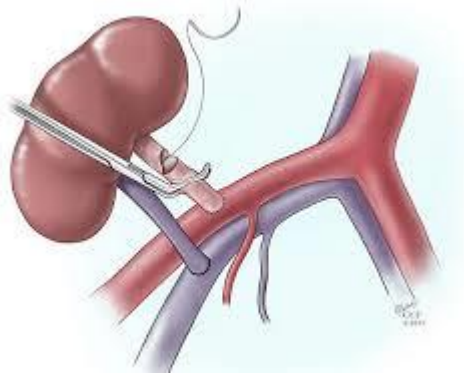
Hypertension as a key risk factor for cardiovascular disease in kidney transplant recipients

Melexopoulou Christina
Department of Nephrology & Renal Transplantation, Laiko General Hospital
National and Kapodistrian University of Athens, Greece

18th Bantao Congress, 21/10/2023

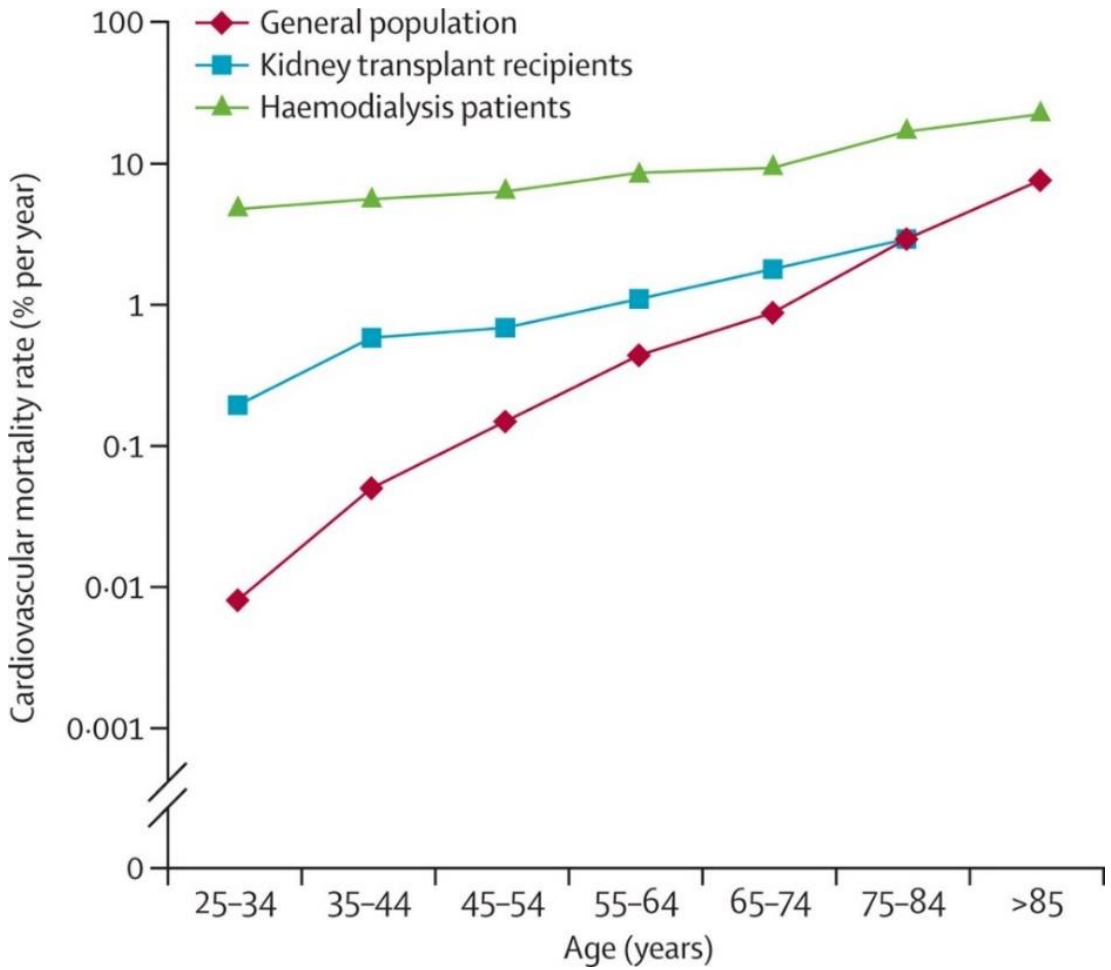
Kidney Transplantation

- Life expectancy
- Cardiovascular benefits
- Quality of life
- Socioeconomic benefits



Rabbat CG et al, J Am Soc Nephrol 2000;11:917
Wolfe RA et al, N Engl J Med 1999; 341:1725
Tonelli M et al, Am J Transplant 2011;11(10):2093-109
Klarenbach SW et al, Nature reviews 2014;10(11):644-52

