Rein et HTA

Risque rénal et cardiovasculaire

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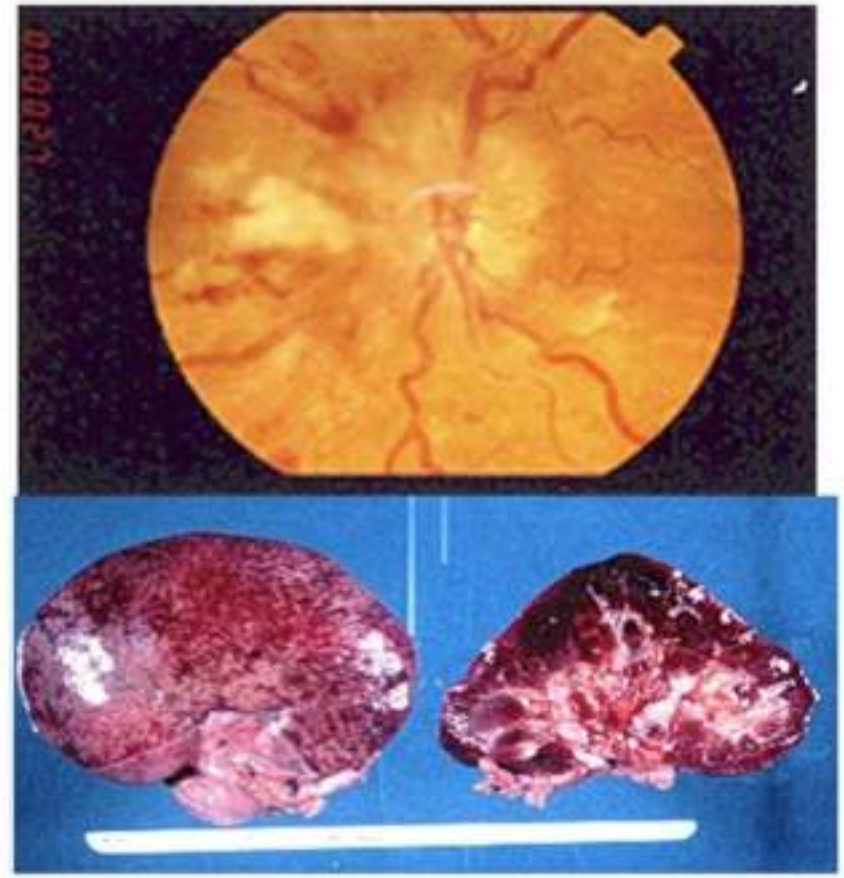
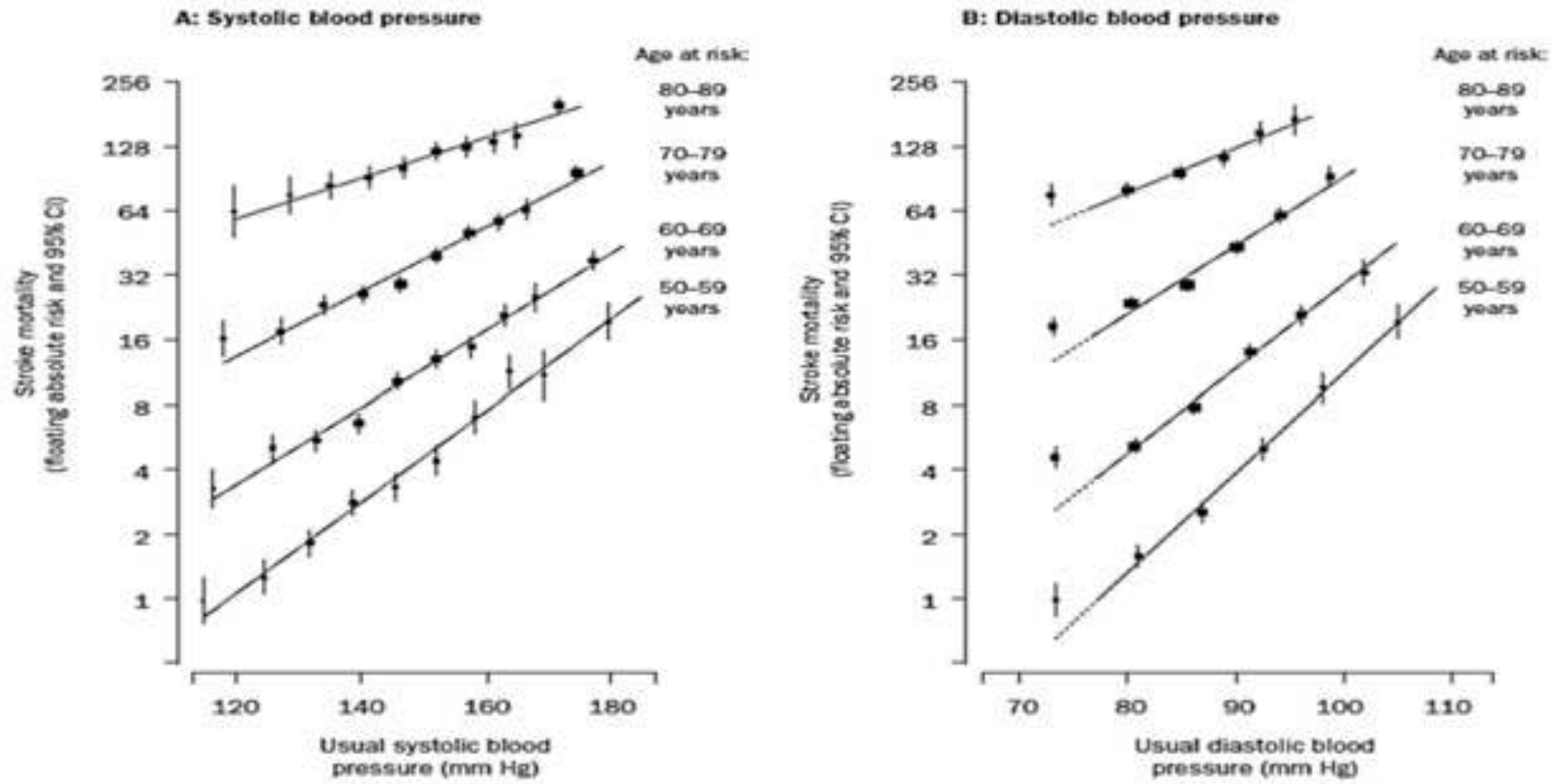
Consequences of uncontrolled hypertension

- Premature death
- Generalized arteriosclerosis and atherosclerosis
- Heart disease
- Stroke
- Malignant Hypertension with kidney failure



Stroke risk rises exponentially with BP



61 prospective studies: > 1 million subjects: Lancet 2002

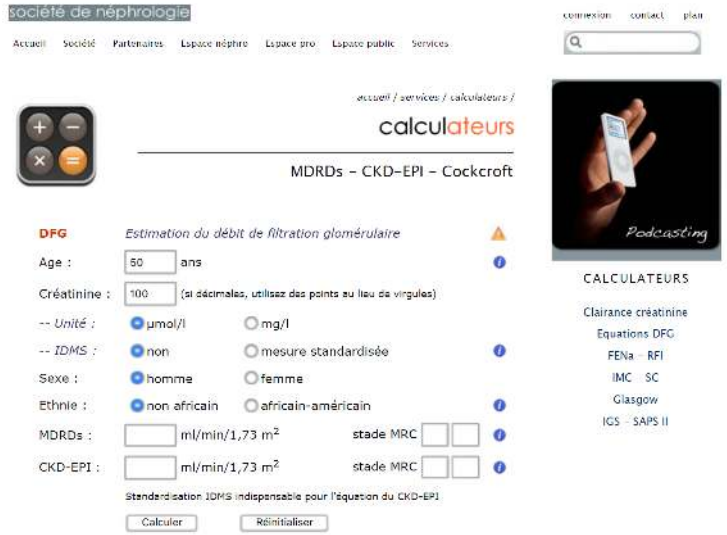
HTA et risque rénal

Comment estimer la fonction rénale

- Méthode des clairances+++
  - Clairance: temps nécessaire à éliminer un élément à 100% d'un vecteur
  - Pour le rein: production connue et stable, élimination strictement glomérulaire sans sécrétion/réabsorption tubulaire
  - Aucun élément naturel possible
  - Inuline, DTPA…: vrai DFG mais cher, difficile donc indications limitées
- Créatinine
  - Ce qui répond le mieux à la définition
  - Dosage peu cher et actuellement devenu reproductible et comparable entre labo (méthode IDMS)
  - Mais clairance de la créatinine (U.V/P): peu fiable, 15% sécrétion tubulaire (↗ si IRC). Reste utile parfois.

Comment estimer la fonction rénale ?

- DFG estimé:
  - G&C à oublier
  - MDRD: mauvais si DFG>60ml/min/1,73m2
  - CKD-EPI recommandation actuelle



Classification de la MRC

Stade	Description	DFG (ml/min/1,73 m²)
1	Maladie rénale chronique* avec fonction rénale normale	≥ 90
2	Maladie rénale chronique* avec insuffisance rénale légère**	60-89
3A	Insuffisance rénale légère à modérée	45-59
3B	Insuffisance rénale modérée à sévère	30-44
4	Insuffisance rénale sévère	15-29
5	Insuffisance rénale terminale	< 15

* Avec marqueurs d'atteinte rénale : protéinurie clinique, hématurie, leucocyturie, ou anomalies morphologiques ou histologiques ou marqueurs de dysfonction tubulaire, persistant plus de 3 mois.

** Un DFG compris entre 60 et 89 ml/min peut être normal chez un sujet âgé.

Classification et estimation du risque rénal

Pronostic, fréquence (nb par an) et stratégie de suivi des maladies rénales chroniques (MRC) en fonction du débit de filtration glomérulaire et de l'albuminurie KDIGO 2012 Traduction Perruche en automne				Albuminurie ou *protéinurie* (mg/g ou mg/mmol)		
				A1	**A2**	**A3**
				Normale à légèrement augmentée	Légèrement à modérément augmentée	Augmentation importante
				<30 ou <*150* <3 ou <*15*	30-300 ou 150-500 3-30 ou *15-50*	>300 ou >*500* >30 ou >*50*
Débit de filtration glomérulaire estimé (formule CKD-EPI 2009) exprimé en ml/mn/1,73m²	**G1**	Normal ou haut	>90	1 si MRC	1 Suivi MG	2 Avis Néphro
	G2	Légèrement diminué	60-89	1 si MRC	1 Suivi MG	2 Avis Néphro
	G3a	Légèrement à modérément diminué	45-59	1 Suivi MG	2 Suivi MG	3 Avis Néphro
	G3b	Modérément à sévèrement diminué	30-44	2 Suivi MG	3 Suivi MG	3 Avis Néphro
	G4	Diminution importante	15-30	3 Avis Néphro	3 Avis Néphro	>=4 Avis Néphro
	G5	Faillite rénale	<15	>=4 Avis Néphro	>=4 Avis Néphro	>=4 Avis Néphro

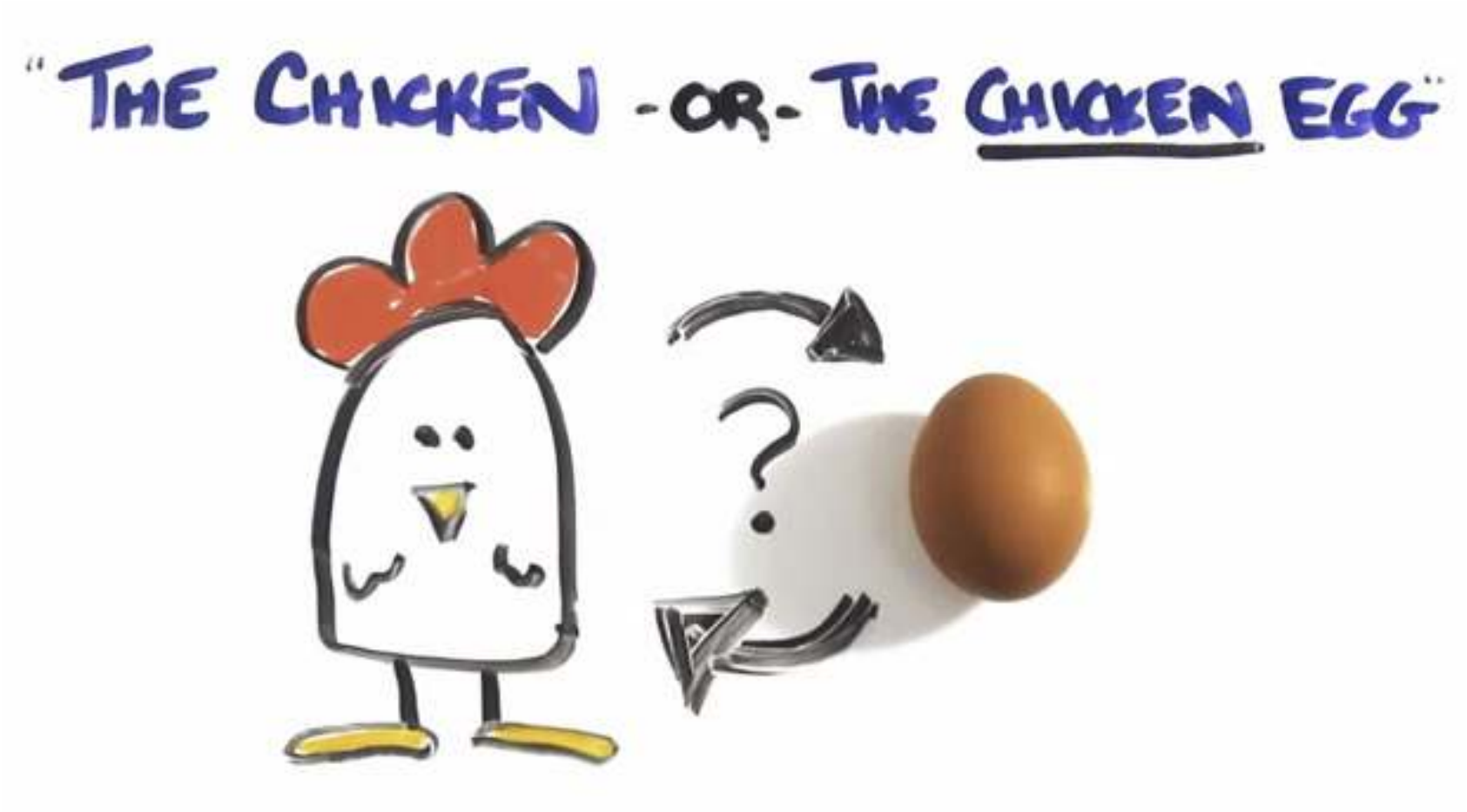
Risque de progression: faible (vert), modéré (jaune), important (orange), très important (rouge)

Kidney inter., Suppl. 3, 2013

Classification et estimation du risque rénal

- Attention! Tenir compte de la vitesse de dégradation de la fonction rénale
  - Lente: <-2ml/min/an avis néphro selon tableau précèdent
  - Modérée: -2 à 5ml/min/an avis néphro souhaitable
  - Rapide: >-5ml/min/an avis néphro urgent

Maladie rénale chronique et HTA



	n	%	Taux brut	Intervalle de confiance à 95% du taux brut
Hypertension artérielle	2 850	25,1	42	[41- 44]
Néphropathie diabétique	2 442	21,5	36	[35- 38]
Inconnu	1 924	17,0	29	[27- 30]
Autre	1 696	15,0	25	[24- 26]
Glomérulonéphrite primitive	1 169	10,3	17	[16- 18]
Polykystose	621	5,5	9	[8- 10]
Pyélonéphrite	552	4,9	8	[8- 9]
Vasculaire	89	0,8	1	[1- 2]

NB : 0 néphropathies manquantes

Incidence de l'IRCT en France: effet de l'HTA

Tableau 1-4. Age des patients à l'initiation du traitement, selon le sexe et la maladie rénale initiale
Age at start of ESRD therapy, by gender and primary diagnosis

Age		n	Moyenne	Ecart-type	Médiane	Min	Max
Selon le sexe	Homme	7 414	67,9	15,5	70,7	0,0	100,2
	Femme	3 929	67,0	16,9	69,9	0,0	96,7
Selon la maladie initiale	Glomérulonéphrite primitive	1 169	59,0	17,7	61,3	0,6	96,7
	Pyélonéphrite	552	63,9	18,7	68,5	0,1	97,0
	Polykystose	621	57,9	12,8	56,2	0,0	90,7
	Néphropathie diabétique	2 442	68,8	12,3	70,4	23,3	93,0
	Hypertension artérielle	2 850	74,3	12,4	76,7	16,0	100,2
	Vasculaire	89	68,6	15,5	72,7	0,0	94,5
	Autre	1 696	61,8	19,1	65,9	0,4	93,0
	Inconnu	1 924	70,5	15,1	72,8	11,0	96,3
Total Pays		11 343	67,6	16,0	70,4	0,0	100,2

Néphroangiosclérose (NAS): quand l'HTA rend les reins malades

Définition:

- Néphropathie d'origine vasculaire
- Conséquence rénale tardive d'une HTA
  - Ancienne
  - Mal contrôlée

Cause majeure d'IRCT

- Mais diagnostic par défaut, preuve histologique rare

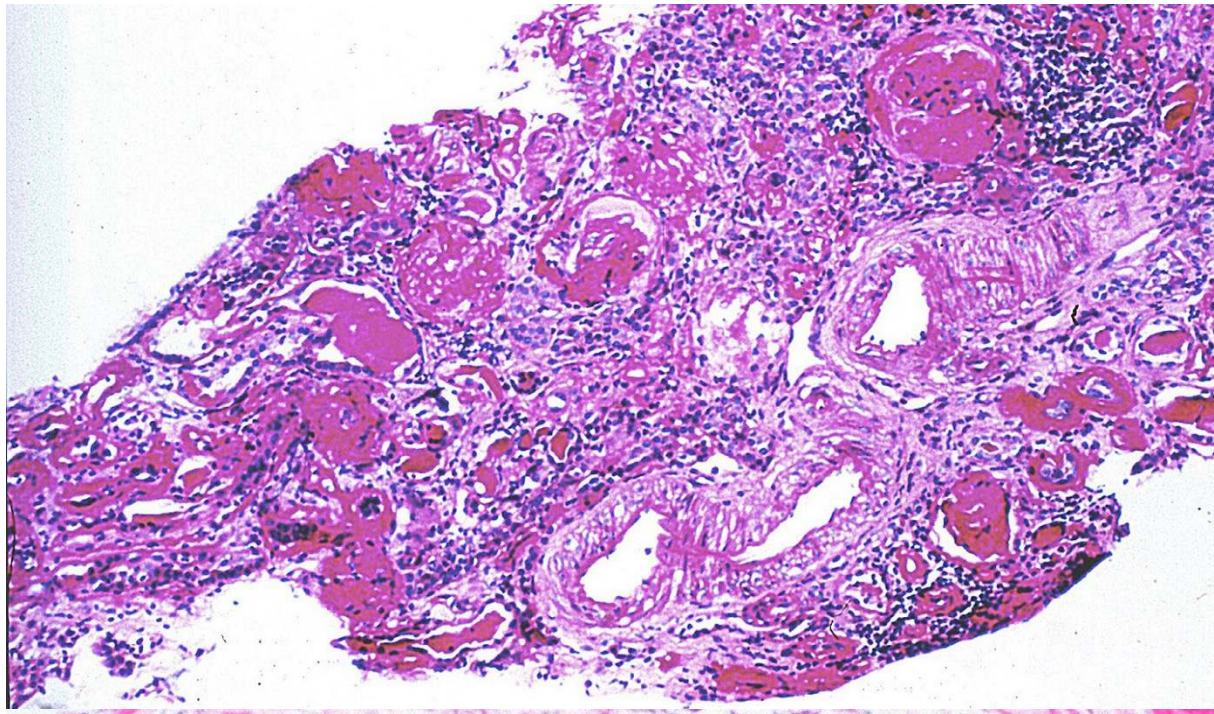
Age++

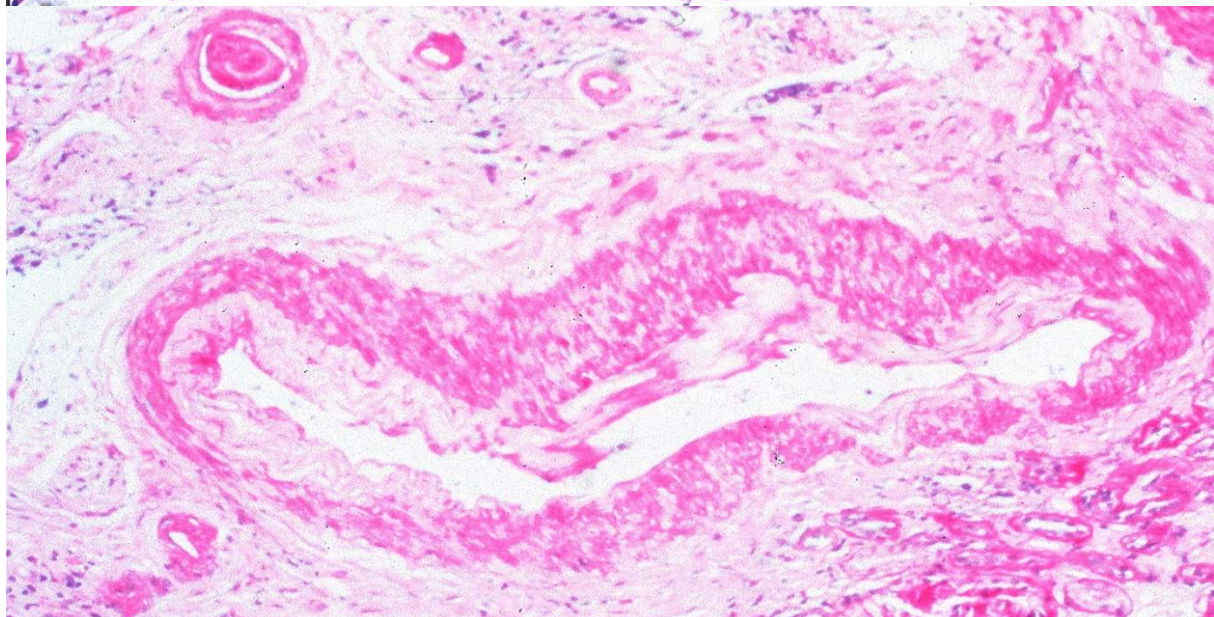
Diagnostic de la NAS

- Souvent d'exclusion+++
- Pas d'élément spécifique, faisceau d'arguments:
  - Terrain: sujet âgé, FDR CV et ATCD CV, race noire
  - HTA ancienne, mal équilibrée, retentissement d'organe (HVG, rétinopathie)
  - Evolution: IRC lentement progressive
  - Syndrome biologique pauvre:
    - Pas de leucocyturie ou d'hématurie
    - Protéinurie absente à modérée (<1g/g en général)
  - Reins harmonieux, symétriques, pas de SAR
- Histologique (rare)

