Management of hypertension in renal transplant patients

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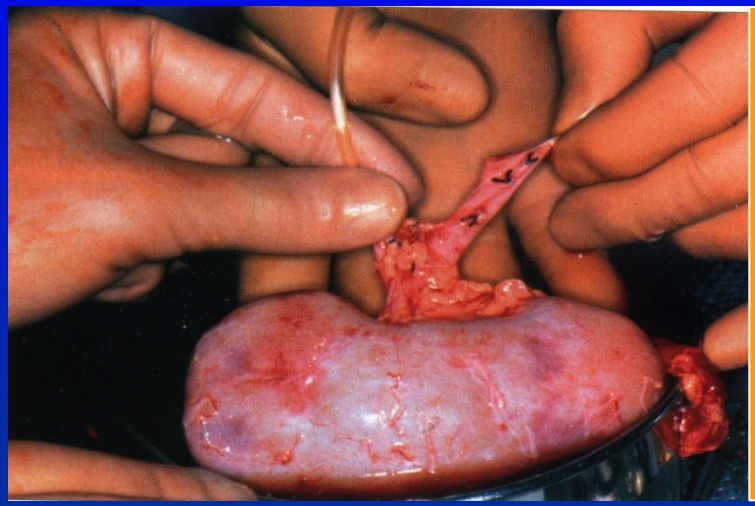
disclosure

- No competing interest in this field



Kidney transplantation
and

HYPERTENSION

Hypertension After Kidney Transplant

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

Am J Kidney Dis. 57(2):331-341. © 2011

44% CV death

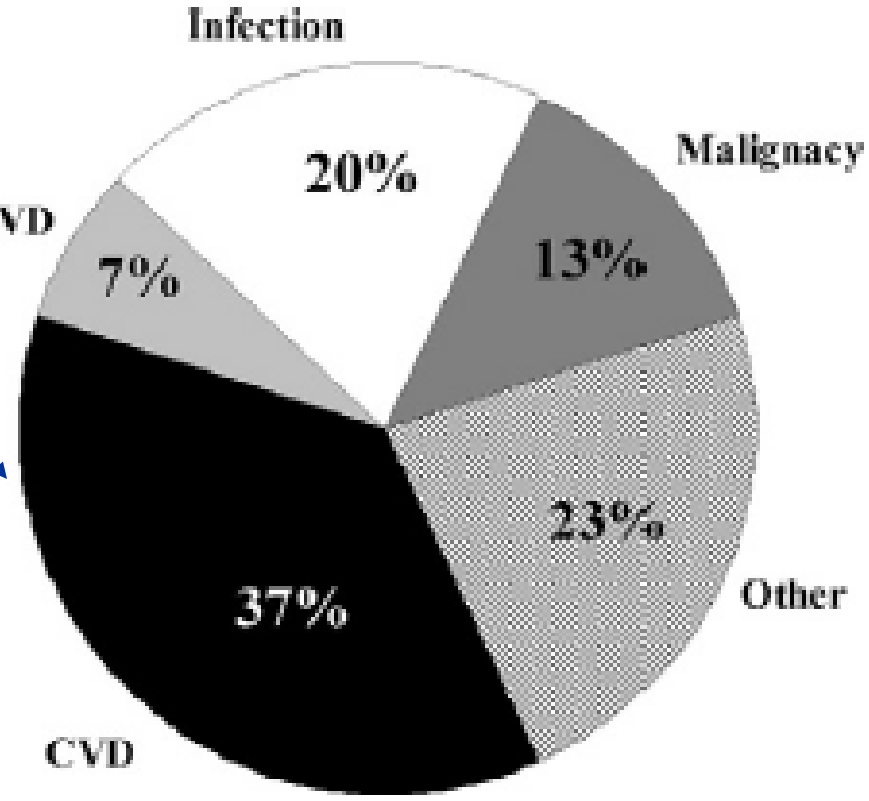


Figure 1. Mortality after kidney transplant. Atherosclerotic disease is the most common cause of death after transplant (44%) and outweighs the contributions from infection and malignancy combined (33%). Abbreviations: CBVD, cerebrovascular disease; CVD, cardiovascular disease. Source: US Renal Data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