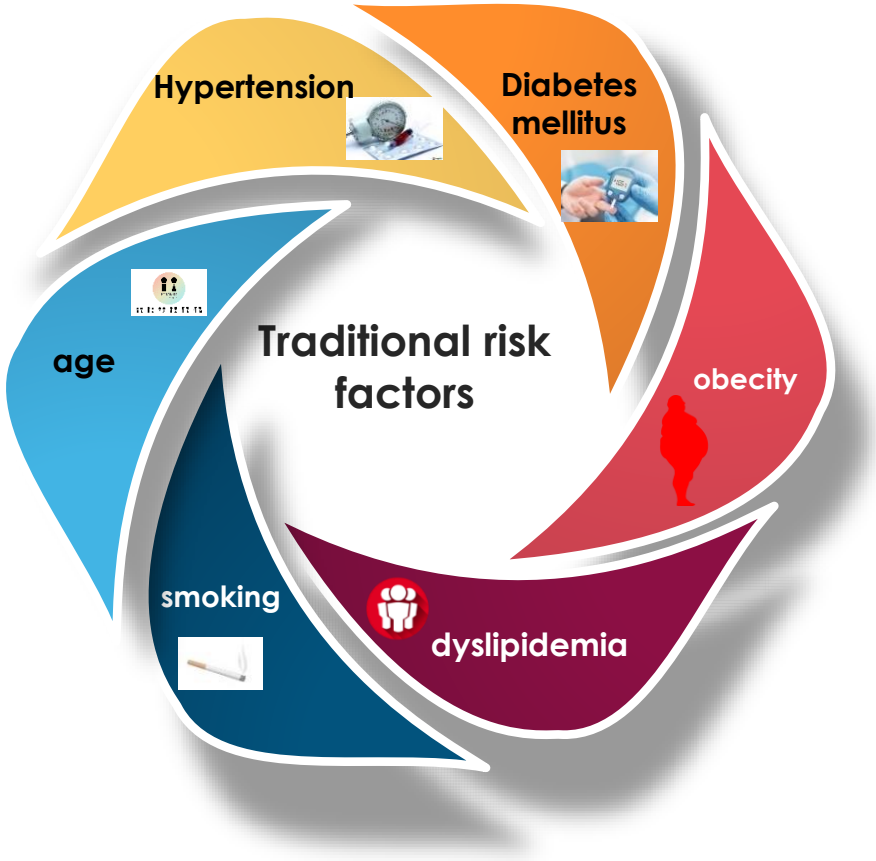
Cardiovascular (CV) mortality in Kidney Transplantation



- Higher risk of CV mortality compared to the general population
- 3-5 fold ↑CV mortality especially in the younger age groups

