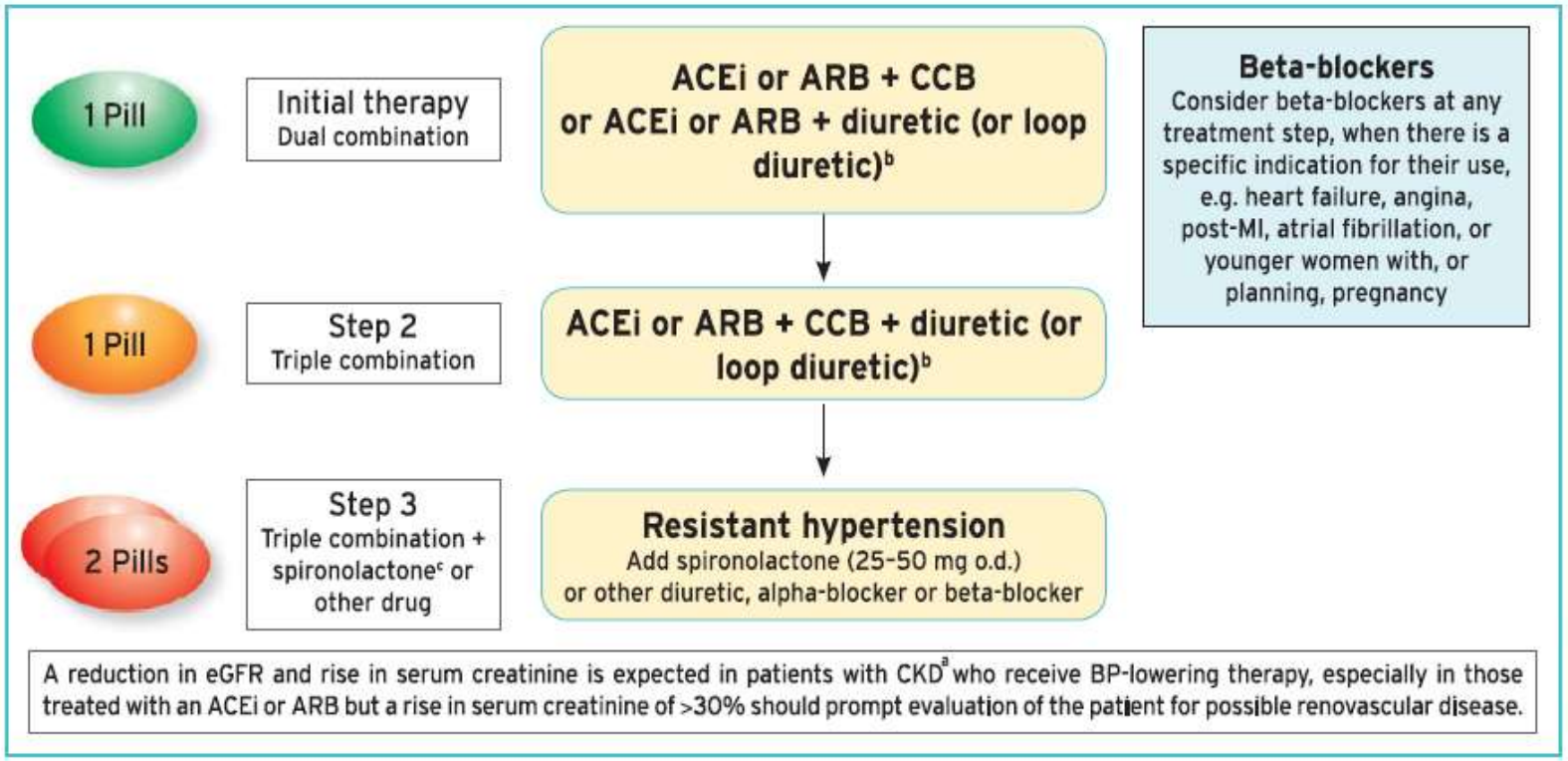


Figure 6 Drug treatment strategy for hypertension and chronic kidney disease. ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BP = blood pressure; CCB = calcium channel blocker; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; MI = myocardial infarction; o.d. = omni die (every day).

