Hypertension in Kidney Transplantation

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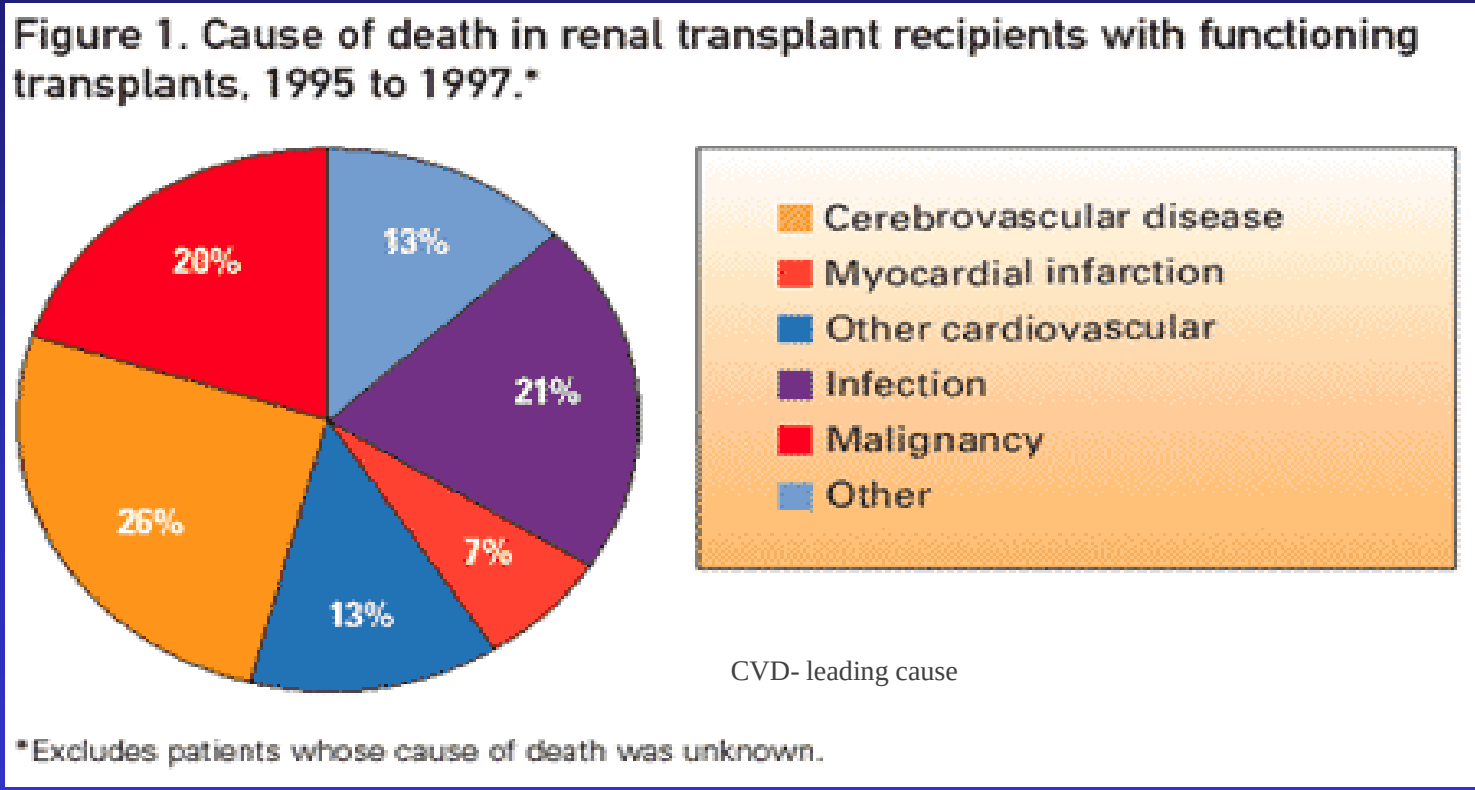
Introduction

Despite marked improvements in short-term graft survival with administration of newer immunosuppressive drugs, long-term morbidity and mortality is still high and offen associated with CVD, the primary cause of death with functioning graft in renal transplant recipients.

Howard RJ, et al. Transplantation 2002; 73:1923-1928
Ojo AO, et al. Kidney Int 2000; 57:307-313

