Controversies In Optimal Iron Use For CKD Anemia Management: Snapshot Of A 2019 KDIGO Conference

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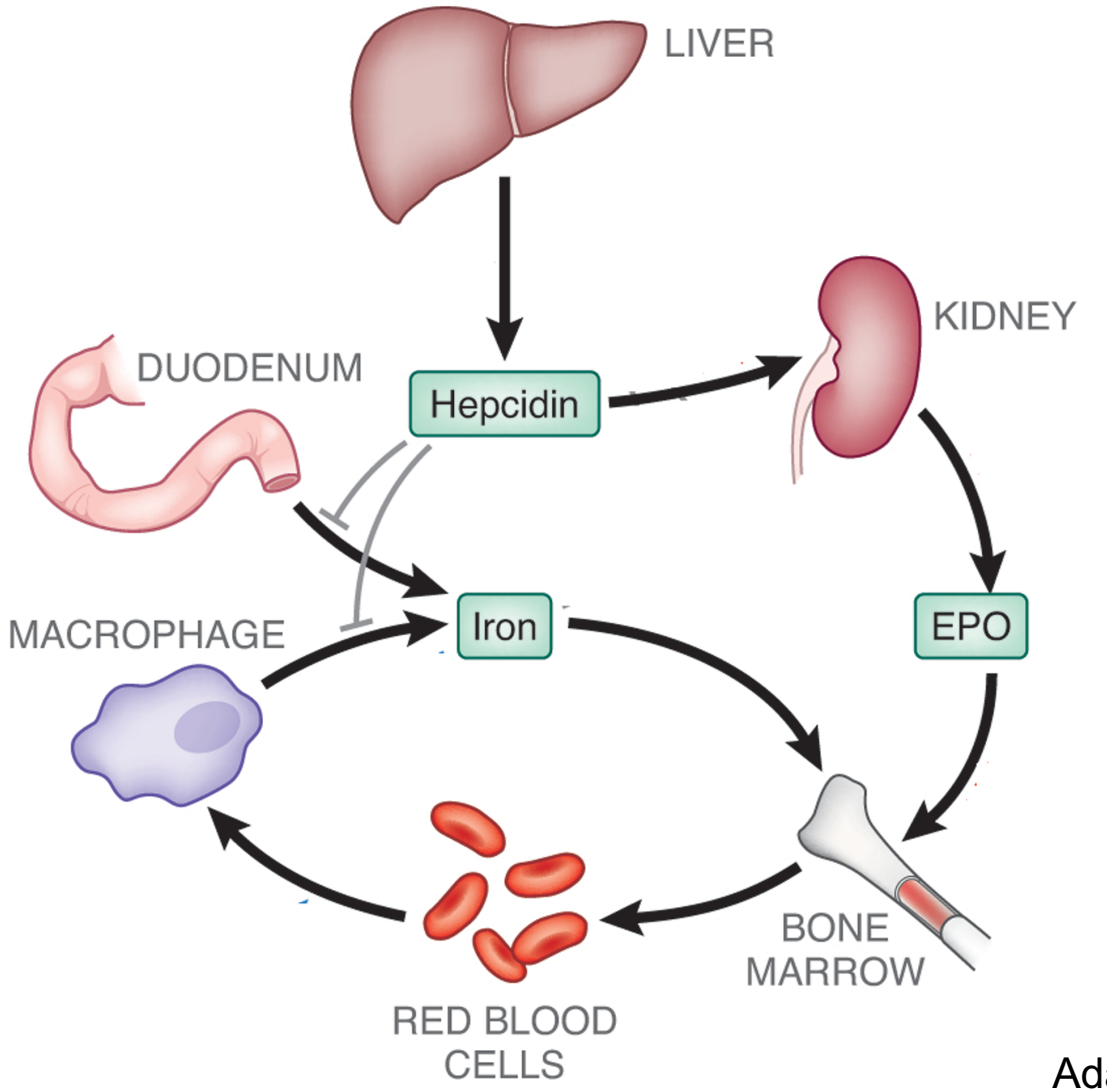
DISCLOSURES

- Employer: Massachusetts General Hospital, Harvard Medical School
- Consultancy agreements: Incyte Corporation; Alnylam Pharmaceuticals
- Ownership Interest: Ferrumax Pharmaceuticals, Inc
- Patents and inventions: Massachusetts General Hospital, Ferrumax Pharmaceuticals, Inc.
- Advisor or membership: Editorial Board: American Journal of Physiology, Renal Physiology; Board of Directors: International BioIron Society; Co-Chair: KDIGO Anemia Guideline Update

ANEMIA OF CKD



Adapted from: Babitt and Lin.
J Am Soc Nephrol. 2012;23(10):1631.

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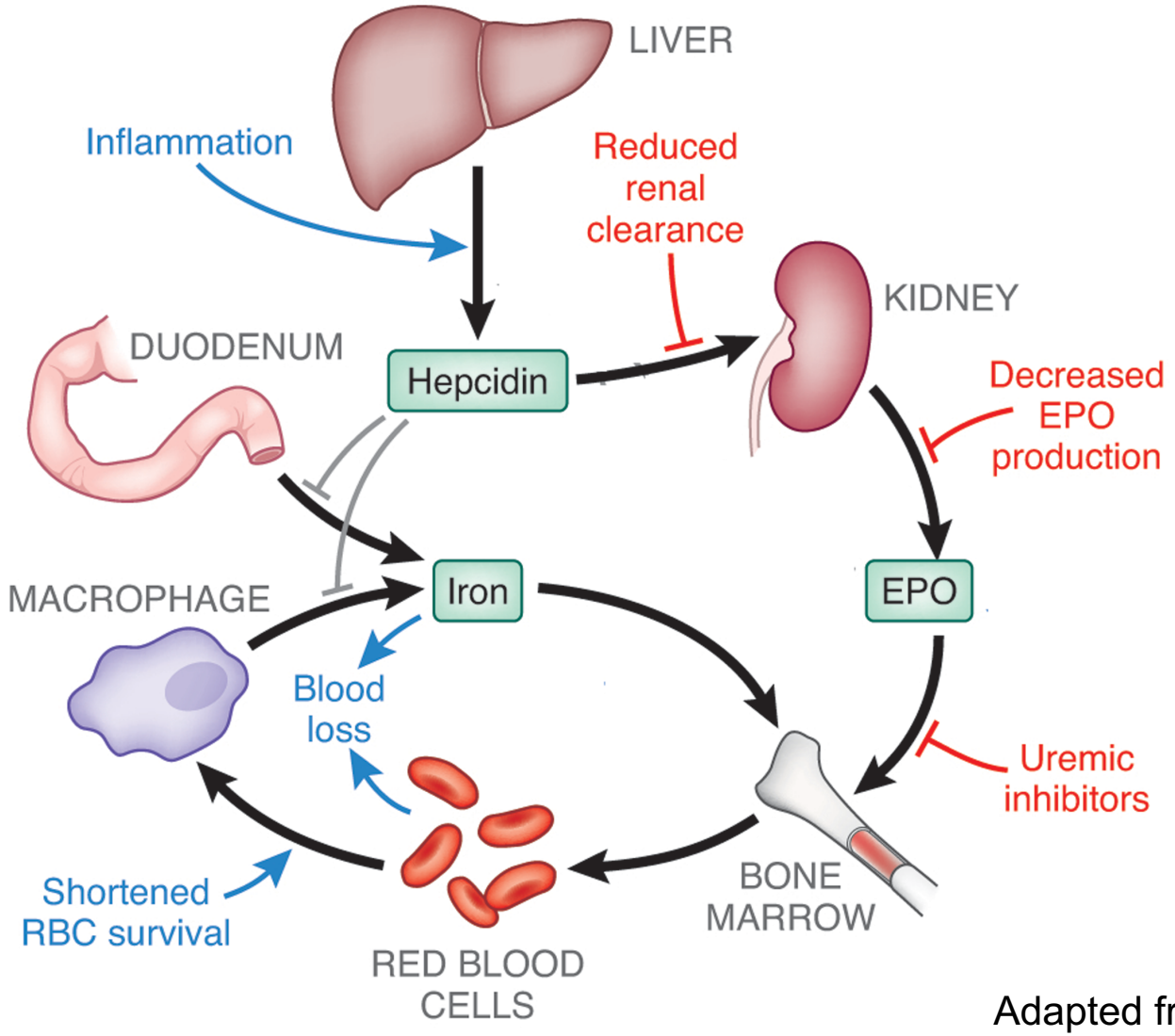

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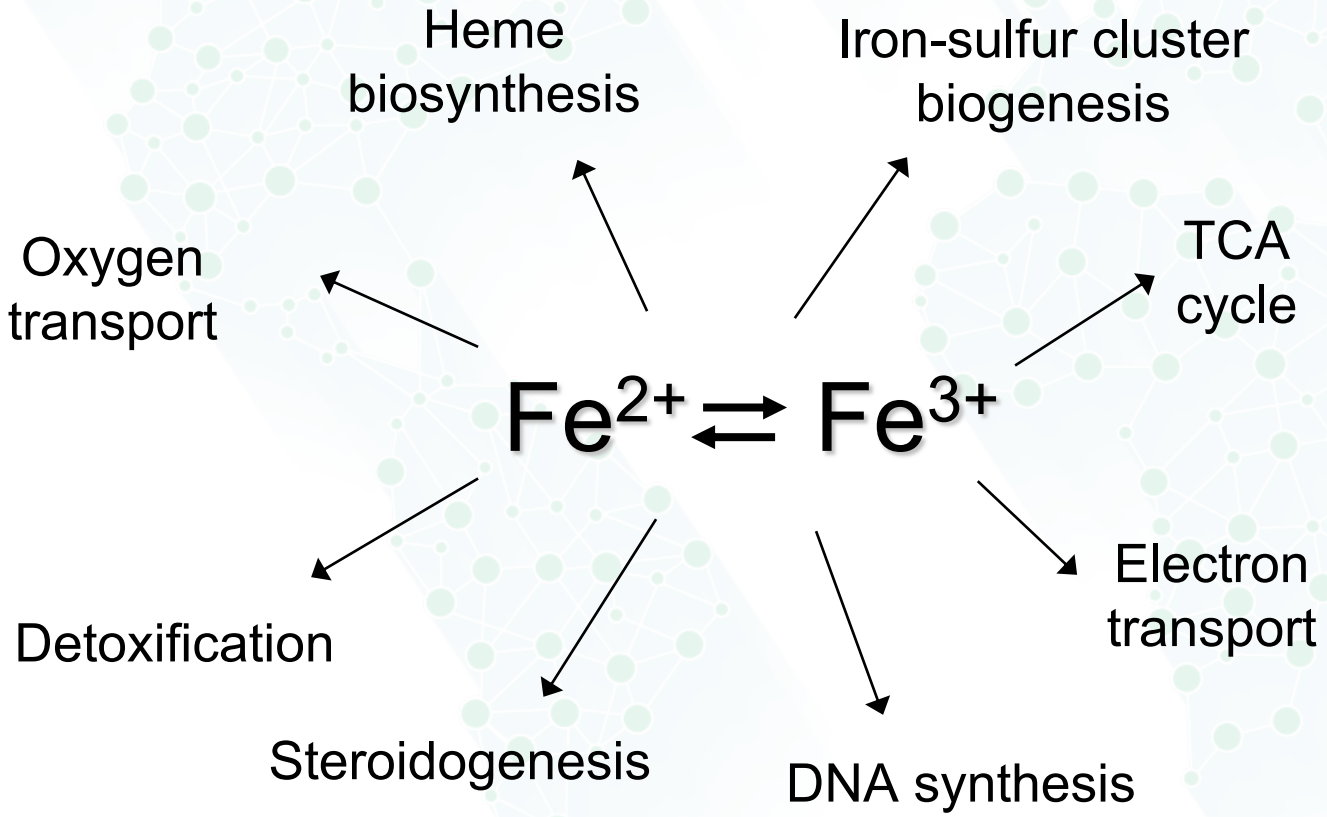
Iron Is An Essential Micronutrient



Iron deficiency may lead to

- Anemia
- Cardiovascular strain
- In fetuses and children:
  - -Developmental defects
  - -Growth retardation
  - -Neurological defects
- Impaired muscle function, exercise tolerance, work performance
- Altered immune function

Adverse Effects of Excess Iron

- Free radical generation, oxidant mediated tissue injury:

  $Fe^{2+} + H_2O_2 \longrightarrow Fe^{3+} + OH^- + OH^{\cdot}$

  - Thalassemia, Hereditary hemochromatosis (cirrhosis, cardiomyopathy, endocrine disorders, arthritis)
  - Diabetes Mellitus
  - Neurodegenerative disorders
  - Cardiovascular Disease
  - Acute Kidney Injury
  - Malignancy
- Infection

KDIGO 2012 GUIDELINES

- Use of iron to treat anemia in CKD
  - Iron status tests recommended at least every 3 months during ESA treatment, more often when initiating/increasing ESAs, blood loss, monitoring response to iron
    - Serum TSAT (= iron/TIBC) (to assess circulating iron available for erythropoiesis
    - Serum ferritin (to assess iron stores)
  - Limitations: TSAT and ferritin have limited sensitivity and specificity in CKD patients of bone marrow iron stores and erythropoietic response to iron supplementation
  - No sufficiently powered interventional trials have tested different triggers for iron supplementation

KDIGO 2012 GUIDELINES

- Use of iron to treat anemia in CKD
  - Balance potential benefits (minimizing transfusions, ESAs, and anemia symptoms), against risks (anaphylactoid and other acute reactions, unknown longer term risk)
  - For adults, trial of IV iron (or 1-3 month trial of oral iron therapy in nondialysis CKD patients) if (2C):
    - an increase in Hgb without starting ESAs or a decrease in ESA is desired AND
    - TSAT < 30% and ferritin ≤ 500 μg/L
  - Continued therapy based on an integrated assessment
  - Insufficient data to recommend any long-term IV dosing strategy
  - Avoid IV iron in patients with active systemic infections (not graded)
  - Caveat: Very limited long-term safety information. Hasn't been exposed to the rigor of large RCTs which has occurred with ESAs

KDIGO Controversies Conference on Optimal Anemia Management in CKD, Barcelona, Dec 2019

- Co-chairs: Tilman B. Drueke, Jodie L. Babitt; Group Leaders: Abhi Kshirsagar, Adeera Levin, Francesco Locatelli, Dorine Swinkels, Volker Haase, Jolanta Malyszko, Michele Eisenga, Der-Cherng Tarng
- Review the latest evidence, explore new and ongoing controversies, propose a research agenda, and assess change implications for the 2012 KDIGO anemia guideline
- The first conference focused largely on iron
- A second conference will be convened in 2021 to discuss novel anemia therpaies, including hypoxia-inducible factor-prolyl hydroxylase inhibitors (HIF-PHIs) once more longer-term outcomes trial data have been accrued.

What is New Since 2012?

New Prospective RCT Data: PIVOTAL

- Prospective RCT in 2141 incident HD patients (0-12 months) comparing
  - Proactive IV iron (400 mg/month iron sucrose) withhold if TSAT >40% or ferritin >700 μg/L
  - Reactive IV iron (0-400mg/month iron sucrose) if TSAT <20% or ferritin <200 μg/L
- Noninferiority trial. Primary endpoints: composite of nonfatal MI, stroke, HF hospitalization or death (time-to-first event analysis)
- Secondary endpoints: components of primary endpoint, ESA dose, transfusions, infection
- Median follow-up 2.1 years

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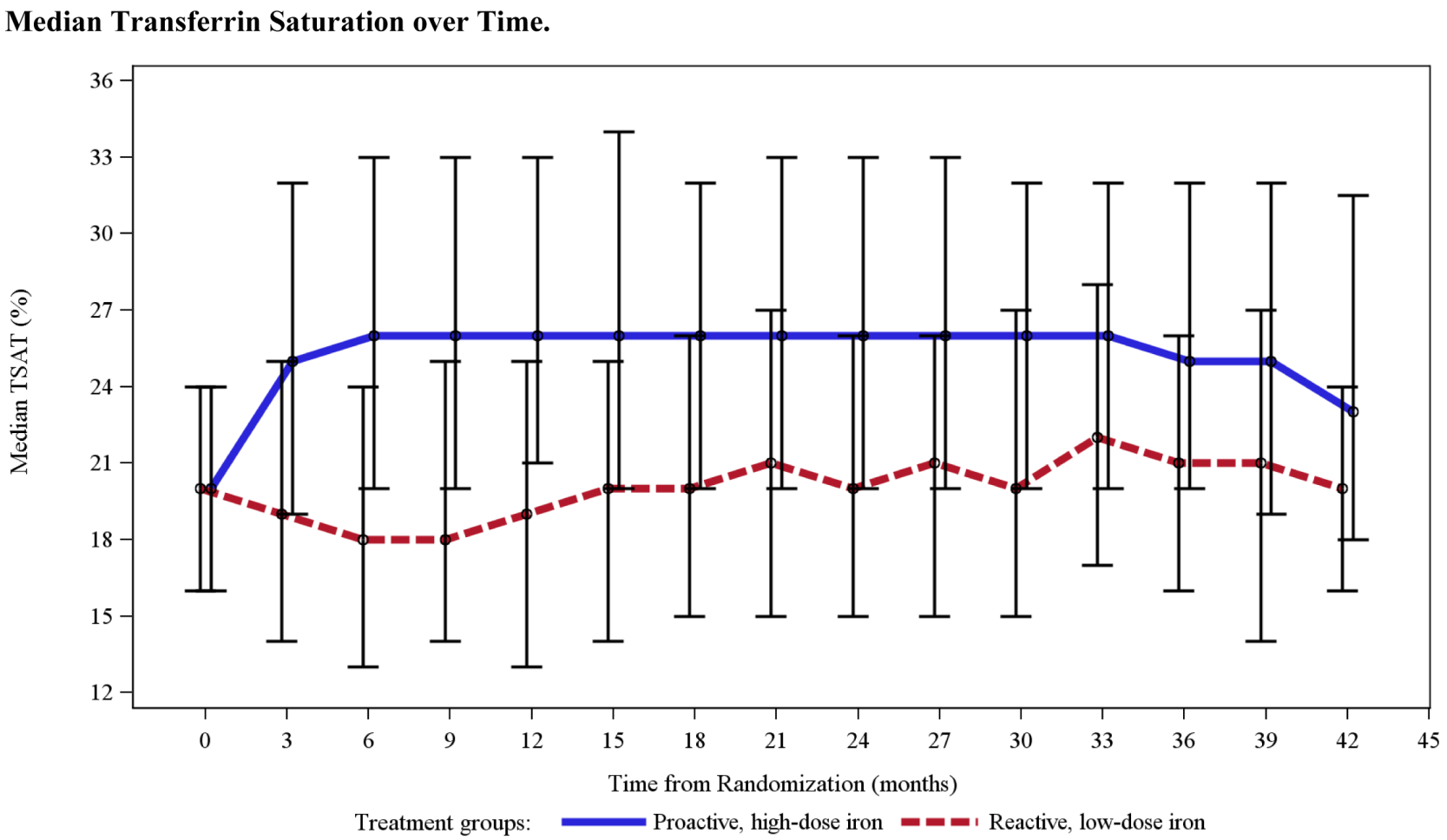

Macdougall *et al. N Engl J Med*. 2019;380(5):447-458.

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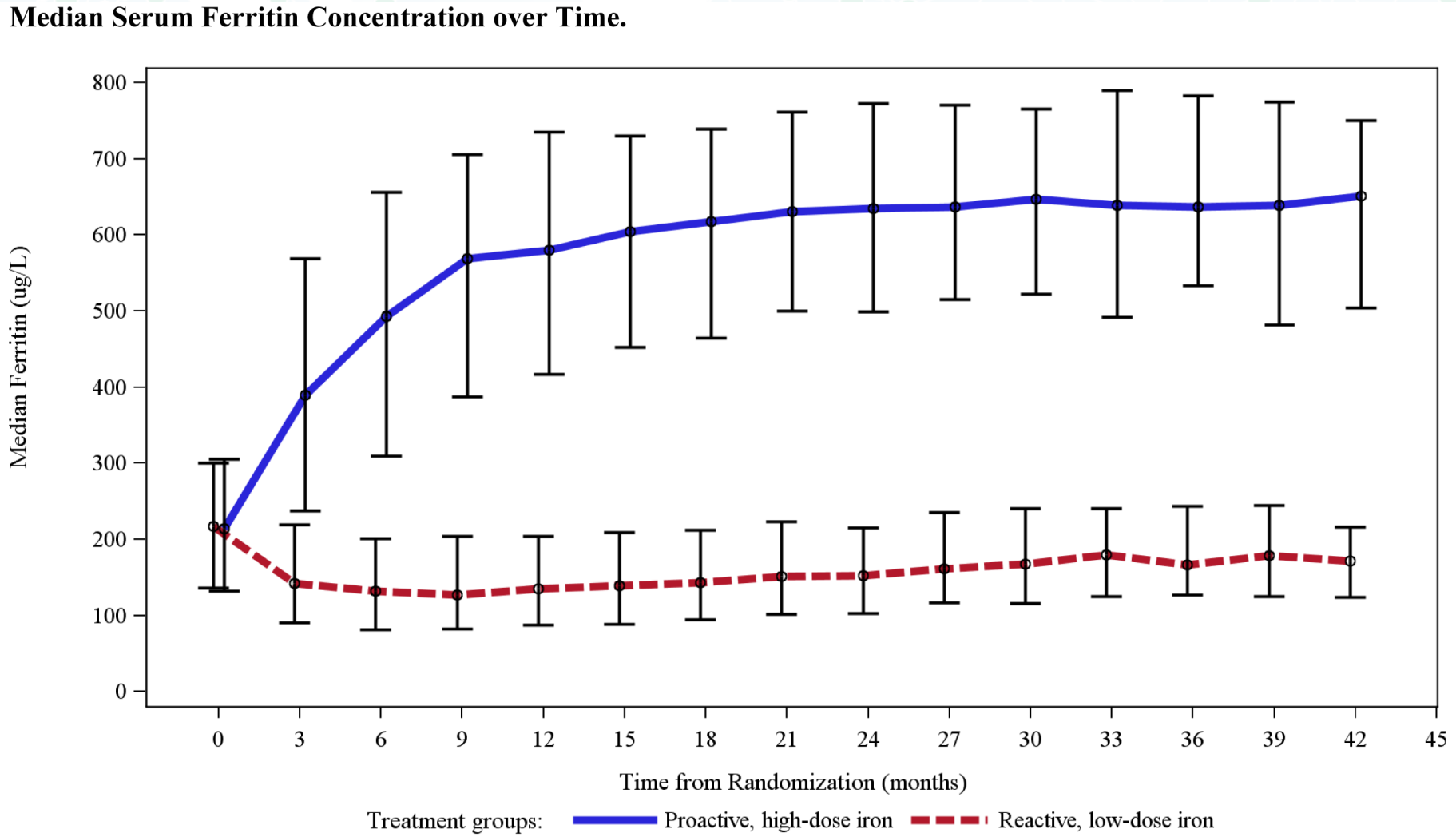

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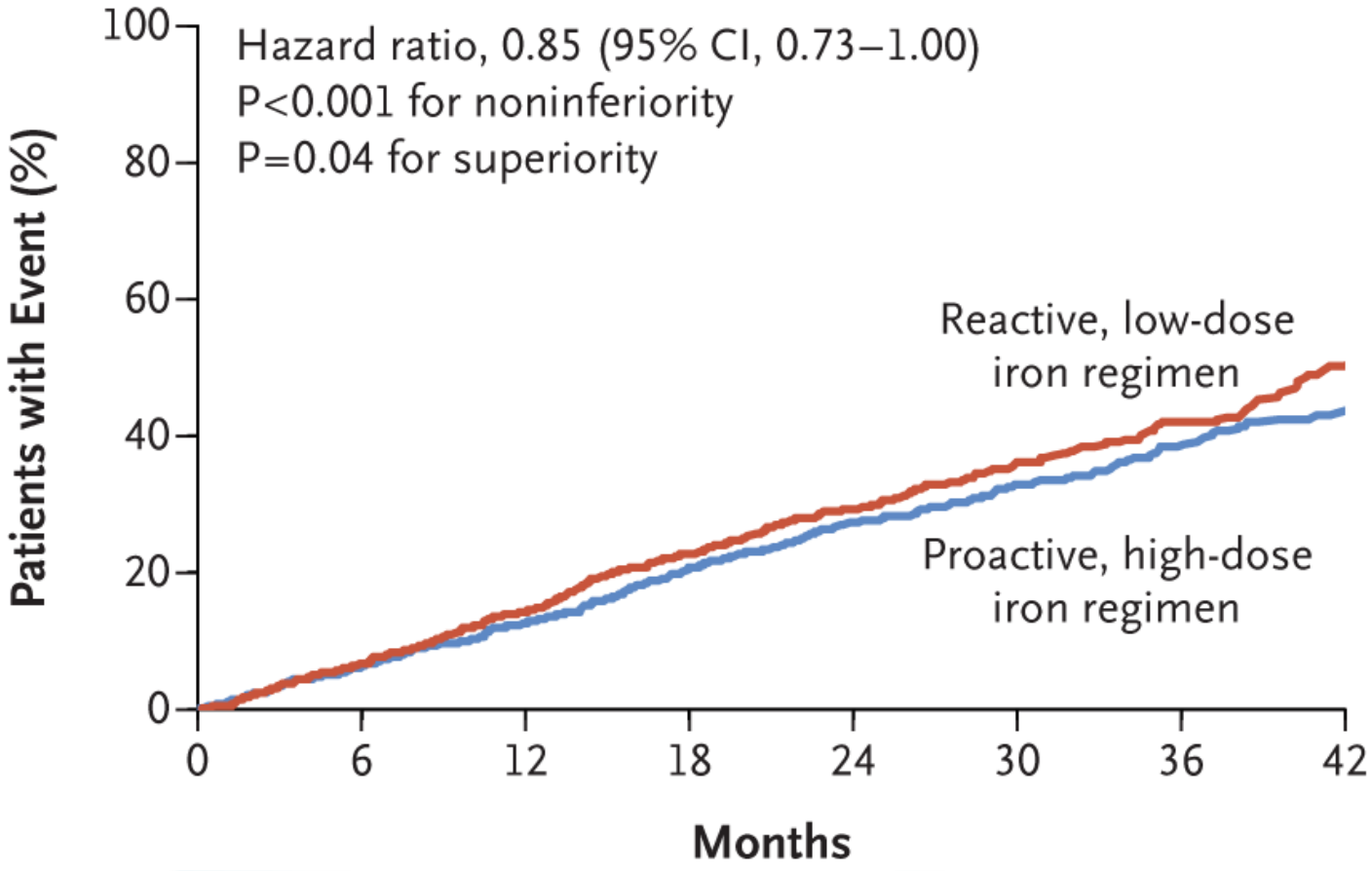
Primary Efficacy End Point composite of nonfatal MI, stroke, HF hospitalization or death (time-to-first event)



