

# Blood Pressure Measurement, Targets, and Pharmacologic Management

KDIGO Controversy Conference  
Lisbon, 2019

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# Conflict of Interest

- Boehringer-Ingelheim (consultant)
- NIH (awardee including SPRINT)
- KDIGO (co-chair, BP in CKD)
- UptoDate (contributor)

# Objectives of This Presentation

- Unsettled or controversial topics
- Not comprehensive literature review
- Focus on BP instead of fluid volume
- HD and PD

# What Are Controversial in BP Management in Maintenance Dialysis Patients?

Almost everything

Yet, we all measure BP  
in dialysis patients

# KDIGO Controversy Conference in New York in March, 2009

- What is the optimal BP treatment target in relation to end-organ damage and outcomes?  
(AKC: Requires large RCT)
- How should anti-hypertensive drugs be used?  
(AKC: Requires large RCT)
- What non-pharmacological therapies can be considered in achieving BP targets?

# BP Measurements

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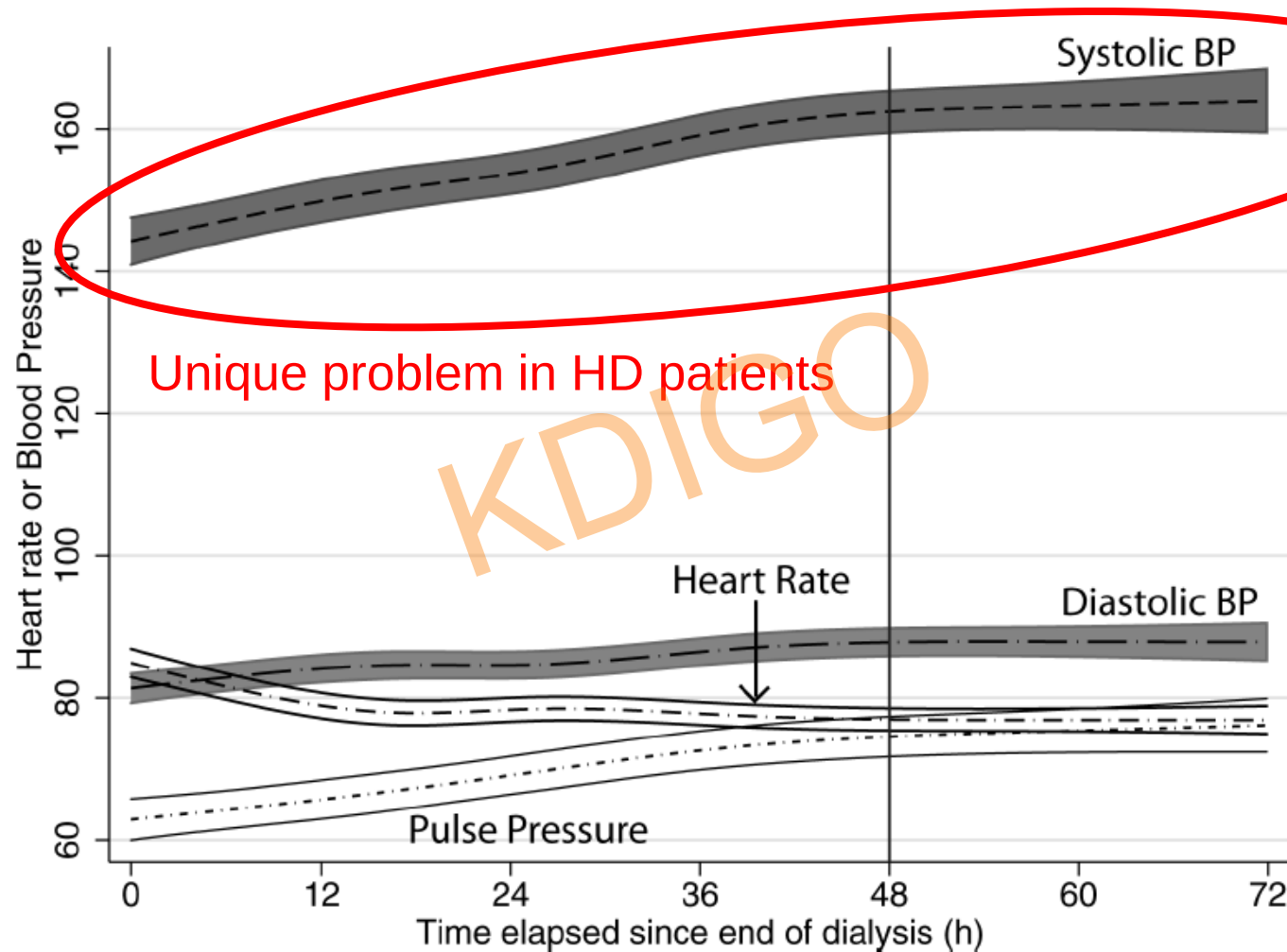
# BP Measurements in Non-Dialysis Patients

- Equipment (manual vs. automated)
- Location (office vs. home)
- Preparations (abstinence from stimulants, rest, body position, ambient temperature)
- Number of readings (random, diurnal, nocturnal dip, 24-hr)
- Reasonable standardizations

## Additional considerations in dialysis patients

- Fluctuations in fluid status (HD > PD)
- Vascular access
- Convenience of geographical location
- Withholding anti-hypertensive medications pre-HD

