

**17. ULUSAL HIPERTANSİYON VE BÖBREK
HASTALIKLARI KONGRESİ
6-10 Mayıs 2015
Antalya**

**Antihypertensive Agents in
Dialysis Patients: Advantages
and Disadvantages**

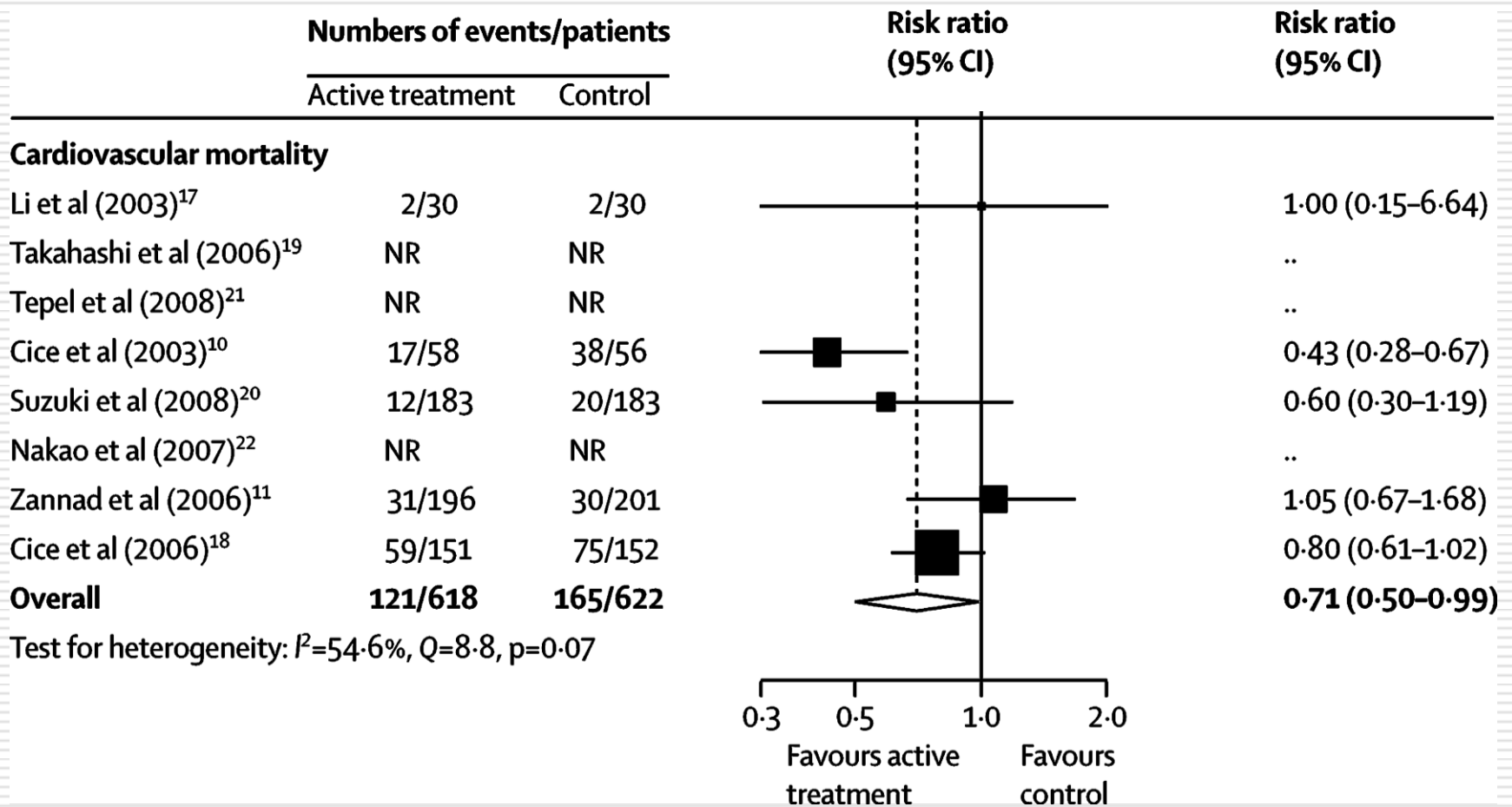
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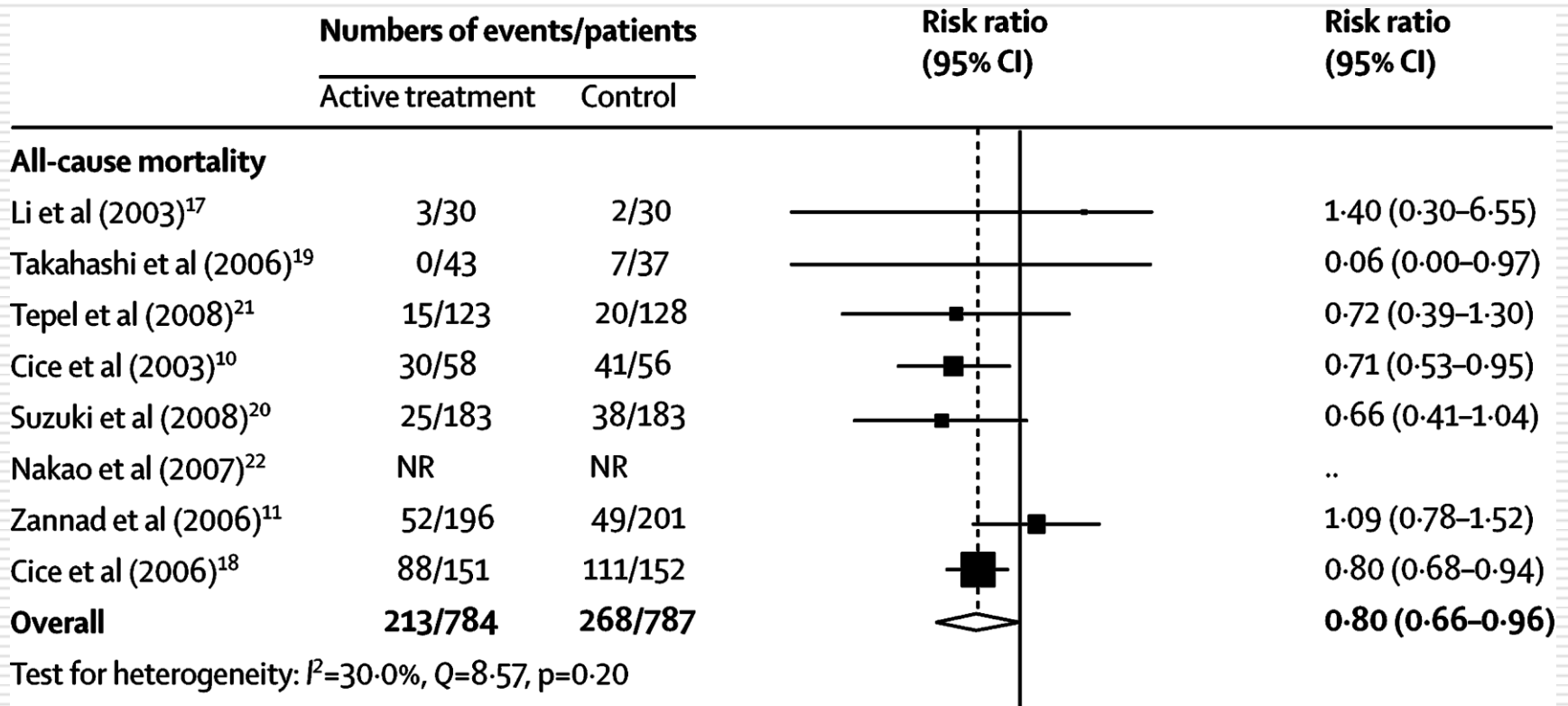
Hypertension in CKD 5D

- 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
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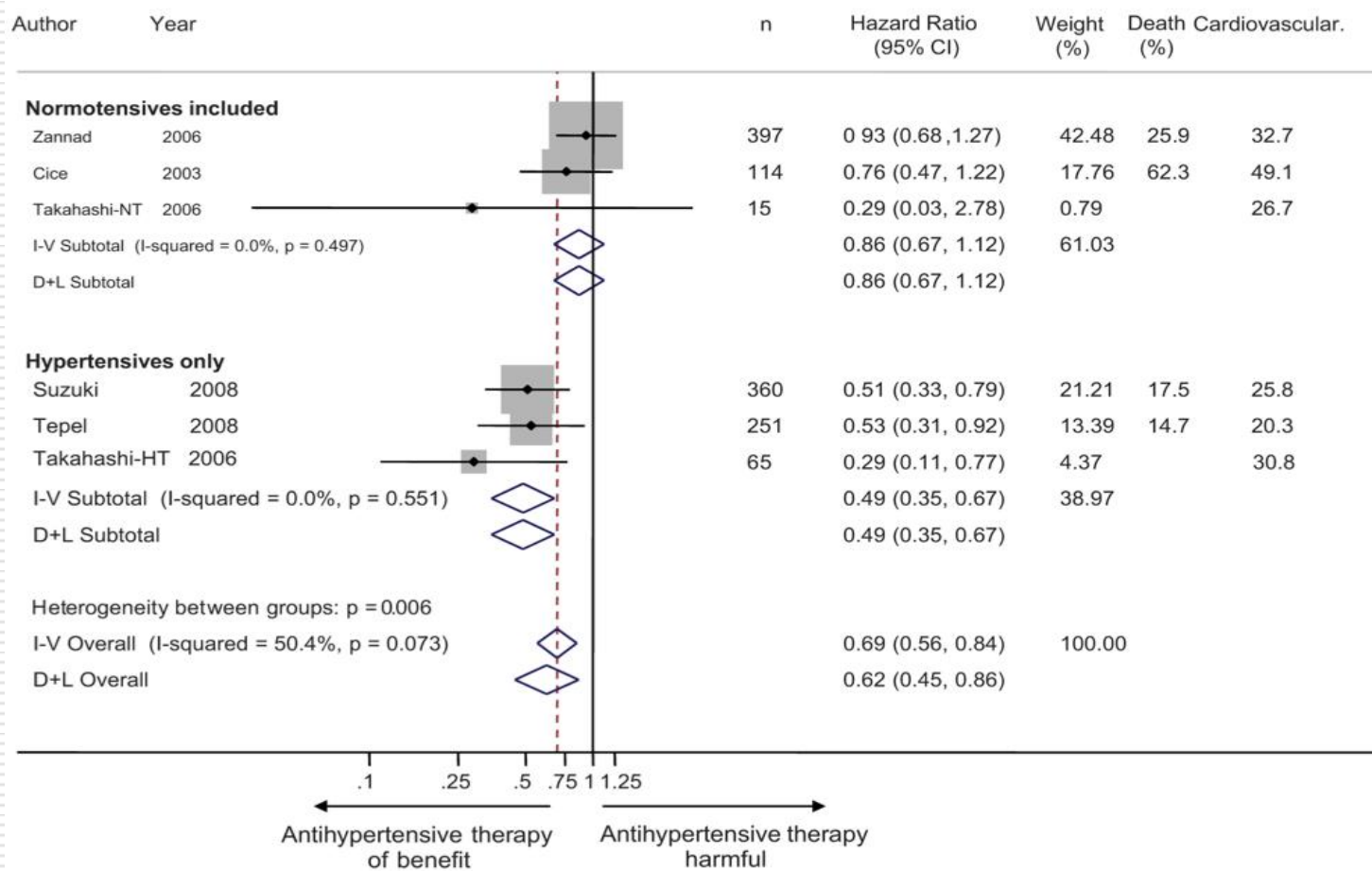
Risk of CV events for BP lowering treatment vs control



Risk of all cause mortality for BP lowering treatment vs control



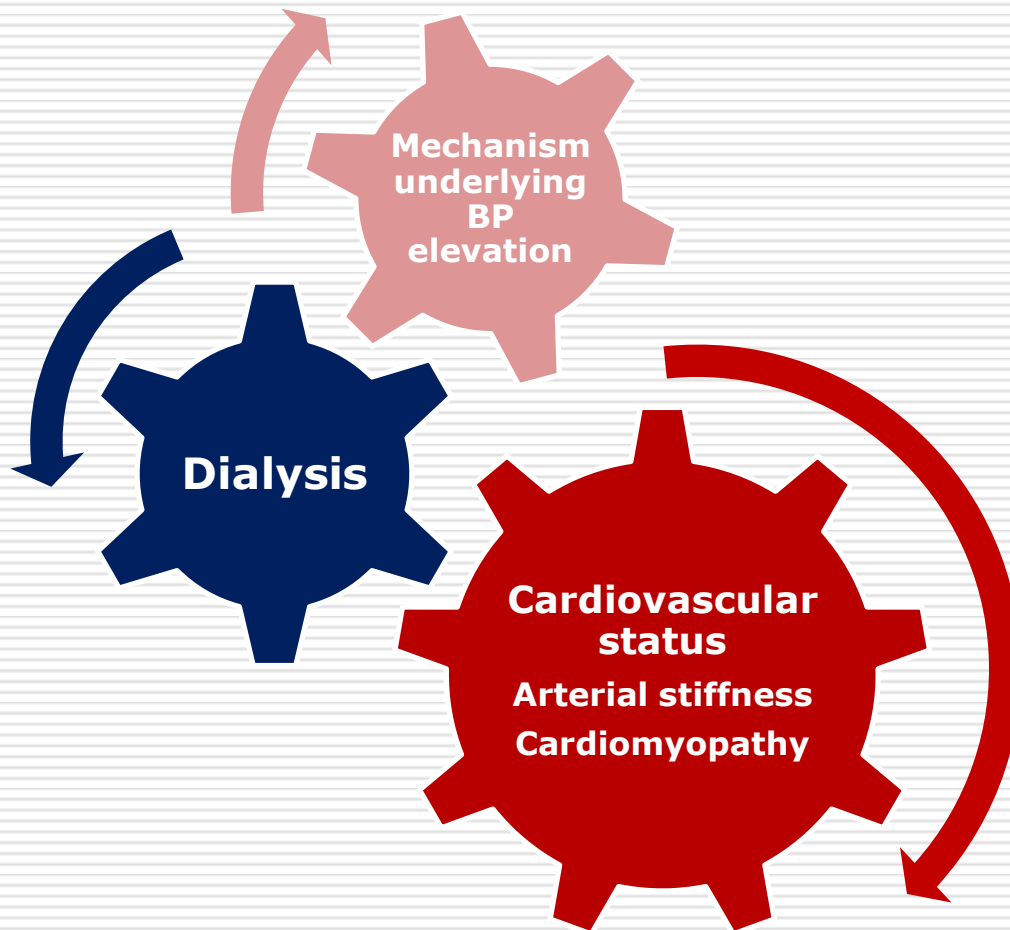
Risk of CV events for BP lowering treatment vs control in CKD 5D