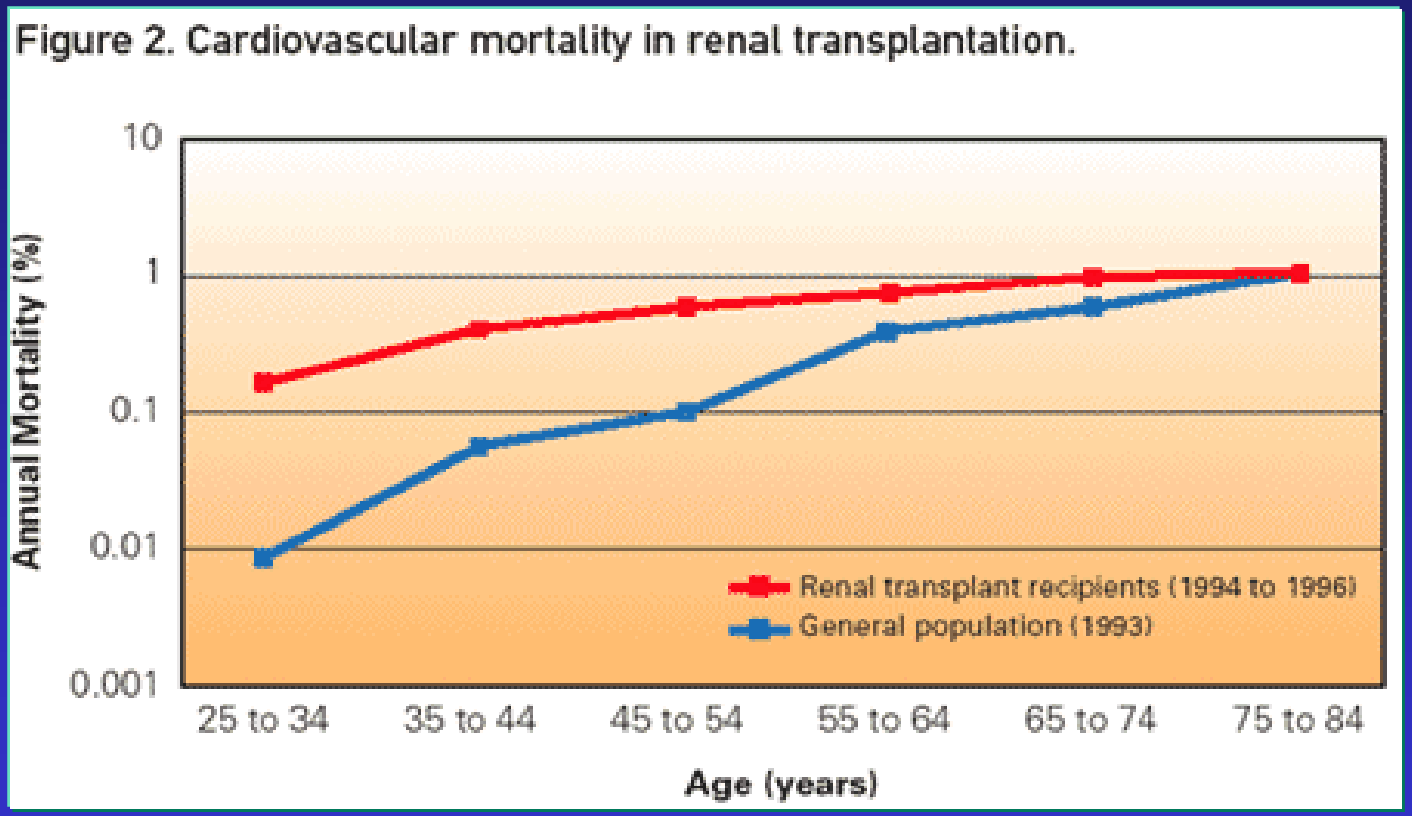
Cerebro and cardio vascular events - most common causes of death in renal transplant recipients with functioning grafts



CVD- leading cause

US Renal Data System. USRDS 2000 Annual Data Report

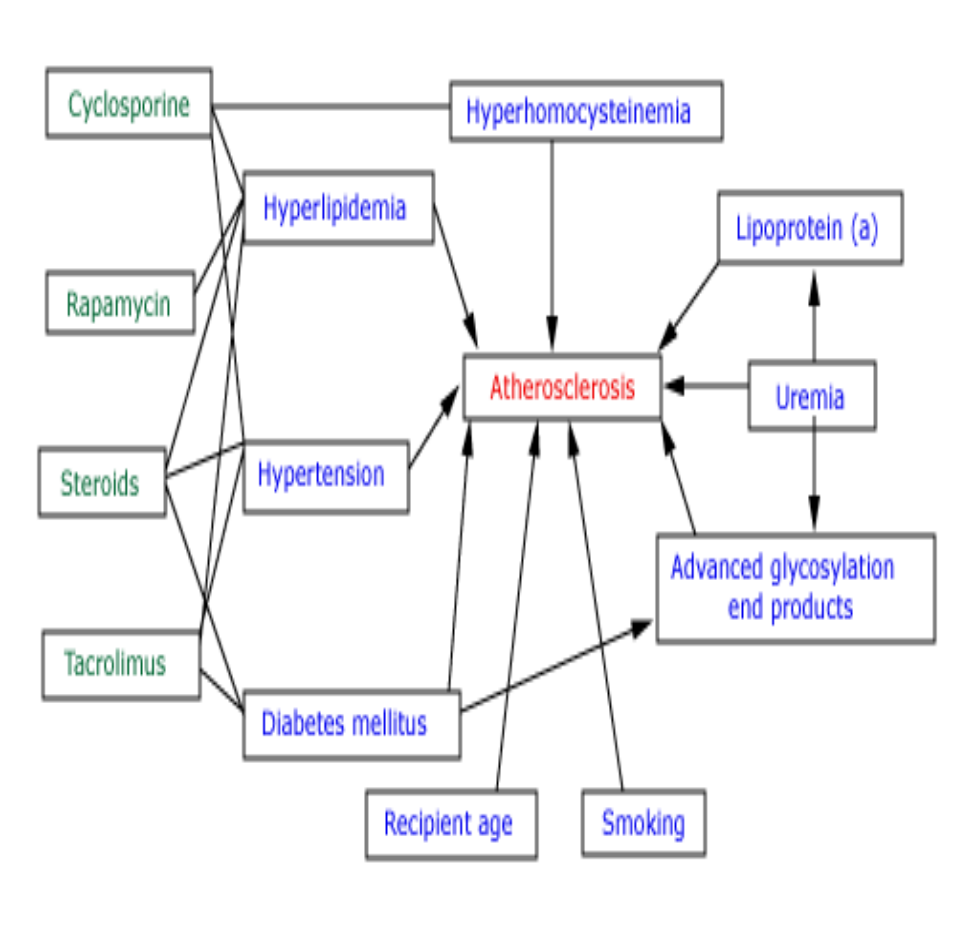
CV morbidity and mortality- much more common among renal transplant recipients compared to the general population



Compared with the general population, CV mortality in transplant pts, stratified by age, is increased almost 10-fold between the ages of 35 and 44 yrs and is at least doubled between the ages of 55 and 64 yrs

US Renal Data System. USRDS 2000 Annual Data Report.

Risk Factors for VD e.g. Atherosclerosis in RTR's



The greater incidence of VD is <u>not</u> entirely explained by traditional risk factors, (age: man>45yrs, women>55yrs, obesity, phisical inactivity , HTN, cigarette smoking, DM, hiperlipidemia, etc).

After Tx, immunosuppresive agents and/or graft dysfunction may increase the risk of VD by causing HTN, hiperlipidemia, or DM.

Kasiske BL et al. J Am Soc Nephrol 2000;11:1735-1743

HTN in kidney transplant recipients

- SBP ≥ 140 and/or DBP ≥ 90 mmHg, or need for treatment with anti-HTN drugs
- incidence: 70% to 90%
- co-morbidity with the greatest concern
- major contributing factor leading to CVD
- HTN also has implications on the health of the graft
- Management of HTN is becoming a crucial issue.

Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation,and Treatment of High Blood Pressure (JNC 7)
Opelz G, et al. Kidney Int 1998; 53: 217-222

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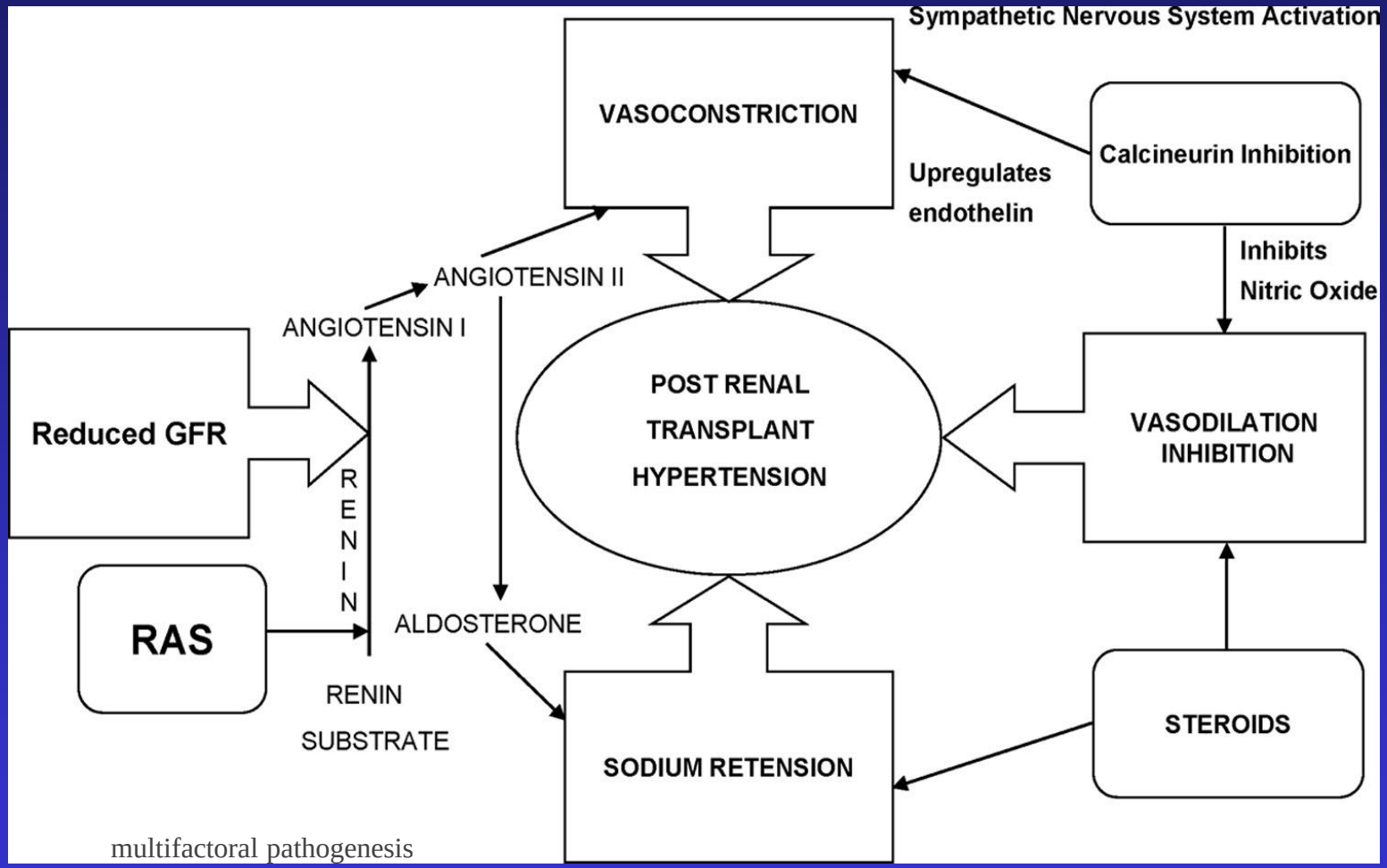
Mechanisms by which HTN is mediated after kidney Tx



multifactoral pathogenesis

American Journal of Kidney Diseases 2011 57, 331-341.

Impact of post-Tx HTN

Kasike et al. 15yrs follow-up study, progressive increase of vascular deseases:

- 23% developed new-onset IHD
- 15% had cerebrovacular event
- 15% developed peripheral vascul.desease
- each increasement in SBP of 10 mmHg above 140 mmHg, associated with RR of 12 % for graft failure, 18% for patient death.

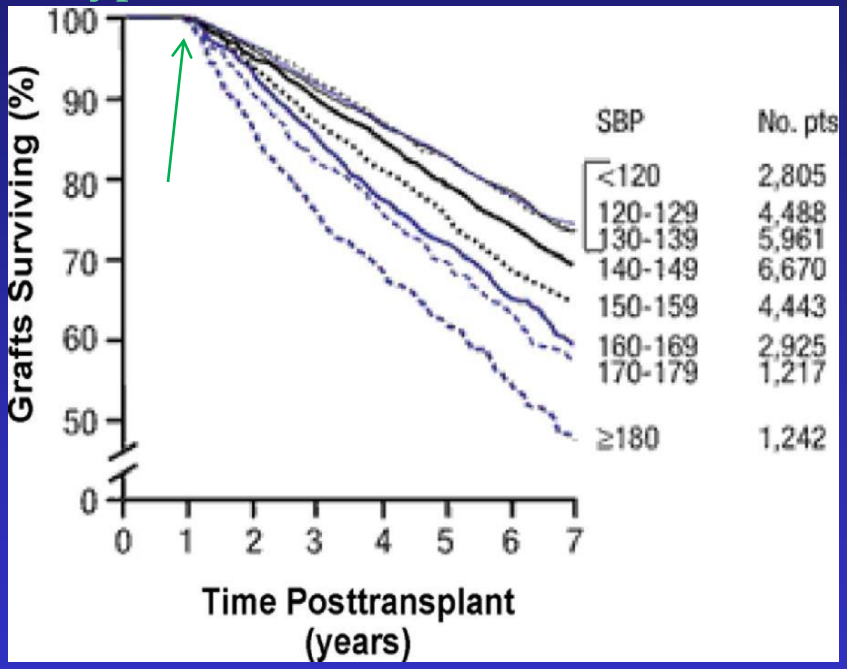
Kasiske BL. , et al. Am J Kidney Dis 2004; 43: 1071-1081 .