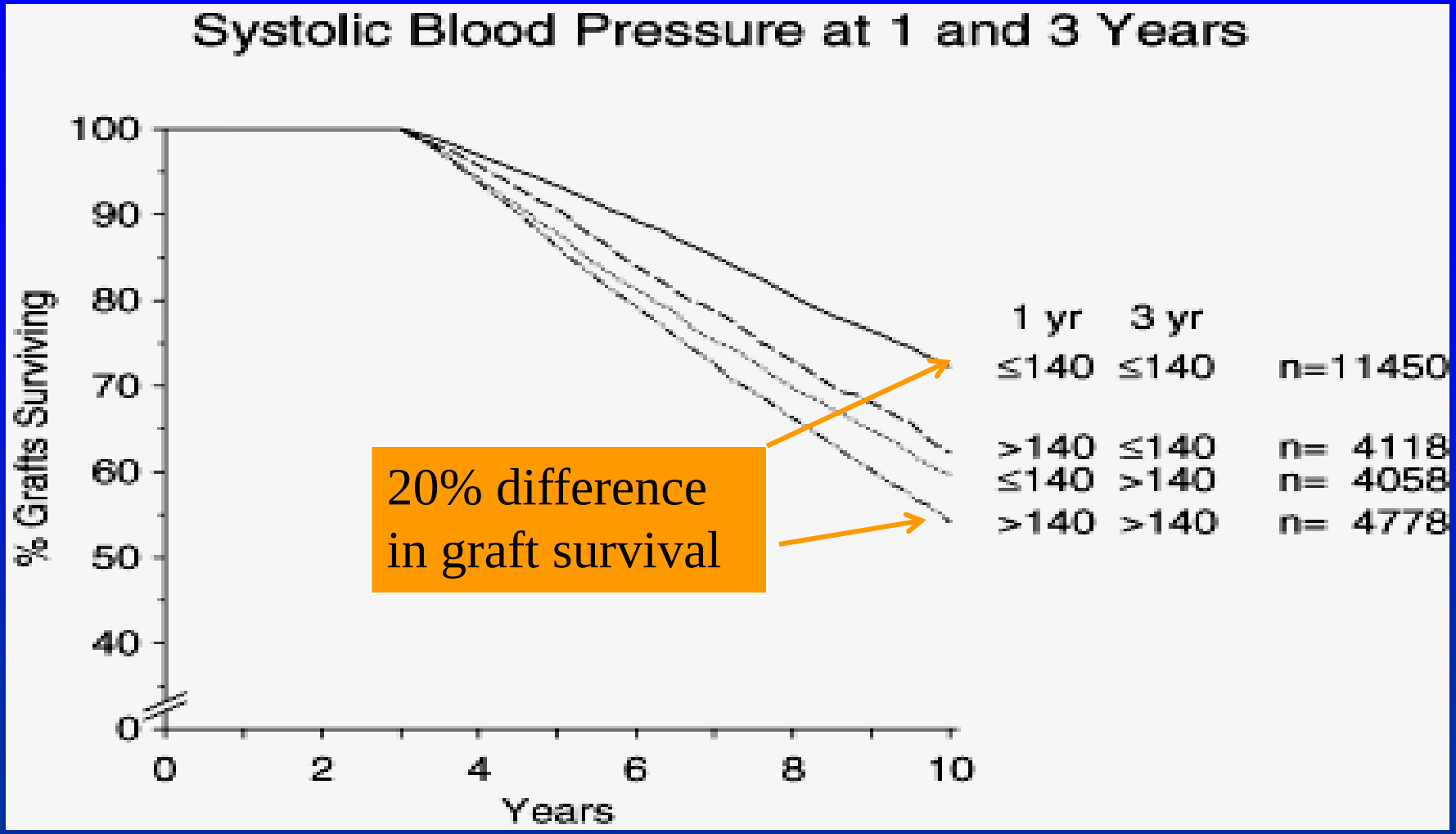
Prevalence of hypertension in solid organ transplantation

Organ	At 1 year	At 5 years
Kidney	~ 80%	~ 95%
Liver	~60-70%	~ 60%
Heart	~ 70%	~ 95%
Lungs	~ 50%	~ 80%

Rev Med Suisse 2009; 5: 1771-7

Adapted from Glatz N.

Office Blood Pressure and kidney graft failure risk in transplanted patients



Opelz et al. Am J Transplant 2005; 5: 2725

Prevalence of different forms of hypertension: true, white coat or masked HTA

N=98 Kidney Tx

HT office >130/80 mmHg

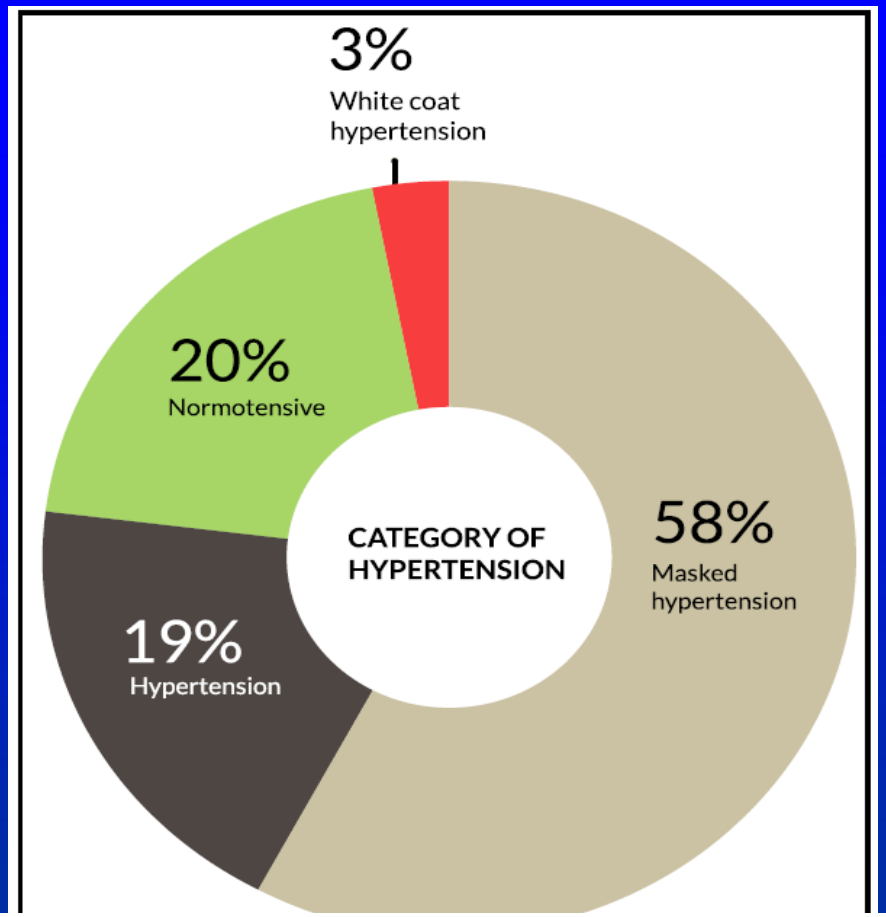
HT ABPM definition:

-Day >130/80 mmHg

-24h >125/75 mmHg

-Night >120/70 mmHg

42% have their antiHTA treatment modified after the ABPM…

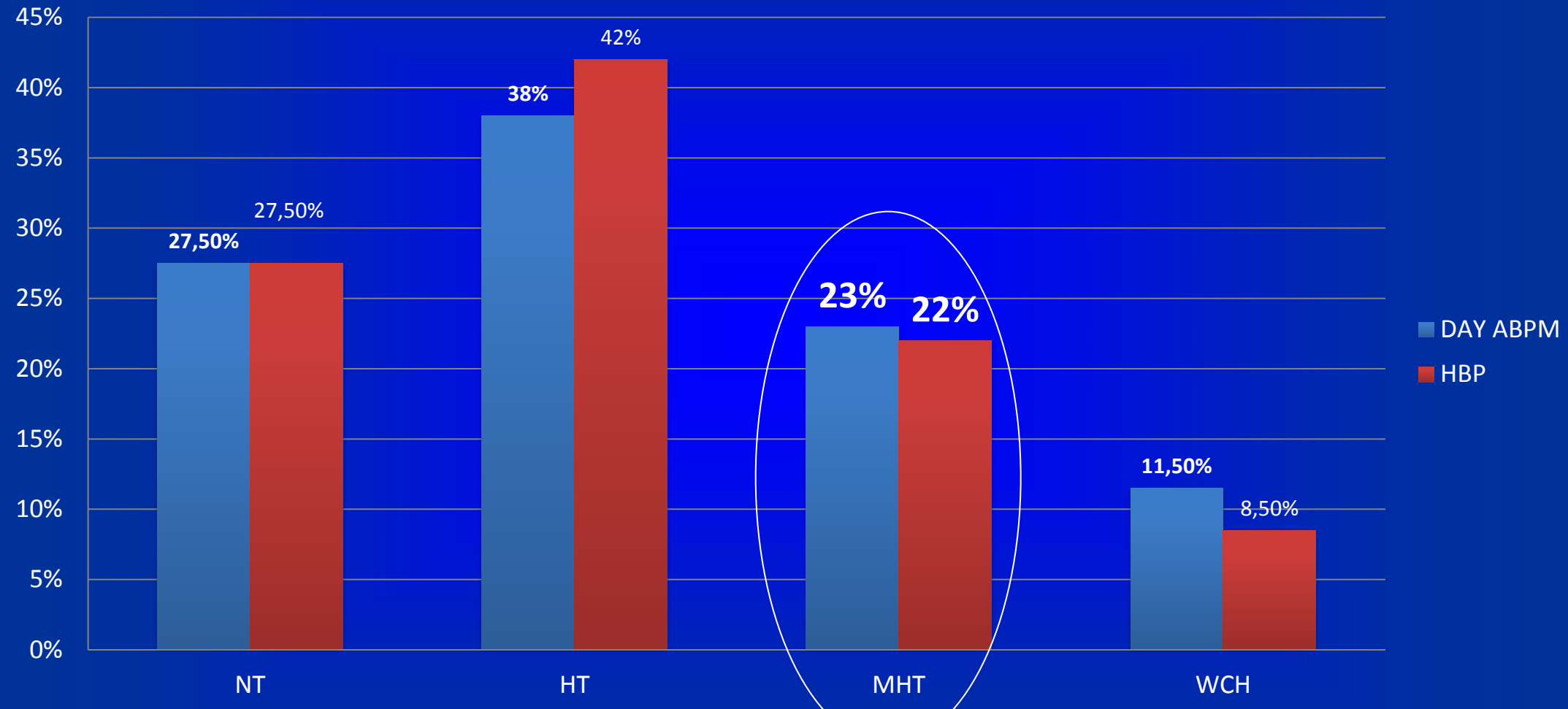


Ambulatory vs Office Blood Pressure Monitoring in Renal Transplant Recipients

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

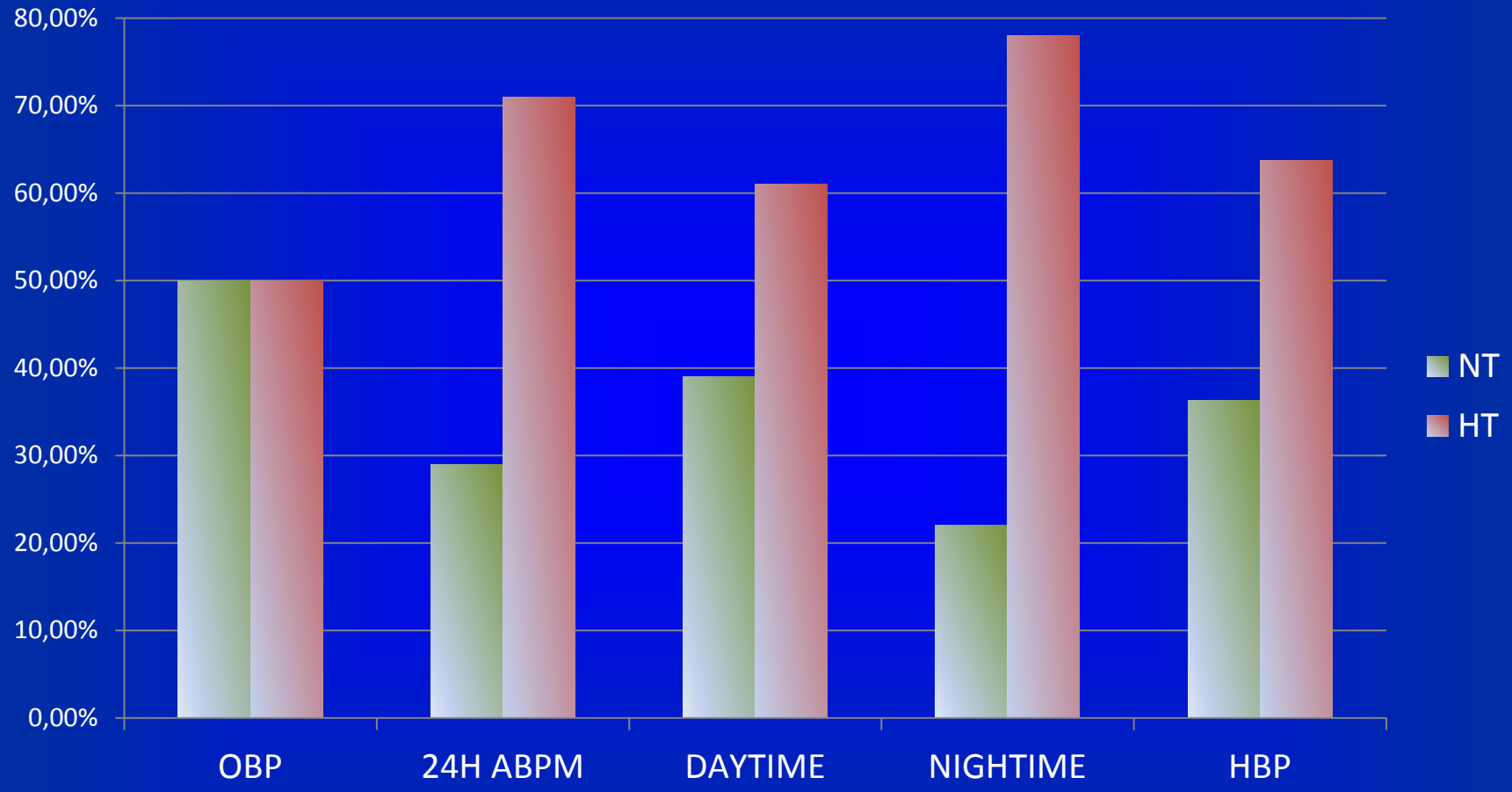
The Journal of Clinical Hypertension Vol 17 | No 1 | January 2015