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



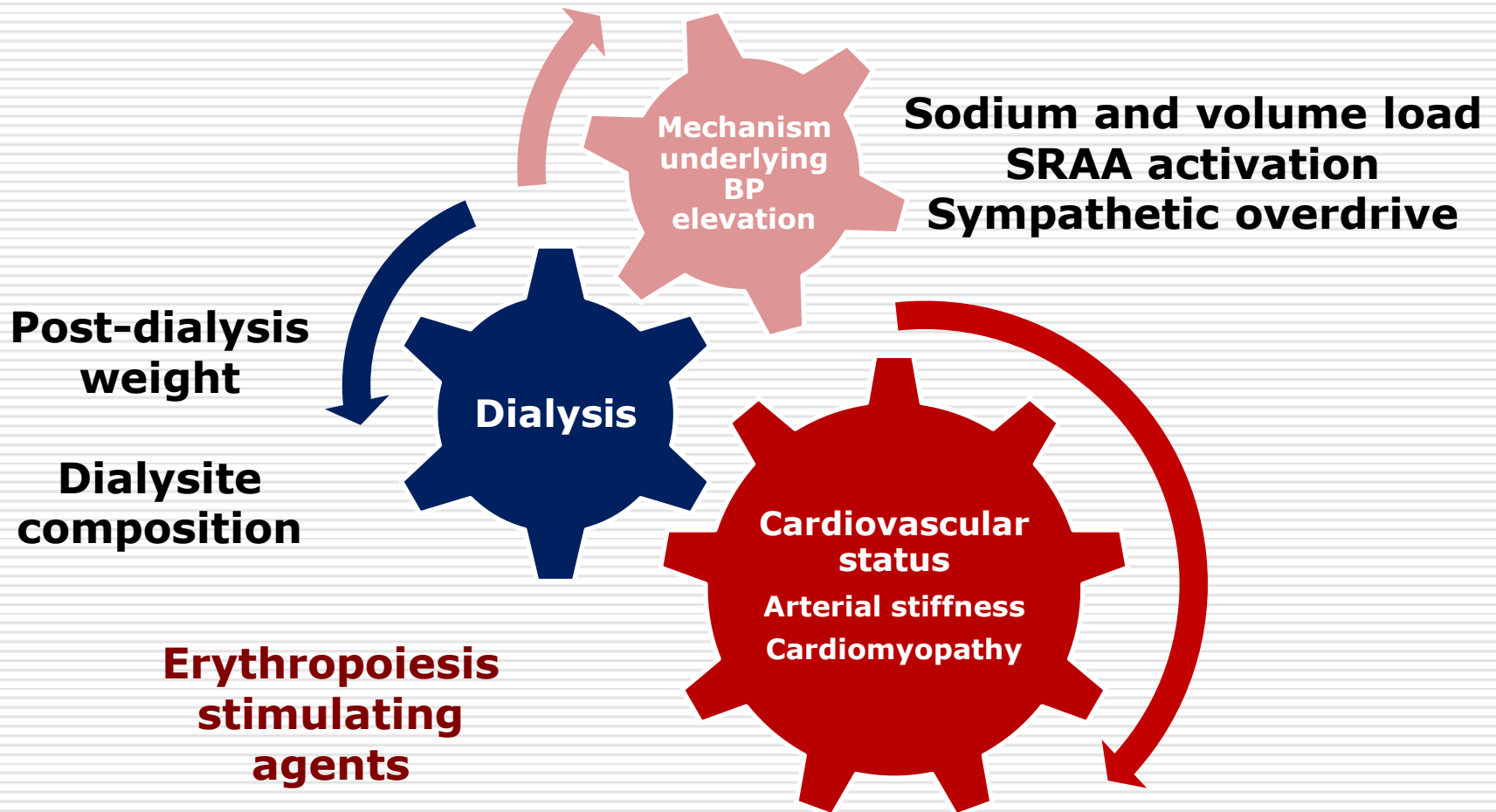
Objective

Reduce morbidity and mortality

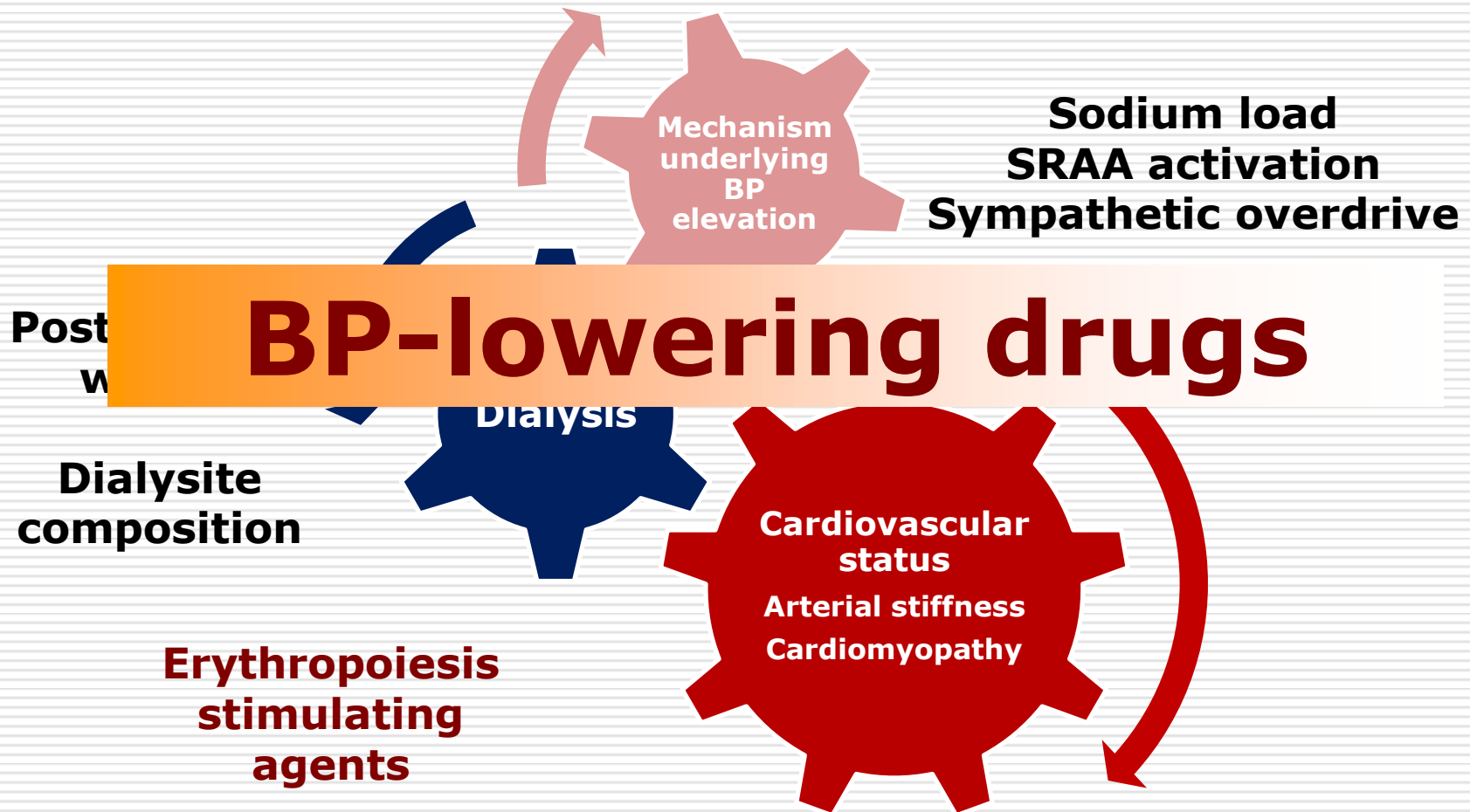
Potential specific problems

Intradialytic hypotension
Vascular access thrombosis
More prone to side effects

Complexity of understanding the prognostic value of BP in CKD 5



Complexity of understanding the prognostic value of BP in CKD 5



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

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.

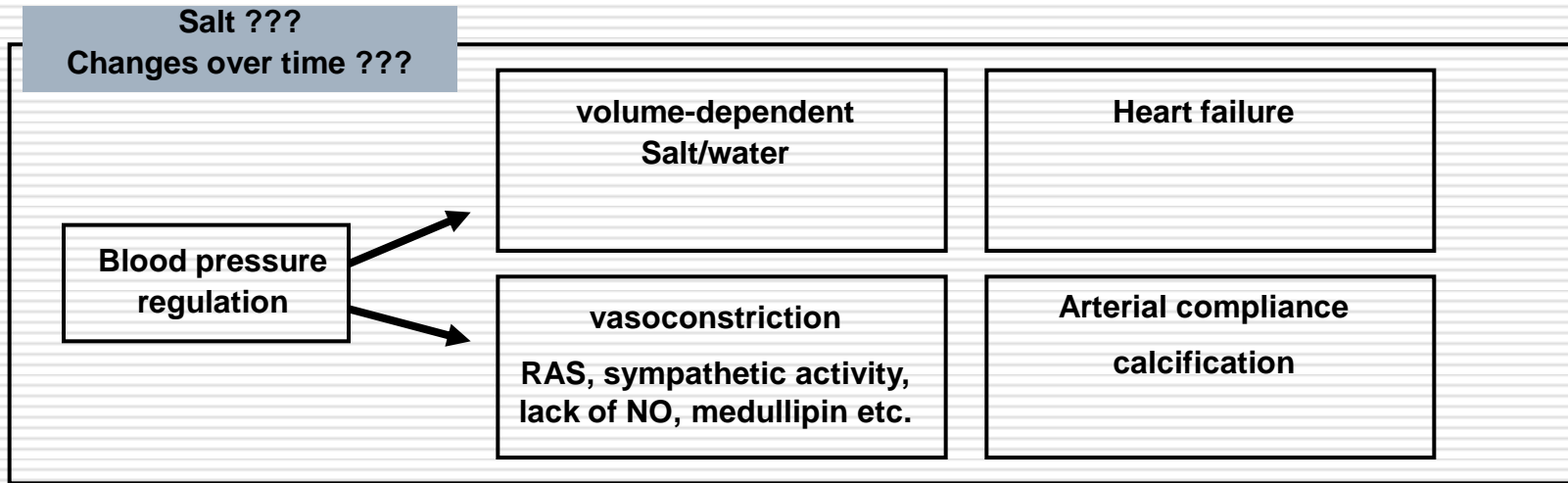
K/DOQI 2009 blood pressure in CKD 5D*

Targets for patients on dialysis are not recommended. Suggested pre-HD <140/90 mmHg; post-HD <130/80 mmHg

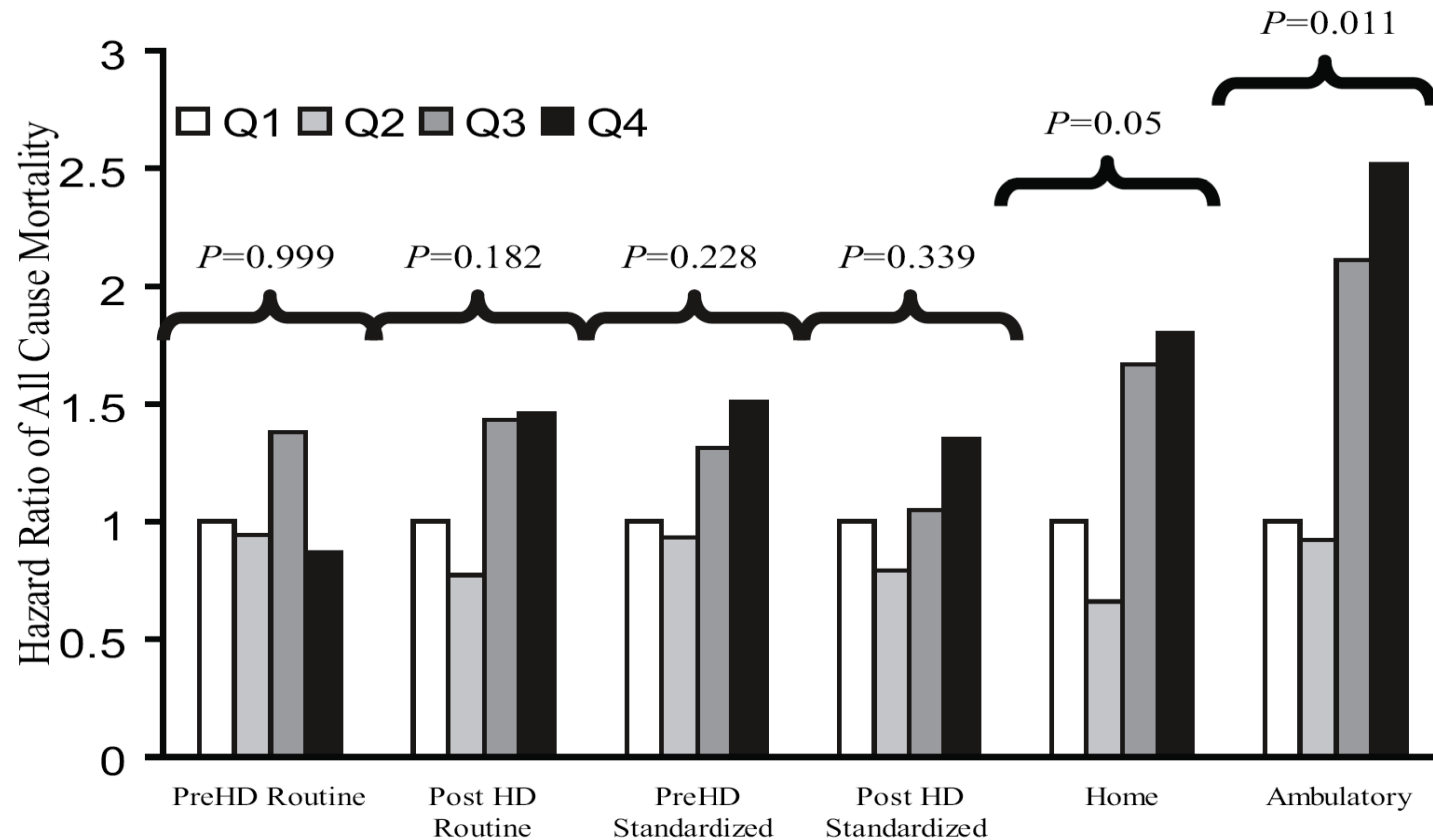
Recommended studies using Home BP

** Blood pressure in chronic kidney disease stage 5D-report from a Kidney Disease: Improving Global Outcomes controversies conference. Levin NW, Kotanko P, Eckardt KU, Kasiske BL, Chazot C, Cheung AK, Redon J, Wheeler DC, Zoccali C, London GM. *Kidney Int.* 2009 (16 December 2009) | doi:10.1038/ki.2009.469*