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New Prospective RCT Data: PIVOTAL

Table 2. Primary and Secondary End Points.*

End Point	Proactive, High-Dose Iron Regimen (N=1093)	Reactive, Low-Dose Iron Regimen (N=1048)	Estimated Treatment Effect (95% CI)	P Value
Primary composite end point†				
Event in the intention-to-treat population — no. (%)	320 (29.3)	338 (32.3)	0.85 (0.73 to 1.00)	<0.001‡
Event in the per-protocol population — no./total no. (%)	313/1080 (29.0)	334/1038 (32.2)	0.85 (0.73 to 0.99)	<0.001‡
Secondary efficacy end points				
Death from any cause and a composite of myocardial infarction, stroke, or hospitalization for heart failure as recurrent events — no. of events (rate per 100 patient-yr)	429 (19.4)	507 (24.6)	0.77 (0.66 to 0.92)§	—
Death from any cause — no. (%)	246 (22.5)	269 (25.7)	0.84 (0.71 to 1.00)	—
Fatal or nonfatal myocardial infarction, fatal or nonfatal stroke, or hospitalization for heart failure — no. (%)	149 (13.6)	168 (16.0)	0.80 (0.64 to 1.00)	—
Fatal or nonfatal myocardial infarction — no. (%)	78 (7.1)	102 (9.7)	0.69 (0.52 to 0.93)	—
Fatal or nonfatal stroke — no. (%)	34 (3.1)	35 (3.3)	0.90 (0.56 to 1.44)	—
Hospitalization for heart failure — no. (%)	51 (4.7)	70 (6.7)	0.66 (0.46 to 0.94)	—
Median monthly dose of erythropoiesis-stimulating agent (IQR) — IU¶	29,757 (18,673 to 48,833)	38,805 (24,377 to 60,620)	−7539 (−9485 to −5582)	—
Blood transfusion				
Any transfusion — no. (%)	198 (18.1)	226 (21.6)	0.79 (0.65 to 0.95)	—
Total no. of units transfused	967	1122	NA‖	—
No. of units transfused per yr	0.43±2.23	0.72±4.26	—	
Least-squares mean change in EQ-5D quality-of-life health index score averaged over time**	−0.04±0.01	−0.05±0.01	0.01 (−0.01 to 0.02)	—
Least-squares mean change in KDQOL overall score averaged over time††	−4.77±0.65	−4.40±0.66	−0.37 (−1.88 to 1.13)	—
Secondary safety end points				
Vascular access thrombosis — no. (%)	262 (24.0)	218 (20.8)	1.15 (0.96 to 1.38)	0.12
Hospitalization for any cause — no. (%)	651 (59.6)	616 (58.8)	1.01 (0.90 to 1.12)	0.90
Hospitalization for infection — no. (%)	323 (29.6)	307 (29.3)	0.99 (0.82 to 1.16)	0.92

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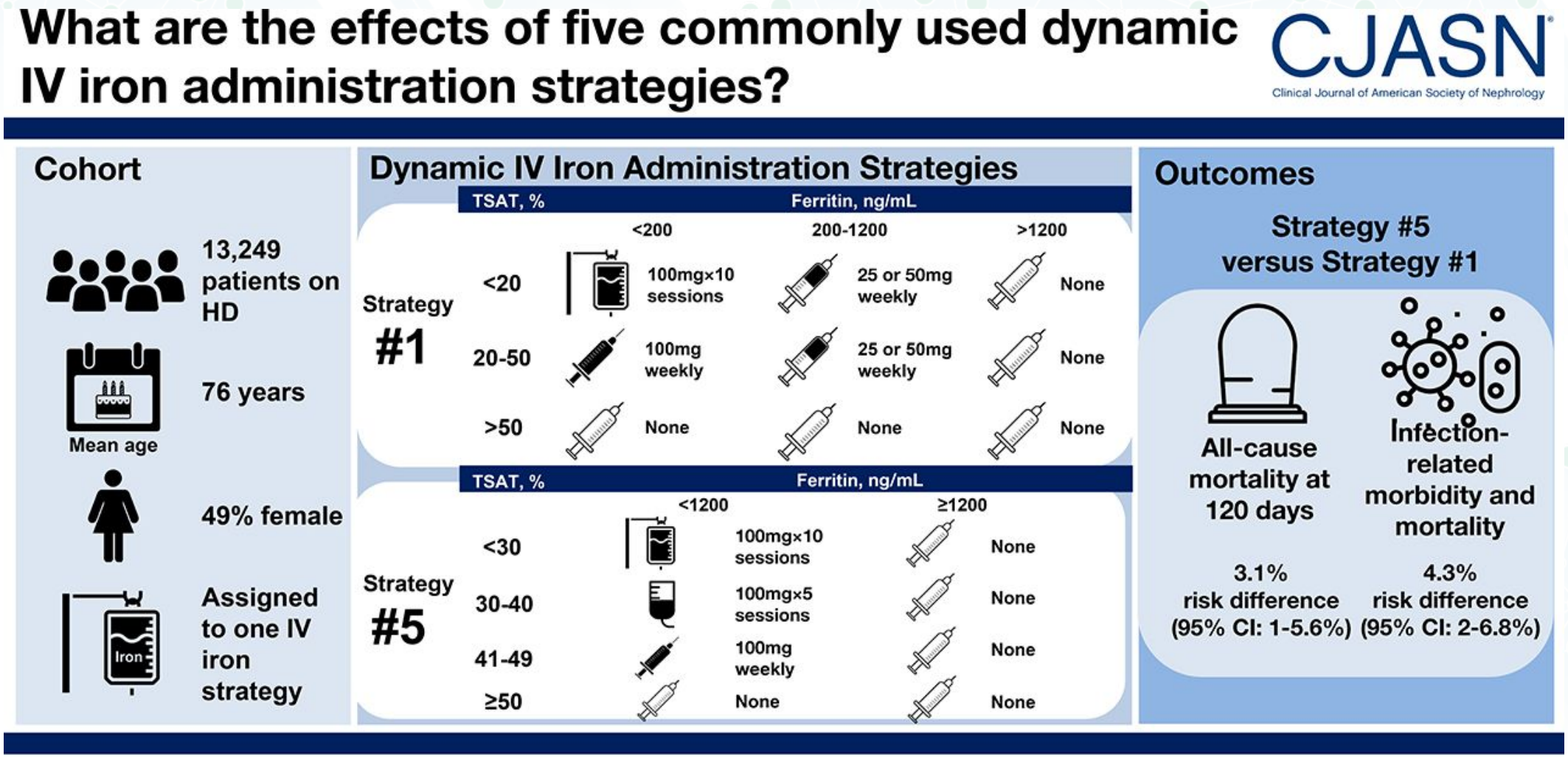
PIVOTAL IMPLICATIONS AND UNANSWERED QUESTIONS

- Avoid ferritin < 200 μg/L and TSAT < 20% in HD patients (this seems harmful)
- Using regular IV iron until ferritin > 700 μg/L or TSAT > 40% resulted in improved outcomes and was safe, leaving open:
  - 400 mg IV iron/month to ferritin 700 μg/L/ TSAT 40% might have been optimal
  - But, it is unknown whether lower, intermediate dose / target strategies might have been sufficient
  - We don't know the upper limit of TSAT and ferritin in terms of safety, ESA dose reduction, patient outcomes. Retrospective, observational data raise concerns that too intensive treatment strategies are associated with an increased risk of mortality and infections.

Potential Risk of High Intensity IV Iron in HD Patients



Conclusions IV iron dosing strategies promoting a high intensity of dose and frequency of IV iron at moderate-to-high levels of iron indices are associated with higher risks of mortality and infection-related events.

Xiaojuan Li, Stephen R. Cole, Abhijit V. Kshirsagar, Jason Fine, Til Stürmer, and M. Alan Brookhart. ***Safety of Dynamic Intravenous Iron Administration Strategies in Hemodialysis Patients.*** CJASN doi: 10.2215/CJN.03970318.
Visual Abstract by Pablo Garcia, MD.

More Unanswered Questions

- There might be differences between ethnicities worldwide. As a example, Japanese HD-patients have generally much lower median ferritin levels than HD-patients in USA and Europe, possibly related to lower inflammation levels, while achieving a similar efficacy.
- What is the optimal treatment regimen for nondialysis CKD patients?
- Is there a benefit to treating iron deficiency beyond anemia treatment?
- The optimal treatment algorithm between relative use of iron therapy and use of ESA in anemic CKD patients has not been established

Iron vs ESA Strategy: Poland Vs Portugal Experience

Table 1 Demographics and laboratory profile

mean (SD)	All	Portugal	Poland	*p**
Number of patients	1247	730	517	–
Age (years)	68 (14)	69 (14)	67 (15)	< 0.01
Hemoglobin (g/dL)	11.0 (1.3)	11.0 (1.3)	11.0 (1.3)	N.S.
TSAT (%)	31.3 (14.5)	28.5 (12.9)	35.3 (15.5)	< 0.001
Ferritin (μg/L)	605.4 (491.5)	497.9 (344.3)	757.1 (613.5)	< 0.001
Weekly dose of ESA (corrected) (U)	4306 (5134)	5154 (6077)	3133 (3068)	< 0.001
Iron dose (mg per month 1)	176 (172)	143 (176)	246 (141)	< 0.001
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Drodz *et al. BMC Nephrol*. 2019;20(1):5.

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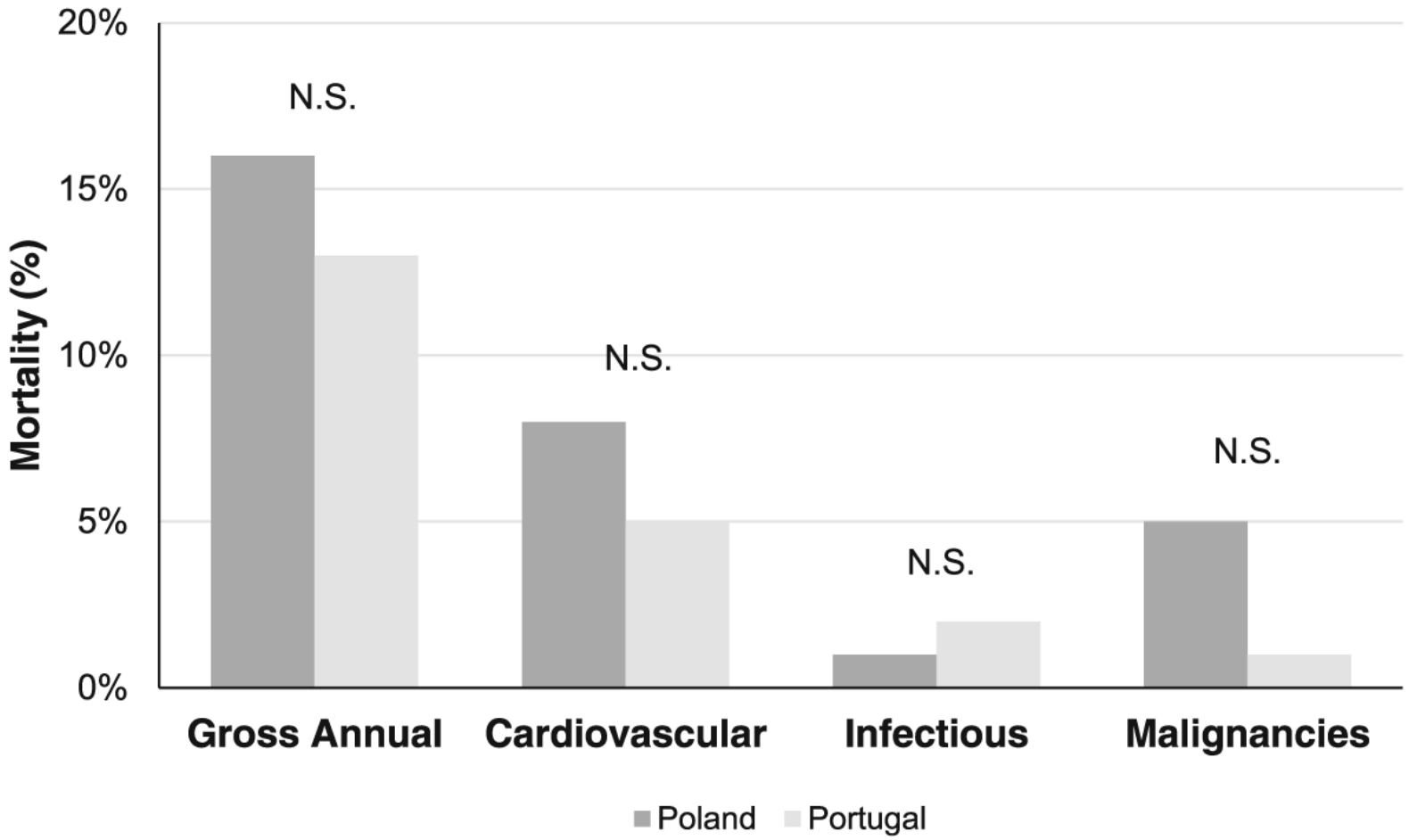
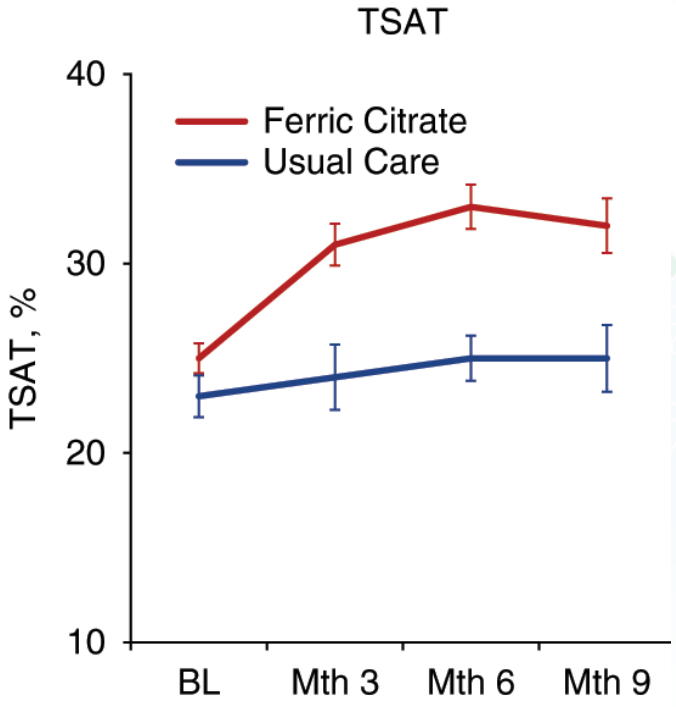


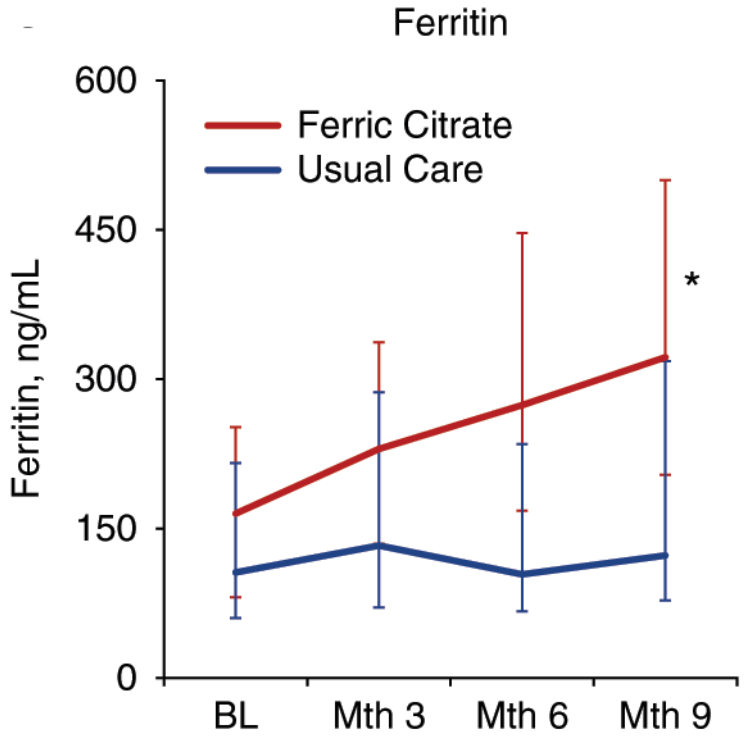
Drodz *et al. BMC Nephrol*. 2019;20(1):5.

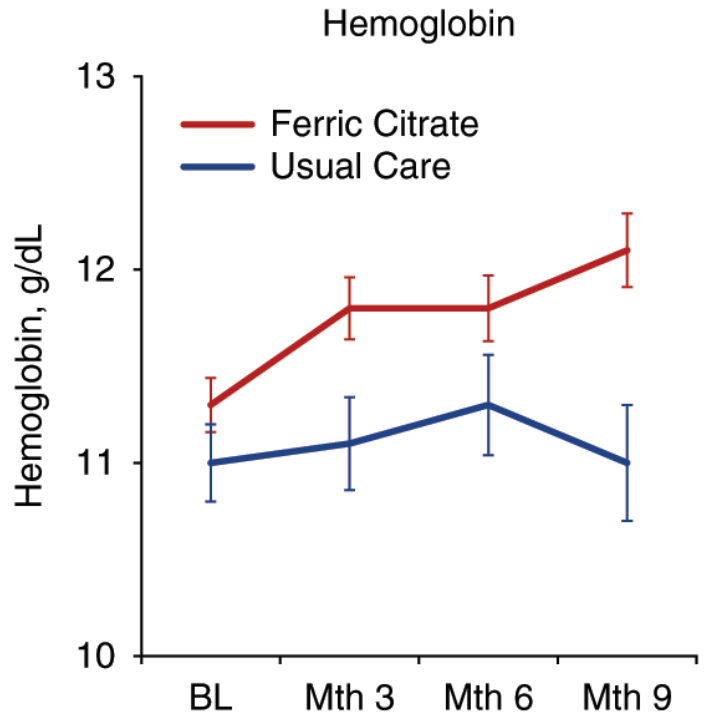
Newer Iron Preparations

- Ferric citrate: dual role as an oral iron compound and phosphate binder. Demonstrated to increase Tsat, ferritin, and Hgb in CKD patients.
- Single center, open label trial, ferric citrate vs usual care, N=203; eGFR<20ml/min

(between-group difference, P<0.001 for each)



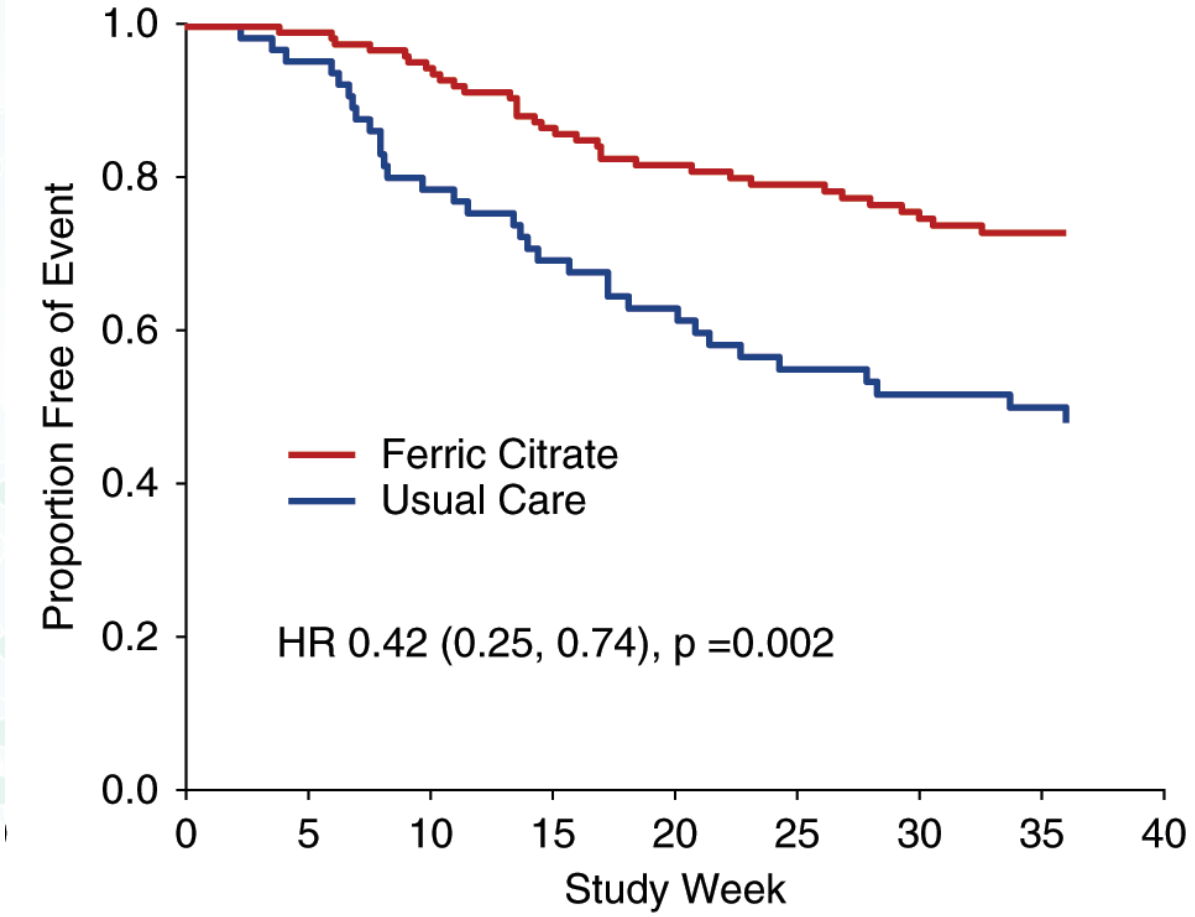




ESA use 15% vs 6% (P=0.03)
IV iron use 17% vs 3% (P=0.001)

Block *et al. J Am Soc Nephrol*. 2019;30(8):1495-1504.

Newer Iron Preparations: Ferric Citrate

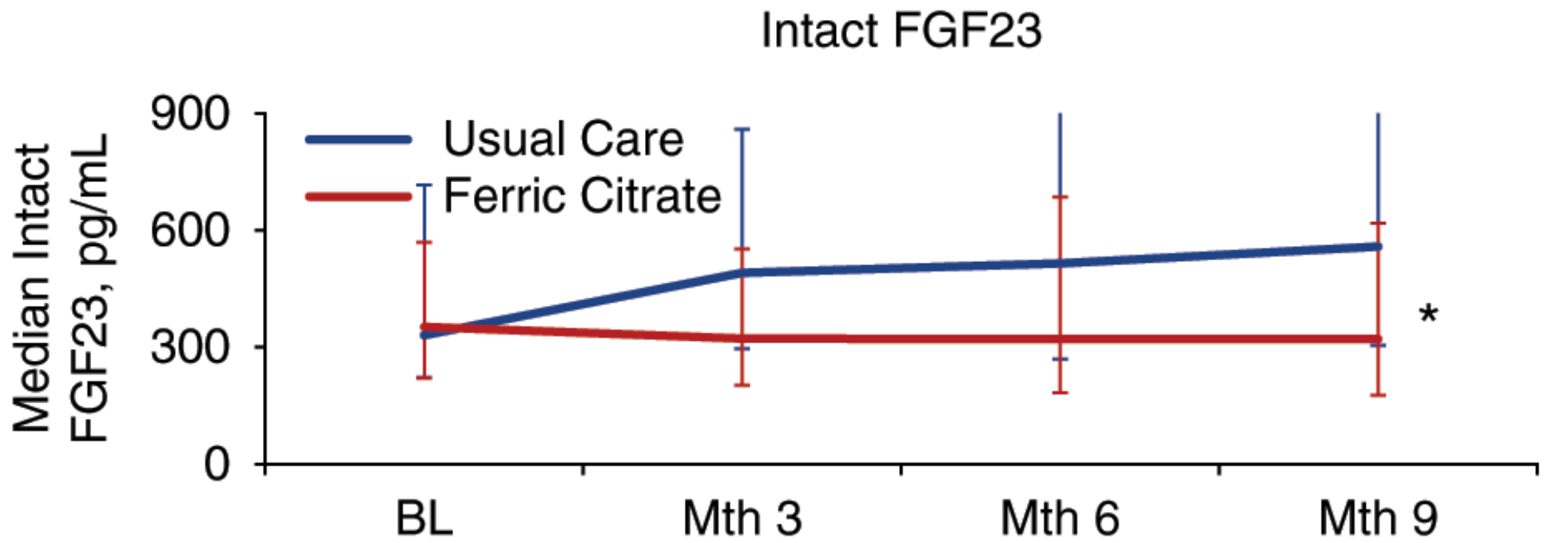


Composite of death, dialysis, transplant

- Interpret with caution; placebo controlled trials needed

Block *et al. J Am Soc Nephrol*. 2019;30(8):1495-1504.

Newer Iron Preparations: Ferric Citrate



Block *et al. J Am Soc Nephrol*. 2019;30(8):1495-1504.

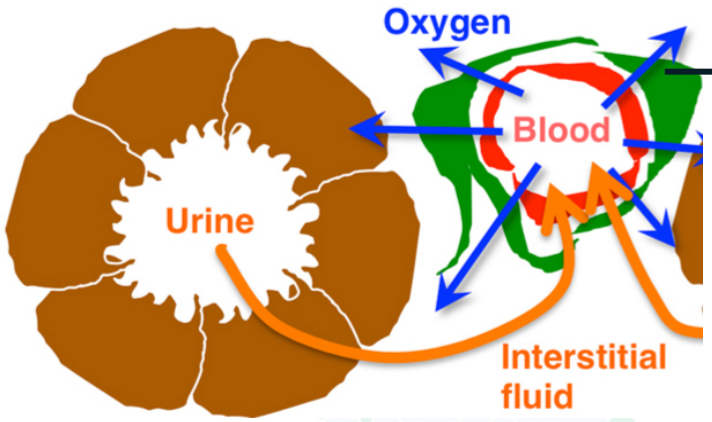
New Recognition Of Links Between Iron, EPO, and FGF23

- Iron deficiency, inflammation and EPO all stimulate FGF23 production.

