

HTA chez le greffé rénal: quelles données pour adapter le traitement?

JM KRZESINSKI

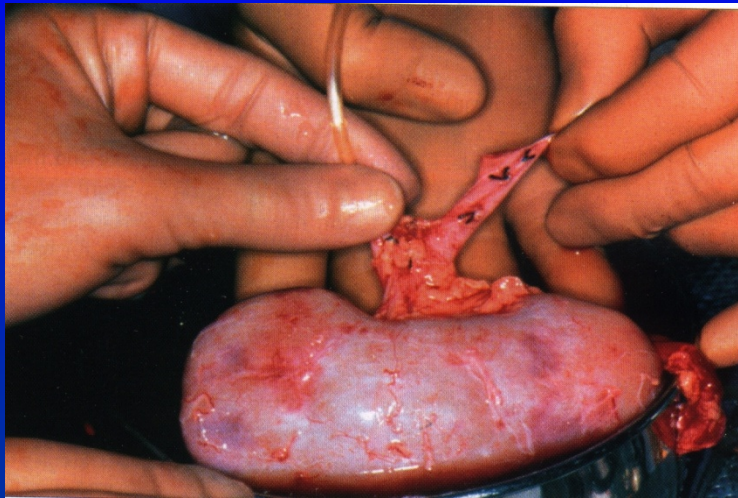
Néphrologie - Dialyse - Transplantation

ULg - CHU Liège

Belgique

Conflit d'intérêt

- Rien à déclarer en relation avec ce thème



Grefte rénale et
HYPERTENSION

44% décès CV

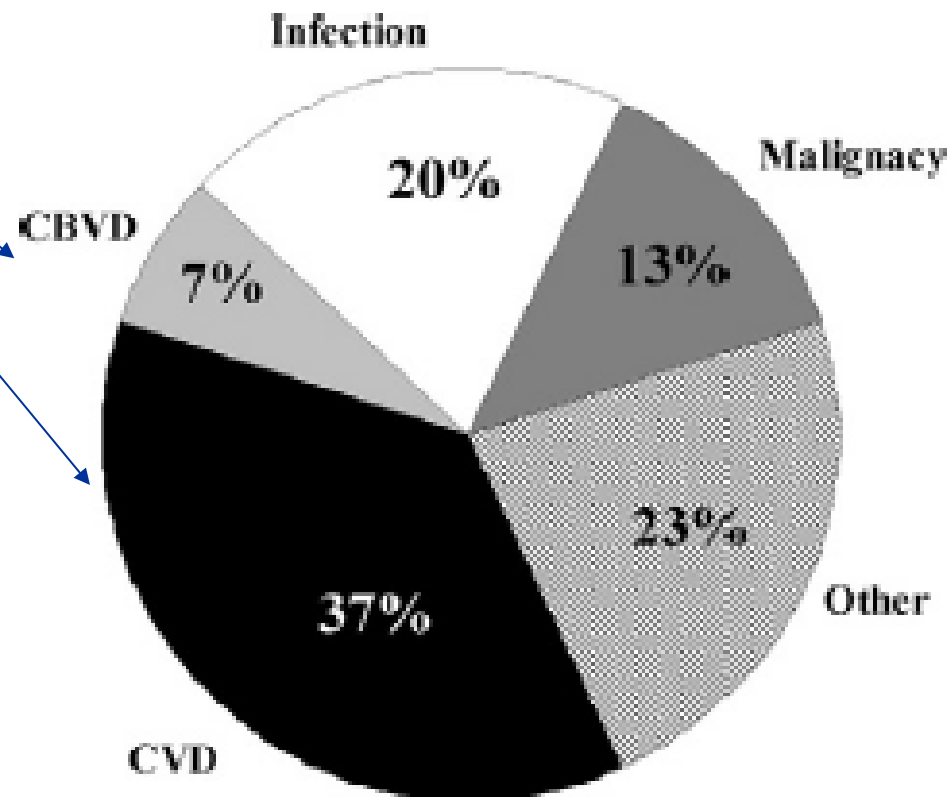


Figure 1. Mortality after kidney transplant. Atherosclerotic disease is the most common cause of death after transplant (44%) and outweighs the contributions from infection and malignancy combined (33%). Abbreviations: CBVD, cerebrovascular disease; CVD, cardiovascular disease. Source: US Renal Data System.³

Table 9.1. Risk factors for posttransplant cardiovascular disease

Risk Factor	Strength of Evidence
Pretransplant cardiovascular disease	++++
Diabetes (including posttransplant diabetes)	++++
Cigarette smoking	+++
Hyperlipidemia	+++
Hypertension	++
Platelet and coagulation abnormalities	++
Allograft dysfunction/rejection	++
Hypoalbuminemia	++
Erythrocytosis	+
Oxygen free radicals	+
Infections	+
Increased homocysteine	+

Prévalence de l'hypertension

Organe	A 1 an	A 5 ans
Rein	~ 80%	~ 95%
Foie	~60-70%	~ 60%
Coeur	~ 70%	~ 95%
Poumons	~ 50%	~ 80%

Box 1. Factors Contributing to Hypertension After Transplant

Recipient Factors

- Pre-existing hypertension & left ventricular hypertrophy
- Body mass index
- Native kidney disease

Donor Factors

- Donor age
- Donor sex
- Donor hypertension

Transplant Factors

- Cold ischemia time
- Warm ischemia time
- Delayed transplant function

Immunotherapy

- Corticosteroids
- Calcineurin inhibitors (cyclosporine > tacrolimus)

Transplant Dysfunction

- Acute rejection
- Antibody-mediated rejection
- Chronic allograft nephropathy
- Thrombotic microangiopathy
- Recurrent or de novo glomerular disease