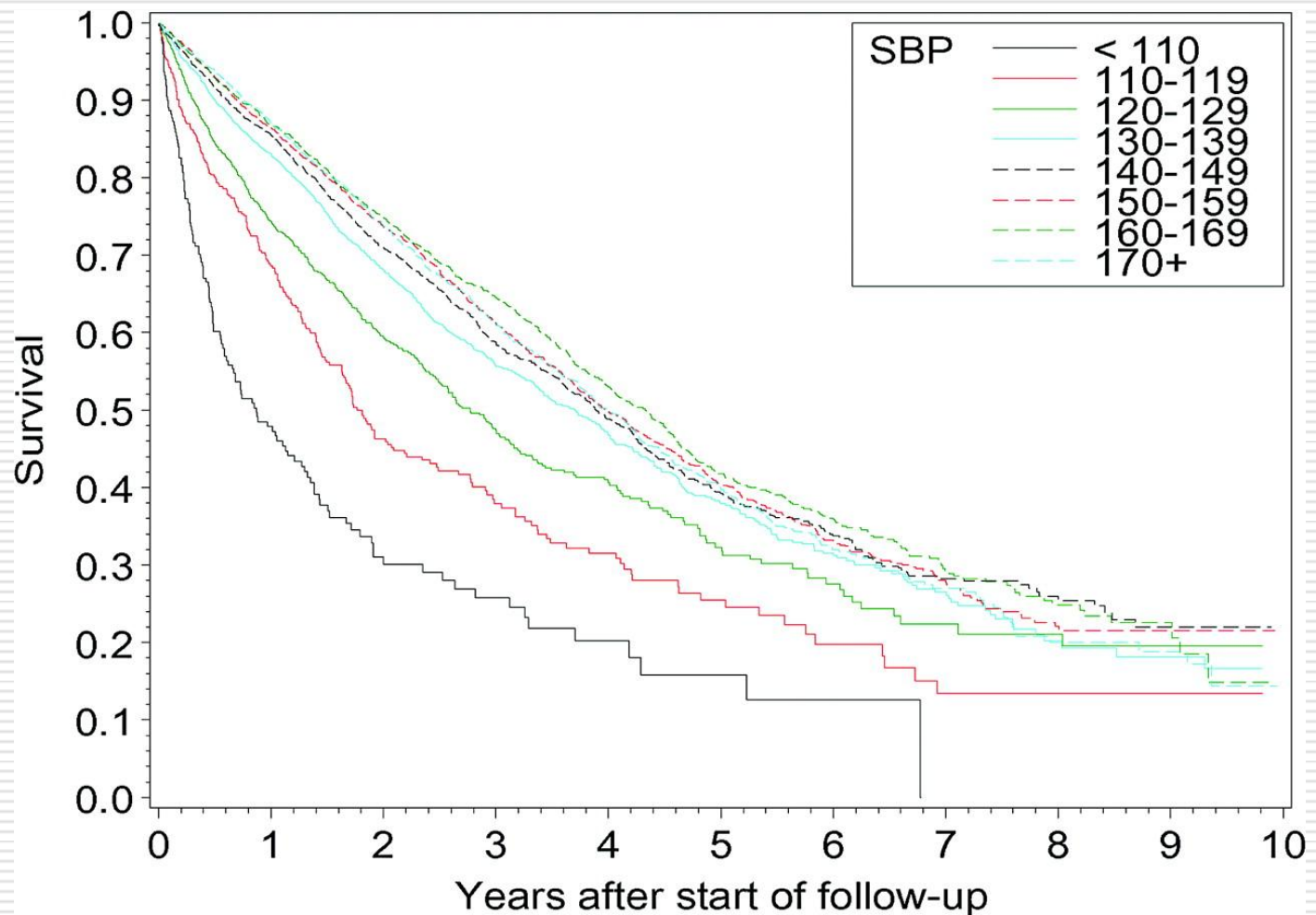
Blood pressure treatment - "conventional" wisdom in ESRD patients



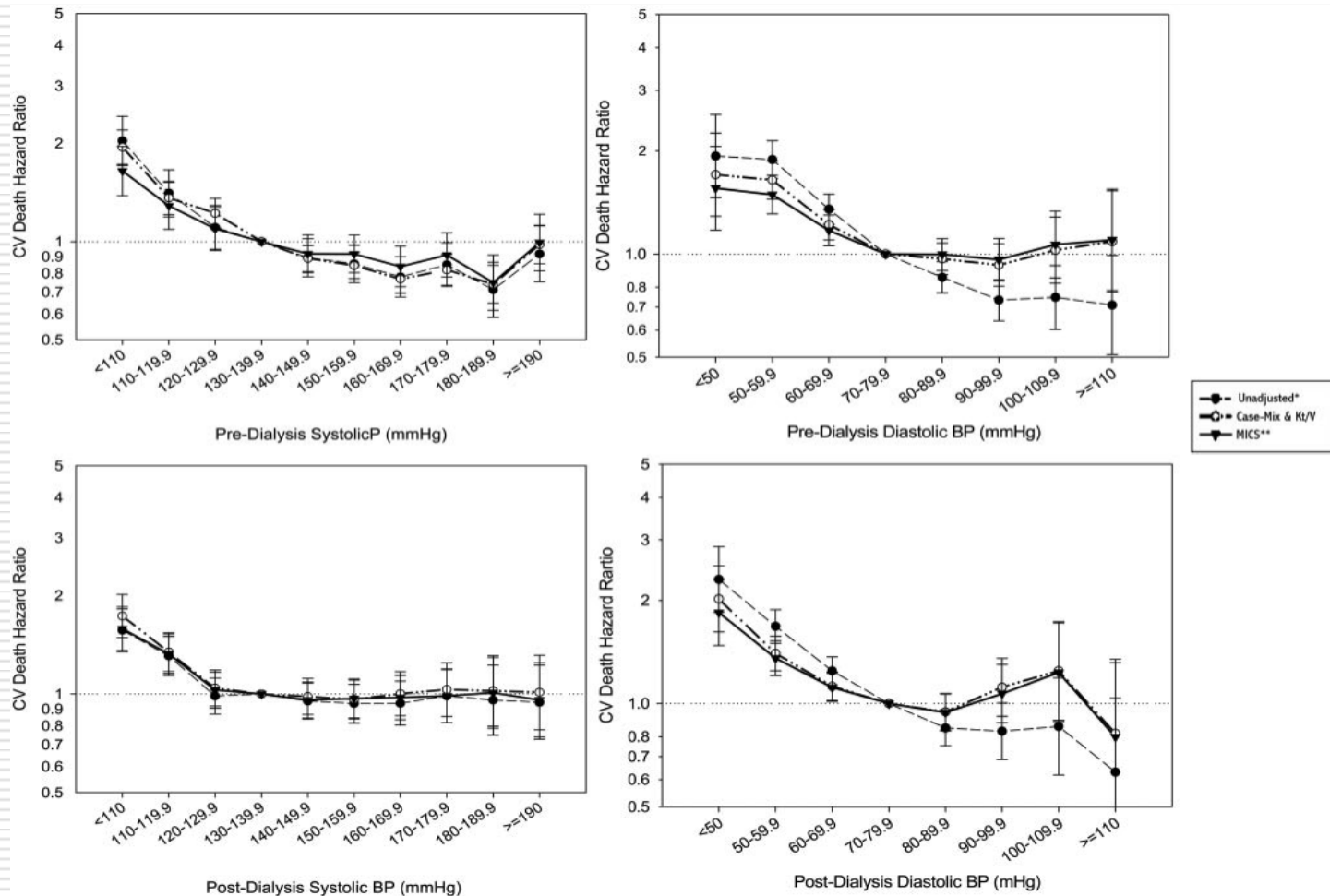
Prognostic value differs when BP measured in different conditions



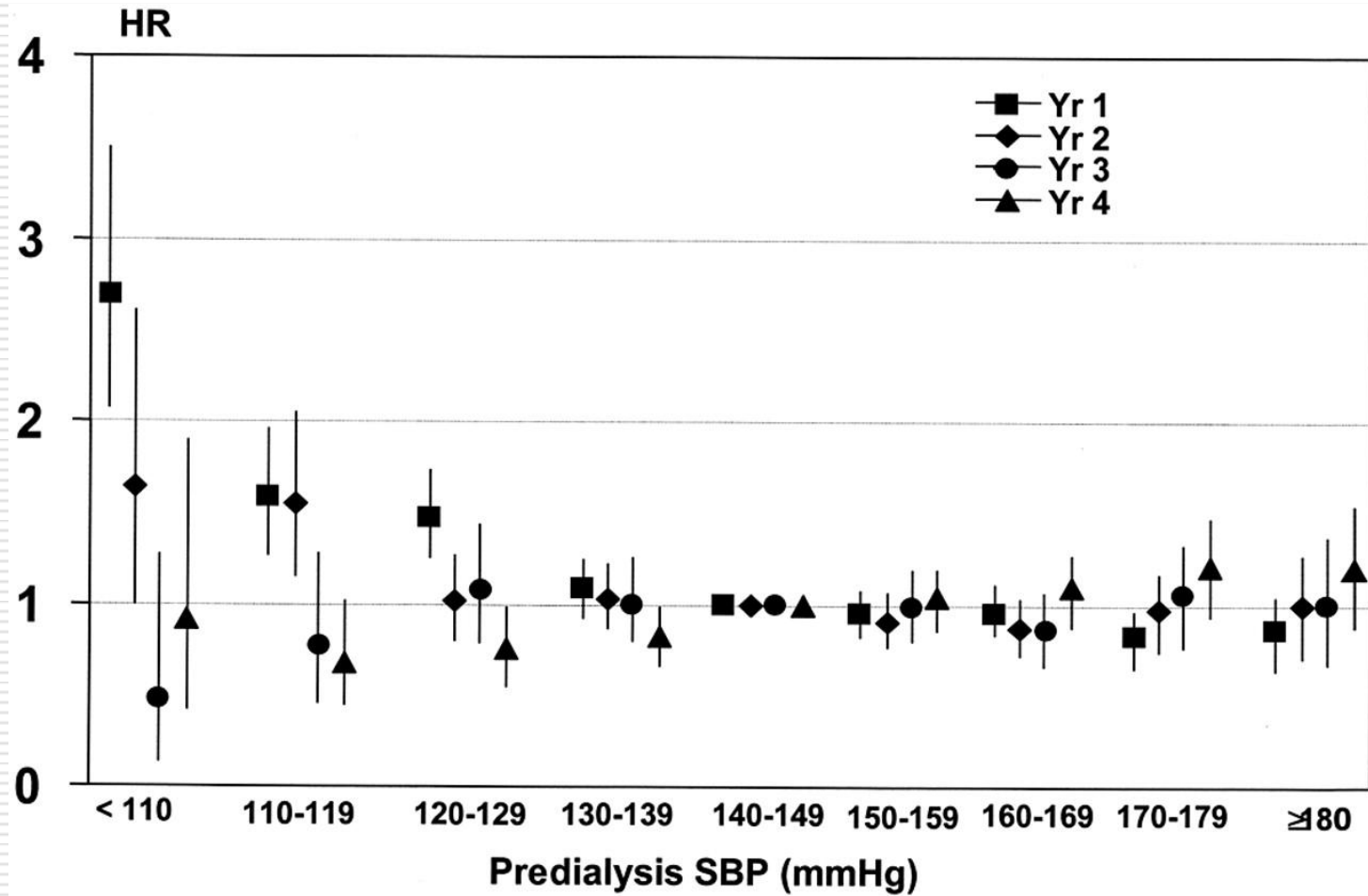
Unadjusted survival by baseline predialysis systolic BP