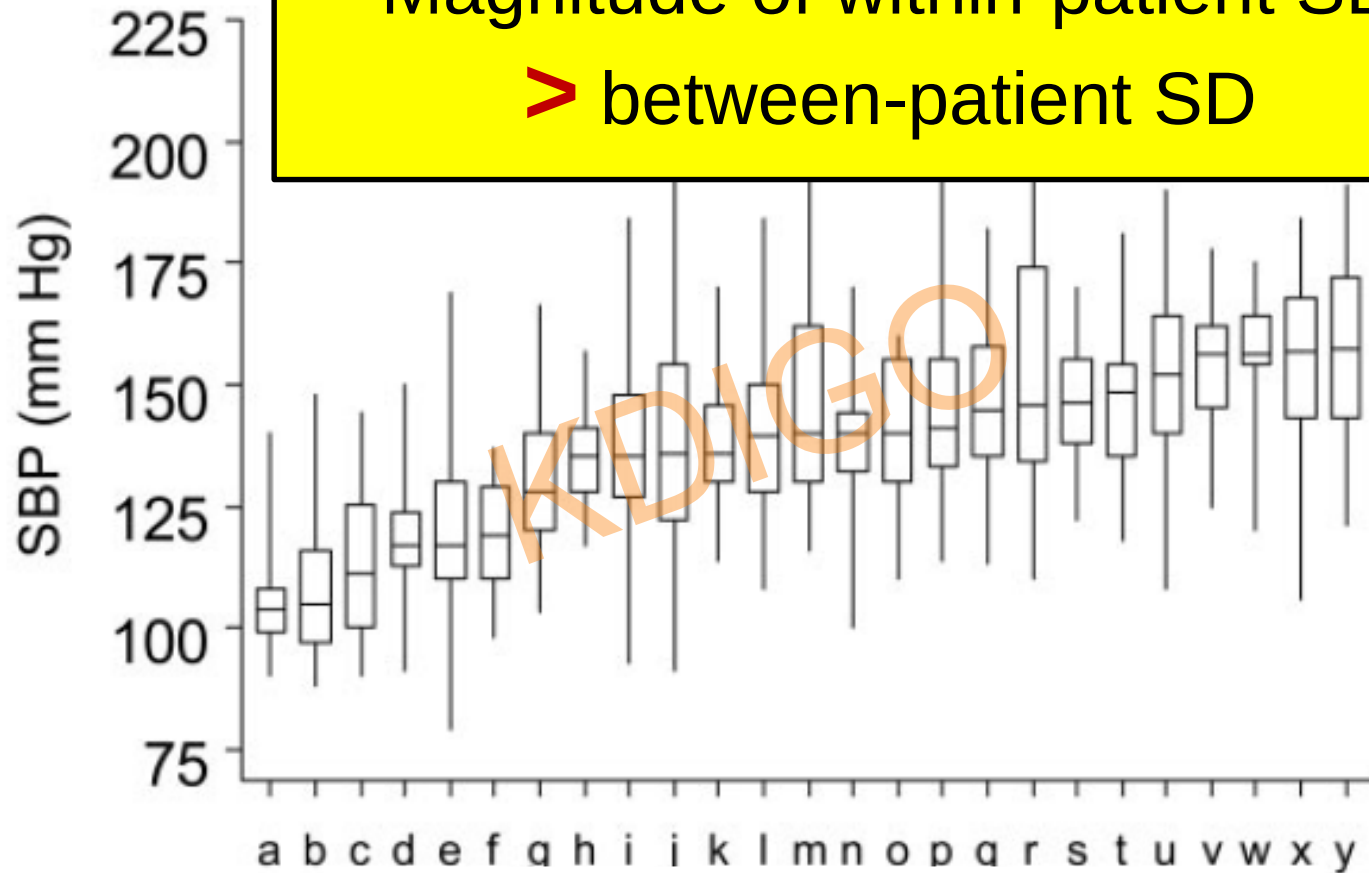
# Increase in Inter-dialytic BP



Unique problem in HD patients

# High Variability in Pre-HD SBP

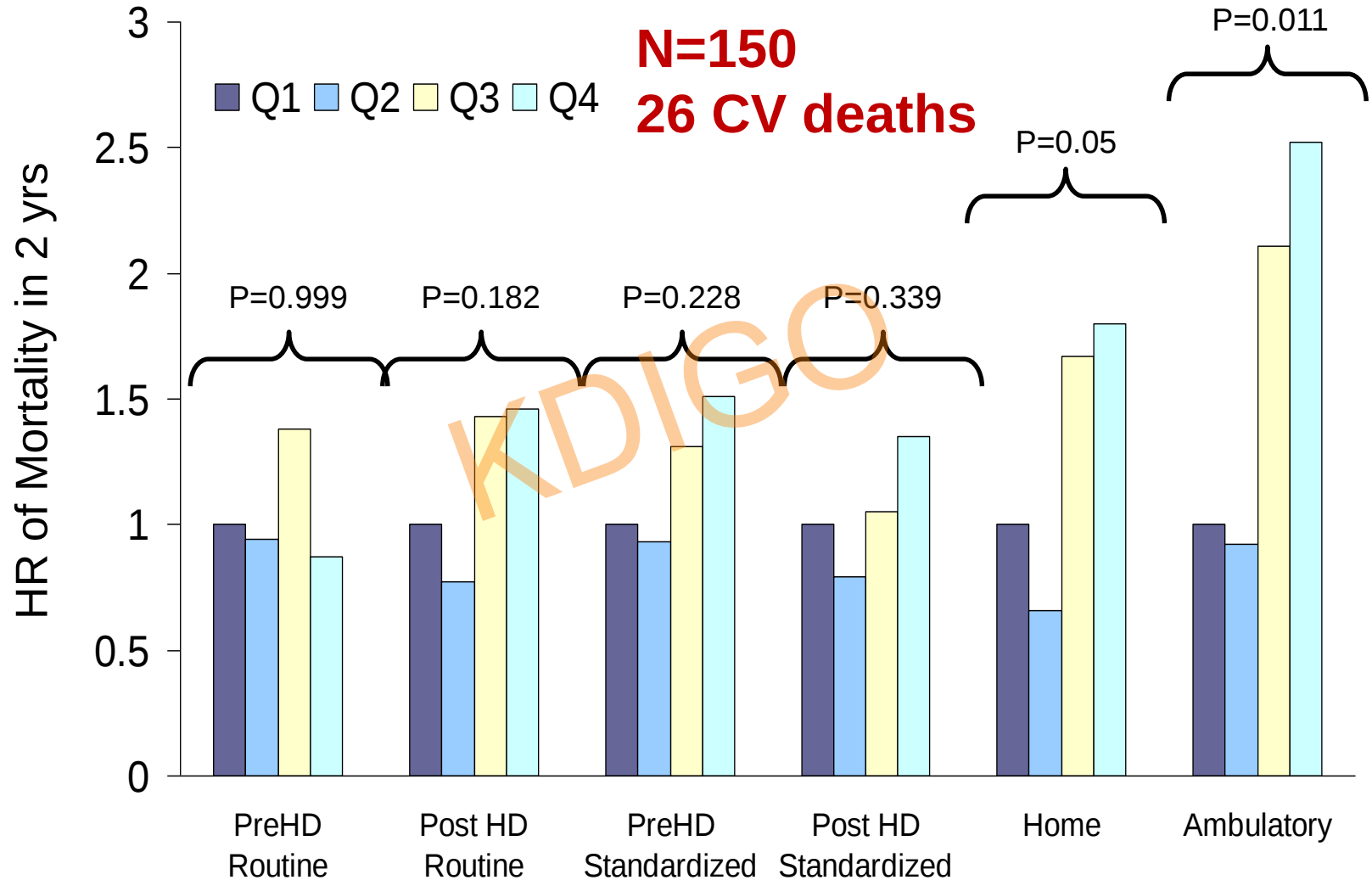
Magnitude of within-patient SD  
> between-patient SD



25 Random HD Patient ID

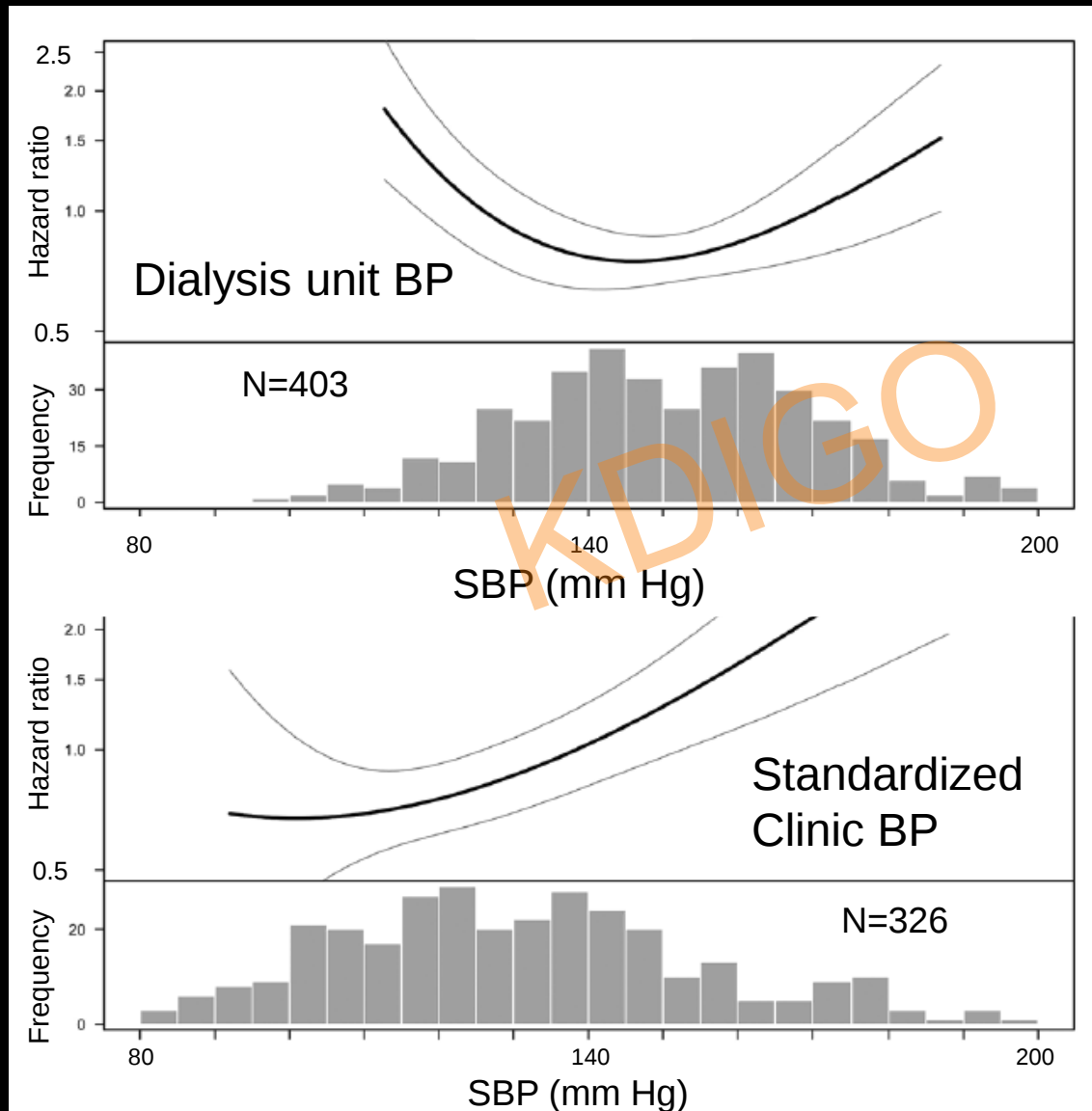
# Prediction of Mortality

## Using Various BP Measurements in HD Patients



# Pre-HD vs. Inter-dialytic Clinic SBP

## Association with Mortality in HD Patients



- CRIC Study

HR 1.26 [1.14-1.40]  
per 10 mm Hg increase

# What Do We Need?

- “Accuracy”
  - What is gold standard?
  - Is it important?
- “Reliability” (reproducibility)
- Association of various BP measurement methods with various clinical outcomes
- Large sample sizes

# Fuzzy Terms in Dialysis Patients

- Prevalence of hypertension (definition?)
- Optimization of BP (and fluid status) (target?)
- Better control of BP (target?)

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# Definition of HTN in HD Patients

- Normative in general population?
- Normative in dialysis population?
- Prognosticative?
- Benefits from BP lowering?

## Harm of “low” BP

- Impaired intradialytic and interdialytic organ perfusion
- Special consideration – loss of residual kidney function

BP Target

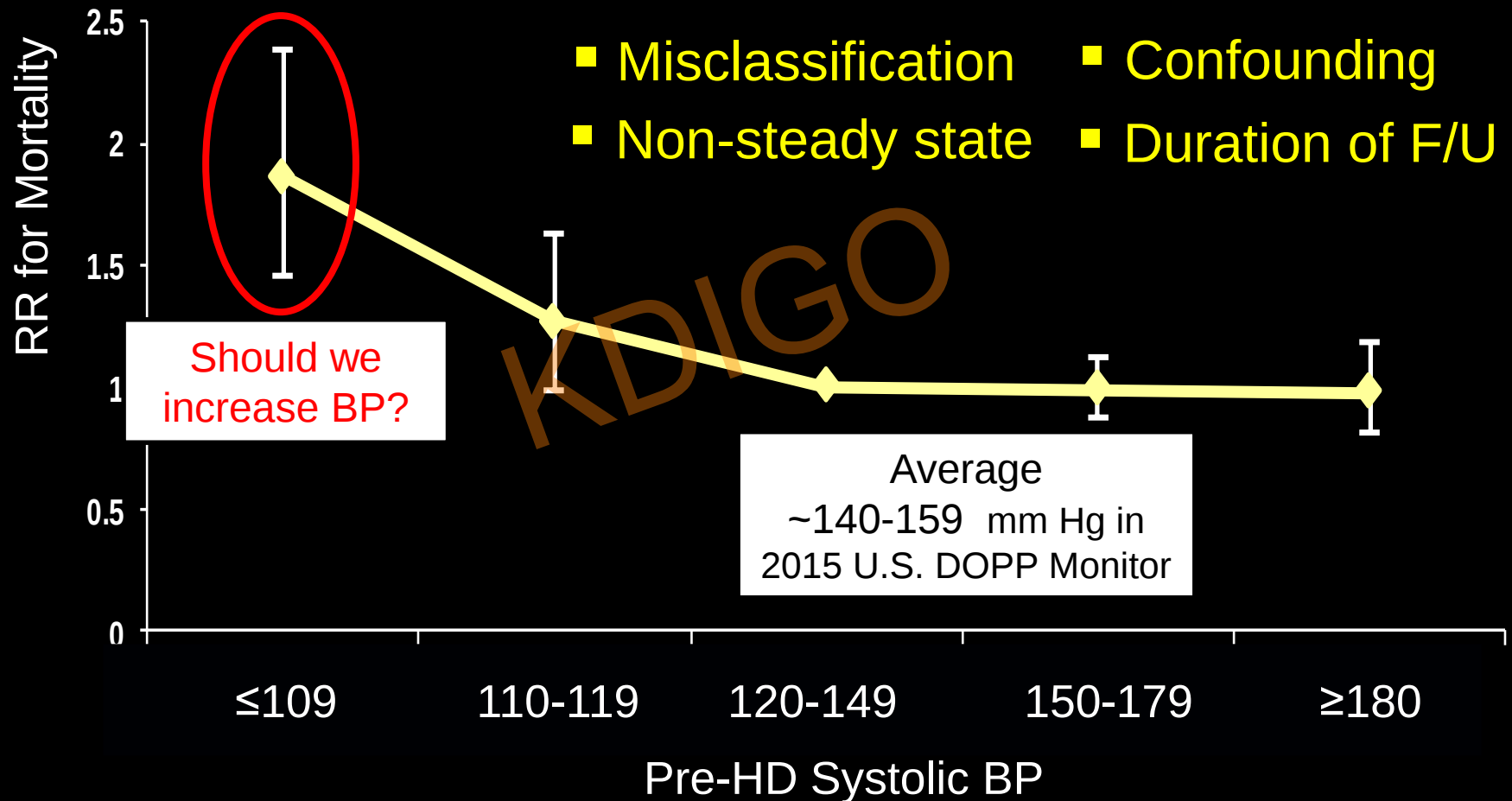
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## 2005 K/DOQI Guideline for CVD in Dialysis