Opelz and Döhler lowering SBP, even after 3 yrs of post Tx HTN, improved survival of both pts and grafts.

Opelz G et al. Am J Transpl 2005; 5: 720-728

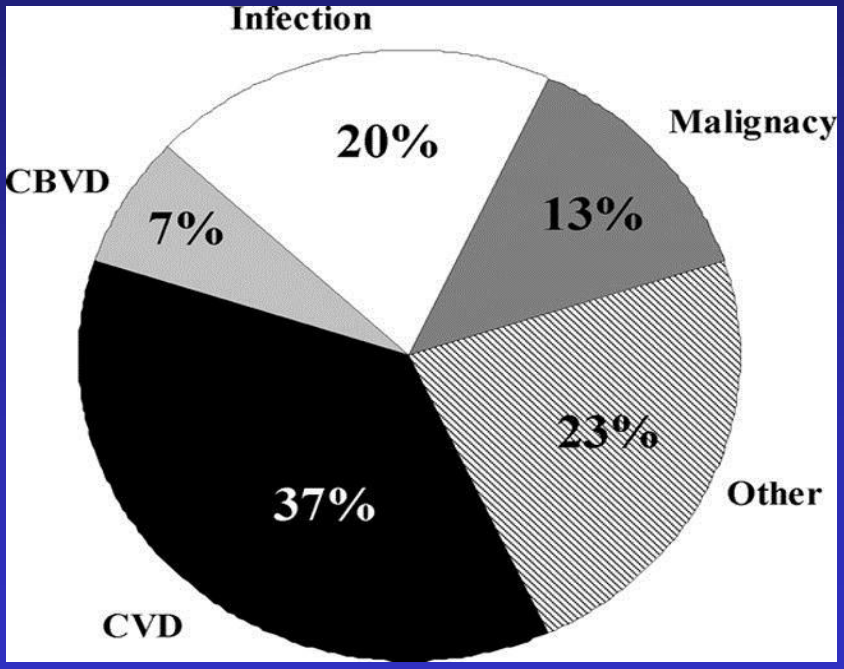
Association of post-Tx HTN with graft and patient survival

Hypertension and Graft survival



Association of hypertension at 1 year with transplant survival. Kidney transplant survival is inversely proportional to blood pressure

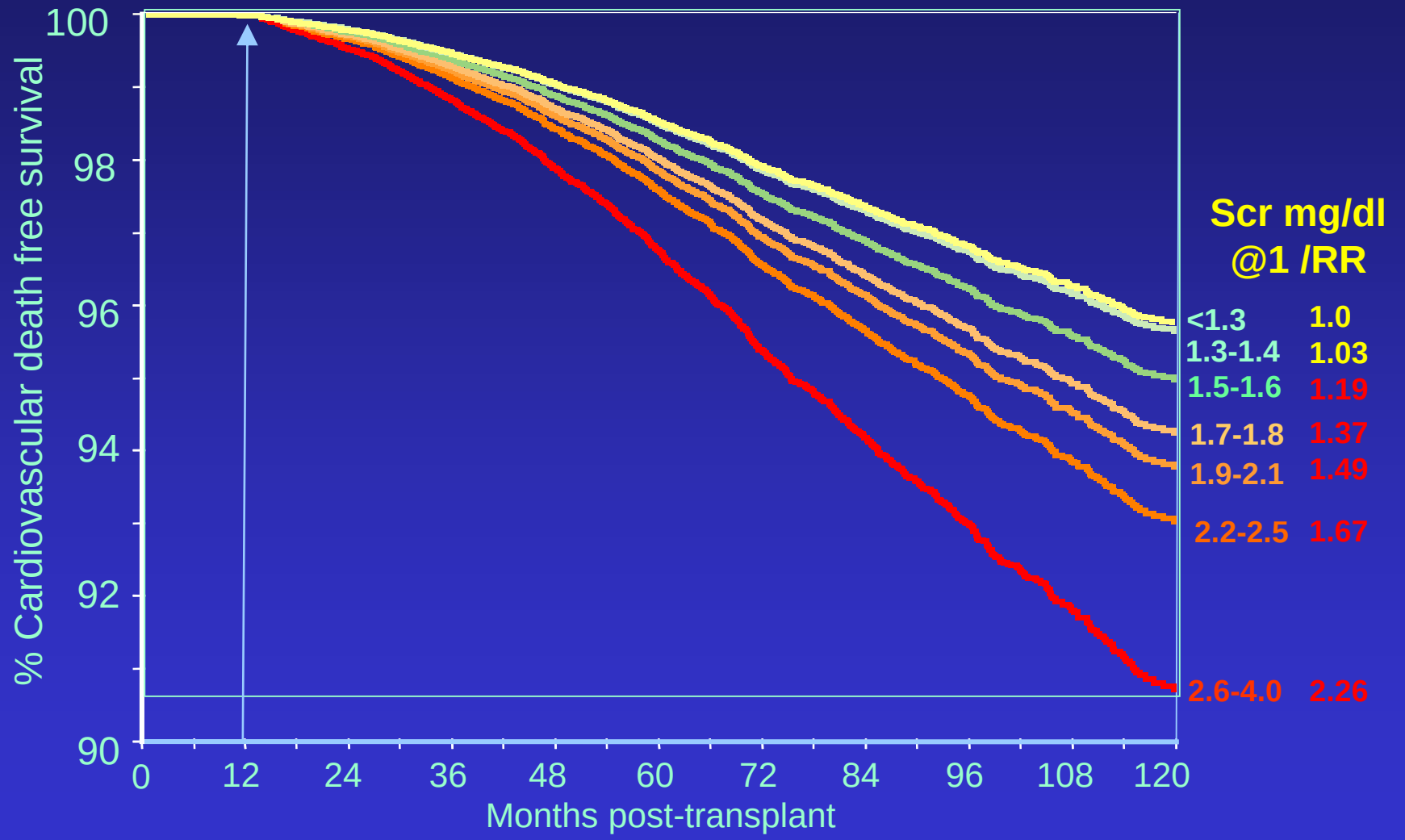
Mortality after kidney transplant



Atherosclerotic disease is the most common cause of death after transplant (44%)

Mahendra M, John PV. Hypertension After Kidney Transplant. **American Journal of Kidney Diseases. 2011 Feb; 57(2):331-341**

Graft function (sCr) is indipendent risk factor for CV death at one year after Tx



Meier-Kriesche, Kaplan *et al.* Transplantation 2003.