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

Time From Start of RRT	No. of Patients	Unadjusted Model		Fully Adjusted Model*			
		RH† (95% CI)	P	RH† (95% CI)	P	P for BP and TWL Status Interaction‡	P for BP and Diabetes Interaction‡
Systolic BP							
180 d-1 y	2,770	0.88 (0.80-0.96)	0.002	0.84 (0.78-0.92)	<0.001	0.04	0.3
Years 2-3	2,642	1.02 (0.98-1.06)	0.4	0.97 (0.93-1.01)	0.2	0.2	0.1
Years 4-5	1,729	1.06 (1.00-1.12)	0.05	0.98 (0.92-1.03)	0.4	0.003	0.02
Years 6+	911	1.14 (1.05-1.23)	0.001	1.10 (1.01-1.19)	0.03	0.5	0.03
Diastolic BP							
180 d-1 y	2,770	0.68 (0.59-0.79)	<0.001	0.78 (0.67-0.91)	0.001	0.3	0.6
Years 2-3	2,642	0.82 (0.76-0.88)	<0.001	0.94 (0.88-1.02)	0.1	0.3	0.2
Years 4-5	1,729	0.82 (0.74-0.91)	<0.001	0.96 (0.87-1.07)	0.5	0.04	0.1
Years 6+	911	0.89 (0.78-1.02)	0.1	0.97 (0.84-1.12)	0.6	0.4	0.1
Mean arterial pressure							
180 d-1 y	2,770	0.73 (0.64-0.84)	<0.001	0.77 (0.67-0.87)	<0.001	0.1	0.8
Years 2-3	2,642	0.91 (0.86-0.97)	0.004	0.95 (0.89-1.01)	0.1	0.2	0.1
Years 4-5	1,729	0.94 (0.86-1.03)	0.1	0.96 (0.88-1.05)	0.4	0.005	0.05
Years 6+	911	1.03 (0.92-1.17)	0.6	1.05 (0.93-1.20)	0.4	0.4	0.03
Pulse pressure							
180 d-1 y	2,770	1.00 (0.90-1.11)	0.9	0.85 (0.76-0.95)	0.003	0.1	0.2
Years 2-3	2,642	1.14 (1.08-1.19)	<0.001	0.98 (0.93-1.03)	0.4	0.3	0.4
Years 4-5	1,729	1.19 (1.12-1.27)	<0.001	0.98 (0.91-1.06)	0.6	0.03	0.1
Years 6+	911	1.29 (1.18-1.41)	<0.001	1.18 (1.06-1.31)	0.002	0.8	0.1

Advantages and disadvantages of antihypertensive treatment in CKD 5

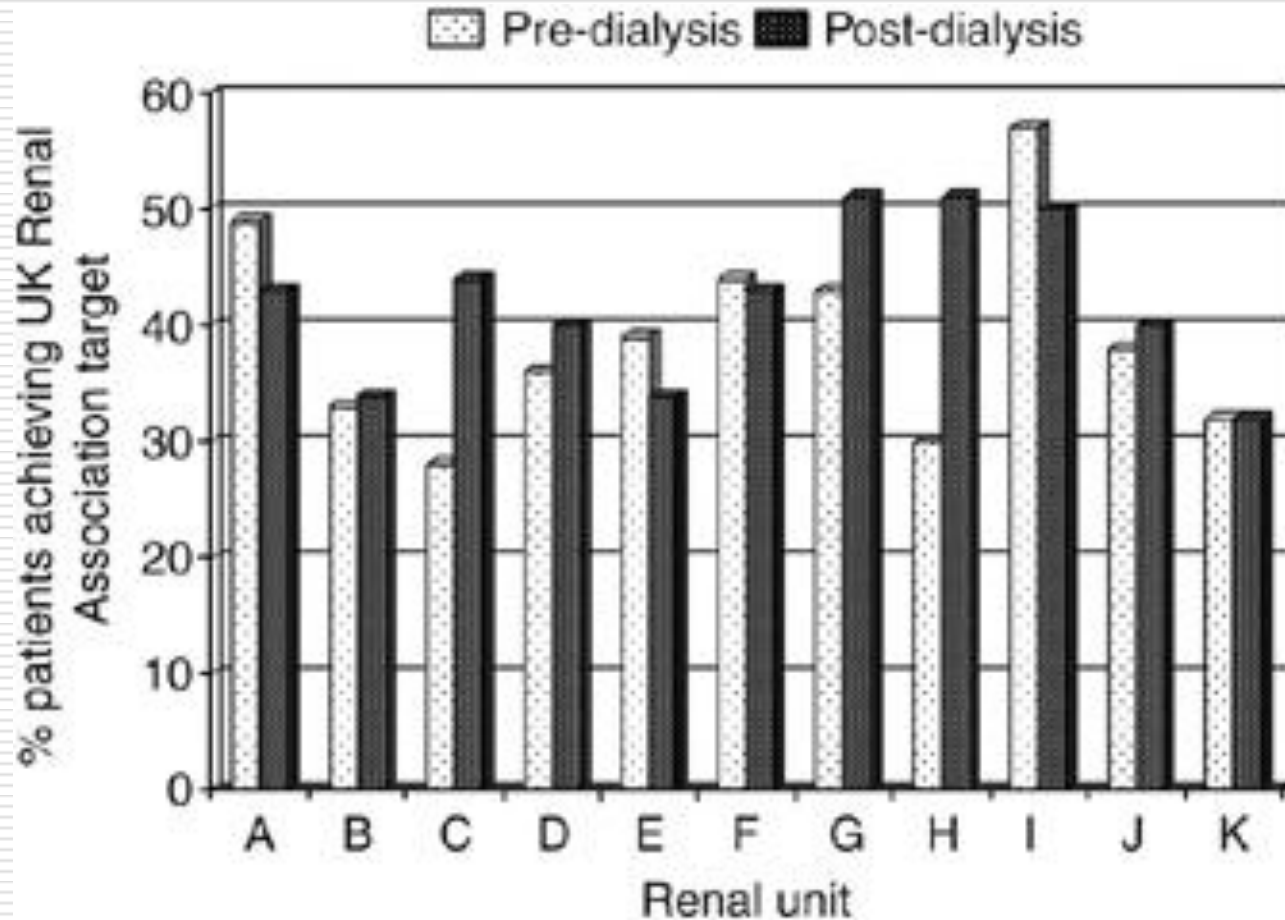
When to initiate Rx and Blood Pressure Goals

Which BP Values should be Targeted

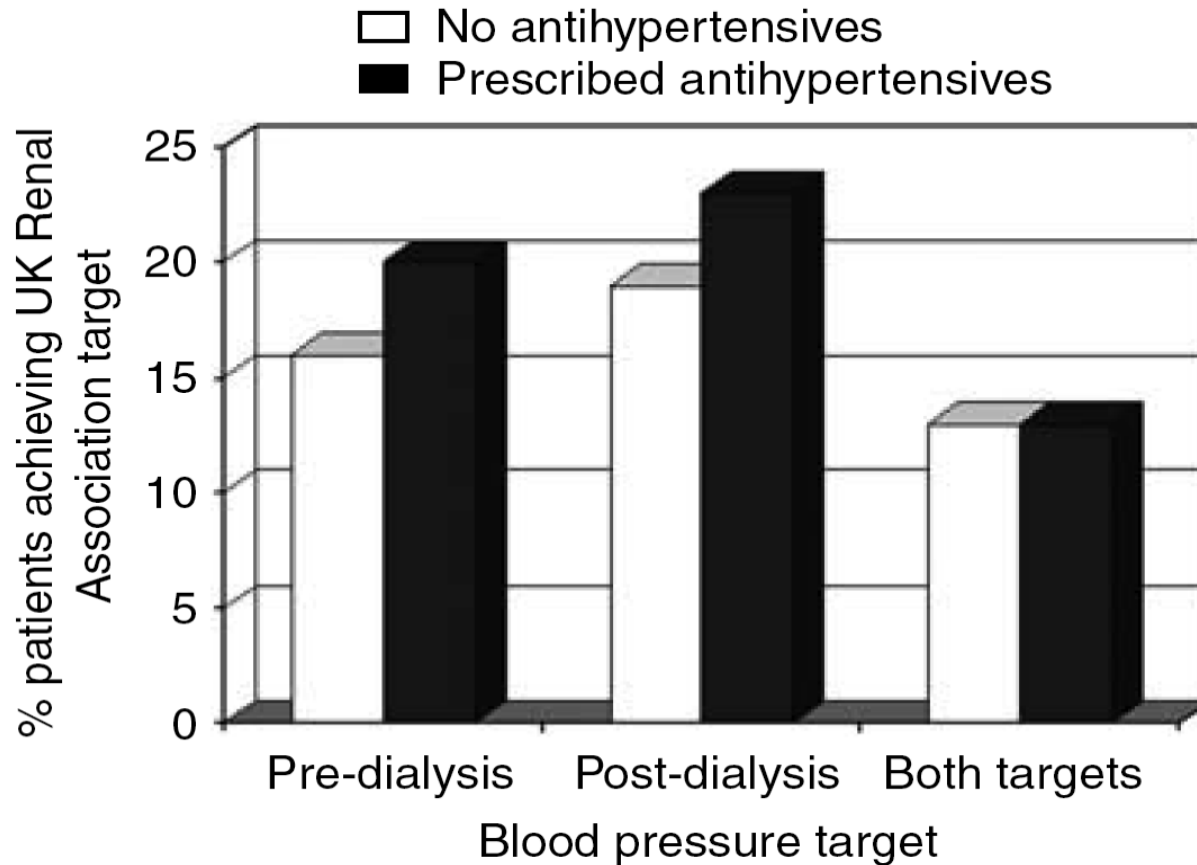
Antihypertensive Treatment in CKD 5

Dose of BP Lowering Drugs in Dyalysis

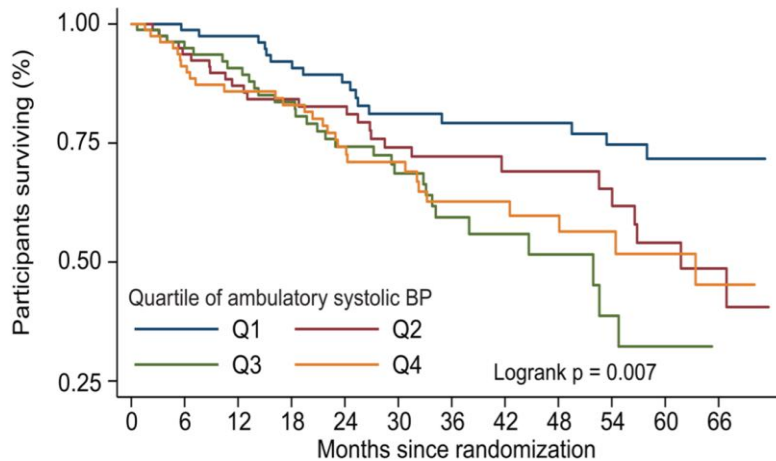
Patients achieving pre- and post-dialysis UK RA blood pressure targets (<140/90 or <130/80 mm Hg)



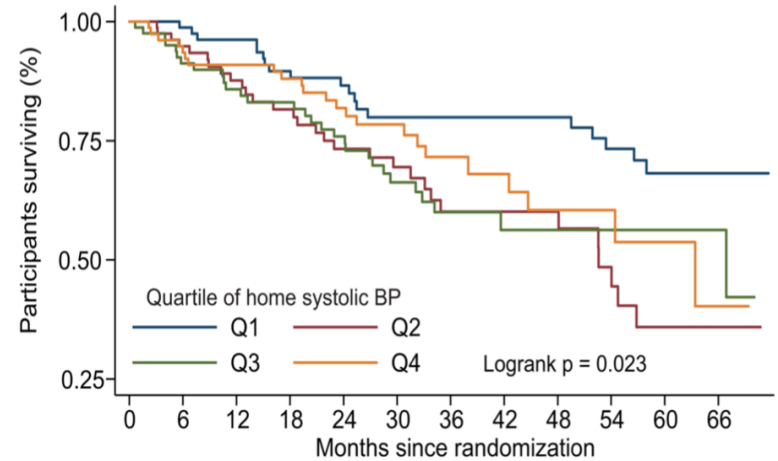
Control rates of pre- and post-HD hypertension by treatment