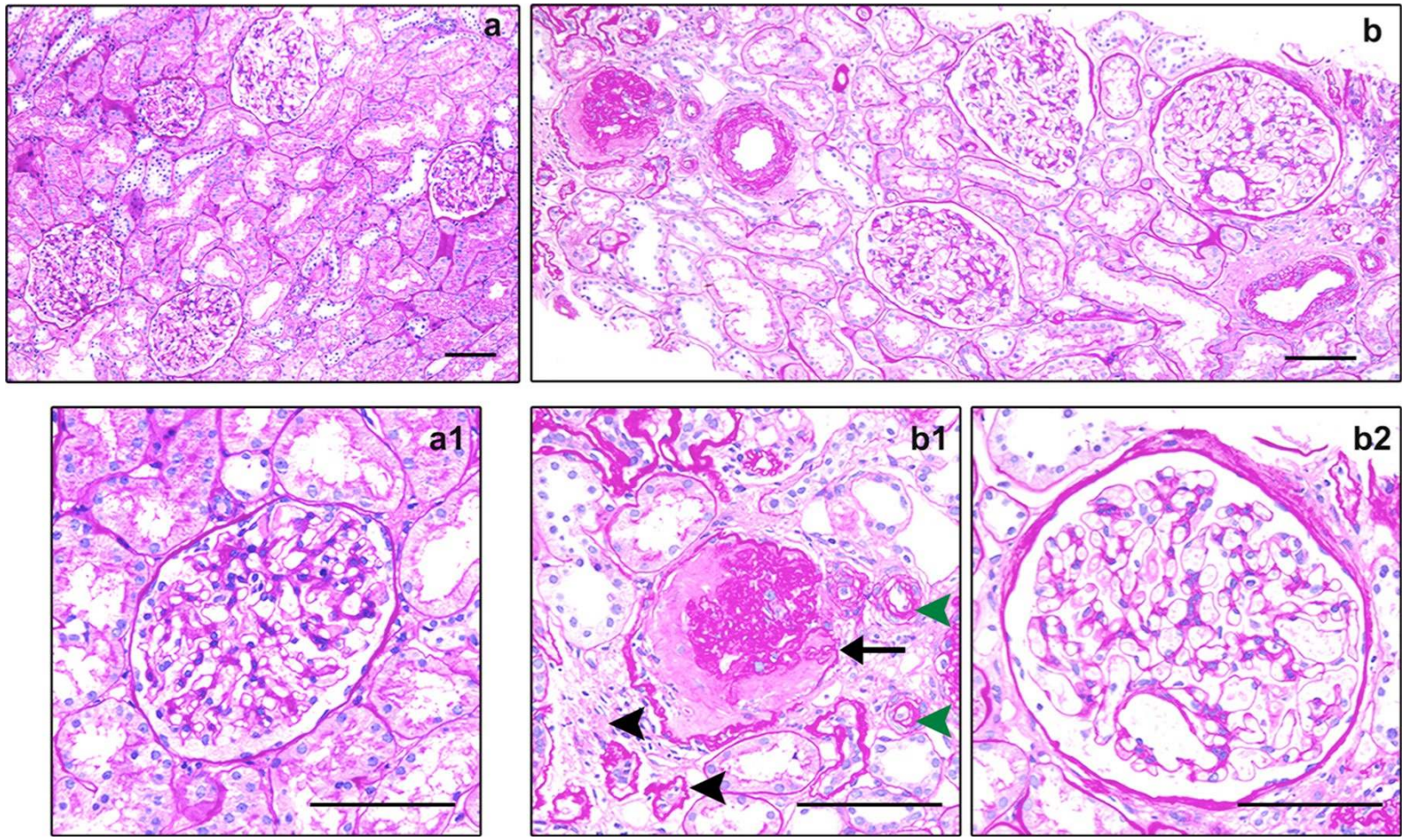
Diagnostic

- Microscopie optique:
  - Lésions vasculaires:
    - Épaississement de la média des artères et artérioles
    - Dépôts hyalins des artérioles afférentes
    - Fibrose intimale
  - Lésions glomérulaires secondaires à l'ischémie
    - Souvent focales, sauf si IRC évoluée
    - Épaississement et plicatures de la MB parfois associés à des lésions d'HSF (secondaire)
    - Glomérulosclérose
  - Lésions tubulo-interstitielles
    - Fibrose interstitielle
    - Atrophie tubulaire
- IF:
  - Pas de dépôts immuns+++
  - IgM et C3 possibles au sein des lésions d'HSF

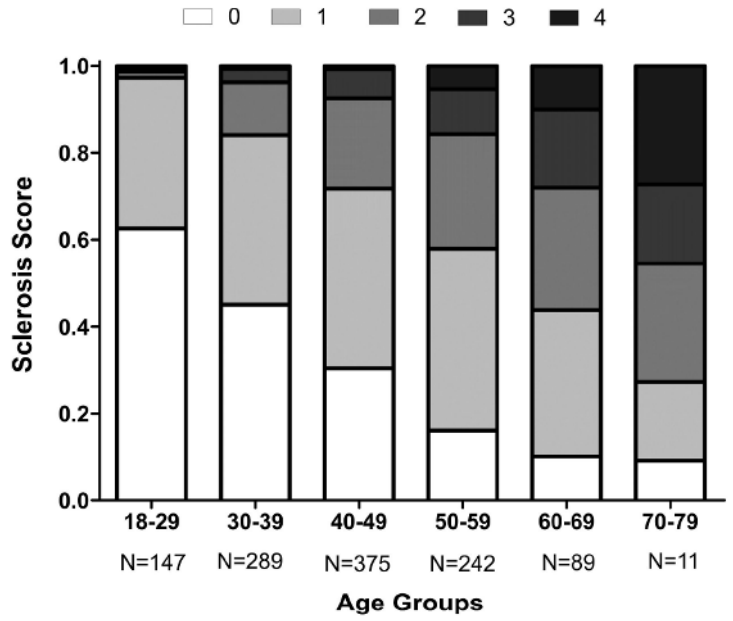




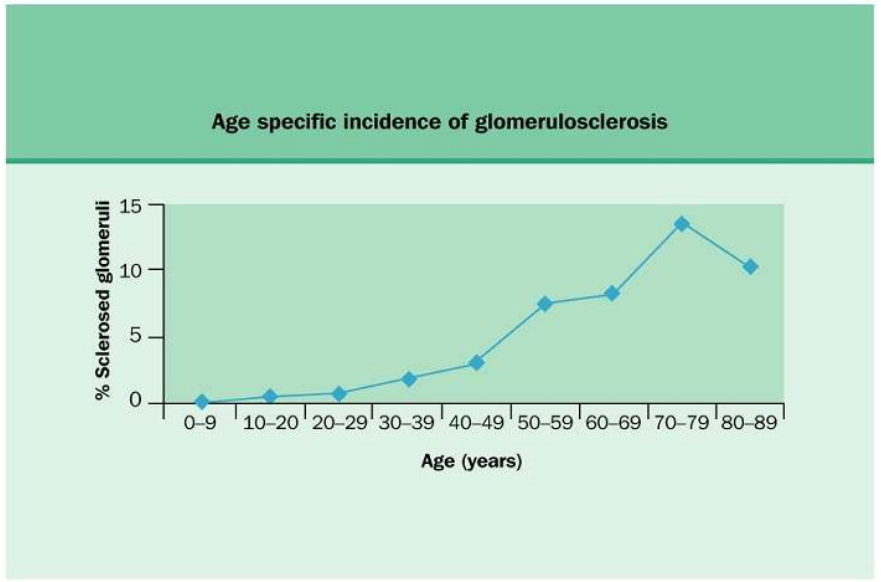
Le vieillissement rénal est associé à des lésions de type NAS

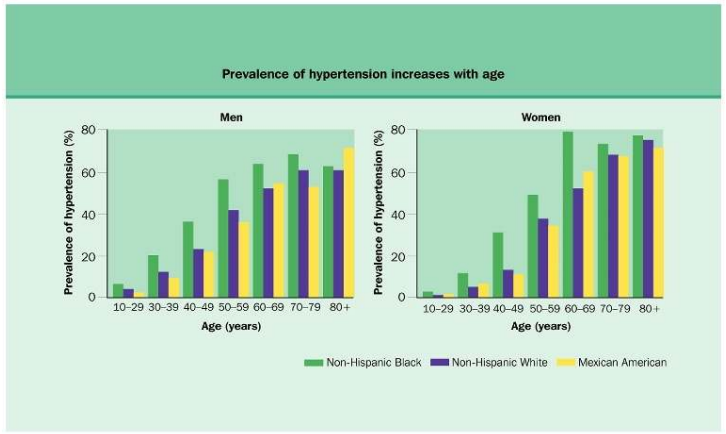


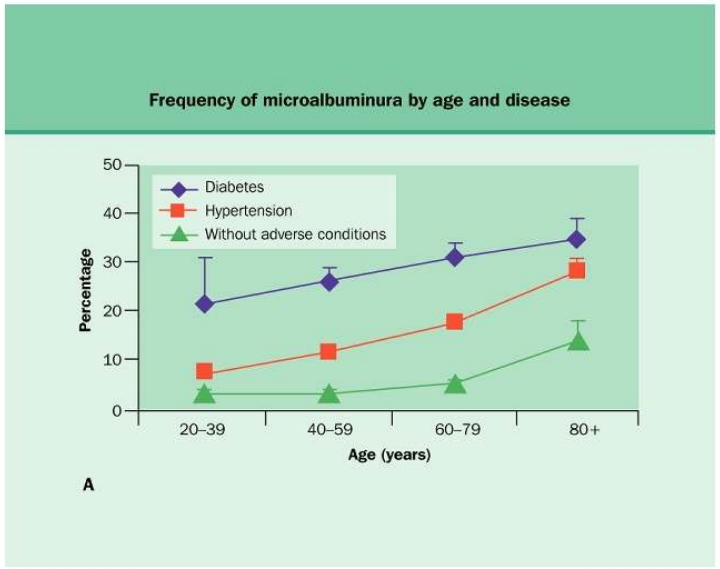
Age et anomalies histologiques

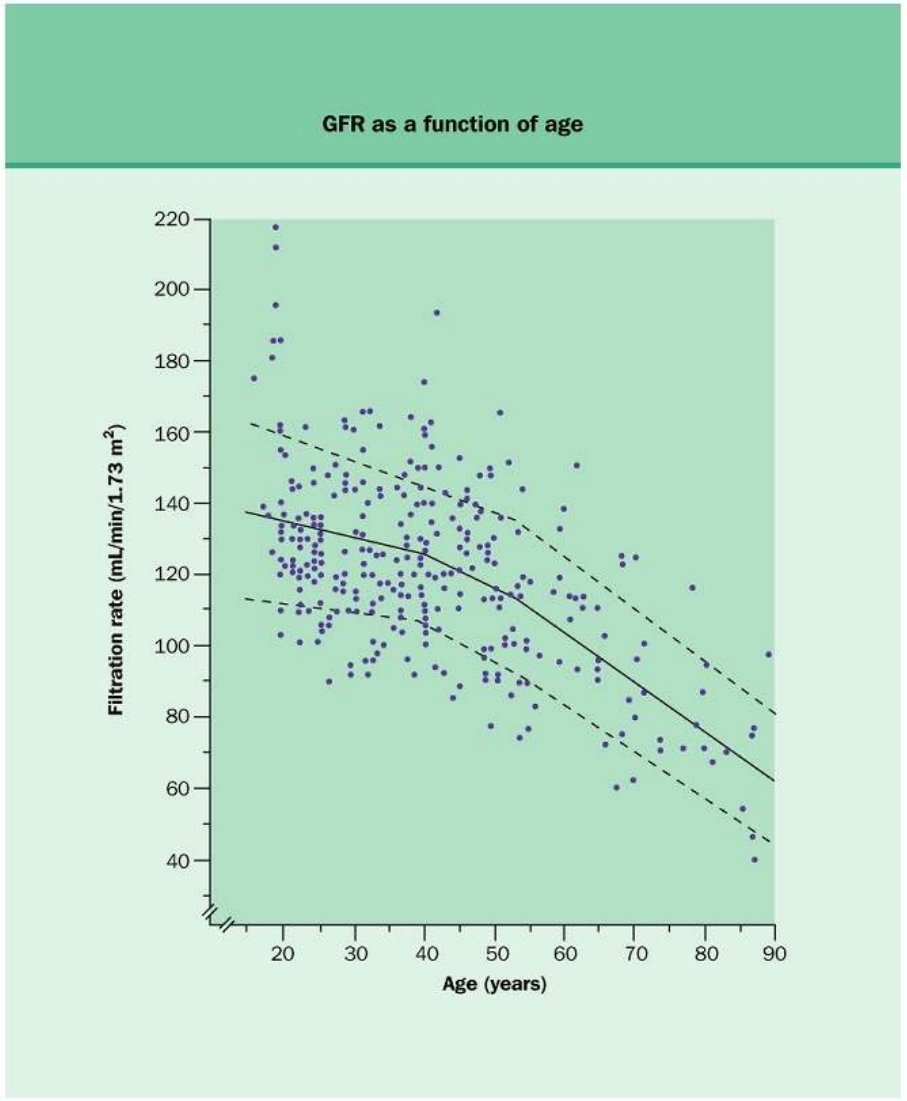


Sclerosis score by age group among 1203 living kidney donors









Sémiologie rénale et âge

Hypertension

Hypertensive Nephrosclerosis as a Relevant Cause of Chronic Renal Failure

Edna Regina Silva Pereira Caetano, Roberto Zatz, Luís Balthazar Saldanha, José Nery Praxedes

- 81 patients HTA grade 2 + IRC
- Tableau clinicobiologique et anamnèse en faveur d'une « NAS bénigne »
- PBR

TABLE 2. Main Histological Diagnoses

Diagnosis	n (%)
HN	53 (65)
BN	18 (22)
MN	35 (43)
Primary nephritis	13 (16)
IgA nephropathy	9 (11)
Membranous glomerulonephritis	2 (3)
Mesangiocapillary glomerulonephritis	1 (1)
Chronic interstitial nephritis	1 (1)
FSGS	15 (19)

Néphroangiosclérose bénigne 22%

78% !

Hypertension 2001

Réanalyse des « Néphropathies Hypertensives »

- Etude rétrospective sur 136 patients
  - Diagnostic de NAS bénigne posé par le néphrologue
  - Diagnostic après réévaluation +/- PBR
    - NAS bénigne 44%
    - Pathologie rénovasculaire et/ou emboles cholestérol 40 %
- Etude prospective sur 58 patients
  - Diagnostic de NAS bénigne posé par le néphrologue
  - Diagnostic après réévaluation +/- PBR
    - NAS bénigne 46%
    - Pathologie rénovasculaire 32 %

Zucchelli *et al*, Kidney Int 1998

Table 4. Final diagnosis of 58 consecutive patients clinically considered as having hypertensive nephrosclerosis

Final diagnosis	*N* patients
Analgesic nephropathy	1
Unsuspected IgA nephropathy	1
Immunotactoid nephropathy	1
Light-chain deposition disease without free light chains in the plasma and urine	1
Unclassified	8
Atheromatous renovascular disease	19
True hypertensive nephrosclerosis	27

HTA secondaires aux MRC

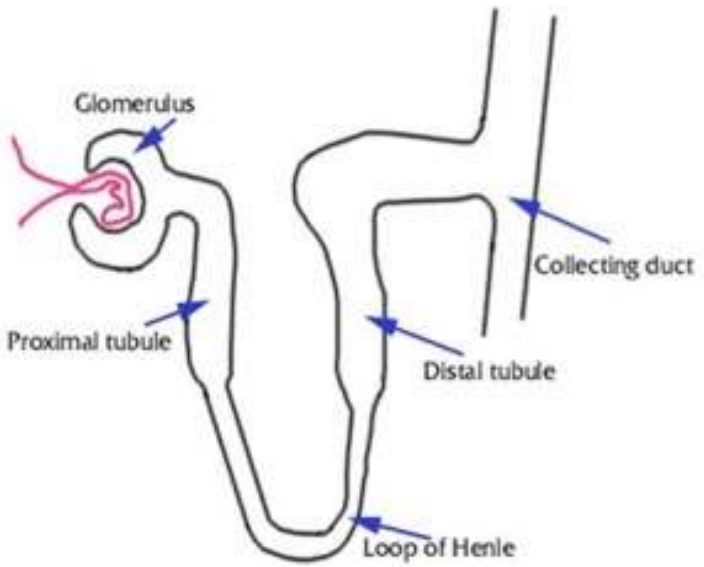
- Maladies vasculaires
  - SAR atheromateuse du fibrodysplasique
  - Embols de cholesterol
- Maladies glomérulaires
  - Symptome classique: NIgA
  - Symptome fréquent: GN avec proliferation endocapillaire (SNA)
  - Symptome possible: GEM
- Maladies héréditaires
  - Kystiques: PKAD, ADPKD (UMOD…)
  - Tubulopathie: Liddle (augmentation activité ENaC), Gordon (WNK1 et WNK4 entraine l'augmentation de l'expression apicale co transport Na/Cl dans TCD)

Les MRC peuvent aggraver une HTA présente

Reduced nephron mass decreases GFR, which increases renin

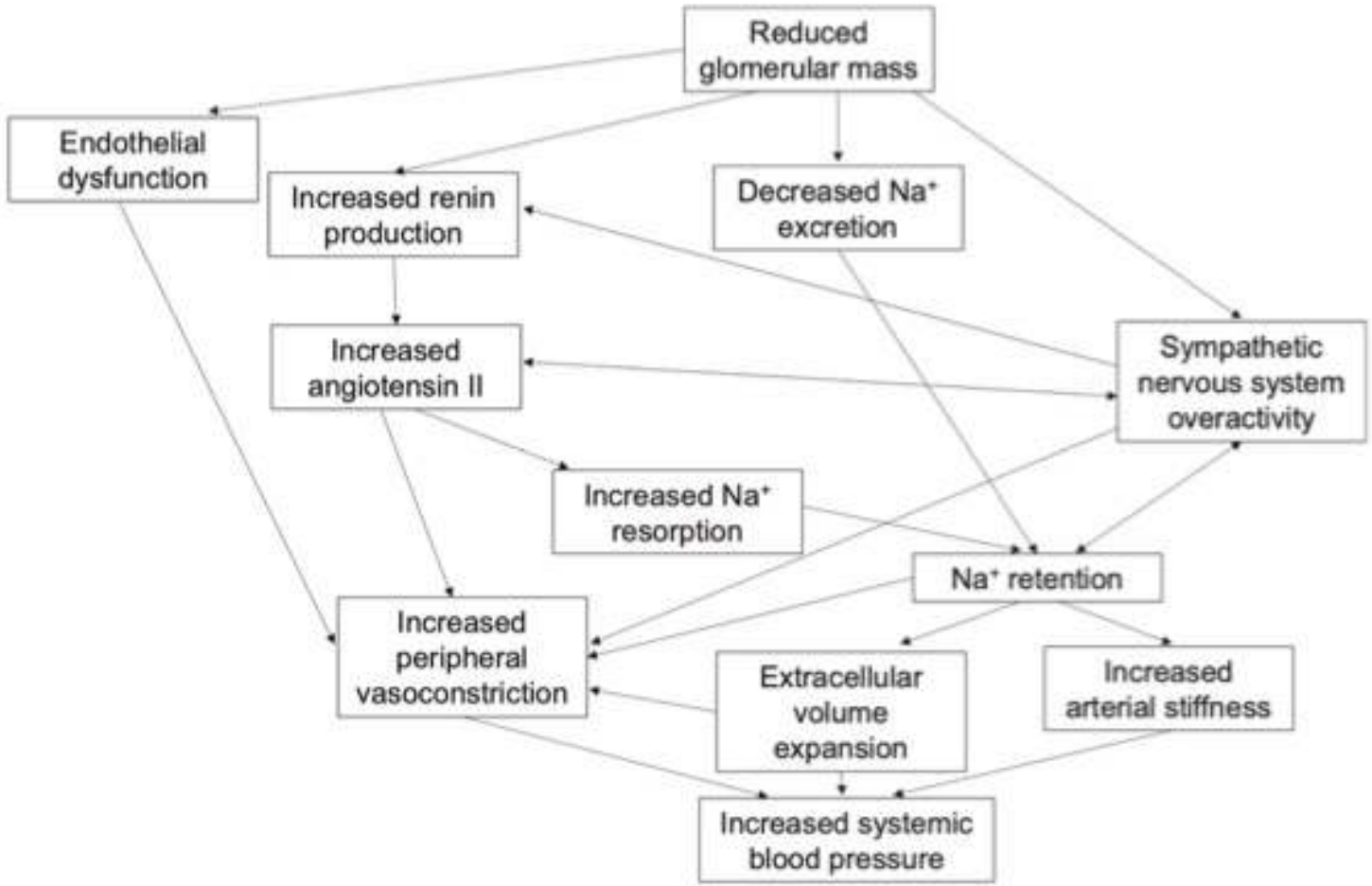
Ang II increase, which causes proximal tubular sodium reabsorption

Chronic sodium retention stimulates vasoconstriction and leads to arterial stiffness



Pathophysiologic mechanisms of hypertension in CKD

Ku AJKD 2019 Core Curriculum 2019



L’HTA augmente t’elle le risque rénal?