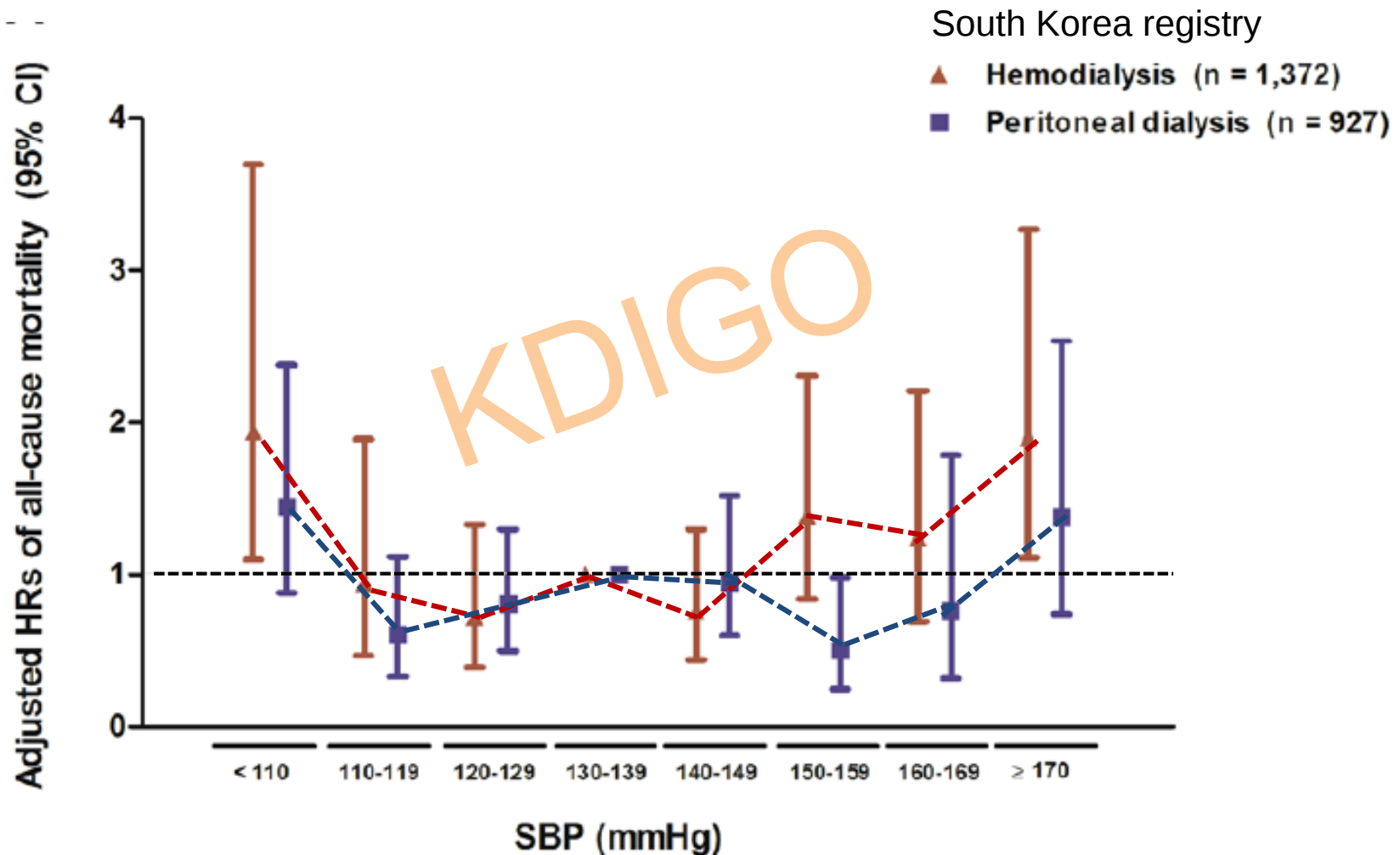
- 12.2. Predialysis and postdialysis blood pressure goals should be  $<140/90$  mmHg and  $<130/80$  mmHg, respectively. (C)

# Association of Pre-HD SBP with Mortality in HD Patients

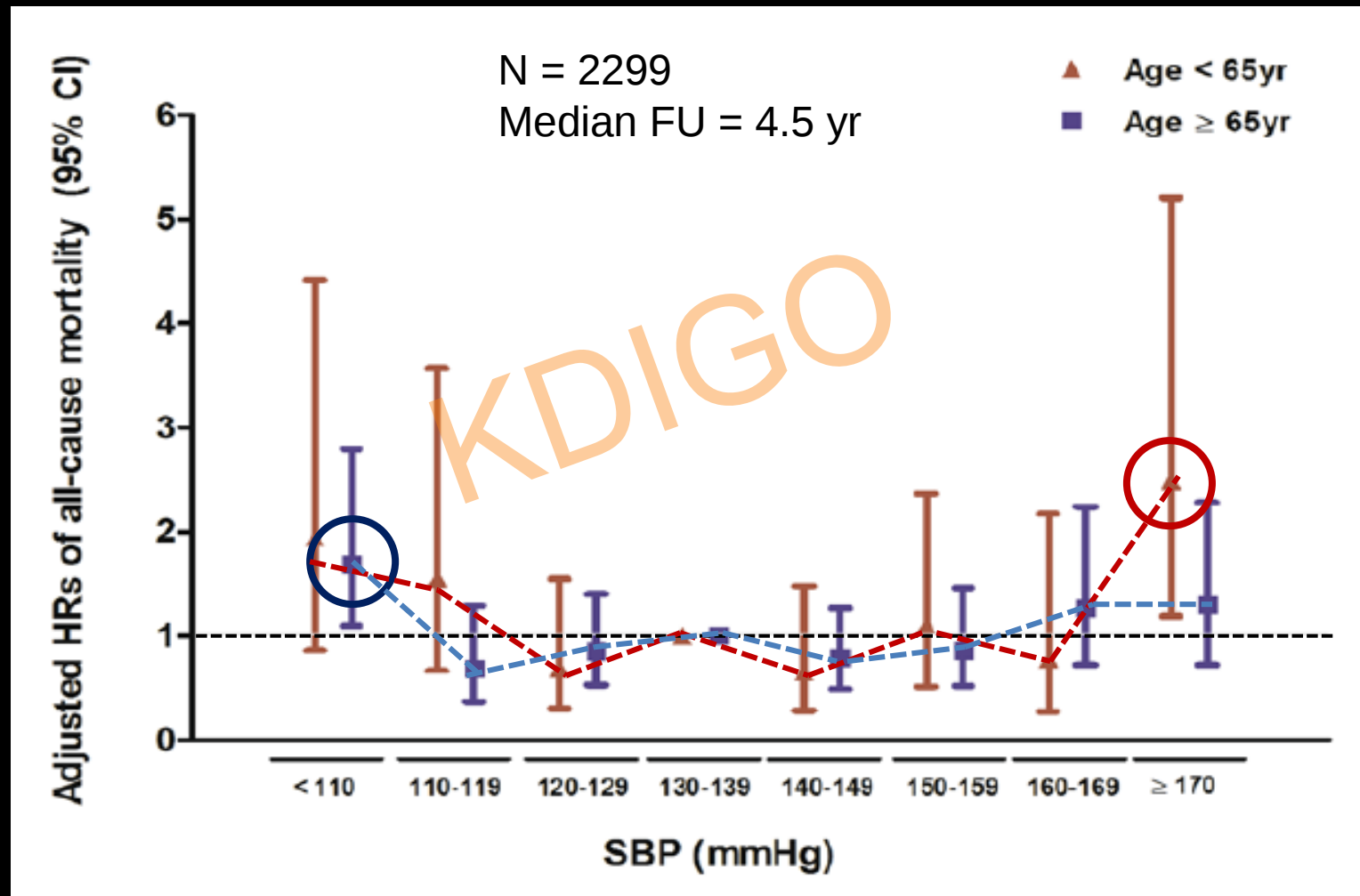
(N=4499)