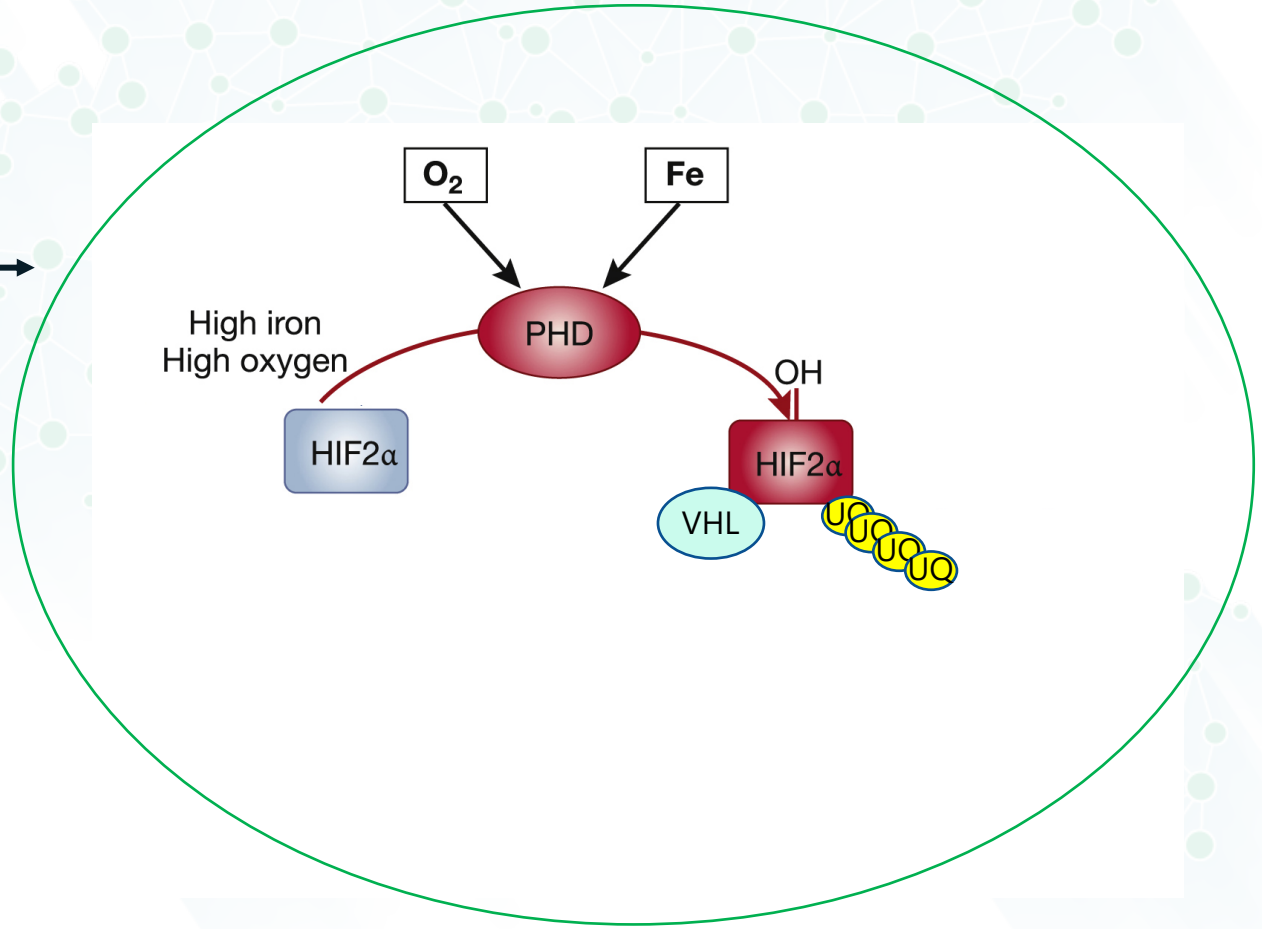
- Certain IV iron preparations cause hypophosphatemia as a consequence of stimulating FGF23 production (ferricarboxymaltose, saccharated iron oxide, iron polymaltose)

Babitt JL and Sitara D. *Curr Opin Nephrol Hypertens*. 2019;28(4):304-310.

New Agents: HIF-PHIs



Renal EPO producing cell



Suzuki and Yamamoto. *Pflugers Arch.* 2016;468(1):3-12.

Adapted from Ganz T. *Kidney Int.* 2018;94(5):851-853.

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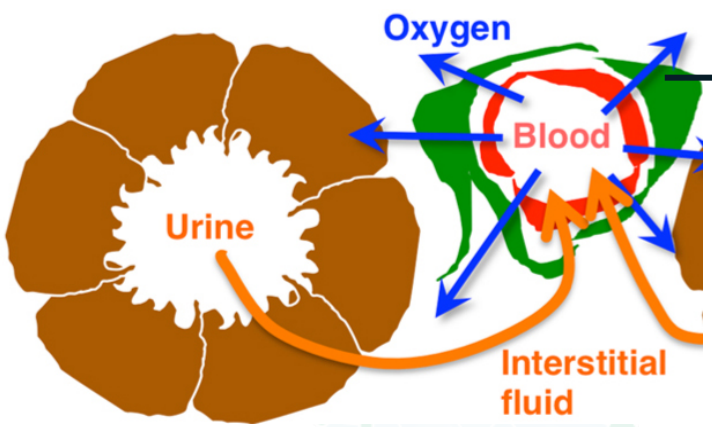

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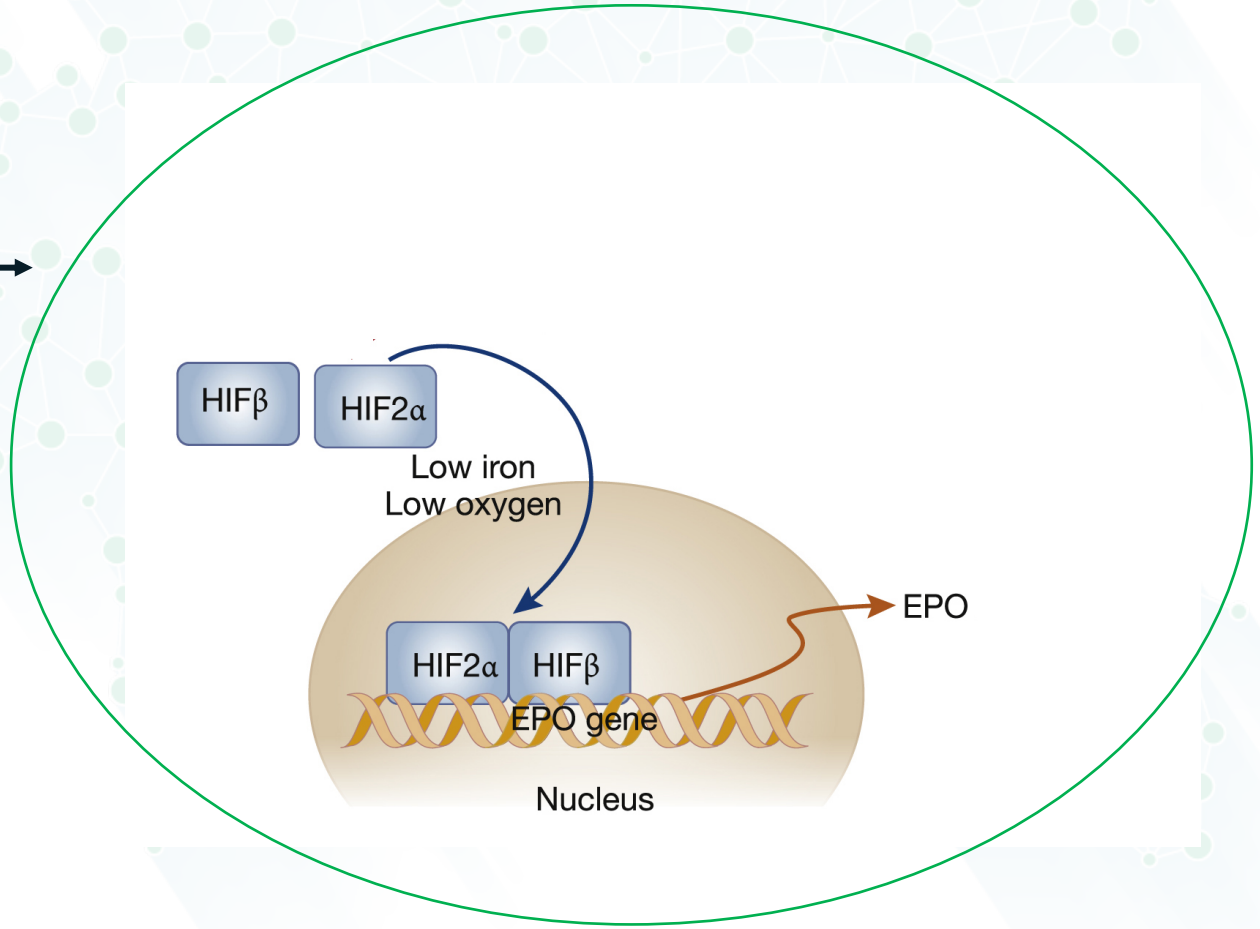

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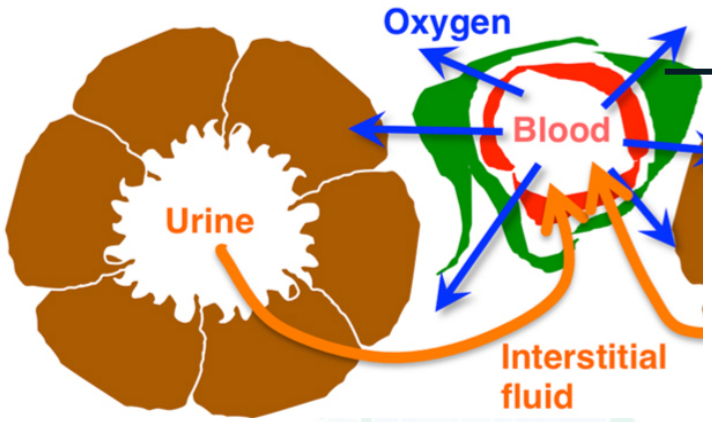

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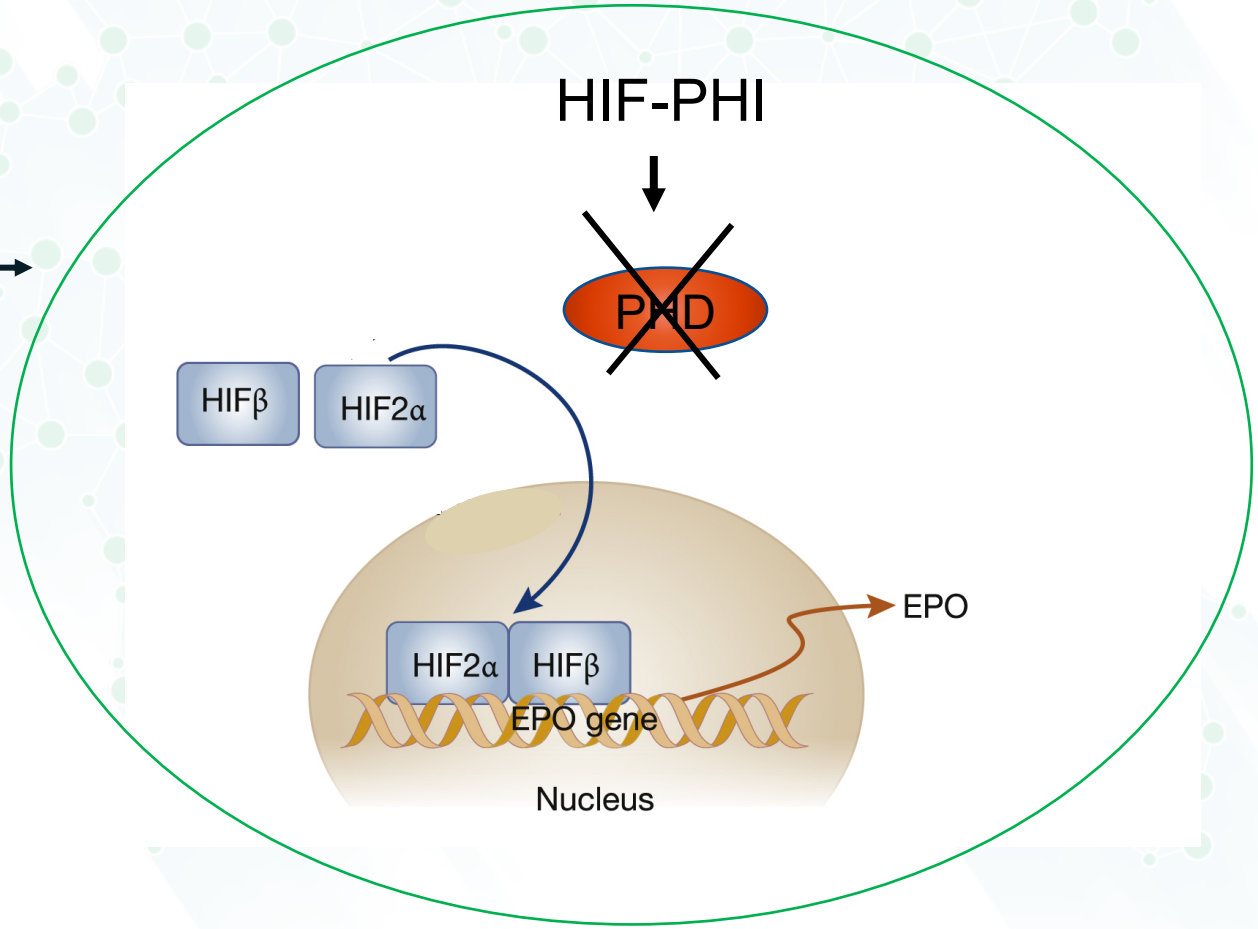

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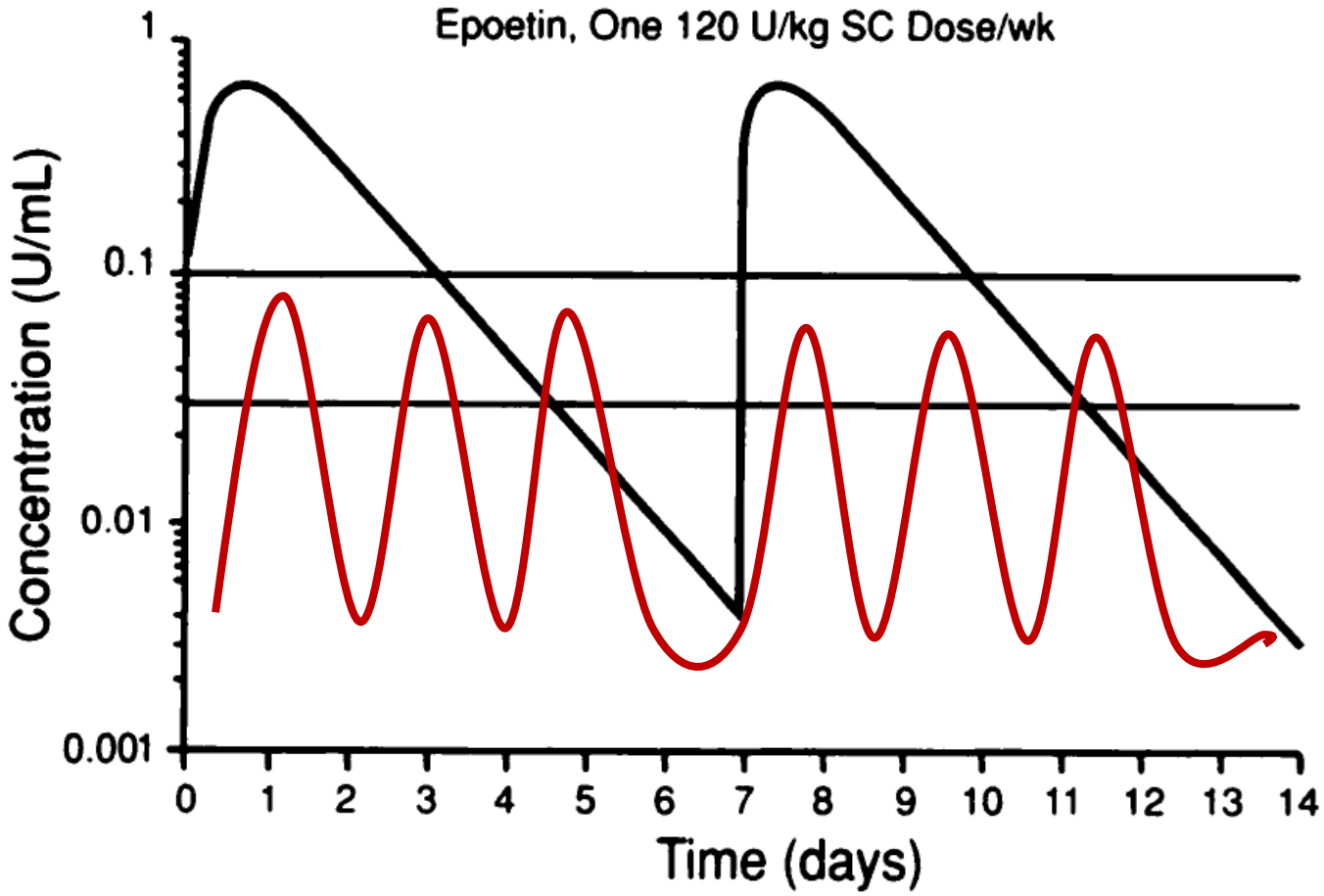
EPO LEVELS FROM EXOGENOUS EPO VS HIF STABILIZERS

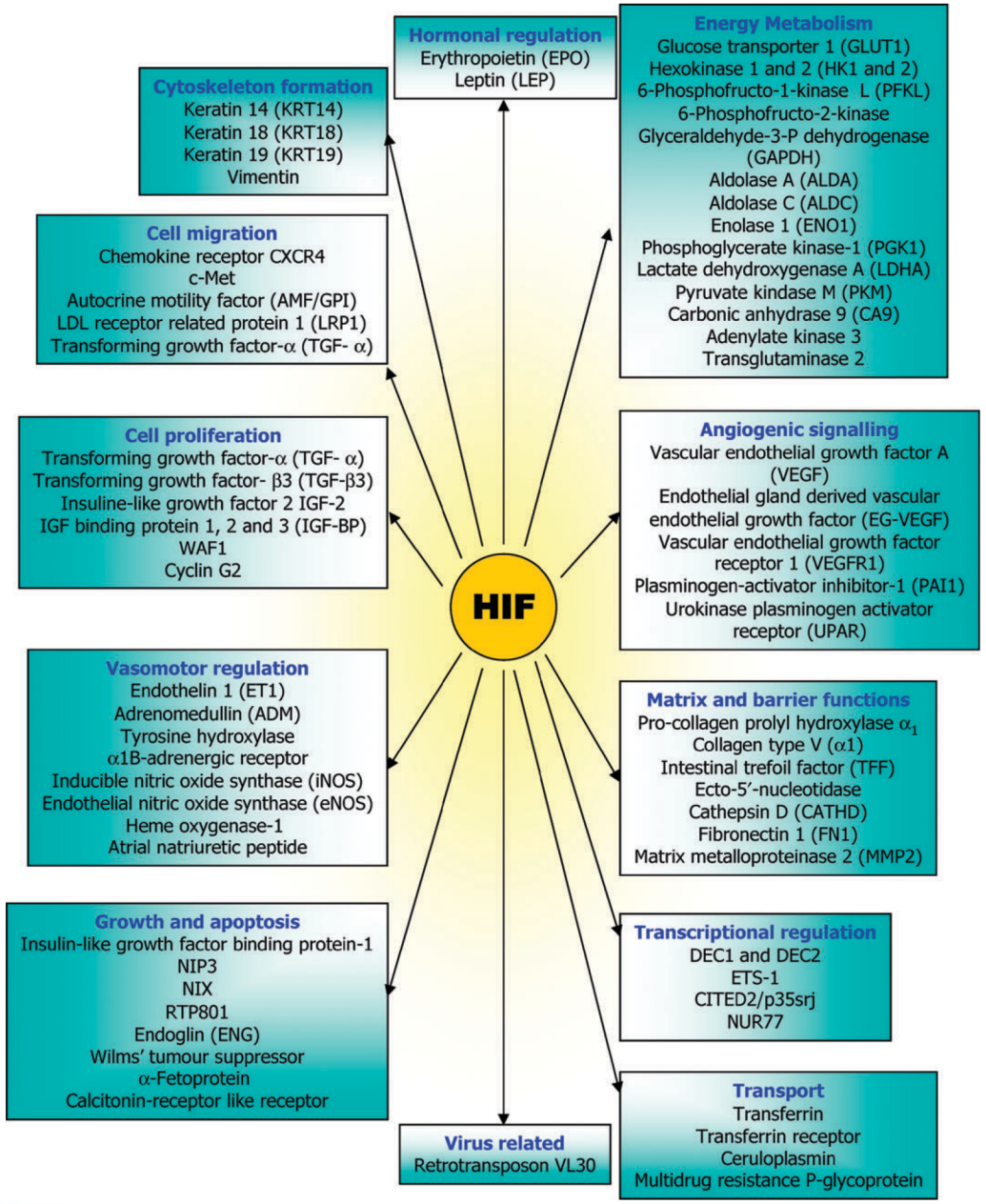


Erythropoiesis range

HIF-PHI

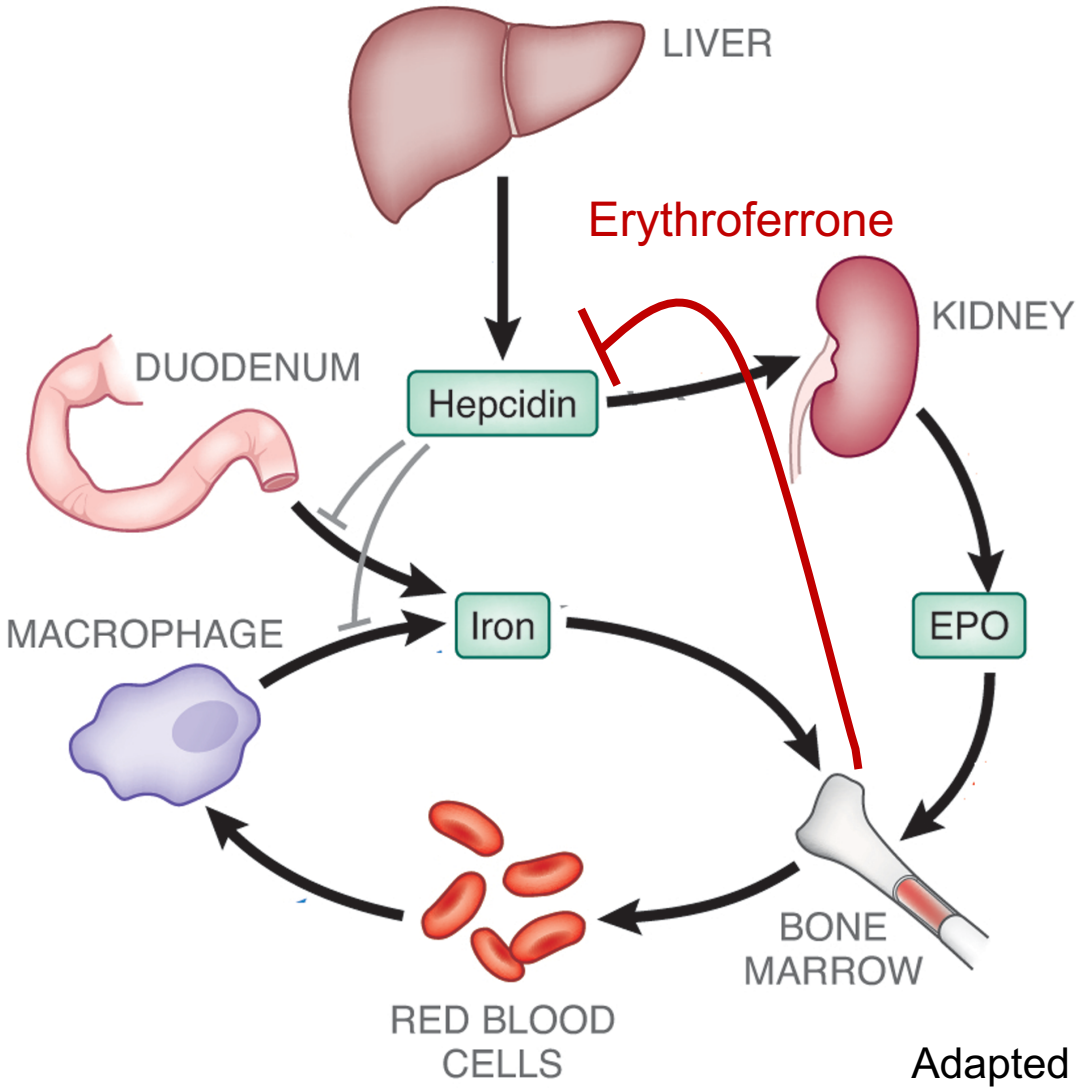
Adapeted from Besarab *et al.* J Am Soc Nephrol. 1992;2(9):1405-16.

HIF Targets



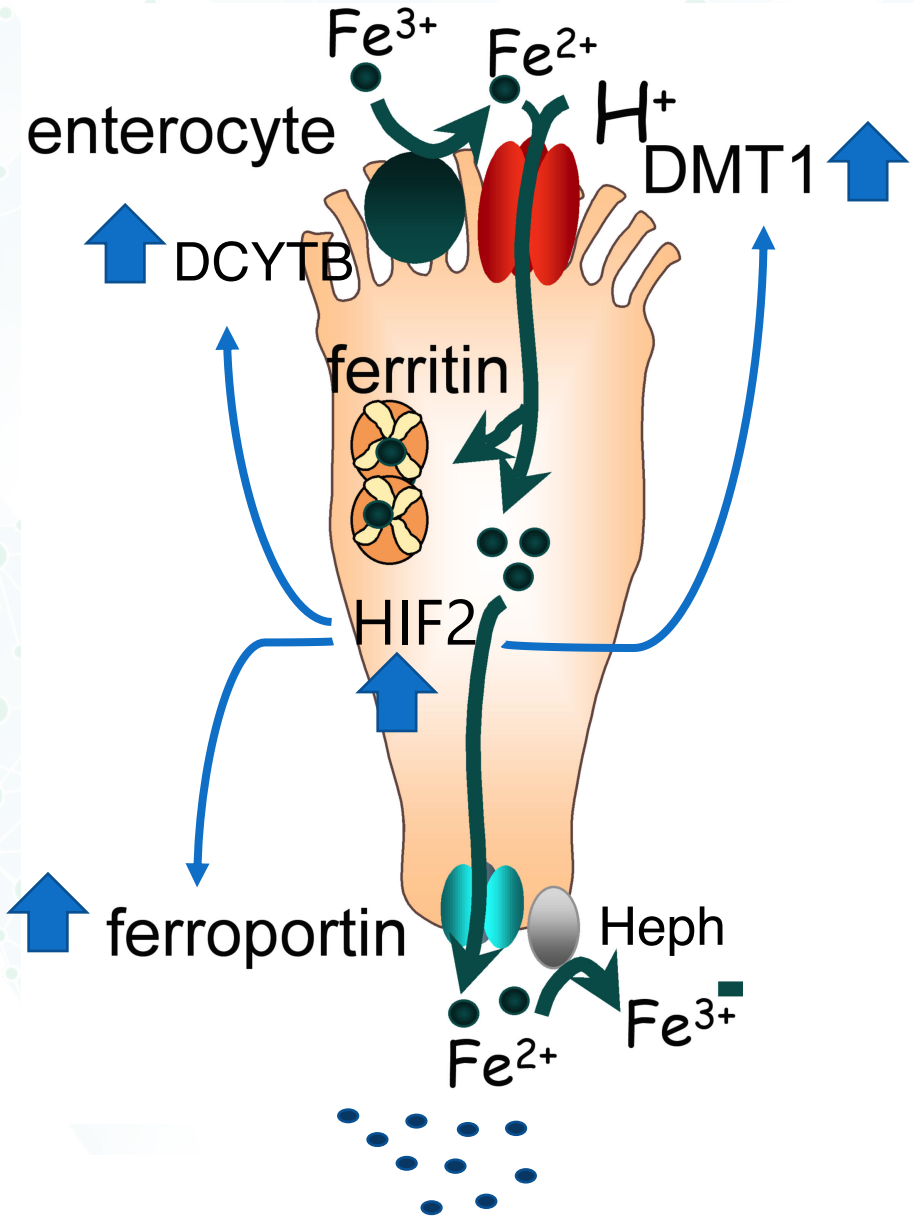
Chowdhury et al. Chem Soc Rev. 2008;37:1308-19.