Baseline Proteinuria (g/d)	Study A Patients (GFR, 25–55 mL/min · 1.73 m²)	Study B Patients (GFR, 13–24 mL/min · 1.73 m²)
	n(%)	
0–0.25	305 (52.1)	81 (31.8)
0.25–1.0	120 (20.5)	63 (24.7)
1.0–3.0	105 (18.0)	70 (27.5)
≥ 3.0	55 (9.4)	41 (16.0)

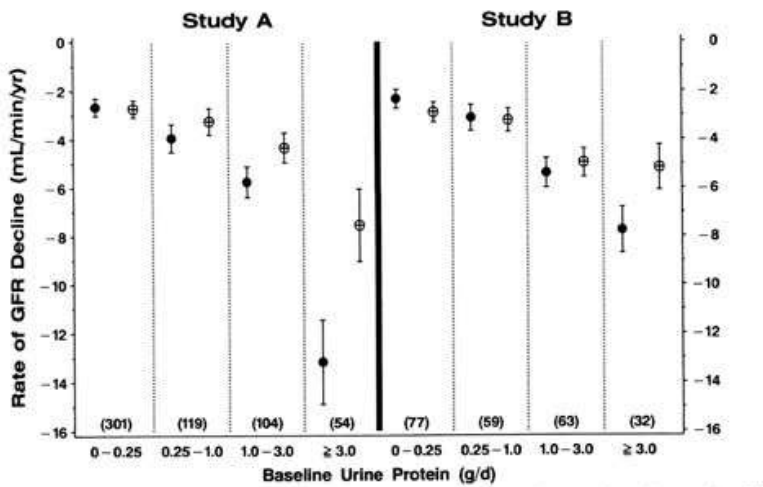
Blood Pressure Control, Proteinuria, and the Progression of Renal Disease

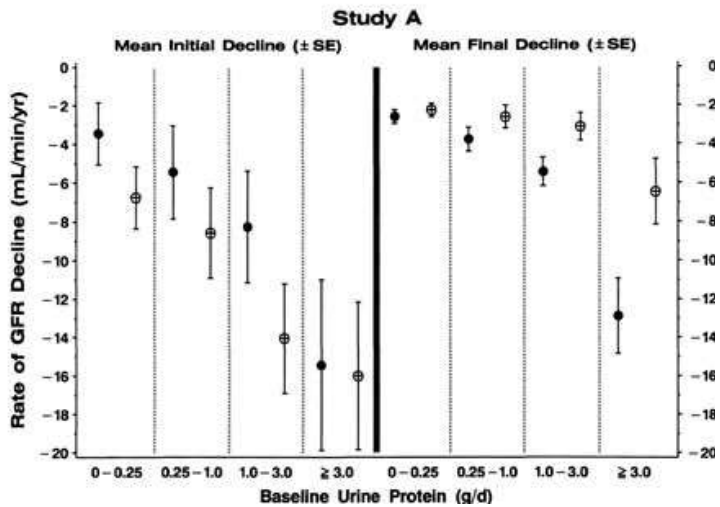
The Modification of Diet in Renal Disease Study

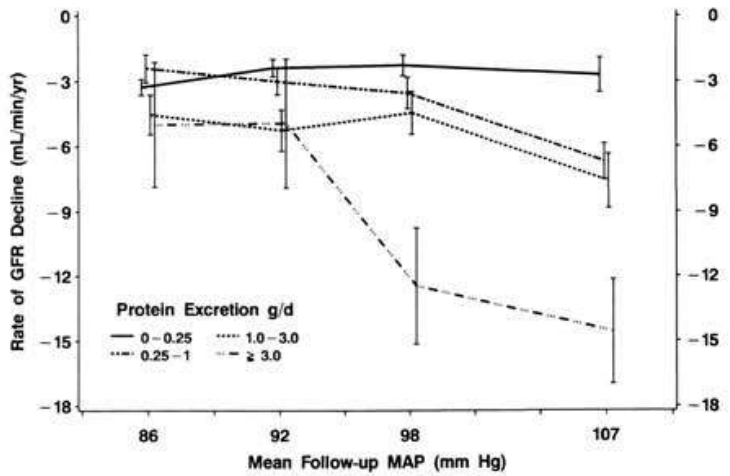
John C. Peterson, MD; Sharon Adler, MD; John M. Burkart, MD; Tom Greene, PhD; Lee A. Hebert, MD; Lawrence G. Hunsicker, MD; Andrew J. King, MD; Saulo Klahr, MD; Shaul G. Massry, MD; and Julian L. Seifter, MD, for the Modification of Diet in Renal Disease (MDRD) Study Group*

Ann Inter Med 1995

840 CKD patients. 2 sous groupes selons DFG.
Dans chaque groupe: double random: cible PAM <107mmHg si age <60 ans ou < 113mmHG vs -15mmHg et apports en proteines (1.3g/Kg vs 0.6g/kg groupe A et 0.6g/dk vs 0.3g/Kg groupe B).







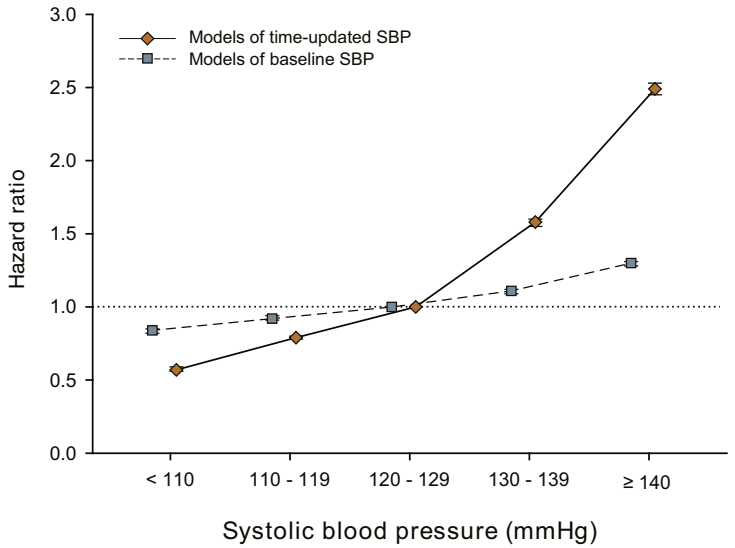
Associations of Systolic Blood Pressure With Incident CKD G3-G5: A Cohort Study of South Korean Adults

Tae Ik Chang, Hyunsun Lim, Cheol Ho Park, Connie M. Rhee, Hamid Moradi, Kamyar Kalantar-Zadeh, Ea Wha Kang, Shin-Wook Kang, and Seung Hyeok Han

AJKD 2020

Korean National Health Insurance Service, >10M (1/5 pop), >40ans, au moins 3 DFG estimés
Suivi 4,7 (3,9 -5,8) ans

Characteristic	Overall	SBP, mm Hg				
		<110	110-119	120-129	130-139	≥140
No.	10,495,570	1,423,596	2,545,558	2,621,866	2,520,637	1,383,913
Age, y	52.7 ± 9.9	49.5 ± 8.4	51.1 ± 9.3	52.3 ± 9.6	54.3 ± 10.1	57.2 ± 10.3
Male sex	49.7%	31.9%	46.2%	52.6%	57.6%	55.7%
Comorbid conditions						
Diabetes	10.3%	6.0%	8.1%	10.1%	12.3%	15.1%
IHD	5.0%	3.3%	4.1%	4.9%	5.7%	7.1%
CHF	0.8%	0.5%	0.7%	0.7%	0.9%	1.2%
CBVD	2.6%	1.6%	2.0%	2.5%	3.2%	4.1%
PAD	0.4%	0.3%	0.3%	0.4%	0.5%	0.6%
COPD	1.8%	1.3%	1.6%	1.7%	2.0%	2.3%
Malignancy	2.6%	2.7%	2.5%	2.5%	2.5%	2.6%
Antihypertensives at BL	8.1%	2.8%	5.0%	7.4%	10.7%	15.3%
ACEi or ARB	3.5%	1.1%	2.1%	3.3%	4.7%	6.8%
CCB	2.2%	0.5%	1.2%	2.0%	3.0%	4.6%
Diuretics	1.7%	0.6%	1.1%	1.6%	2.3%	3.2%
Antihypertensives at last visit	15.0%	4.2%	8.3%	12.9%	20.1%	33.2%
ACEi or ARB	6.6%	1.8%	3.6%	5.6%	8.8%	14.8%
CCB	4.8%	0.9%	2.3%	4.0%	6.7%	11.6%
Diuretics	2.7%	0.8%	1.5%	2.4%	3.6%	6.0%
Statins at BL	4.0%	2.5%	3.3%	4.1%	4.8%	5.5%
Statins at last visit	8.3%	5.1%	6.8%	8.2%	9.9%	11.7%
Smoking status						
Never	63.6%	73.7%	65.4%	61.6%	59.2%	61.5%
Former	15.8%	9.9%	14.1%	16.8%	18.5%	18.2%
Current	20.6%	16.4%	20.5%	21.6%	22.3%	20.2%
Alcohol intake						
0 g/d	57.1%	65.9%	59.2%	55.7%	53.3%	53.9%
1-19 g/d	30.2%	27.8%	30.4%	31.3%	31.0%	28.5%
≥20 g/d	12.7%	6.3%	10.4%	13.1%	15.7%	17.6%
Physical activity						
<600 MET-min/wk	48.2%	50.4%	48.1%	47.4%	47.2%	49.3%
600-3,000 MET-min/wk	43.4%	42.3%	43.8%	44.1%	43.8%	41.7%
>3,000 MET-min/wk	8.4%	7.3%	8.1%	8.5%	8.9%	9.0%
Proteinuria	4.6%	3.8%	3.8%	4.3%	4.8%	6.9%
SBP, mm Hg	123.3 ± 15.0	101.2 ± 5.2	113.2 ± 3.4	122.5 ± 3.1	132.7 ± 3.2	149.1 ± 9.8
BMI, kg/m^2	24.0 ± 3.4	22.5 ± 2.7	23.5 ± 2.8	24.1 ± 2.9	24.6 ± 4.5	25.1 ± 3.2
eGFR, mL/min/1.73 m^2	88.2 ± 14.3	90.6 ± 14.6	89.0 ± 14.4	88.4 ± 14.3	87.2 ± 14.1	86.1 ± 14.0
LDL-C, mg/dL	118.6 ± 73.0	116.2 ± 65.0	118.2 ± 79.8	118.9 ± 61.9	119.5 ± 75.2	119.7 ± 82.4
HDL-C, mg/dL	55.5 ± 26.9	57.2 ± 25.7	55.9 ± 26.8	55.3 ± 26.6	54.8 ± 27.0	54.9 ± 28.4
Triglycerides, mg/dL	137.6 ± 101.8	106.7 ± 75.8	125.9 ± 90.7	138.9 ± 101.2	151.6 ± 108.5	163.0 ± 120.0



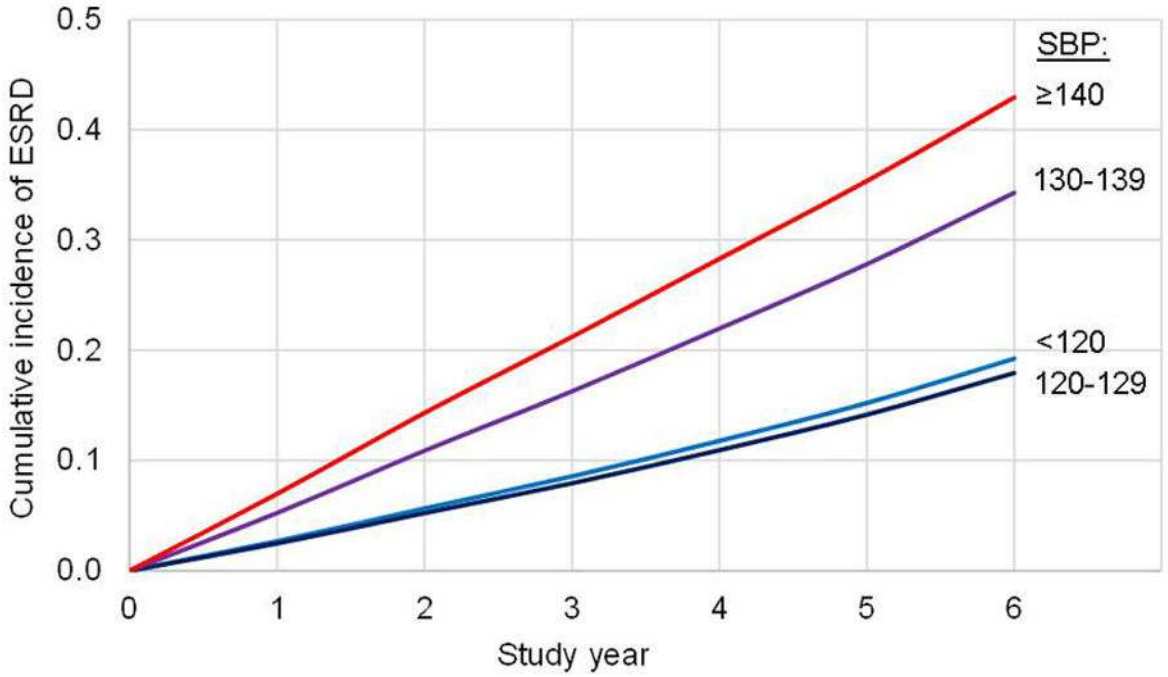
Model	HR (95% CI)	*P*
Time-Updated SBP		
Continuous model, per 10 mm Hg increase	1.35 (1.35-1.36)	<0.001
Categorical model		
<110 mm Hg	0.57 (0.56-0.59)	<0.001
110-119 mm Hg	0.79 (0.78-0.80)	<0.001
120-129 mm Hg	1.00 (reference)	
130-139 mm Hg	1.58 (1.55-1.60)	<0.001
≥140 mm Hg	2.49 (2.45-2.53)	<0.001
Baseline SBP		
Continuous model, per 10 mm Hg greater	1.09 (1.09-1.10)	<0.001
Categorical model		
<110 mm Hg	0.84 (0.82-0.85)	<0.001
110-119 mm Hg	0.92 (0.91-0.94)	<0.001
120-129 mm Hg	1.00 (reference)	
130-139 mm Hg	1.11 (1.09-1.12)	<0.001
≥140 mm Hg	1.30 (1.28-1.31)	<0.001

Time-updated systolic blood pressure and the progression of chronic kidney disease: Findings from the Chronic Renal Insufficiency Cohort (CRIC) Study

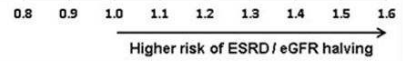
Amanda H Anderson, PhD, MPH, **Wei Yang, PhD**, **Raymond R Townsend, MD**, **Qiang Pan, MA**, **Glenn M Chertow, MD, MPH**, **John W Kusek, PhD**, **Jeanne Charleston, BSN, RN**, **Jiang He, MD, PhD**, **RadhaKrishna Kallem, MD, MPH**, **James P Lash, MD**, **Edgar R Miller III, MD, PhD**, **Mahboob Rahman, MD, MS**, **Susan Steigerwalt, MD**, **Matthew Weir, MD**, **Jackson T Wright Jr, MD, PhD**, **Harold I Feldman, MD, MSCE**, and **CRIC Study Investigators***

Ann Int Med 2015

Chronic Renal Insufficiency Cohort, US. N= 3708. Suivi 5,7 (4,6 - 6,7) ans



Subgroup	N	Event Rate (95% CI) per 1,000 person-years	P-value for Interaction
Overall	3,708	59.9 (56.1-63.6)	
Age ≤ 55	1,146	76.5 (68.8-84.2)	0.74
Age > 55	2,562	52.8 (48.6-57.1)	
Men	2,026	66.1 (60.8-71.5)	0.21
Women	1,682	52.5 (47.3-57.7)	
NH Black	1,548	75.9 (69.3-82.5)	0.20
NH White	1,585	34.8 (30.6-39.0)	
No Diabetes	1,926	35.8 (31.9-39.7)	0.63
Diabetes	1,782	91.6 (84.7-98.6)	
eGFR > 45	1,699	21.6 (18.4-24.7)	0.48
eGFR ≤ 45	2,009	102.1 (95.2-109.1)	
Urine PCR ≤ 0.25	2,034	15.1 (12.6-17.5)	0.31
Urine PCR > 0.25	1,674	136.3 (127.4-145.2)	
No ACE/ARB	1,159	53.1 (46.8-59.5)	0.90
ACE/ARB	2,549	62.9 (58.3-67.6)	
No Ca Channel Blocker	2,203	45.9 (41.7-50.1)	0.54
Ca Channel Blocker	1,505	82.3 (75.3-89.3)	



Forest plot of crude event rates (95% confidence intervals) and multivariable-a hazard ratios per 10 mmHg increase in mean SBP over time on development o halving of eGFR overall and by subgroups using marginal structural models.

The impact of hypertension on chronic kidney disease and end-stage renal disease is greater in men than women: a systematic review and meta-analysis

BMC nephrol 2020

Misghina Weldegiorgis[1,2*] and Mark Woodward[1,2,3]

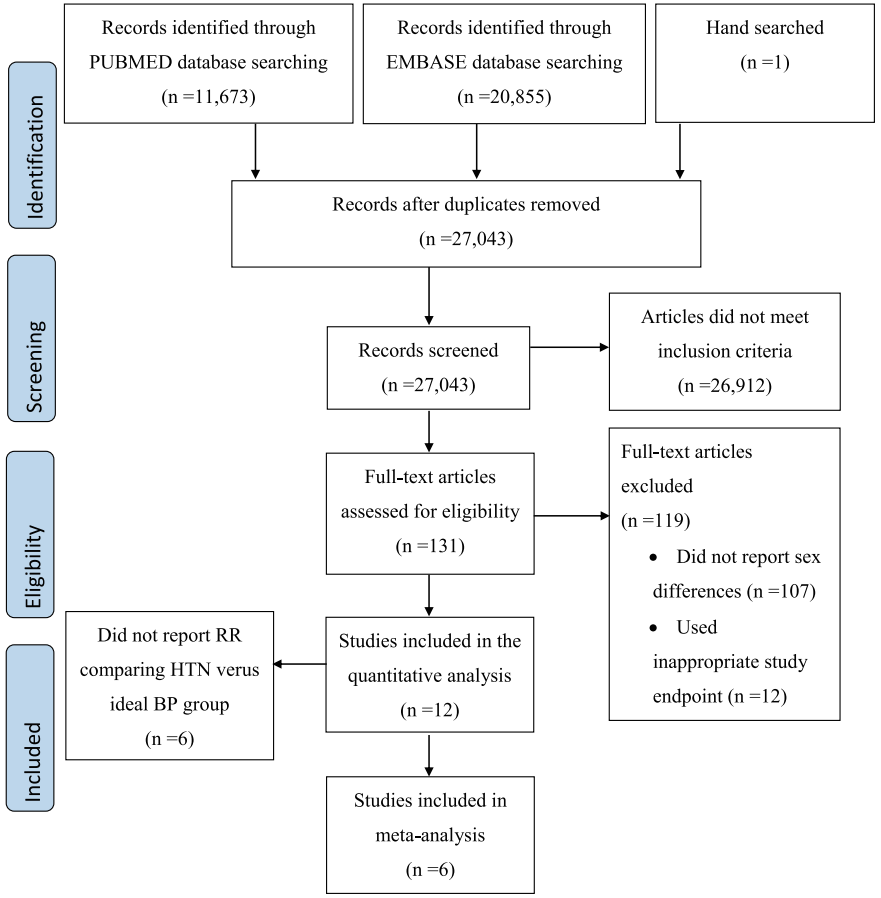
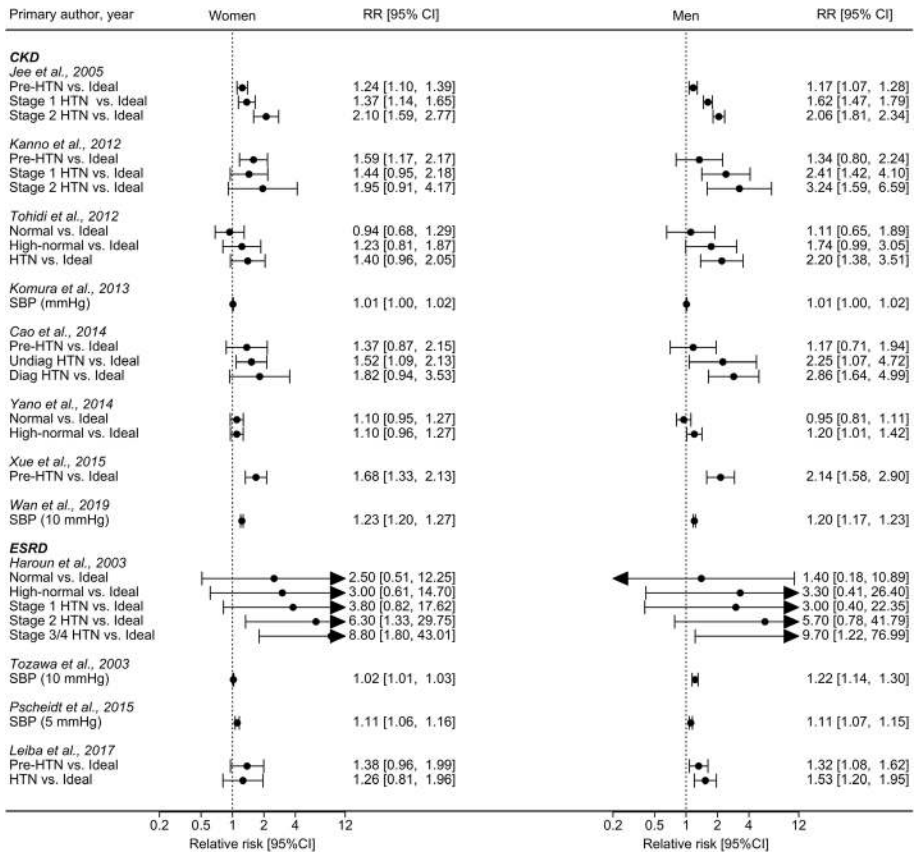