Risk factors of post-transplant HTN

- General-population risk factors
  (obesity, smoking, alcohol, excessive salt intake)
- Pre-existing essential hypertension
- Renal dysfunction : DGF, AR, CAN, GN, ON
  lymphocele, ureteral stenosis…
- Renal-transplant artery stenosis
- Effects of native kidneys
- Hypertensive donor
- Immunosuppressive drugs

Mailloux LU et al. Am J Kidney Dis. 1998;32(suppl 3):S120–S141.
Kew CE II et al. J Renal Nutrition. 2000;10:3–6.

Pre-existing essential hypertension

Two studies: pre -Tx HTN indipendent risk factor for post -Tx HTN at 3 mo and 1 yr after Tx.

Perez Fontan M, et al Am J Kidney Dis 1999;33(1):21-8.

Budde K, Waiser J, Fritsche L, et al. Transplant Proc 1997;29:209-110.

Renal dysfunction

important cause of post Tx HTN, mechanisms: salt and water retention, innappropriate activation of RAS, increase of sympathetic activity, IRI, oxidative stress…

Haas M, Mayer G. Nephrol Dial Transplant 1997;12:395-8.

Transplant Renal Artery Stenosis

- 12-20% causes of post-Tx HTN
- occurs between 3-24 months post Tx
- risk factors: harvesting and operative complications, atherosclerotic disease, CMV infection, DGF
- important to detect early and correct
- both transluminal balloon angioplasty and surgical bypass have been reported with excellent success.

Benoit G, et al Transplant renal artery stenosis: Transpl Int 1990,3:137

The presence of native kidney

Hypersecretion of renin, increase in sympathetic activity

Laparoscopic bill. nefrectomy (not recimmended currently)

Midtvedt K, et al. Nephrol Dial Transplant 1996;11:2045-9.

Role of hypertenzive donor on post-Tx HTN

In a study of 85 pts, elevations in BP and increased anti-HTN requirements post-transplant occurred much more frequently in recipients **WITHOUT** a FHX who received a kidney from a donor **WITH** a FHX.

Guidi E, J Am Soc Nephrol 1996

KDIGO Guidelines

The most current and widely recognized recommendations are the KDIGO (Kidney Disease: Improving Global Outcomes) guidelines, which recommend that:

- BP be measured during each office visit.
- BP be maintained at < 130 mm Hg systolic and < 80 mm Hg diastolic for:
  - pts 18 years of age and older
  - those under 18 who fall below the 90th percentile for gender, age, and height.

KDIGO Guidelines

- Physicians are not limited by the guidelines to any class of anti-HTN agent.
- Pts should be monitored for adverse effects and drug interactions.
- If proteinuria is detected, use of ACEI or ARB is recommended as first-line therapy.

The guidelines also recommend that practitioners:

- identify ideal BP targets
- measure the effect that minimizing proteinuria has on progression of CKD
- determine the effects of ACEIs and ARBs on patient and graft survival.

Post Transplant HTN Management

Table 6. Guidelines for Altering Treatment Regimens in Renal Transplant Recipients With Hypertension

Posttransplant Hypertension	Possible Interventions
• Seen in up to 90% of patients • Risk factor for graft loss • Goal blood pressure: – 130/80 mm Hg with diabetes – 125/75 mm Hg with proteinuria – 130/85 mm Hg without proteinuria or diabetes	• Lifestyle modifications include: – diet low in fat and sodium – exercise – smoking cessation – weight reduction • Taper or withdraw steroids • Consider conversion from cyclosporine to tacrolimus

National Heart, Lung, and Blood Institute. The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Bethesda, NIH publication 98-4080.

Antihypertensive agents

Table 1. Main anti-hypertensive agents used in renal transplant recipients.

Drugs	Advantages	Adverse events
Calcium channel blockers (CCB) early post Tx period dihydropyridinic CCB preffered	Reduce arteriolar vasoconstriction Reverse ventricular hypertrophy **CNI toxicity**	Peripheral oedema Gastro-oesophageal reflux Gingival hypertrophy Non-dihydropyridine CCB increase cyclosporin blood levels
ACE-inhibitors Angiotensin receptor blockers not recommended in the early, graft dysfunction (byCNI)	Prevent heart failure ,**LVD= regression of LVH** Prevent intimal thickening **e.g. atherosclerosis** Antiproteinuric effect **antiproliferative**	Small increase in creatinine **Diltiazem, Verapamil** Anaemia Hyperkalaemia Oligoanuria in transplant artery stenosis
Beta-blockers first line Th in pts with CVD, resistant HTA	Cardioprotective	Hyperlipaemia Increased risk of diabetes Poor correction of hypoglycaemia in diabetics Increase cardiovascular risk?
Alpha-antagonists Central agents	Control of benign prostatic hypertrophy Rapid onset	Dry mouth Bradycardia Rebound hypertension Sedation
Diuretics **immediate post-TX loop diuretics +- other drugs,urine output <50 ml/h.**	Reduce extracellular overload Synergize with other antihypertensive drugs	Hypokalaemia Hyperlipaemia Hyperuricaemia

CHD,DM

CAN: diuretics + CCBs. ACEs or ARBs when GFR > 30 ml/min.

The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Bethesda, NIH publication 98-4080.