Foley RN, et al. Am J Kidney Dis 1998; 32 (5 suppl 3): S112–19

Pretransplant Cardiovascular Risk Factors



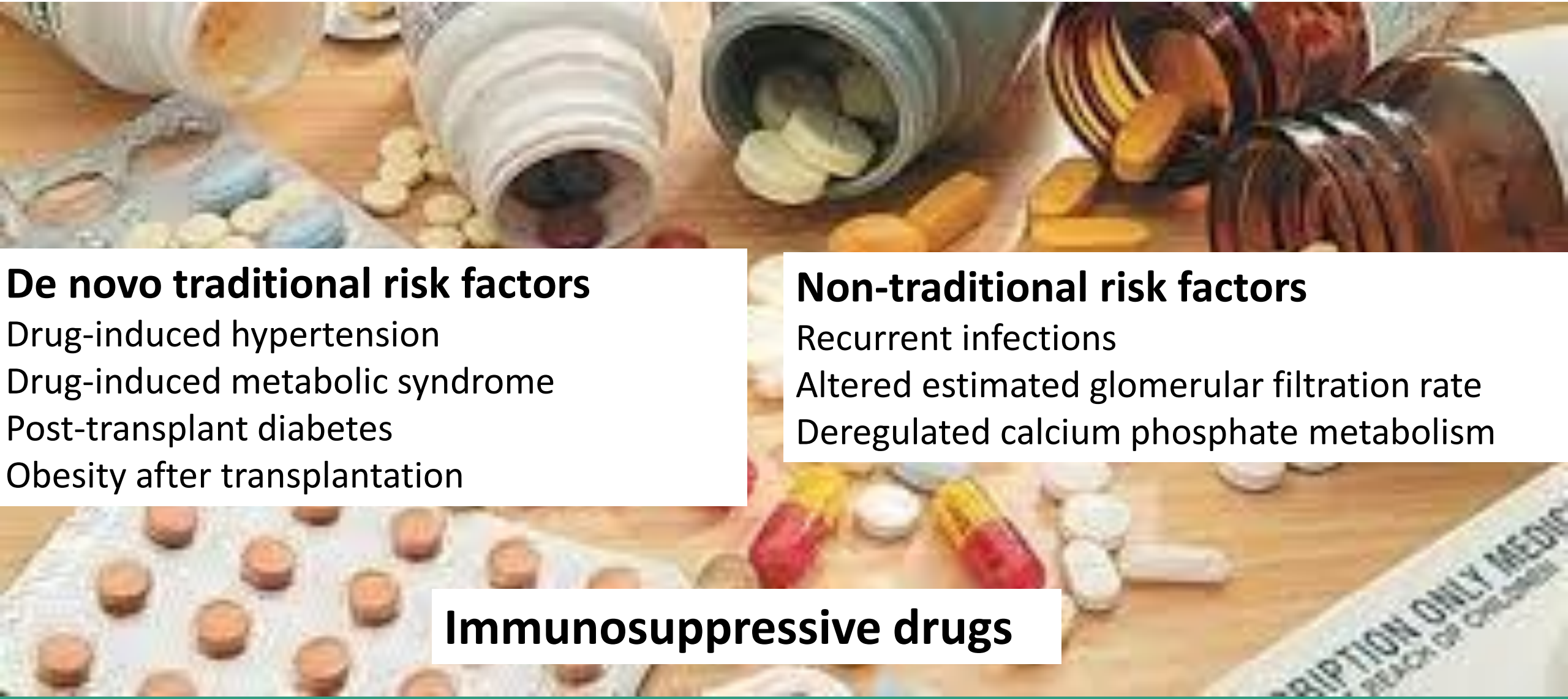
Pre-existing heart failure
Left ventricular hypertrophy
Coronary artery disease

Non-traditional risk factors

- Anemia
- Proteinuria
- Systemic inflammation
- Hyperhomocysteinemia
- Arteriovenous fistula

Rao N et al. Seminars in Nephrology 2018, 38:291-297

Post-transplant Cardiovascular Risk Factors



De novo traditional risk factors

Drug-induced hypertension
Drug-induced metabolic syndrome
Post-transplant diabetes
Obesity after transplantation

Non-traditional risk factors

Recurrent infections
Altered estimated glomerular filtration rate
Deregulated calcium phosphate metabolism

Immunosuppressive drugs

Rangaswami et al. NDT 2019, 34:760-773

Reggiani, Moroni and Ponticelli, J. Pers. Med. 2022, 12, 1200

Hypertension after Kidney Transplantation

Definition of Post-Transplant Hypertension

- Persistently high BP or normotension with the use of antihypertensive medications

High Blood Pressure
>130/80 mmHg

Blood pressure target

KDIGO/KDOQI: ≤130/80

ACC/AHA: ≤130/80

ESC/ESH: No specific recommendation

ERA-EDTA: <125/75 if proteinuria present

NHF Australia: No specific recommendation

HTN Canada: ≤140/90

KDIGO Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease. Kidney International (2021) 99,S1-S87

Epidemiology of Hypertension Post-Transplant

- Prevalence: 70-90% of renal Tx recipients

Demographic risk factors

- pretransplant hypertension
- elevated body mass index
- male sex
- African-American race
- older donor age

Transplant-specific risk factors

- delayed graft function (DGF)
- calcineurin inhibitor (CNI)
- glucocorticoid use
- recurrent disease
- acute rejection
- post-transplant proteinuria

