Antihypertensive Agents in Dialysis Patients: Advantages and Disadvantages

Josep Redon. MD, PhD, FAHA
Scientific Director
INCLIVA Research Institute
University of Valencia
Hypertension in CKD 5D

- Frequent condition with major implications for survival
- Hypertension largely increases cardiovascular risk (x10-x20)
- Grounded evidences about values to treat and goals to achieve are not available
### Risk of CV events for BP lowering treatment vs control

#### Numbers of events/patients

<table>
<thead>
<tr>
<th></th>
<th>Active treatment</th>
<th>Control</th>
<th>Risk ratio (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Cardiovascular mortality</td>
<td></td>
<td></td>
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<tr>
<td>Li et al (2003)(^{17})</td>
<td>2/30</td>
<td>2/30</td>
<td>1.00 (0.15–6.64)</td>
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<tr>
<td>Takahashi et al (2006)(^{19})</td>
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<tr>
<td>Cice et al (2003)(^{10})</td>
<td>17/58</td>
<td>38/56</td>
<td>0.43 (0.28–0.67)</td>
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<tr>
<td>Suzuki et al (2008)(^{20})</td>
<td>12/183</td>
<td>20/183</td>
<td>0.60 (0.30–1.19)</td>
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<tr>
<td>Nakao et al (2007)(^{22})</td>
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<td>30/201</td>
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<td>Cice et al (2006)(^{18})</td>
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<tr>
<td><strong>Overall</strong></td>
<td><strong>121/618</strong></td>
<td><strong>165/622</strong></td>
<td><strong>0.71 (0.50–0.99)</strong></td>
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</tbody>
</table>

Test for heterogeneity: \(I^2=54.6\%\), \(Q=8.8\), \(p=0.07\)

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*Heerspink et al. Lancet 2009;373:1009-1015*
### Risk of all cause mortality for BP lowering treatment vs control

<table>
<thead>
<tr>
<th>Numbers of events/patients</th>
<th>Risk ratio (95% CI)</th>
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<tr>
<td><strong>Active treatment</strong></td>
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<tr>
<td>All-cause mortality</td>
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<td>Cice et al (2003)(^{10})</td>
<td>30/58</td>
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<td>Suzuki et al (2008)(^{20})</td>
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<td>Zannad et al (2006)(^{21})</td>
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<tr>
<td>Cice et al (2006)(^{18})</td>
<td>88/151</td>
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<td><strong>Overall</strong></td>
<td>213/784</td>
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</table>

Test for heterogeneity: \(I^2=30.0\%, Q=8.57, p=0.20\)

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*Heerspink et al. Lancet 2009;373:1009-1015*
Risk of CV events for BP lowering treatment vs control in CKD 5D

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>n</th>
<th>Hazard Ratio (95% CI)</th>
<th>Weight (%)</th>
<th>Death Cardiovascular (%)</th>
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<td><strong>Normotensives included</strong></td>
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<tr>
<td>Zannad</td>
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<td>397</td>
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<td>0.76 (0.47, 1.22)</td>
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<td>Takahashi-NT</td>
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<td>0.29 (0.03, 2.78)</td>
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<tr>
<td>I-V Subtotal (I-squared = 0.0%, p = 0.497)</td>
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<td>0.86 (0.67, 1.12)</td>
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<td>D+L Subtotal</td>
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<td><strong>Hypertensives only</strong></td>
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<td>Suzuki</td>
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<tr>
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<td>I-V Subtotal (I-squared = 0.0%, p = 0.551)</td>
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<td>0.49 (0.35, 0.67)</td>
<td>38.97</td>
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<td>D+L Subtotal</td>
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<tr>
<td>Heterogeneity between groups: p = 0.006</td>
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<tr>
<td>I-V Overall (I-squared = 50.4%, p = 0.073)</td>
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<td>0.69 (0.56, 0.84)</td>
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<td>D+L Overall</td>
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Agarwal and Sinha. Hypertension 2009;53:860-866
Hypertension in CKD 5D

- Frequent condition with major implications for survival
- Hypertension largely increases cardiovascular risk (x10-x20)
- Grounded evidences about values to treat and goals to achieve are not available
- Balance between benefit and harm is complex
Complexity of understanding the prognostic value of BP in CKD 5

Objective
Reduce morbidity and mortality

Potential specific problems
Intradialytic hypotension
Vascular access thrombosis
More prone to side effects
Complexity of understanding the prognostic value of BP in CKD 5