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

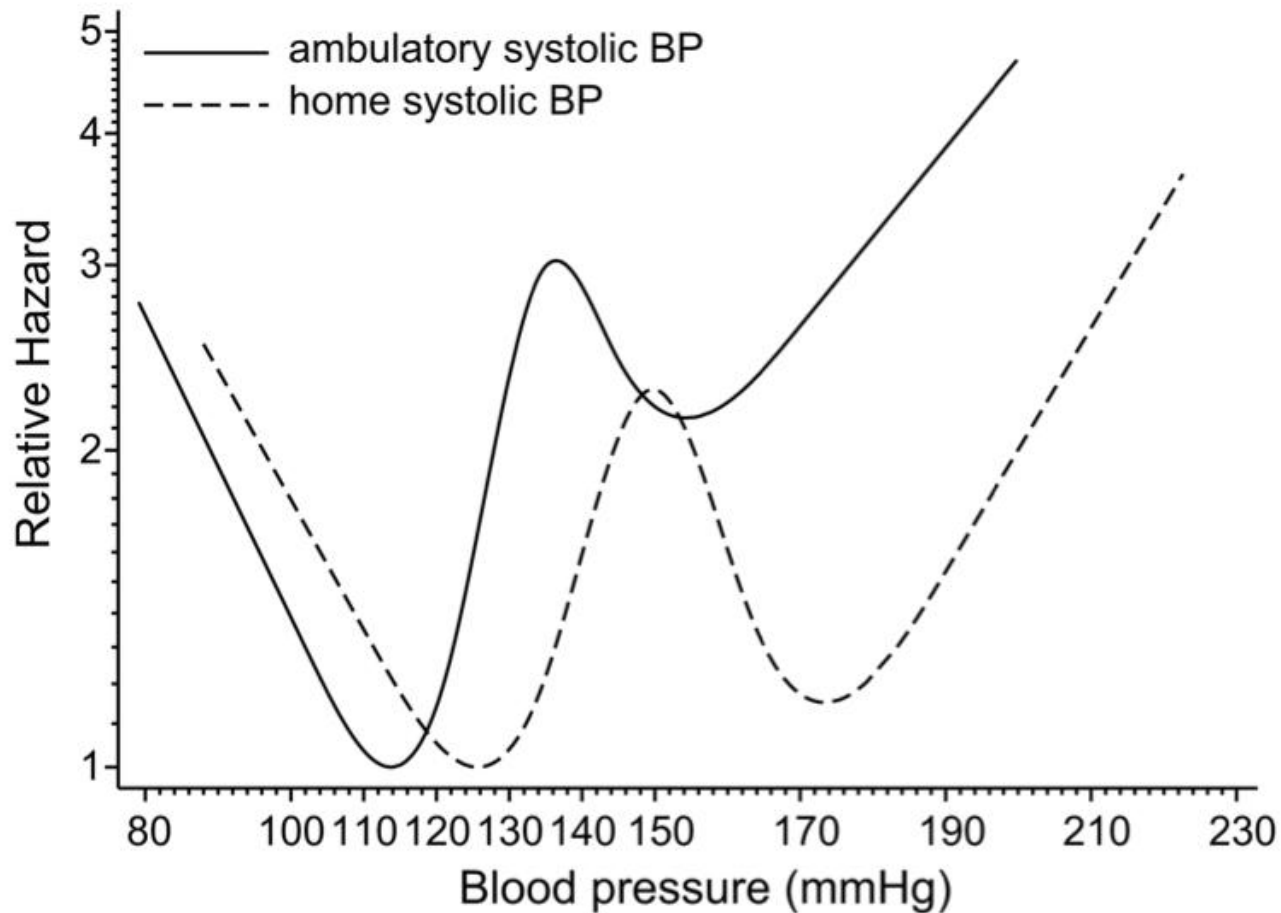


Number at risk	0	6	12	18	24	30	36	42	48	54	60	66
Quartile 1	82	78	74	67	54	44	40	36	35	33	16	12
Quartile 2	81	72	64	55	51	39	30	22	19	18	10	8
Quartile 3	82	72	64	56	45	36	20	13	12	6	2	0
Quartile 4	81	72	61	58	48	37	27	21	18	12	9	4



Number at risk	0	6	12	18	24	30	36	42	48	54	60	66
Quartile 1	81	78	73	64	53	45	42	38	37	33	18	15
Quartile 2	81	69	60	50	42	35	24	20	17	12	4	2
Quartile 3	81	72	63	59	51	36	25	14	13	13	9	6
Quartile 4	80	72	64	60	49	37	24	18	15	9	4	1

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



Advantages and disadvantages of antihypertensive treatment in CKD 5

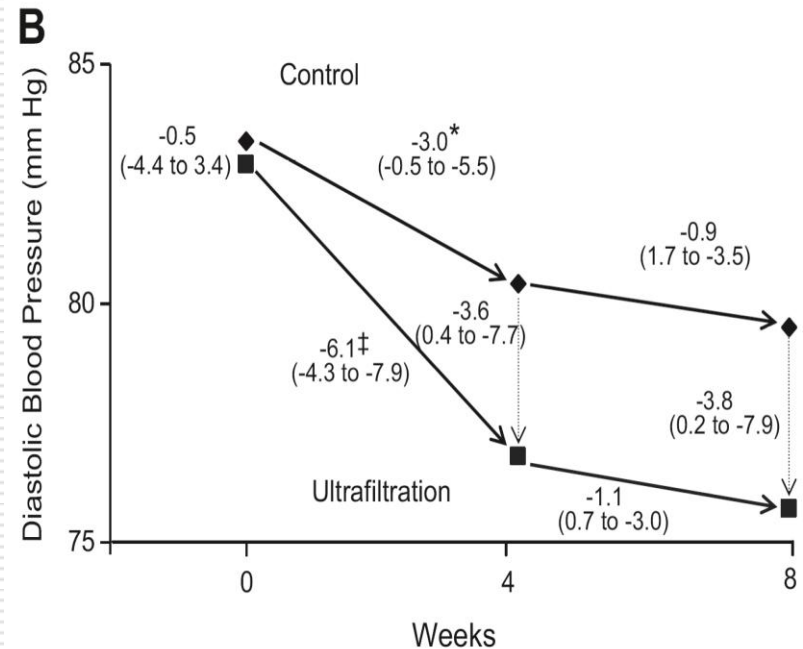
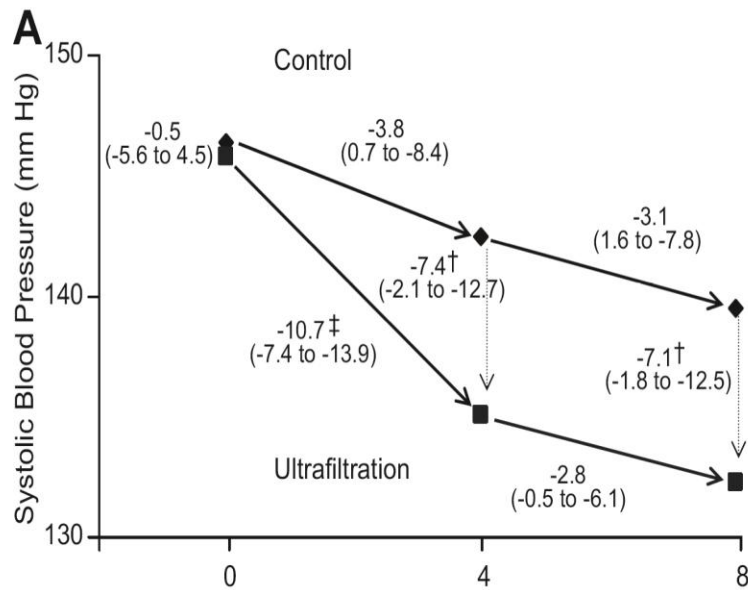
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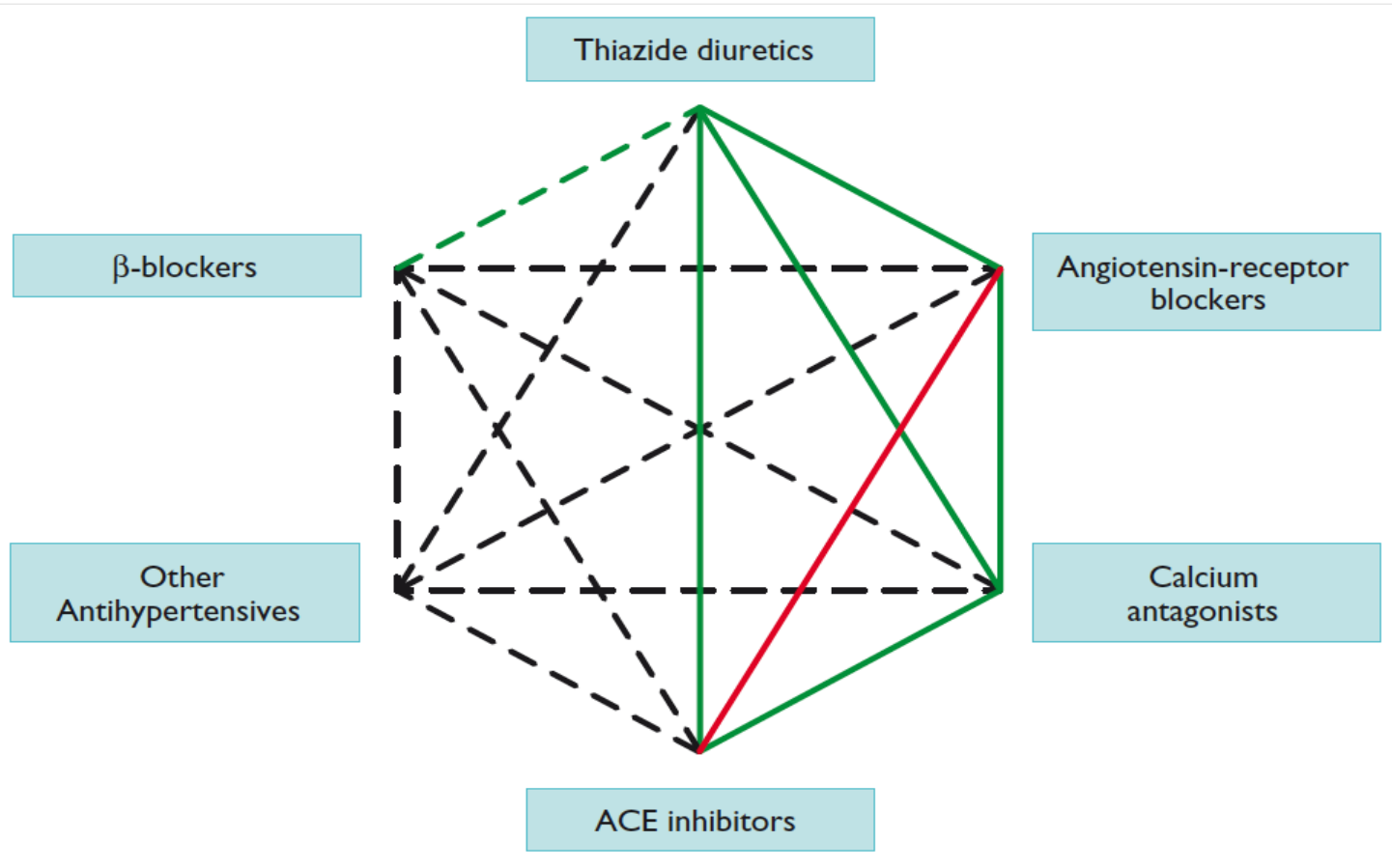
Antihypertensive Treatment in CKD 5

Dose of BP Lowering Drugs in Dyalisis

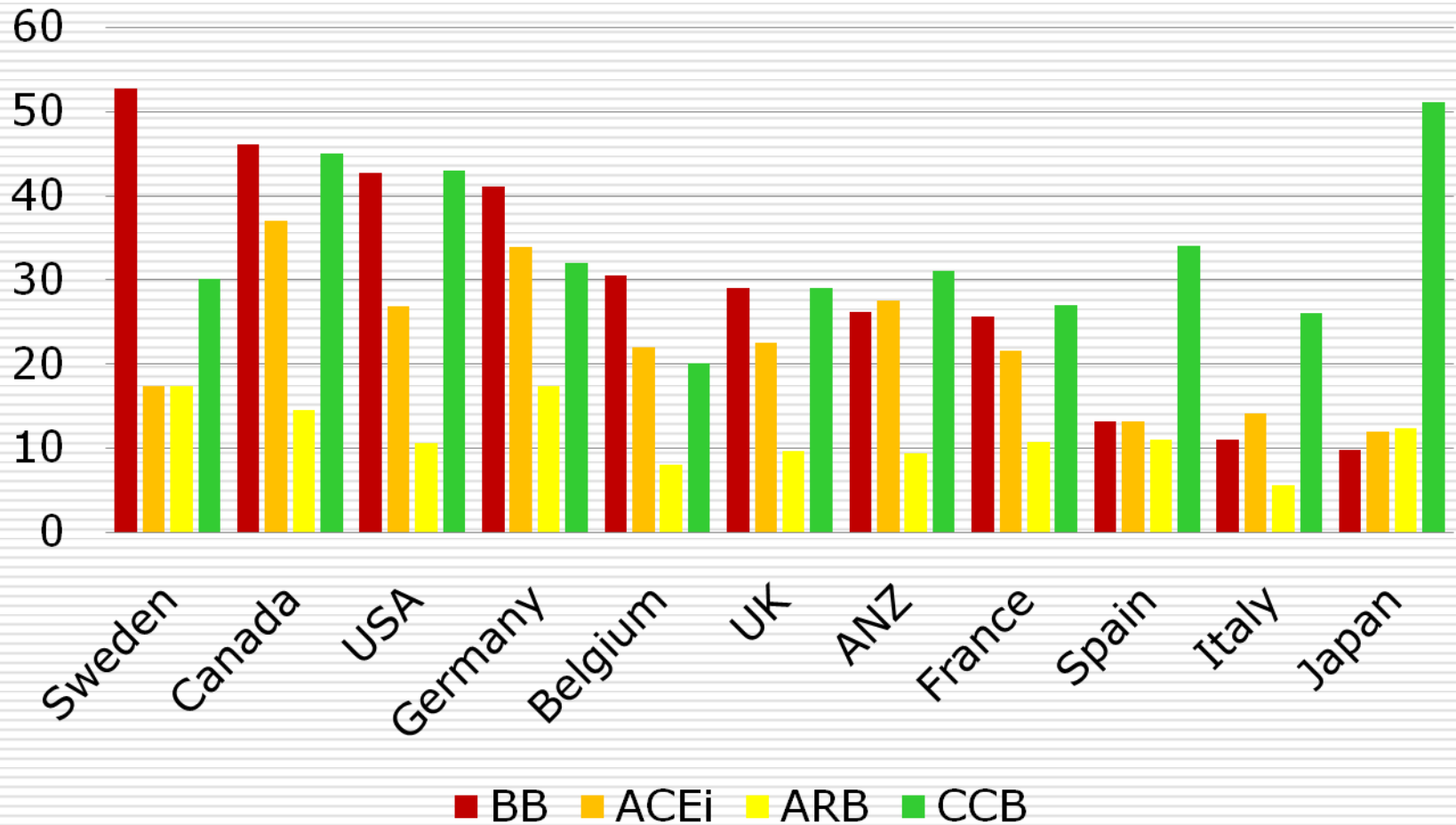
The effect of dry weight reduction on interdialytic ambulatory BP in hypertensive hemodialysis pts.