Transplant Renal Artery Stenosis

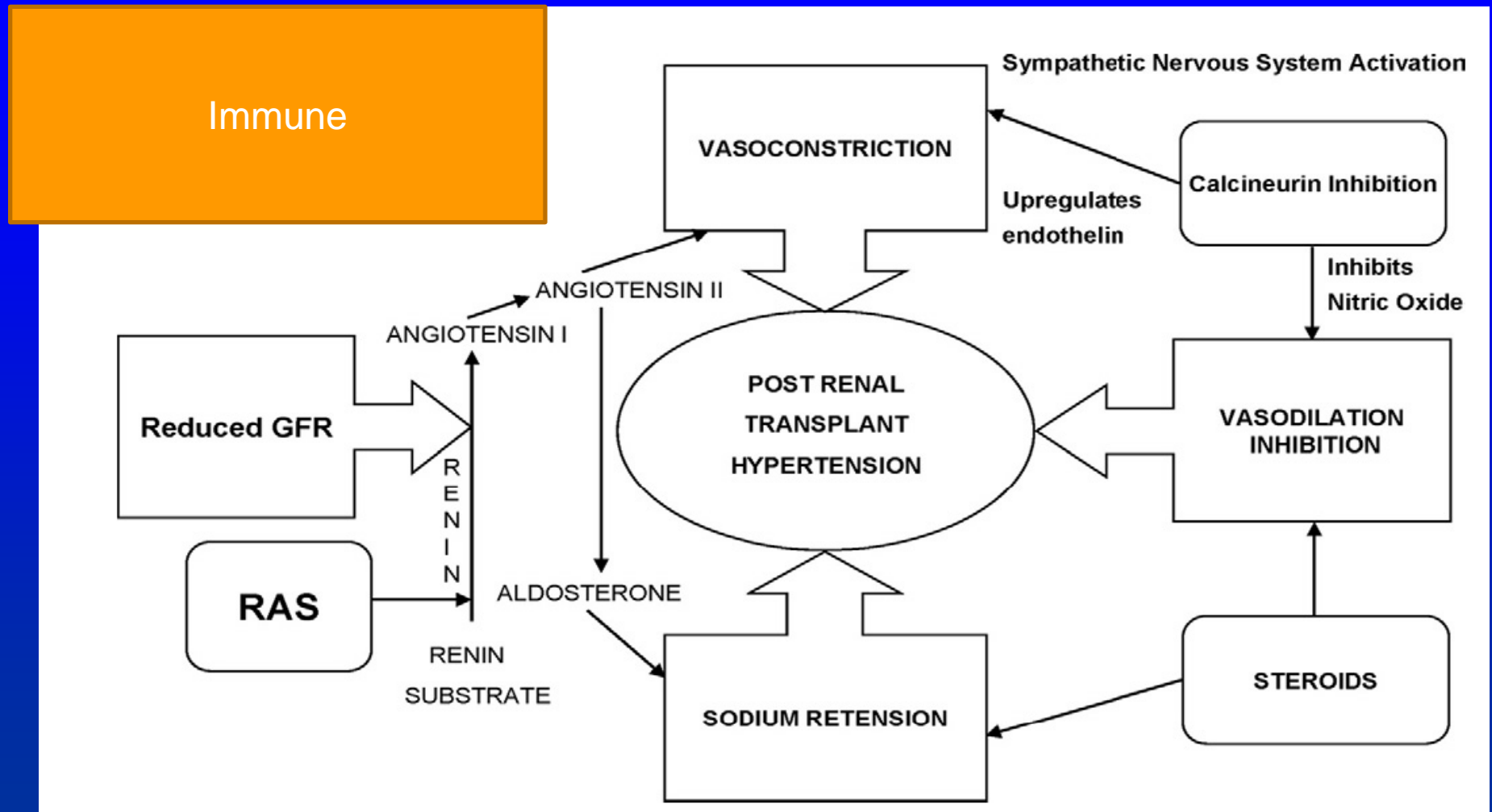
Transplant obstruction

- Ureteric stenosis
- Lymphocele

Hypertension After Kidney Transplant

Mahendra Mangray, MD, and John P. Vella, MD, FRCP

HTA post-transplantation: mécanismes potentiels



Hypertension After Kidney Transplant

Mahendra Mangray, MD, and John P. Vella, MD, FRCP

Contrôle de l'HTA chez le greffé

- La normalisation de la PA en consultation (<130/80 mmHg) chez le greffé rénal hypertendu est faible: de 10 à 50% selon les études.
- Une certaine inertie thérapeutique existe.
- La mesure de la PA en dehors de la consultation est utile (automesure, MAPA/24h) pour valider la réalité des chiffres.

Prévalence respective de l'hypertension vraie, de celle de la blouse blanche ou masquée

N=98 Tx rénale

HTcabinet >130/80 mmHg

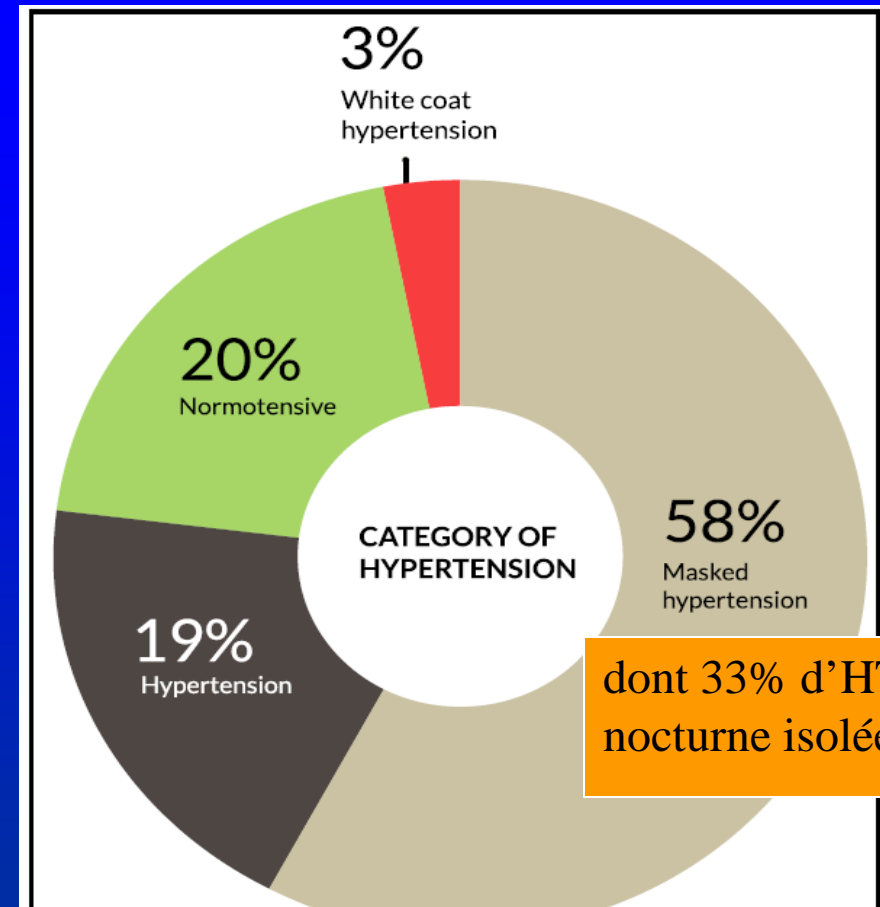
HT MAPA définie par :

-J >130/80 mmHg

-24h >125/75 mmHg

-Nuit >120/70 mmHg

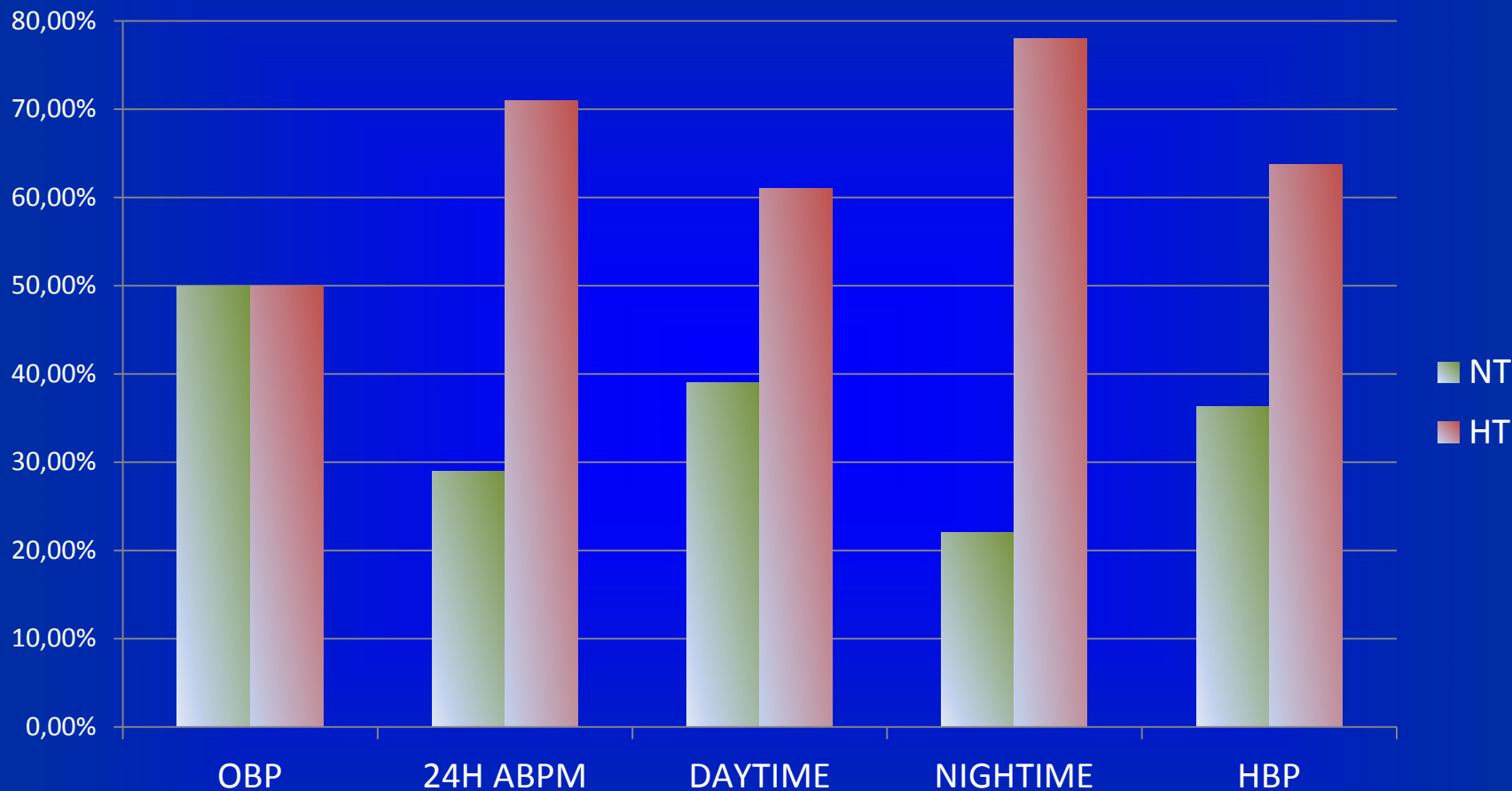
42% ont leur traitement changé après la MAPA...