Weir M. J Am Soc Nephrol. 2015 Jun; 26(6): 1248–1260

Blood Pressure Measurement

Improving the diagnosis → better therapeutic approach

Office BP measurement
Home BP readings
Ambulatory BP monitoring (***ABPM)***

Halimi J. J Hypertens. 2021 Aug 1;39(8):1513-1521

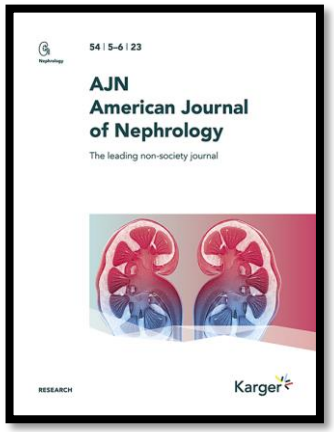
Blood Pressure Measurement

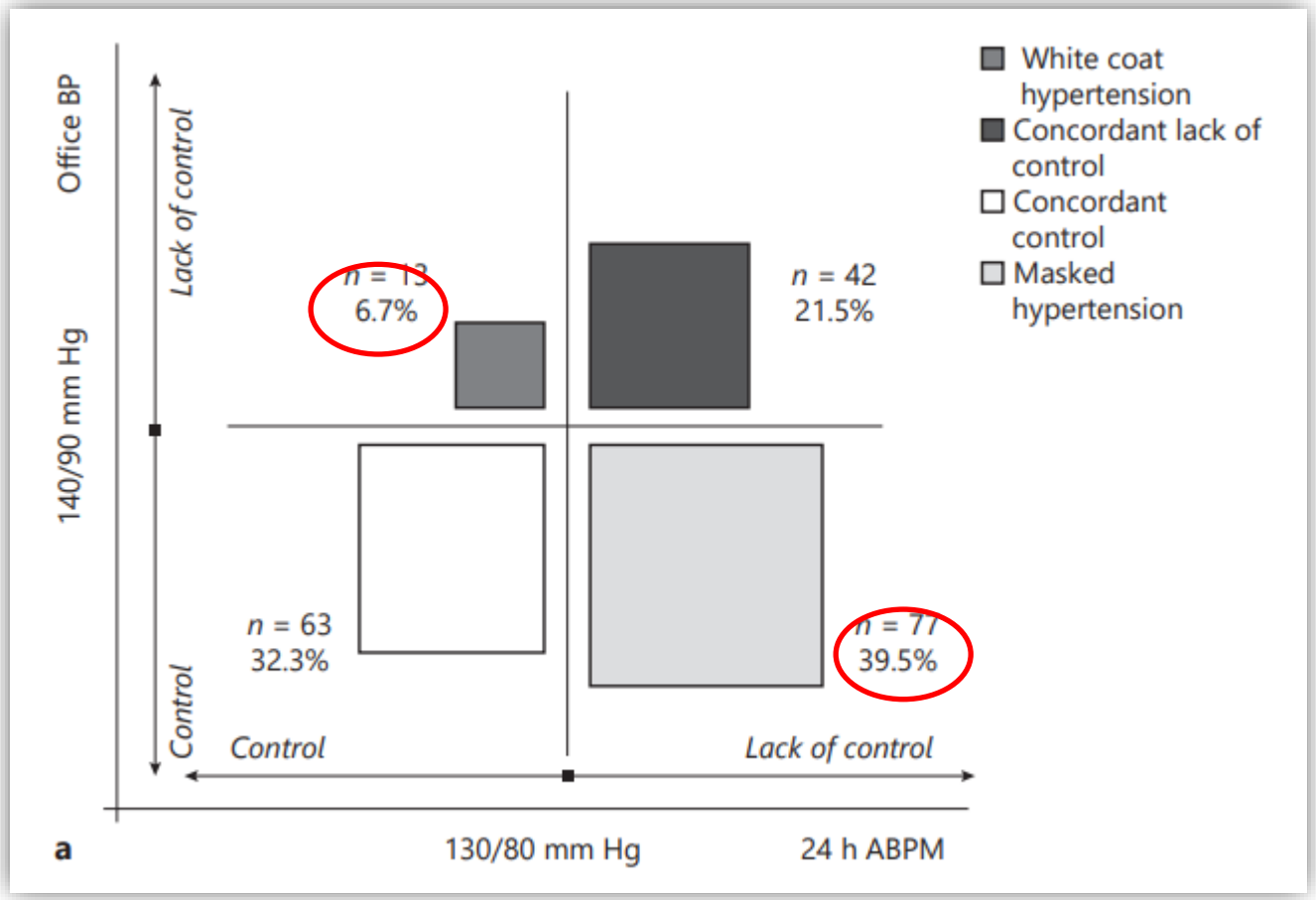
Recommendation 1.2: We suggest that out-of-office BP measurements with ambulatory BP monitoring (ABPM) or home BP monitoring (HBPM) be used to complement standardized office BP readings for the management of high BP (2B)

- **White-coat hypertension**
- **Masked hypertension**
- **Abnormal day-night BP patterns**
  (Non-dipping and Reverse dipping)

KDIGO Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease. Kidney International (2021) 99,S1-S87

Diagnostic Performance of Office versus Ambulatory Blood Pressure in Kidney Transplant Recipients