HIF-PHIs AND EPO SUPPRESS HEPCIDIN TO INCREASE IRON AVAILABILITY



Adapted from: Babitt and Lin.
J Am Soc Nephrol. 2012;23(10):1631.

HIF2α DIRECTLY TARGETS INTESTINAL IRON TRANSPORT PROTEINS



HIF-PHIs: Phase 3 Trials

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Roxadustat Treatment for Anemia in Patients Undergoing Long-Term Dialysis

N. Chen, C. Hao, B.-C. Liu, H. Lin, Caili Wang, C. Xing, X. Liang, G. Jiang, Zhengrong Liu, X. Li, L. Zuo, L. Luo, J. Wang, M. Zhao, Zhihong Liu, G.-Y. Cai, L. Hao, R. Leong, Chunrong Wang, C. Liu, T. Neff, L. Szczech, and K.-H.P. Yu

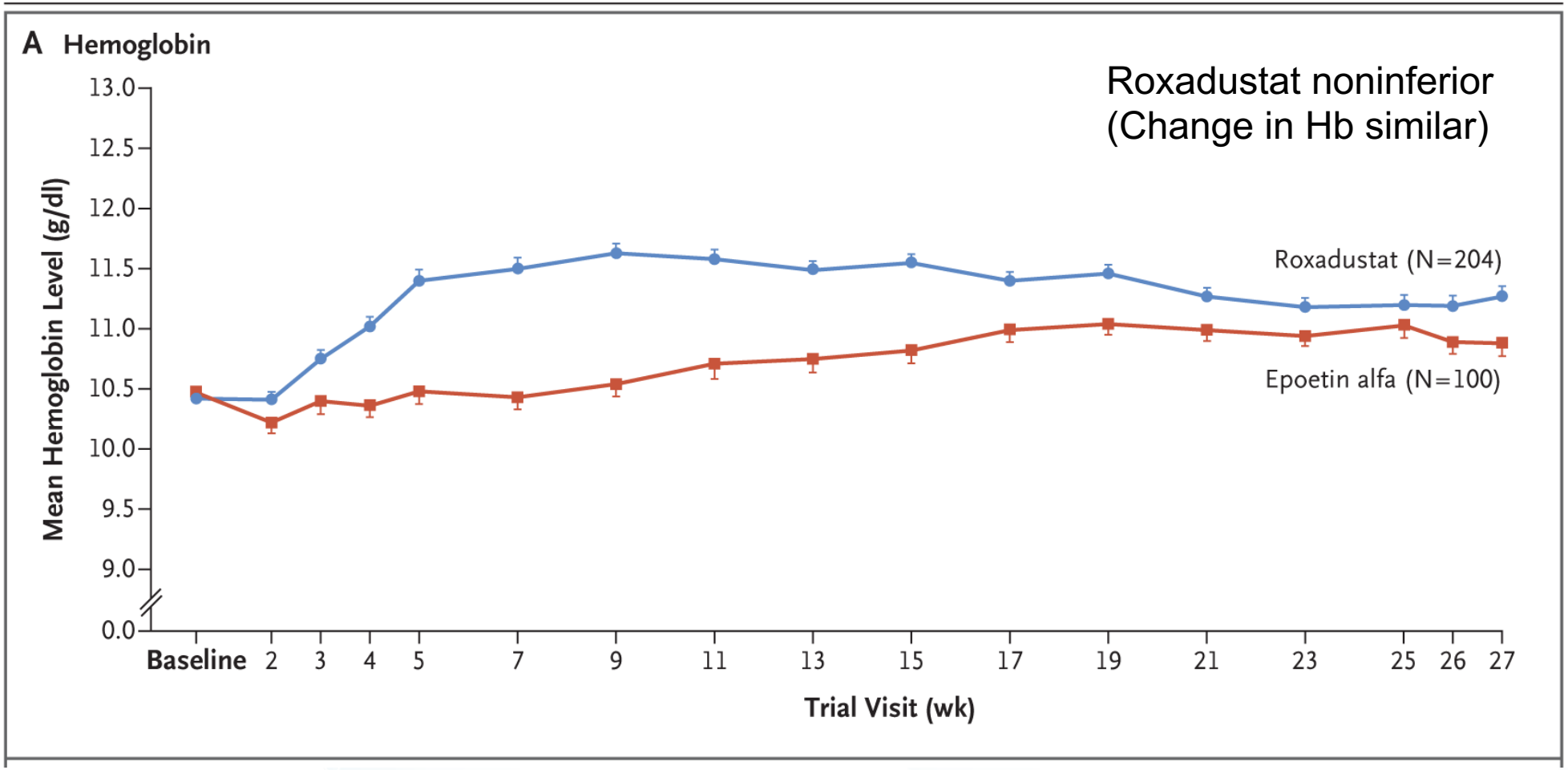
N ENGL J MED 381;11 NEJM.ORG SEPTEMBER 12, 2019

HIF-PHIs: Phase 3 Trials

- Prospective, open label, randomized control trial of Roxadustat vs active therapy with epoetin alfa
- Noninferiority trial
- Duration 26 weeks. N=305 assigned 2:1 to Roxadustat vs EPO. Dose adjusted to achieve Hb target 10-12. No IV iron allowed (except rescue therapy)
- Primary end point: change in Hb level from baseline to end of study (avg of weeks 23-27)
- Secondary endpoints: change in iron biomarkers, change in cholesterol, Hb effect based on inflammatory status (CRP), exacerbation of HTN, change in MAP

Chen N *et al. N Engl J Med.* 2019;381(11):1011-1022.

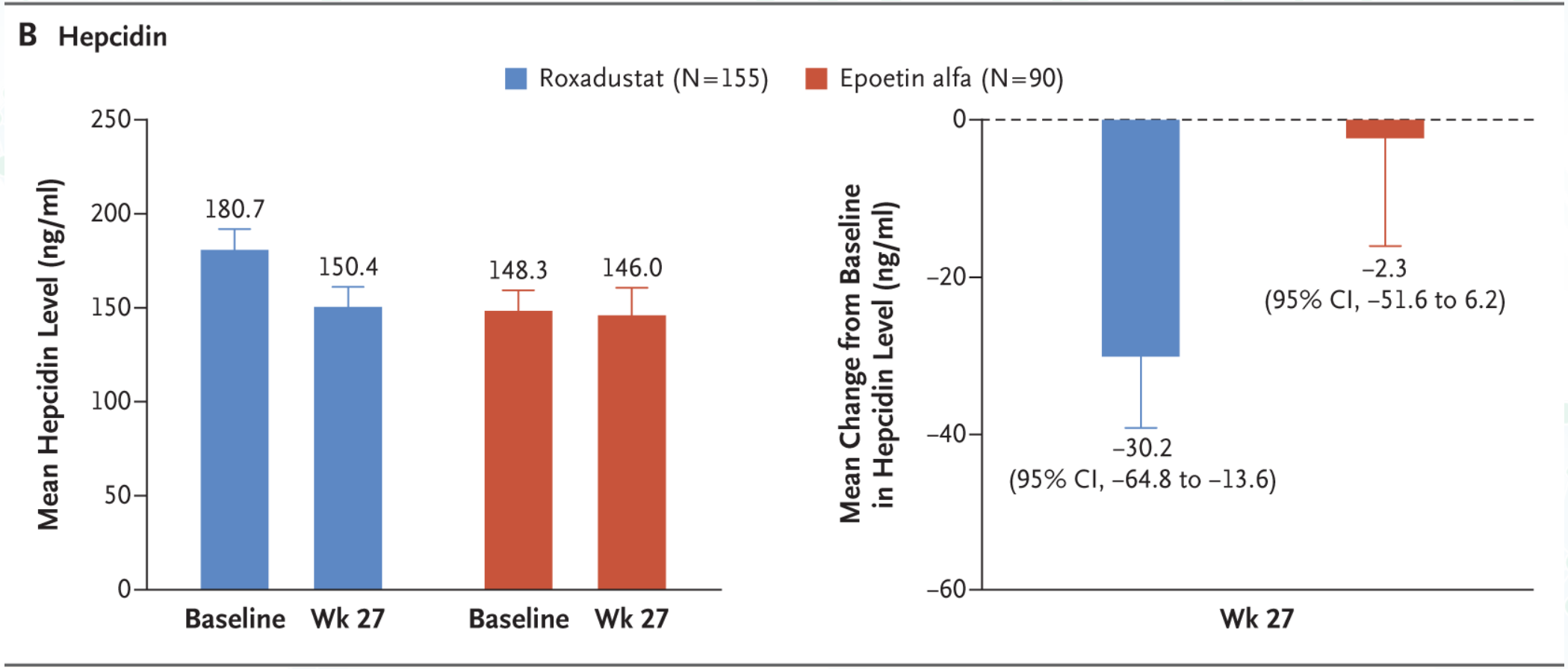
HIF-PHIs: Phase 3 Trials



Percentage of patients with Hb response, Hb above lower target, need for rescue therapy also similar

Chen N *et al. N Engl J Med.* 2019;381(11):1011-1022.

HIF-PHIs: Phase 3 Trials



Chen N *et al. N Engl J Med.* 2019;381(11):1011-1022.

HIF-PHIs: Phase 3 Trials

Another phase 3 trial of roxadustat vs darbepoetin alfa in Japanese HD patients

Parameter	Roxadustat (n=150)	Darbepoetin alfa (n=151)
Week 0	26.441 (21.502)	24.446 (20.988)
Week 4	25.344 (26.584)	21.605 (19.694)
Week 12	25.469 (24.711)	22.490 (28.579)
Week 24	27.665 (24.640)	23.241 (26.472)
EoT	28.749 (28.220)	23.845 (26.127)
Change from Week 0 to EoT	2.308 (27.279)	–0.600 (27.061)

Akizawa et al. J Am Soc Nephrol. 2020;31(7):1628-1639.

HIF-PHIs: Phase 3 Trials

Table 2. Mean Change from Baseline in Iron Biomarker Levels at Week 27 (Intention-to-Treat Population).*

Variable	Roxadustat		Epoetin Alfa		Treatment Difference (95% CI)
	End-of-Treatment Assessment	Change from Baseline	End-of-Treatment Assessment	Change from Baseline	
Iron					
No. of patients	160	160	94	94	
Mean (μmol/liter)	15.2±8.1	0.1±8.3	10.6±4.0	−3.7±7.2	
Least-squares mean (μmol/liter)		0.6±0.7		−3.9±0.5	4.4±0.7 (3.0 to 5.9)
Transferrin					
No. of patients	160	160	94	94	
Mean (g/liter)	2.29±0.66	0.40±0.48	1.86±0.45	−0.04±0.36	
Least-squares mean (g/liter)		0.38±0.05		−0.05±0.04	0.43±0.05 (0.32 to 0.53)
Total iron-binding capacity					
No. of patients	160	159	94	93	
Mean (μmol/liter)	57.4±16.5	10.0±11.9	46.6±11.3	−1.1±9.0	
Least-squares mean (μmol/liter)		9.5±1.2		−1.2±1.1	10.7±1.3 (8.1 to 13.3)
Transferrin saturation					
No. of patients	160	159	94	93	
Mean (%)	28.0±15.8	−5.7±15.4	23.0±8.5	−7.6±13.8	
Least-squares mean (%)		−4.5±1.2		−8.7±1.0	4.2±1.4 (1.5 to 6.9)
Ferritin					
No. of patients	160	160	94	94	
Mean (μg/liter)	373±470	−119±208	294±294	−136±220	
Least-squares mean (μg/liter)		−99±19		−133±21	35±24 (−12 to 82)

* Plus–minus values are means ±SD or least-squares means ±SE. Baseline values are provided for patients who had paired values at week 27 for comparison. To convert the values for iron to micrograms per deciliter, divide by 0.1791.

Chen N *et al. N Engl J Med.* 2019;381(11):1011-1022.

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Chen N *et al. N Engl J Med.* 2019;381(11):1011-1022.

CONCLUSIONS

- A lot has changed since 2012: New RCTs and other clinical trials, new iron agents, new biologic insights
- Many unanswered questions. More research is needed.
- New guidelines will be needed.
- Stay tuned for our paper.
- KDIGO Controversies Conference on Novel Anemia Therapies, December 2021

THANK YOU

KDIGO

John Davis
Michael Cheung
Melissa Thompson
Wolfgang Winkelmayer
Michel Jadoul
Tanya Green
Danielle Green
Jennifer King

Conference Leaders

Tilman Drüeke
Abhi Kshirsagar
Adeera Levin
Francesco Locatelli
Dorine Swinkels
Volker Haase
Jolanta Malyszko
Michele Eisenga
Der-Cherng Tarng
All conference attendees!

2021 Annual Dialysis Virtual Conference

KDIGO Guidelines for Hypertension Management in CKD (ND)

KDIGO Guideline Co-Chairs:

Alfred K. Cheung, MD

University of Utah

Johannes F.E. Mann, MD

KfH Kidney Center

DISCLOSURES

- Alfred Cheung has received
  - Consultancy/contributions: Boehringer Ingelheim, UptoDate
  - Research grants from National Institutes of Health for SPRINT trial

Work Group & Process

- International representations
- Extensive experiences (CKD, HTN)
- Evidence Review Team (Cochrane Kidney Transplant)
- Rigorous “GRADE” (Grading of Recommendations Assessment, Development and Evaluation) methodology

What is New Since 2012 KIDGO Guideline

- SPRINT (Systolic Blood Pressure Intervention Trial), SPRINT-CKD and SPRINT-MIND
- Large meta-analysis of BP trials in CKD and non-CKD populations
- More work and emphasis on techniques of BP measurement

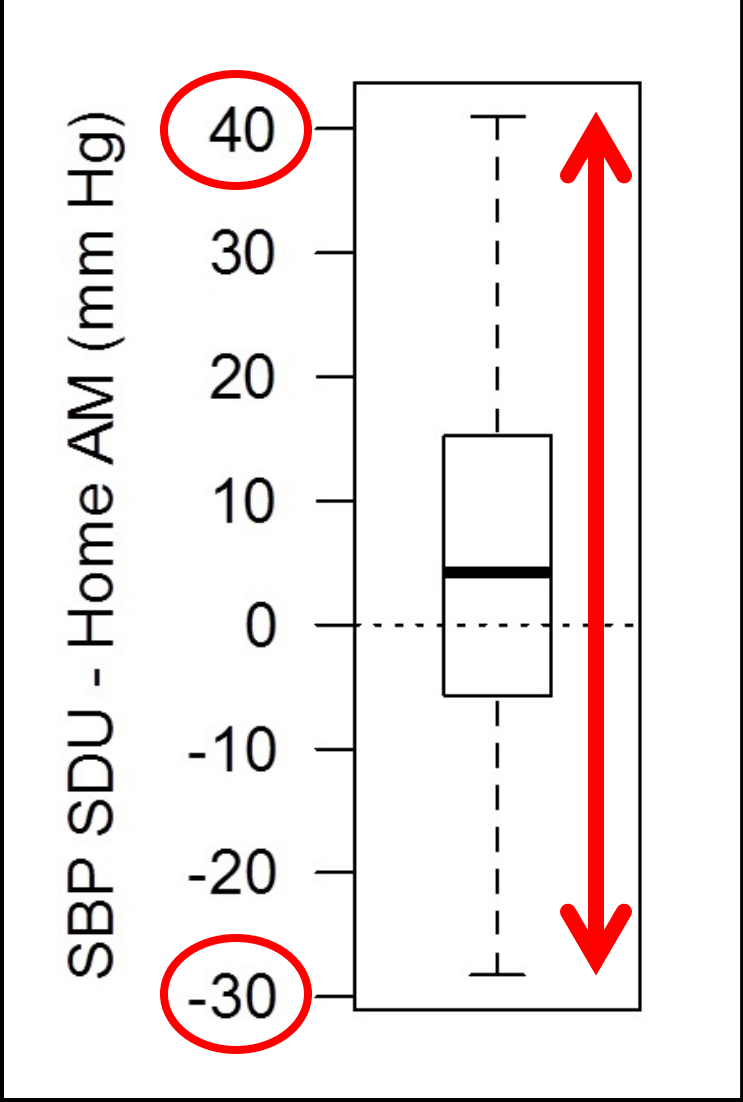
Public Commentary

- Jan 31 – Mar 2, 2020
- All commentaries carefully considered
- Revision submitted for publication

Why Exclude Dialysis Patients in Guideline?

- Lack of larger RCT targeting BP with hard clinical outcomes
- Very poor correlation between predialysis BP with “steady-state” interdialytic BP values

Standardized Dialysis Unit vs. Home SBP



- Blood Pressure in Dialysis (BID) Trial (pilot RCT)
- Standardized Dialysis Unit (SDU) BP measurement and home measured per AHA guidelines (3 readings after 5 min rest), both using oscillometric device
- N = 2512 pairs of mid-week pre-HD and next home BP in 121 patients

Miskulin, ASN, 2017

Guideline Chapters

- Chapter 1. BP Measurement
- Chapter 2. Lifestyle Treatment for Lowering BP in CKD Patients
- Chapter 3. BP Management in CKD ND Patients with and without Diabetes
- Chapter 4. BP Management in Kidney Transplant Recipients
- Chapter 5. BP Management in Children with CKD

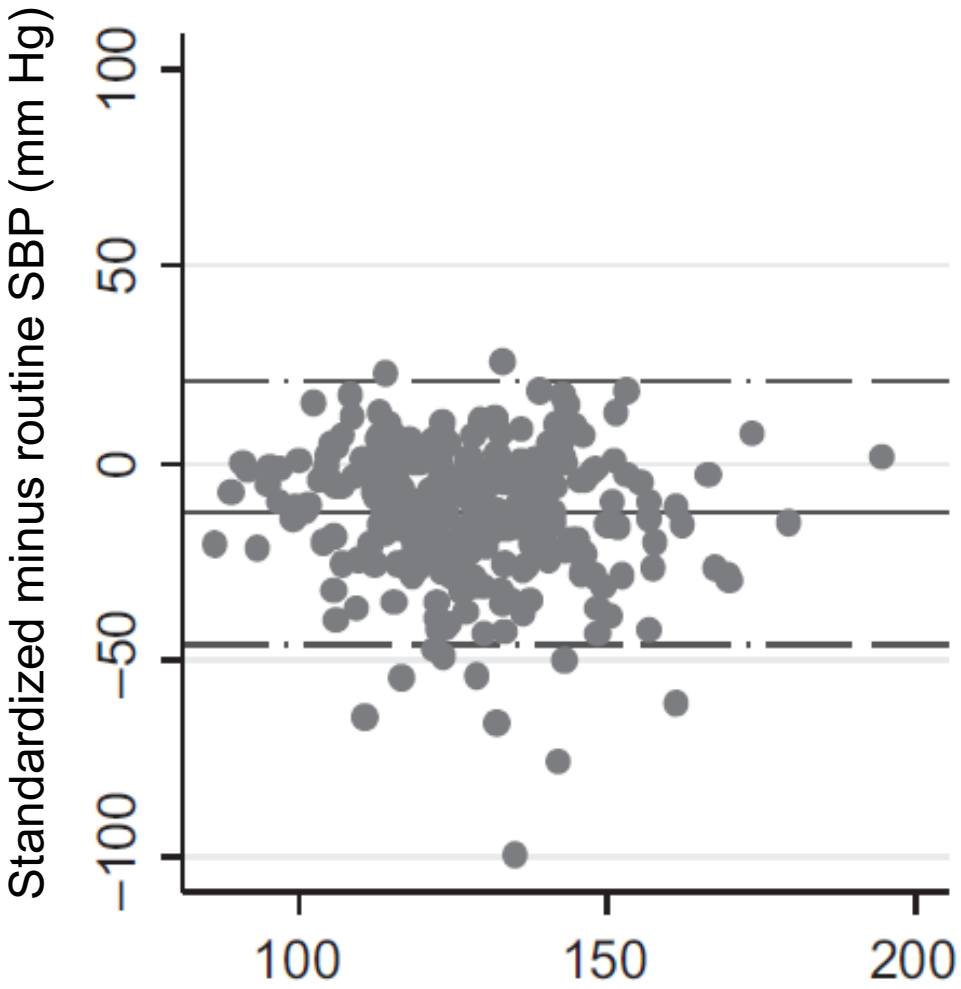
BP Measurement

Recommendation 1.1. We recommend standardized office BP in preference to routine office BP for the management of high BP in adults (1B).

STANDARDIZED BP MEASUREMENT

- **Key is proper preparations**
  - Abstinence from caffeine, exercise and smoking for >30 min
  - Feet on floor; arm and back supported
  - Keep quiet (and not talked to) and relaxed for >5 min
  - Correct cuff size and position
  - Validated equipment *(not necessarily automated)*
- Advantages
  - Employed in large RCTs (e.g., ACCORD and SPRINT)
  - Minimizes over-treatment or under-treatment of high BP
- Disadvantages
  - Requires staff training and retraining
  - Requires more time of patients, staff and clinic

Poor Correlation Between Routine and Standardized Office BP



- N = 275 **CKD**
- eGFR 29±10 ml/min/1.73m^2
- Bland-Altman plot with limits of agreement

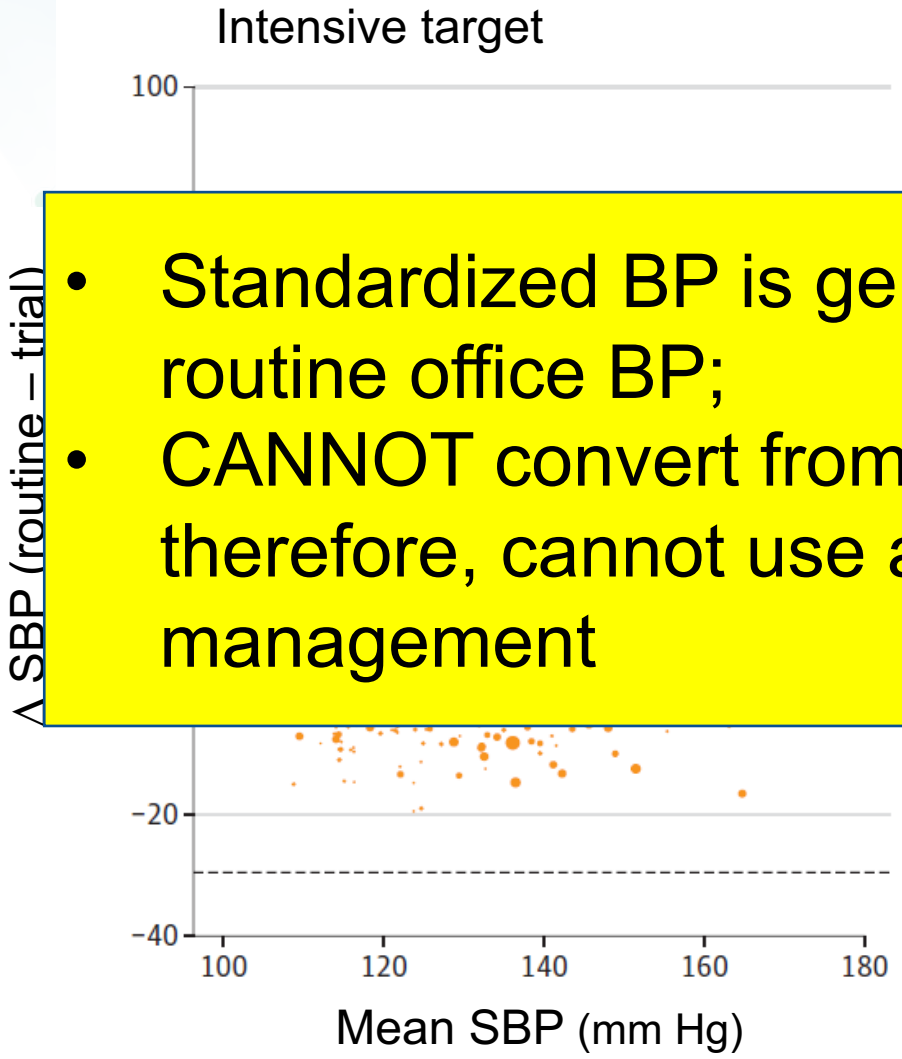
← **+20.7 mm Hg**

← -12.7 mm Hg

← **-46.1 mm Hg**

Agarwal, JAHA, 2017

Poor Concordance in SBP between Trial and Routine Clinical Practice Measurements in SPRINT



- Standardized BP is generally lower (but can be higher) than routine office BP;
- CANNOT convert from one to the other *in individual patient,* therefore, cannot use a correction factor for clinical BP management

Drawz, JAMA IM, 2020

BP Measurement: Practice Points

Oscillometric BP device may be preferable to manual device for standardized office BP measurement.

Automated office BP (AOBP), either attended or unattended, may be preferred method of *standardized* office BP measurement.