- Post-dialysis weight
- Dialysite composition
- Erythropoiesis stimulating agents
- Sodium and volume load
- SRAA activation
- Sympathetic overdrive
- Cardiovascular status
- Arterial stiffness
- Cardiomyopathy
- Mechanism underlying BP elevation
Complexity of understanding the prognostic value of BP in CKD 5

BP-lowering drugs

Post-dialysis weight
Dialysis
Dialysite composition
Erythropoiesis stimulating agents
Cardiovascular status
Arterial stiffness
Cardiomyopathy
Mechanism underlying BP elevation
Sodium load
SRAA activation
Sympathetic overdrive
Advantages and disadvantages of antihypertensive treatment in CKD 5

When to initiate Rx and Blood Pressure Goals

Which BP Values should be Targeted

Antihypertensive Treatment in CKD 5

Dose of BP Lowering Drugs in Dialysis
Definition of Hypertension in K/DOQI guides

**K/DOQI 2005 guidelines on cardiovascular disease in dialysis patients**
Predialysis and postdialysis blood pressure goals should be <140/90mmHg and <130/80mmHg respectively (C)

**K/DOQI 2006 update of hemodialysis adequacy guidelines**
Focus on volume control, dietary sodium restriction and avoidance of high dialysate sodium

DO NOT recommend specific blood pressure targets in hemodialysis patients

**K/DOQI 2007 clinical practice guidelines for diabetes and CKD**
Target blood pressure in diabetes and CKD stages 1-4 should be <130/80mmHg (B)

Targets for patients on dialysis are not recommended.

**K/DOQI 2009 blood pressure in CKD 5D**
Targets for patients on dialysis are not recommended. Suggested pre-HD <140/90 mmHg; post-HD <130/80 mmHg

Recommended studies using Home BP

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Blood pressure treatment - “conventional” wisdom in ESRD patients

- Blood pressure regulation
  - volume-dependent Salt/water
  - vasoconstriction RAS, sympathetic activity, lack of NO, medullipin etc.
- Heart failure
  - Arterial compliance calcification

Salt ???
Changes over time ???

What is the “real” RR ???

Acute changes ???

HD HD HD

HD HD HD
Prognostic value differs when BP measured in different conditions

Alborzi et al. CJASN 2007;2:1228-1234
Unadjusted survival by baseline predialysis systolic BP

Association between BP and 15-month CV death in 40 933 MHD patients (95% confidence interval bars are depicted)

Hazard ratios (HR) for all-cause mortality by baseline predialysis SBP

# Blood pressure and mortality risk in peritoneal dialysis

## Time-Stratified Cox Proportional Hazards Model for Components of BP

<table>
<thead>
<tr>
<th>Time From Start of RRT</th>
<th>No. of Patients</th>
<th>Unadjusted Model</th>
<th>Fully Adjusted Model*</th>
<th>$P$ for BP and TWL Status Interaction‡</th>
<th>$P$ for BP and Diabetes Interaction‡</th>
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<tr>
<td></td>
<td>RH† (95% CI)</td>
<td>$P$</td>
<td>RH† (95% CI)</td>
<td>$P$</td>
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<td><strong>Systolic BP</strong></td>
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<td>180 d-1 y</td>
<td>2,770</td>
<td>0.88 (0.80-0.96)</td>
<td>0.002</td>
<td>0.84 (0.78-0.92)</td>
<td>&lt;0.001</td>
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<td>Years 2-3</td>
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<td>0.97 (0.93-1.01)</td>
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<td>Years 4-5</td>
<td>1,729</td>
<td>1.06 (1.00-1.12)</td>
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<td>0.98 (0.92-1.03)</td>
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<td>Years 6+</td>
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<td>1.14 (1.05-1.23)</td>
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<td>1.10 (1.01-1.19)</td>
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<td><strong>Diastolic BP</strong></td>
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<td>180 d-1 y</td>
<td>2,770</td>
<td>0.68 (0.59-0.79)</td>
<td>&lt;0.001</td>
<td>0.78 (0.67-0.91)</td>
<td>0.001</td>
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<td>0.94 (0.88-1.02)</td>
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<td>Years 4-5</td>
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<td>0.96 (0.87-1.07)</td>
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<td><strong>Mean arterial pressure</strong></td>
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<tr>
<td>180 d-1 y</td>
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<td>0.73 (0.64-0.84)</td>
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<td>0.77 (0.67-0.87)</td>
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<td>Years 4-5</td>
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<td>0.94 (0.86-1.03)</td>
<td>0.1</td>
<td>0.96 (0.88-1.05)</td>
<td>0.4</td>
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<td>911</td>
<td>1.03 (0.92-1.17)</td>
<td>0.6</td>
<td>1.05 (0.93-1.20)</td>
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<td><strong>Pulse pressure</strong></td>
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<td>180 d-1 y</td>
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<td>0.98 (0.93-1.03)</td>
<td>0.4</td>
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<td>Years 4-5</td>
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<td>0.98 (0.91-1.06)</td>
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<td>1.18 (1.08-1.31)</td>
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*Adjusted for age, sex, race, diabetes, and time since start of RRT.