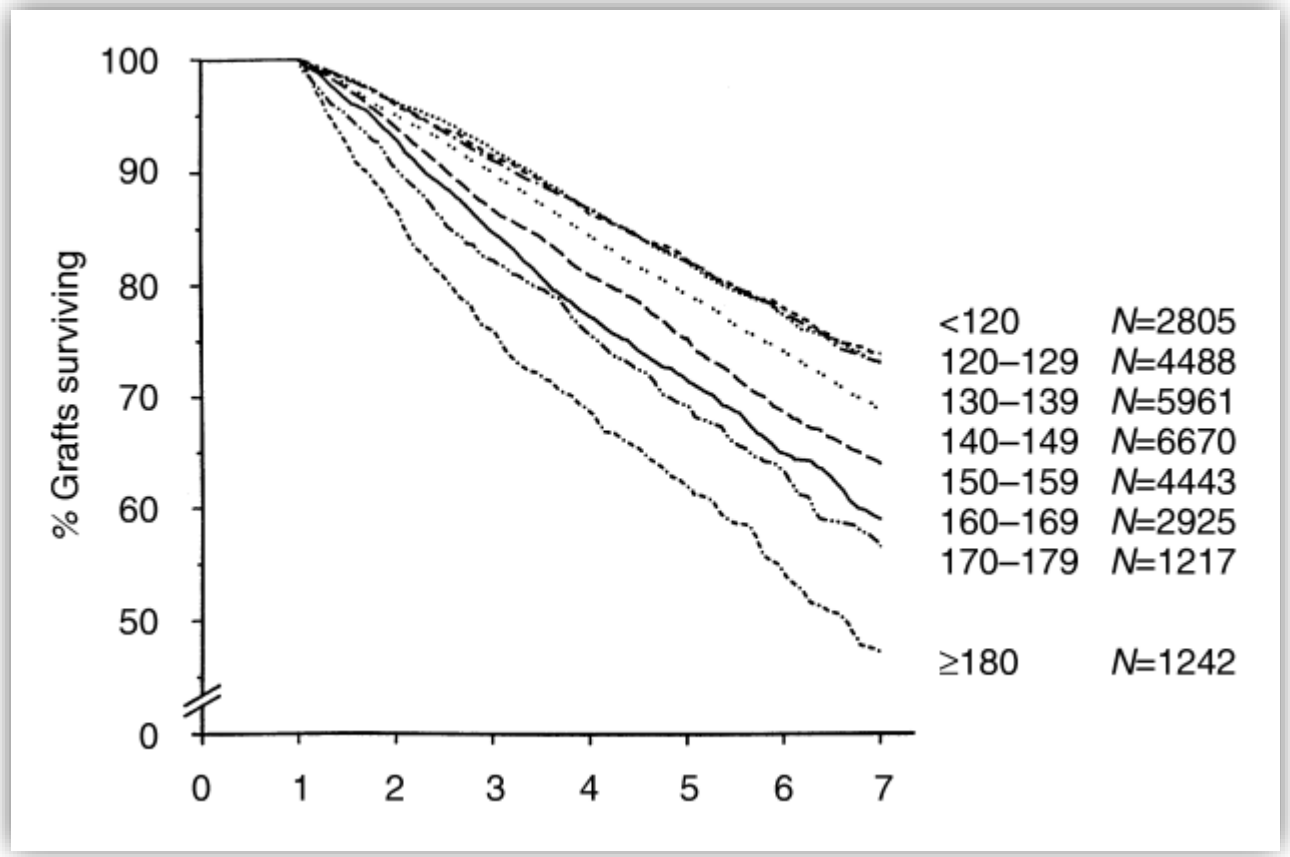
- Hypertension prevalence by office BP was 88.3% with ESC/ESH compared to 94.1 at relevant ABPM thresholds
- **White-coat** and **masked hypertension** were diagnosed in 6.7 and 39.5% of patients

Korogiannou M,……. Marinaki S. Am J Nephrol 2021;52:548–558

Impact of Post-Transplant Hypertension on Renal and Cardiovascular Risk

Is post-transplant hypertension “a silent killer” ?