- **May increase likelihood of adherence to proper BP measurement protocols**
- **Removes potential sources of inaccuracies with manual measurement**
- **May reduce white-coat effect**
- **Frees staff to complete other duties**
- **Used in large RCTs and prospective cohort studies**

But, probably not as important as proper preparations

BP Measurement

Recommendation 1.2. We suggest that out-of-office BP measurements be used with ambulatory BP monitoring (ABPM) or home BP monitoring (HBPM) to complement standardized office BP readings for the diagnosis and management of high BP. (2B)

- Weak recommendation since no large outcomes trials based on out-of-office BP

BP Management in CKD ND Patients with and without Diabetes – **BP Targets**

Recommendation 3.1.1. We suggest that adults with CKD and high BP be treated with a target systolic blood pressure (SBP) of less than 120 mm Hg, using *standardized* office BP measurement (2B)

INDIVIDUALIZATION IS KEY

Benefits and ha

- Diabetes
- CKD Stag
- Heavy proteinuria
- Individuals with SBP 120-129 mm Hg
- Patients with very low baseline diastolic BP (DBP) (e.g., <50 mm Hg)
- Very old (e.g., >90 yrs) or very frail in nursing home
- Severe hypertension (e.g., SBP <150 mm Hg on >4 drugs)

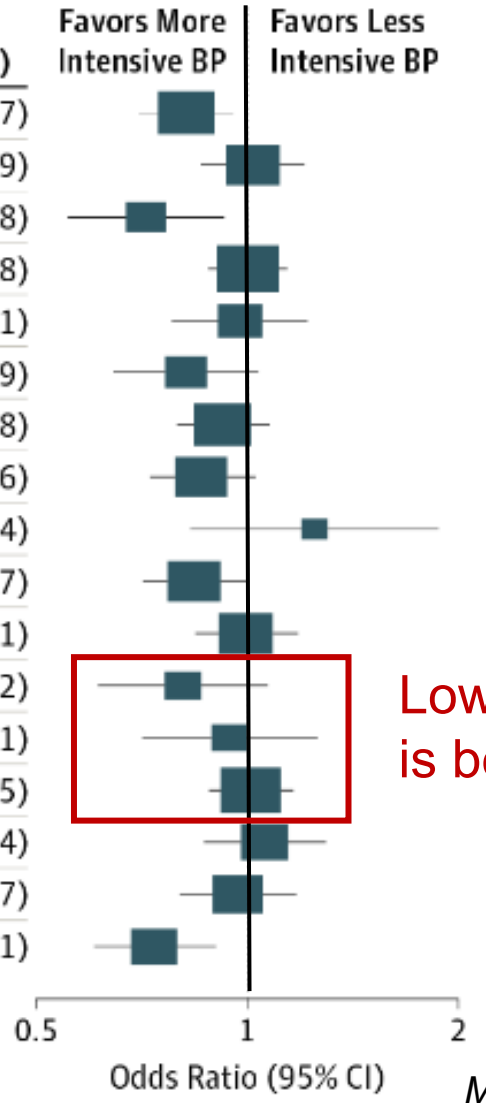
Should this be separated into 2 different recommendations?

Effect of Intensive BP Lowering on Risk of Mortality in **CKD**

18 RCTs

Subgroup		No. of Trials	No. of Deaths/Total No. More Intensive BP	No. of Deaths/Total No. Less Intensive BP	Odds Ratio (95% CI)	*P* Value for Heterogeneity
Drug vs placebo		5	328/2976	395/3006	0.819 (0.700-0.957)	.06
Defined BP arms		13	256/4375	314/5467	1.020 (0.860-1.209)	
Follow-up	<3 y	4	112/1223	153/1242	0.718 (0.555-0.928)	.38
Median 3.6 yr	≥3 y	14	472/6128	556/7231	1.002 (0.882-1.138)	
Diabetes	Yes	6	174/1428	178/1431	0.977 (0.781-1.221)	
	No	6	131/2552	156/2515	0.818 (0.644-1.039)	.29
Severe renal dysfunction	Yes	10	307/4960	403/6051	0.925 (0.793-1.078)	
	No	8	277/2468	306/2395	0.863 (0.726-1.026)	.56
Baseline SBP	<140 mm Hg	6	55/929	44/916	1.247 (0.830-1.874)	
	140-160 mm Hg	8	275/3293	315/3225	0.842 (0.710-0.997)	
	>160 mm Hg	4	254/3129	350/4302	0.998 (0.843-1.181)	.14
Achieved SBP	<125 mm Hg	4	97/1602	116/1575	0.811 (0.613-1.072)	
	125-135 mm Hg	8	96/1542	101/1538	0.945 (0.708-1.261)	
	>135 mm Hg	6	391/4207	492/5360	1.014 (0.882-1.165)	
SBP difference	≤6 mm Hg	7	175/2550	244/3750	1.059 (0.866-1.294)	
	>6 to <12 mm Hg	7	229/2434	228/2359	0.971 (0.800-1.177)	.06
	≥12 mm Hg	4	180/2367	237/2364	0.761 (0.621-0.931)	

OR=0.86



Lower is better

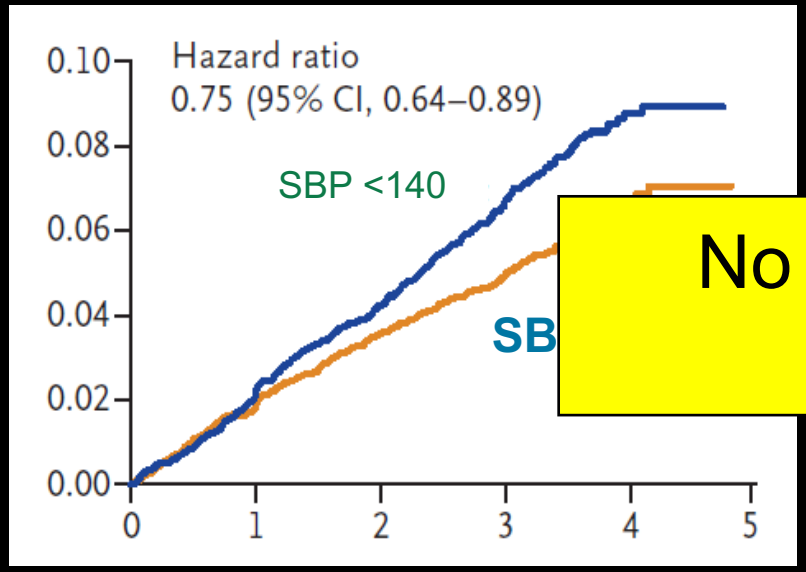
- Heterogeneity in intensity of BP lowering

Malhotra, JAMA IM 2017

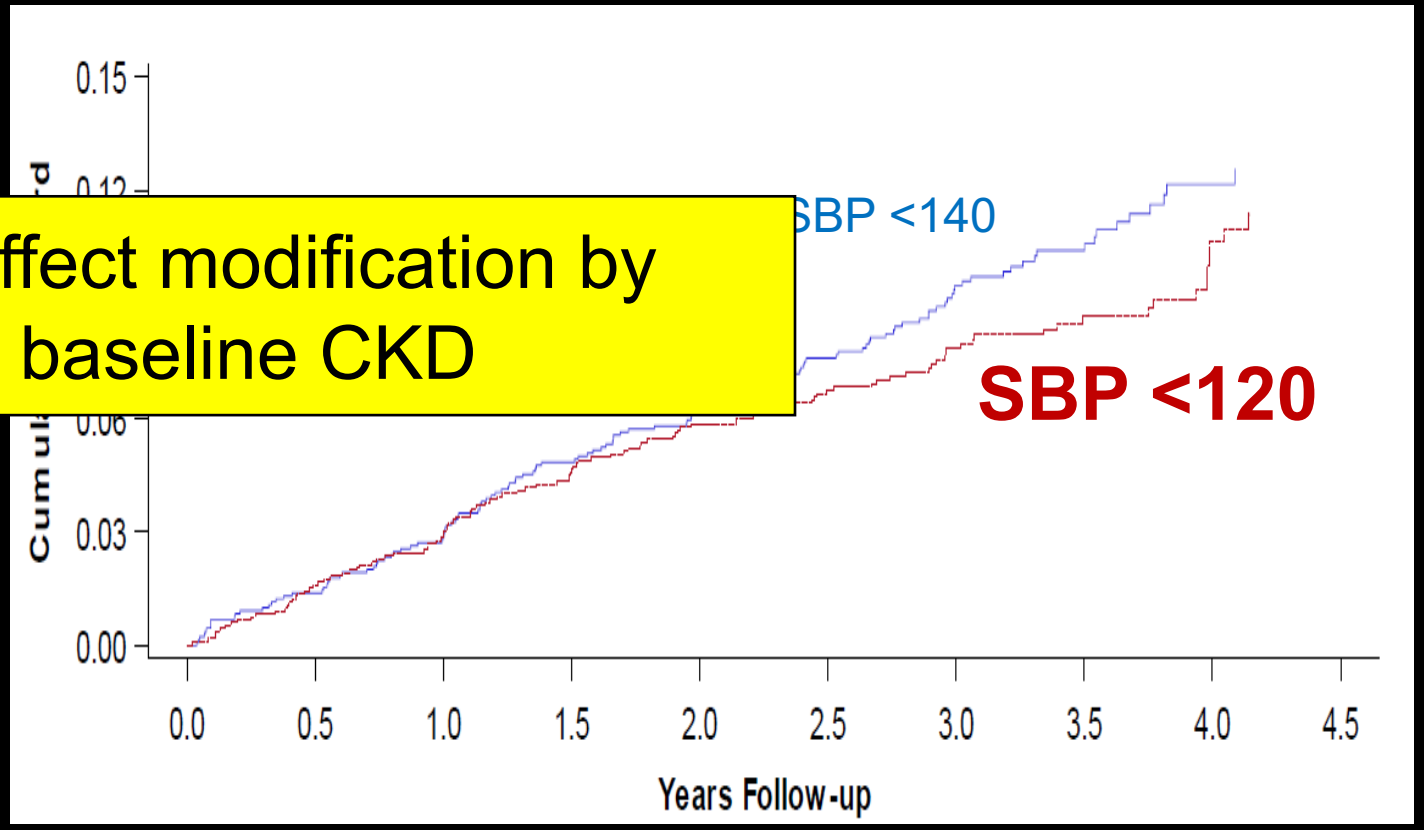
SPRINT (Target SBP <120 mm Hg vs. <140 mm Hg)

Primary Outcome (Cardiovascular events = MI, ACS, stroke, CHF, CV death)

Entire Cohort



CKD subgroup



No effect modification by baseline CKD

- Similar results for all-cause mortality (HR 0.72; 95% CI 0.53-0.99)

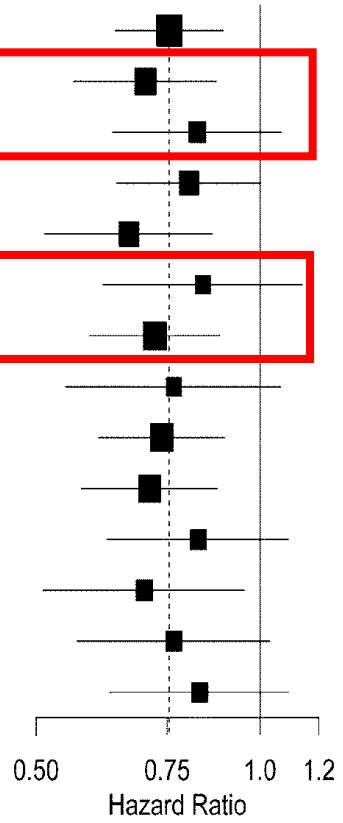
SPRINT, NEJM, 2015

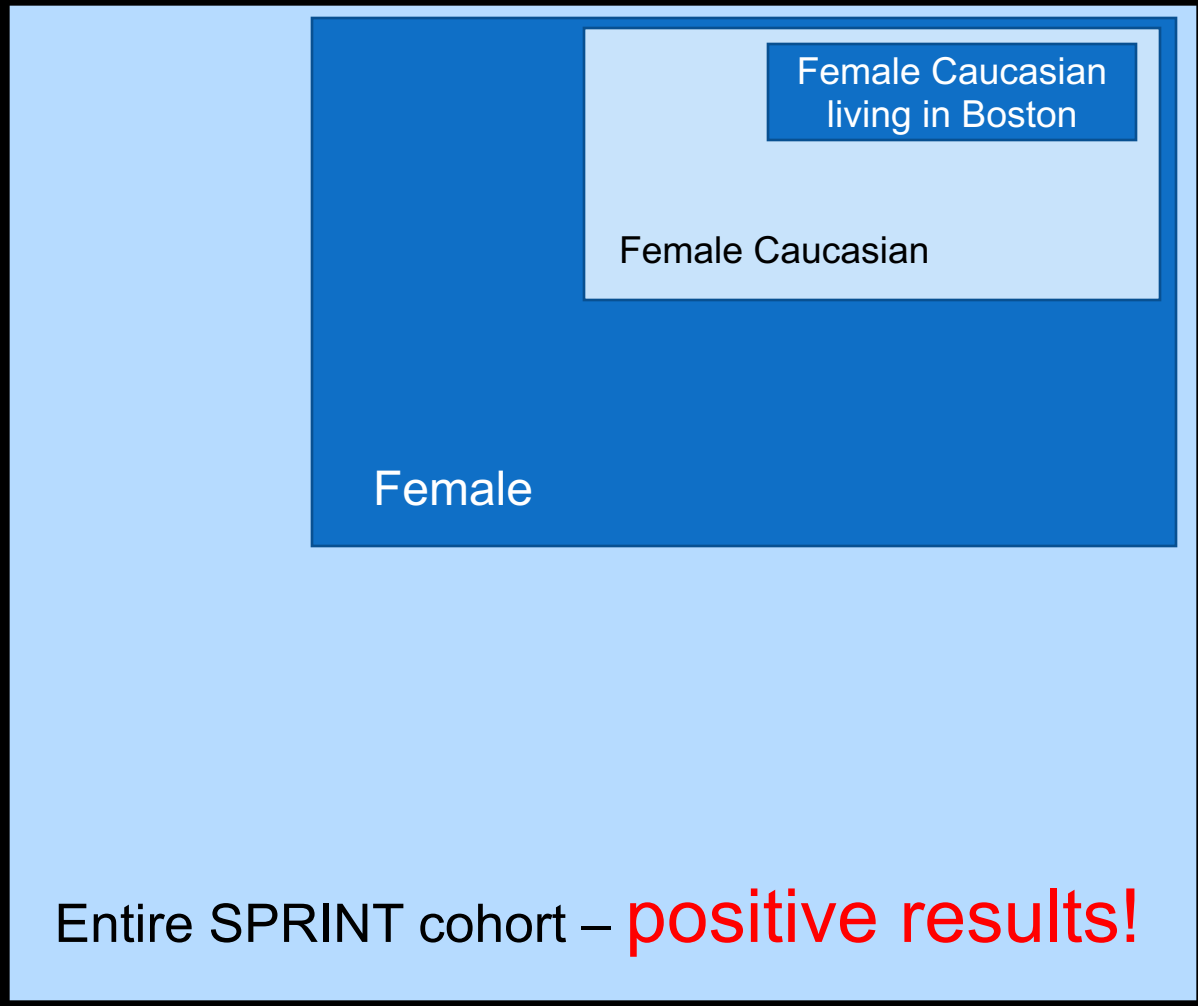
Cheung, JASN, 2017

How far can you go in interpretation of subgroup analysis

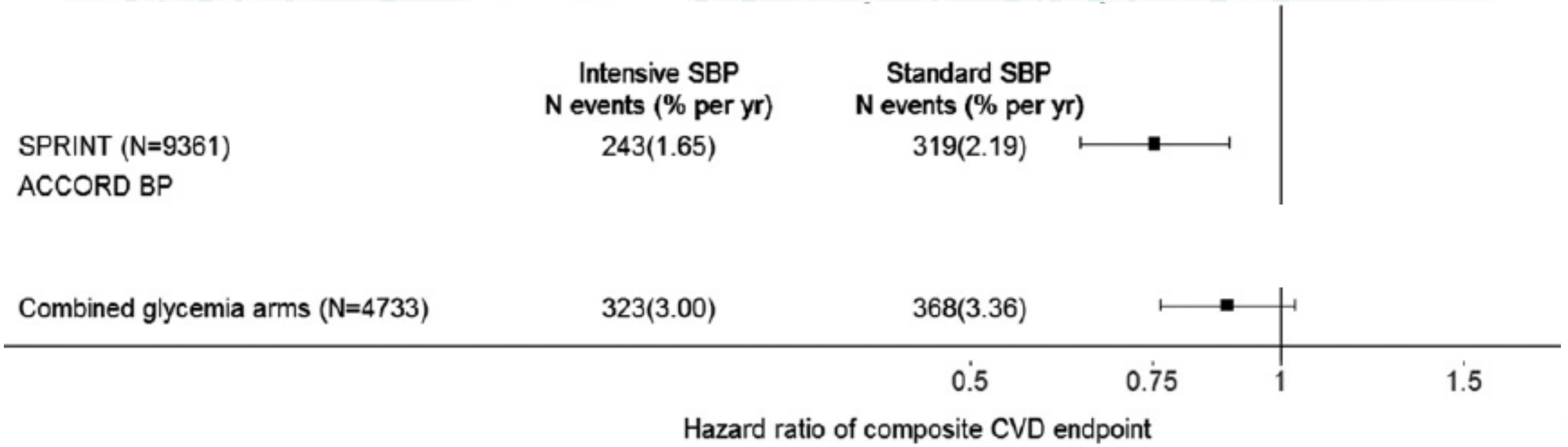
Subgroup	HR	P*
Overall	0.75 (0.64,0.89)	
No Prior CKD	0.70 (0.56,0.87)	0.36
Prior CKD	0.82 (0.63,1.07)	
Age < 75	0.80 (0.64,1.00)	0.32
Age ≥ 75	0.67 (0.51,0.86)	
Female	0.84 (0.62,1.14)	0.45
Male	0.72 (0.59,0.88)	
African−American	0.77 (0.55,1.06)	0.83
Non African−American	0.74 (0.61,0.90)	
No Prior CVD	0.71 (0.57,0.88)	0.39
Prior CVD	0.83 (0.62,1.09)	
SBP ≤ 132	0.70 (0.51,0.95)	0.77
132 < SBP < 145	0.77 (0.57,1.03)	
SBP ≥ 145	0.83 (0.63,1.09)	

*Unadjusted for multiplicity





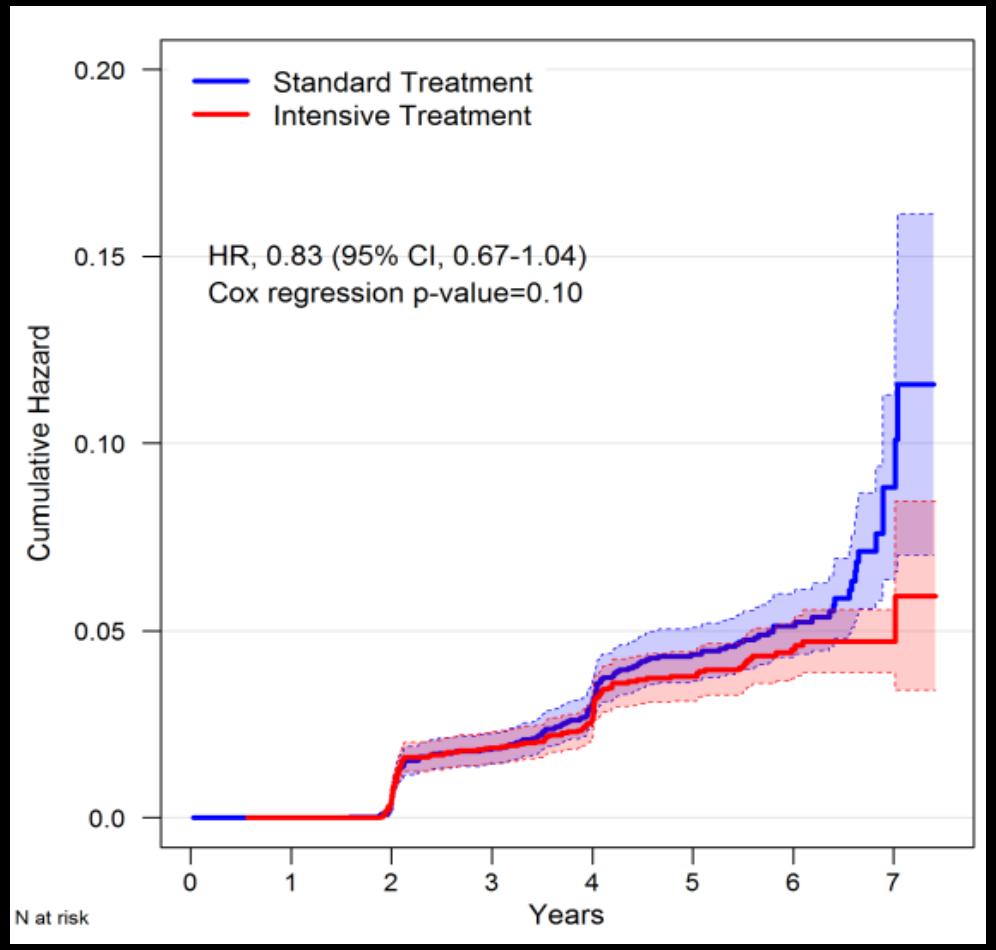
Effect of Intensive SBP Lowering (<120 mm Hg) on CVD



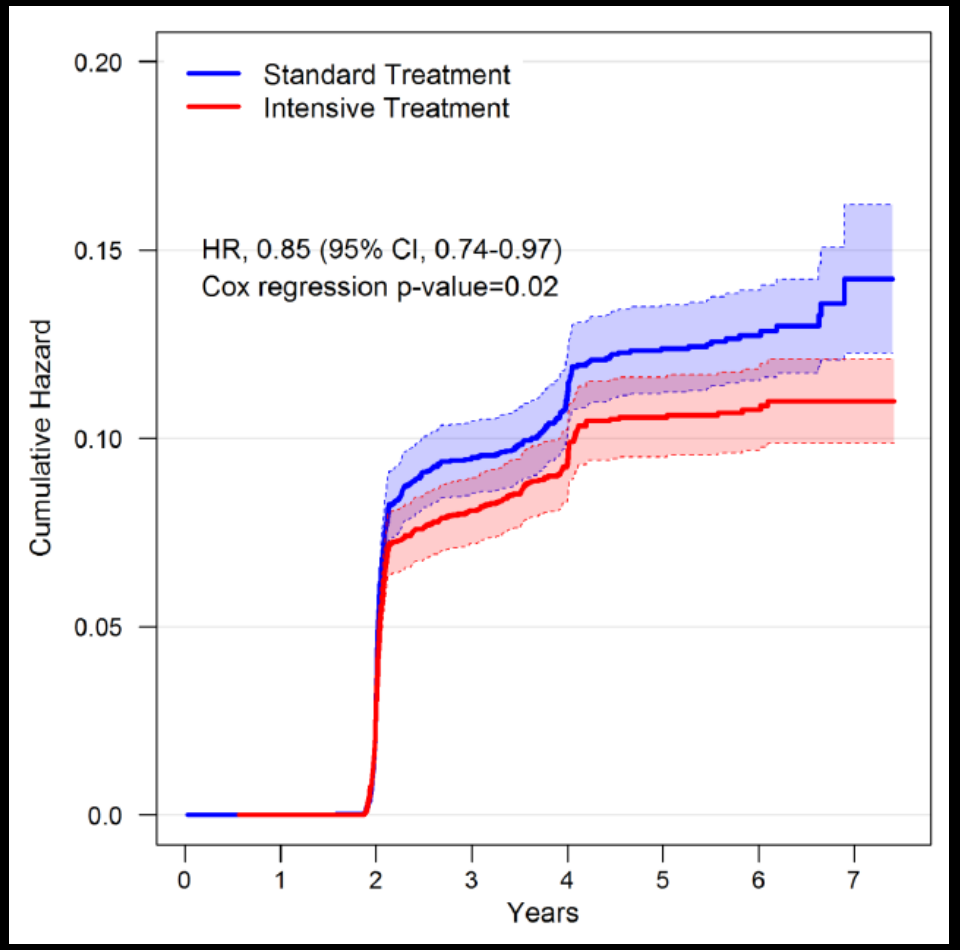
Beddhu, JAHA, 2018

Effect of Intensive SBP on Cognition in Entire SPRINT Cohort

Probable Dementia



Composite of Probable Dementia or Mild Cognitive Impairment



SPRINT, JAMA, 2019

Adverse Events in CKD Subgroup in SPRINT

	No. (%) of Participants with AE			
	Intensive BP	Standard BP	HR	P
Hypotension	51 (3.8)	38 (2.9)	1.34	0.17
Syncope	54 (4.1)	42 (3.2)	1.28	0.22
Injurious fall	125 (9.4)	138 (10.5)	0.90	0.40
K <3.0 mmol/l	30 (2.2)	16 (1.2)	1.87	0.04
K >5.5 mmol/l	106 (8.0)	78 (5.9)	1.36	0.04
Serious adverse events	627 (47.1)	640 (48.1)	0.98	0.67

Cheung, JASN, 2017

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K >5.5 mmol/l	106 (8.0)	78 (5.9)	1.36	0.04
Serious adverse events	627 (47.1)	640 (48.1)	0.98	0.67
AKI/ARF	**114 (8.6)**	**78 (5.9)**	**1.46**	**0.01**

