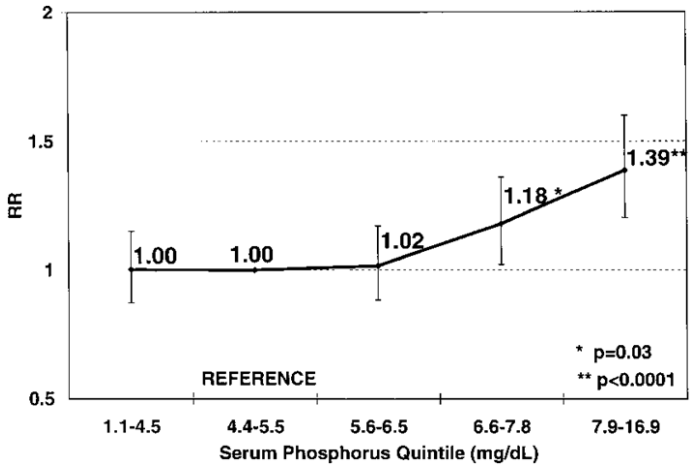
Trials to Build an Evidence Base for Phosphate Management in ESKD

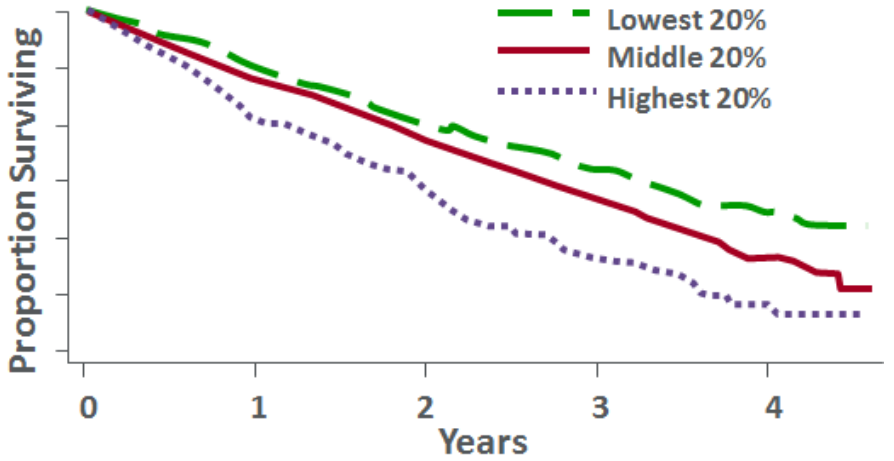
Myles Wolf, MD, MMSc

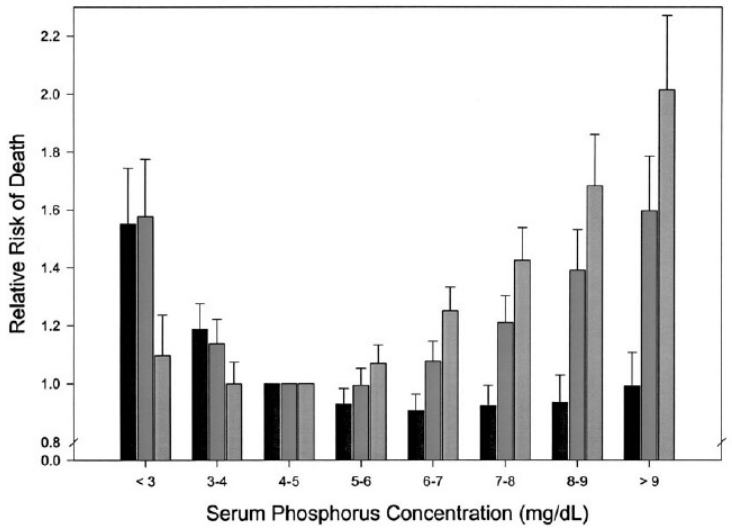
DISCLOSURES

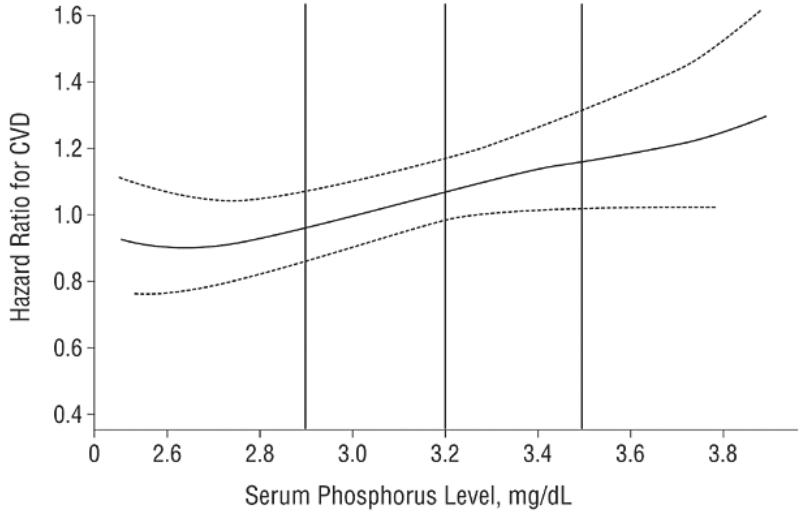
- Consultant: Bayer, Enyo, Launch, Jnana, Pharmacosmos, Reata
- Scientific Advisory Board: Unicycive, Walden
- Board of Directors: Akebia