Ambulatory vs Office Blood Pressure Monitoring in Renal Transplant Recipients

Jafar Ahmed, MBChB; Valerie Ozorio, MBChB; Maritza Farrant, MBChB; Walter Van Der Merwe, MBChB, FRACP

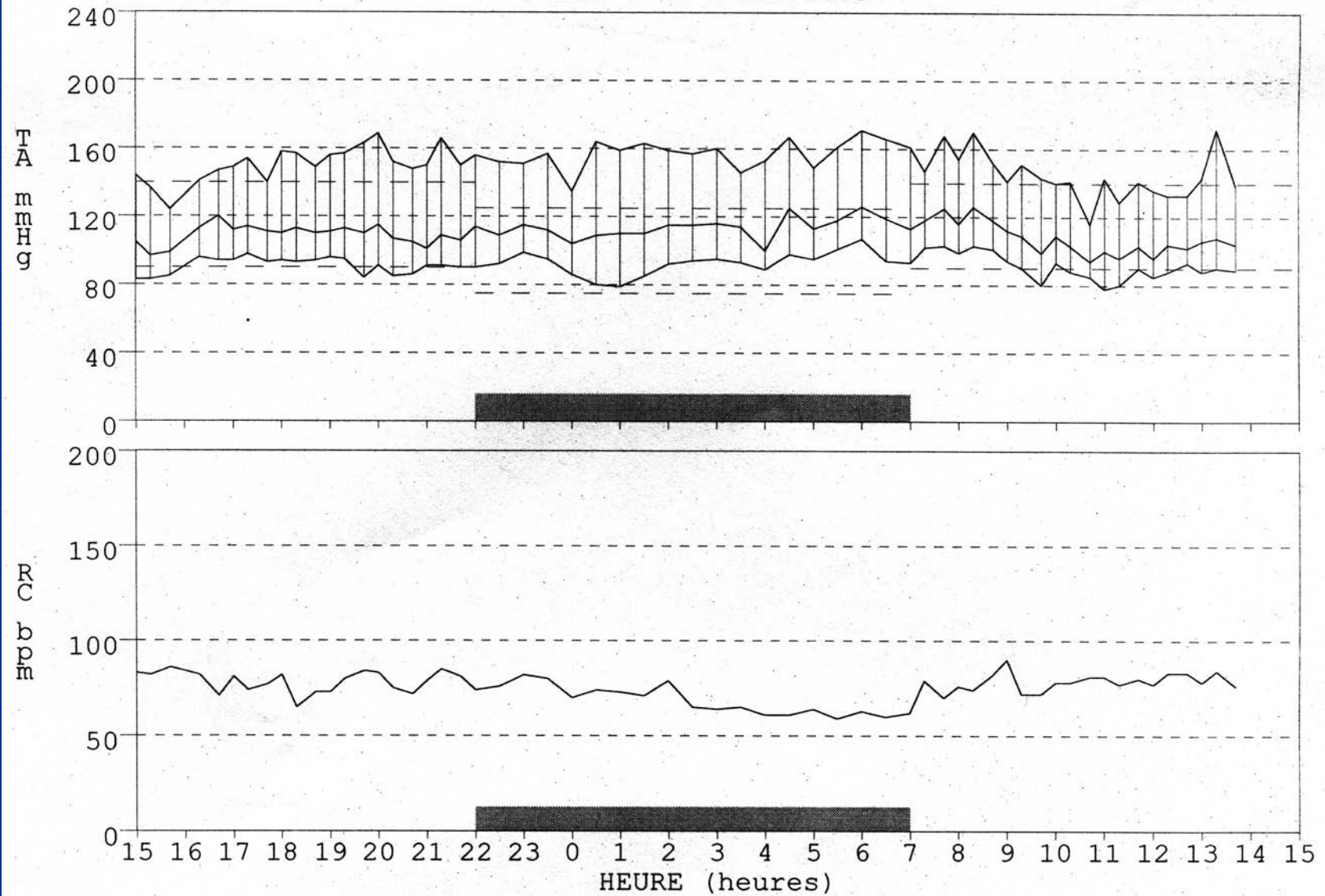
Blood Pressure control in treated hypertensive Ktr according to office and out-of-clinic BP measurements



Baseline visit-N=70, personal data

56 ans, DFG 65 ml/min, 7 ans
de greffe en moy, 2 antiHT

Jour 1 : 18.08.2009



Moyenne de jour : 147/91 mmHg; FC : 78
Moyenne de nuit : 158/93 mmHg; FC : 69

Research Article

Abnormal circadian blood pressure pattern 1-year after kidney transplantation is associated with subsequent lower glomerular filtration rate in recipients without rejection

Hani M. Wadei, MD^{a,*}, Hatem Amer, MD^b, Matthew D. Griffin, MBBCh^c, Sandra J. Taler, MD^b, Mark D. Stegall, MD^d, and Stephen C. Textor, MD^b

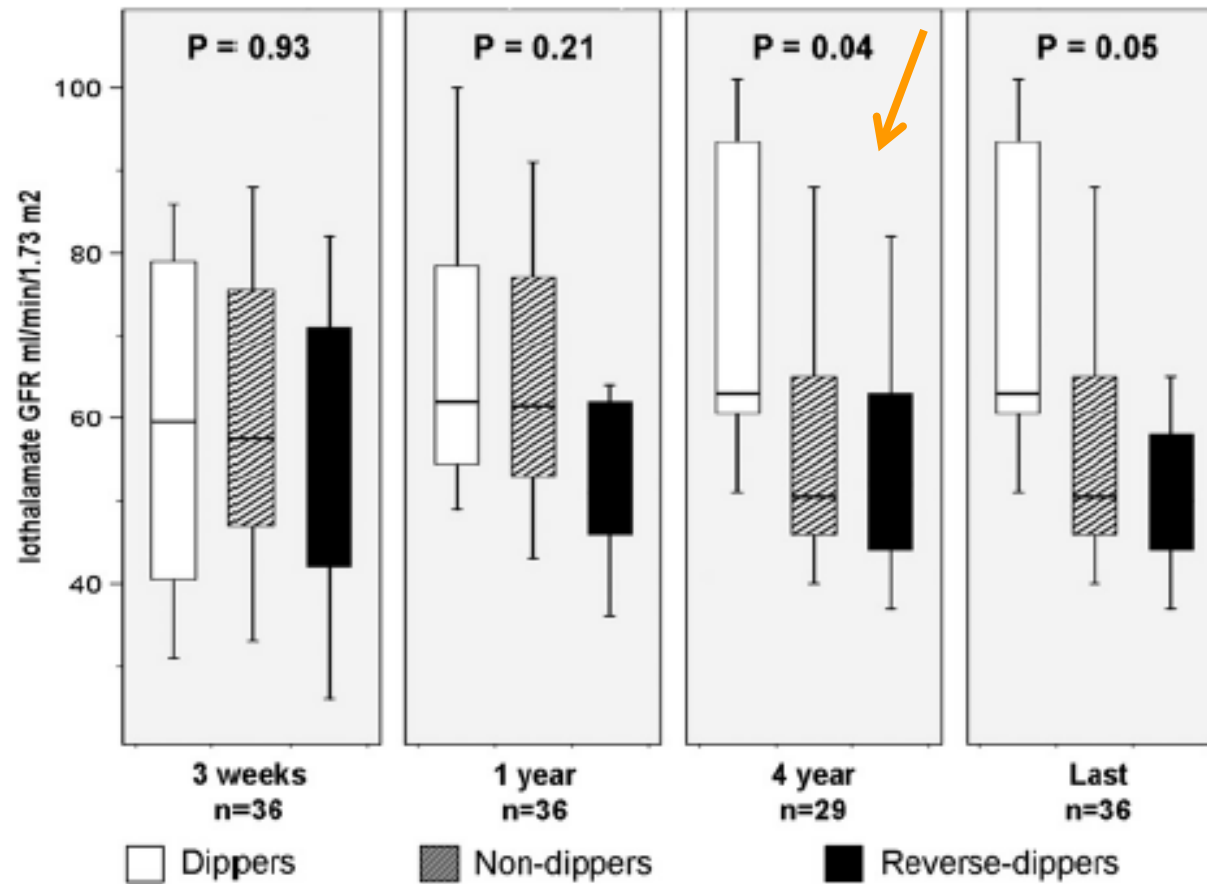
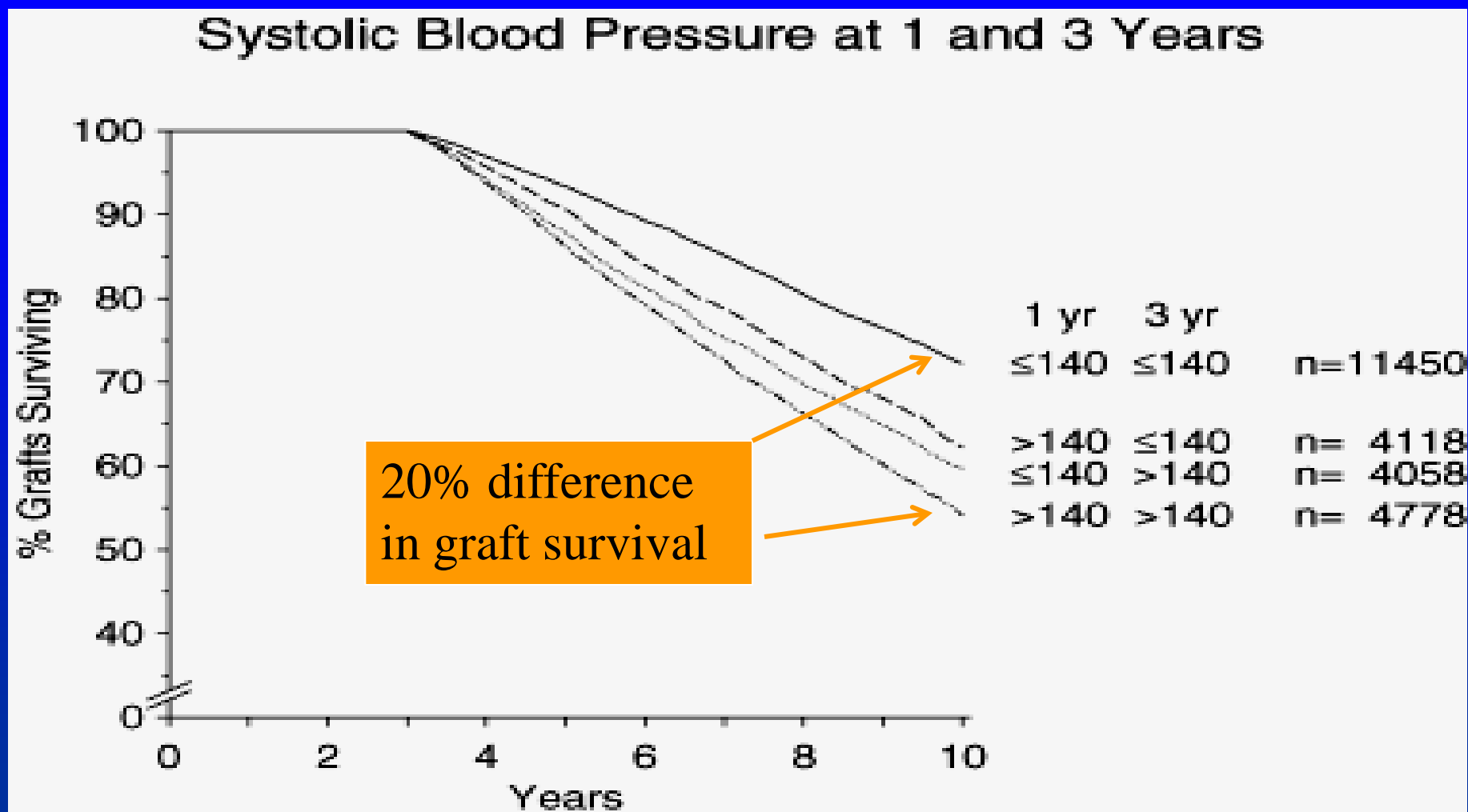