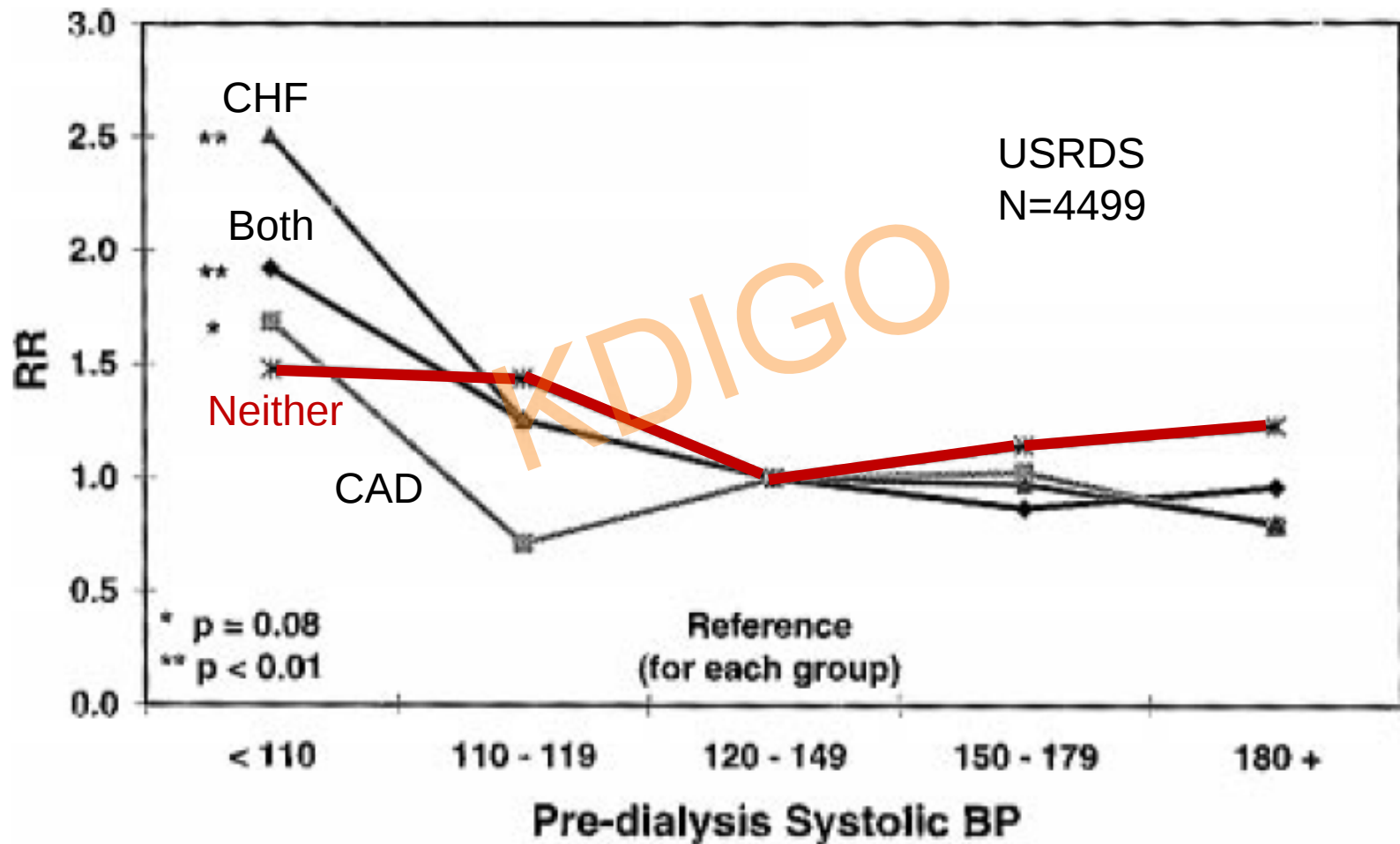
# Association between SBP and **Mortality** Risk in HD and PD Patients



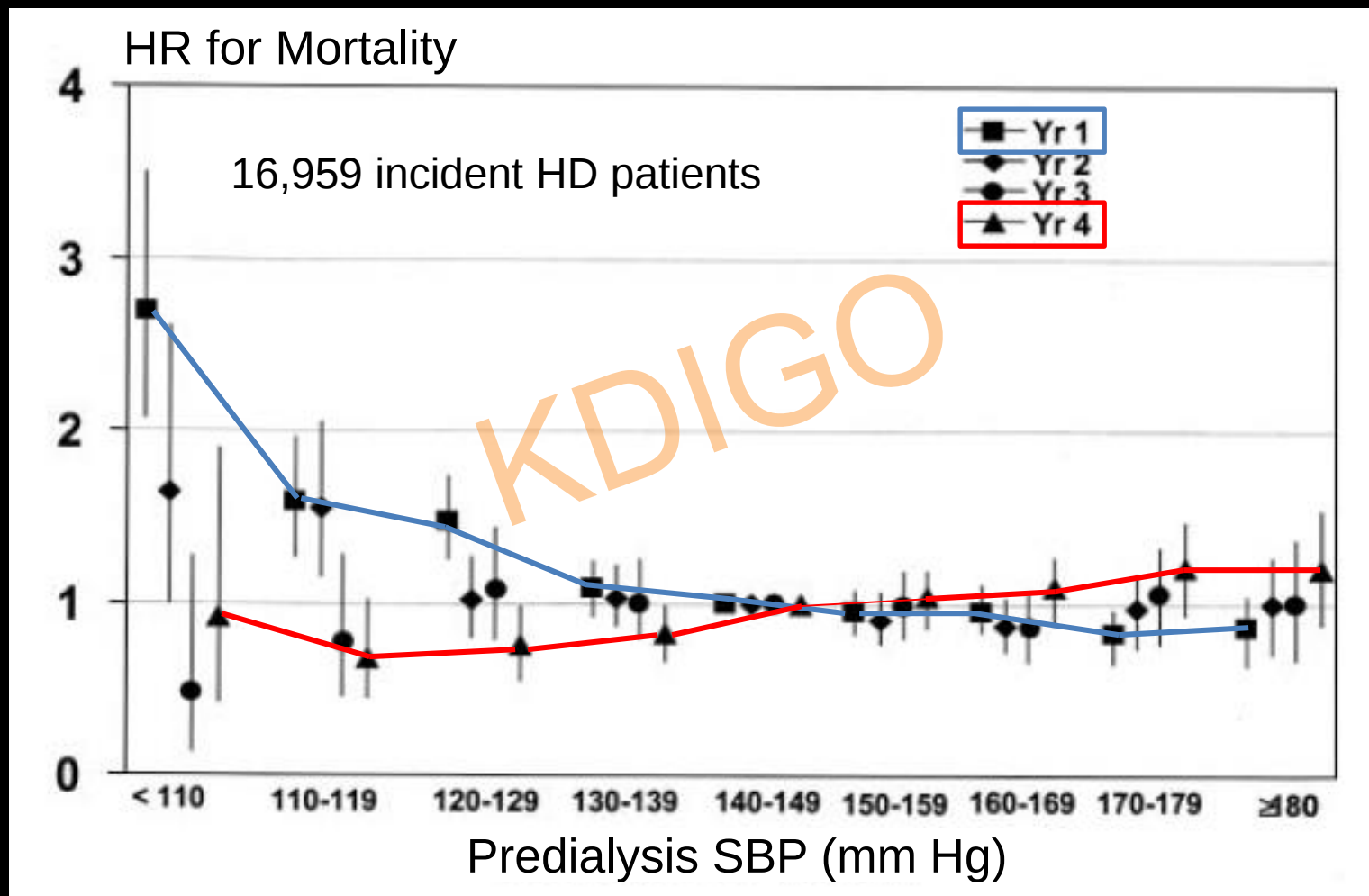
# Association between SBP and **Mortality** Risk May Varies with **Age** in Dialysis (HD+PD) Patients