Table 1 Characteristics of studies included in quantitative analysis

Primary author, year	Country	Baseline study, year	Follow-up, years	N (% Female)	Age, year	Systolic blood pressure categories (mmHg)				Total events (% Female)	
						< 120n (% Female)	120–129 n (% Female)	130–139n (% Female)	≥140n (% Female)		
Jee et al (2005)[a,] [17]	Korea	1990–1992	10[b]	157,377 (33.6)	35–59[d]	55,940 (53.3)	67,307 (26.2)		34,135 (15.8)	5478 (27.9)	***CKD***
Kanno et al (2012)[a,] [18]	Japan	1993–2007	6.5[b]	2150 (63.4)	60.3[b]	586 (75.8)	815 (61.2)		749 (56.2)	461 (62.7)	
Tohidi et al (2012)[a,] [19]	Iran	1999–2001	9.9[b]	3313 (56.1)	≥ 20[b]	NA	NA	NA	NA	723 (71.5)	
Komura et al. (2013) [20]	Japan	1999	10[b]	1506 (68.6)	58.2[b]	NA	NA	NA	NA	466 (28.9)	
Cao et al (2014)[a,] [21]	China	2006–2011	4.5[c]	1703 (46)	45.6[b]	828 (64.2)	546 (31.7)		329 (24.0)	194 (31)	
Yano et al. (2014) [22]	Japan	2008	3[b]	42,625 (63.8)	60[c]	17,759 (68.6)	14,064 (60.9)	10,802 (59.5)	NA	2142 (57.4)	
Xue et al. (2015) [23]	China	2006–2007	3.9[c]	32,385 (27.2)	46.4[b]	12,351 (36.3)	20,034 (21.6)		NA	601 (54.9)	
Wan et al. (2019) [24]	China	2011–2012	6[c]	156,469 (58.5)	64.3[b]	NA	NA		NA	30,993 (NA)	
Haroun et al (2003)[a,] [25]	US	1974	20[b]	23,534 (59.2)	NA	3686 (78.8)	5333 (65.7)	4513 (54.8)	10,002 (50.5)	143 (NA)	***ESRD***
Tozawa et al. (2003) [26]	Japan	1983–1984	17[b]	98,759 (52.5)	50[b]	23,187 (64.8)	22,835 (48.9)	16,840 (45.9)	35,897 (50.1)	400 (42.3)	
Pscheidt et al. (2015) [27]	Austria	1988–2005	17.5[b]	185,341 (53.9)	38.9[c]	117,658 (NA)	NA	NA	67,506 (NA)	403 (39.2)	
Leiba et al (2017)[a,] [28]	Israel	1977–2013	16.8[c]	2,194,635 (41.7)	16–19[d]	1,465,733 (43.4)	442,077 (36.5)		286,825 (41)	690 (23.3)	

Abbreviation: N Total number of individuals in the study, *n* Number of individuals in each blood pressure category, *SD* Standard deviation, *IQR* Interquartile range, *NA* Not available. *Note:* [a] studies included in the meta-analysis (in bold); [b], mean; [c], median; [d], range



Weldegiorghis BMC Nephrol 2020

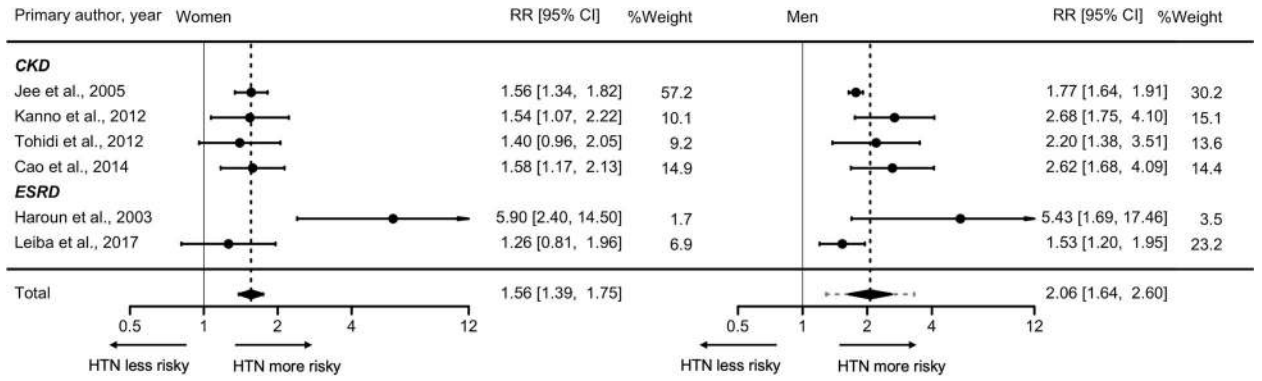


Fig. 3 The maximum-adjusted pooled relative risk and 95% confidence intervals for chronic kidney disease and end-stage renal disease in women (left panel) and men (right panel), comparing individuals with Hypertension versus ideal blood pressure

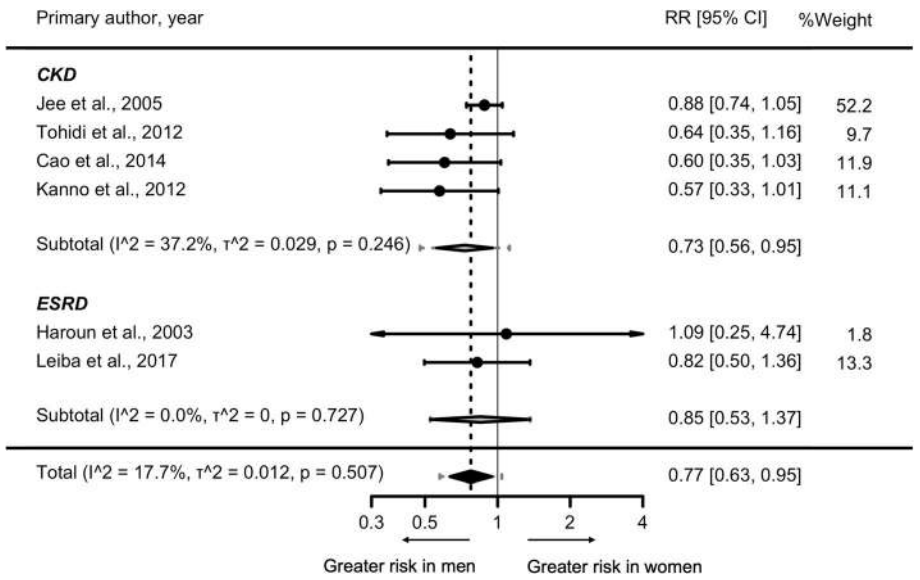


Fig. 4 The maximum-adjusted women-to-men relative risk ratio and 95% confidence intervals for chronic kidney disease and end-stage renal disease, comparing individuals in Hypertension versus ideal blood pressure

La correction de l’HTA diminue t’elle le risque rénal?

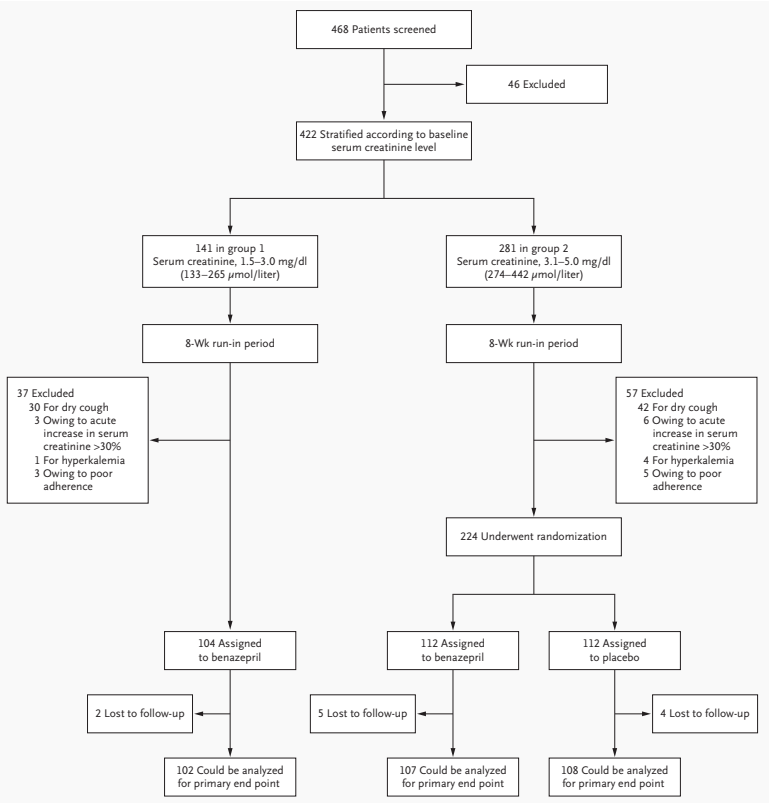
The NEW ENGLAND JOURNAL of MEDICINE

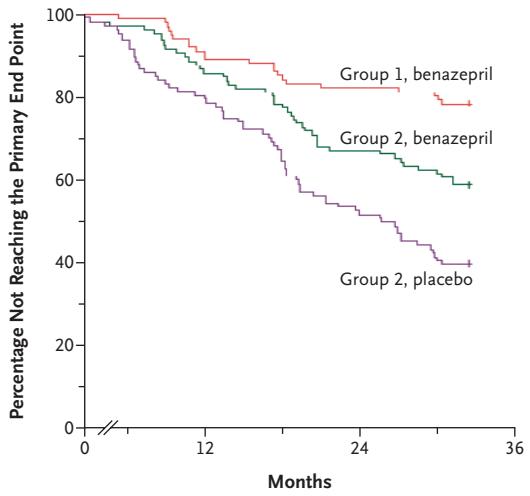
ORIGINAL ARTICLE

Efficacy and Safety of Benazepril for Advanced Chronic Renal Insufficiency

Fan Fan Hou, M.D., Ph.D., Xun Zhang, M.D., Guo Hua Zhang, M.D., Ph.D., Di Xie, M.D., Ping Yan Chen, M.D., Wei Ru Zhang, M.D., Ph.D., Jian Ping Jiang, M.D., Min Liang, M.D., Ph.D., Guo Bao Wang, M.D., Zheng Rong Liu, M.D., and Ren Wen Geng, M.D.

Diminution de 43% des evenements rénaux
Independent du contrôle tensionnel

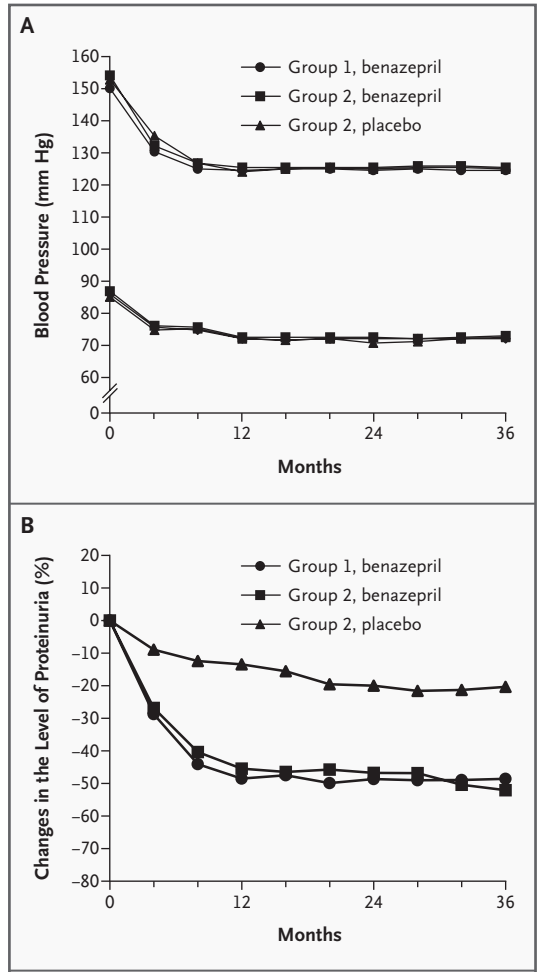




No. at Risk				
Group 1, benazepril	102	96	84	40
Group 2, benazepril	107	96	73	32
Group 2, placebo	108	88	59	22

Figure 2. Kaplan–Meier Estimates of the Percentage of Patients Not Reaching the Primary Composite End Point of a Doubling of the Serum Creatinine Level, End-Stage Renal Disease, or Death.

Group 1 had a serum creatinine level of 1.5 to 3.0 mg per deciliter, and group 2 had a serum creatinine level of 3.1 to 5.0 mg per deciliter at baseline.



J Am Soc Nephrol 12: 2832–2837, 2001

ACE Inhibitors to Prevent End-Stage Renal Disease: When to Start and Why Possibly Never to Stop: A *Post Hoc* Analysis of the REIN Trial Results

PIERO RUGGENENTI,*† ANNALISA PERNA,* and GIUSEPPE REMUZZI*†
on behalf of Gruppo Italiano di Studi Epidemiologici in Nefrologia (GISEN)

analyse post-hoc de l'étude REIN (Ramipril Efficacy In Nephropathy)
322 patients non diabétioques, CKD avec Pu

Parameter	Lowest		Middle		Highest	
	Conventional	Ramipril	Conventional	Ramipril	Conventional	Ramipril
Patients *n*	55	52	56	52	46	61
GFR (ml/min per 1.73 sqm)						
range	10.5 to 32.7	13.6 to 32.6	32.7 to 50.6	33.0 to 50.8	50.9 to 101.0	51.7 to 100.9
mean ± SD	23.4 ± 5.3	25.0 ± 5.2	41.1 ± 5.2	41.0 ± 5.2	63.0 ± 10.0	67.0 ± 13.3
Clinical parameters						
age (yr)	50.3 ± 13.6	49.5 ± 12.3	52.3 ± 14.3	48.8 ± 14.0	46.3 ± 12.8	48.8 ± 14.0
male gender (%)	71%	73%	68%	87%	78%	77%
systolic BP (mmHg)	147.4 ± 17.0	149.4 ± 17.8	146.1 ± 18.9	142.9 ± 16.8	143.5 ± 16.0	144.1 ± 20.0
diastolic BP (mmHg)	89.3 ± 11.1	92.0 ± 12.7	90.5 ± 11.0	89.2 ± 9.6	90.8 ± 10.9	89.6 ± 12.5
mean BP (mmHg)	108.7 ± 11.1	111.2 ± 13.2	109.0 ± 12.6	107.1 ± 10.7	90.8 ± 10.7	107.7 ± 14.0
Diagnosis						
glomerular disease (%)	35%	50%	52%	60%	57%	64%
APKD or interstitial nephritis (%)	11%	10%	9%	2%	2%	6%
other or unknown (%)	54%	40%	39%	38%	41%	30%
Laboratory parameters						
serum creatinine (mg/dl)	3.2 ± 0.7	3.1 ± 0.9	2.0 ± 0.4	2.0 ± 0.4	1.5 ± 0.3	1.4 ± 0.3
creatinine clearance (ml/min per 1.73 sqm)	29.4 ± 9.2	31.0 ± 12.5	46.8 ± 11.8	48.3 ± 12.1	67.5 ± 15.7	71.1 ± 19.1
proteinuria (g/24 h)	3.7 ± 2.2	4.1 ± 3.3	3.2 ± 2.3	3.6 ± 2.9	3.1 ± 2.3	2.8 ± 2.0
total cholesterol (mg/dl)	238.8 ± 59.5	237.9 ± 54.0	250.7 ± 51.1	243.8 ± 68.0	245.4 ± 53.2	247.0 ± 83.0
triglycerides (mg/dl)	192.8 ± 126.0	195.7 ± 133.9	174.4 ± 94.4	172.2 ± 94.6	168.9 ± 96.6	214.9 ± 216.9
potassium (mEq/l)	4.7 ± 0.6	4.5 ± 0.6	4.4 ± 0.6	4.3 ± 0.5	4.3 ± 0.5	4.4 ± 0.4

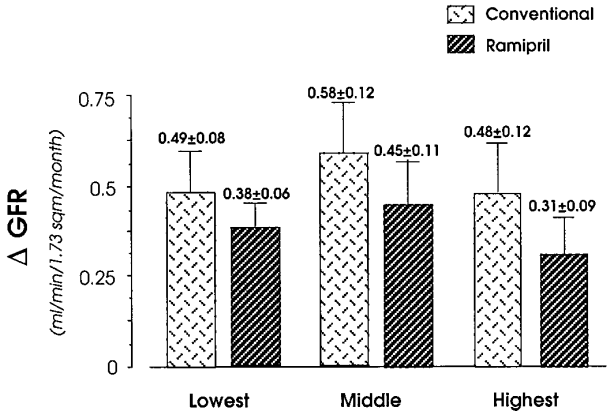


Figure 1. GFR decline in 322 patients with proteinuric, chronic nephropathies according to treatment and tertiles of basal GFR. There were no significant differences among the groups. Values are mean ± SEM.

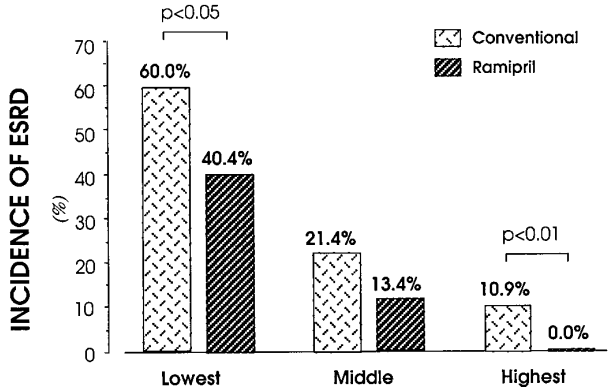


Figure 2. Incidence of end-stage renal disease (ESRD) in 322 patients with proteinuric, chronic nephropathies according to treatment and tertiles of basal GFR.

"Ramipril decreased GFR by 22%, 22%, and 35% and the incidence of ESRD by 33% (P 0.05), 37%, and 100% (P 0.01) in the lowest, middle, and highest tertiles, respectively .
Thus, disease progression and response to ACE inhibition do not depend on severity of renal insufficiency".