Figure 1. Box plots representing median (solid line) and inter quartile range of GFR at 3 weeks, at 1 and 4 years, and at last follow-up in 36 kidney transplant recipients with no rejection and with normal histology grouped according to dipping status. Non- and reverse dippers had lower kidney function compared with dippers at 4 years and at last follow-up. Corresponding values of glomerular filtration

Cible de PA chez le greffé rénal?

- Aucune étude randomisée contrôlée n'a été menée pour connaître la meilleure cible de PA!

Pression artérielle et risque de perte du greffon rénal (étude registre, donneurs cadavériques)



Chapter 5: Blood pressure management in kidney transplant recipients (CKD T)

KDIGO

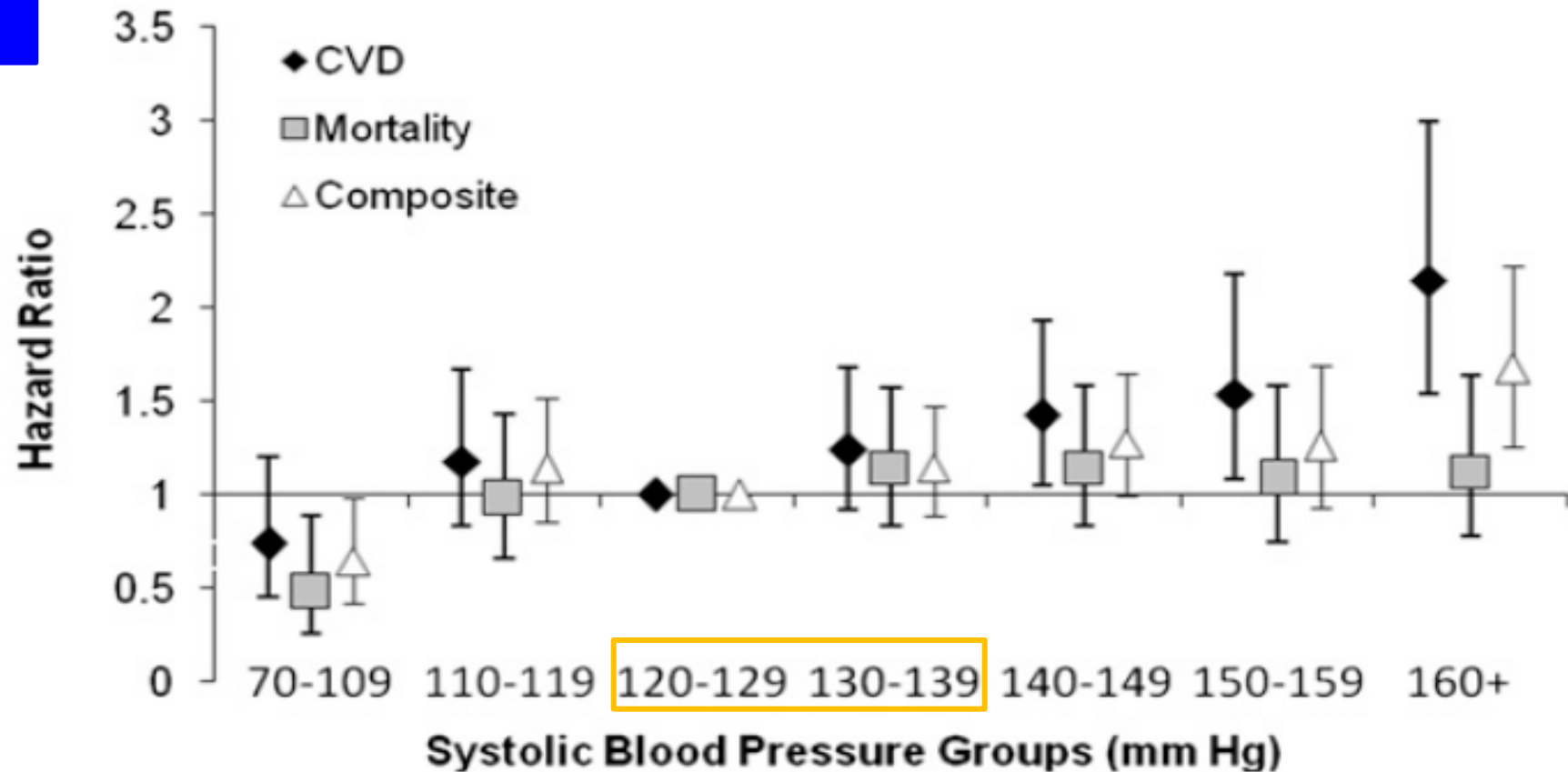
Kidney International Supplements (2012) **2**, 370–371; doi:10.1038/kisup.2012.55

5.1: We suggest that adult kidney transplant recipients whose office BP is consistently > 130 mm Hg systolic or > 80 mm Hg diastolic be treated to maintain a BP that is consistently ≤ 130 mm Hg systolic and ≤ 80 mm Hg diastolic, irrespective of the level of urine albumin excretion. (2D)