# Paradoxical Association Not Seen in HD Patients Without Heart Disease

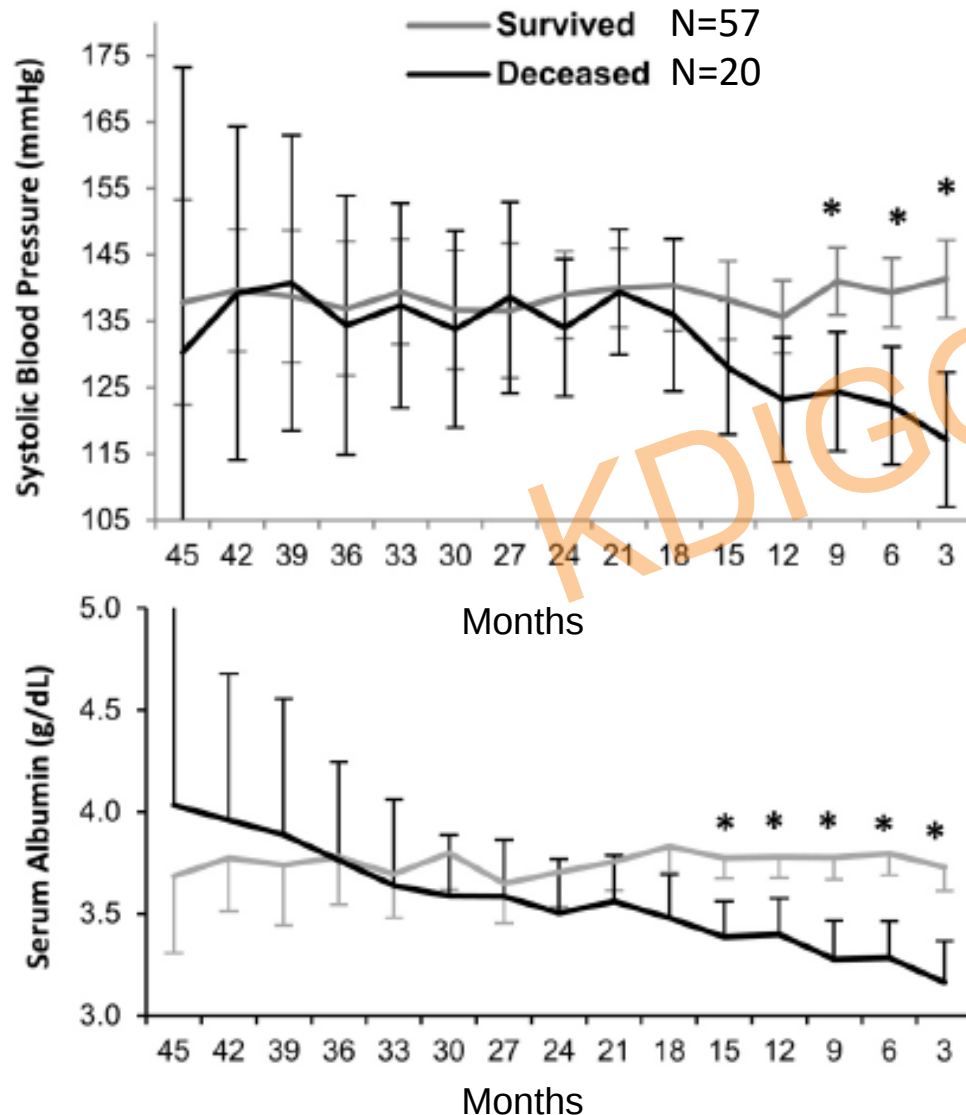


# Association of Predialysis SBP with Mortality Risk Depends on HD Vintage



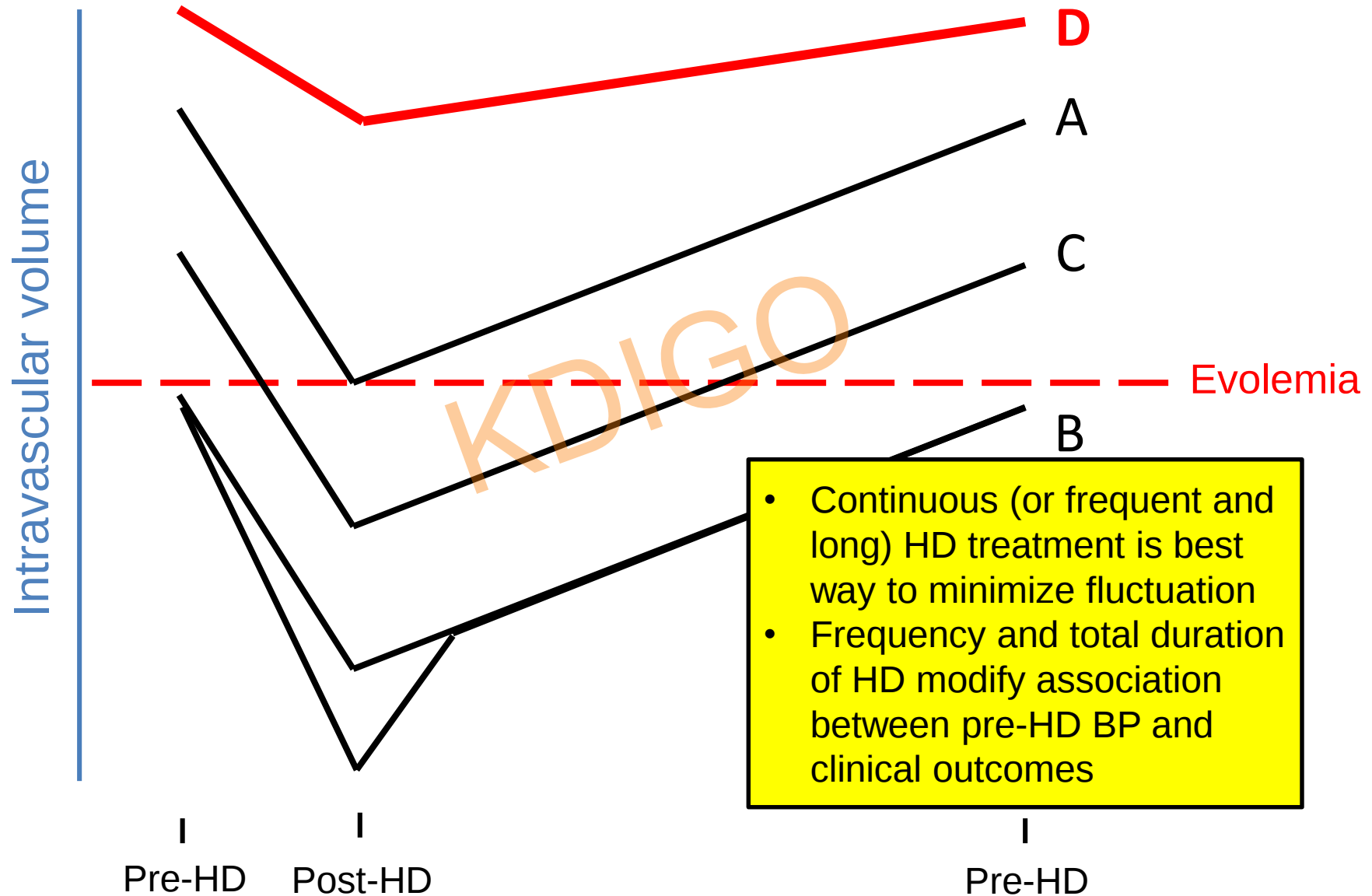
# Association of BP with Death in PD Patients

## Effect of F/U Duration and Cardiac Function

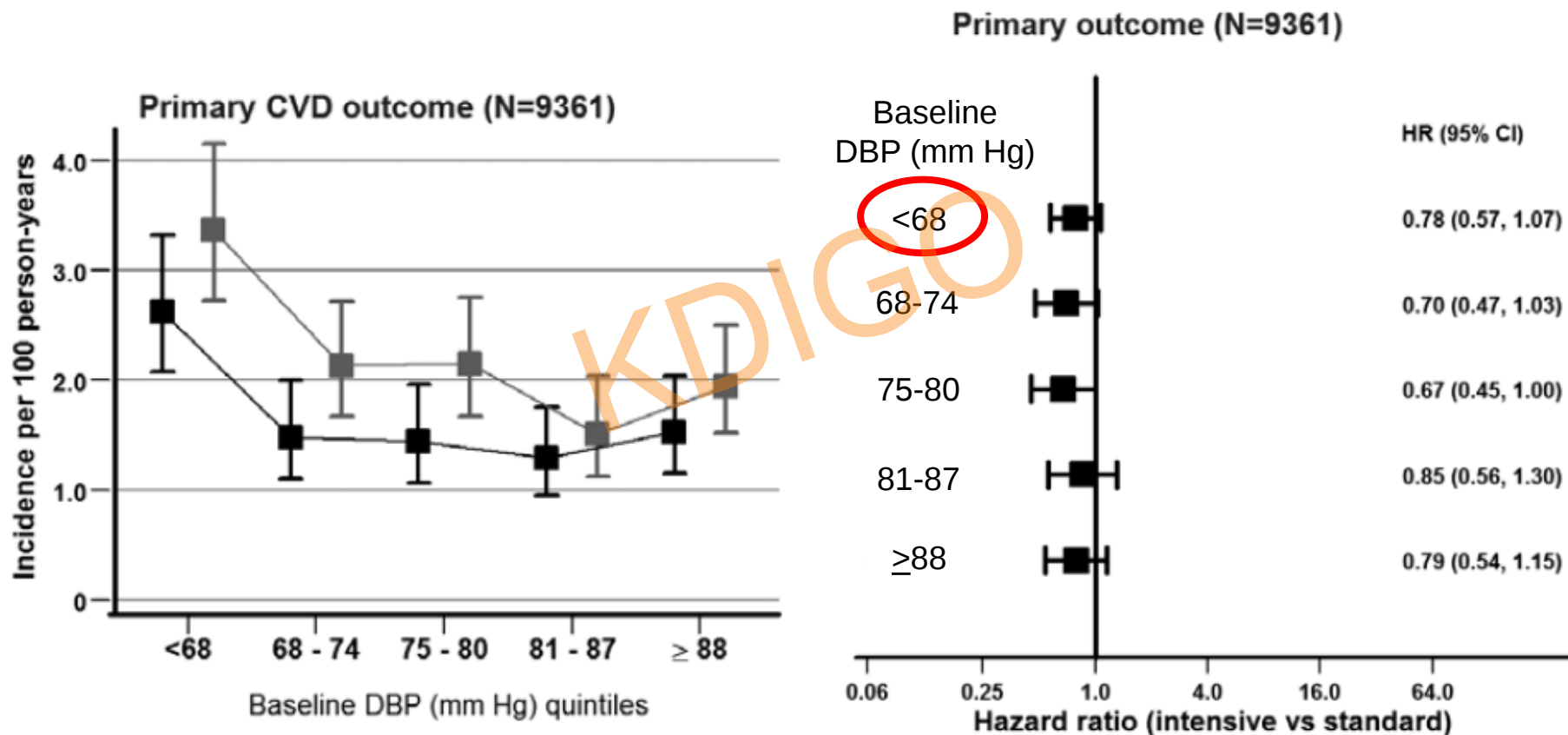


- RR for death = 7.3 [1.5-35.7] for SBP <120 mm Hg (vs. SBP 140-159 mm Hg)
- RR = 3.4 [0.7-17.7] after adjustment for ejection fraction

# Never Consistently Euvolemic



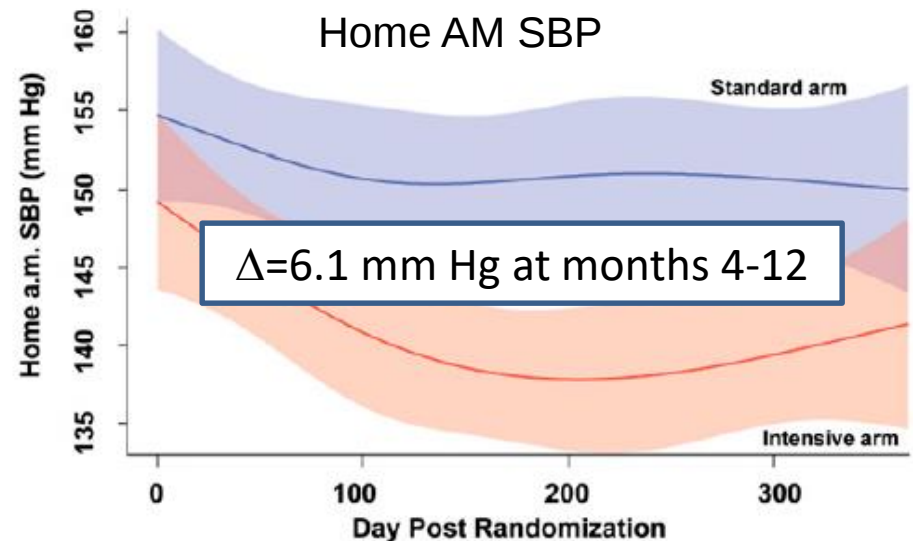
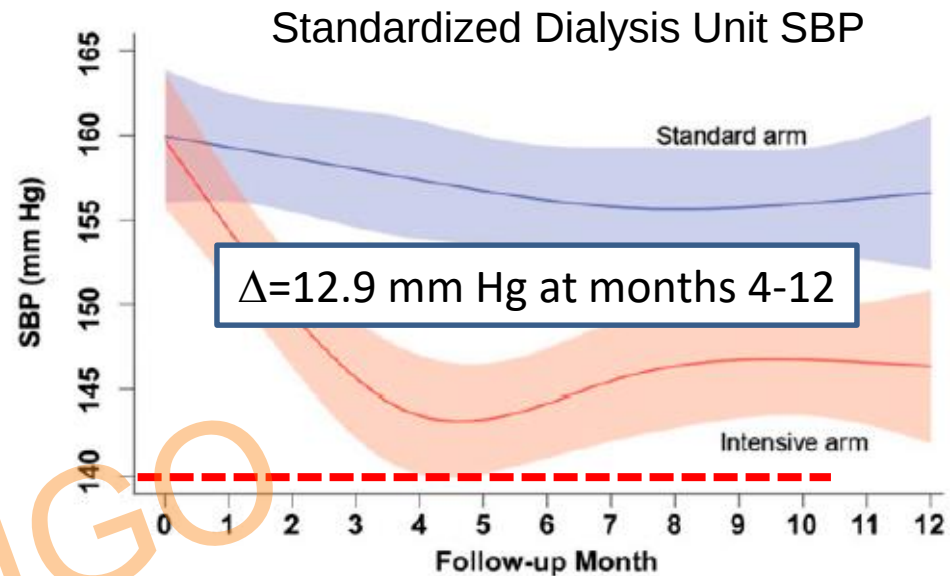
# Effect of Intensive vs. Standard SBP on Clinical Outcomes by Baseline DBP Quintiles in SPRINT