Phosphate & mortality: ESRD, CKD, non-CKD



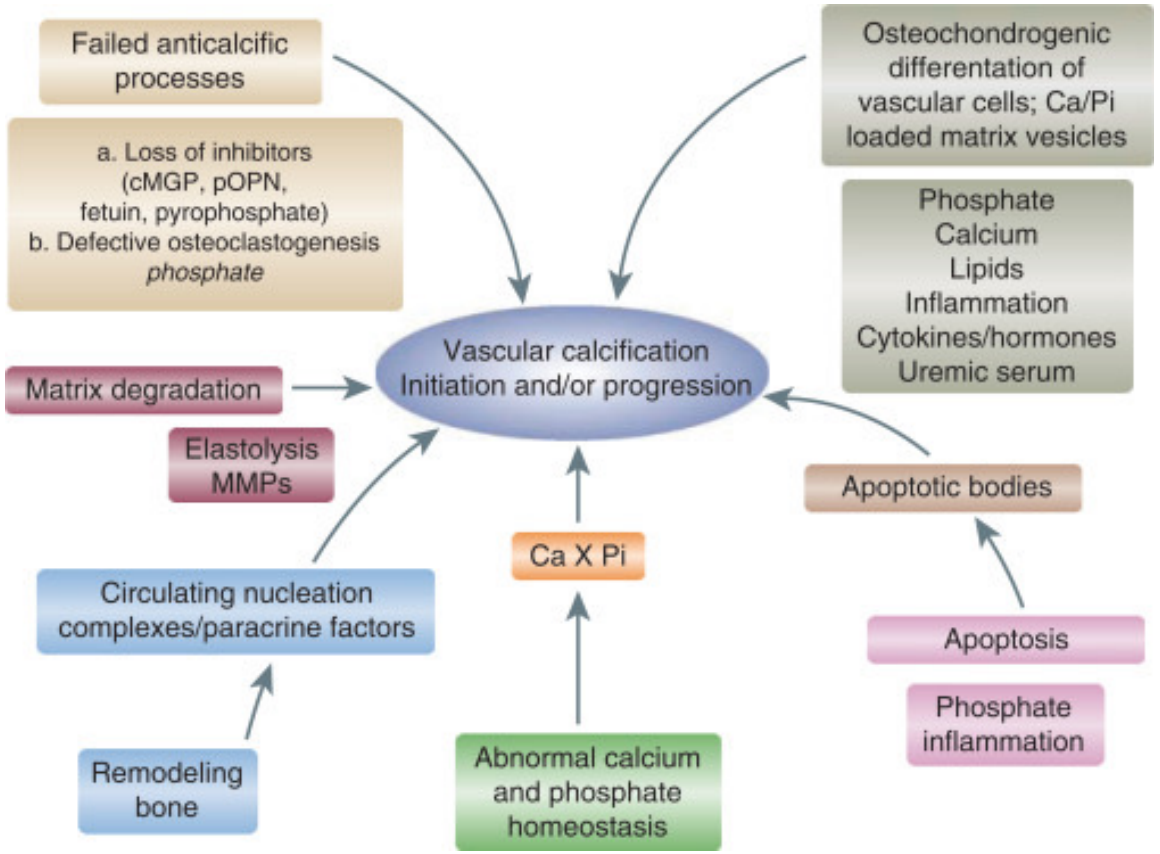


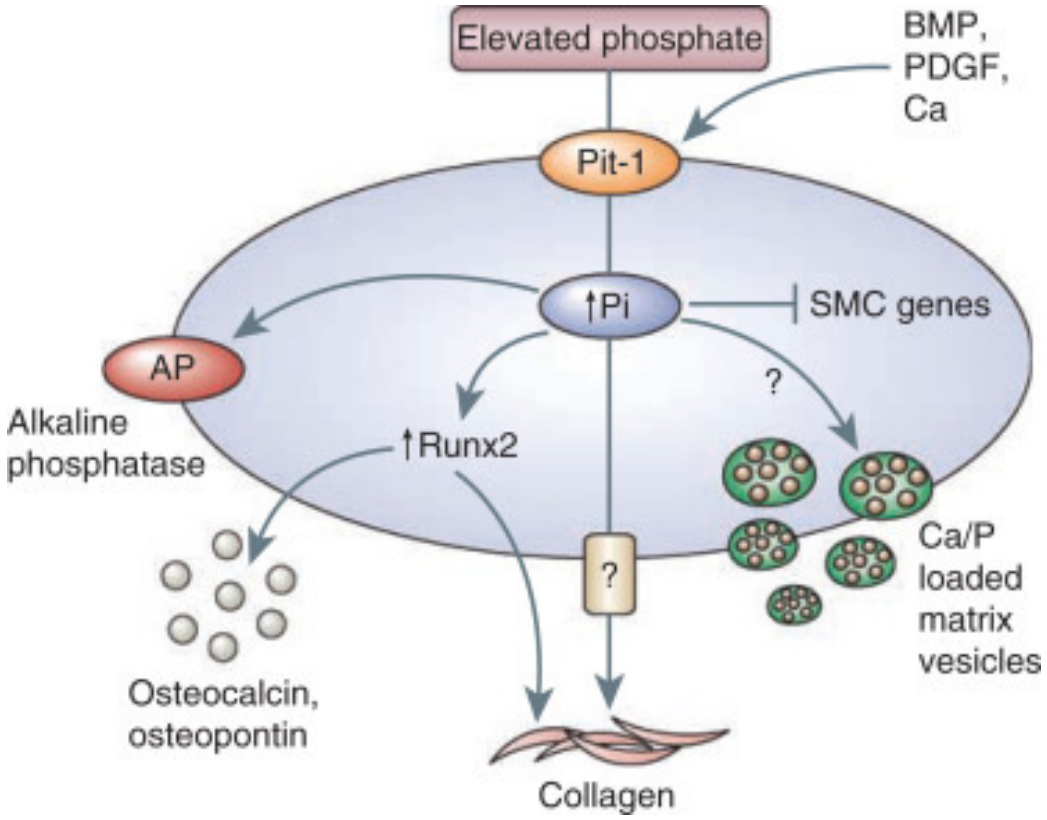




Block GA, AJKD 1998; Block GA, JASN 2004; Kestenbaum B, JASN 2005; Dhingra R, Arch Intern Med 2007