Treatment of post transplant HTN

- For years, CCBs have been the backbone of treating the post-Tx HTN.
- Currently, dihydropyridine CCBs (amlodipine) remain a mainstay of anti-HTN treatment.
- Amlodipine: mitigates CNI-related vasoconstriction and lowers BP effectively, enhances the immunosuppressive effect by blocking the entry of Ca++ into the activated T cells, reducing the need for higher doses of CyA or TAC.

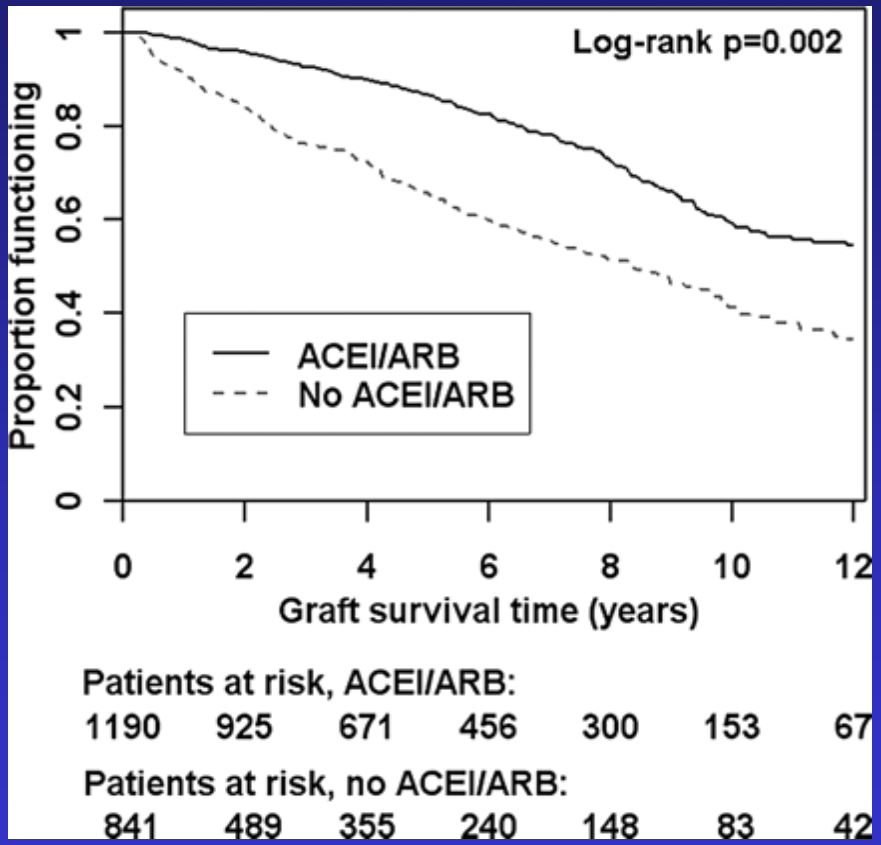
  Emerging evidence suggests that other drug classes may have promise in the transplant population.

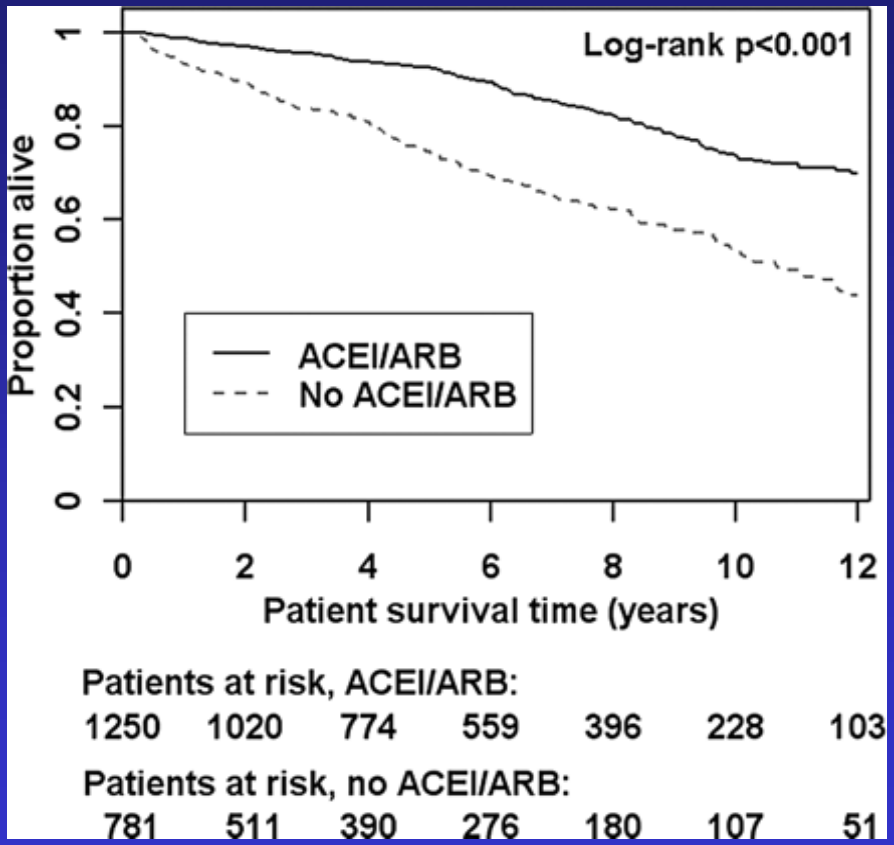
Treatment of post transplant HTN

- Heinze et al. found an increase in both patient and graft survival with the use of ACEIs.
- Weir reported a decrease in proteinuria with the use of ACEIs and ARBs.
- A 2009 Cochrane Database review by Cross et al. showed that treatment with CCBs diminished graft loss and improved GFRs.