We need large RCTs to determine BP targets in dialysis patients

# BP in Dialysis (BID) Pilot Trial

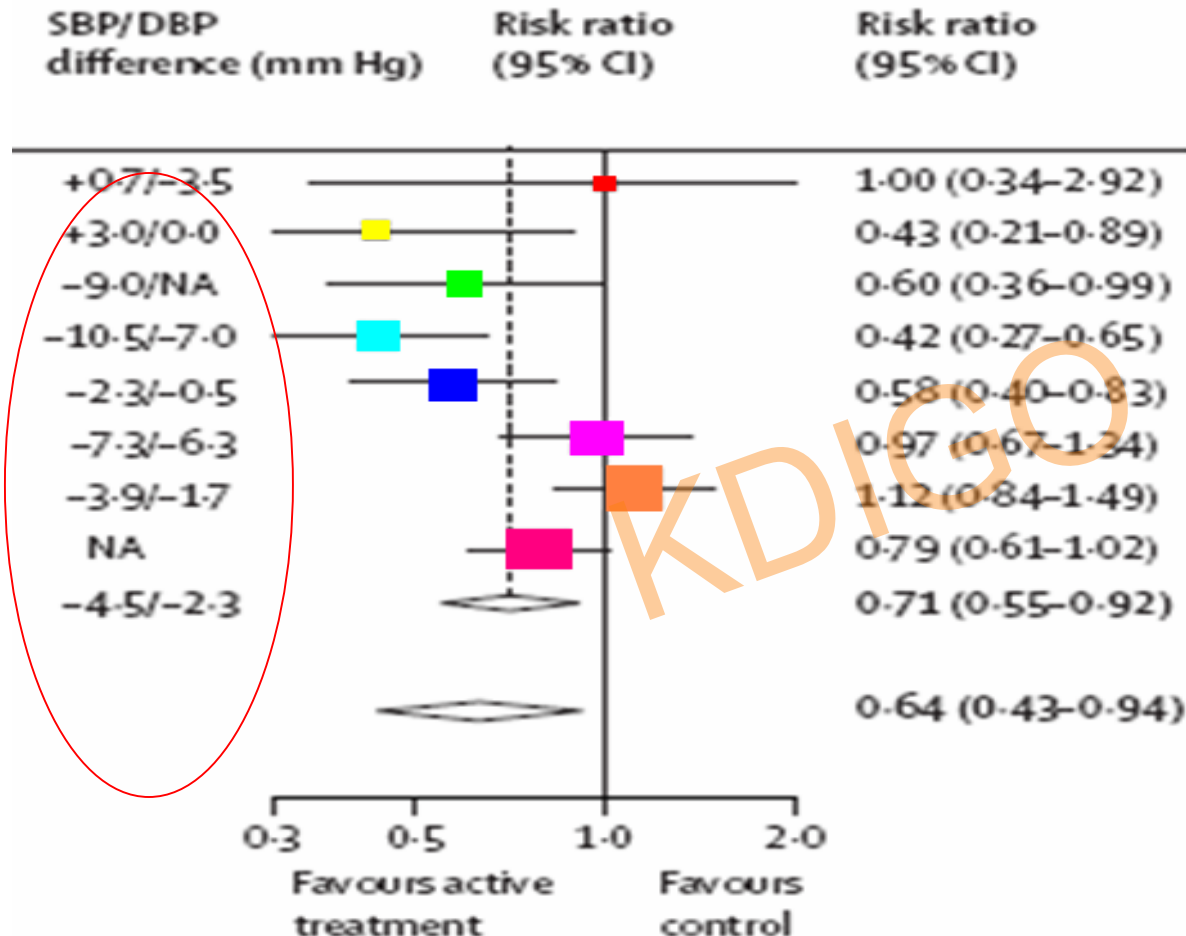
- 126 HD patients randomized to  
Pre-HD SBP 110-140 mm Hg  
vs. 155-165 mm Hg
- More intradialytic hypotensive  
symptoms in intensive SBP arm
- Not powered for clinical  
outcomes, but risks were  
numerically *higher* in intensive  
SBP arm for MACE,  
hospitalization and (3x higher)  
vascular access thrombosis



# Pharmacotherapy

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# Lowering BP in dialysis patients is beneficial

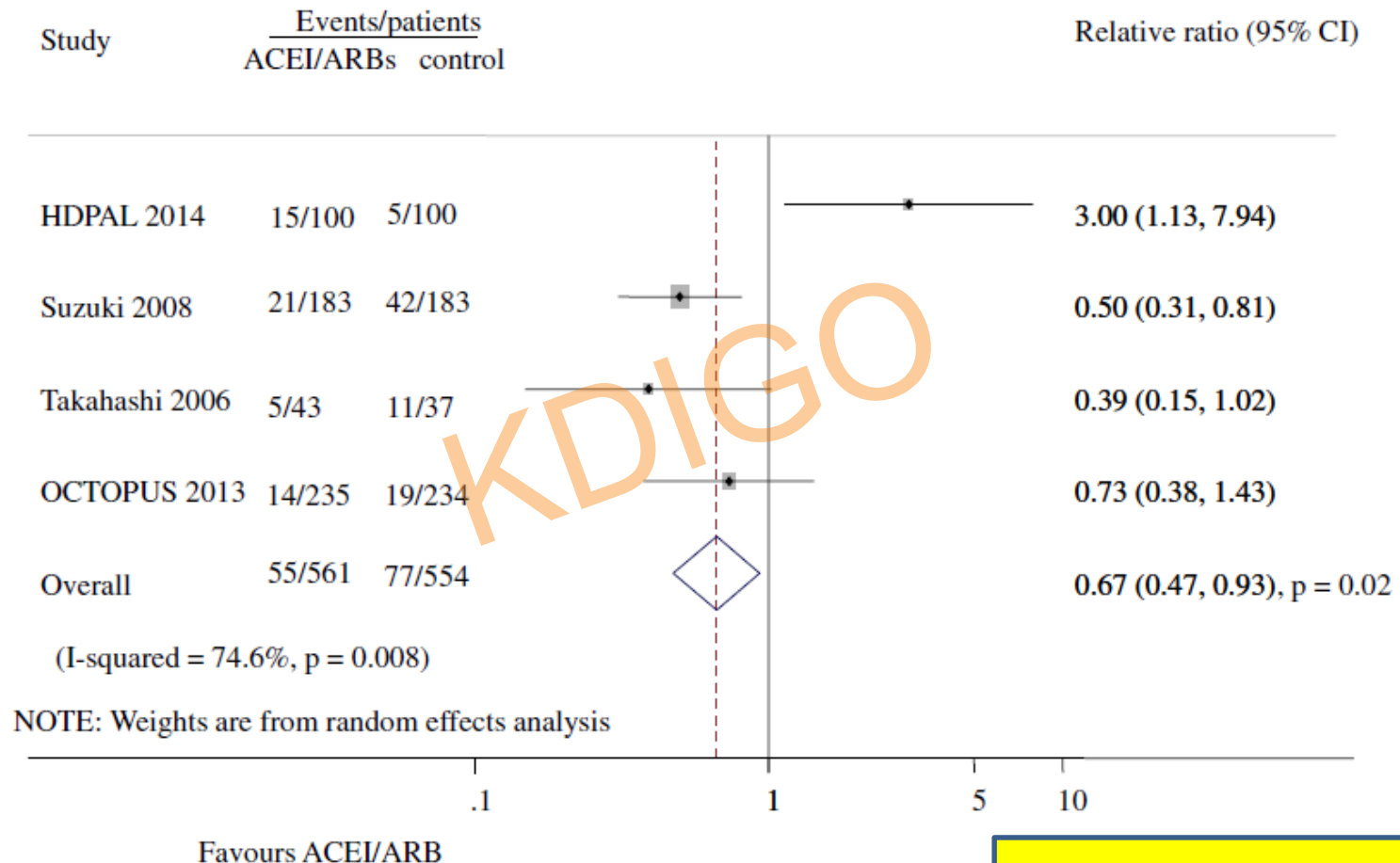


## Caveats:

- Heterogeneous study design
- Pre-dialysis BP
- **None was BP trial**
- Interventions were specific agents (RAAS blocker, BB, CCB), **not** targeting BP