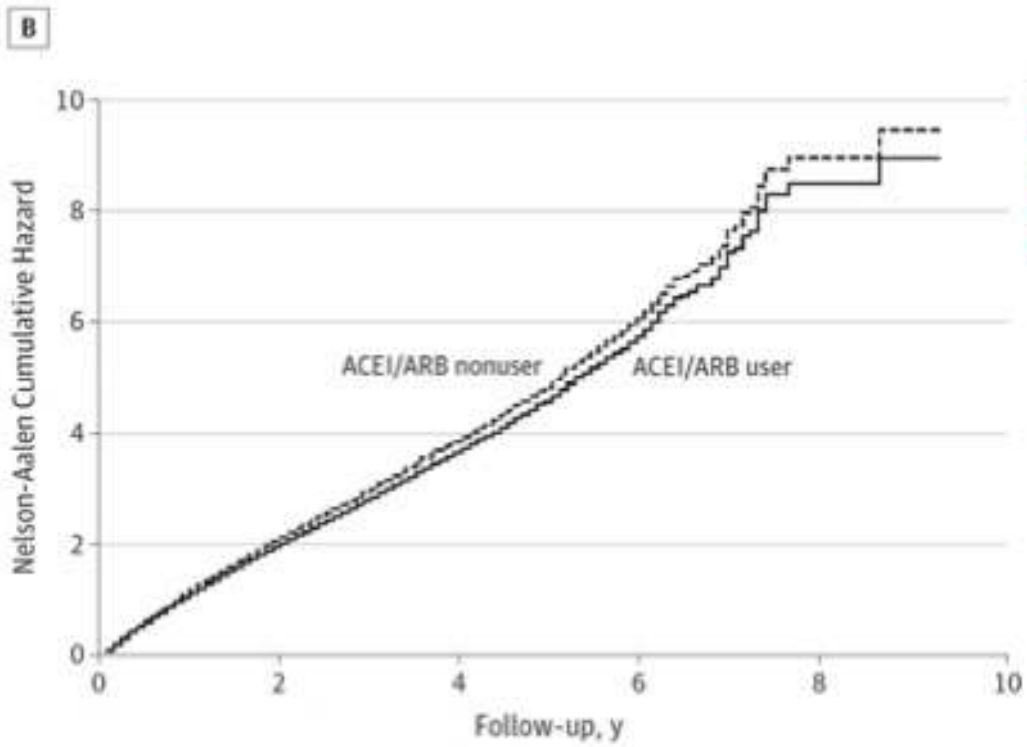
Table 3. Serious adverse events leading to patient withdrawal

	Lowest Tertile		Middle Tertile		Highest Tertile	
	Conventional	Ramipril	Conventional	Ramipril	Conventional	Ramipril
Death	0	1	1	1	0	1
Cardiovascular events	2	0	1	1	2	2
Worsening of renal function	2	1	1	0	0	0
Hyperkalemia	1	2	0	1	0	0
Cough	1	1	0	0	1	1
Uncontrolled BP	0	1	2	0	0	1
Cancer	0	0	2	2	0	0
Other	1	1	1	1	2	2
Total	7	7	8	6	5	7

Effets secondaires, IRA et hyper K très rares

Even among predialysis CKD5, ACEI/ARB was beneficial

Hsu, Ta-Wei. JAMA IM 2014;174(3):347-354



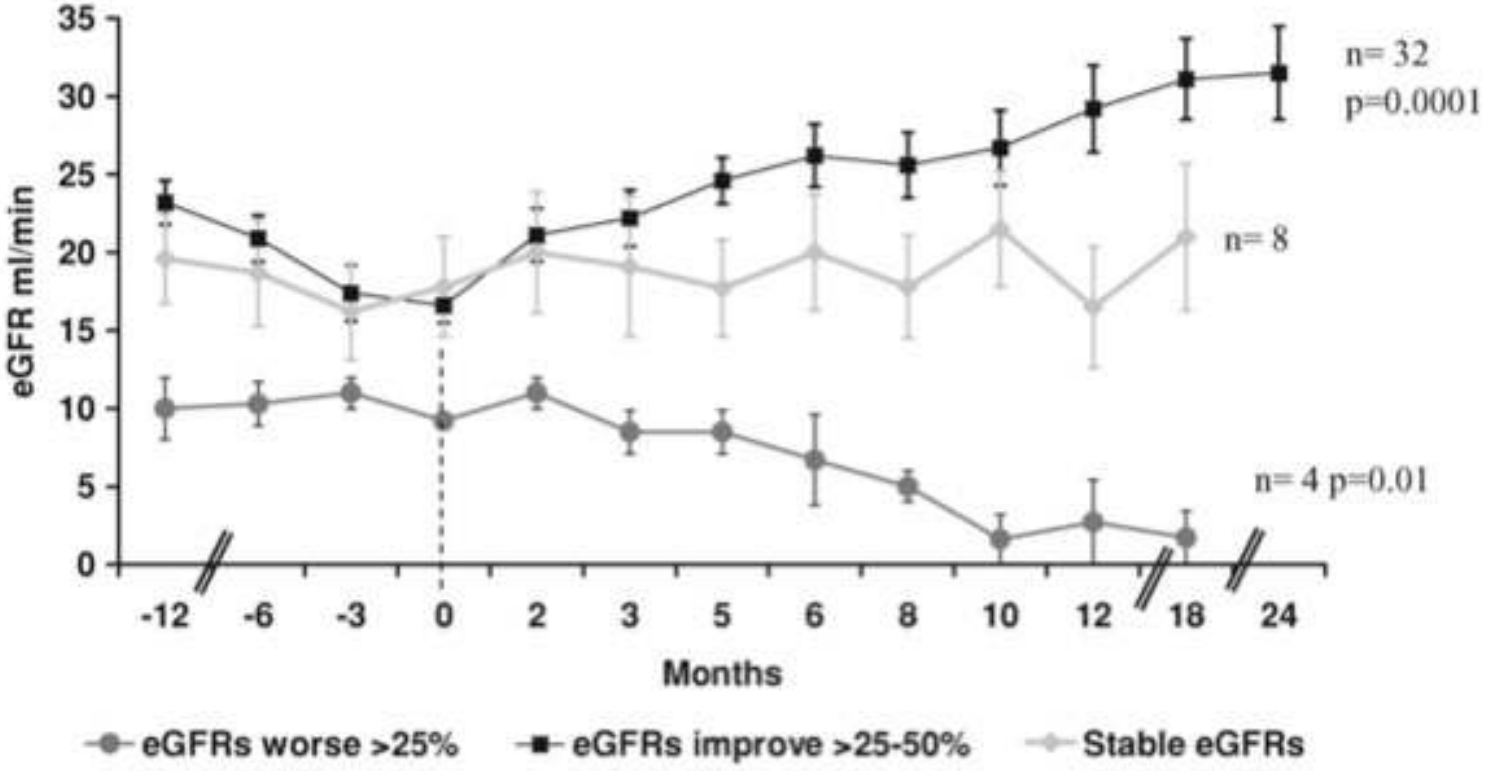
HR 0.93 (0.91-0.96) of dialysis initiation or death

Also higher rates of hyperkalemia-associated hospitalizations

RR = 1.31 (1.21-1.43)

Anecdotally, we stop ACE/ARB frequently to delay dialysis

Ahmed NDT 2010; 25: 39277-3982



Mais étude avec nombreux biais: selection (73ans de moyenne, 46% DS), mesure PA seulement en CS (effet BB chez le sujets âgés et risque épisodes d'hypoPA / IRA) donc amélioration de la perfusion rénale
Maladie rénovasculaire mal définie (seul critère asymérie rénale), seulement 5/52 SAR "présumée"
Faible nombre
7 insuffisants cardiaques: 4 DC

Other pharmacologic agents use in CKD

Diuretics:

- Helps with fluid overload, may prevent hyperkalemia with RAS inhibitors
- Classic teaching states loop diuretics more effective than thiazides when eGFR < 30 (though some studies refute this)

Calcium Channel Blockers:

- Nondihydropyridine (diltiazem, verapamil) can also have proteinuria reduction

Beta blockers:

- Best in patients with concomitant heart failure or atrial fibrillation

Medications	CKD-Related Indications	Other Potential Indications	Common Side Effects	Potential Contraindications	Other Considerations
Diuretics					
Thiazide (eg, hydrochlorothiazide, chlorthalidone, metolazone)	Fluid overload; may improve proteinuria if used in combination with RAS inhibitors	Kidney stone prevention (hypercalciuria); Gordon syndrome; NDI	Hyperuricemia; hypercalcemia; hyponatremia; hypokalemia; hyperglycemia (with long-term use)	Gout; hypercalcemia	May be less effective when eGFR is <30 although some studies have shown these agents remain effective even with low eGFR
Loop (eg, furosemide, bumetanide, torsemide)	Fluid overload	Heart failure; hypercalcemia	Hearing loss; hypokalemia; hypocalcemia; hyponatremia	Gout; sulfonamide-related hypersensitivity	Bumetanide and torsemide have better intestinal absorption than furosemide
Potassium-sparing (triamterene, amiloride)	Fluid overload; hypokalemia	Refractory hypomagnesemia; lithium toxicity/NDI	Hyperkalemia; metabolic acidosis	Pregnancy	
RAS Blockade					
ACEi (first-line agents if proteinuria)	Proteinuria reduction; delays progression of CKD	Heart failure with reduced ejection fraction; post–myocardial infarction	Cough; angioedema; hyperkalemia; leukopenia; anemia	Pregnancy; bilateral renal artery stenosis	
ARBs (first-line agents if proteinuria)	Proteinuria reduction; delays progression of CKD	Uric acid lowering (losartan) or gout; similar to ACEi	Cough (less than with ACEi); angioedema; hyperkalemia	Pregnancy; bilateral renal artery stenosis	
β-Blockers					
Selective (metoprolol, nebivolol)		Heart failure; atrial fibrillation; migraines; essential tremors; anxiety disorders; angina	Bradycardia; hyperkalemia; fatigue; depression; sexual dysfunction	Asthma; COPD; 2nd or 3rd degree heart block	
Combined α-β (carvedilol, labetalol)		Heart failure; atrial fibrillation	Bradycardia; hyperkalemia; fatigue; depression; sexual dysfunction	2nd or 3rd degree heart block	May be better tolerated in lung disease than selective β-blockers
Calcium Channel Blockers					
Dihydropyridine (amlodipine, nifedipine)		Raynaud, esophageal spasms	Lower-extremity edema; gingival hypertrophy		May worsen proteinuria
Nondihydropyridine (diltiazem, verapamil)	Proteinuria reduction	Atrial fibrillation	Constipation; gingival hyperplasia	2nd or 3rd degree heart block	↑ calcineurin and mTOR inhibitor levels
Other					
α-Blockers		Benign prostatic hypertrophy; kidney stone passage	Orthostasis		
Central α-adrenergic agonists (clonidine)			Sedation; bradycardia; dry mouth; rebound hypertension	Depression	
Vasodilators (minoxidil, hydralazine)			Headache; tachycardia; lupus-like syndrome (hydralazine); edema; pericardial effusion	Post–myocardial infarction; heart failure	
Direct renin inhibitors (aliskiren)	Proteinuria reduction; if not tolerating ACEi or ARB			Bilateral renal artery stenosis	Not recommended for use in combination with ACEi or ARBs

Table 2 (Cont'd). Selected Indications and Considerations in the Choice of Antihypertensive Agents for Patients With CKD

Medications	CKD-Related Indications	Other Potential Indications	Common Side Effects	Potential Contraindications	Other Considerations
Aldosterone antagonists (spironolactone, eplerenone)	Proteinuria reduction	Cirrhosis with ascites; polycystic ovarian syndrome; hyperaldosteronism	Hyperkalemia; metabolic acidosis; gynecomastia		May be useful in addition to ACEi or ARB for proteinuria reduction

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate (in mL/min/.173 m^2); mTOR, mammalian target of rapamycin; NDI, nephrogenic diabetes insipidus; RAS, renin-angiotensin system.

Ku E, AJKD 2019

Table 4. Summary of the major clinical trials with BP intervention for adverse kidney outcome

Trial	Number		BP target (achieved), mm Hg		Main outcomes		Key findings
	Active	Standard	Active	Standard			
MDRD [59]	432	408	MAP < 92, SBP/DBP < 125/75 (93.3, 126/77)	MAP < 107, SBP < 140 (98.4, 134/81)	GFR decline		↓29%[a]
					KFRT or death		NR
ABCD [65]	237	243	SBP/DBP < 130/80 (128/75)	SBP/DBP < 140/90 (137/81)	CCl		NR
					Albuminuria	Normoalbuminuria to microalbuminuria	↓
						Microalbuminuria to overt albuminuria	↓
REENAL *post hoc* [66]	*Post hoc* analysis categorized SBP into < 130 (n = 169), 130–139 (n = 209), 140–159 (n = 610), 160–179 (n = 373), and ≥ 180 mmHg (n = 152)				Composite 2XSCr, KFRT, or death		HR (95% CI) vs. SBP < 130 mmHg: 1.08 (0.83–1.40), 1.49 (1.18–1.90), 2.74 (2.12–3.54), and 3.51 (2.50–4.93)
REIN-2 [28]	167	168	SBP/DBP < 130/80 (130/80)	SBP/DBP < 135/90 (134/82)	KFRT		NR
IDNT *post hoc* [67]	*Post hoc* analysis categorized SBP into < 145 (n = 391), 145–158 (n = 411), 159–170 (n = 383), and > 170 mmHg (n = 405)				Composite 2XSCr or KFRT		RR vs. SBP > 170 mmHg: 0.55, 0.92, 0.66, and 0.70
ADVANCE [47]	5,569	5,571	SBP 145–135[b]	SBP 145–140[b]	Composite macroalbuminuria, 2XSCr, KFRT, renal-cause death, or microalbuminuria		↓21%
					Composite macroalbuminuria, 2XSCr, KFRT, renal-cause death		↓18%[c]
					Microalbuminuria		↓21%
ACCORD [26]	2,362	2,371	SBP < 120 (119.3)	SBP < 140 (133.5)	Serum creatinine elevation[d]		NR
					Decreased eGFR < 30 mL/min/1.73 m^2		NR
AASK [58]	540	554	SBP/DBP < 130/80 (130/78)	SBP/DBP < 140/90 (141/86)	Composite 2XSCr, KFRT, or death		↓27%[e]
SPRINT [24]	4,678	4,683	SBP < 120 (123.3)	SBP < 140 (136.2)	Participants with baseline CKD	Composite ≥ 50% reduction eGFR to < 60 mL/min/1.73 m^2, long-term dialysis, or KT	NR

Table 5. Summary of major intervention trials with RAS blockers and new potential drugs for kidney outcomes

Trial	Number	Main inclusion criteria	Intervention	Control	Main outcome	Key findings	BP by intervention, mmHg	
							Baseline	Follow-up
RAS blockers								
Lewis et al. [68]	409	Diabetic nephropathy	Catopril	Placebo	2XSCr	↓48% risk	SBP 135	SBP 128–134
IDNT [70]	1,715	Type 2 diabetic nephropathy	Irbesartan	Placebo	Composite 2X SCr, KFRT, or all-cause death	↓20% risk	160/87	140/77
			Irbesartan	Amlodipine		↓23% risk	159/87	141/77
RENAAL [71]	1,513	Type 2 diabetic nephropathy	Losartan	Placebo	Composite 2X SCr, KFRT or death	↓16% risk	152/82	140/74
BENEDICT [72]	904	DM without microalbuminuria	Trandolapril + verapamil	Placebo	% Microalbuminuria	5.7% vs. 10%	151/88	139/80
			Trandolapril	Placebo		6.0% vs. 11.9 %	151/88	139/81
Mineralocorticoid receptor antagonists								
Bianchi et al. [87]	165	CKD treated with RASi	Spironolactone + RASi	RASi	Proteinuria reduction eGFR decline (mL/min/1.73 m²)	↓54.2% −6.2 vs. −9.0	133/79	127/76
FIDELIO-CKD [92]	5,734	CKD, T2DM	Finerenone + RASi	RASi	Kidney failure[a], eGFR decrease ≥ 40%, or renal death	↓18% risk	SBP 138	
Endothelin receptor antagonists								
DUET [85]	109	FSGS, eGFR > 30 mL/min/1.73 m², UPCR ≥ 1.0 g/g	Sparsentan	Irbesartan	Proteinuria reduction FSGS PR	↓26% ↓19% risk	132/84	120/75
SONAR [84]	2,648	CKD, T2DM, albuminuria	Atrasentan	Placebo	2XSCr or KFRT	↓35% risk	136/75	139/-
SGLT2 inhibitors								
EMPA-REG *post hoc* [78]	7,020	T2DM, eGFR ≥ 30 mL/min/1.73 m²	Empagliflozin	Placebo	Macroalbuminuria, 2XCr, RRT, or renal death 2XCr with eGFR ≤ 45 mL/min/1.73 m²	↓39% risk ↓44% risk	Patients with eGFR < 60 mL/min/1.73 m²: 136/75 Patients with eGFR ≥ 60 mL/min/1.73 m²: 135/77	-

Rein et risque cardiovasculaire

De nombreuses études sur le risque cardiovasculaire et sa prévention

- **ALLHAT** (Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial),
- **SEARCH** (Study Evaluating Additional Reductions in Cholesterol and Homocysteine),
- **TNT** (Treating to New Targets),
- **IDEAL** (Incremental Decrease in Endpoints Through Aggressive Lipid Lowering),
- **ALLIANCE** (Aggressive Lipid Lowering Initiation Abates New Cardiac Events),
- **PROVE IT** (Pravastatin or Atorvastatin in Evaluation and Infection Therapy),

… depuis une décade (2)

- **PROSPER** (Prospective Study of Pravastatin in the Elderly at Risk),
- **FIELD** (Fenofibrate Intervention and Event Lowering in Diabetes),
- **CARDS** (Collaborative Atorvastatin Diabetes Study),
- **ASPEN** (Atorvastatin as Prevention of Coronary Heart Disease Endpoints in Patients with Non-Insulin-Dependent Diabetes Mellitus),
- **SPARCL** (Stroke Prevention by Aggressive Reduction in Cholesterol Levels),
- **ACCORD** (Action to Control Cardiovascular Risk in Diabetes).
- **ALERT** (Assessment of Lescol in Renal Transplantation),

… depuis une décade (3)

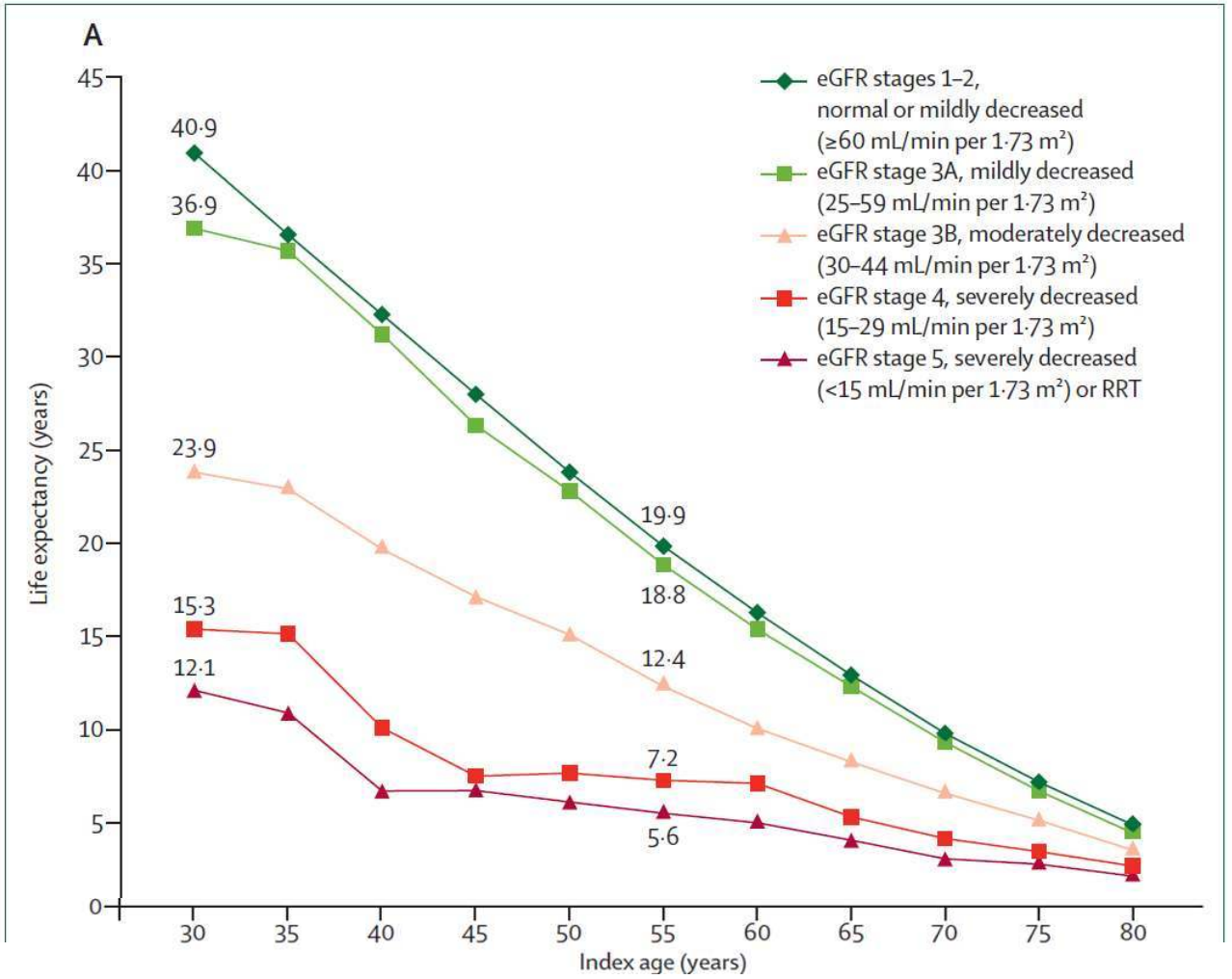
- **4D** (Die Deutsche Diabetes Dialyse Studie),
- **PREVEND IT** (Prevention of REnal and Vascular ENdstage Disease Intervention Trial),
- **AURORA** (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events),
- **SHARP** (Study of Heart and Renal Protection).