BP phenotypes according to out-of-clinic measurements



Baseline visit (N=70), personal data

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



Baseline visit-N=70, personal data

Journal of the American Society of Hypertension 5(1) (2011) 39–47

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]

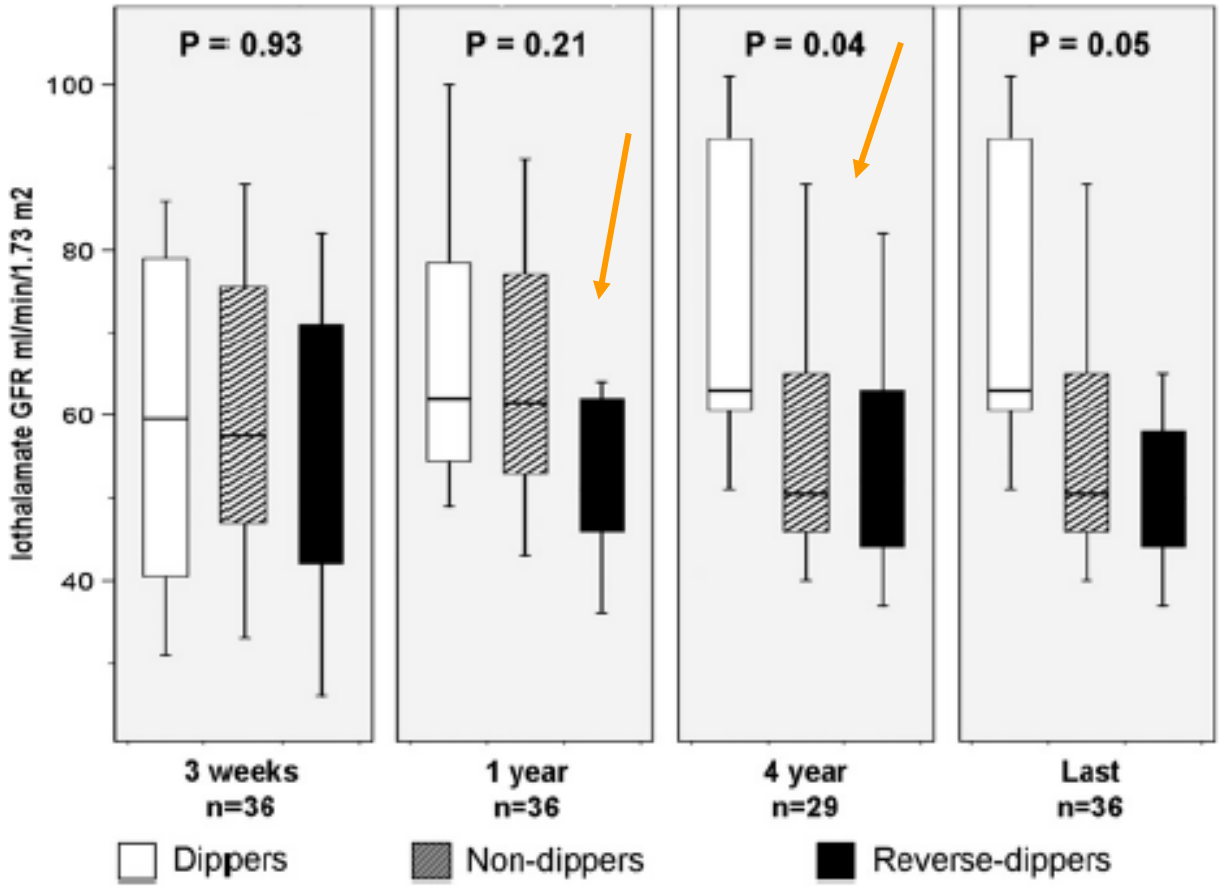


Figure 1. Box plots representing median (solid line) and inter quartile range of GFR at 3 weeks, at 1 and 4 years, and at last follow-up in 36 kidney transplant recipients with no rejection and with normal histology grouped according to dipping status. Non- and reverse dippers had lower kidney function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

Am J Kidney Dis. 57(2):331-341. © 2011

Hypertension After Kidney Transplant

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

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)