Combined N=1,679 in 8 trials

# Effect of ACEI/ARB on **CHF** in HD/PD Patients



- Meta-analysis of 11 RCTs and 1856 patients

NOT BP TRIALS

# Removal of Antihypertensive Drugs by HD

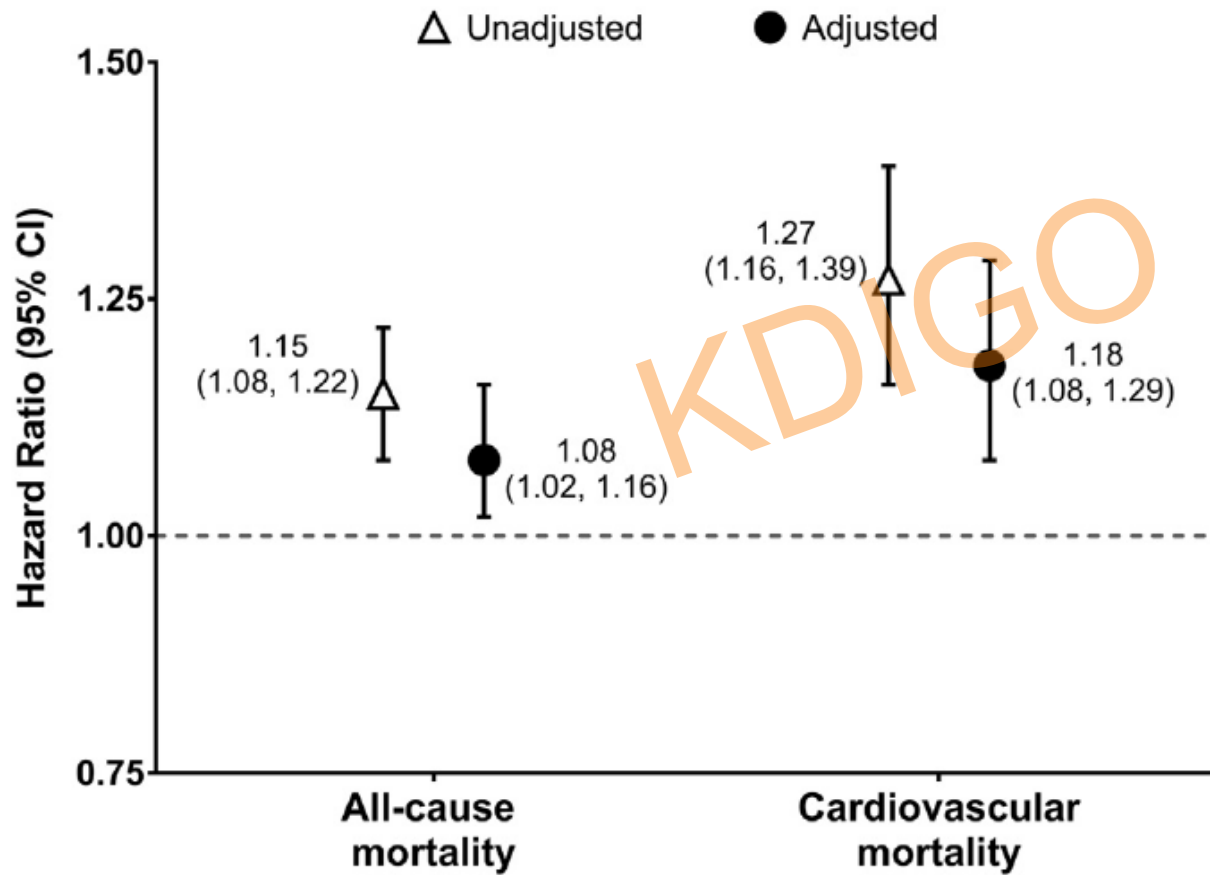
|                   |      |
|-------------------|------|
| <b>ACE-I</b>      |      |
| Benazepril        | <30% |
| Enalapril         | 35%  |
| Fosinopril        | 2%   |
| Lisinopril*       | 50%  |
| Ramipril          | <30% |
| <b>β-Blockers</b> |      |
| Atenolol*         | 75%  |
| Carvedilol        | None |
| Labetalol         | <1   |
| Metoprolol        | High |
| <b>Other</b>      |      |
| Clonidine         | 5%   |
| Hydralazine       | None |
| Minoxidil         | Yes  |

|             |      |
|-------------|------|
| <b>ARB</b>  |      |
| Losartan    | None |
| Candesartan | None |
| Eprosartan  | None |
| Telmisartan | None |
| Valsartan   | None |
| Irbesartan  | None |
| <b>CCB</b>  |      |
| Amlodipine  | None |
| Diltiazem   | <30% |
| Nifedipine  | Low  |
| Nicardipine | ?    |
| Felodipine  | No   |
| Verapamil   | Low  |

# $\beta$ -Blocker Dialyzability and Mortality in HD Patients

- Propensity-matched retrospective cohort study using administrative database in Canada
- Highly-dialyzable  $\beta$ -blockers (atenolol, metoprolol, acebutolol; N=3294) vs. lowly-dialyzable  $\beta$ -blockers (propranolol, bisoprolol; N=3294)
- Initiating highly-dialyzable  $\beta$ -blockers were associated with higher risk of death in 180 days (RR 1.4 [1.1-1.8])

# Carvedilol vs. Metoprolol with 1-Year Mortality in HD Patients



- 9558 carvedilol (low dialyzability) + 17506 metoprolol (high dialyzability)
- Inverse-probability weighting
- Carvedilol had higher rate of IDH (IRR 1.10 [1.09-1.11])

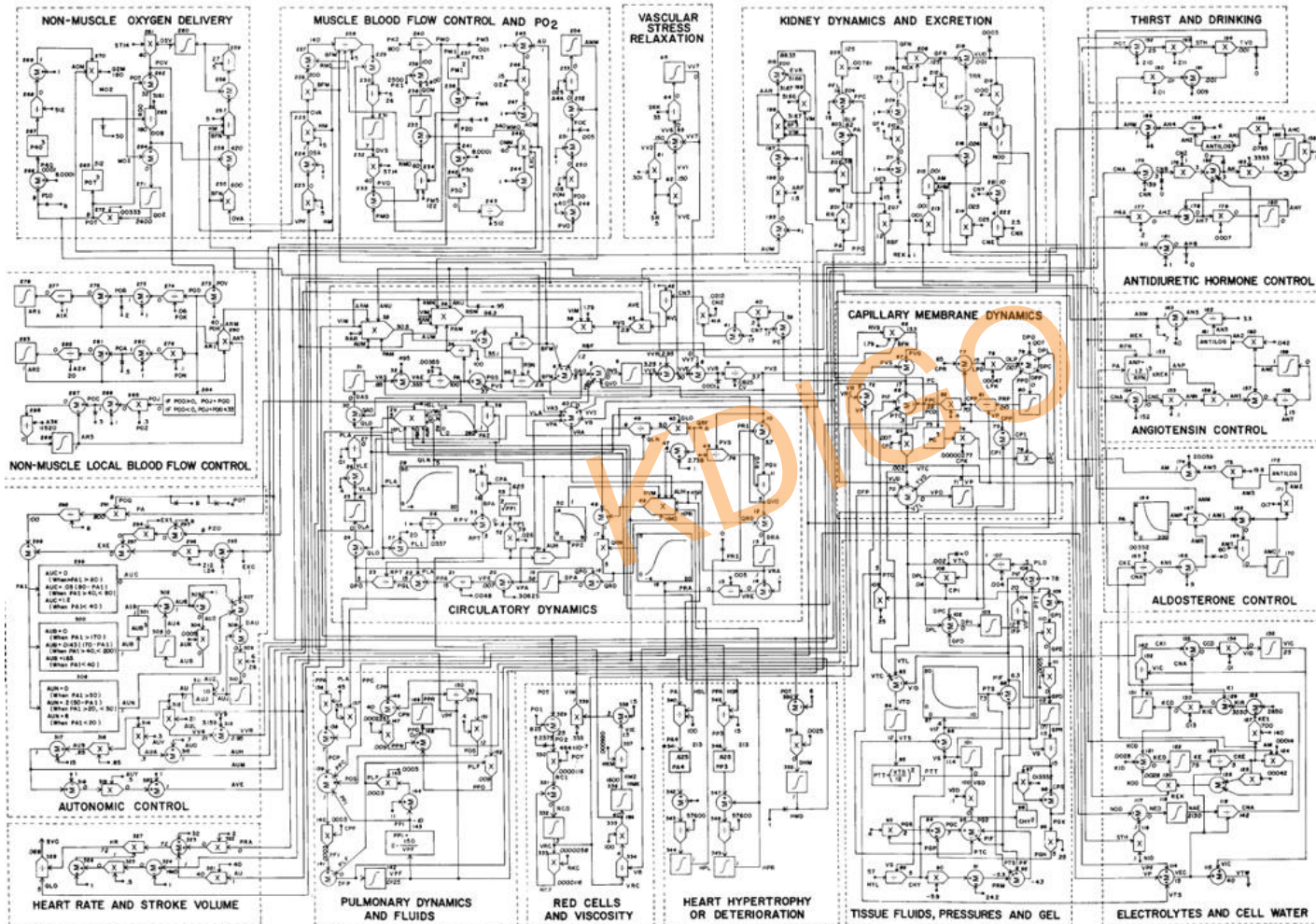
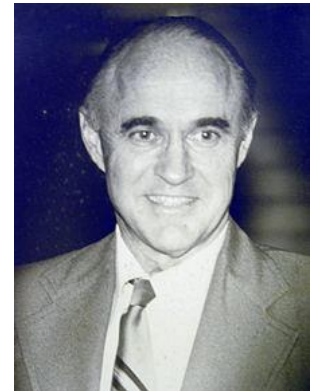
# How much of HTN in Dialysis Patients is volume-dependent?