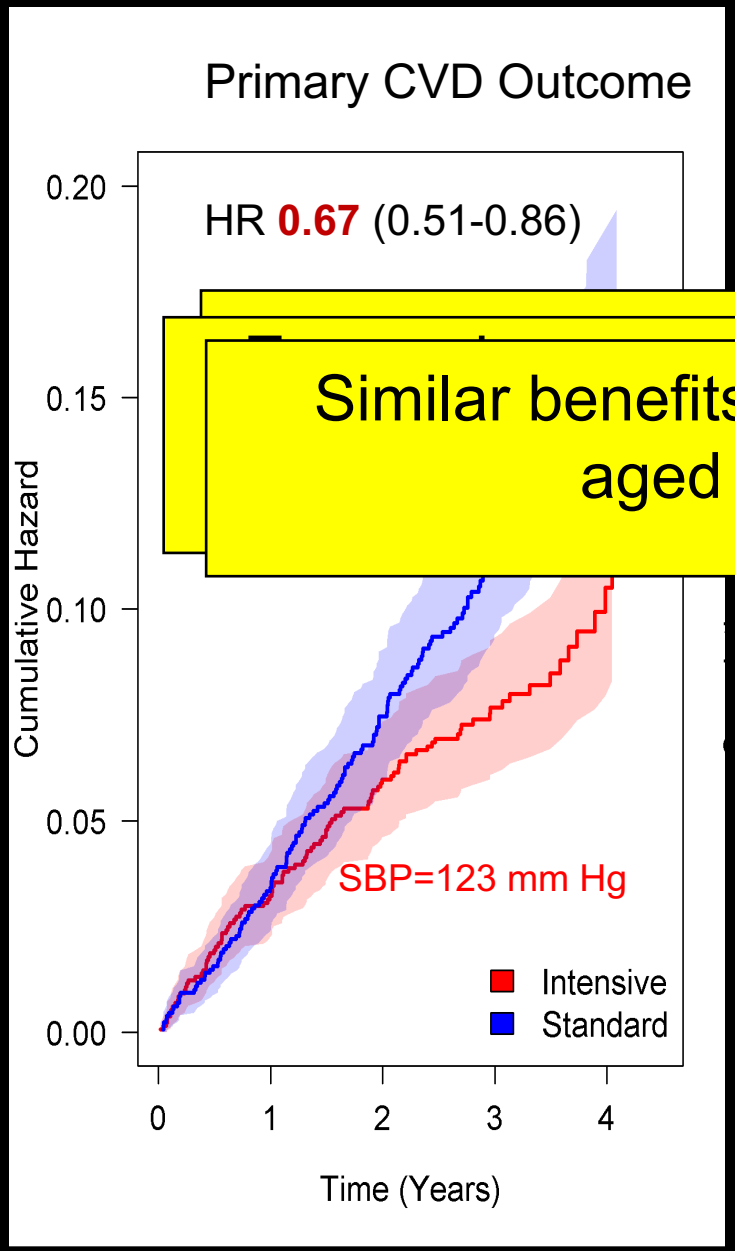
Cheung, JASN, 2017

Severities and Courses of AKI in Entire SPRINT Cohort

	Intensive BP	Standard BP	
No. participants with AKI events	179	109	HR 1.64 [1.30-2.10]
↑ ≥0.3 mg/dL or 1.5-2.0x (modified KDIGO Stage 1)	128 (59.5%)	81 (62.8%)	
Complete resolution of AKI event (within 20% of baseline)	169 (90.4%)	86 (86.9%)	
AKI requiring RRT	8 (4.5%)	6 (5.5%)	
ESRD	2 (1.1%)	3 (2.8%)	

Rocco, AJKD, 2017

Outcomes in SPRINT-Seniors (>75 yr) Cohort (N=2,636)



Similar benefits in **CKD** patients aged >75 yrs

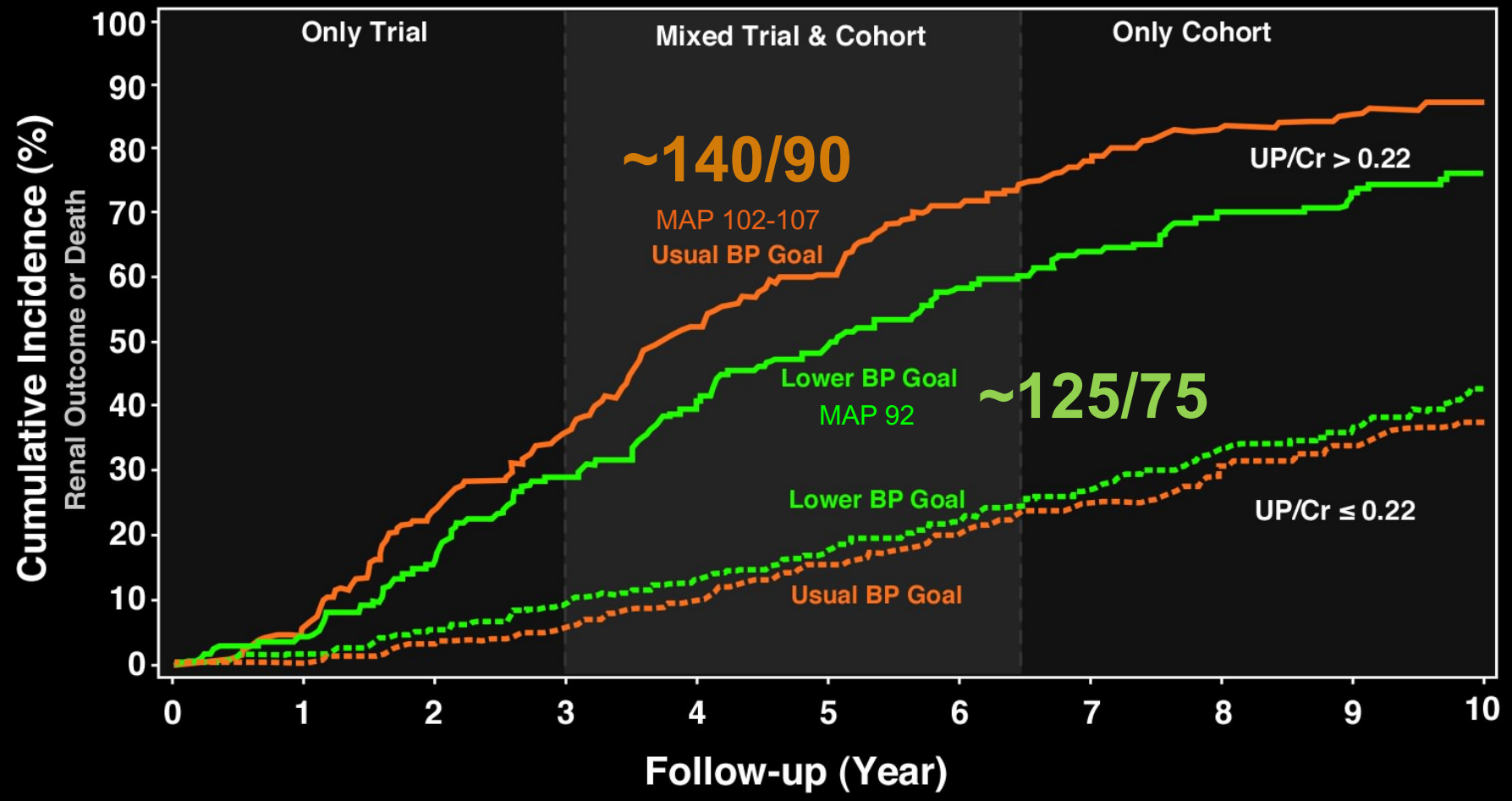
Cheung, JASN, 2017

Williamson, JAMA, 2016

Effects of Intensive BP Lowering on Kidney Outcomes

Renoprotection Associated with Lower BP Goal in AASK

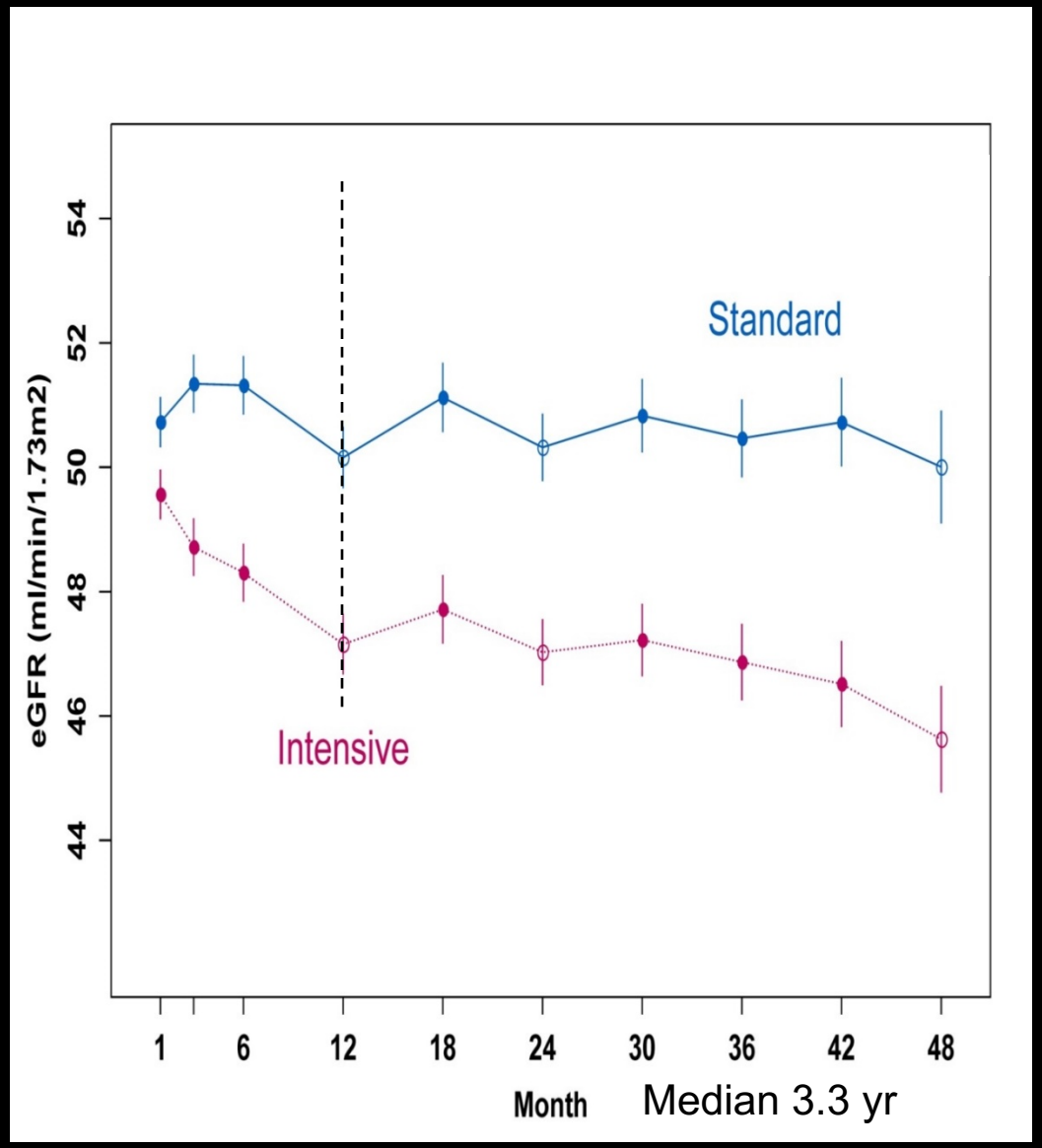
(African-American Study of Kidney Disease & HTN)



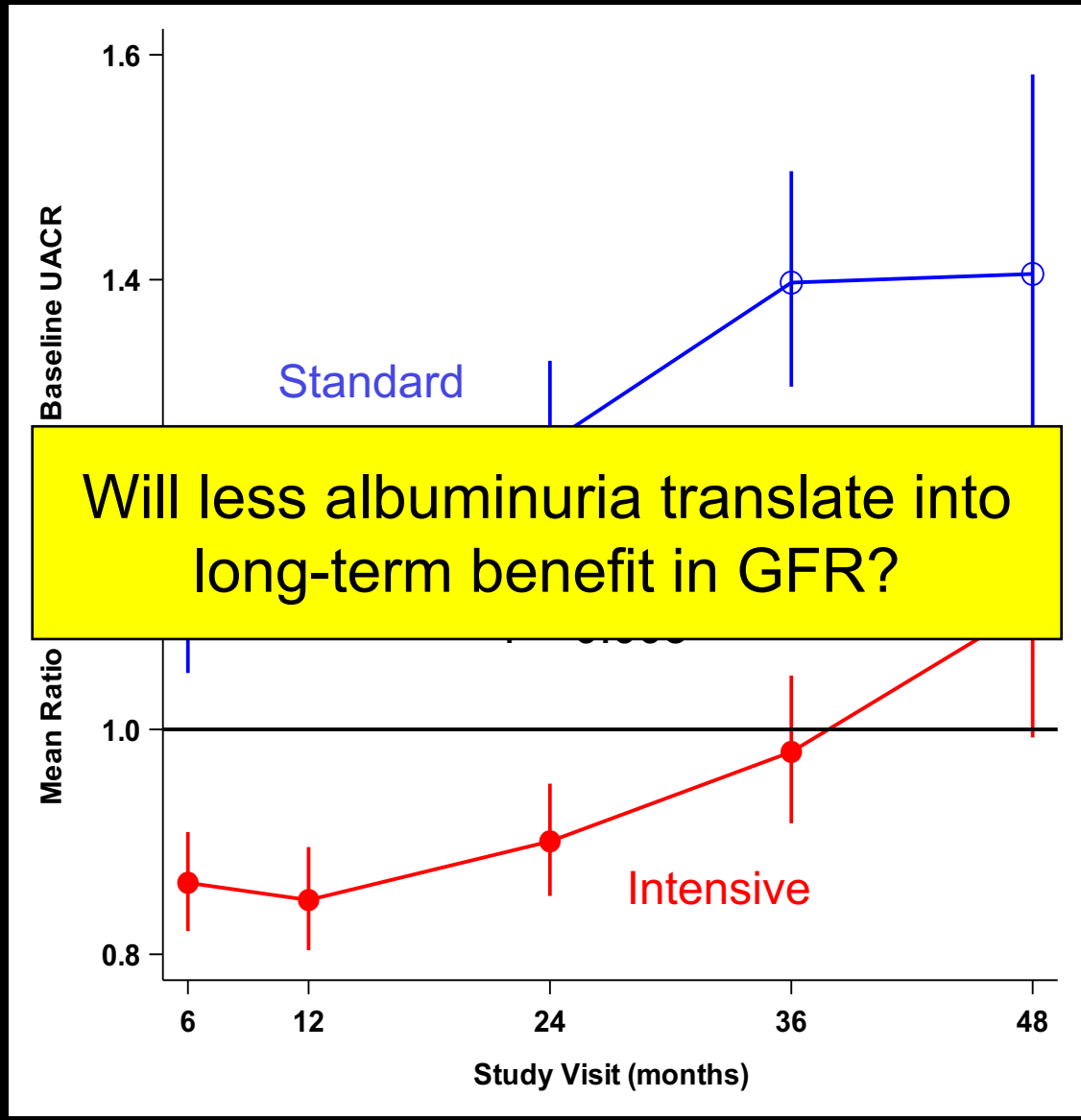
N=1,094

Appel, NEJM, 2010

eGFR over Time in CKD Subgroup in SPRINT



Urinary Albuminuria-to-Creatinine Ratio (UACR) over Time



Cheung, JASN, 2017

Summary of Rationales for Target SBP <120 mm Hg in CKD

- Must be standardized measurement (routine BP is too erratic)
- SBP <120 mm Hg seems to have favorable *CV, brain and survival* benefits; and favorable benefit/risk ratio (even for >75 yrs old)
- Uncertainty in: DM, eGFR <20 ml/min/1.73m^2, proteinuria >1 g/d, very old, very frail

  Optimal SBP in these conditions are uncertain and may not be <130 mm Hg or <140 mm Hg

- General guidelines are useful, but individualization is key

QUESTION AND ANSWER

GRADING RECOMMENDATIONS

- GRADE methodology
- The quality of the evidence – Level A, B, C, D
  - Study limitations
  - Inconsistency
  - Indirectness
  - Imprecision
  - Publication bias

- Strength of the recommendation – “We recommend” or “We suggest”

  One face-to-face meeting – New Orleans Jan 2019
  - Balance of benefits and harms
  - Quality of the evidence
  - Patient values and preferences
  - Resources and other considerations

EVIDENCE REVIEW

- PICO QUESTIONS (Population, Intervention, Comparator, Outcome)
- Focus on RCTs
- Some focused observational study reviews

Critical outcomes	Important outcomes
All-cause mortality	Doubling serum creatinine
Cardiovascular mortality	Acute kidney injury
End-stage kidney disease	Falls
Cardiovascular events - MI, stroke, HF	Fatigue
Dementia or cognitive impairment	Body weight
	Blood pressure

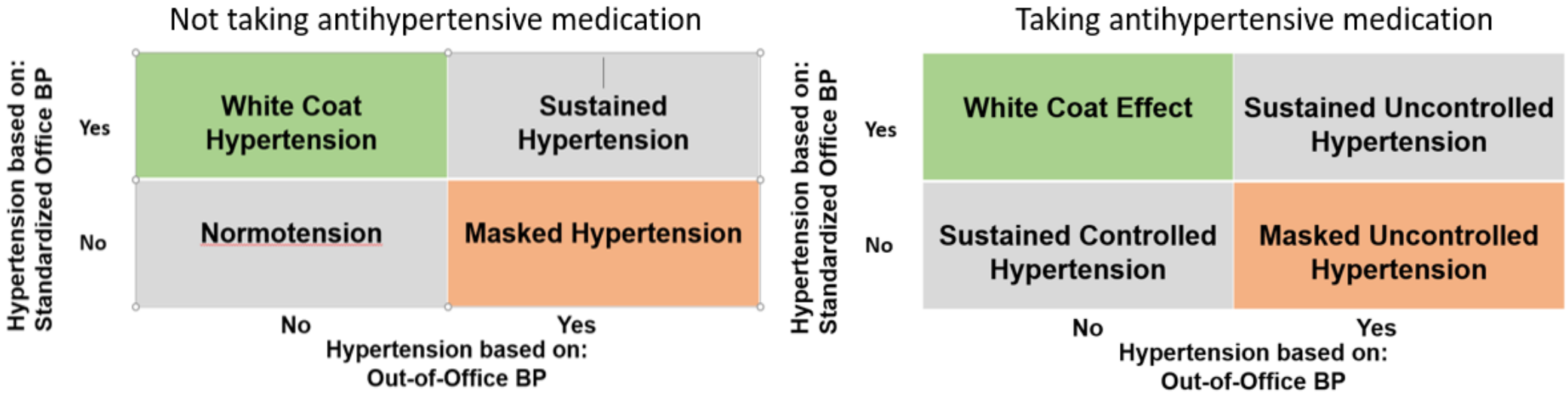
PICO QUESTIONS

Population	Intervention	Comparator	Outcome
Blood Pressure Measurement			
• Patients with CKD • General Population	**Oscillometric (office-based) BP (unattended or attended), ambulatory BP, home oscillometric monitors**	Auscultatory office-based BP monitoring	Sensitivity, specificity, negative predictive value, positive predictive value; Cost-effectiveness

BP Measurement

Recommendation 1.2. We suggest that out-of-office BP measurements be used with ambulatory BP monitoring (ABPM) or home BP monitoring (HBPM) to complement standardized office BP readings for the diagnosis and management of high BP. (2B)

- BP status may differ when based on standardized office vs. out-of-office BP



- Weak recommendation since no large outcomes trials based on out-of-office BP

Population	Intervention	Comparator	Outcome
BP Management in CKD ND with and without Diabetes			
• Adults with CKD with and without diabetes	• **Low BP target**	• Standard BP target	• Critical and important outcomes
• Adults with CKD with and without diabetes	• **ACEi, ARB, aldosterone antagonists**	• Placebo or standard of care	• Critical and important outcomes
• Adults with CKD with and without diabetes	• **Non-RAAS inhibition (alpha blockers, beta-blockers, CCB, DRI, diuretics)**	• Placebo or RAASi	• Critical and important outcomes
• Adults with and without diabetes	• **Dual RAASi**	• Mono RAASi	• Critical and important outcomes
• Adults with chronic hyperkalemia	• **Potassium binders**	• Placebo or standard of care	• Critical and important outcomes, hospitalization, hypokalemia

Population	Intervention	Comparator	Outcome
BP Management in Kidney Transplant Recipients			
• Kidney transplant recipients	• **Low protein diet**	• Usual protein diet	• Critical and important outcomes
• Kidney transplant recipients	• **Low salt diet**	• Normal salt diet	• Critical and important outcomes, sodium excretion, SCr
• Kidney transplant recipients	• **Dietary modification (including dietary advice or lifestyle management)**	• Standard of care (including lifestyle advice) or any other dietary pattern	• Critical and important outcomes
• Kidney transplant recipients and high BP	• **Any exercise intervention >8 weeks duration**	• Standard of care	• Critical and important outcomes, BMI, quality of life

Population	Intervention	Comparator	Outcome
BP Management in Kidney Transplant Recipients			
• Adults and children kidney transplant recipients	• **Low BP target**	• Standard BP target	• Critical and important outcomes
• Adults and children kidney transplant recipients	• **RAAS inhibition (ACEi, ARB, aldosterone antagonists) or non-RAAS inhibition (alpha blockers, beta-blockers, CCB, DRI, diuretics)**	• Placebo or standard of care	• Critical and important outcomes
• Kidney transplant recipients with chronic hyperkalemia	• **Potassium binders**	• Placebo or standard of care	• Critical and important outcomes, hospitalization, hypokalemia

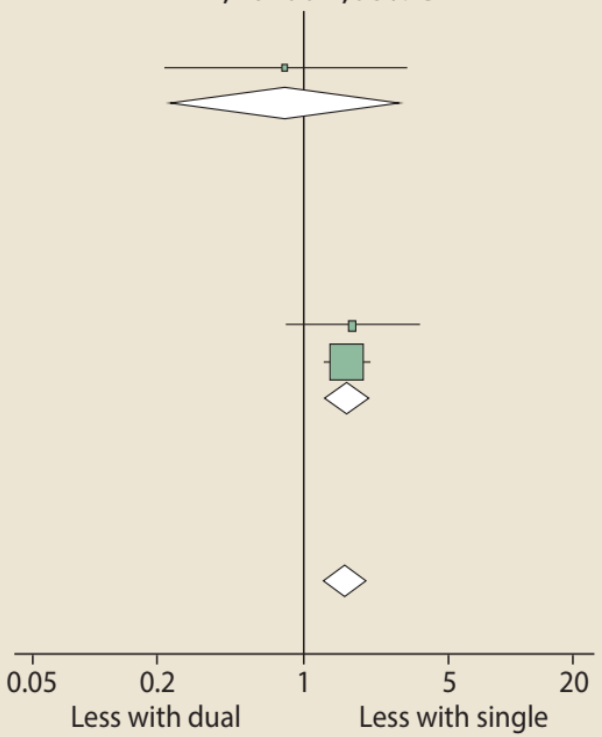
Population	Intervention	Comparator	Outcome
BP Management in Children with CKD			
• Children with CKD	• **Low BP target**	• Standard BP target	• Critical and important outcomes
• Children with CKD	• **RAAS inhibition (ACEi, ARB, aldosterone antagonists) or non-RAAS inhibition (alpha blockers, beta-blockers, CCB, DRI, diuretics)**	• Placebo or standard of care	• Critical and important outcomes, SCr

Blood Pressure Management in CKD ND Patients with and without Diabetes – Dual RAASi

Recommendation 3.3.1. We recommend not treating with any combination of ACEi, ARB, and direct renin inhibitor therapy in patients with CKD with or without diabetes *(1B).*

AKI Events

Study or subgroup	Dual Events	Dual Total	Single Events	Single Total	Weight	Risk ratio M–H, Random, 95% CI
6.8.1 Mildly increased albuminuria						
ONTARGET 2008	3	447	8	983	3.3%	0.82 [0.22, 3.09]
Subtotal (95% CI)		447		983	3.3%	0.82 [0.22, 3.09]
Total events	3		8			
Heterogeneity: not applicable						
Test for overall effect: Z = 0.29 (P = 0.78)						
6.8.2 Moderately increased albuminuria						
ONTARGET 2008	13	1084	15	2177	10.6%	1.74 [0.83, 3.64]
VA–NEPHRON–D 2009	130	724	80	724	86.1%	1.63 [1.25, 2.10]
Subtotal (95% CI)		1808		2901	96.7%	1.64 [1.28, 2.09]
Total events	143		95			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.03$, df = 1 (P = 0.86); $I^2 = 0\%$						
Test for overall effect: Z = 3.96 (P = < 0.0001)						
Total (95% CI)		**2255**		**3884**	**100.0%**	**1.60 [1.26, 2.04]**
Total events	952		715			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.03$, df = 2 (P = 0.60); $I^2 = 0\%$						
Test for overall effect: Z = 3.84 (P = 0.0001)						
Test for subgroup differences: $Chi^2 = 1.00$, df = 1 (P = 0.32); $I^2 = 0\%$						



PICO QUESTIONS

Population	Intervention	Comparator	Outcome
Patients with CKD General population	Automated BP measurement Ambulatory BP measurement	Office-based BP measurement	Differences, sensitivity, specificity
Adults, children, and elderly with CKD Transplant recipients	Lower BP target (<120/80 mm Hg; <130/90 mm Hg, etc.)	Standard BP target	Critical and important outcomes
Adults, children, and elderly with CKD Transplant recipients	Antihypertensive medication	Placebo or active control	Critical and important outcomes
Adults and children with CKD Transplant recipients	Diet (salt intake, dietary patterns)	Placebo or normal diet	Critical and important outcomes
Adults and children with CKD Transplant recipients	Exercise	Placebo or no exercise	Critical and important outcomes

Practice Points

- New feature for KDIGO
- Consensus statement based on workgroup experiences and perhaps limited evidence
- Not graded for evidence or recommendation
- Supplement “Recommendations”

Lifestyle Treatment for Lowering BP in CKD ND Patients – Salt Intake

Recommendation 2.1.1. We suggest targeting salt intake to <90 mmol (<2 g) per day of sodium (corresponding to 5 g of sodium chloride) among CKD patients with high BP (2C).

Practice Point 2.1.1. Dietary sodium restriction is usually not appropriate for patients with sodium-wasting nephropathy.

Practice Point 2.1.2. The DASH-type diet or use of salt substitutes which are rich in potassium may not be appropriate for patients with advanced CKD or those with hyporeninemic hypoaldosteronism because of the potential for hyperkalemia.

Watch out for sodium-containing medications)

Lifestyle Treatment for Lowering BP in CKD ND Patients – Physical Activity

Recommendation 2.2.1. **We suggest that patients with high BP and CKD undertake moderate-intensity physical activity for a cumulative duration of at least 150 minutes per week, or to a level compatible with their cardiovascular and physical tolerance (2C).**

Practice Point 2.2.1. **Consider the cardiorespiratory fitness status, physical limitations, cognitive function, and risk of falls when deciding on the implementation and intensity of physical activity interventions in individual patients.**

Practice Point 2.2.2. **The form and intensity of physical activity should be considered and modified as necessary in individual patients. There may still be important health benefits even if physical activity falls below targets proposed for the general population.**

BP Management in Kidney Transplant Recipients (CKD G1T-G5T)

Recommendation 4.1. We recommend that a dihydropyridine *calcium channel blocker (CCB)* or an *ARB* be used as the first-line antihypertensive agent in adult kidney transplant recipients (1C).

Practice Point 4.1. Treat adult kidney transplant recipients with high BP to a target BP that is *<130 mm Hg systolic and <80 mm Hg diastolic* using standardized office BP measurement (see Recommendation 1.1.).

BP Management in CKD ND Patients with and without Diabetes – **Treatment with RAS Inhibitors**

Recommendations 3.2.1., 3.2.2 and 3.2.3.