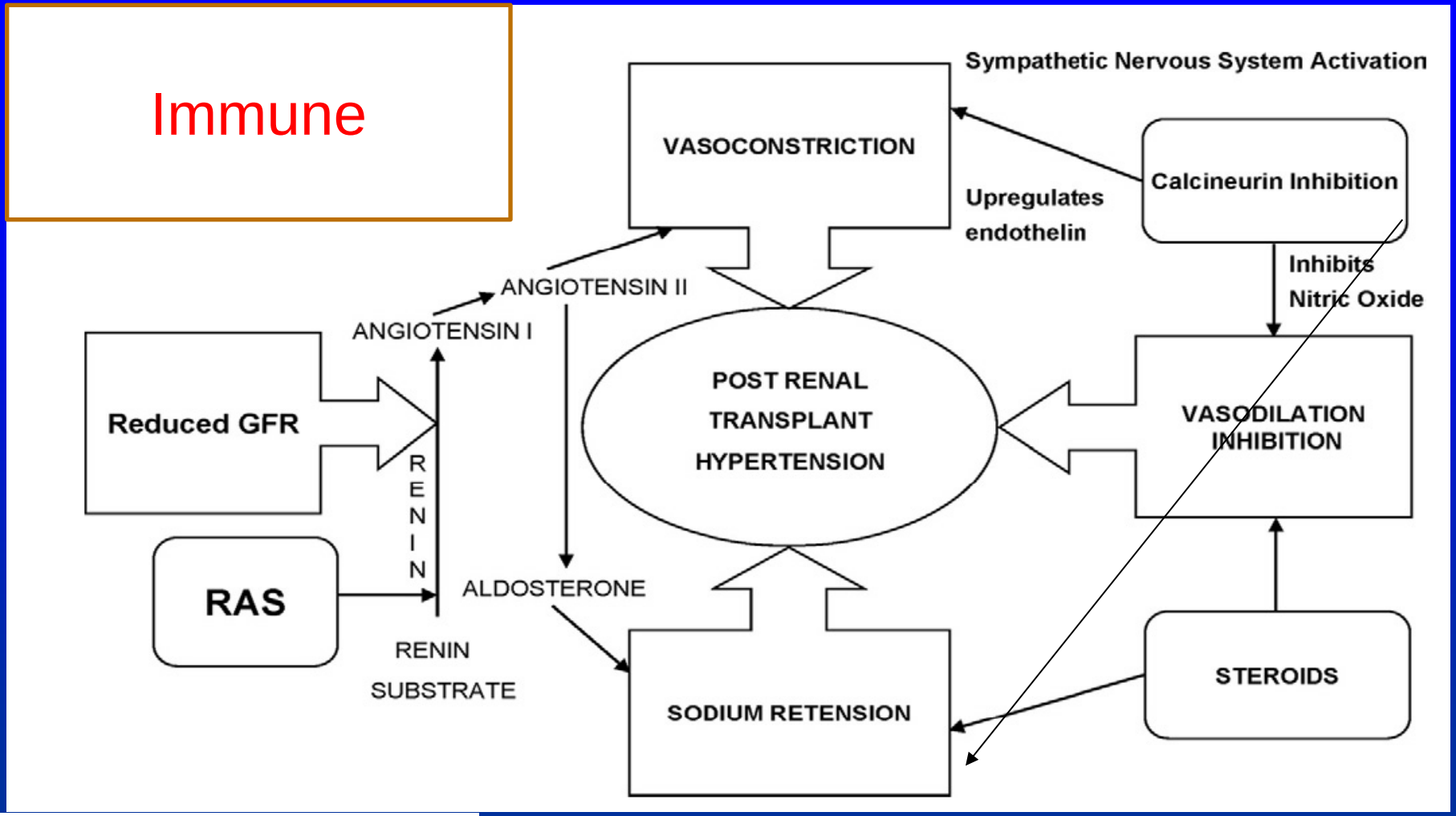
Transplant Dysfunction
- Acute rejection
- Antibody-mediated rejection
- Chronic allograft nephropathy
- Thrombotic microangiopathy
- Recurrent or de novo glomerular disease

Transplant Renal Artery Stenosis

Transplant obstruction
- Ureteric stenosis
- Lymphocele

Post-transplant HTA:potential mechanisms

Immune



Hypertension After Kidney Transplant

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Am J Kidney Dis. 57(2):331-341

Optimal BP target?

- HT in KT is prevalent, multifactorial and associated with a bad prognosis.
- However, no RCT have been realized to examine optimal levels of BP in KTR to prolong graft survival or limit the risk of CV events

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

KDIGO

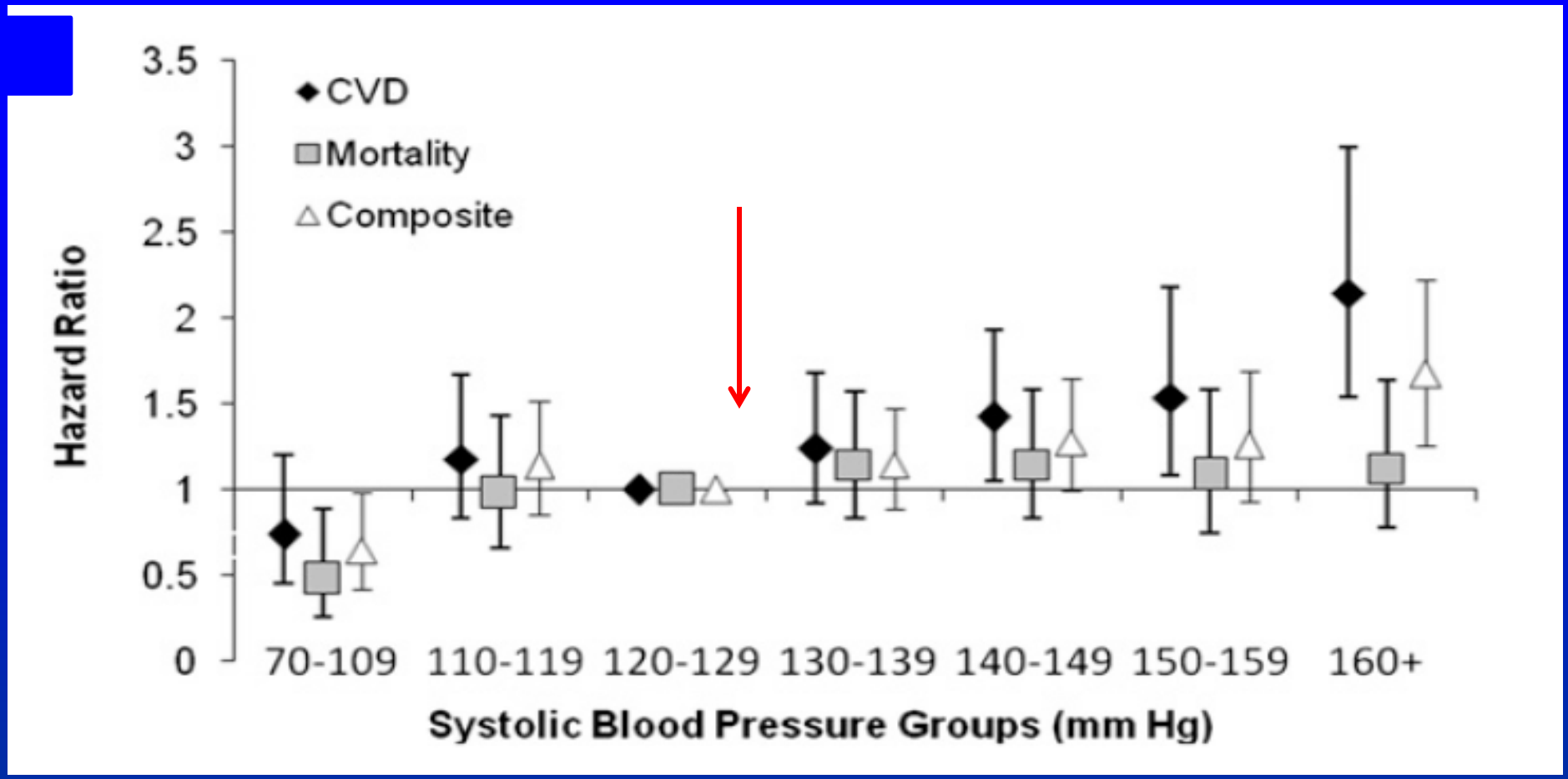
Kidney International Supplements (2012) **2,** 370–371; doi:10.1038/kisup.2012.55