KDIGO: 130/80 mmHg

No recommendation for the BP target in KTR in JNC8 , 2014 or ESH/ESC, 2013

Etude Favorit: impact de la PAS sur le risque de décès et complication CV

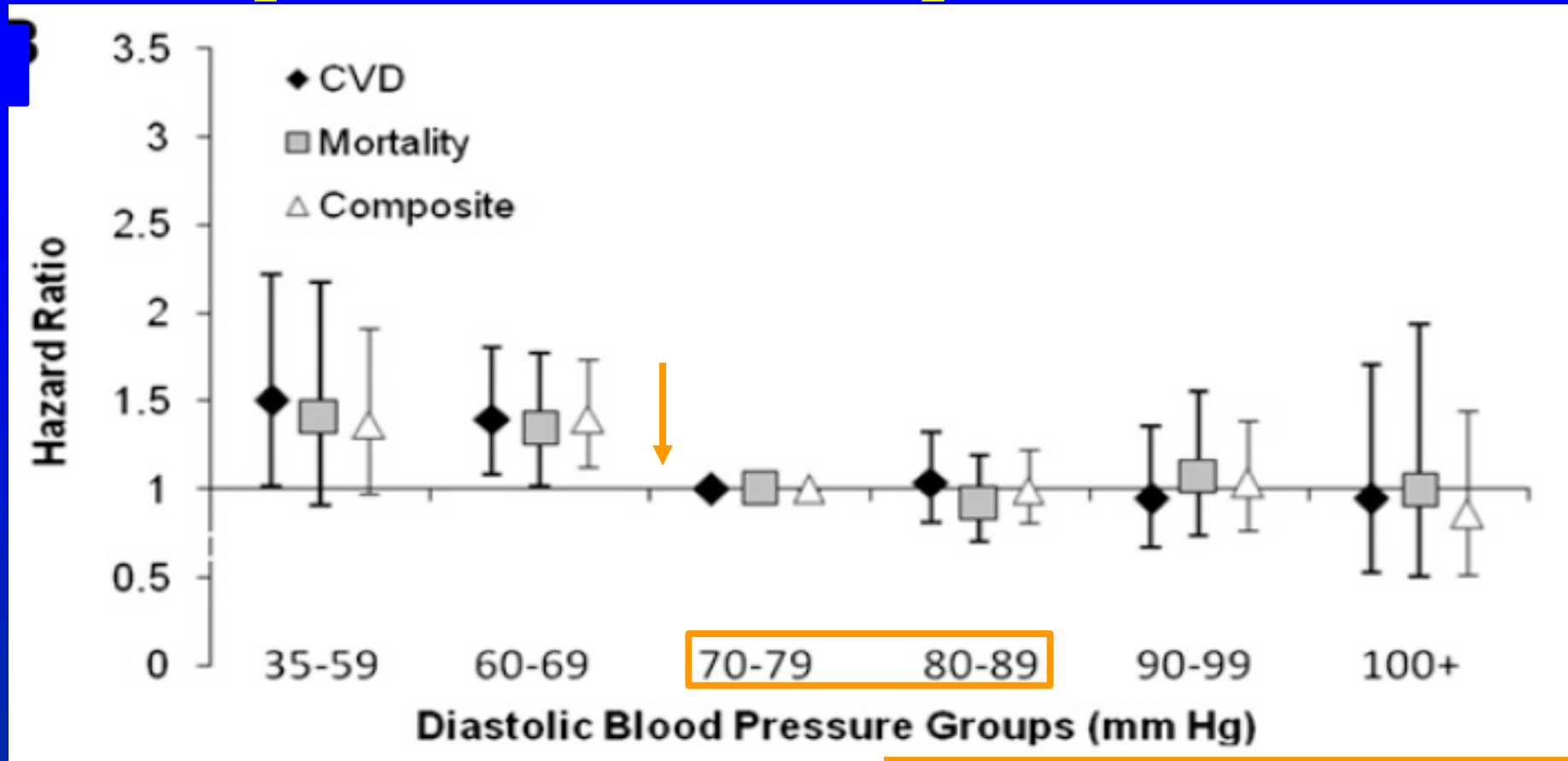


BP, Cardiovascular Disease, and Death in the Folic Acid for Vascular Outcome Reduction in Transplantation Trial

Myra A. Carpenter,* Alin John,[†] Matthew R. Weir,[‡] Stephen R. Smith,[§] Lawrence Hunsicker,^{||} Bertram L. Kasiske,[¶] John W. Kusek,^{**} Andrew Bostom,^{††} Anastasia Ivanova,* Andrew S. Levey,[†] Scott Solomon,^{‡‡} Todd Pesavento,^{§§} and Daniel E. Weiner[†]

Analyse a posteriori, 3474 greffés rénaux prévalents

Etude Favorit: impact de la PAD sur le risque de décès et complication CV



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Analyse a posteriori, 3474 greffés rénaux prévalents

Combined effects of SBP and DBP on CVD

Systolic BP and Diastolic BP Category ^a	<i>n</i>	CVD	
		HR (95% CI)	<i>P</i> Value
Low_Low	324	1.19 (0.83 to 1.70)	0.34
Low_Mod	325	1.13 (0.75 to 1.72)	0.56
Mod_Low	298	1.57 (1.14 to 2.17)	0.01
Mod_Mod	1034	Reference	—
Mod_High	128	0.62 (0.27 to 1.44)	0.27
High_Low	124	1.82 (1.24 to 2.67)	0.002
High_Mod	741	1.50 (1.16 to 1.95)	0.002
High_High	494	1.65 (1.17 to 2.32)	0.004

SBP: Low:<120 mmHg; Mod:120-139 mmHg; High: ≥140 mmHg
 DBP: Low:< 70 mmHg; Mod: 70-89 mmHg; High: ≥ 90 mmHg

Particularités du traitement de l'HTA chez le greffé rénal

- Changements hygiéno-diététiques
- Agents antihypertenseurs
- Changement de l'IS

Original Article

Sodium intake and blood pressure in renal transplant recipients

Else van den Berg^{1,2}, Johanna M. Geleijnse^{1,3}, Elizabeth J. Brink^{1,4}, Marleen A. van Baak^{1,5},
Jaap J. Homan van der Heide², Rijk O.B. Gans⁶, Gerjan Navis² and Stephan J.L. Bakker^{1,2}

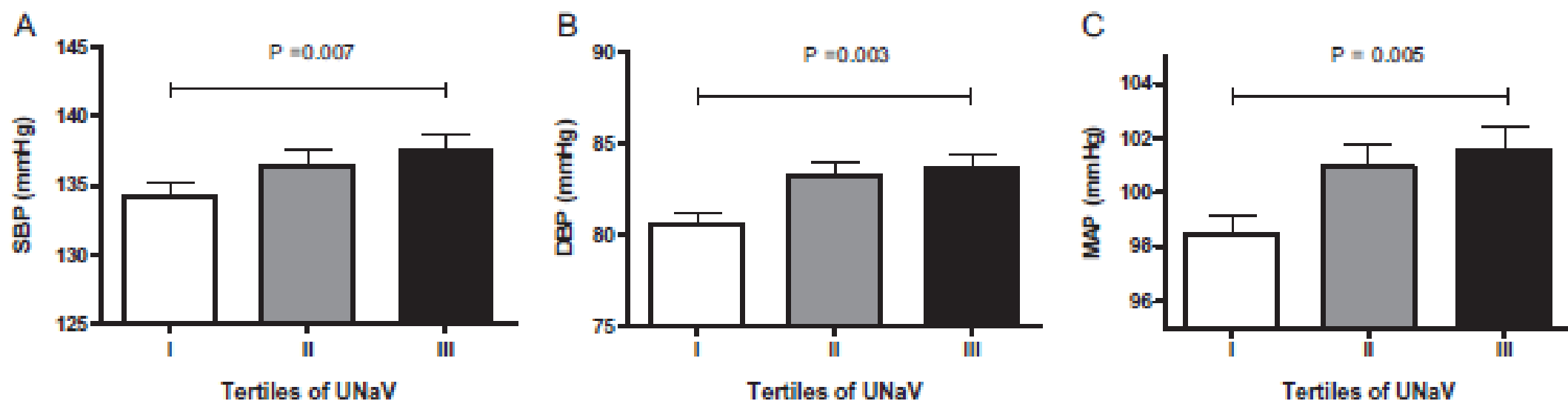


Fig. 2. SBP, DBP and MAP of RRT according to gender-stratified tertiles of urinary sodium excretion. (A) SBP; (B) DBP; (C) MAP. Values are mean with SEM. UNaV, urinary sodium excretion.