We suggest treatment with RASi (ACEi or ARB) for people with CKD and high BP

Variable levels of evidence (1B – 2C), depending on eGFR and albuminuria level (particularly strong evidence for those with heavy albuminuria)

- Algorithm for add-on antihypertensives is being considered by KDIGO WG

BP Management in CKD ND Patients with and without Diabetes – **Treatment with RAS Inhibitors**

Practice Point 3.2.1. RASi (ACEi or ARB) should be administered using *maximally recommended doses* to achieve the benefits described because the proven benefits were achieved in trials using these doses.

Practice Point 3.2.4. Mineralocorticoid receptor antagonists are effective for management of refractory hypertension but may cause decline in kidney function or hyperkalemia, particularly among patients with low eGFR (consider K binders).

Overall Summary

MAJOR UPDATES

- Emphasis on standardized BP measurement because they are used in large RCTs to examine BP targets
- SBP target <120 mm Hg with emphasis on individualization and caveats

OTHERS

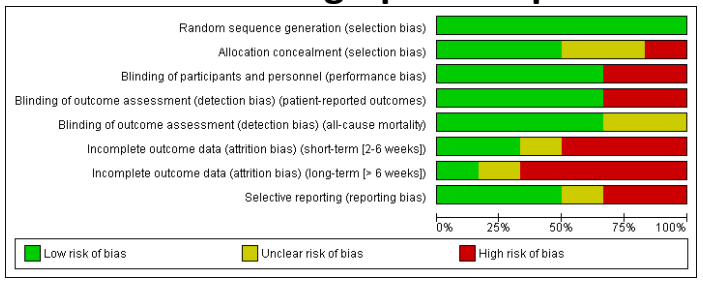
- Limit salt intake and moderate intensity physical activity
- No significant change in use of RASi, with strongest evidence in patients with heavy albuminuria
- BP targets for kidney transplant recipients remain to be <130/<80 using standardized office BP measurement
- BP target for children remains to be 24h MAP by ABPM to ≤50th percentile for age, sex, and height in normal pediatric normogram

EVIDENCE SYNTHESIS

- Standard Cochrane methods – Two independent reviewers
  - Data abstraction
  - Critical appraisal – using validated tools

- Data-analysis
  - Random effects meta-analysis and generic inverse variance
    - Relative risk for dichotomous outcomes
    - Mean difference for continuous outcomes
  - Heterogeneity assessed using the I^2 statistic

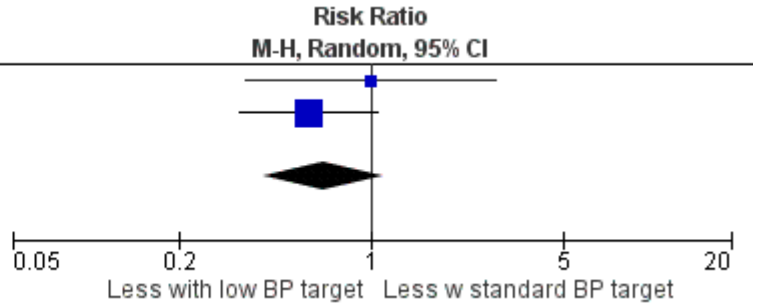
Risk of bias graph example



Forest plot example – BP target – CV Mortality

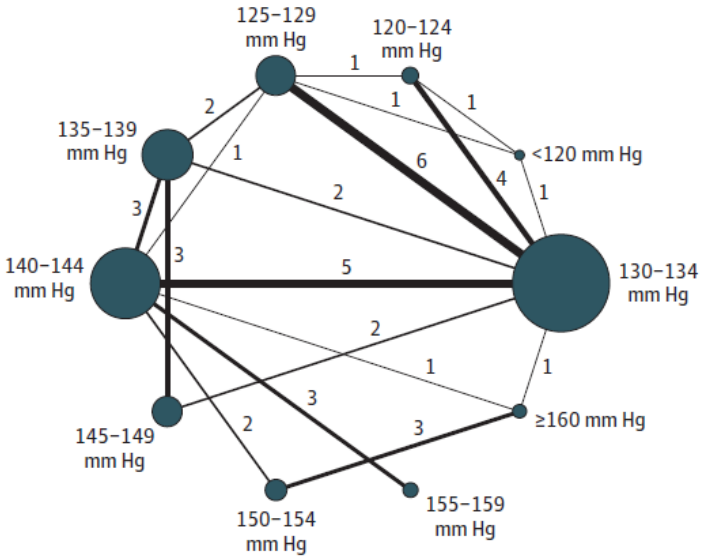
Study or Subgroup	Low BP target Events	Total	Standard BP target Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
ACCORD Study 2016	7	867	7	859	23.6%	0.99 [0.35, 2.81]
SPRINT CKD 2017	18	1330	30	1316	76.4%	0.59 [0.33, 1.06]
Total (95% CI)		**2197**		**2175**	**100.0%**	**0.67 [0.40, 1.11]**
Total events	25		37			

Heterogeneity: Tau² = 0.00; Chi² = 0.71, df = 1 (P = 0.40); I² = 0%
Test for overall effect: Z = 1.55 (P = 0.12)

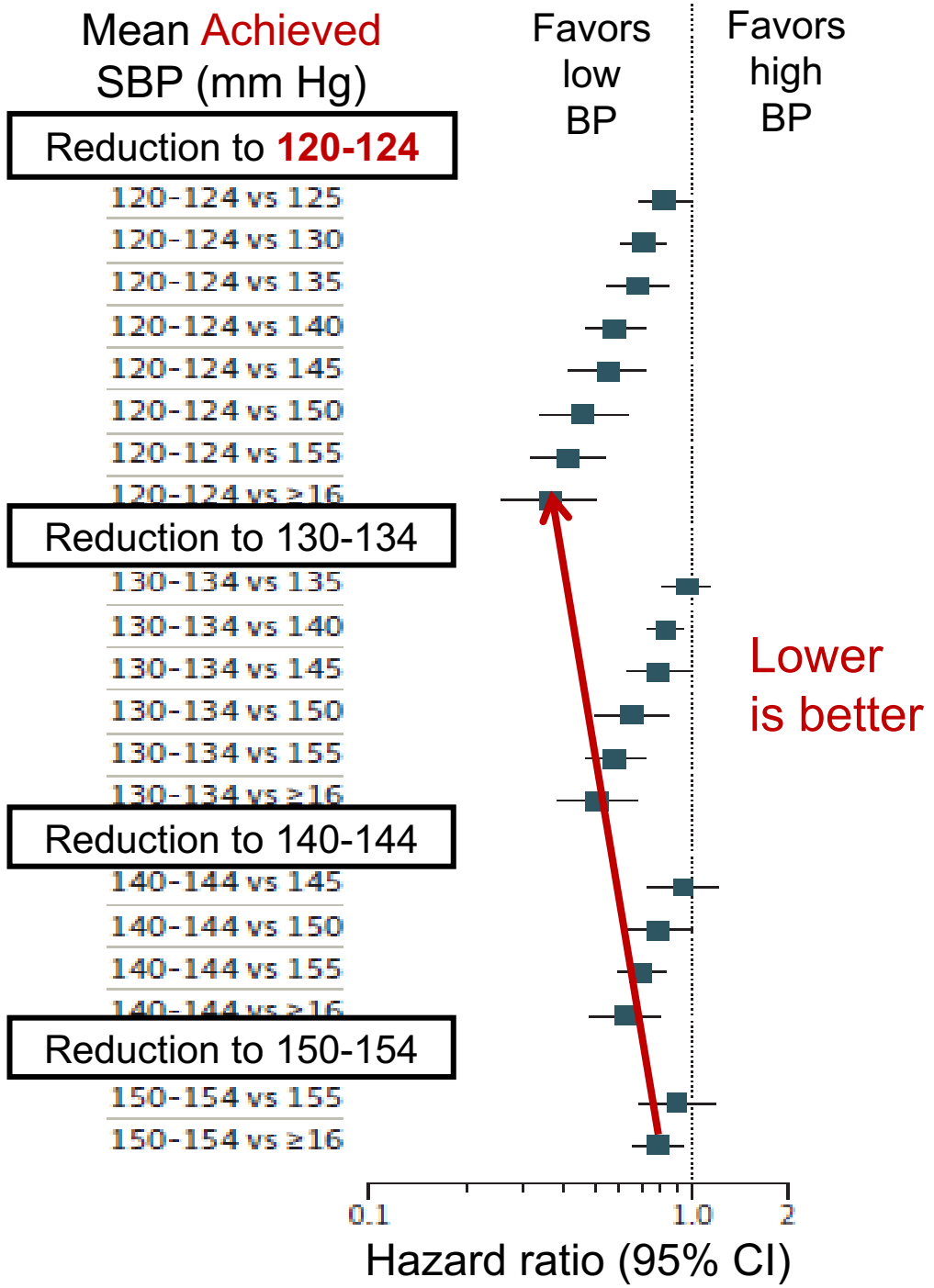


Network Meta-analysis of Effects of SBP Reduction on Major CV Events

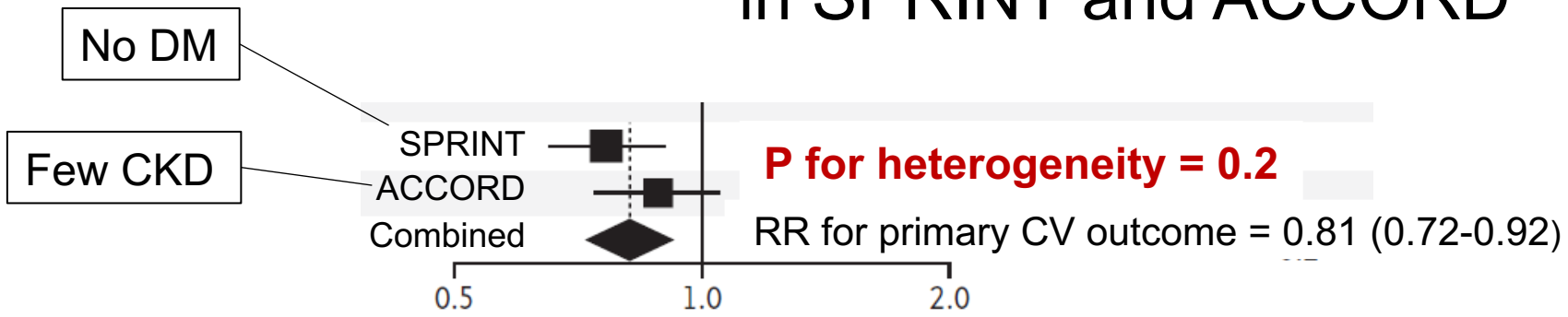
- 42 RCTs including 144,220 patients
- General population



Bundy, JAMA Cardiology, 2017

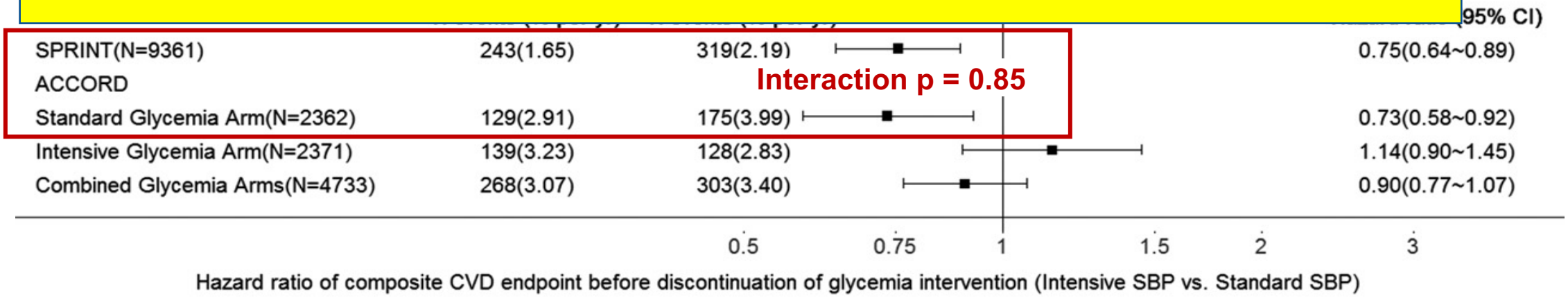


Effects of Intensive SBP Control (<120 mm Hg vs. <140 mm Hg) in SPRINT and ACCORD



- Effect of intensive SBP lowering seems to be similar between DM and non-DM
- Is DM CKD similar to non-DM CKD - Uncertain

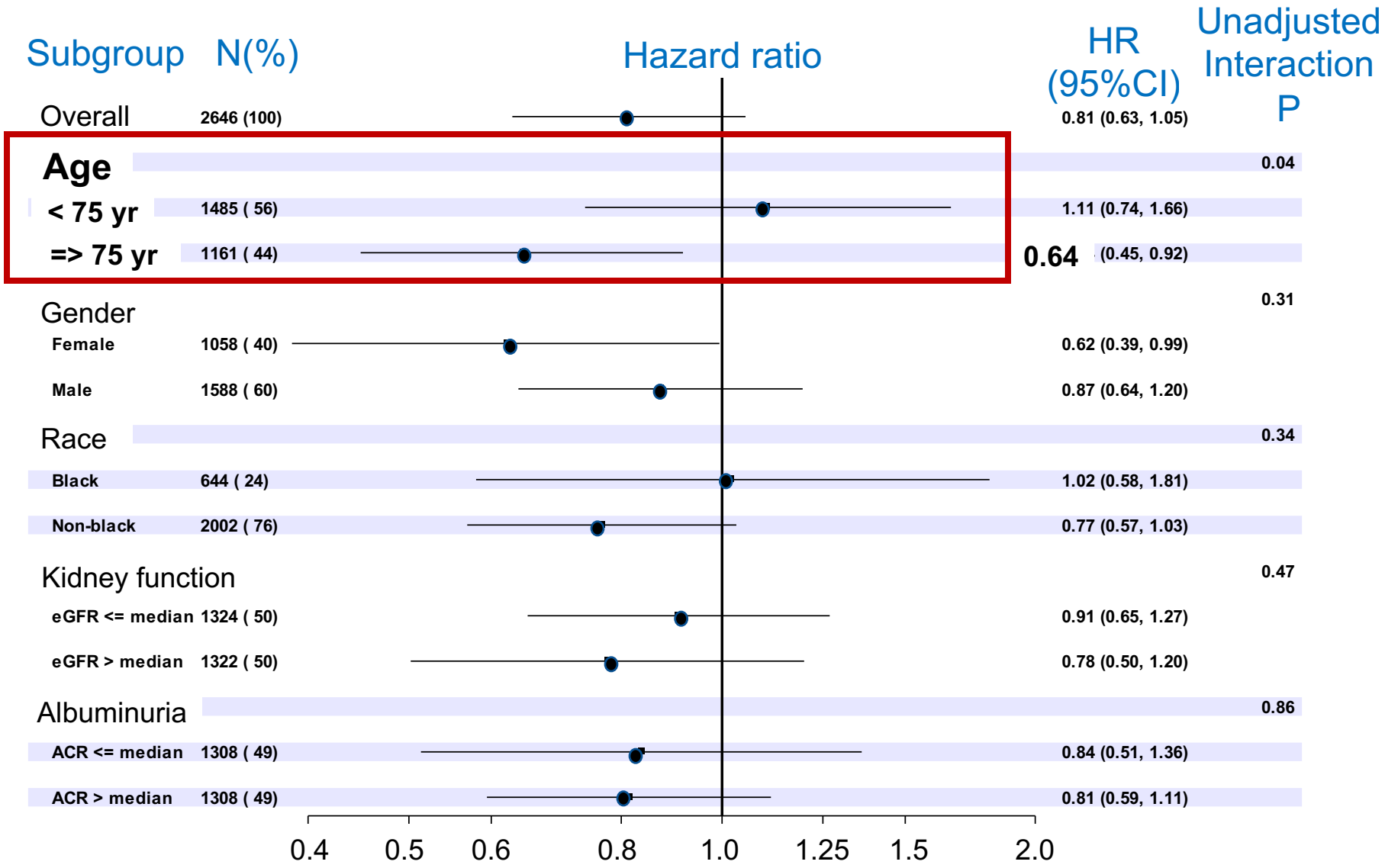
JM, 2015



Beddhu, JAHA, 2018

Primary CVD Outcome with Intensive SBP in **CKD Subgroup** Stratified by Baseline Characteristics

(Subgroups within CKD subgroup)



Unpublished

BP Management in Children with CKD

Recommendation 5.1. **We suggest that, in children with CKD, BP should be treated to lower 24-hour mean arterial pressure (MAP) by ABPM to less than or equal to the 50th percentile for age, sex, and height (2C)**

Practice Point 5.1. **We suggest monitoring BP once a year with ABPM, and monitoring every 3-6 months with standardized auscultatory office BP**

Practice Point 5.2. **Use ACEi or ARB as first-line therapy for high BP in children with CKD. These drugs lower proteinuria and are usually well tolerated**

Population	Intervention	Comparator	Outcome
Lifestyle Interventions			
• Adults with CKD	• **Low protein diet**	• Usual protein diet	• Critical and important outcomes
• Adults with CKD with and without diabetes	• **Low salt diet**	• Usual salt diet	• Critical and important outcomes, sodium excretion, SCr, BMI
• Adults with CKD	• **Dietary modifications (including dietary advice or lifestyle management**)	• Standard of care (including lifestyle advice) or any other dietary pattern	• Critical and important outcomes
• Adults with CKD and high BP	• **Any exercise intervention >8 weeks duration**	• Standard of care	• Critical and important outcomes, fat mass, quality of life

Guideline Format

KDIGO guidelines continue to use the GRADE methodology, but we have strengthened the link between evidence and the recommendations themselves.

Guidelines now include a mix of recommendations and "Practice Points" to help clinicians better evaluate and implement the guidance from the expert Work Group.

All recommendations follow a consistent and structured format and are similar in style to previous KDIGO recommendations.

Practice Points are a new addition to KDIGO guidance, and may be formatted as a Table, a Figure, or an Algorithm to make them easier to use in clinical practice.

Guidelines will be published in print form and simultaneously posted online in MAGICapp; the online format will facilitate rapid updates as new evidence emerges.

Blood pressure management in dialysis:
Conclusions from a KDIGO Controversies Conferences

DRAFT

Annual Dialysis Conference
March 6, 2021

Jennifer E. Flythe, MD, MPH
Associate Professor of Medicine
University of North Carolina School of Medicine

Annual Dialysis Conference
presented by the *University of Missouri Division of Nephrology*

KIDNEY DISEASE · IMPROVING GLOBAL OUTCOMES · KDIGO

UNC HEALTH CARE
KIDNEY CENTER

Disclosures

- **Funding**: NIH/ NIDDK, NIH/ NHLBI, PCORI, Robert Wood Johnson Foundation, and Renal Research Institute (a subsidiary of Fresenius Medical Care)

- **Speaking Honorarium**: Fresenius Medical Care, American Society of Nephrology, National Kidney Foundation, multiple universities

- **Consulting:** Fresenius Medical Care, AstraZeneca, NxStage Medical

Outline

- KDIGO Controversies Conference overview
- Blood pressure (BP) measurement in dialysis
- BP management in dialysis
  - Targets
  - Treatment

KDIGO Controversies Conference

Annual Dialysis Conference

presented by the *University of Missouri Division of Nephrology*

UNC HEALTH CARE

KIDNEY CENTER

BP and Volume Management in Dialysis

February 2019; Lisbon, Portugal

KIDNEY DISEASE · IMPROVING GLOBAL OUTCOMES ® KDIGO

Conference background

- BP and volume status are thought to be key mediators of poor outcomes among individuals receiving maintenance dialysis.
- There is global interest in expanding the definition of “adequate dialysis”, a concept traditionally defined by small molecule clearance, to other aspects of dialysis care, including BP and volume management.
- KDIGO Dialysis Controversies Conferences (Dialysis Initiation, January 2018; Madrid, Spain): proposed a shift toward more individualized or personalized dialysis care.
- Conference sought to build on the Dialysis Initiation Conference by considering how BP and volume status management could be optimized and individualized across dialysis modalities and resource settings.

Conference overview

- Examine BP measurement and targets for individuals receiving maintenance dialysis;
- Pharmacologic interventions for BP abnormalities; dialysis prescriptions as they relate to BP and volume;
- Extracellular volume assessment and management with a focus on technology-based solutions; and
- Volume-related patient symptoms and experiences and non-pharmacologic interventions for BP and volume abnormalities.

Conference overview

- Examine BP measurement and targets for individuals receiving maintenance dialysis;
- Pharmacologic interventions for BP abnormalities; dialysis prescriptions as they relate to BP and volume;
- Extracellular volume assessment and management with a focus on technology-based solutions; and
- Volume-related patient symptoms and experiences and non-pharmacologic interventions for BP and volume abnormalities.

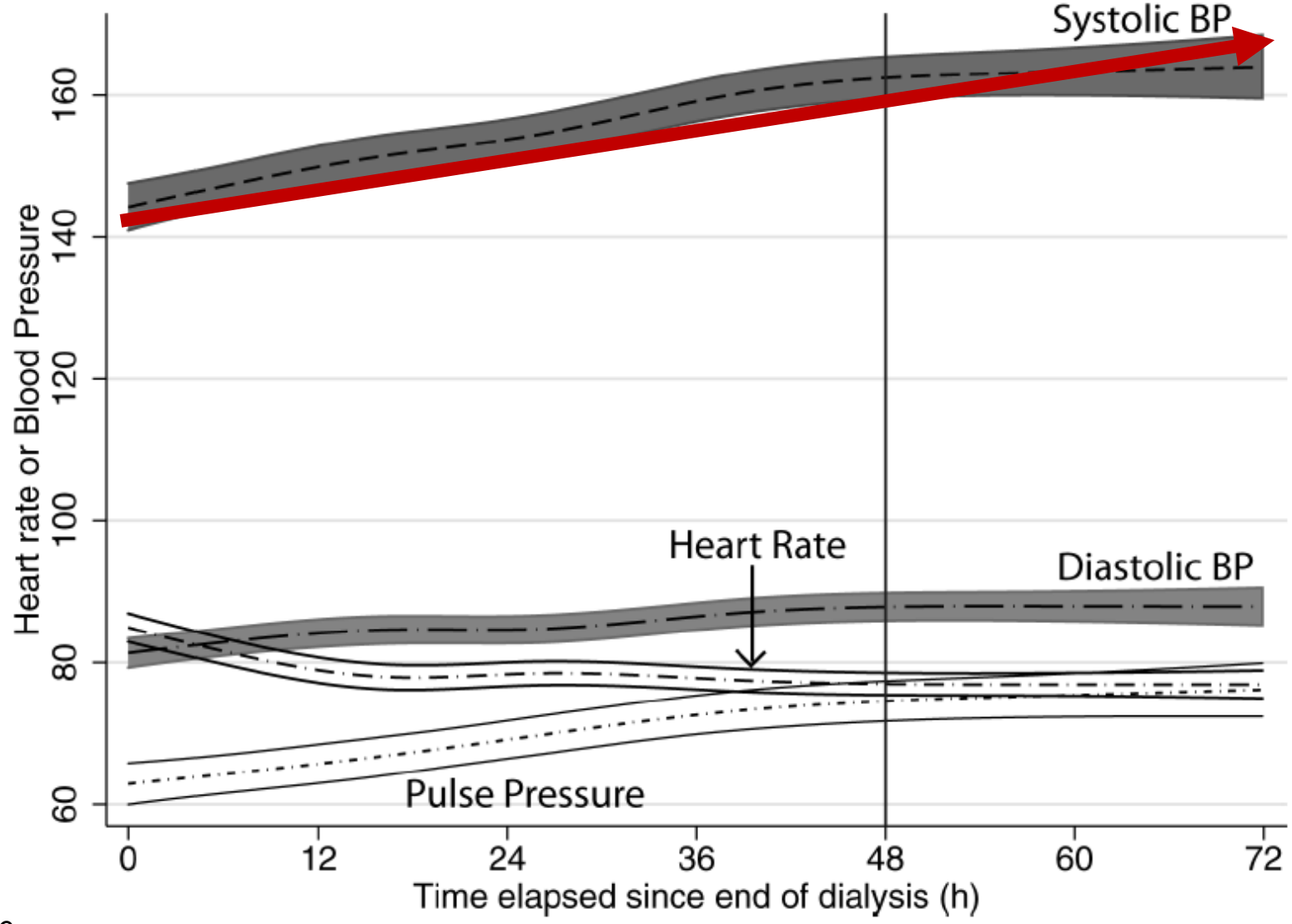
BP Measurement

How and when should BP be measured among individuals receiving dialysis?

When should we measure BP?

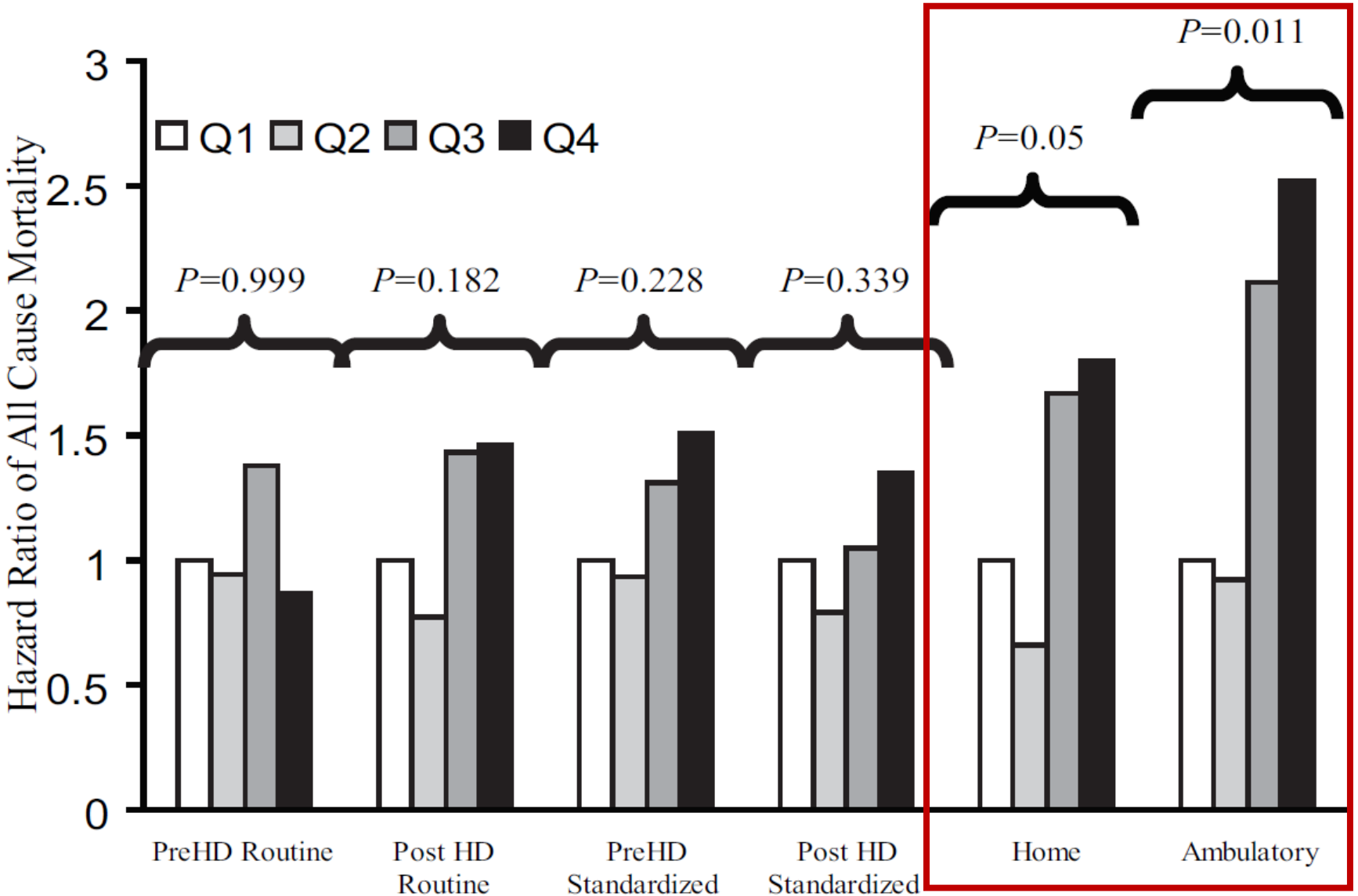
- Routine dialysis clinic BP measurements
  - Pre-, intra- and post-dialysis
- Standardized dialysis clinic BP measurements
  - Pre- and post-dialysis
- Ambulatory BP monitoring (ABPM)
- Home BP measurements

BP increases in inter-dialytic period (HD)



Agarwal. Am J Kid Dis, 2009.