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 2012: <130/80 mmHg

ESH 2013 or JNC8 2014: No recommendation for the BP target in KTR!

SBP: impact on CV events and death

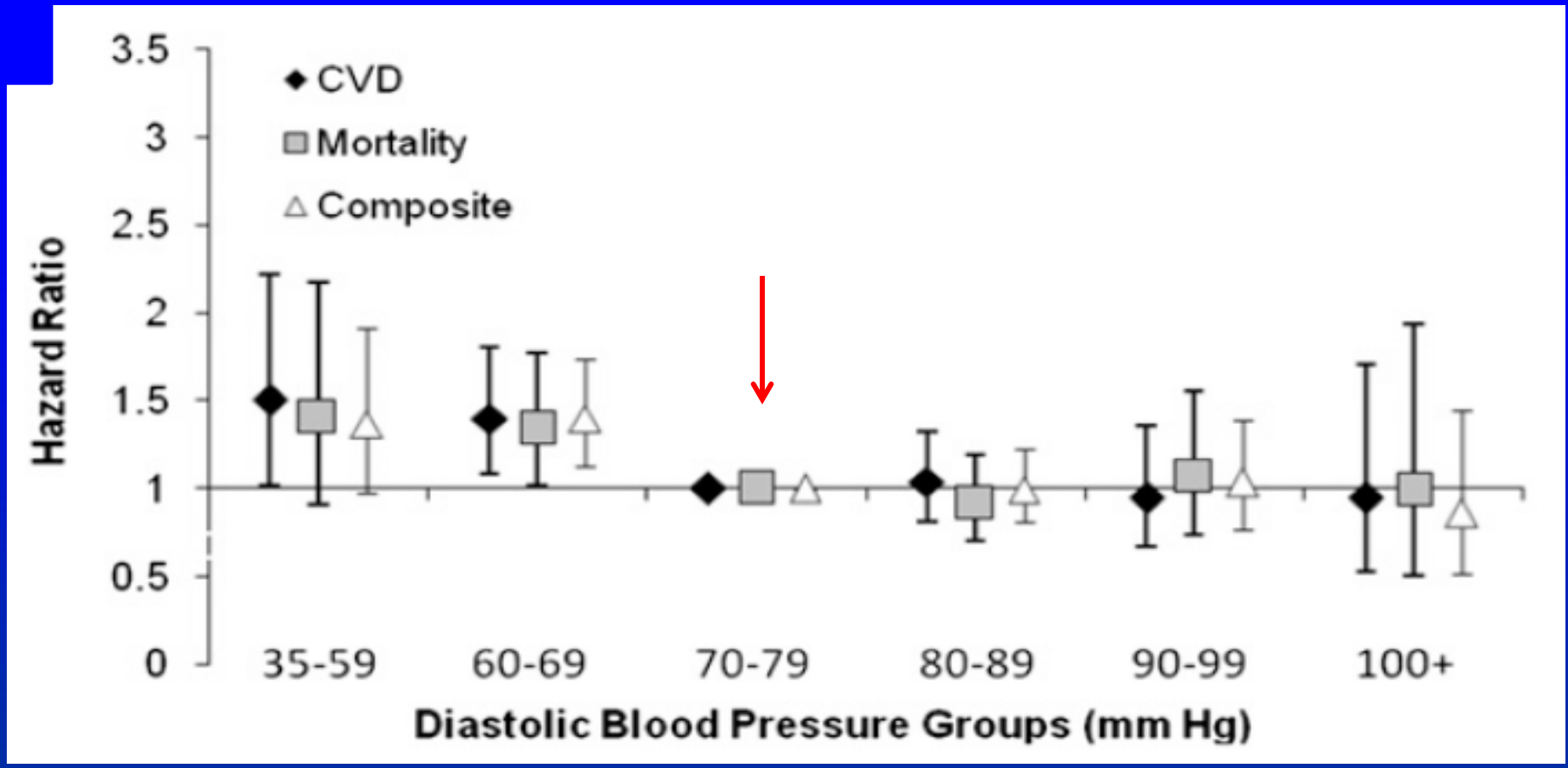


BP, Cardiovascular Disease, and Death in the Folic Acid for Vascular Outcome Reduction in Transplantation Trial