Post-Transplant BP and kidney graft outcome



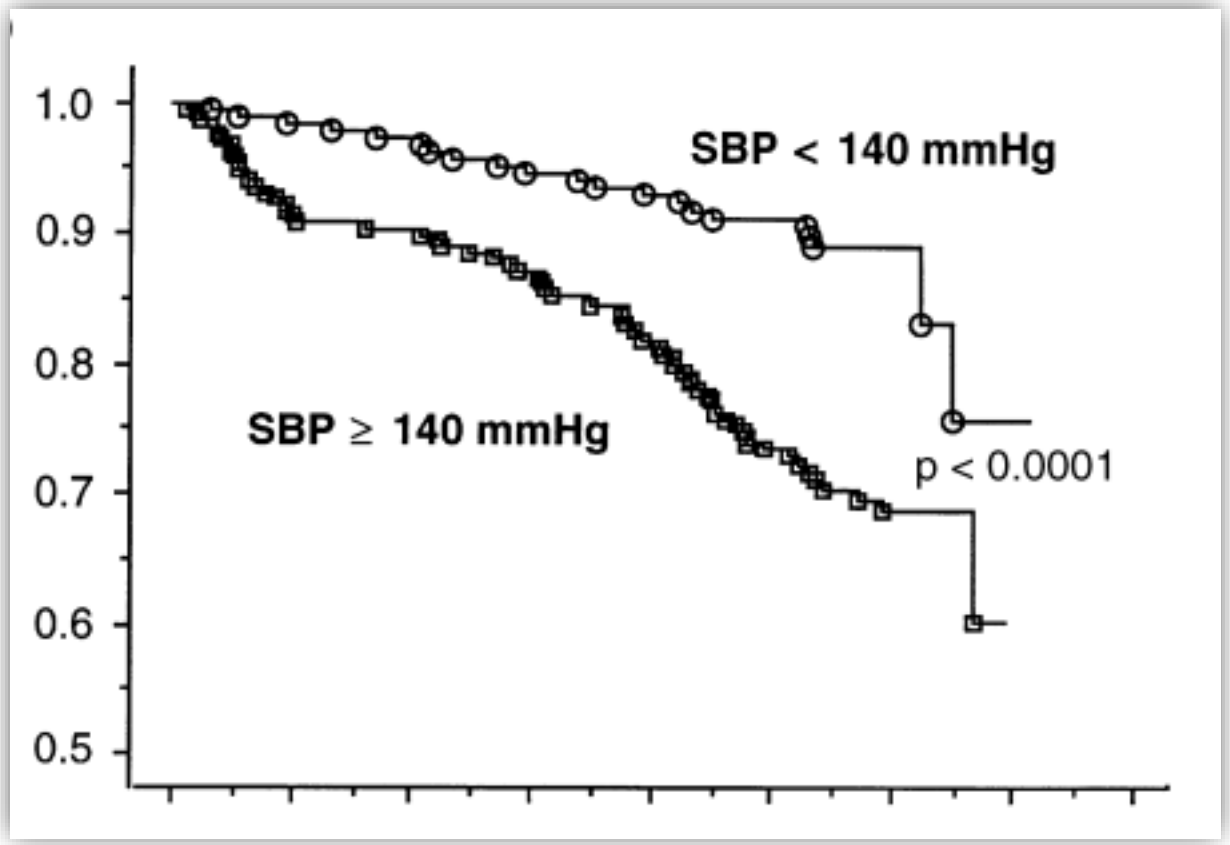
- 29,751 patients from 262 transplant centers (the Collaborative Transplant Study)
- Influence of BP post-Tx on long-term kidney graft outcome