Treatment approach to KT hypertension

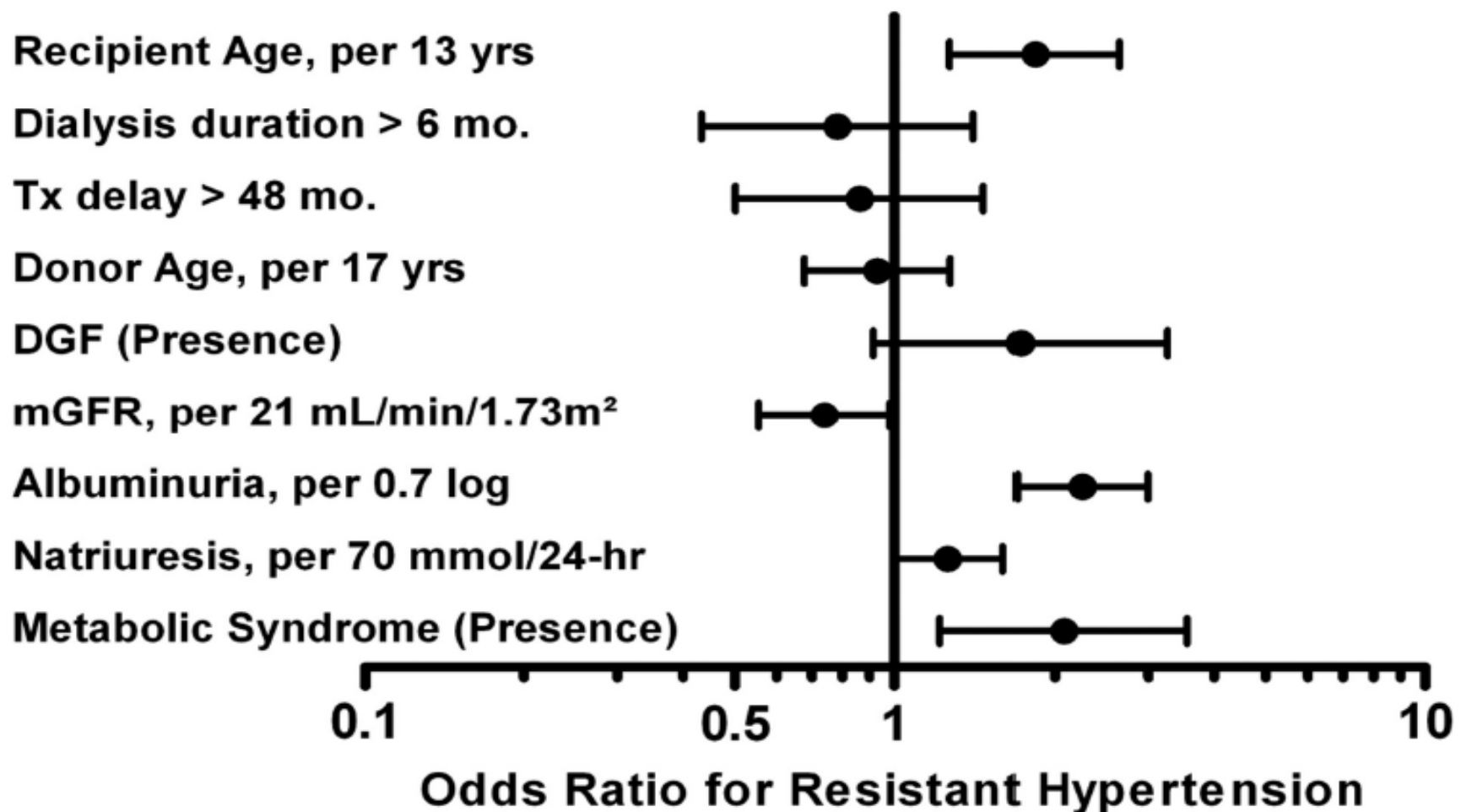
- Therapeutic lifestyle changes
 - Higher potassium diet?

Table 4 Coefficients of partial correlation between urinary Na⁺ and K⁺ excretion and Home systolic blood pressure

Pearson correlations	Partial correlation coefficient	P
N = 49		
Home SBP with urinary Na ⁺ Controlled for: age, BMI, smoking habit, antirejection drugs and urinary K ⁺	0.30	0.074
Home SBP with urinary K ⁺ Controlled for: age, BMI, smoking habit, antirejection drugs and urinary Na ⁺	-0.48	0.002

Facteurs de risque pour l'HTA résistante

Transplantation 2015;99: 1016–1022



Approche thérapeutique chez l'HT greffé

- **Médicament:** Chaque classe est possible.
- Le traitement doit être individualisé mais souvent une association de molécules est requise pour atteindre la cible.

Intérêt potentiel de chaque classe d'antiHTA chez le patient transplanté

- **Diurétique**: surcharge hydrosodée, renforcement d'effet antiHTA
- **Bbloqueur**: coronaropathie
- **AC nonDHP**: réduction besoins en ICN, angor
- **AC DHP**: protection rénale si ICN
- **IEC-ARA2**: néphropathie chronique greffon, protéinurie, érythrocytose, haut risque CV

Effets secondaires des antiHTA gênants en transplantation

- **Diurétique:** déshydratation, troubles ioniques et dysfonction sexuelle, diabète, dyslipidémie
- **BBloqueur:** dysfonction sexuelle, dyslipidémie
- **AC non DHP:** élévation des taux d'ICN
- **AC DHP:** hypertrophie gingivale avec ICN
- **IEC-ARA2:** IRA si SAR > ou déshydratation, anémie, hyperkaliémie

Antihypertensives for kidney transplant recipients

N Cross et al Transplantation July 2009

RAS Blockers or DHP CCB:

- - Lower GFR with RAS Blockers
 - - reduction of proteinuria and hemoglobin
 - - small increase in kalemia
 - - not higher risk for graft loss!
-
- Interest of RAS Blockers in proteinuric patients (CAN)?

Ramipril versus placebo in kidney transplant patients with proteinuria: a multicenter, double-blind, randomized controlled trial (G Knoll et al)

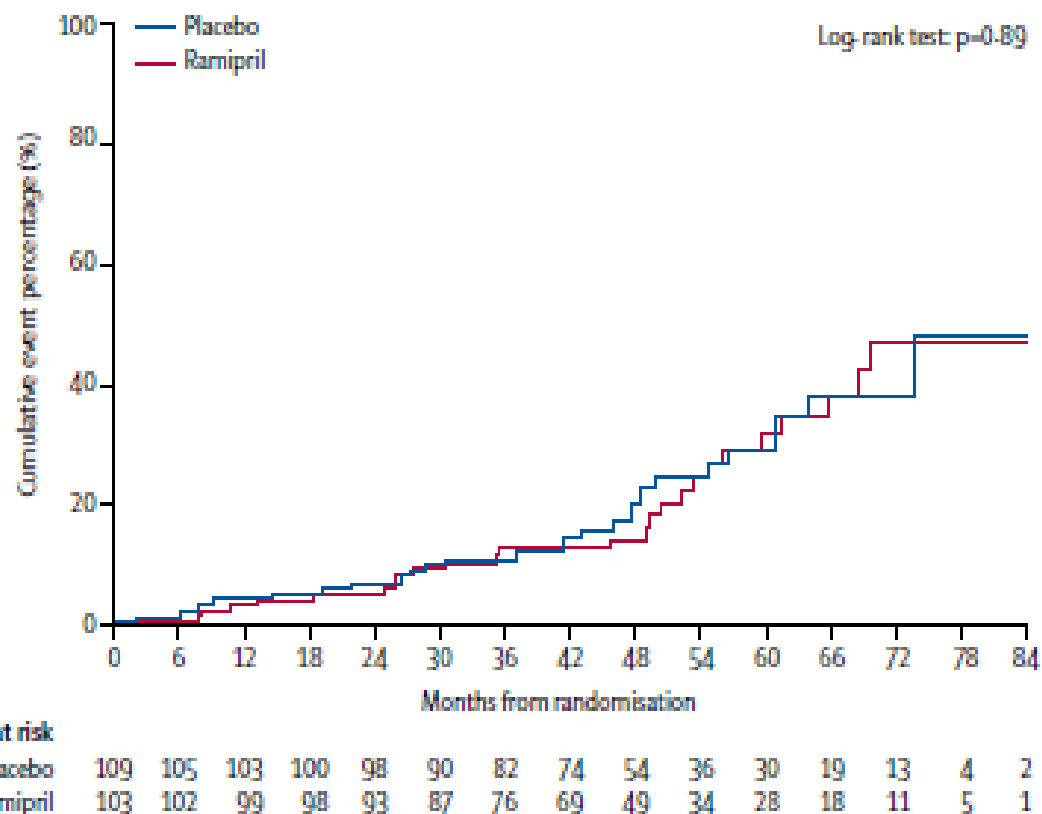
- Study conducted in Canada and New Zealand, with adult renal transplant recipients at least 3-months post-transplant with an eGFR of 20 mL/min/1.73m² or greater and proteinuria 0.2 g per day or greater,
- They were randomly assigned to receive either ramipril (5 mg orally twice daily) or placebo for up to 4 years, with an extended period of 4y.