MRC et risque cardiovasculaire

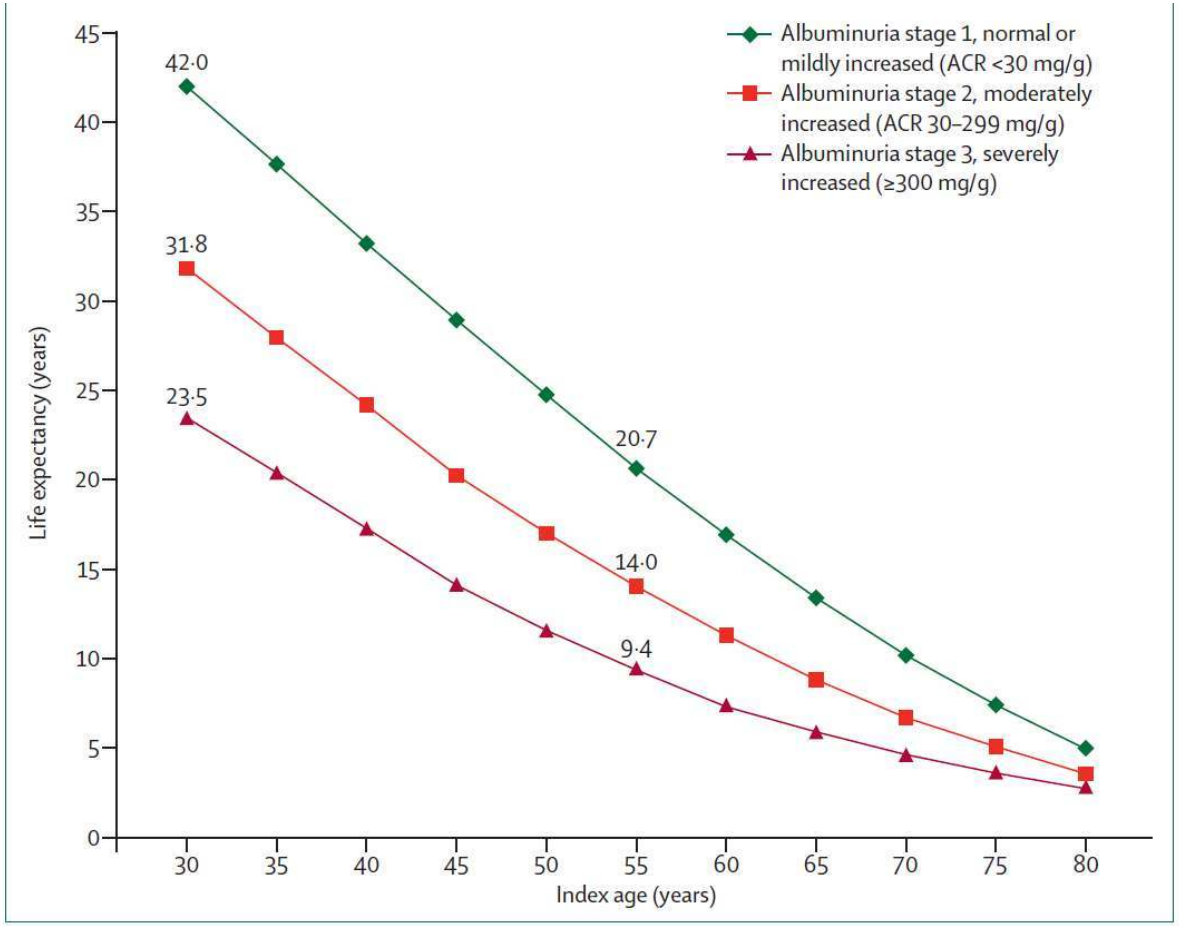
- In patients with CKD, the increased cardiovascular risk is **multifactorial** and is due partly to pathophysiological processes **specific to CKD** that make prevention of cardiovascular disease by standard interventions directed at single traditional risk factors difficult; therefore, innovative strategies need to be investigated (eg, the targeting of non-traditional cardiovascular risk factors, early prevention, and multifactorial intervention strategies)

Gansevoort RT et al. Lancet 2013; 382: 339–52

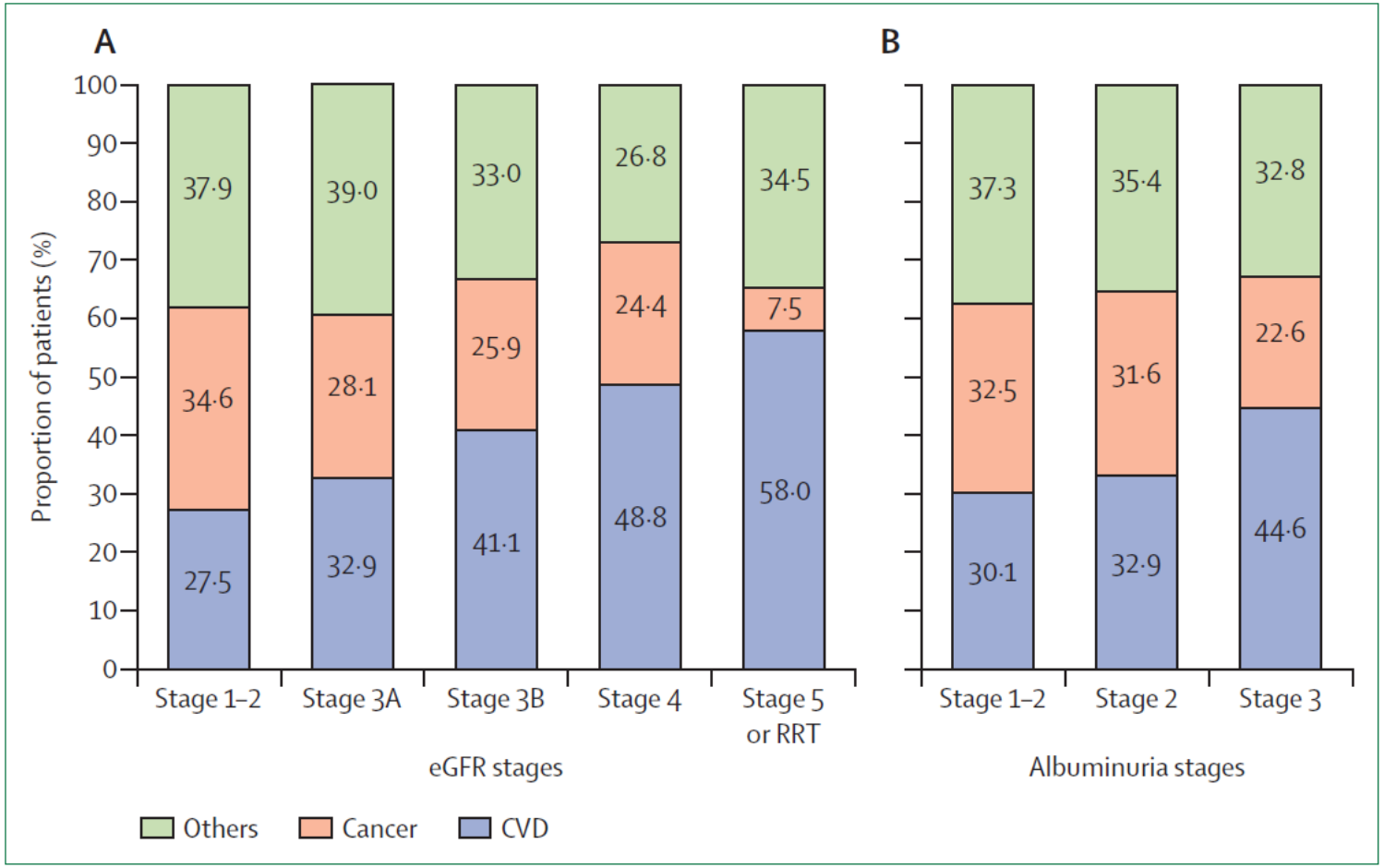
Stade de MRC et espérance de vie selon l'âge



Stade de MRC et espérance de vie selon l'albuminurie



Stade de la MRC et décès CV

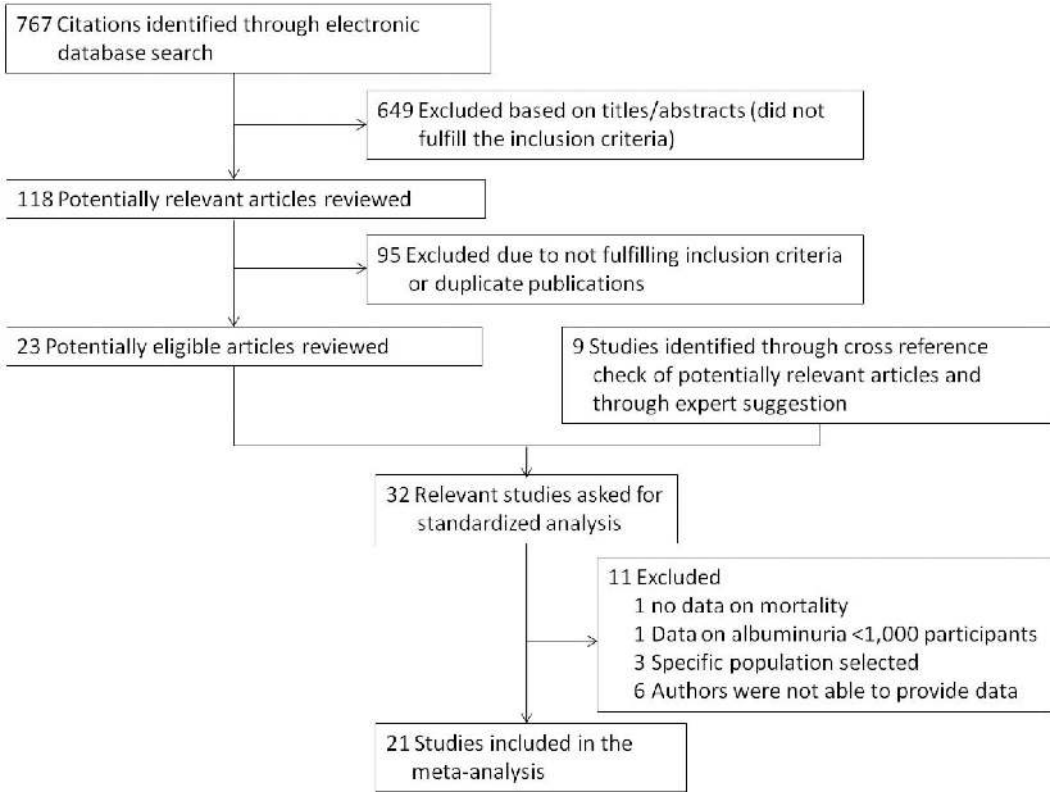


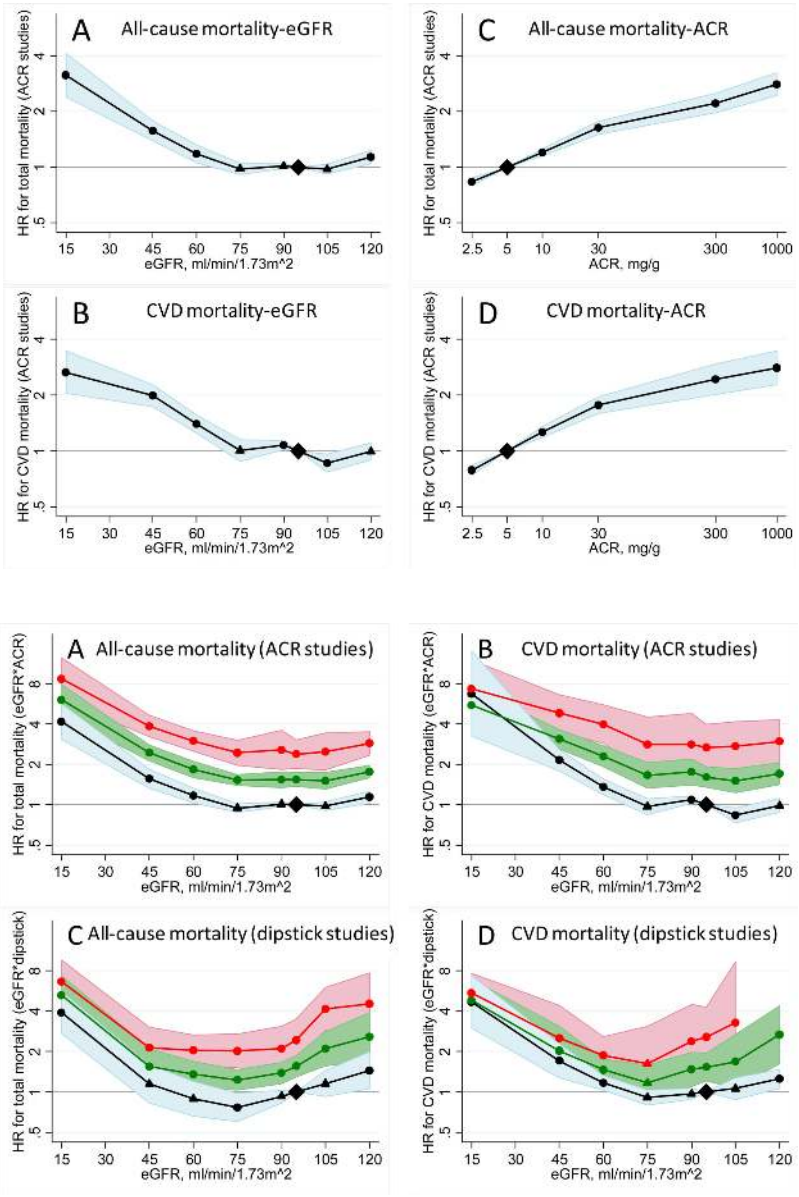
Turin TC et al. *Nephrol Dial Transplant* 2012; **27:** 3182–86. Turin TC et al. *Am J Kidney Dis* 2013; **61:** 646–68.

Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality: a collaborative meta-analysis of general population cohorts

Matsushita K, Lancet 2010

14 études avec ACR : 105872 patients
7 études avec Pu à la BU: 1128310 patients





Fonction rénale, protéinurie et mortalité cardiovasculaire

- The adjusted risk of cardiovascular mortality is **more than doubled** *at the upper end of the microalbuminuria category* (30–299 mg/g), compared with the risk in individuals with normal albuminuria.
- **Albuminuria** *even at the upper end of the normal range* (threshold 30 mg/g) confers **CV risk**.
- Thus, even **slight increases** in albuminuria require clinical attention.
- A wide variety of specific CVD have been associated with estimated impaired kidney function.

Table 3. Summary of the major clinical trials with BP intervention for cardiovascular outcomes and mortality

Trial	Number		BP target (achieved), mm Hg		Diabetes	CKD	Main outcomes	Key findings (risk reduction vs. standard group)
	Active	Standard	Active	Standard				
HOT [42]	DBP (achieved), mm Hg ≤ 80 (81.1) (n = 6,262) ≤ 85 (83.2) (n = 6,264) ≤ 90 (85.2) (n = 6,264)				1,503 (8)	1,367 (7)[a]	Composite nonfatal MI, nonfatal stroke, or CVD death	NR (↓51 vs. ≤ 90 mm Hg among diabetic patients)
UKPDS [41]	758	390	< 150/85 (144/82)	< 160/90 (154/87)	1,148 (100)	198 (17)[b]	All-cause mortality	NR
							MI	NR
							Stroke	↓44%
							PVD	NR
							Microvascular disease[c]	↓37%
ACCORD [26]	2,362	2,371	SBP < 120 (119.3)	SBP < 140 (133.5)	4,733 (100)	403 (9)	Composite nonfatal MI, nonfatal stroke, or death from CVD	NR
SPRINT [24]	4,678	4,683	SBP < 120 (121.4)	SBP < 140 (136.2)	None	2,646 (28)	Composite MI, ACS, stroke, HF, or CVD death	↓25%
HOPE-3 [27]	6,356	6,349	SBP < 130 (128)	SBP < 140 (134)	731 (8)	348 (3)	Composite cardiovascular death, nonfatal MI, or nonfatal stroke	NR
SPRINT post hoc analysis in CKD [37]	1,330	1,316	SBP < 120 (123.3)	SBP < 140 (136.9)	None	2,646 (100)	Composite MI, ACS, stroke, HF, or CVD death	NR
							Composite MI, ACS, stroke, HF, CVD death, or all-cause death	NR
							All-cause death	↓28%

Values are presented as number (%).

BP, blood pressure; CVD, cardiovascular disease; HOT, Hypertension Optimal Treatment; DBP, diastolic blood pressure; MI, myocardial infarction; NR, no reduction in relative risk; UKPDS, UK Prospective Diabetes Study Group; PVD, peripheral vascular disease; ACCORD, Action to Control Cardiovascular Risk in Diabetes; SBP, systolic blood pressure; SPRINT, Systolic Blood Pressure Intervention Trial; ACS, acute coronary syndrome; HF, heart failure; HOPE-3, Heart Outcomes Prevention Evaluation-3.

[a]Definition of CKD: serum creatinine > 115 μmol/L.

[b]Definition of CKD: albuminuria ≥ 50 mg/L.

[c]Retinopathy requiring photocoagulation, vitreous hemorrhage, and fatal or nonfatal renal failure.

Meta-Analysis: Intensive BP lowering reduces mortality in patients with CKD 3-5

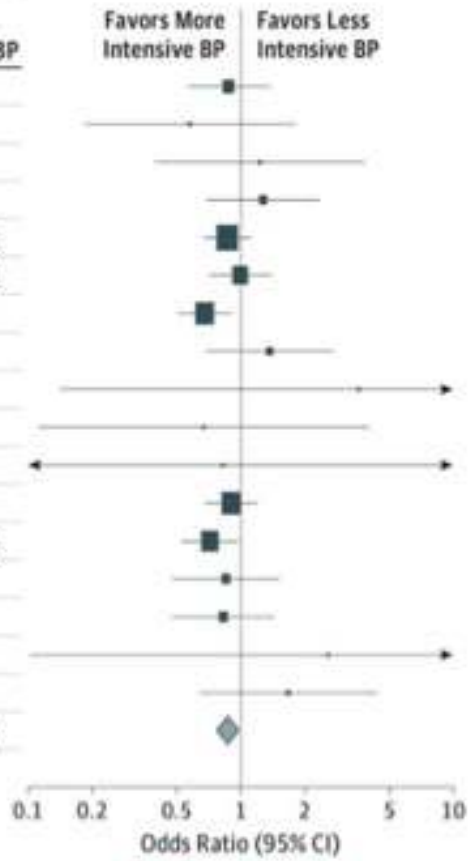
Malhotra JAMA IM 2017

18 trials

Source	Odds Ratio (95% CI)	Score	No. of Deaths/Total No. More Intensive BP	No. of Deaths/Total No. Less Intensive BP	P Value
Wright et al,[14] 2002	0.874 (0.554-1.380)	-0.578	37/540	43/554	.56
Estacio et al,[24] 2000	0.575 (0.182-1.820)	-0.941	5/62	9/68	.35
Schrier et al,[26] 2002	1.227 (0.398-3.865)	0.349	6/57	7/80	.73
Cushman et al,[32] 2010	1.271 (0.685-2.360)	0.761	26/208	20/198	.45
Heerspink et al,[27] 2010	0.862 (0.662-1.123)	-1.102	117/1010	135/1023	.27
Lonn et al,[37] 2016	0.993 (0.699-1.410)	-0.039	49/1220	97/2399	.97
Beckett et al,[30] 2008	0.676 (0.502-0.911)	-2.570	83/788	121/816	.01
Klahr et al,[13] 1994	1.366 (0.681-2.742)	0.878	20/432	14/408	.38
Mant et al,[34] 2016	3.588 (0.140-91.945)	0.772	1/26	0/30	.44
Ruggenenti et al,[22] 2005	0.667 (0.110-4.042)	-0.441	2/167	3/168	.66
Schrier et al,[25] 2002	0.825 (0.050-13.701)	-0.134	1/41	1/34	.89
SHEP Cooperative Research Group,[28] 1991	0.900 (0.670-1.209)	-0.700	96/879	103/859	.48
Wright et al,[17] 2015	0.714 (0.519-0.982)	-2.072	70/1330	95/1316	.04
Benavente et al,[33] 2013	0.850 (0.468-1.544)	-0.534	24/216	25/195	.59
Staessen et al,[29] 1997	0.826 (0.470-1.451)	-0.665	26/242	29/228	.51
Toto et al,[23] 1995	2.566 (0.101-64.993)	0.572	1/42	0/35	.57
UK Prospective Diabetes Study Group,[35] 1998	1.667 (0.626-4.435)	1.023	20/68	7/35	.31
Overall	0.859 (0.764-0.965)	-2.560	584/7451	709/8473	.01

Heterogeneity: $\tau^2 = 0\%$; $P = .77$; $I^2 = 0\%$

1293 deaths / 15924



OR = 0.86

Quelles sont les cibles?
Recommandations?