- Do not know (not in CKD or non-CKD either)
- Probably quite a bit
- Probably varies among individuals

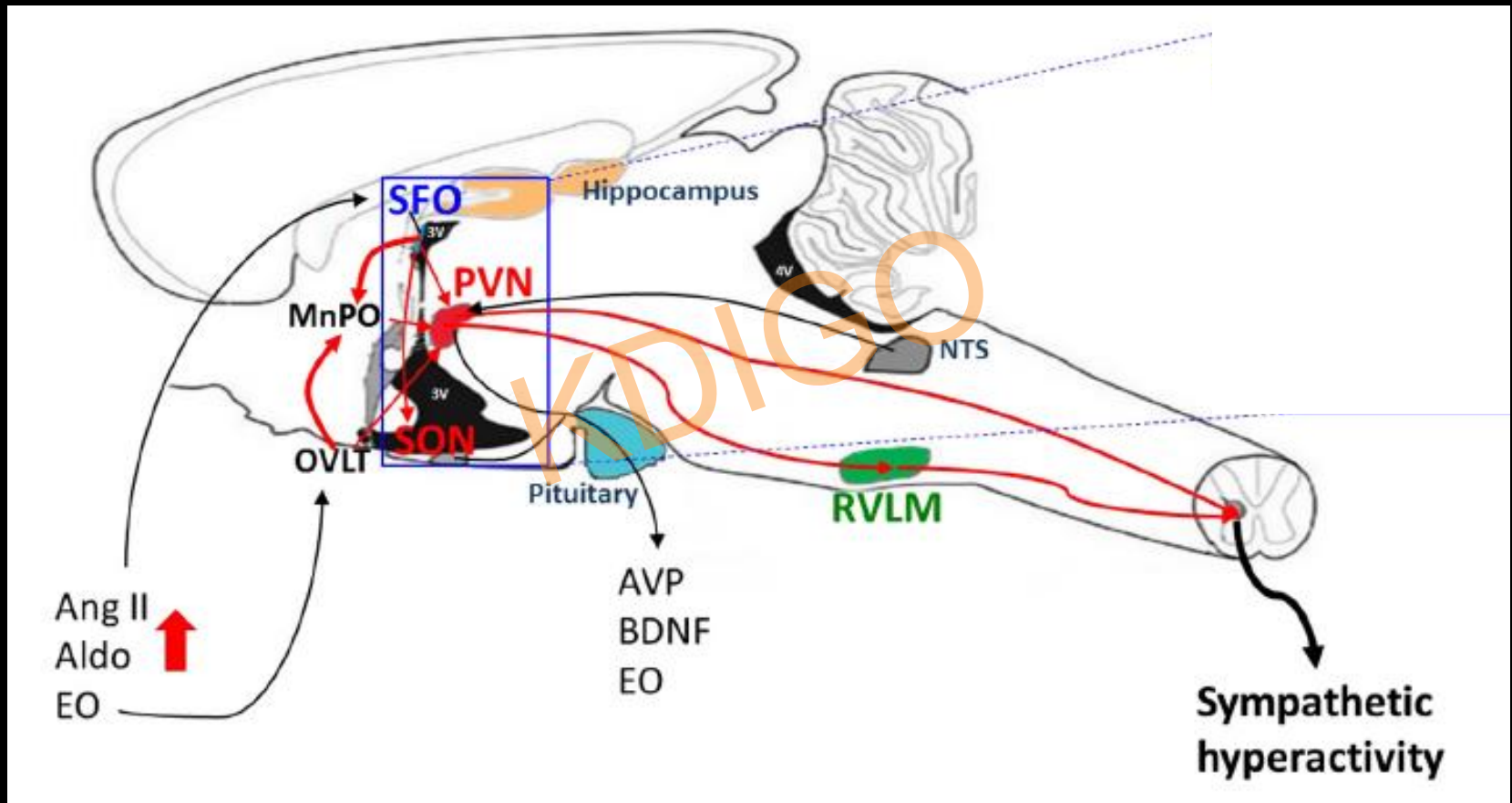
# Volume-Independent Blood Pressure Increase in HD Patients

- Arterial stiffness (e.g., calcification)
- Sympathetic over-activity (kidney ischemia, CHF, decreased renalase)
- Other mediators (RAAS, ET-1/NO ratio)
- ESA (increases sensitivity to Ang II and NE and increases ET-1)
- Sleep apnea (contributes to impaired nocturnal dipping)

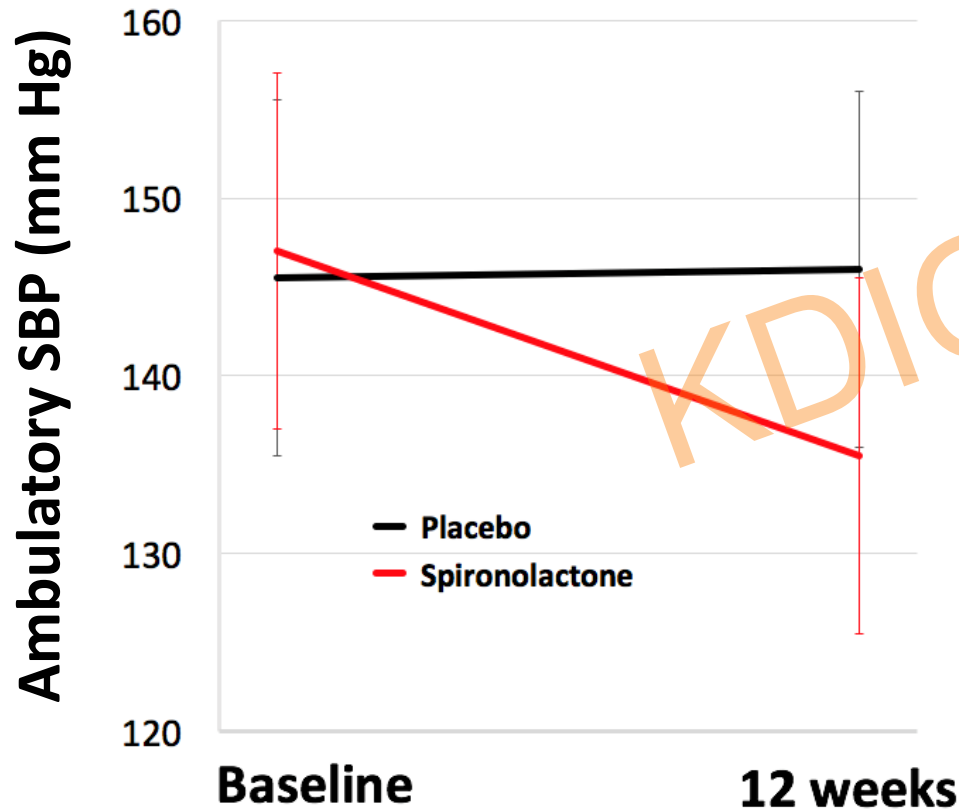
# Circulation: Overall Regulation



# Endocrine and Paracrine Ang II and Aldosterone in CNS Modulate Sympathetic Outflow

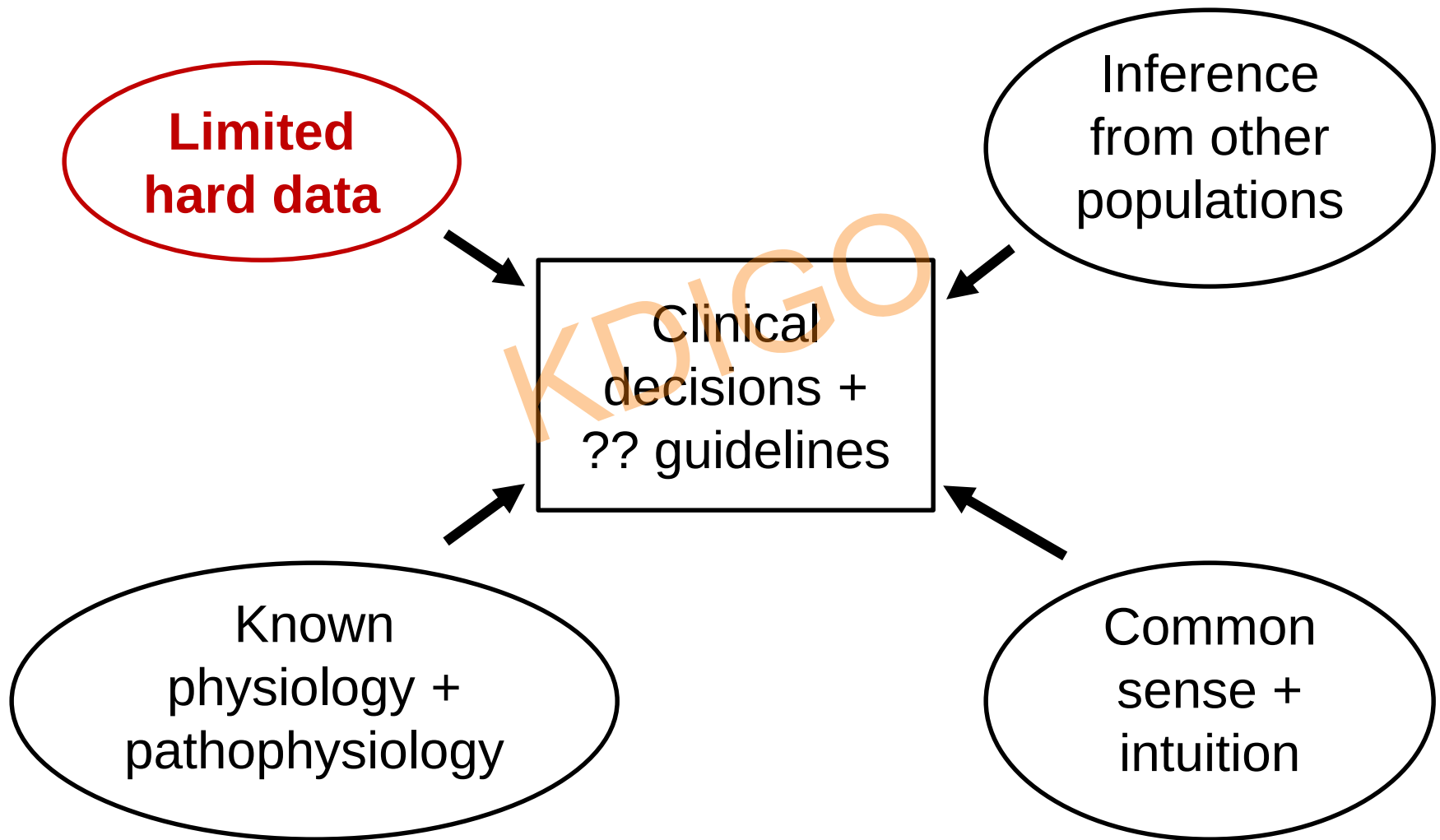


# Effects of Spironolactone on BP in Dialysis Patients



- Double-blinded RCT of 76 patients on HD or PD x 56 mos
- ~78% had urine volume <100 ml/24 hr
- ABP ~146/90 on 5 drugs
- Spironolactone 25 mg vs. placebo as add-on
- No  $\Delta$  in BW and serum  $K^+$

# How do we decide what to do with BP in dialysis patients?



# Conclusions

- BP Measurements for dialysis patients
  - Peri-HD measurements are convenient, but not reliable
  - Should move towards home or clinic measurements for clinical use and research
- BP Target for dialysis patients
  - Unknown, but be leery of U-shape curve in observational studies
  - Needs large RCTs
- Pharmacotherapy for dialysis patients
  - No clear winner among anti-hypertensive agents
  - CV outcomes and preservation of residual kidney function should be considered