Kaplan-Meier estimates of actual graft and patient survival

ACEI/ARB therapy was associated with longer graft an pts survival





Gerhard Opelz, Bernd Döhler . Am J Transp., November, 2005. 10.1111/j.1600-6143.2005.01093

Systematic Review of RAS Blockade in Kidney Transplantation

- 21 randomized trials
- n=1549
- median follow-up: 27 months
- eGFR decreased by 5.8 ml/min
- Hct decreased by 3.5 %
- proteinuria decreased by 470 mg/day
- no change in serum potassium
- not enough power to see an effect on patient or graft survival

Hiremath S, et. al AmJ Transplant 2007; 7:2350-2360

Use of ARBs/ACEIs in the pre-Tx period

- The excess RAAS activity in cadaveric kidney donor and recipient are important contributors to the pathogenesis of DGF.
- Administration of ACEI/ARB to cadaveric kidney donors immediately before nephrectomy, preserves intrarenal hemodynamics and decreases the number of postoperative ARF episodes from 25% to 58%.

Blumenfeld et al. Am J Hypert 2001; 14:1270
Lorenz M et al. Am J Med 2004; 43:1070
Formica RN, et al. Transplant Proc 2004; 36: 2675-2678
Midtvedt K, et al. Transplantation 2001; 72: 1787

What about the use of Renin blockers in transplant recipients?

One concern about Aliskiren use is the drug–drug interaction with Cys, where P-glycoprotein mediated drug transport is inhibited resulting in a several-fold increase in aliskiren exposure: risk of renal impairment, hypotension, and hyperkalemia.

Packag insert. Tekturna (aliskiren). East Hanover, NJ: Novartis, Pharmaceutical Corp. 2009

Managing HTN in Rt recipients

- **Control of associated risk factors**
  Lipids (statins, fibrates)
  Insulin resistance: insulin sensitizers (metformin, glitazones)
  Platelet aggregation: aspirin, others?
  Hyperhomocisteinemia: folic acid, vit. B6, B12
- **Modification and minimization of immunosuppression**

Chobanian AV et al. LAMA 2003; 289: 2560-2572
Calhoun DA, et al. Hypertension 2008; 51: 1403-1419

Maintaining immunosuppression: Corticosteroids

- sodium retention , pl.volume expansion,
- increased: cardiac output, renal vasc. resistance,
  sensitivity to ET-1 & Ag II, density of glucocorticoid receptors,
  renin secretion in hypertensive recipients, and
- decreased production of Pgl

Minimization or withdrawal of CS`s as soon as possible!

incidence of HTN induced by CS`s is 15%.
high doses of CS`s can directly cause HTN
long term maintenance dose may aggravate HTN
conversion from every day to alternate day may cause reduction of BP.

- There is question if CSs withdrawal is associated with lower BP ?

Goodwin JE, et al. J Am Soc Nephrol 2008; 19: 1291-1299
Opelz G et al. Am J Transpl 2005; 5: 720-728

Maintaining immunosuppression: CNIs

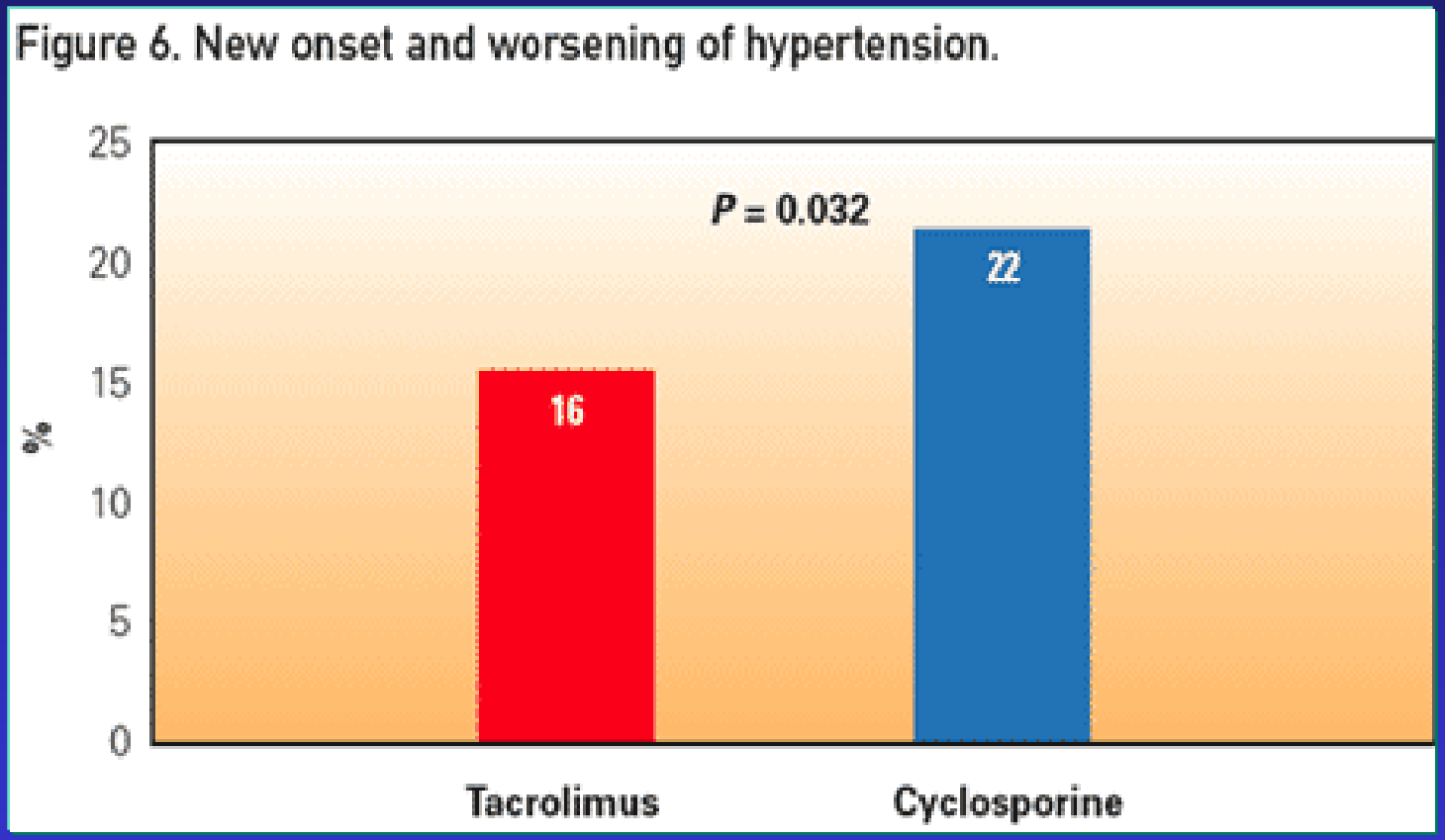
- increased systemic vascular resistance
- by activation of RAS , ET, Trx, NO, Prostacyclin
- constriction of afferent arterioles
- reduction of GFR and renal blood flow
- excess plasma volume from sodium retention

Reduce or avoid CNIs !!