Post-Tx BP is a highly significant predictor of long-term kidney graft outcome

Opelz G et al. Kidney International, Vol. 53 (1998), pp. 217–222

Post-Transplant BP and Cardiovascular Disease

survival from ischemic heart disease

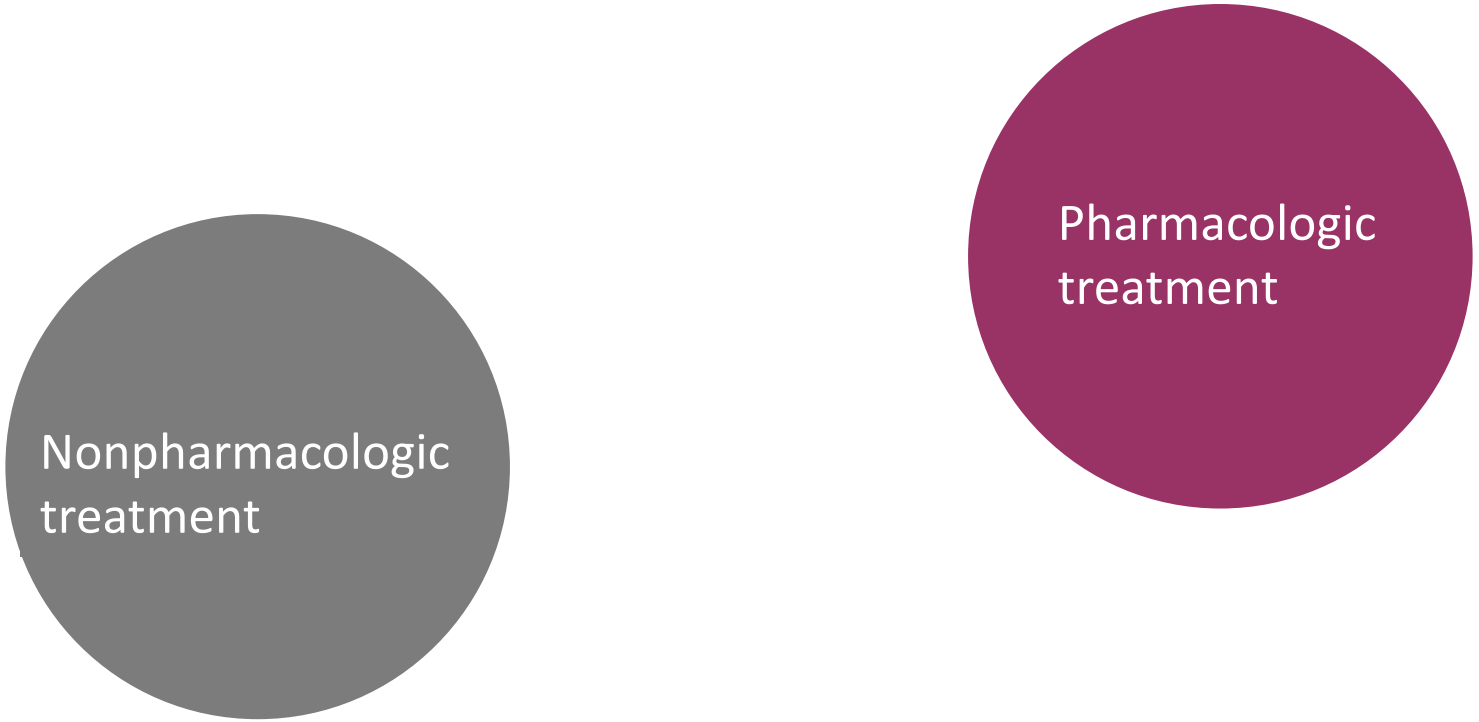


- cross-sectional Norway study
- 405 renal transplant patients
- 5 yr follow-up

Post-transplant hypertension is associated with higher risk for cardiovascular events
(LVH, myocardial infarction, congestive heart failure)

Aakhus S. Clin Transplant. 2004 Oct;18(5):596-604

Treatment of Post-Transplant Hypertension



Lifestyle Changes

Lose weight

Move more

Limit alcohol

Focus on nutrition

Don’t smoke.

Cut salt

De-stress

Pharmacological Therapy

All categories of antihypertensives may be used

- Average number of antihypertensives after Tx: 2.25±1.03 (vs 3.5 in CKD)

- There are no randomized controlled trials that determine optimal antihypertensive therapy in kidney Tx
- The choice of treatment should be individualized by evaluating the patient's comorbidities, drug to drug interactions, and efficacy/tolerability index of the drug.

Ari E et al. Current Hypertension Reports (2021) 23: 21

Calcium-Chanel-blockers, CCB's

- Most widely accepted and prescribed as 1st line therapy, particular in the first 6 months post-transplantation
- Neutralize the vasoconstrictive effects of CNI's: ↓ vascular resistance, ↑GFR

Metanalysis, 29RCT's, n=2262 pts
CCB's vs placebo

↓ allograft loss, ↑GFR

DH-CCB's: "Initial drug of choice in KTR?"
Non-DH-CCB's (verapamil, diltiazem): **increase** blood levels of CNI's and mTORi's

Cross NB et al.Cochrane Database Syst Rev.2009;3:CD003598

Renin-Angiotensin-Aldosterone-System Blockers (RAAS)

- Should be considered beyond the first few months of transplantation
- Benefit to diabetic and/or proteinuric patients and also for post-transplant erythrocytosis
- Help maintain graft functions by reducing intra-glomerular pressure and proteinuria in the long term.

Contrary to expectations studies of RAAS blockers → **NO benefit in allograft or patient survival**

Philipp T et al. results from SECRET. NDT. 2010;25:967–76
Ibrahim HN et alJ Am Soc Nephrol. 2013;24:320–27

Paoletti E et al. Transplantation. 2013;95:889–95
Knoll GA et al.. Lancet Diabetes Endocrinol. 2016;4:318–26

β - Blockers

- Commonly used drugs after KTx with cardioprotective effects
- Consider selection in recipients with coronary artery disease or arrythmia
- Counteract the reflex tachycardia induced by other drugs (CCB's, vasodilators)
- The possible protective mechanism of beta-blocker is via mitigation of the sympathetic nervous system, which is stimulated in failed native kidneys
- Beta-blockers decrease proinflammatory cytokines, which are known to increase the risk for atherosclerosis

Wadei HM, Textor SC. In: Weir MR, Lerma EV, eds. Kidney Transplantation: Practical Guide to Management. New York, NY: Springer Science+Business Media; 2014:205–24.