ESH-ESC Guidelines 2013: Antihypertensive drug classes

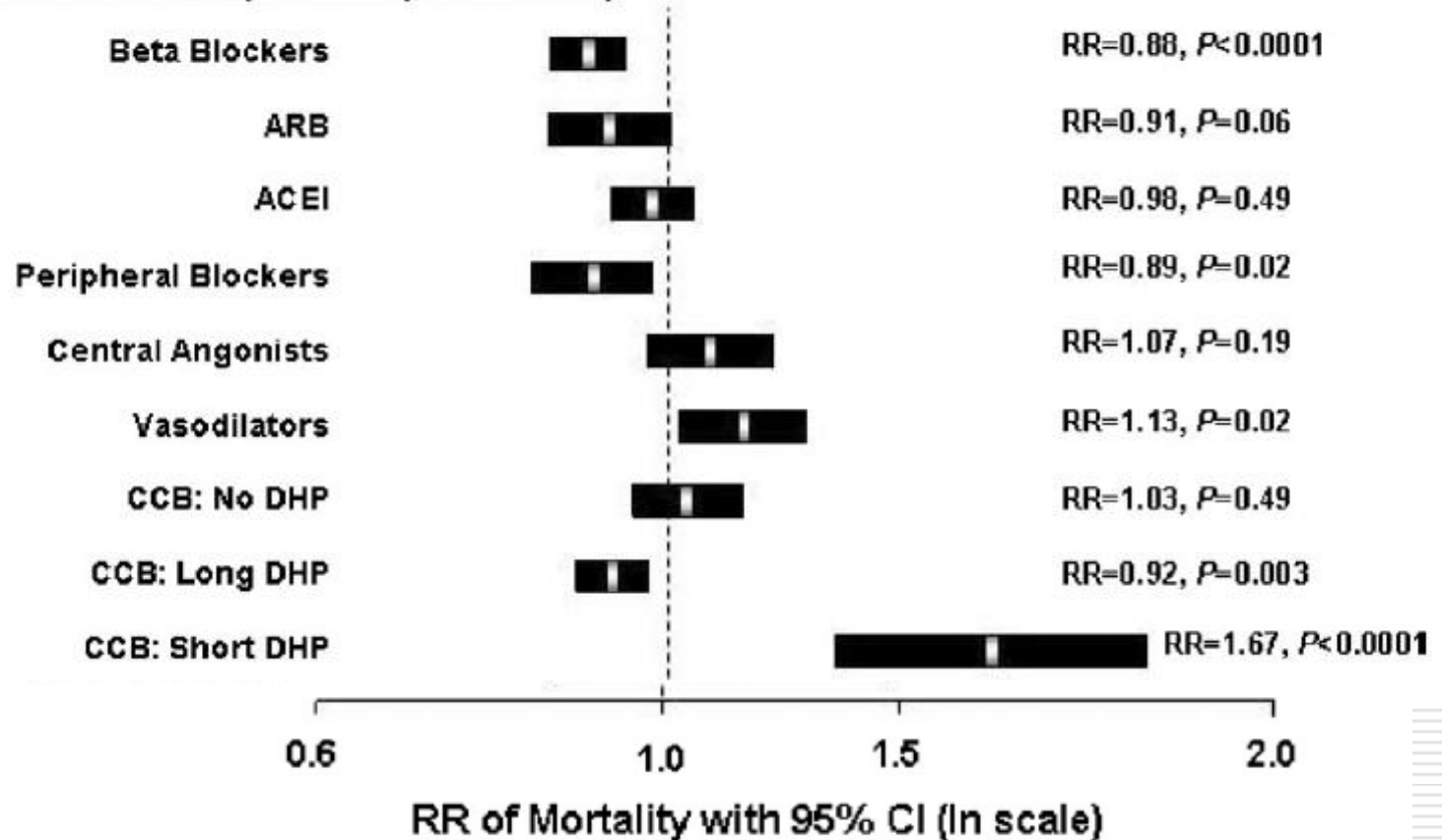


Use of antihypertensive classes by country in CKD 5D (DOPPS I-II)



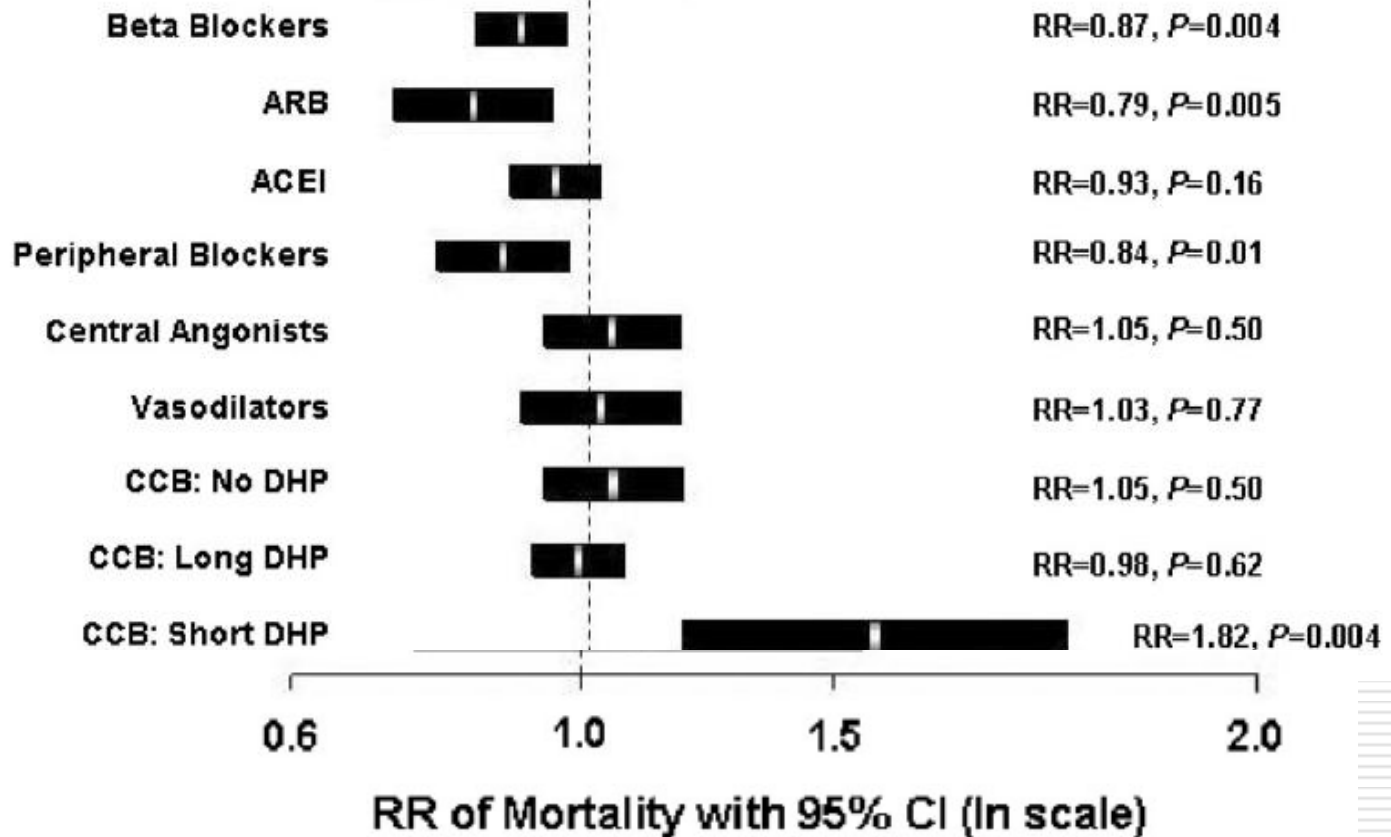
Antihypertensive classes and all-cause mortality in CKD 5D (DOPPS I-II)

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



Antihypertensive drug classes and CV mortality in CKD 5D (DPPDS I-II)

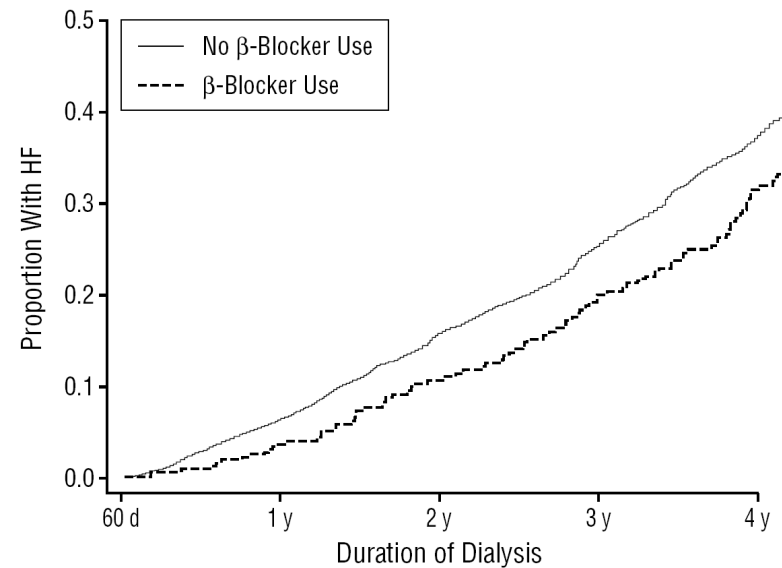
Analysis of Patient-Level Prescription Data (AHA vs. none):



Observational studies of beta blockers

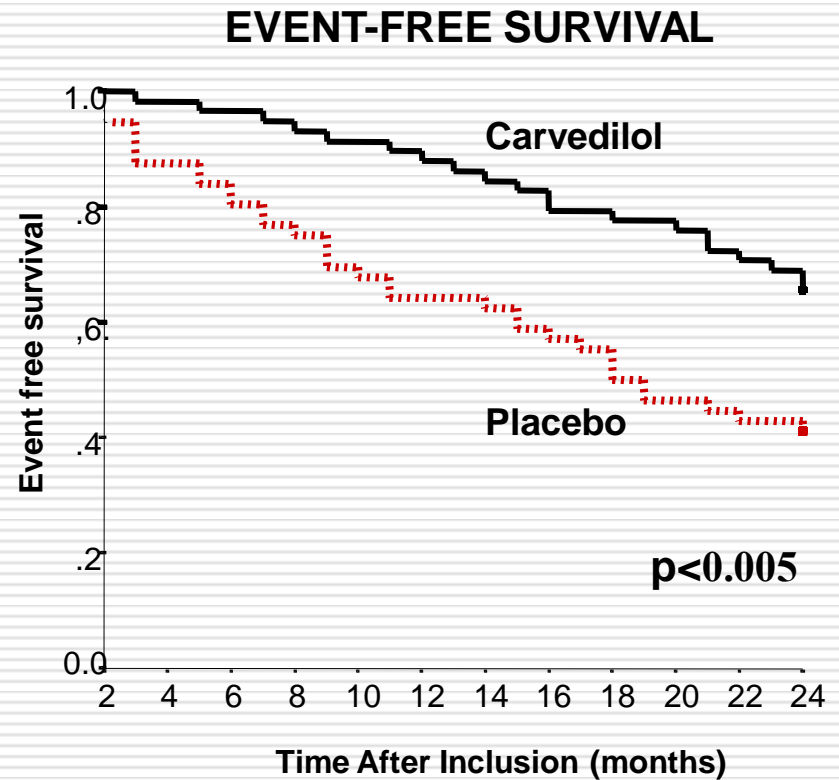
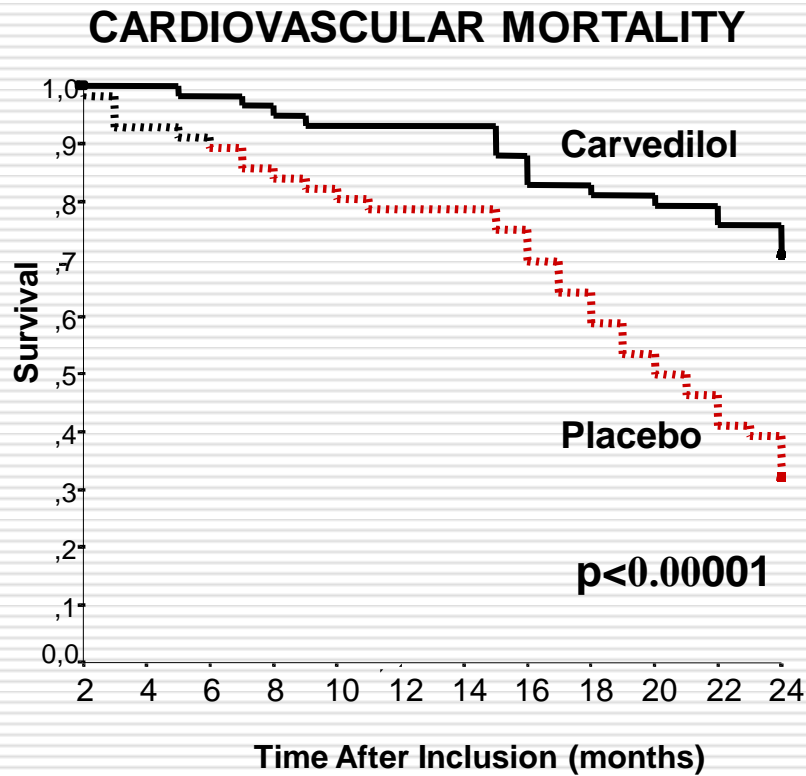
(Analyses of the Dialysis Morbidity and Mortality Studies DMMS conducted by the US Renal Data System)

- 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.**



No. at Risk	60 d	1 y	2 y	3 y	4 y
No β -Blocker Use	1280	1109	926	735	579
β -Blocker Use	298	274	238	201	156