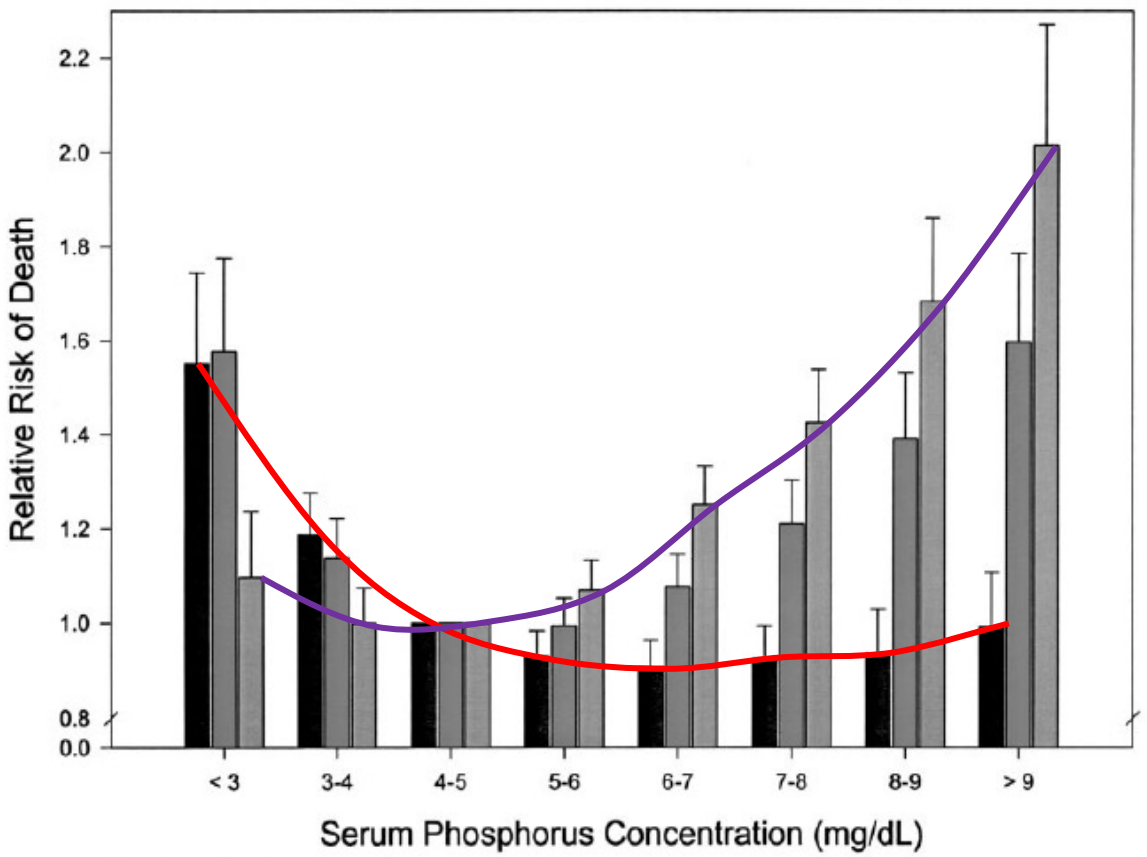
Phosphate and arterial calcification

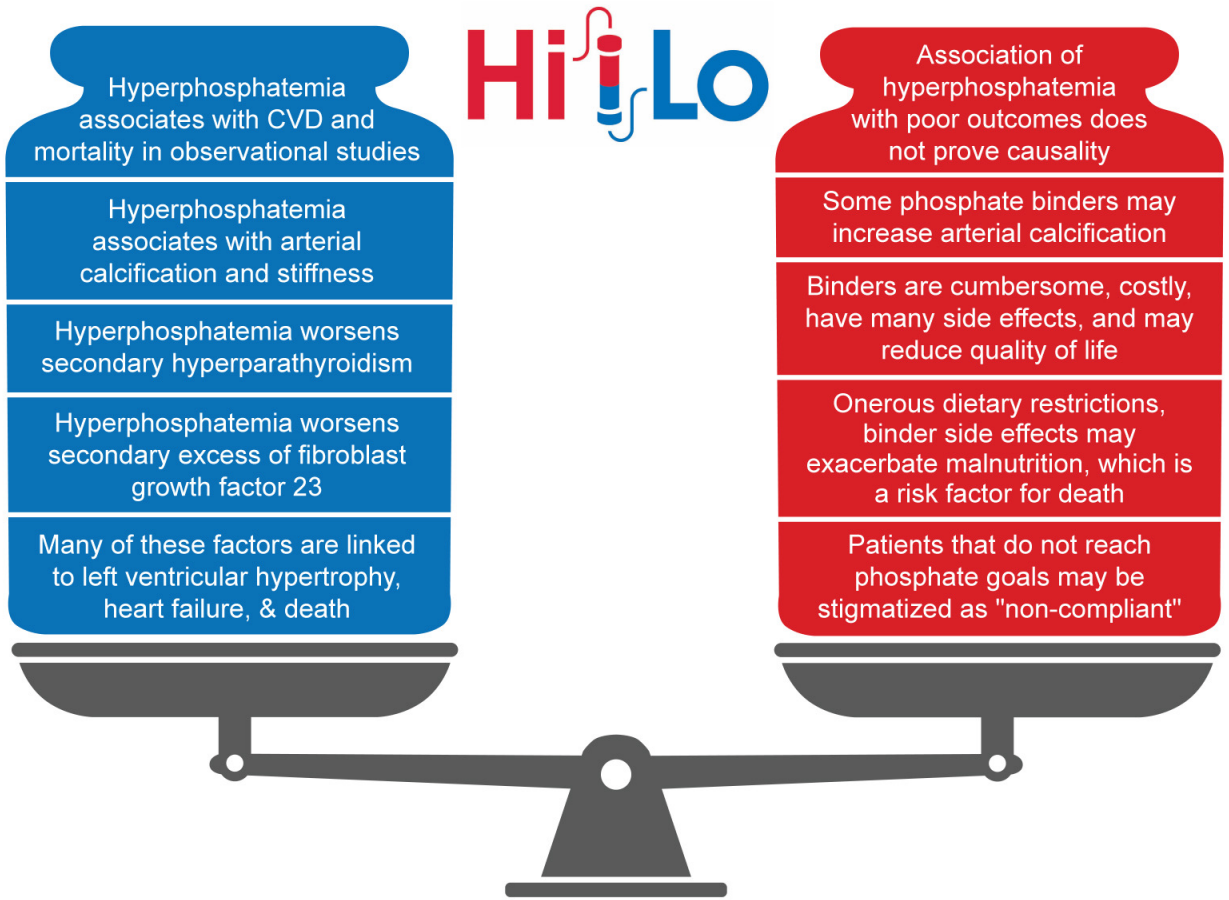




Giachelli CM. Kidney Int 2009

Hemodialysis: serum phosphate & mortality





Block et al. J Am Soc Nephrol 2004; Edmonston D et al. Am J Kidney Dis 2021

Current state

HiLo
A Pragmatic Trial Sponsored by the National Institutes of Health

Based on *preclinical* & *observational* data, *opinion-based* guidelines: Maintain P <5.5 mg/dl using binders, diet

But…there is no proof that lowering high phosphate in individual patients helps improve their outcomes!

HD: Ideal Setting for Pragmatic Trials

- Highly accessible study population
- Frequent & regular clinical encounters
- Highly granular & uniform data collection as part of routine clinical care
- Infrastructure of dialysis provider organizations allows for:
  - Centralized implementation
  - Inclusion of large number of facilities with broad geographic distribution
- Many unanswered questions about fundamental aspects of dialysis care

HiLo: Pragmatic trial of higher vs lower P in HD

PHOSPHATE

Pragmatic randomized trial of High Or Standard PHosphAte Targets in End-stage kidney disease

Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

www.phri.ca

High-level comparison of trial designs

HiLo
A Pragmatic Trial Sponsored by the National Institutes of Health

HiLo

- Pragmatic
- Targets: <5.5 vs >6.5 mg/dl
- Non-study clinicians drive Rx
- Data collected: clinical only
- Outcome: Hierarchical win ratio
  - Death, all cause
  - Hospitalizations, all cause
- No outcome adjudication

PHOSPHATE

- Pragmatic
- Targets: <4.65 vs 6.2–7.75 mg/dl
- Non-study clinicians drive Rx
- Data collected: clinical only
- Outcome: Time to first event
  - CV death, non-fatal MI, coronary revasc, stroke, PAD event
- Outcomes are adjudicated

Primary outcome: All-cause mortality & hospitalization

HiLo
A Pragmatic Trial Sponsored by the National Institutes of Health

- All-cause mortality is a gold standard outcome in clinical trials.
- Hospitalization is also extremely important to all stakeholders: patients, families, clinicians, dialysis providers, payers/Medicare.
- HyperP contributes to multiple complications that result in hospitalization.
- Hospitalization is an accepted endpoint in other therapeutic areas.
- Will be collecting real-time outcomes using EHR data.