Lifestyle modification remains first step

Target salt intake to < 2 g per day among CKD patients with high BP

DASH diet can lead to moderate declines in BP by ~ 10 mm Hg
(though high potassium diets despite evidence of benefit may place patients with advanced CKD at risk of hyperkalemia)

Weight loss can reduce BP by ~5 mm Hg for every 5-kg weight loss

Limiting alcohol intake

⚠ 2g Na = 6g NaCl

KDIGO= “outlayer”

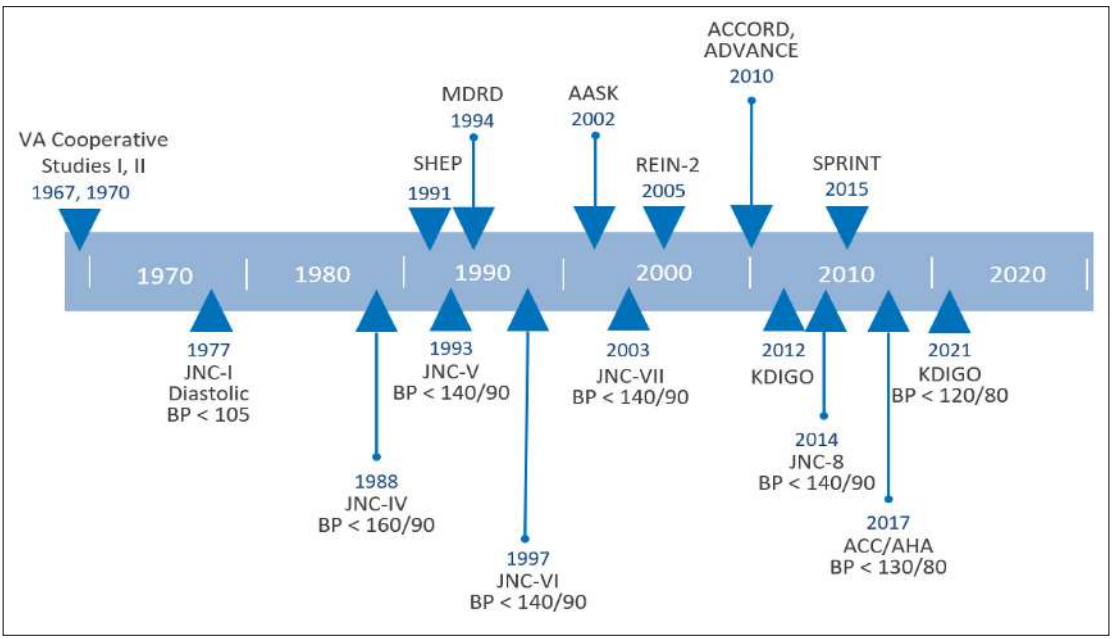


Table 1. Guideline comparisons of goal BP and first-line treatment for CKD patients with hypertension

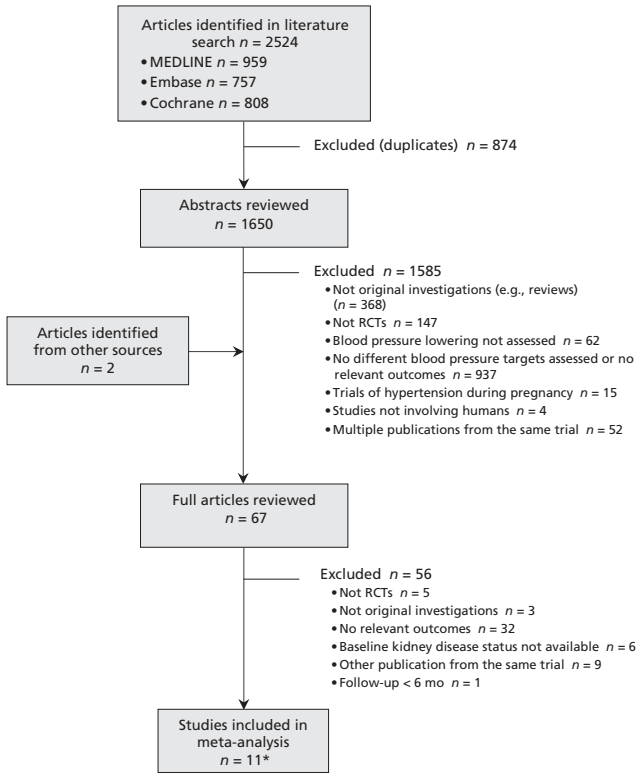
Guideline	BP target in CKD patients without proteinuria, mmHg	BP target in CKD patients with proteinuria, mmHg	Recommended first-line treatment
ISHIB [35]	< 130/< 80	< 130/< 80	Diuretic or CCB
NICE [19]	< 140/< 90	< 130/< 80	ACEi or ARB
JNC8 [18]	< 140/< 90	< 140/< 90	ACEi or ARB
ACC/AHA [32]	< 130/< 80	< 130/< 80	ACEi
ESC/ESH [34]	SBP 130–139	SBP 130–139	ACEi or ARB
ISH [33]	< 130/< 80	< 130/< 80	ACEi or ARB
Hypertension Canada [22]	SBP < 120	SBP < 120	ACEi or ARB
KDIGO [25]	SBP < 120	SBP < 120	ACEi or ARB

BP, blood pressure; CKD, chronic kidney disease; ISHIB, International Society on Hypertension in Blacks; CCB, calcium channel blocker; NICE, National Institute for Health and Clinical Excellence; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; JNC8, Eighth Joint National Committee; ACC/AHA, American College of Cardiology/American Heart Association; ESC/ESH, European Society of Cardiology and the European Society of Hypertension; SBP, systolic blood pressure; ISH, International Society of Hypertension; KDIGO, Kidney Disease: Improving Global Outcomes.

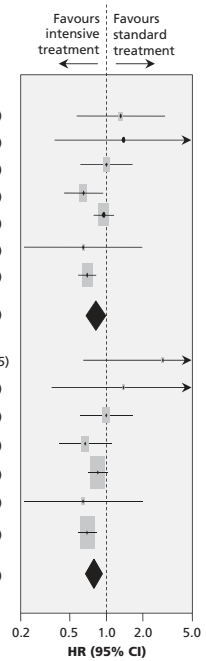
Lee JY, KJIM 2021

Effects of intensive blood pressure lowering on the progression of chronic kidney disease: a systematic review and meta-analysis

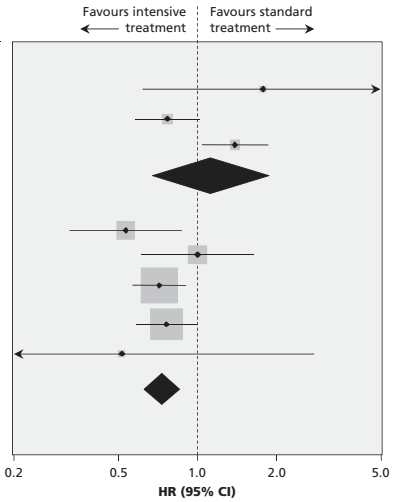
Jicheng Lv CMAJ 2013



Study	Treatment, no. of events/patients: Intensive	Standard	Systolic BP, mm Hg, intensive/standard: Baseline	Achieved	HR (95% CI)
Composite outcome					
Toto et al.[21]	11/42	7/35	124/122	133/138	1.31 (0.57–3.02)
Schrier et al.[28]	5/41	3/34	143/142	90/101	1.38 (0.36–5.37)
Ruggenenti et al.[14]	38/169	34/169	137.0/136.4	129.6/133.7	1.00 (0.61–1.64)
Wühl et al.[18]	46/189	69/196	NA	NA	0.65 (0.45–0.94)
Appel et al.[13]	213/540	209/554	152/149	128/141	0.95 (0.78–1.15)
Hayashi et al.[27]	5/1230	8/1269	1717/171.8	135.9/145.6	0.64 (0.21–1.97)
Klahr et al.[17]	306/432	310/408	130/131	126.2/133.8	0.69 (0.59–0.83)
Overall (I^2 = 38.1%)	624/2643	640/2665	156.3/156.4	131.7/141.5	0.82 (0.68–0.98)
ESKD					
Toto et al.[21]	7/42	2/35	124/122	133/138	2.92 (0.65–13.15)
Schrier et al.[28]	5/41	3/34	143/142	90/101	1.38 (0.36–5.37)
Ruggenenti et al.[14]	38/169	34/169	137.0/136.4	129.6/133.7	1.00 (0.61–1.64)
Wühl et al.[18]	22/189	34/196	NA	NA	0.67 (0.41–1.10)
Appel et al.[13]	238/540	256/554	152/149	128/141	0.85 (0.71–1.02)
Hayashi et al.[27]	5/1230	8/1269	171.7/171.8	135.9/145.6	0.64 (0.21–1.97)
Klahr et al.[17]	306/432	310/408	130/131	126.2/133.8	0.69 (0.59–0.83)
Overall (I^2 = 21.6%)	621/2643	647/2665	156.3/156.4	131.7/141.5	0.79 (0.67–0.93)



Patient subgroup	Treatment, no. of events/patients: Intensive	Standard	HR (95%CI)
Without baseline proteinuria			
Wühl et al.[18]	NA/33	NA/41	1.78 (0.62–5.14)
Klahr et al.[17]	128/210	133/201	0.77 (0.58–1.02)
Appel et al.[13]	98/357	83/376	1.39 (1.04–1.86)
Overall (I^2 = 78.2%)	226/600	216/618	1.12 (0.67–1.87)
With baseline proteinuria			
Wühl et al.[18]	NA/67	NA/59	0.53 (0.33–0.87)
Ruggenenti et al.[14]	38/169	34/169	1.00 (0.61–1.64)
Klahr et al.[17]	178/221	177/207	0.71 (0.56–0.91)
Appel et al.[13]	114/181	126/176	0.76 (0.58–0.99)
Hayashi et al.[27]	2/224	4/230	0.51 (0.09–2.78)
Overall (I^2 = 0.0%)	332/862	341/841	0.73 (0.62–0.86)



Can intensive BP control increase ESRD progression risk?

Ku. JASN 2017

Table 2. Association between percentage decline in renal function in the AASK participants (*n*=899) from time of randomization until month 3 and risk of ESRD

Renal Function Decline, %	Strict BP Arm				Usual BP Arm			
	N	ESRD Incidence[a] (95% CI)	Unadjusted HR (95% CI)	Adjusted HR[b] (95% CI)	*N*	ESRD Incidence[a] (95% CI)	Unadjusted HR (95% CI)	Adjusted HR[b] (95% CI)
AASK	448				451			
<5	271	2.9 (2.4 to 3.6)	1.00 (0.75 to 1.34)	0.94 (0.70 to 1.25)	319	2.9 (2.4 to 3.5)	1.0 (Reference)	1.0 (Reference)
5 to <20	139	3.6 (2.7 to 4.7)	1.26[c] (0.90 to 1.76)	1.19[c] (0.84 to 1.68)	98	6.3 (4.8 to 8.1)	2.22[c] (1.60 to 3.09)	1.83[c] (1.30 to 2.57)
≥20	38	9.8 (6.7 to 14.4)	3.58 (2.32 to 5.52)	3.04 (1.95 to 4.77)	34	10.4 (6.9 to 15.7)	3.83 (2.43 to 6.04)	2.56 (1.60 to 4.11)
MDRD	388				373			
<5	190	7.1 (6.0 to 8.5)	0.93 (0.73 to 1.19)	0.88 (0.68 to 1.13)	182	7.6 (6.4 to 9.0)	1.0 (Reference)	1.0 (Reference)
5 to <20	150	9.7 (8.1 to 11.7)	1.28[c] (0.99 to 1.64)	1.08[c] (0.84 to 1.40)	136	12.6 (10.5 to 15.1)	1.66[c] (1.29 to 2.13)	1.62[c] (1.25 to 2.11)
≥20	48	15.5 (11.5 to 20.9)	2.03 (1.44 to 2.87)	1.57 (1.09 to 2.24)	55	17.3 (13.0 to 23.7)	2.39 (1.71 to 3.35)	1.48 (1.04 to 2.1)

[a]Per 100 person-years.

[b]Adjusted for age, sex, baseline heart disease, antihypertensive drug assignment (ACE inhibition versus other agents), baseline eGFR category, baseline proteinuria category, and baseline MAP. Model is additonally adjusted for race for MDRD participants.

[c]HRs are statistically significantly different comparing strict with usual BP arms ($P<0.05$).

Lowering eGFR < 20% within 3-4 months with strict BP control not associated with development of ESRD

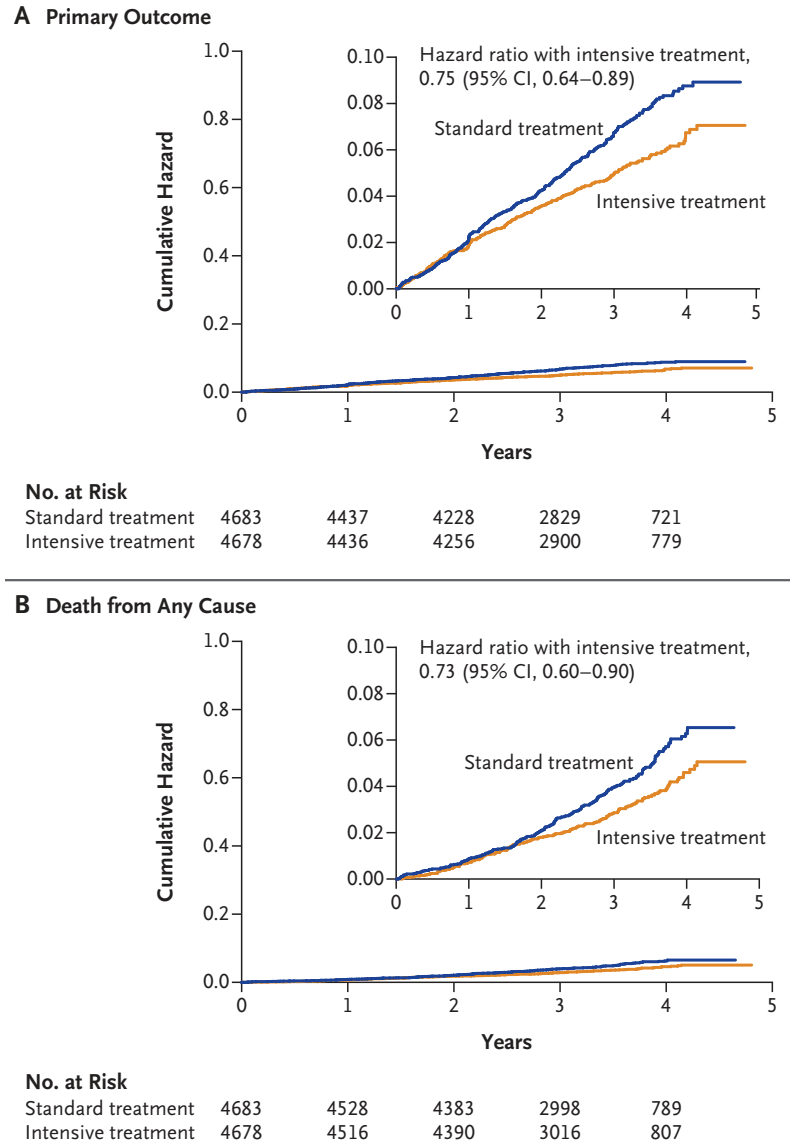
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 26, 2015 VOL. 373 NO. 22

A Randomized Trial of Intensive versus Standard Blood-Pressure Control

The SPRINT Research Group*

- 9361 patients non diabétiques randomisés
- Ttt standards (PAS <140mmHg) vs intensif (PAS<120mmHG)
- Critère composite: SCA, IDM, IC, AVC, mort de cause CV
- Suivi médian 3.3 ans
- Choix des ttt anti HTA selon un algorythme



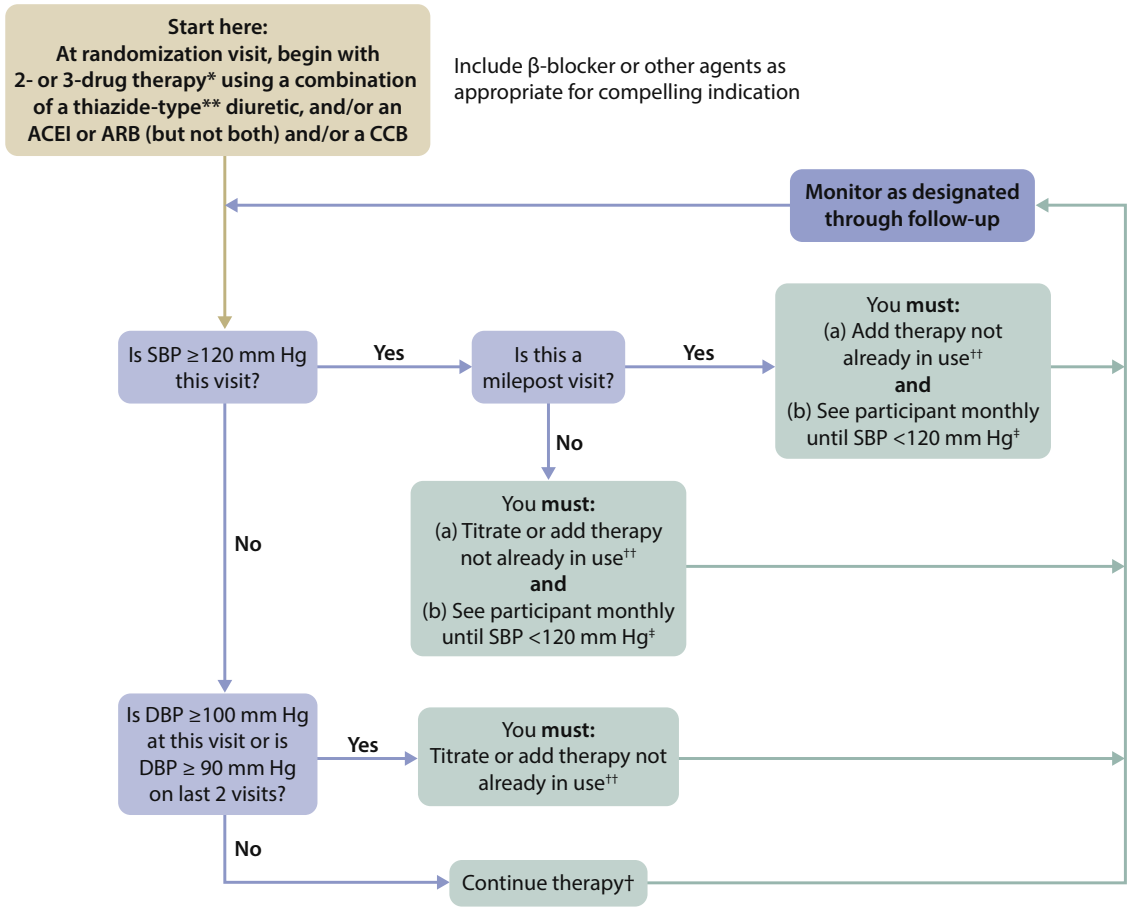


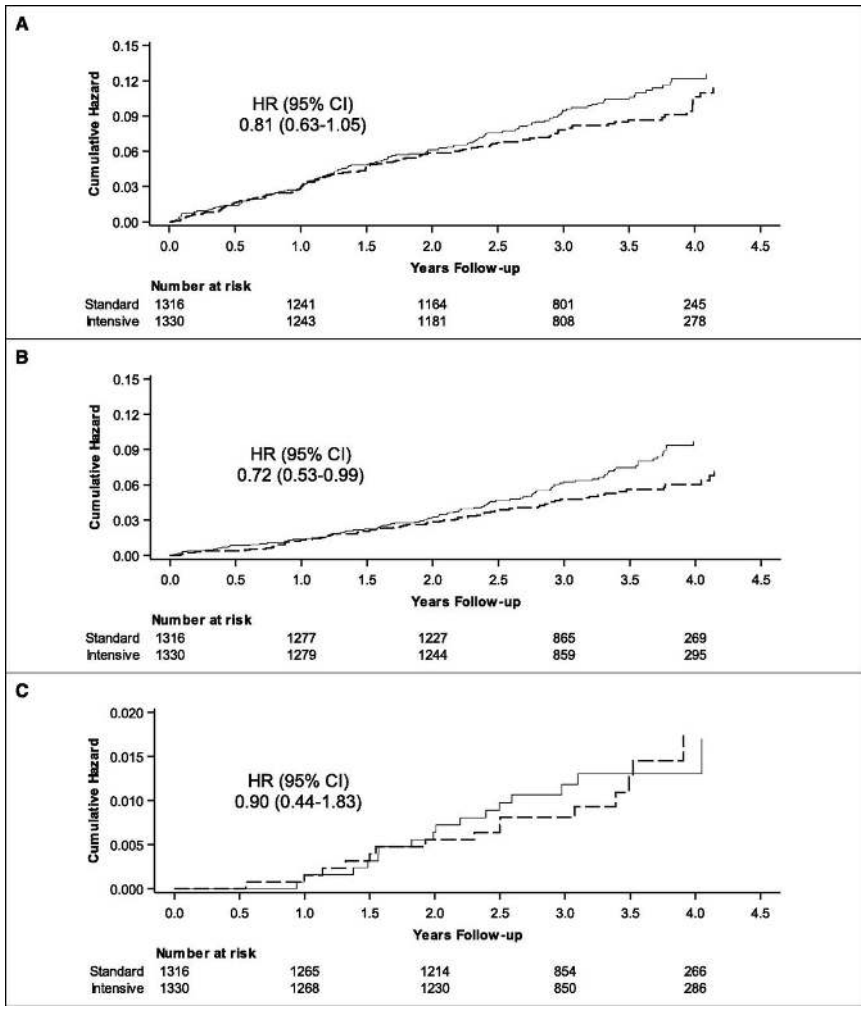
Figure 3 | Treatment algorithm for intensive SBP arm (target SBP <120 mm Hg) in SPRINT trial protocol. From *The New England Journal of Medicine*, the SPRINT Research Group, A Randomized Trial of Intensive Versus Standard Blood-Pressure Control, Volume 373, Pages 2103–2116, Copyright © 2015 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[2] ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium-channel blocker; CKD, chronic kidney disease; DBP, diastolic blood pressure; SBP, systolic blood pressure; SPRINT, Systolic Blood Pressure Intervention Trial. *May begin with a single agent for participants aged ≥75 years with SBP <140 mm Hg on 0–1 medications at study entry. A second medication should be added at the 1-month visit if participant is asymptomatic and SBP ≥130 mm Hg. **May use loop diuretic for participants with advanced CKD. †Unless side effects warrant change in therapy. ††Consider adding a fifth antihypertensive medication. ‡Or until clinical decision is made that therapy should not be increased further.