‡Time-stratified on patient years of RRT (180 d-1-2, 2-3, 3-5, 5-10, >10).
Advantages and disadvantages of antihypertensive treatment in CKD 5

When to initiate Rx and Blood Pressure Goals

Which BP Values should be Targeted

Antihypertensive Treatment in CKD 5

Dose of BP Lowering Drugs in Dialysis
Patients achieving pre- and post-dialysis UK RA blood pressure targets (<140/90 or <130/80 mm Hg)

Control rates of pre- and post-HD hypertension by treatment

Prognostic value of home and ambulatory BP of all cause mortality in dialysis

Agarwal R. Hypertension 2010;55:763-768
Prognostic value of home and ambulatory BP of all cause mortality in dialysis

Agarwal R. Hypertension 2010;55:763-768
Advantages and disadvantages of antihypertensive treatment in CKD 5

- When to initiate Rx and Blood Pressure Goals
- Which BP Values should be Targeted
- Antihypertensive Treatment in CKD 5
- Dose of BP Lowering Drugs in Dyalisis
The effect of dry weight reduction on interdialytic ambulatory BP in hypertensive hemodialysis pts.

Agarwal et al. Hypertension 2009;53:500-507
ESH-ESC Guidelines 2013: Antihypertensive drug classes

Mancia et al. Journal of Hypertension 2013;31:1281-1357
Use of antihypertensive classes by country in CKD 5D (DOPPS I-II)

Lopes et al. Nephrol Dial Transp 2009;24:2809-2816
Antihypertensive classes and all-cause mortality in CKD 5D (DOPPS I-II)

Lopes et al. Nephrol Dial Transpl 2009;24:2809-2816
Antihypertensive drug classes and CV mortality in CKD 5D (DPPDS I-II)

Analysis of Patient-Level Prescription Data (AHA vs. none):

- Beta Blockers: RR=0.87, P=0.004
- ARB: RR=0.79, P=0.005
- ACEI: RR=0.93, P=0.16
- Peripheral Blockers: RR=0.84, P=0.01
- Central Angonists: RR=1.05, P=0.50
- Vasodilators: RR=1.03, P=0.77
- CCB: No DHP: RR=1.05, P=0.50
- CCB: Long DHP: RR=0.98, P=0.62
- CCB: Short DHP: RR=1.82, P=0.004

RR of Mortality with 95% CI (ln scale)

Lopes et al. Nephrol Dial Transpl 2009;24:2809-2816
Observational studies of beta blockers
(Analyses of the Dialysis Morbidity and Mortality Studies DMMS conducted by the US Renal Data System)

- 2550 pts observed 60 days after dialysis
- In patients WITHOUT a history of HF, use of beta blockers was associated with lower subsequent risk of de novo HF, combined HF and cardiac death and all cause death.
- Beta-blockers were used by only 20% of patients in this cohort regardless of the presence of previous HF.

Carvedilol in patients on hemodialysis CV mortality and all cause hospitalization

CARDIOVASCULAR MORTALITY

EVENT-FREE SURVIVAL

Carvedilol
Placebo

Carvedilol
Placebo

p<0.00001

p<0.005

Time After Inclusion (months)

Time After Inclusion (months)

Cice et al. JACC 2003; 41:1438-1444
ACE inhibitors after MI in patients on HD ESRD Database + Cooperative CV Project Database

Association of medication classes with 30-day mortality after Myocardial infarction in pts with ESRD

Berger et al. JACC 2003;42:201-208
Fosinopril in Dialysis (FOSIDIAL) Study

Zannad et al. Kidney International 2006; 70: 1318-1324
ARBs (candesartan) on CV Events and mortality in hemodialysis patients

Takahasi et al. Nephrol Dial Transpl 2006;21:2507-2512
Atenolol vs lisinopril in hemodyalisis: Impact in LVH and CV events

Agarwal et al. Nephrol Dial Transp 2014;29:672-681
Atenolol vs lisinopril in hemodialysis: Impact in LVH and CV events

Agarwal et al. Nephrol Dial Transp 2014;29:672-681
Selection of antihypertensive drugs in CKD 5D