[a]CKD is defined as an eGFR <60 mL/min/1.72 m^2 with or without proteinuria.

[b]Use loop diuretics when eGFR is <30 mL/min/1.72 m^2, because thiazide/thiazide-like diuretics are much less effective/ineffective when eGFR is reduced to this level.

[c]Caution: risk of hyperkalaemia with spironolactone, especially when eGFR is <45 mL/min/1.72 m^2 or baseline K^+ ≥4.5 mmol/L.

The overdriven glomerulus as a cardiovascular risk factor

Carmine Zoccali, Francesca Mallamaci

Kidney International
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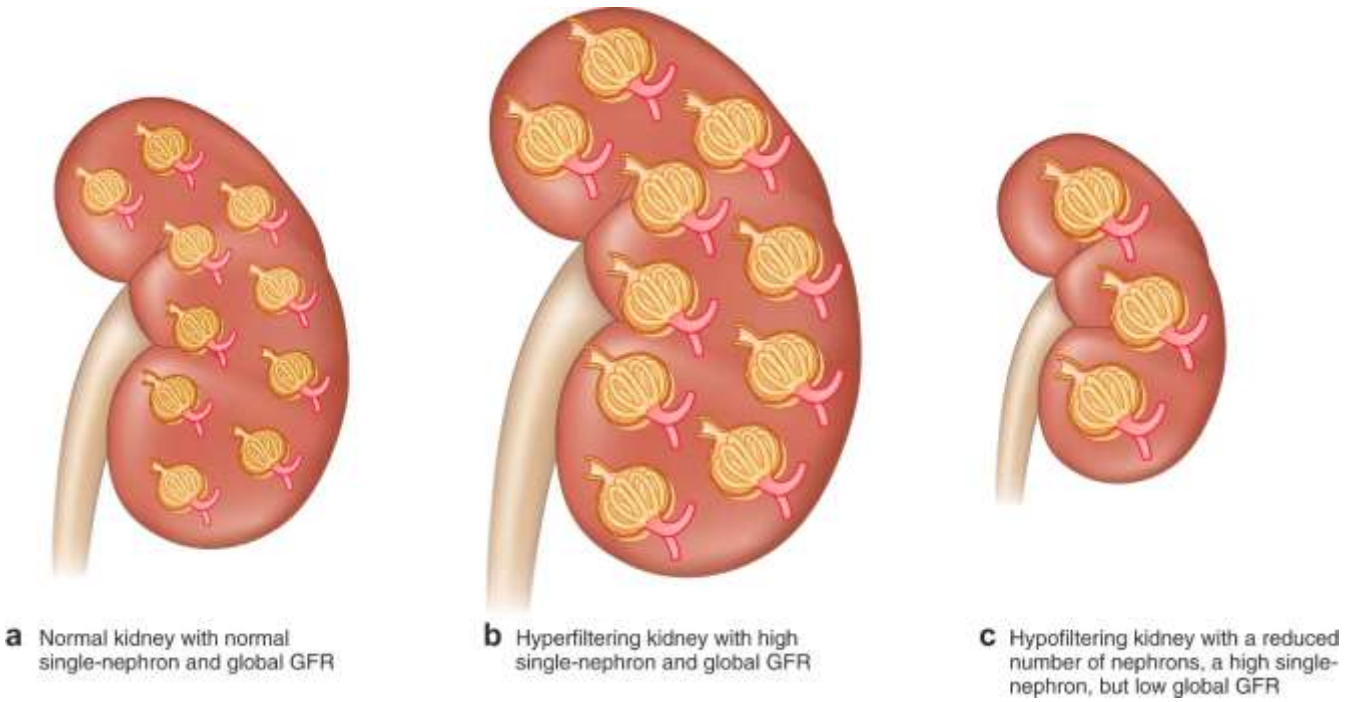

a Normal kidney with normal single-nephron and global GFR

b Hyperfiltering kidney with high single-nephron and global GFR

c Hypofiltering kidney with a reduced number of nephrons, a high single-nephron, but low global GFR