	PI	R
Measured DTPA GFR (mL/min)	65.1 (27.6)	65.9 (25.0)
Corrected (mL/min/1.73m ²)	58.6 (24.1)	59.8 (21.9)
Blood pressure		
Systolic blood pressure (mm Hg)	135 (17)	135 (16)
Diastolic blood pressure (mm Hg)	78 (10)	77 (9)
<130/80	32 (29%)	35 (34%)
Serum potassium (mmol/L)	4.3 (0.5)	4.3 (0.6)
Serum creatinine (umol/L)	142 (54)	138 (51)
Haemoglobin (g/L)	129 (17)	131 (14)
Proteinuria (mg per day)	400 (270-720)	430 (270-813)

Ramipril versus placebo in kidney transplant patients with proteinuria: a multicentre, double-blind, randomised controlled trial

www.thelancet.com/diabetes-endocrinology Published online October 23, 2015

Greg A Knoll*, Dean Fergusson*, Michaël Chassé, Paul Hebert, George Wells, Lee Anne Tibbles, Darin Treleaven, David Holland, Christine White, Norman Muirhead, Marcelo Cantarovich, Michel Paquet, Bryce Kiberd, Sita Gourishankar, Jean Shapiro, Ramesh Prasad, Edward Cole, Helen Wilmore, Valerie Cropp, Debora Hooper, Tim Ramsay, John Gill



	Placebo (n=109)	Ramipril (n=103)	p value
Total	24 (22%)	39 (38%)	0.02
Angioedema	0	1 (1%)	0.49
Cough	0	4 (4%)	0.05
Hyperkalemia*	1 (1%)	5 (5%)	0.11
Anemia*	22 (20%)	25 (24%)	0.51
Other	1 (1%)	4 (4%)	0.20

*Hyperkalemia defined as serum potassium ≥ 6.0 mmol/L; anaemia defined as haemoglobin < 100 g/L

Table 3: Adverse events

Lower BP in the ramipril group (-5/-3 mmHg)

Figure 2: Time to the primary outcome of doubling serum creatinine, end-stage renal disease or death during the extension phase of the study

Interpretation Treatment with ramipril compared with placebo did not lead to a significant reduction in doubling of serum creatinine, end-stage renal disease, or death in kidney transplant recipients with proteinuria. These results do not support the use of angiotensin-converting enzyme inhibitors with the goal of improving clinical outcomes in this population.

Inhibiteurs du SRA

- Doivent idéalement être évités dans les 3 premiers mois de greffe vu le risque:
 - d'ignorer un rejet
 - d'IRA fonctionnelle
 - d'hyperkaliémie.

Influence d'une modification de l'IS

- Arrêt des corticostéroïdes:
 - Petite diminution de la prévalence de l'HTA (-10%), effet plus net sur l'Hypercholestérolémie (-24%) et sur le risque de Diabète (-36%) (Pasqual et al T 2006, Woodle et al Ann Surg 2008)
 - Augmentation légère du risque de rejet aigu mais pas d'effet sur la fonction du greffon au long cours.
- ICN:
 - PA plus basse si réduction de dose, conversion de la Ciclosporine en Tacrolimus ou substitution(après 3mois).

How to manage HT according to the KTR period?

- **During the 1st month after KT:** role of volume overload, high dose of CST and CNI, DGF, technical problem (Kinking transplant renal artery, Page Kidney).

Best antiHT choice : CCB, Bblocker and sometimes diuretics.

Target BP : 140-150 mmHg

- **Between the 1st and the 4th month after KT:**

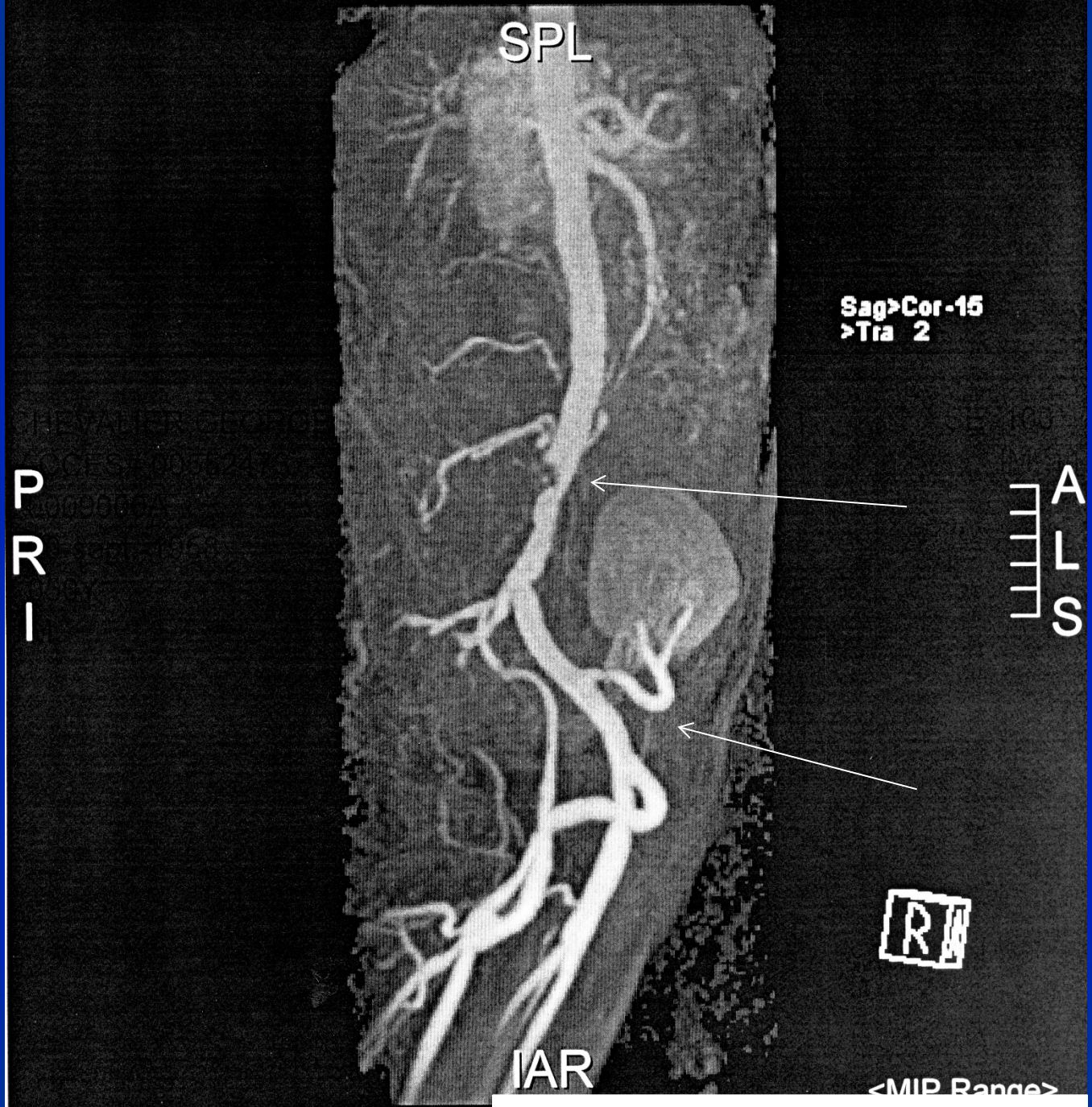
Target SBP <140 mmHg,

Look for 2ary HT (TRAS and other classic forms of 2ary HT)

- **After the 4th month of KT:** look for all CV risk factors,
target SBP <130 mmHg if possible

Transplant RAS

- 1-23% of KTR (**en moyenne 12%**) (Audard et al Am J HTA 2006)
- **RF:** CMV infection, DGF, surgical techniques, humoral rejection
- **Clinical presentation** similar to native Kidney RAS
- **Diagnosis:** Colour doppler sonography (sometimes MRI angiography)
- Conventional angiography (gold standard confirmation test)
- Biopsy of the graft could be useful before angioplasty (CAN)
- **Treatment:** possible spontaneous regression !,
angioplasty (with or without stent placement): (J Transplantation 2011)
 - high technical success (88-100%),
 - some complications of the procedure (3-25%)



MR angiography

Hypertension en Transplantation Rénale: Conclusions

- L'HTA est fréquente , souvent multifactorielle et sa prise en charge est importante pour le pronostic.
- Le recours aux techniques de mesure de la PA en dehors de la consultation est nécessaire.
- La cible de la PA est d'autant plus basse que l'on s'éloigne de la date de la Transplantation (cible de la PA proposée <130/80 mmHg après le 1^{er} trimestre).
- Rôle de l'alimentation dans l'approche thérapeutique et des AC DHP et Bêtabloquant. Changer l'IS peut être bénéfique.
- Si résistance au traitement, rechercher une cause secondaire, une mauvaise adhérence à la diététique et aux médicaments.