- Among the drug groups the **first step** should be:
  - **Beta-blockers** if CHD or CHF exists
  - **ACEi** if CHF
- **24-hour** antihypertensive **activity** is recommended for once-a-day Tx
- **Second step**, frequently needed, should combine a drug with additive effect and reduction of side effects
- Not favour the use **single-pill** combinations
Second step of combining antihypertensive drugs for CKD 5D
Advantages and disadvantages of antihypertensive treatment in CKD 5

- When to initiate Rx and Blood Pressure Goals
- Which BP Values should be Targeted
- Antihypertensive Treatment in CKD 5
- Dose of BP Lowering Drugs in Dyalisis
Antihypertensive drugs in CKD 5D under dialysis

Dose reduction?

Drug pharmacokinetics
## Dose correction due to metabolism of the drug

<table>
<thead>
<tr>
<th>ACEi</th>
<th>β-blockers</th>
<th>Vasodilators</th>
<th>Central agents</th>
<th>ARBs</th>
<th>CCBs</th>
<th>α-blockers</th>
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<tbody>
<tr>
<td></td>
<td>bisoprolol</td>
<td>esmolol</td>
<td>diazoxide</td>
<td>clonidine</td>
<td>candesartan</td>
<td>all</td>
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<td>metoprolol</td>
<td>minoxidil</td>
<td>guanabenz</td>
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<td>α-blockers</td>
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</tbody>
</table>

- Full dose
- 25% dose reduction
- 50% dose reduction
- 50-75% dose reduction

Redon et al. Blood Purf 2010
Antihypertensive drugs in CKD 5D under dialysis

- Dose reduction?
- Dialysis removal?

Molecular weight
Protein binding
Water solubility
Intercompartmental exchange
## Dose correction due to permeability

<table>
<thead>
<tr>
<th>ACEi</th>
<th>β-blockers</th>
<th>Vasodilators</th>
<th>Central agents</th>
<th>ARBs</th>
<th>CCBs</th>
<th>α-blockers</th>
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</thead>
<tbody>
<tr>
<td>fosinopril</td>
<td>bisoprolol</td>
<td>diazoxide</td>
<td>clonidine</td>
<td>candesartan</td>
<td>all</td>
<td>doxazosin</td>
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<tr>
<td>benazepril</td>
<td>esmolol</td>
<td>minoxidil</td>
<td>guanabenz</td>
<td>eprosartan</td>
<td>dihydropyridin</td>
<td>prazosin</td>
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<td></td>
<td>labetalol</td>
<td>nitroprusiate</td>
<td>guanethidine</td>
<td>irbesartan</td>
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<td>terazosin</td>
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<td>betaxolol</td>
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</tbody>
</table>

### Central agents

- clonidine
- guanabenz
- guanethidine

### ARBs

- candesartan
- eprosartan
- irbesartan
- losartan
- olmesartan
- telmisartan
- valsartan

### CCBs

- all
- dihydropyridin
- veramapil
- diltiazem

### α-blockers

- doxazosin
- prazosin
- terazosin

### Vasodilators

- diazoxide
- minoxidil
- nitroprusiate

### β-blockers

- bisoprolol
- esmolol
- labetalol
- metoprolol
- pindolol
- timolol
- acebutolol
- betaxolol

### No removal

- quinapril
- ramipril
- trandolapril

### 30% removal

- captopril
- enalapril
- lisinopril
- perindopril

### 50% removal

- atenolol
- carvedilol
- nadolol
- sotalol

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Redon et al. Blood Purf 2010
Antihypertensive drugs in CKD 5D under dialysis

Dose reduction?
Dialysis removal?
Dialysis technique

Mode of solute transport
Membrane
Flow rate
Time of dialysis
Benefits beyond BP reduction

- Glucose and lipid metabolism:
  - CCB neutral
  - ACEi-ARB at least neutral
- RAAS blockade:
  - Reduction of LVH and arterial remodeling
- Sympathetic overdrive reduction with BB
- Intracellular calcium load with CCB
- Compliance:
  - Better in drugs without side effects (ARB)
Major problems before randomized prospective trials

- What is (are) the blood pressure measurement(s) a diagnosis of HTN is based upon?
- Do we have to subclassify according to heart failure (or other)?
- How to account for „time on dialysis“?
- Role of dialysis regime?
Conclusions

- Treatment of hypertension is a big challenge for nephrologists in CKD 5D
- Grounded information about values to treat and goals is lacking
- Sound treatment requires cardiovascular assessment
- Drugs combined with appropriate volume management achieve success
- Compelling indications, dosage and membrane permeability are key elements for setting Tx