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†

J Am Soc Nephrol **25:** 1554–1562, 2014

DBP: impact on CV events and death



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Treatment approach to hypertension

- Therapeutic lifestyle changes[1]
- Antihypertensive agents[1]
- Alter immunosuppressive regimen[2]

[1]K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. Am J Kidney Dis 2004; 43:S1-290
[2]Fellström B. BioDrugs 2001;15:261-78

Therapeutic lifestyle changes (similar to ESH 2013)

- Salt restriction (<100 mmol/d)
- Moderation of alcohol intake
- Regular exercise (5-7 d/ w)
- Reduction of weight if BMI > 25 Kg/m^2

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

Saint-Remy A et al BMC Nephrology 2012; 13: 121

Influence of IS modification

- Steroids cessation:
- small decrease in BP prevalence (-10%), higher effect on hypercholesterolemia (-24%) and on DM risk(-36%) (Pasqual et al T 2006, Woodle et al Ann Surg 2008)
- small risk of Acute Rejection without significant effect on long term graft function.
- CNI:
- Lowering BP by either reducing CNI dose, converting Cyclosporine to Tacrolimus or by substituting it (after 3m).

Treatment approach to KT hypertension

- Drug treatment: each class is possible according to the patient, but most patients require more than one agent to achieve BP control targets

Potential advantage but also risk of antiHT drugs in KTR

- Diuretics attenuate saline retention but can create functional AKI, hypoK and Mg, sexual trouble
- BBlockers decrease morbidity and mortality after MI and in CHF (KTR have high CV risk) but can generate
- sexual dysfunction, dyslipidemia, DM risk
- Non DHP CCB: increase in CNI blood concentration, So can spare drug use but if not adapted caused nephrotoxicity
- DHP CCB attenuate the nephrotoxicity of CNI but can create gum hypertrophy

Inhibitors of RAS (RASI)

ACEI or AIIRA could be useful in proteinuric patients, in post-transplant erythrosis or when LVH

But there is a controversial interest for their use for graft survival !

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. Winkelmayer,‖ 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.

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)?

Some trials comparing RASI and other Treatment in KT with HT

Some more recent randomized trials:

- 1. SECRET study (3y)(Philipp et al NDT 2010): no significant benefit on kidney function by candesartan but it is safe with higher effect on lowering of BP and proteinuria
- 2. Ibrahim et al (JASN 2013) (5y): no statistical significant benefit with losartan on IF/TA, but well tolerated and can reduce the doubling serum creatinine rate.

3. Ramipril versus placebo in kidney transplant patients with proteinuria: a multicenter, double-blind, randomized controlled trial (G Knoll et al Lancet diabetes-endocrine 2015)

- Study in Canada and New Zealand, adult renal TR at least 3-months post-transplant with an eGFR of 20 mL/min/1·73m^2 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.

	Pl	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, Prasad, Edward Cole,

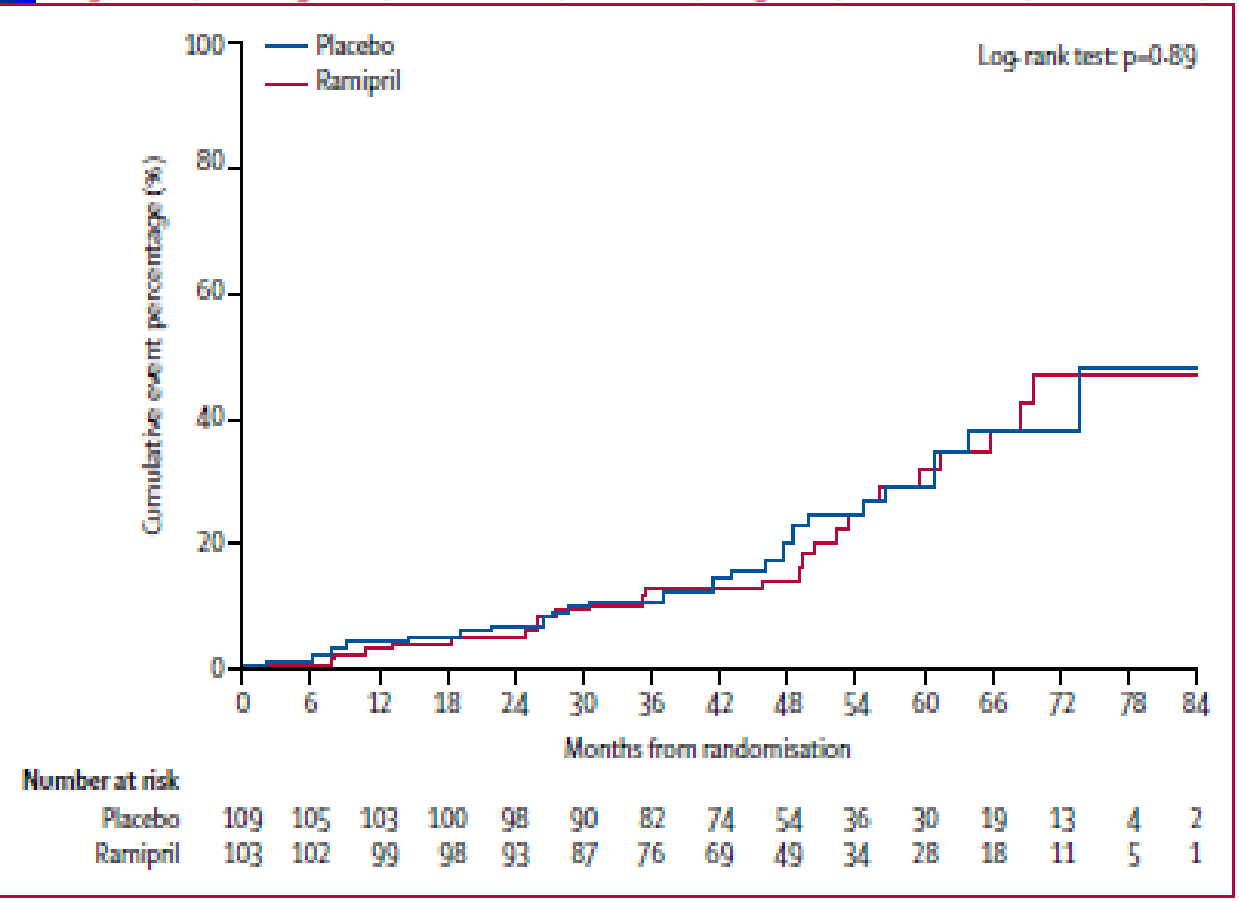


Figure 2: Time to the primary outcome of doubling serum creatinine, end-stage renal disease or death during the extension phase of the study

	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)

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.