Mortality prediction w/ different BP msmts (HD)



Alborzi. Clin J Am Soc Nephrol, 2007.

When should we measure BP?

- ***Home BP monitoring***
  - Recommended by AHA and European Society of HTN
  - Correlates more closely with ABPM than pre- and post-HD BPs
  - Better predictor of all-cause and CV mortality (vs. peri-dialytic)

- Timing
  - Consider: BID (AM and PM) after mid-week HD for 4 days

- Feasible?
  - **BID Study**: 22% of participants achieved ≥4 home msmts/month

Is home BP feasible?

- 4-month parallel pilot feasibility RCT (N=50)
  - Home BP vs. pre-HD BP q 2weeks
  - Target systolic BP: 140-100 mmHg (dry weight and med adjustment)
  - Outcomes: adherence, acceptability, clinical outcomes

Time-point	2 home BP readings
Overall (across 16 weeks)	94%
Week 4	92%
Week 8	96%
Week 12	100%
Week 16	96%

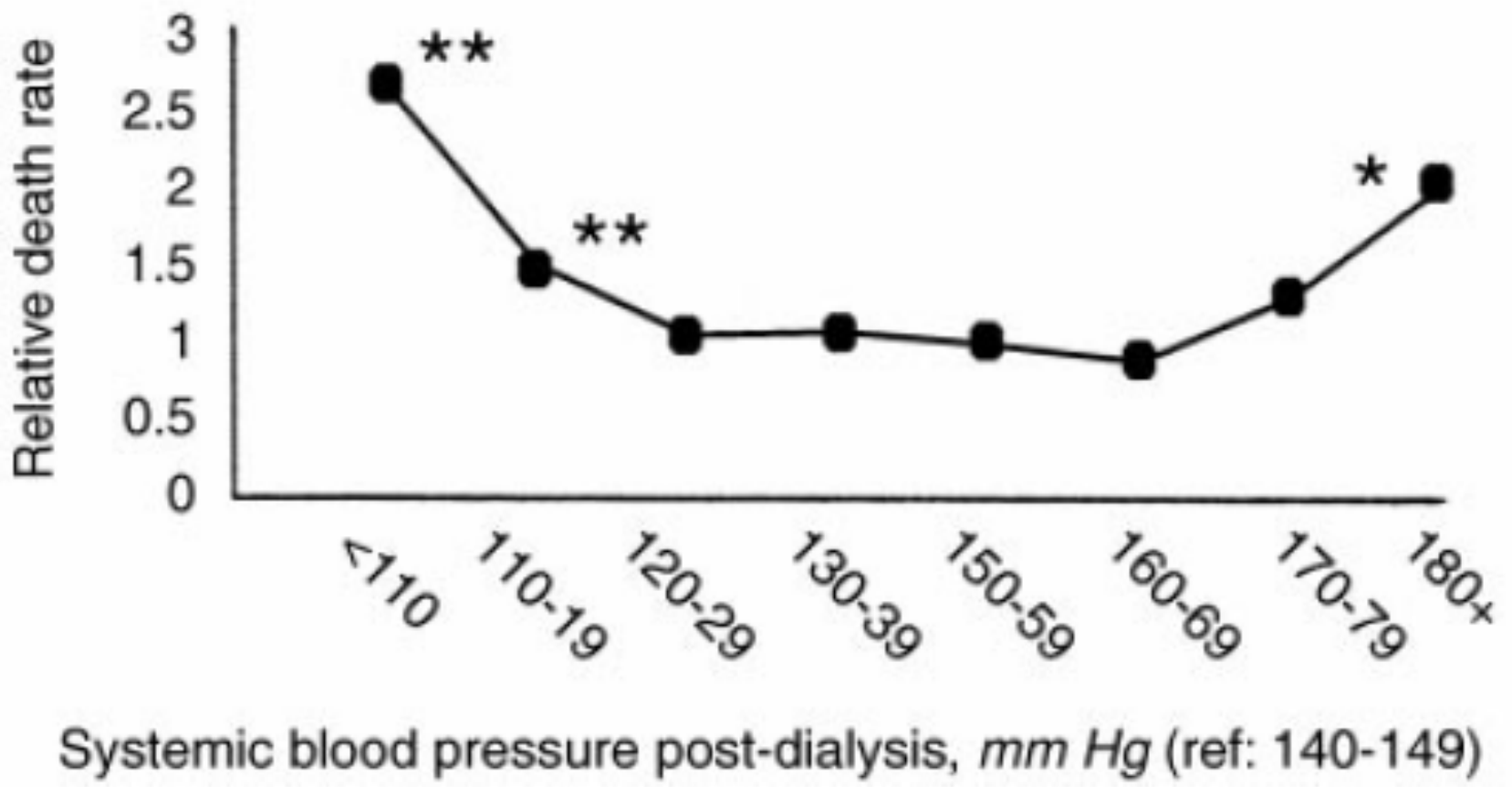
Bansal. Am J Kid Dis, 2020.

BP Management: Targets

Threshold for the diagnosis of hypertension?
Optimal definition of intradialytic hypotension?
Optimal definition of intradialytic hypertension?

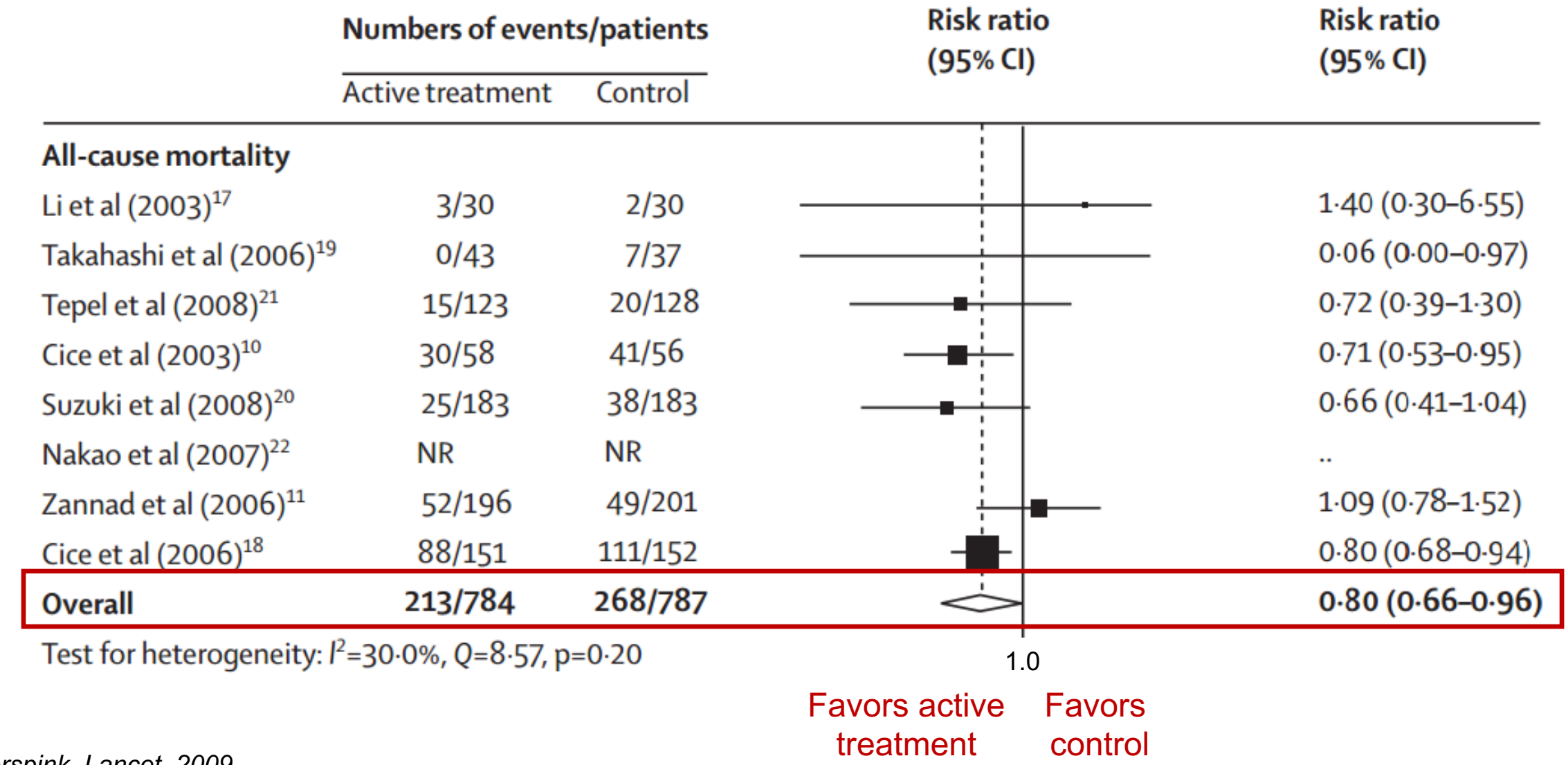
Blood pressure: U-shaped mortality association

- U.S. (N=5,433)



Zager. Kid Int, 1998.

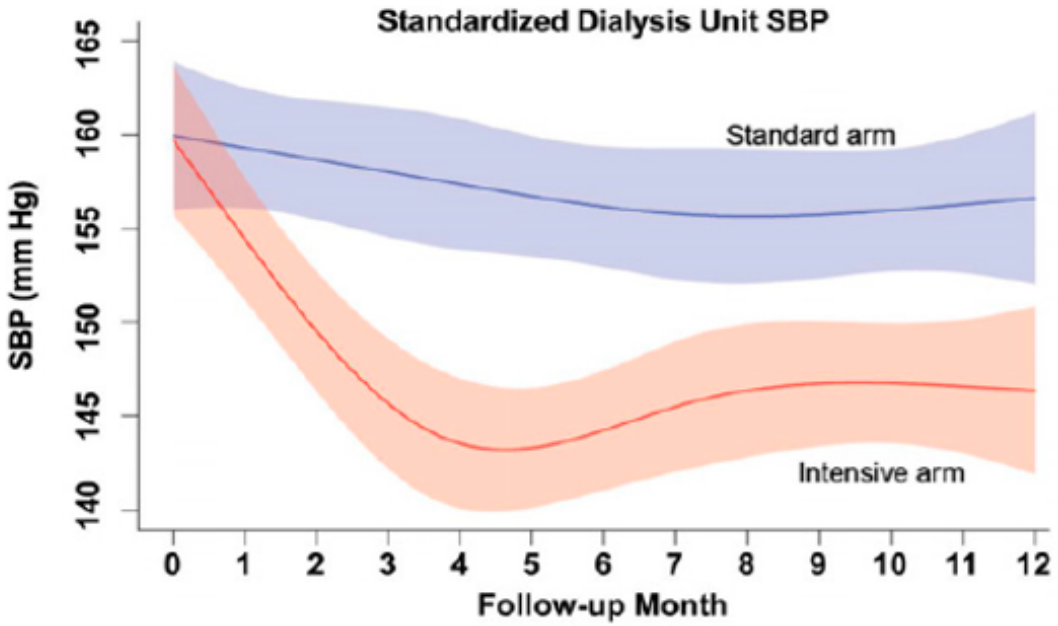
Lowering BP reduces all-cause mortality



Heerspink. Lancet, 2009.

Blood pressure in Dialysis (BID) pilot study

- 126 hypertensive hemodialysis patients:
  - Standardized pre-HD SBP 110-140 mmHg (intensive)
  - Standardized pre-HD SBP 155-165 mmHg (standard)



Intradialytic events	HR (95% CI) of recurrent events*
SBP <90 mmHg	1.30 (1.10-1.52)
Cramps	1.16 (1.04-1.30)
Nausea/ vomiting	1.41 (1.02-1.94)

*Intensive vs. standard (reference) arm.

Miskulin. J Am Soc Nephrol, 2017.

Definition of hypertension and treatment targets

- Thresholds for BP treatment and BP treatment goals among individuals receiving HD can only be established on the basis of prospective randomized trials.

- ***Current evidence does <u>not</u> meet this standard***

- In the absence of high-level, dialysis-relevant evidence, it is reasonable to extrapolate BP thresholds and targets for interdialytic BP (i.e. not pre- or post-dialysis measurements) from current hypertension guidelines for the general population.

Definition of hypertension and treatment targets

- 2017 ACC/AHA Guidelines: target **130/80 mmHg**

- 2018 ESH/ESC Guidelines:
  - SBP target **<130 mmHg** for <65 years
  - SBP target **130-140 mmHg** for all others

- 2017 ERA-EDTA Recommendations:
  - Home BP **≥135/85 mmHg** AM and PM msmts over 6 non-HD days (2-wk pd)
  - ABPM average BP **≥130/80 mmHg** over 24h on non-HD day

An individualized approach is necessary.
Consider intradialytic and interdialytic BP patterns, volume management, co-morbidities, and frailty.

Intradialytic *hypo*tension

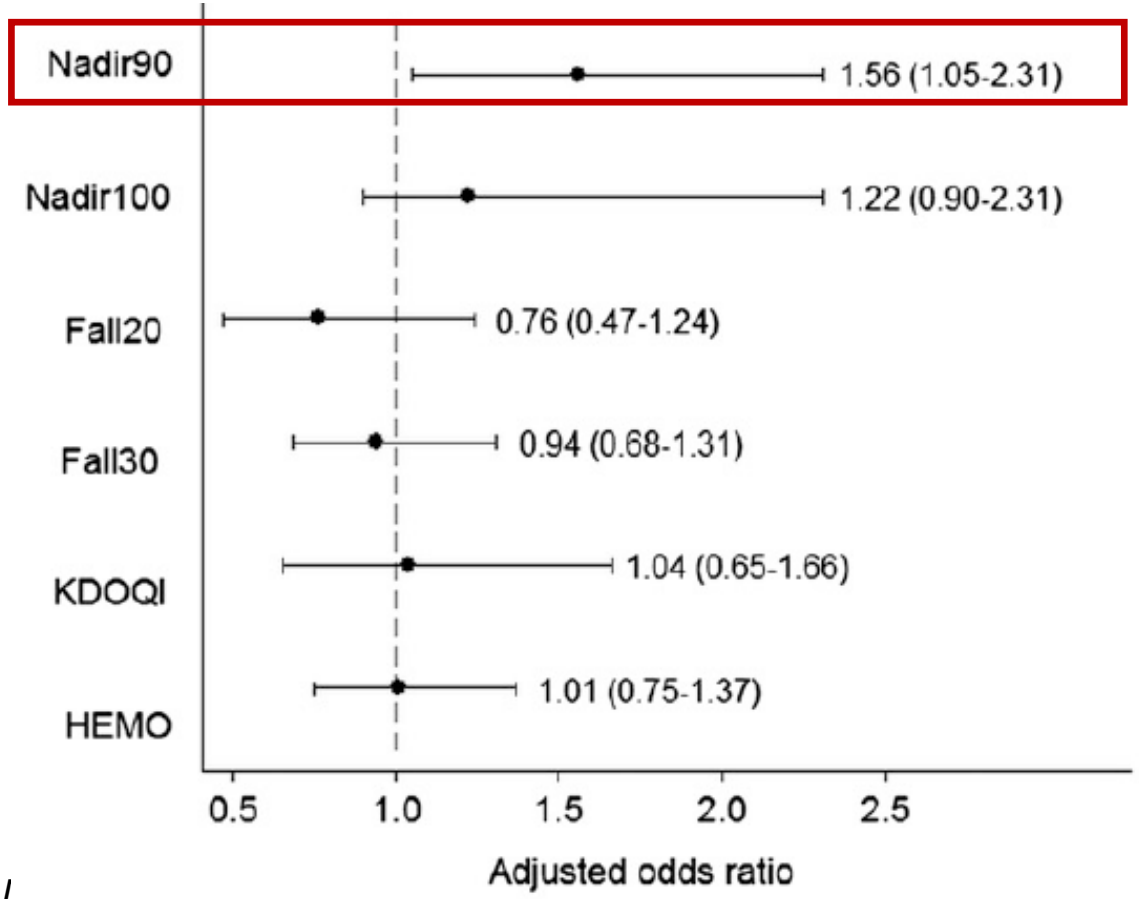
- Prevalence: 15-50% of HD treatments (definition-dependent)
- Serious complication of HD associated with:
  - Vascular access thrombosis
  - Inadequate dialysis dose
  - Hospitalizations and mortality

Guideline definition	Other definitions and notes
Intradialytic hypotension	
KDOQI 2005 Guidelines[11] Decrease in SBP ≥ 20 mm Hg or mean BP ≥ 10 mm Hg with associated symptoms (cramping, headache, lightheadedness, vomiting, or chest pain) or need for intervention (reduction in UF or administration of fluids)	• SBP drop accompanied by interventions (saline bolus administration, UF reduction, or blood pump flow reduction) • SBP drop of a certain degree (20, 30, or 40 mm Hg) • Nadir intradialytic SBP below a threshold value (90, 95, or 100 mm Hg) A nadir SBP < 90 mm Hg and a nadir SBP < 100 mm Hg in patients with pre-dialysis SBP > 160 mm Hg is most potently associated with mortality.[4]

Flythe/KDIGO. Kid Int, 2020.

Intradialytic *hypo*tension

- Dialysis Org. Cohort (N=10,392 prevalent HD patients)
- Definition met in >30% of HD treatments



Any symptomatic ↓ in SBP
or
nadir intradialytic SBP <90 mmHg

should prompt reassessment of BP and volume management

Flythe. J Am Soc I[illegible]

Intradialytic *hyper*tension

- Prevalence: 5-15% of HD treatments (definition-dependent)
- Serious complication of HD associated with:
  - Hospitalizations and mortality

Guideline definition	Other definitions and notes
Intradialytic hypertension	
None	• BP rise of any degree during the second or third intradialytic hour • SBP rise > 15 mm Hg within or immediately post-dialysis • SBP rise > 10 mm Hg from pre- to post-dialysis • Rising intradialytic BP that is unresponsive to volume removal

An SBP rise >10 mmHg from pre- to post-HD in the hypertensive range in at least 4 of 6 consecutive HD treatments
should prompt reassessment of BP and volume management

Flythe/KDIGO. Kid Int, 2020.

BP Management: Treatment

When should anti-HTN agents be used?
How should anti-HTN agents be selected?

When should anti-HTN meds be used?

- **Purpose: BP lowering**
  - ***FIRST:*** on-pharmacological treatments
  - If still not at BP goal, then add / titrate BP medications
  - If BP medications are interfering with volume management, reduce BP medications to allow more volume removal
- **Purpose: Cardioprotection**
  - Reasonable to initiate/continue BP medication if given for CV indication
  - Would NOT reduce UF to allow increase in BP medications

Optimizing volume status takes priority

Flythe/KDIGO. Kid Int, 2020.

Non-pharmacologic management of hypertension

- Hypertension management requires adequate control of excess sodium and fluid volume.
- Initiation or intensification of anti-hypertensive therapy in a volume-expanded state impedes achievement of post-HD euvolemia.

Sodium	Fluid	Other
↓ dietary sodium	Dry weight assessment -Frequent -New technologies?	Longer dialysis duration
↓ interdialytic sodium loading	Careful probing of dry weight	More frequent dialysis

Georgianos. Nat Rev Nephrol, 2016.

How should anti-HTN be selected?

Patient heterogeneity and scarcity of comparative evidence precludes recommending any one medication class over another for all patients.

- Antihypertensive medications considered first-line in the general population (e.g., β-blockers, ACEIs/ARBs, and calcium channel blockers) can also be considered first-line to lower BP in patients receiving dialysis.

- It is reasonable to choose medication based on patient characteristics, cardiovascular indications, and availability

Flythe/KDIGO. Kid Int, 2020.

How should anti-HTN be selected?

Medication Class	Evidence for Use
Hypertension	
ACEIs / ARBs	• *RCT*: Fosinopril did not reduce cardiovascular events and death compared with placebo in patients on HD with left ventricular hypertrophy.[145] • *RCT:* Inconsistent results related to ARBs and cardiovascular outcomes.[146-149] • *Meta-analysis:* ACEI/ARBs may reduce left ventricular mass index.[150] • *RCT:* May preserve residual kidney function, especially in PD patients.[151, 152]
β-blockers	• *RCT:* Fewer heart failure hospitalizations with the β-blocker atenolol compared to the ACEI lisinopril in HD patients with hypertension and left ventricular hypertrophy.[153] • *RCT:* Lower risk of death and cardiovascular death with carvedilol *vs.* placebo in HD patients with dilated cardiomyopathy who were also receiving digoxin and ACEI or ARB.[154]
Calcium channel blockers	• *RCT:* Amlodipine reduced cardiovascular events compared with placebo in HD patients with hypertension.[155]
Diuretics	• *Prospective:* May help preserve residual diuresis and limit fluid overload.[71, 156] • *Prospective:* Minimal effect on central hemodynamic indices and should not be considered an antihypertensive medication in the setting of dialysis.[157] • *Observational:* Continuation of loop diuretics after HD initiation associated with lower IDWG and lower intradialytic hypotension and hospitalization rates.[158]
Mineralocorticoid receptor antagonists	• *RCT:* Some trials in patients on dialysis have shown benefit on cardiovascular outcomes with spironolactone *vs.* placebo,[159-161] while others have not.[162] • *Ongoing RCTs:* Spironolactone and cardiovascular outcomes in HD patients (ACHIEVE and ALCHEMIST).[163]

Flythe/KDIGO. Kid Int, 2020.

Anti-HTN selection: dialyzability

Class and Agents	Removal with hemodialysis	Supplement post-dialysis
Beta-blockers		
Atenolol	50%	25-50 mg
Carvedilol	None	None
Metoprolol	50%	50 mg
Calcium channel-blockers	None	None
ACE-inhibitors		
Fosinopril	None	None
Lisinopril	50%	2.5-5 mg
Enalapril	50%	2.5-5 mg
Angiotensin receptor-blockers	None	None
Central alpha-agonists		
Clonidine	5%	None
Methyldopa	60%	250-500 mg
Alpha-1-blockers	None	None
Vasodilators		
Hydralazine	25-40%	None
Minoxidil	None	None

Denker. Semin Dial, 2015 and Levin. Kidney Int, 2009.

Anti-HTN selection: dialyzability

- **No RCTs regarding dialyzability and outcomes**

- It is reasonable to consider intradialytic BP patterns with regards to dialyzability of anti-HTN medications
  - Use **dialyzable** medications if intradialytic ***hypo***tension
  - Use **non-dialyzable** medications if intradialytic ***hyper***tension

Flythe/KDIGO. Kid Int, 2020.

Anti-HTN therapy should be individualized

- **Always need to consider individual patient characteristics**
  - Heart failure with reduced EF: carvedilol
  - A-fib: beta-blocker
  - BPH: alpha blocker if residual kidney function
  - Residual kidney function: ACEI/ARB especially for PD
  - Propensity for intradialytic *hypo*- or *hyper*tension: consider dialyzability
  - Orthostatic hypotension: avoid alpha-blockers, hydralazine, minoxidil
  - High pill burden: if intradialytic hemodynamics stable, consider longer acting, once daily dosing

Flythe/KDIGO. Kid Int, 2020.

Anti-HTN therapy selection: summary

- Medications considered 1st line in general population (ACEI/ARB, beta-blockers, calcium channel blockers) should be considered in ESKD
- Lack of evidence precludes recommending any one particular agent over another
- Consider other CV indication when making treatment choice
- Possible preference for ACEi/ARB to preserve RKF, especially in PD
- Consider intradialytic BP patterns with regards to dialyzability of anti-HTN medications

Flythe/KDIGO. Kid Int, 2020.

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OFFICIAL JOURNAL OF THE INTERNATIONAL SOCIETY OF NEPHROLOGY

Kidney International (2020) **97,** 861–876

www.kidney-international.org

KDIGO executive conclusions

Blood pressure and volume management in dialysis: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference

OPEN

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Kidney International (2020) 97, 861-876.

Flythe. Kid Int, 2020.

Summary

- Managing BP in dialysis requires an individualized approach with integration of numerous clinical, dialysis treatment, and patient factors
- Clear need for RCTs and additional study in this area

Modality	Recommendations
BP measurements, targets, and pathophysiology	
HD and PD	Investigate the optimal BP target/threshold for hypertension treatment
HD and PD	Assess the agreement and prediction of standardized (attended or unattended) in-office BP readings, averaged intradialytic BP readings, and scheduled home BP readings with ABPM and clinical outcomes
HD and PD	Assess the acceptability and feasibility of ABPM
HD and PD	Investigate strategies to reduce BP variability
BP agent selection	
HD and PD	Hypertension: Conduct head-to-head RCTs of different medication classes on BP, including 44-h ABPM, and clinical and patient-reported outcomes (i.e., ARB vs. BB or ARB vs. BB vs. CCB)
HD and PD	Hypertension: Conduct RCTs on the effect of diuretics on RKF, BP, and CV outcomes
HD	Hypotension: Conduct larger, longer RCTs on effectiveness of midodrine

Questions?