- Replace CyA by using less: hypertensive and nephrotoxic drugs (AZA, MMF, Sirolimus, Tacrolimus,)

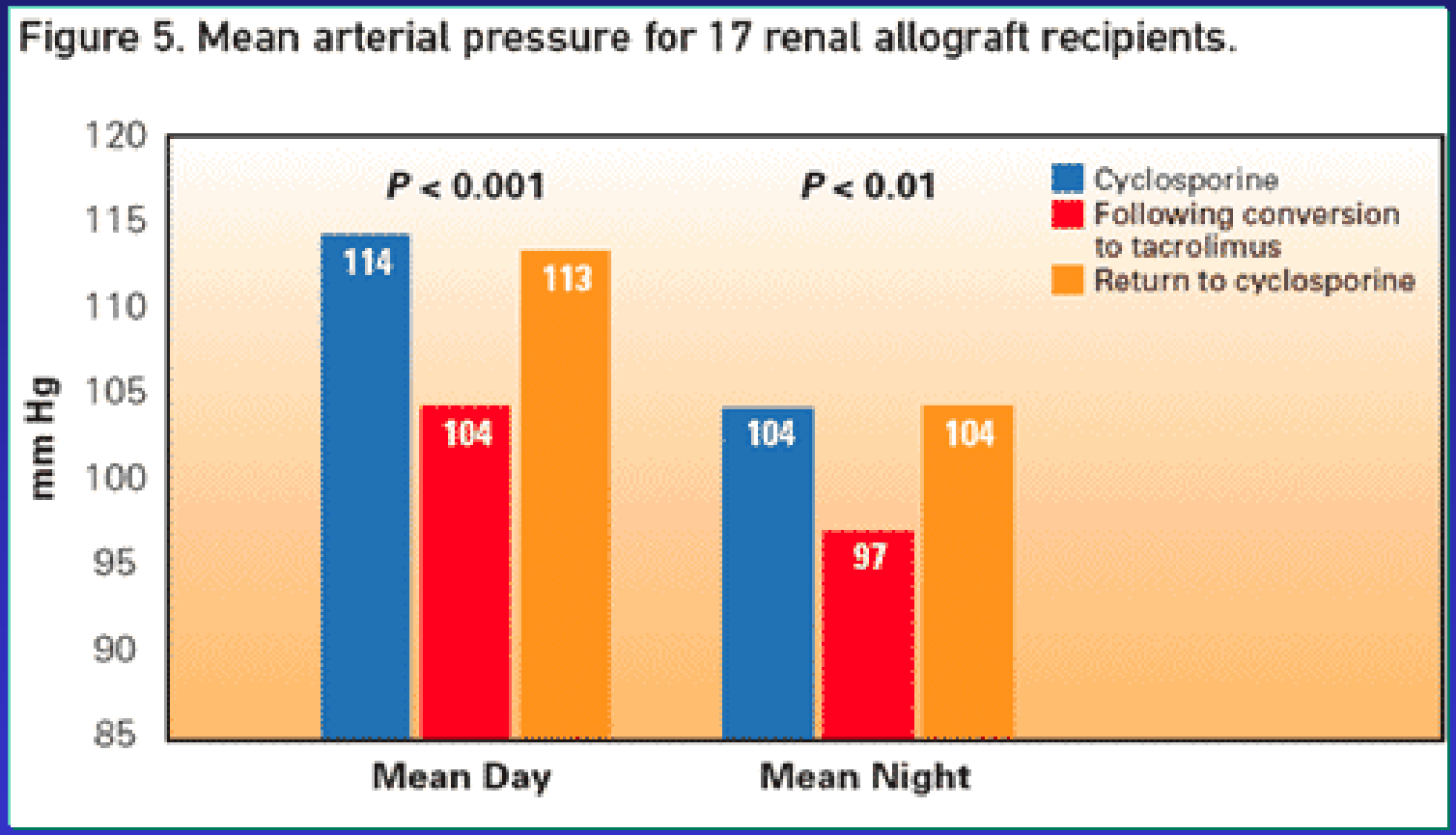
Van den Dorpel et al. Hypertension 1996;28:304-307
De Matos et al. Am J Kidney Dis 1996; 28:631-637

Significantly lower BP in pts treated TAC v.s. CyA



Margreiter R. Efficacy and safety of tacrolimus compared with ciclosporin microemulsion in renal transplantation: a randomised multicentre study. Lancet. 2002;359:741-746.

Improvement of MBAP in patients switched from CyA to TAC



Ligtenberg G, Hene RJ, Blankestijn PJ, Koomans HA. Cardiovascular risk factors in renal transplant patients: cyclosporin A versus tacrolimus. J Am Soc Nephrol. 2001;12:368-373.

Summary

- HTN is highly prevalent after kidney Tx and may contribute to CV morbidity and mortality, thereby influencing on graft and patient outcome and survival.
- Management od post-Tx HTN include: lifestyle modification and treatment of concominant CV risk fastors such as diabetes , huperlipidemia, hyperhomocysteinemia, etc.
- Optimal first line anti-HTN therapy consist: thiazide diuretics, CCBs, and/or beta-blockers.
- In proteinuric patients ACEIs and ARBs are recommended.

Summary

- Maintenance therapy with a low dose of corticosteroids may avoid some immunologic risk while improving HTN.
- Conversion from CyA to TAC/ Sirolimus , or CNI withdrawal with conversion to Rapamycin may lead to decreased BP in the stable post-Tx patient.
- **"We are doing all right,"** but there is much room for continued study of the risk factors and treatment of HTN in renal transplant recipients.

Thank You