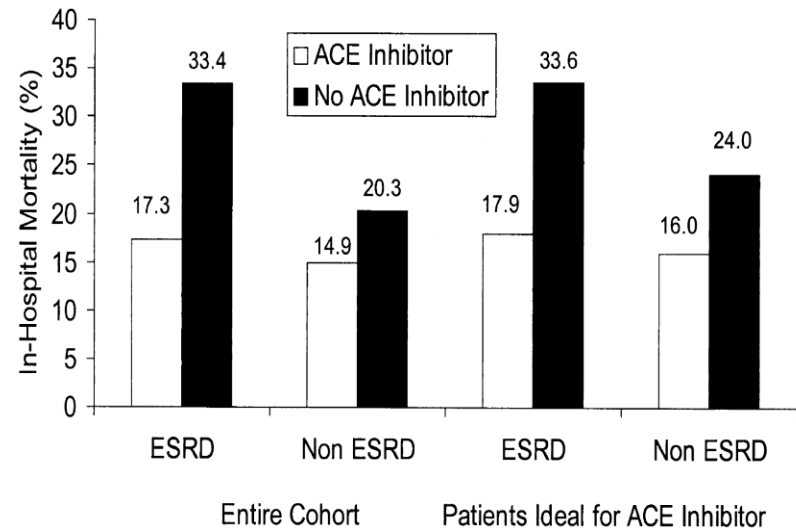
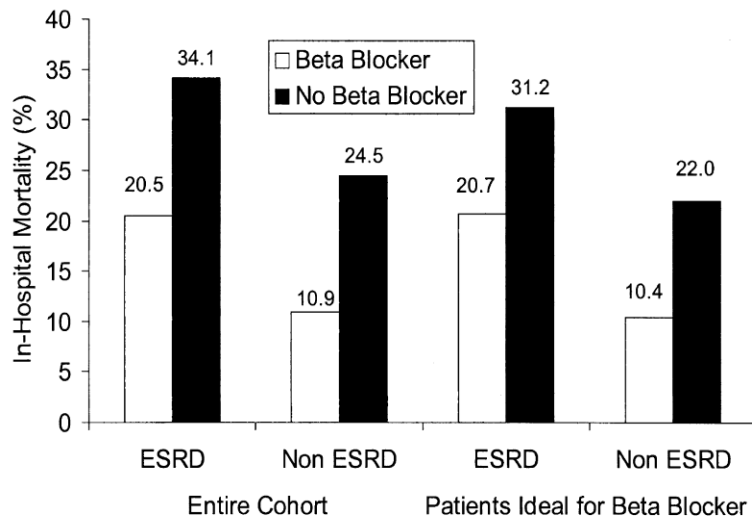
Carvedilol in patients on hemodialysis CV mortality and all cause hospitalization



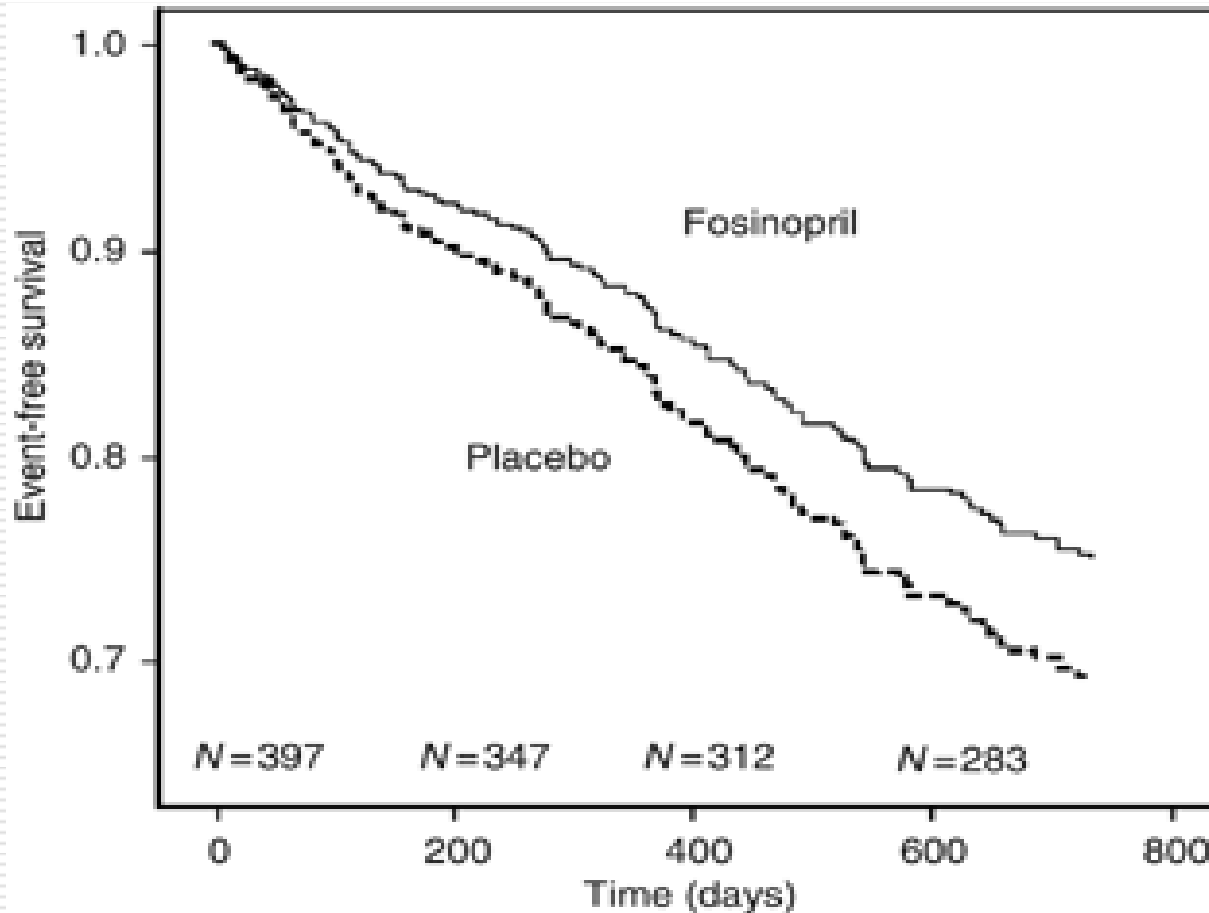
ACE inhibitors after MI in patients on HD

ESRD Database + Cooperative CV Project Database

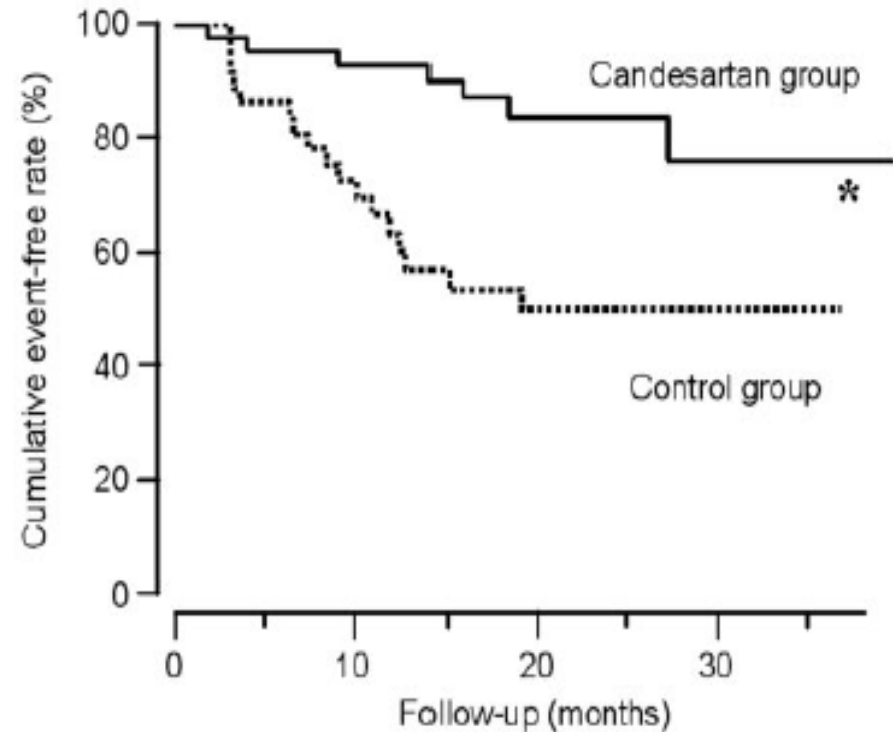
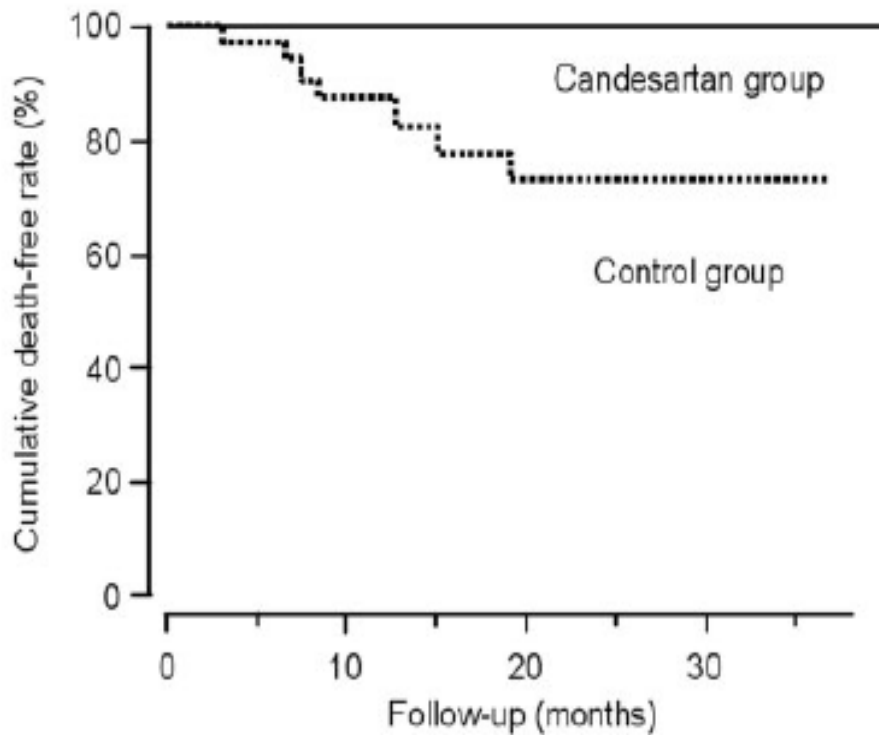
Association of medication classes with 30-day mortality after Myocardial infarction in pts with ESRD



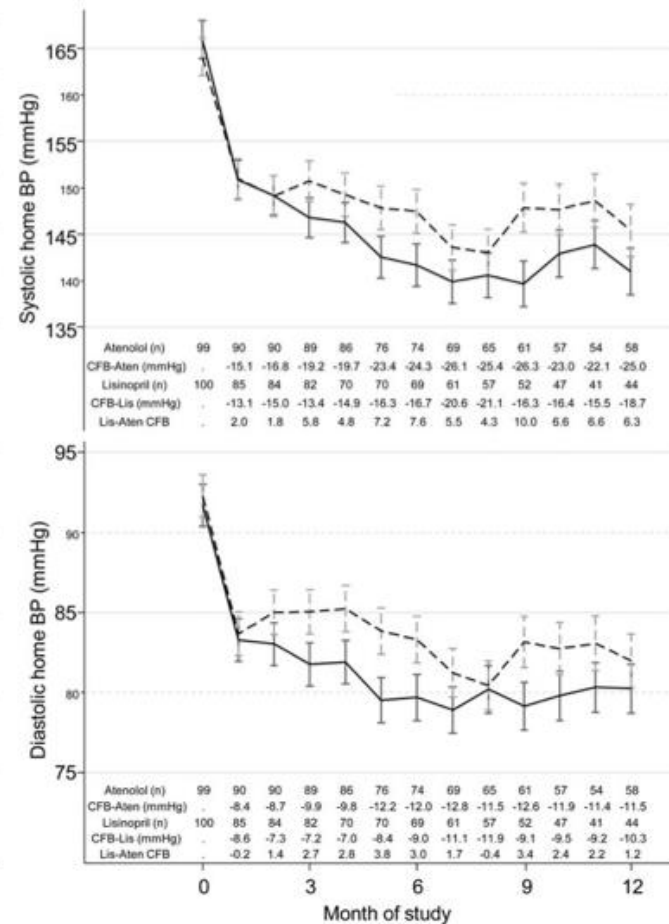
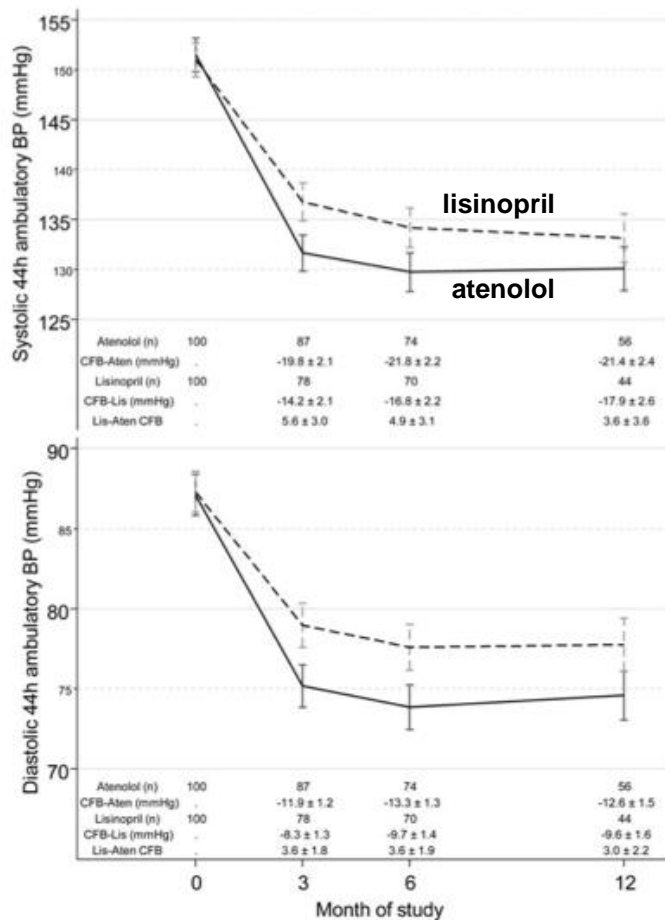
Fosinopril in Dialysis (FOSIDIAL) Study