How to manage HT according to the KTR period?

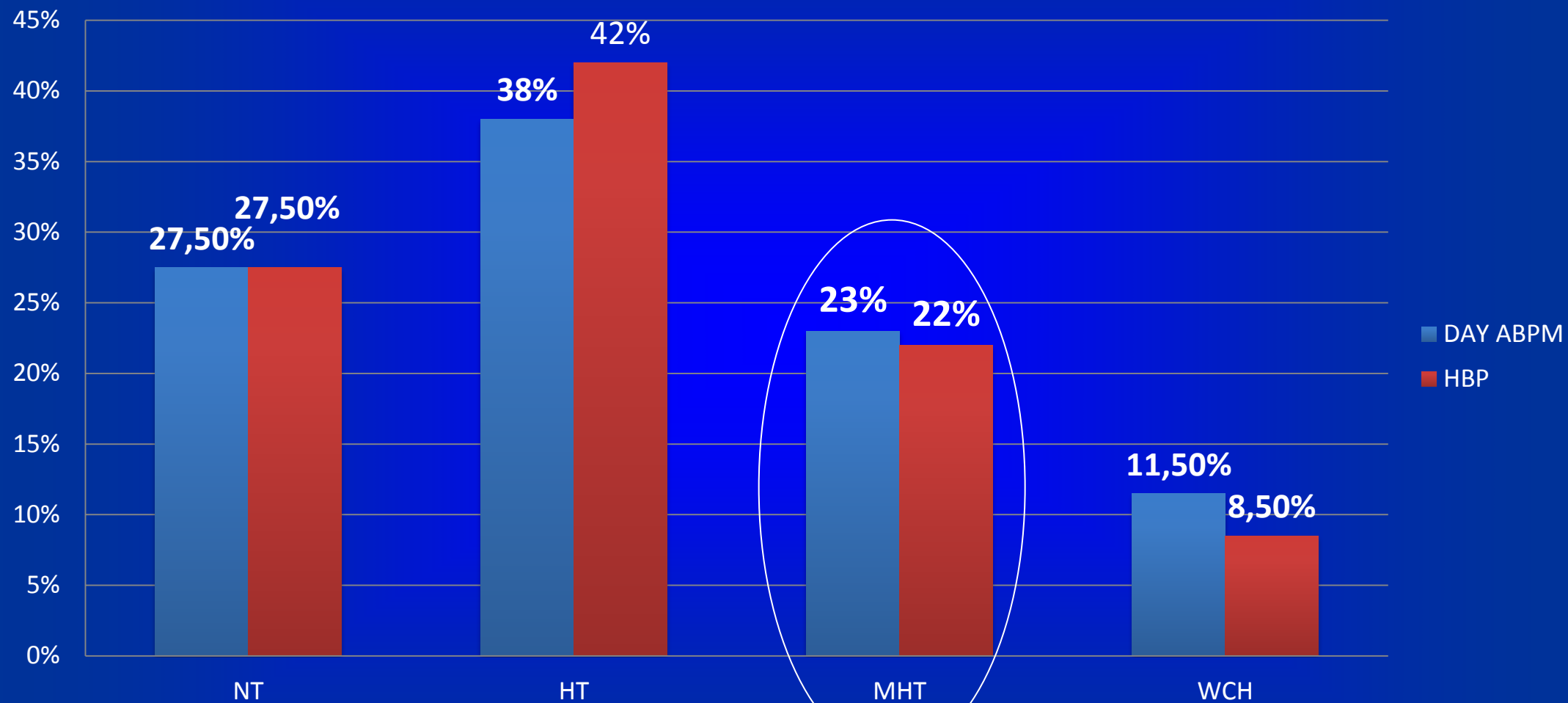
If uncontrolled HT,

- check for drug compliance and true HT by out-of-the clinic BP measurements,
- check for salt, potassium intakes and weight change,
- try to modify IS therapy,
- look for secondary HT (SAS, TRAS, endocrine diseases,..)
- introduce spironolactone if kalemia is correct
- discuss for bilateral native nephrectomy if resistant HT.

General characteristics KTR from Liège, all treated for HTA

	Mean \pm sd	min-max
N	70	
Men/women (N)	43/27	
Age (years)	56 \pm 11.5	33-76
Graft survival (years)	7.0 \pm 6.6	1-25
Hemodialysis vintage (years)	2.7 \pm 3.7	1 m -7.9 y
GFR (ml/min)	65.6 \pm 24	26-133
BMI (kg/m ²)	25.8 \pm 4.7	16-37
BMI \geq 30	(21%)	
Diabetes (N,%)	19 (27)	
Current smokers (N,%)	9 (13)	
Office SBP (mmHg)	136 \pm 14	107-175
Office DBP (mmHg)	83 \pm 12	50-108
N antiHT drugs	2 \pm 1	1-5

BP phenotypes (ref:OBP) according to out-of-clinic measurements



Baseline visit (N=70), personal data

Angiotensin-Converting Enzyme Inhibitor or Angiotensin II Type 1 Receptor Antagonist Therapy Is Associated with Prolonged Patient and Graft Survival after Renal Transplantation

Georg Heinze,* Christa Mitterbauer,[†] Heinz Regele,[‡] Reinhard Kramar,[§]
Wolfgang C. Winkelmayr,^{||} Gary C. Curhan,[¶] and Rainer Oberbauer[†]

**Core Unit of Medical Statistics and Informatics, Departments of [†]Nephrology and [‡]Pathology, Medical University of Vienna, Vienna, and [§]Austrian Dialysis and Transplant Registry, Hospital Wels, Wels, Austria; and ^{||}Division of Pharmacoepidemiology and Pharmacoeconomics and Renal Division, and [¶]Channing Laboratory, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts*

J Am Soc Nephrol 17: 889–899, 2006.

No Improvement of Patient or Graft Survival in Transplant Recipients Treated with Angiotensin-Converting Enzyme Inhibitors or Angiotensin II Type 1 Receptor Blockers: A Collaborative Transplant Study Report

Gerhard Opelz,* Martin Zeier,[†] Gunter Laux,* Christian Morath,[†] and Bernd Döhler*
*Departments of *Transplantation Immunology and [†]Nephrology, University of Heidelberg, Heidelberg, Germany*

J Am Soc Nephrol 17: 3257–3262, 2006.

Facteurs de risque d'Insuffisance rénale ou de mort en transplantation rénale

Creatinine doubling, all-cause ESRD, or death

Variable	HR (95% CI)	P-value
Plasma aldosterone	0.998 (0.99, 1.003)	0.43
Plasma renin activity	1.02 (0.90, 1.1)	0.74
Losartan	0.48 (0.21, 1.0)	0.07
Tacrolimus + rapamycin	2.37 (0.98, 5.7)	0.05
Caucasian donor	0.18 (0.07, 0.4)	< 0.01
< 3 HLA matches	3.79 (1.56, 9.1)	< 0.01
Hypertension	6.97 (2.23, 21.7)	< 0.01
Acute rejection (ever)	3.98 (1.80, 8.8)	< 0.01

Table 3. Variables related to 1-year systolic blood pressure by linear regression analysis.

	β	95% CI	p
Recipient age (years)	0.321	0.144–0.499	<0.001
Recipient sex (male)	5.958	1.589–10.326	0.008
Body mass index (kg/m ²)	0.214	–0.265–0.694	0.379
Recipient diabetes	6.660	1.738–11.582	0.008
Donor age (years)	0.062	–0.087–0.212	0.412
eGFR (ml/min/1.73 m ²)	–0.156	–0.300–0.011	0.036
Delayed graft function	4.709	0.192–9.225	0.041
1-year acute rejection	1.683	–3.176–6.541	0.496
Cyclosporine	9.143	4.907–13.379	<0.001
1-year urinary sodium excretion (per 100 mmol/day)	3.529	0.725–6.334	0.014