Sodium-glucose cotransporter 2 inhibitors (SGLT2) and blood pressure

Based on 24-h ambulatory blood pressure monitoring studies, **SGLT2i reduced systolic and diastolic blood pressure by 4–6 and 1.5–3 mmHg**, respectively. This effect is most probably due to natriuresis

Reference		HbA1c (%)		eGFR (ml/min)		Blood pressure (mmHg)	
		Baseline	Follow up	Baseline	Follow up	Baseline	Follow up
Kwon and Kong[15]		7.9 ± 1.3	7.4 ± 1.1 at 3 M	71.1 ± 20.1	71.5 ± 25.8 at 12 M	NR	NR
Rajasekeran et al.[9]	KTR	8.6 ± 1.4	−0.84 ± 1.2 ($p = .07$)	78 ± 18.2	−4.3 ± 12.2 ($p = .3$)	NR	SBP: −6.5 ± 10.8 ($p = .13$) DBP: −4.8 ± 12 ($p = .3$)
	SPKTR	7.4 ± 1.1		60 ± 14			
Beshyah et al.[16]		8.8	7.8	84	95	115/70	NR
Schwaiger et al.[8]		6.7 ± 0.7	7.1 ± 0.8 ($p = .03$)	54.0 ± 23.8	53.5 ± 13.3 at 12 M	SBP: 150 ± 26, DBP: 86 ± 14	SBP: 140 ± 20 ($p = .36$) **DBP: 76 ± 11 ($p = .02$)**
AlKindi et al.[10]		9.34 ± 1.36	7.41 ± 1.44 ($p < .05$)	75.75 ± 13.38	69.88 ± 14.70	SBP: 135 ± 9.5, DBP: 80.6 ± 10.1	SBP: 126 ± 11.5 DBP: 74.8 ± 7.3
Attallah and Yassine[11]		8.1 ± 0.2	7.1 ± 0.15	95.3 ± 15.97[+]	97.25 ± 14.84[+]	NR	SBP: −4.2 at 3 M
Halden et al.[12]	Empagliflozin	6.9 (6.5, 8.2)	6.7 (6.3, 7.5) ($p = .025$)	66 (57, 68)	61 (56, 67)	SBP: 136 (131, 147) DBP: 76 (71, 82)	SBP: 142 (126, 148) DBP: 76 (70, 82)
	Placebo	6.8 (6.1, 7.2)	6.9 (6.4, 7.4)	59 (52, 72)	59 (52, 67)	SBP: 135 (127, 146) DBP: 78 (74, 85)	SBP:137 (132, 143) DBP: 80 (74, 86)
Mahling et al.[13]		7.3 (6.4–7.8)	7.1 (6.6–7.5)	57 (47, 73)	NA	SBP: 135, DBP: 80	SBP: −3 (−36, 1), DBP: NR
Shah et al.[14]		8.5 ± 1.5	7.6 ± 1.0 ($p < .05$)	86 ± 20[a]	83 ± 18[a]	SBP: 142 ± 21 DBP: 81 ± 9	SBP: 134 ± 17 ($p < .05$) DBP: 79 ± 8
Kong et al.[17]		7.5 ± 1.1	7.1 ± 1.0 at 6 M ($p = .011$)	60.3 ± 17.0	59.3 ± 14.5	NR	NR
Song et al.[18]		NR	−0.53 ± 1.79 ($p = .1189$)	66.7 ± 20.6	−1 at 3 M +1 at 6 M	NR	NR

SGLT2 & Kidney Transplantation

Kanbay M et al. Nephrology. 2021;26:1007–1017

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes

Finerenone had **modest effects on blood pressure**: the changes in mean systolic blood pressure from baseline to month 1 and to month 12 were **–3.0 and –2.1 mm Hg**, respectively

NIH U.S. National Library of Medicine
ClinicalTrials.gov

The EFfect of FinErenone in Kidney TransplantiOn Recipients:
The EFFEKTOR Study (Estimated Study Completion Date :December 2025)

Bakris G et al. N Engl J Med 2020; 383:2219-2229

Take home message

Optimal BP control is more important than the use of a specific choice of antihypertensive drug class

Weir MR. J Am Soc Nephrol. 2015;26:1248–1260

Inadequacy of Cardiovascular Risk Factor Management in Chronic Kidney Transplantation -- Evidence from the FAVORIT Study

Clinical TRANSPLANTATION
The Journal of Clinical and Translational Research

- N=2,817 Tx patients with ↑ blood pressure (>130/80 mm Hg)
- 90% were using at least one BP lowering medication and 61% were taking two or more medications
- From patients in medication, 70% had BP of >130/80 mm Hg and 44% had BP>140/90 mm Hg

Uncontrolled hypertension in about 50% of Tx patients on medication

Carpenter M et al. Clin Transplant. 2012 ; 26(4): E438–E446

Conclusions

- The issue of hypertension is frequently underestimated by kidney transplant recipients and their physicians

- Hypertension is a crucial risk factor for progression of CKD and the development of cardiovascular disease, so strict blood pressure control is central in the management of Tx patients

Hypertension is an important modifiable risk factor

Thank you