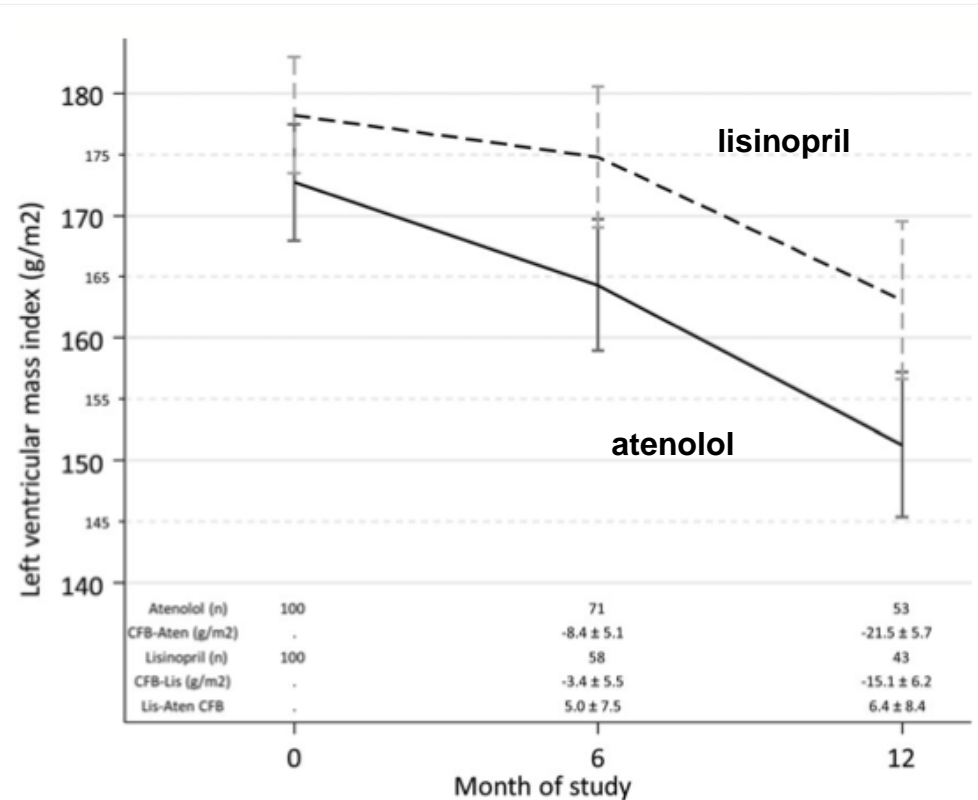
ARBs (candesartan) on CV Events and mortality in hemodialysis patients



Atenolol vs lisinopril in hemodialysis: Impact in LVH and CV events



Atenolol vs lisinopril in hemodialysis: Impact in LVH and CV events



Atenolol > Lisinopril

CV events

2.36 (p=0.001)

CV events (combined)

2.29 (p=0.021)

Heart failure

3.13 (p=0.021)

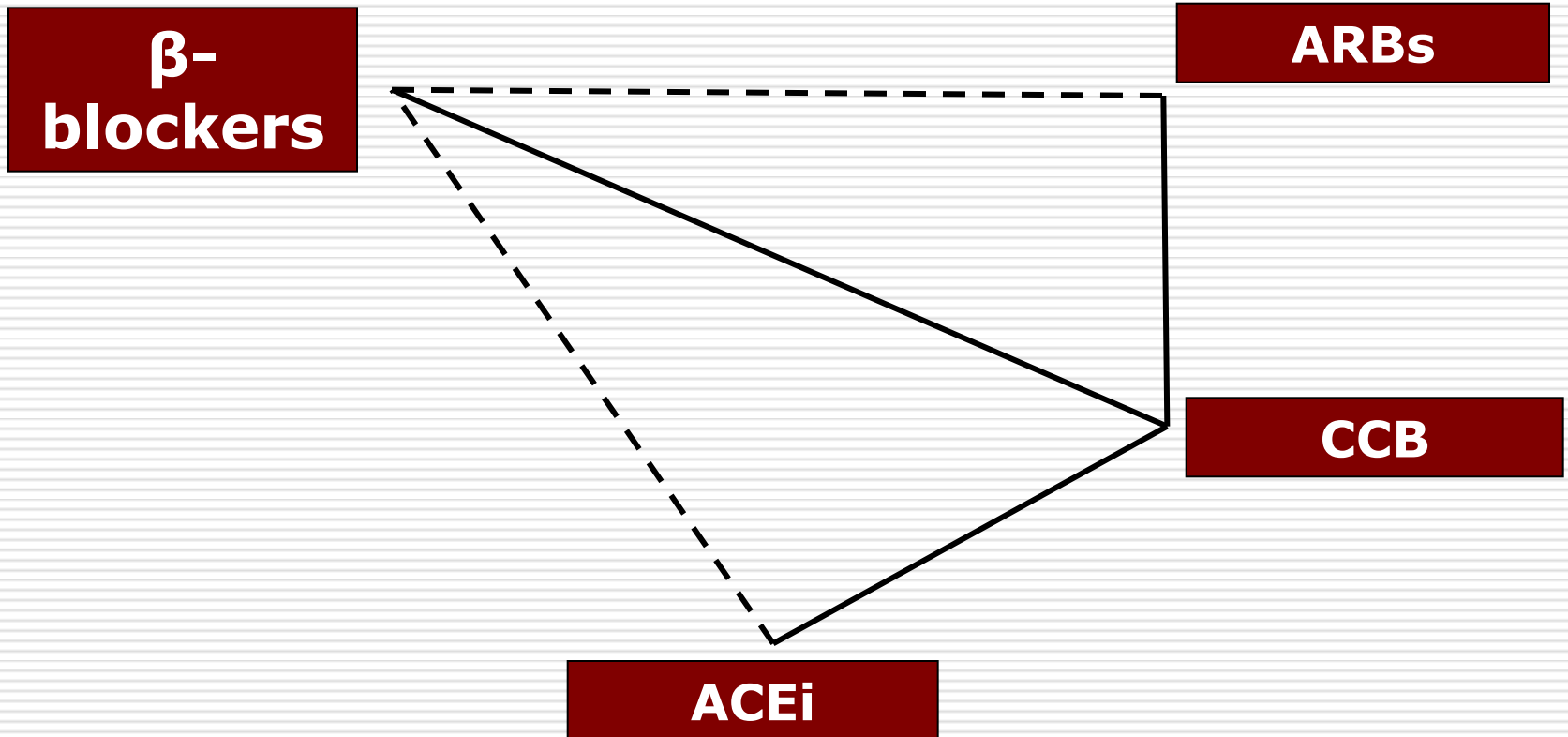
Hospitalization

1.61 (p=0.002)

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 Dialysis

Antihypertensive drugs in CKD 5D under dialysis



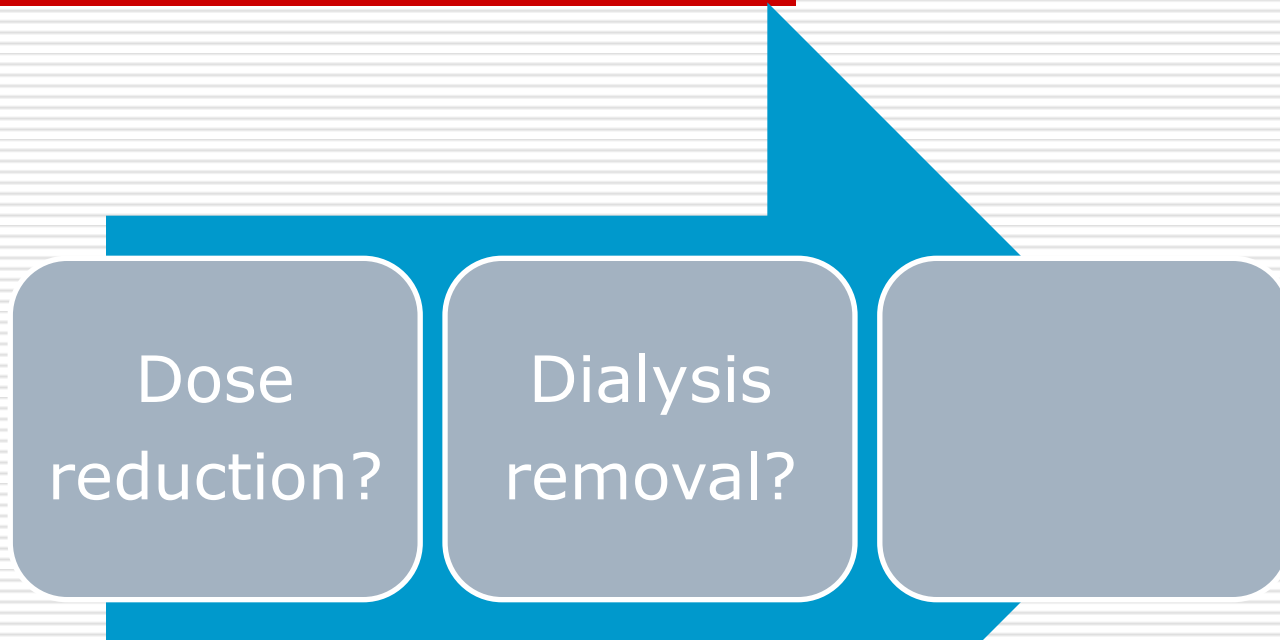
Dose
reduction?

**Drug
pharmacokinetics**

Dose correction due to metabolism of the drug

ACEi	β -blockers	Vasodilators	Central agents	ARBs	CCBs	α -blockers
	bisoprolol esmolol labetalol metoprolol pindolol timolol	diazoxide minoxidil nitroprusiate	clonidine guanabenz	candesartan eprosartan irbesartan losartan olmesartan telmisartan valsartan	all dihydropirydin veramapil diltiazem	doxazosin prazosin terazosin
Full dose						
fosinopril benazepril	acebutolol betaxolol					
25% dose reduction						
	atenolol carvedilol	hidralazine	guanethidine methyldopa			
50% dose reduction						
captopril enalapril lisinopril perindopril quinapril ramipril trandolapril	nadolol sotalol					
50-75% dose reduction						

Antihypertensive drugs in CKD 5D under dialysis

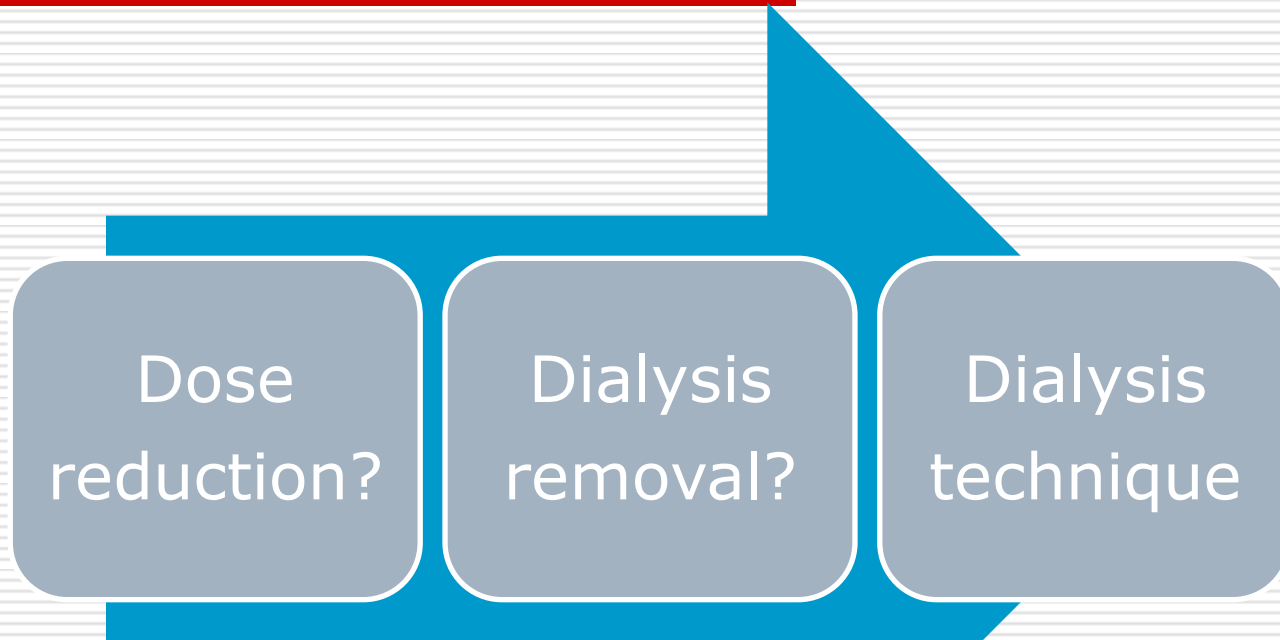


Molecular weight
Protein binding
Water solubility
Intercompartmental exchange

Dose correction due to permeability

ACEi	β -blockers	Vasodilators	Central agents	ARBs	CCBs	α -blockers
fosinopril benazepril	bisoprolol esmolol labetalol metoprolol pindolol timolol acebutolol betaxolol	diazoxide minoxidil nitroprusiate	clonidine guanabenz guanethidine	candesartan eprosartan irbesartan losartan olmesartan telmisartan valsartan	all dihydropyridin veramapil diltiazem	doxazosin prazosin terazosin
						No removal
quinapril ramipril trandolapril						30% removal
captopril enalapril lisinopril perindopril	atenolol carvedilol nadolol sotalol	hidralazine	methyldopa			
						50% removal

Antihypertensive drugs in CKD 5D under dialysis



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
-