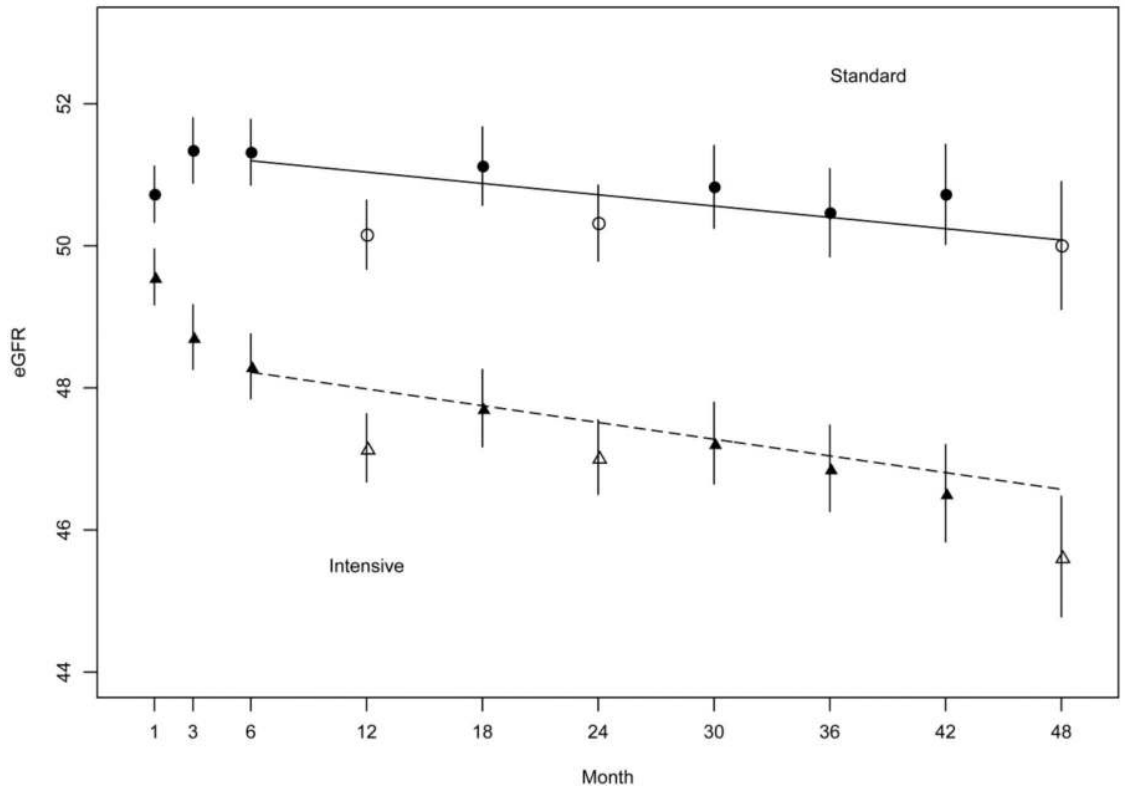
Analyse post-hoc de SPRINT chez patients CKD: 2646 patients

A: main <SPRINT outcome

B: all cause of death

C: main kidney outcome, -50% DFG / ESRD. Chez seulement 15 vs 16 patients





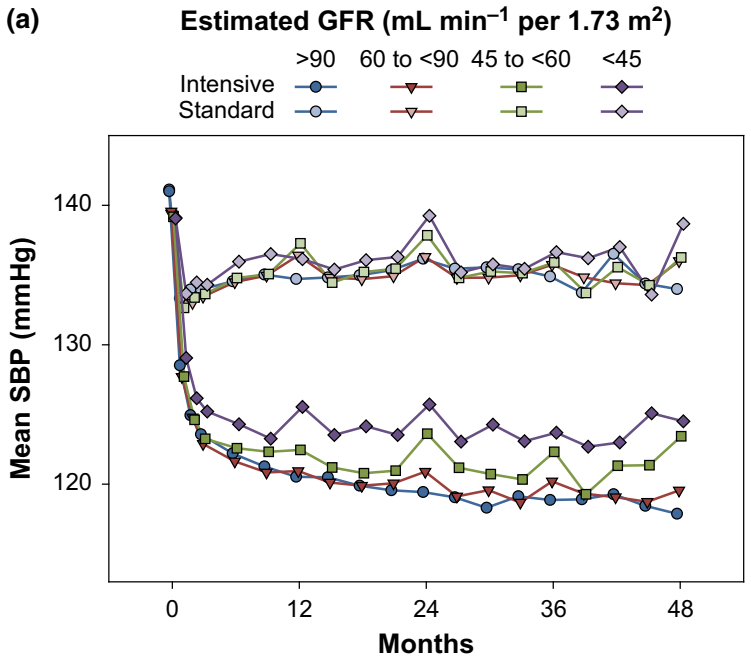
Cible basse:

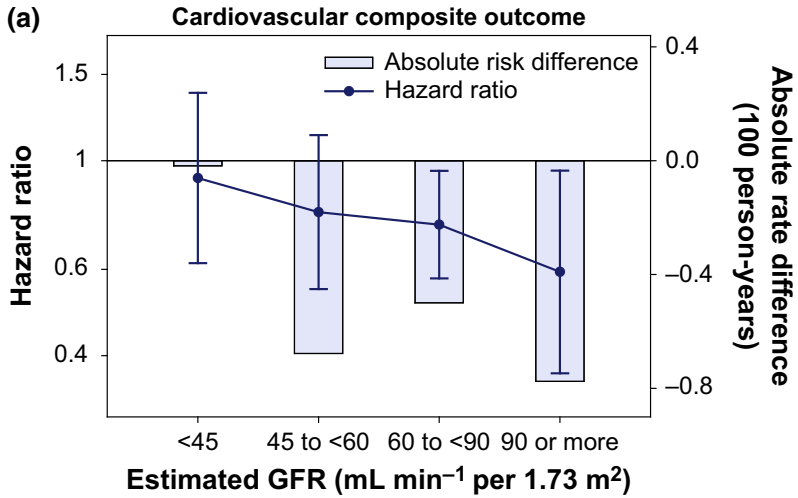
*Cardioprotection aussi chez IRC

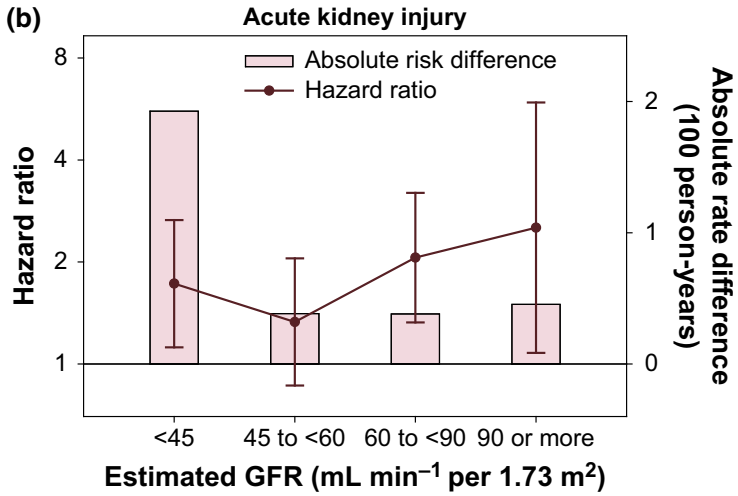
*Néphroprotection non retrouvée

Cheung AK, JASN 2017

Autre analyse post-hoc de SPRINT: effet du niveau de DFG sur le rapport bénéficie/risque d'un contrôle strict de la PA







Le bénéfice CV est attenué par des DFG bas
Risque d'IRA augmenté si DFG bas

Obi Y, J of Int Med 2018

Table 2. Major recent studies investigating blood pressure targets

Study	*N*	CV risk	Years of follow-up	BP target	Key results
ACCORD [7]	4733	High	4.7	SBP <120 vs. SBP <140	No significant difference in CVD events overall Significantly less CV events/death in intensive BP-standard glycemia arm
SPRINT, Main Outcomes [8]	9361	High	3.26	SBP <120 vs. SBP <140	Significantly less CV events and CV deaths in intensive arm
SPRINT, AKI Outcomes [14▪]	9361	High	3.26	SBP <120 vs. SBP <140	AKI more frequent in intensive arm Most AKI were stage 1 Most had complete or partial recovery
SPRINT, CKD Cohort [12▪▪]	2646	High	3.3	SBP <120 vs. SBP <140	Less CV events/death in intensive arm in those with GFR <60 and age ≥75 No difference in incident ESRD or decline in kidney function ≥50% but few events
SPRINT, Tubular injury markers [13▪]	978	High	4	SBP <120 vs. SBP <140	Biomarkers of kidney injury were not higher in intensive BP group
HOPE-3 [15]	12705	Intermediate	5.6	Candesartan + HCTZ vs. placebo	Patients with higher baseline blood pressure had reduction in CV events; no difference in those with lower baseline blood pressure

ACCORD, Action to Control Cardiovascular Risk in Diabetes; AKI, acute kidney injury; CKD, chronic kidney disease; CV, cardiovascular; ESRD, end-stage renal disease; HOPE-3, Heart Outcomes Prevention Evaluation-3; SPRINT, Systolic Pressure Intervention Trial.

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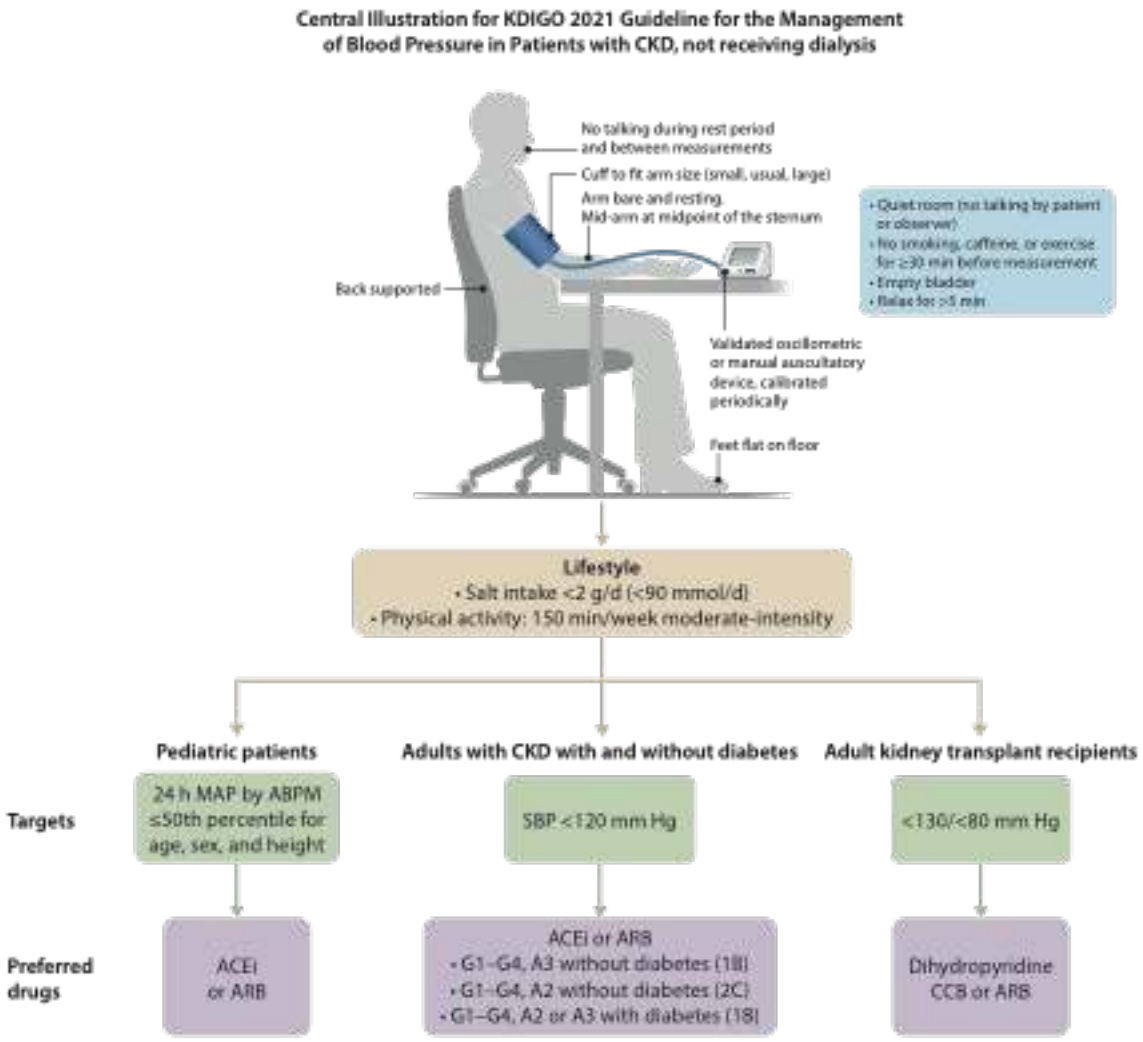
Executive summary of the KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease



Chapter 1: Blood pressure measurement	
• **Recommendation 1.1**	We recommend standardized office BP measurement in preference to routine office BP measurement for the management of high BP in adults (*1B*).
• **Recommendation 1.2**	We suggest that out-of-office BP measurements with ambulatory BP monitoring (ABPM) or home BP monitoring (HBPM) be used to complement standardized office BP readings for the management of high BP *(2B)*.
Chapter 2: Lifestyle interventions for lowering blood pressure in patients with CKD not receiving dialysis	
• **Recommendation 2.1.1**	We suggest targeting a sodium intake <2 g of sodium per day (or <90 mmol of sodium per day, or <5 g of sodium chloride per day) in patients with high BP and CKD *(2C)*.
• **Recommendation 2.2.1**	We suggest that patients with high BP and CKD be advised to undertake moderate-intensity physical activity for a cumulative duration of at least 150 minutes per week, or to a level compatible with their cardiovascular and physical tolerance *(2C)*.
Chapter 3: Blood pressure management in patients with CKD, with or without diabetes, not receiving dialysis	
• **Recommendation 3.1.1**	We suggest that adults with high BP and CKD be treated with a target systolic blood pressure (SBP) of <120 mm Hg, when tolerated, using standardized office BP measurement *(2B)*.
• **Recommendation 3.2.1**	We recommend starting renin-angiotensin-system inhibitors (RASi) (angiotensin-converting enzyme inhibitor [ACEi] or angiotensin II receptor blocker [ARB]) for people with high BP, CKD, and severely increased albuminuria (G1–G4, A3) without diabetes *(1B)*.
• **Recommendation 3.2.2**	We suggest starting RASi (ACEi or ARB) for people with high BP, CKD, and moderately increased albuminuria (G1–G4, A2) without diabetes (*2C*).
• **Recommendation 3.2.3**	We recommend starting RASi (ACEi or ARB) for people with high BP, CKD, and moderately-to-severely increased albuminuria (G1–G4, A2 and A3) with diabetes (*1B*).
• **Recommendation 3.3.1**	We recommend avoiding any combination of ACEi, ARB, and direct renin inhibitor (DRI) therapy in patients with CKD, with or without diabetes *(1B)*.
Chapter 4: Blood pressure management in kidney transplant recipients (CKD G1T–G5T)	
• **Practice Point 4.1**	Treat adult kidney transplant recipients with high BP to a target BP of <130 mm Hg systolic and <80 mm Hg diastolic using standardized office BP measurement (see Recommendation 1.1).
• **Recommendation 4.1**	We recommend that a dihydropyridine calcium channel blocker (CCB) or an ARB be used as the first-line antihypertensive agent in adult kidney transplant recipients (*1C*).
Chapter 5: Blood pressure management in children with CKD	
• **Recommendation 5.1**	We suggest that in children with CKD, 24-hour mean arterial pressure (MAP) by ABPM should be lowered to ≤50th percentile for age, sex, and height *(2C)*.

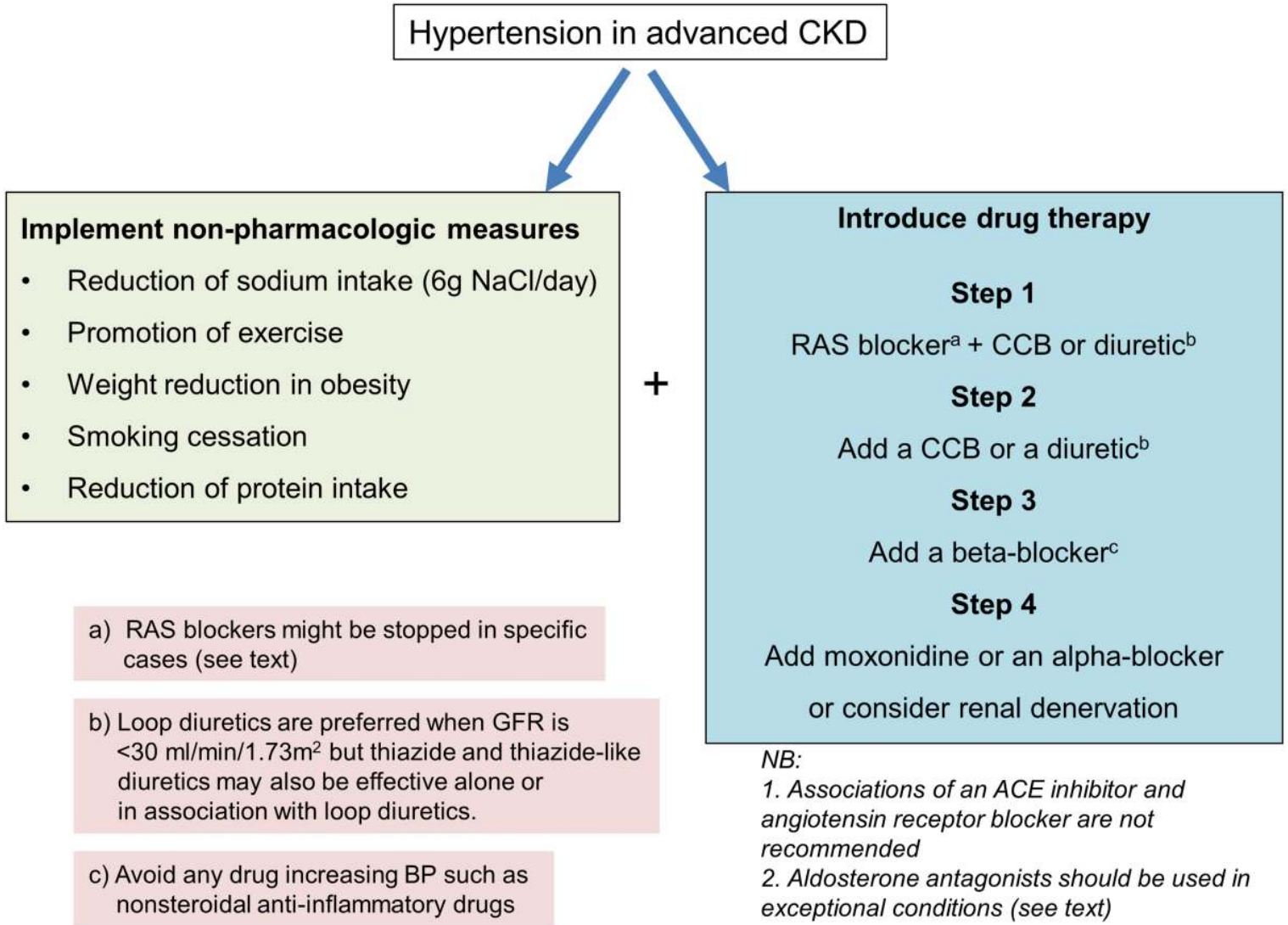


Figure 1 Schematic representation of a possible strategy to manage hypertension in severe CKD.

Is the KDIGO Systolic Blood Pressure Target <120 mm Hg for Chronic Kidney Disease Appropriate in Routine Clinical Practice?

Indranil Dasgupta, Carmine Zoccali

Hypertension 2022

- The KDIGO target systolic BP <120 mmHg target is based on CKD subgroup analysis of a single randomized controlled trial (SPRINT).
- The target is not generalisable as SPRINT excluded people with diabetes (also not supported by ACCORD trial), ADPKD, GN on immunosuppression, proteinuria >1 g/day and CKD stages 4 (very few patients included) & 5.
- The target refers to standardized BP and not to routine office BP.
- Standardized BP measurement is important for initiating and monitoring treatment of hypertension, but is challenging to implement outside specialist hypertension and research clinics.
- The target will increase the risk of adverse events in the multi-morbid, frail and elderly CKD population, especially if applied to routine BP measurement.
- The target will be difficult to achieve in the majority of CKD patients based on current evidence.
- The target systolic BP <120 mmHg recommended by KDIGO is an outlier among the contemporary international hypertension guidelines and will perplex clinicians.

Conclusions

- HTA est un important facteur de risqué CV et renal
- HTA participle à la progression de l'IRC
- IRC est associé à une augmentation du risqué CV dès le stade 3a.
- Le risqué de DC de cause CV chez les patients au stade 3 > risqué d'IRCT
- Donc contrôle HTA fondametal dans la MRC
- Cible <120mmHg de PAS par les KDIGO
    - Basée sur 1 seule étude bien conduit dans la population générale (SPRINT) et ses études post-hoc dans l'IRC.

Merci de votre attention