Management of hypertension in renal transplant patients

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disclosure

• No competing interest in this field

Kidney transplantation and
HYPERTENSION
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.
<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Strength of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretransplant cardiovascular disease</td>
<td>++++</td>
</tr>
<tr>
<td>Diabetes (including posttransplant diabetes)</td>
<td>++++</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>+++</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>+++</td>
</tr>
<tr>
<td>Hypertension</td>
<td>++</td>
</tr>
<tr>
<td>Platelet and coagulation abnormalities</td>
<td>++</td>
</tr>
<tr>
<td>Allograft dysfunction/rejection</td>
<td>++</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>++</td>
</tr>
<tr>
<td>Erythrocytosis</td>
<td>+</td>
</tr>
<tr>
<td>Oxygen free radicals</td>
<td>+</td>
</tr>
<tr>
<td>Infections</td>
<td>+</td>
</tr>
<tr>
<td>Increased homocysteine</td>
<td>+</td>
</tr>
</tbody>
</table>
# Prevalence of hypertension in solid organ transplantation

<table>
<thead>
<tr>
<th>Organ</th>
<th>At 1 year</th>
<th>At 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td>~80%</td>
<td>~95%</td>
</tr>
<tr>
<td>Liver</td>
<td>~60-70%</td>
<td>~60%</td>
</tr>
<tr>
<td>Heart</td>
<td>~70%</td>
<td>~95%</td>
</tr>
<tr>
<td>Lungs</td>
<td>~50%</td>
<td>~80%</td>
</tr>
</tbody>
</table>

Adapted from Glatz N.  

*Rev Med Suisse 2009; 5: 1771-7*
Office Blood Pressure and kidney graft failure risk in transplanted patients

20% difference in graft survival

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…
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
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, Hatem Amer, MD, Matthew D. Griffin, MBCh, Sandra J. Taler, MD, Mark D. Stegall, MD, and Stephen C. Textor, MD

**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 rate (GFR) are expressed in ml/min/1.73 m².
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

Diagram showing the mechanisms of post-transplant hypertension with pathways involving reduced GFR, RAS, angiotensin, aldosterone, sodium retention, and vasodilation inhibition. Key factors include sympathetic nervous system activation, calcineurin inhibition, and steroids.
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.
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 $\leq 130$ mm Hg systolic and $\leq 80$ mm Hg diastolic, irrespective of the level of urine albumin excretion. (2D)
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†
DBP: impact on CV events and death

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

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Treatment approach to hypertension

- Therapeutic lifestyle changes\(^1\)
- Antihypertensive agents\(^1\)
- Alter immunosuppressive regimen\(^2\)

\(^2\)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/m²
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

<table>
<thead>
<tr>
<th>Pearson correlations</th>
<th>Partial correlation coefficient</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 49</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Home SBP with urinary Na⁺ Controlled for: age, BMI, smoking habit, antirejection drugs and urinary K⁺</td>
<td>0.30</td>
<td>0.074</td>
</tr>
<tr>
<td>Home SBP with urinary K⁺ Controlled for: age, BMI, smoking habit, antirejection drugs and urinary Na⁺</td>
<td>-0.48</td>
<td>0.002</td>
</tr>
</tbody>
</table>
Influence of IS modification

- **Steroids cessation:**
  - small decrease in BP prevalence (-10%), higher effect on hypercholesterolemia (-24%) and on DM risk (-36%)
  - 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. Winkelmayrer,‖ 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


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

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.

- Study in Canada and New Zealand, adult renal TR 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.

### Table

<table>
<thead>
<tr>
<th>Measure</th>
<th>Placebo (P)</th>
<th>Ramipril (R)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measured DTPA GFR (mL/min)</td>
<td>65·1 (27·6)</td>
<td>65·9 (25·0)</td>
</tr>
<tr>
<td>Corrected (mL/min/1·73m²)</td>
<td>58·6 (24·1)</td>
<td>59·8 (21·9)</td>
</tr>
<tr>
<td>Blood pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>135 (17)</td>
<td>135 (16)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>78 (10)</td>
<td>77 (9)</td>
</tr>
<tr>
<td>&lt;130/80</td>
<td>32 (29%)</td>
<td>35 (34%)</td>
</tr>
<tr>
<td>Serum potassium (mmol/L)</td>
<td>4·3 (0·5)</td>
<td>4·3 (0·6)</td>
</tr>
<tr>
<td>Serum creatinine (umol/L)</td>
<td>142 (54)</td>
<td>138 (51)</td>
</tr>
<tr>
<td>Haemoglobin (g/L)</td>
<td>129 (17)</td>
<td>131 (14)</td>
</tr>
<tr>
<td>Proteinuria (mg per day)</td>
<td>400 (270–720)</td>
<td>430 (270–813)</td>
</tr>
</tbody>
</table>
Ramipril versus placebo in kidney transplant patients with proteinuria: a multicentre, double-blind, randomised controlled trial

Greg A Knoll*, Dean Fergusson*, Michael Chassé, Paul Hebert, George Wells, Lee Anne Tibbles, Darin Treleaven, David Holland, Christine White, Yasod, Edward Cole.

Table 3: Adverse events

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (n=109)</th>
<th>Ramipril (n=103)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>24 (22%)</td>
<td>39 (38%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Angioedema</td>
<td>0</td>
<td>1 (1%)</td>
<td>0.49</td>
</tr>
<tr>
<td>Cough</td>
<td>0</td>
<td>4 (4%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Hyperkalemia*</td>
<td>1 (1%)</td>
<td>5 (5%)</td>
<td>0.11</td>
</tr>
<tr>
<td>Anemia*</td>
<td>22 (20%)</td>
<td>25 (24%)</td>
<td>0.51</td>
</tr>
<tr>
<td>Other</td>
<td>1 (1%)</td>
<td>4 (4%)</td>
<td>0.20</td>
</tr>
</tbody>
</table>

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

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.

Lower BP in the ramipril group (-5/-3 mmHg)
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 CCBI and/or BBBlocker.

• Don’t forget poor compliance and secondary HTA if resistance!
Thank you for your attention

Questions?