Inhibitors of RAS (RASI)

- However, RASI should be avoided in the early post-transplantation period due to hemodynamic effect on GFR and K homeostasis and in any situation characterized by hemodynamic instability.

How to manage HT according to the KTr period?

- During the 1st month after KTr: 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 KTr:

  Target SBP <140 mmHg,

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

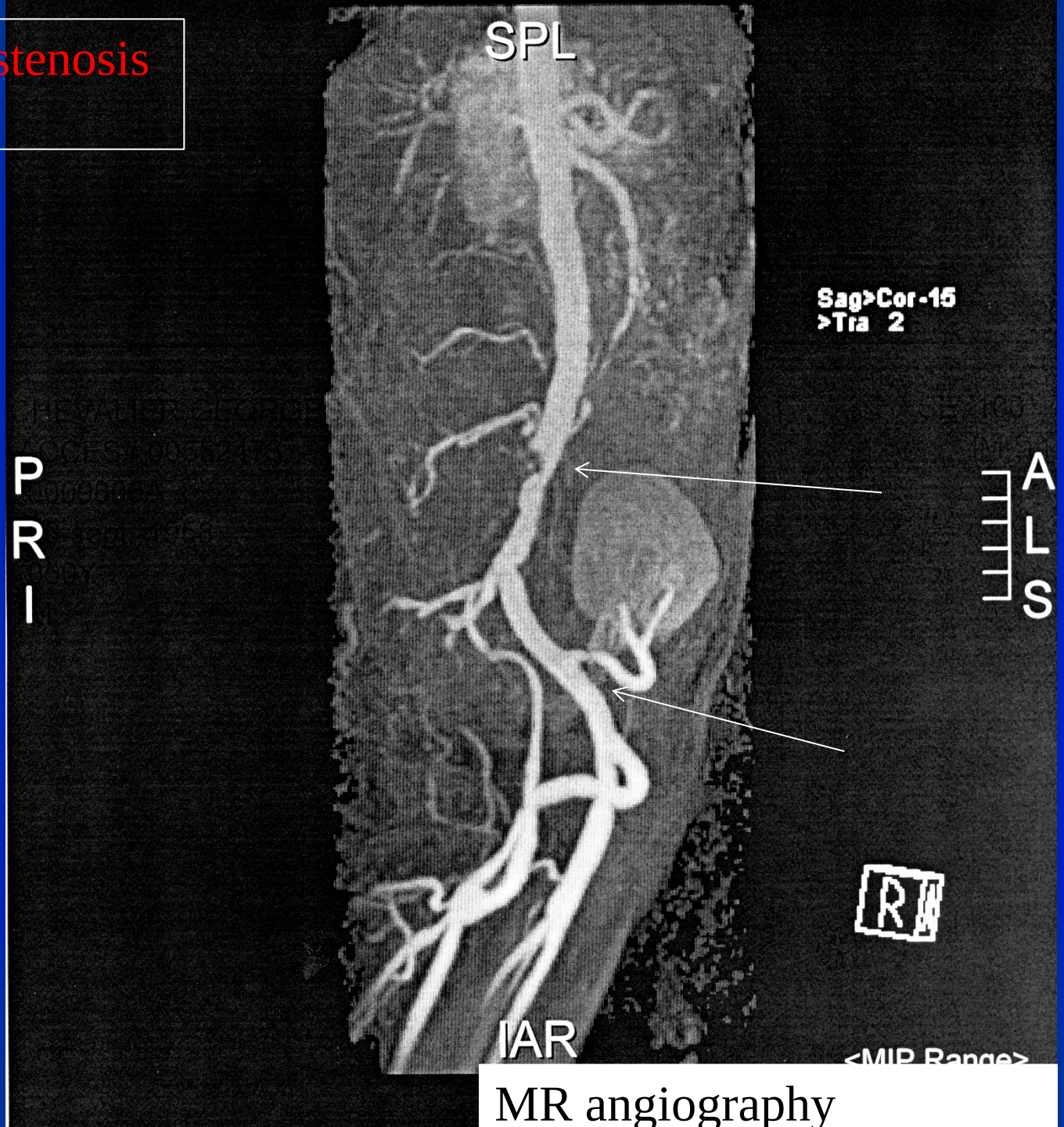
- After the 4th month of KTr: look for all CV risk factors, target SBP <130 mmHg if possible

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 disorders,..)
- introduce spironolactone if kalemia is correct
- discuss for bilateral native nephrectomy if remaining resistant HT.

Renal artery stenosis



MR angiography

Transplant RAS

- 1-25% of KTR
- 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%),
  - lower clinical success (67-90%)
  - some complications of the procedure (3-25%)

Hypertension in KTr: Conclusions

- Hypertension is frequent , often multifactorial and a risk factor for development of CVD and poor graft function.
- A global strategy is needed to manage high BP and the CV risk, improving the accuracy of BP measurements.
- Similar management is proposed as in the general population, but with a suggested BP target <130/80 mmHg.
- Further improvement in BP control could be achieved by tapering or discontinuation of steroids and/or CNI (especially cyclosporine).
- The first line antihypertensive therapy seems CCBl and/or BBlocker.
- Don’t forget poor compliance and secondary HTA if resistance !

Thank you for your attention

Questions?