Wins, losses and ties: Death Hospitalization

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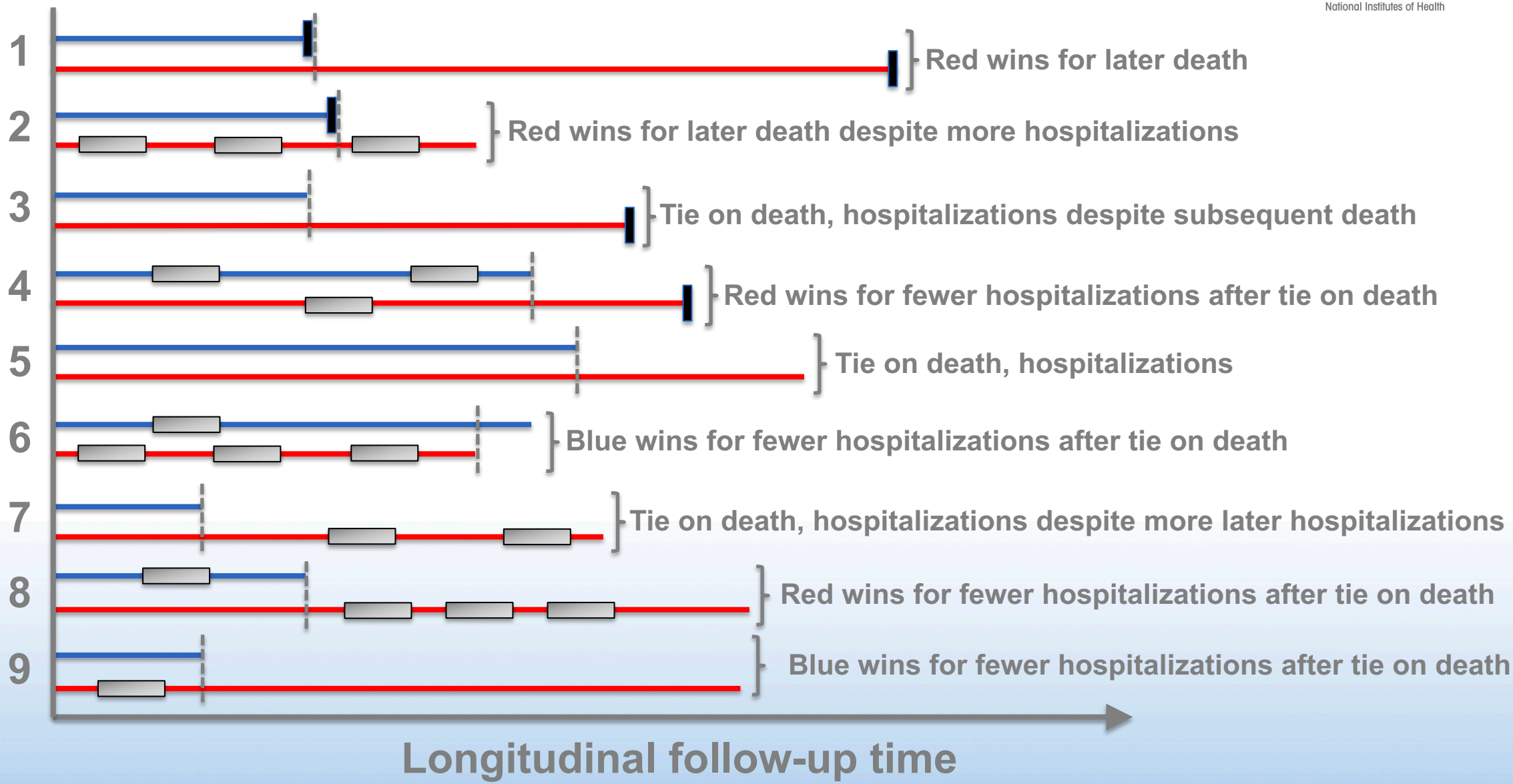
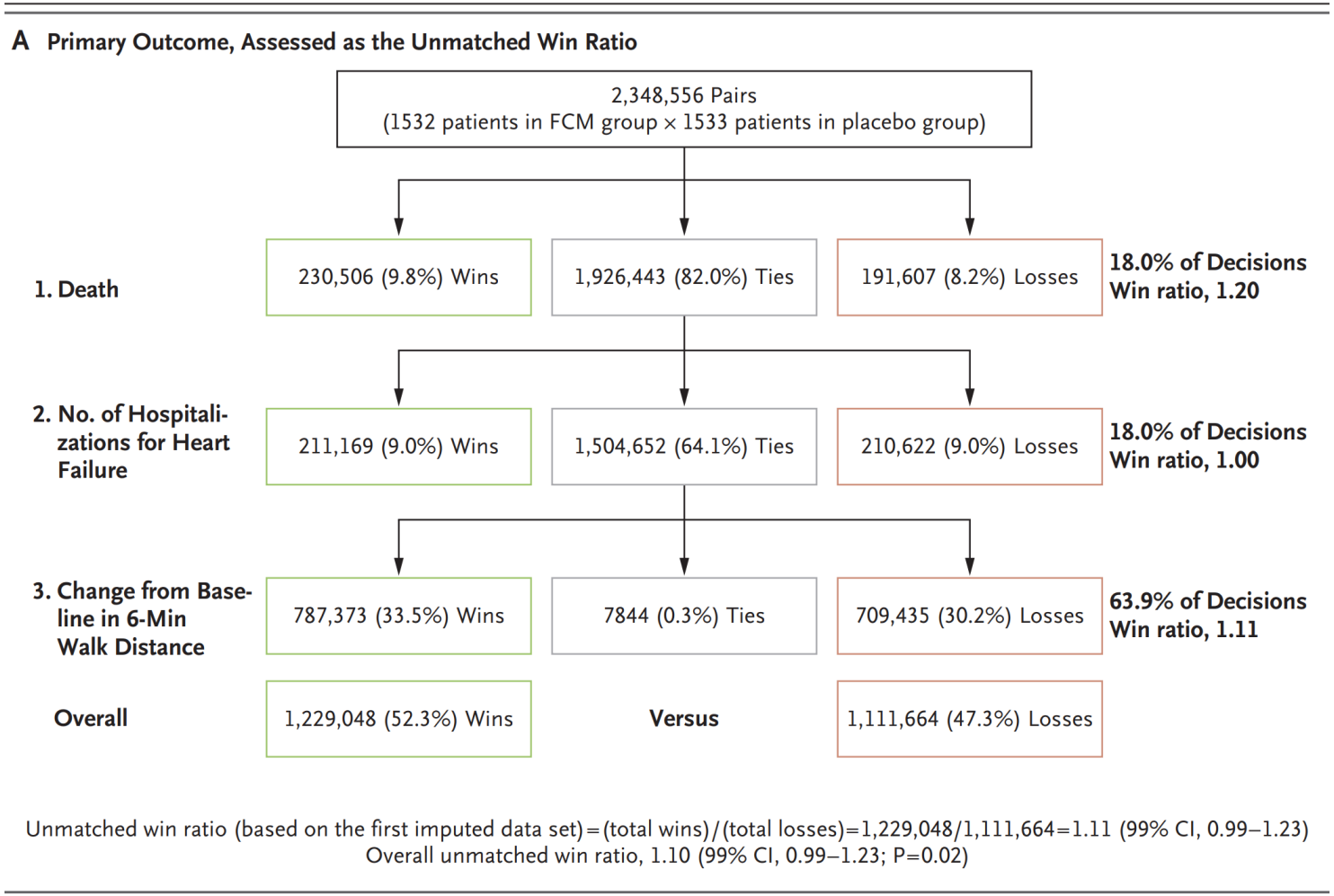


Win ratio in use: HEART-FID Trial



Mentz RJ et al. NEJM 2023

Informed Consent

HiLo
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Informed Consent needed: the “research involves more than minimal risk”

- We use “eConsent:”
  - A relatively new pragmatic approach to clinical trial design
  - Informed consent obtained electronically by smart phone, tablet or computer
  - HiLo offers both written and video-based consent materials
  - Dialysis facility staff are asked to refer patients to the HiLo website

45 CFR Part 46 (“The Common Rule”)

At 10% enrollment…

HiLo
A Pragmatic Trial Sponsored by the National Institutes of Health

- Imbalance in baseline characteristics between Hi and Lo arms

	Hi N=255	Lo N=179
Mean age, years	57.5 ± 13.8	61.6 ± 13.9
Mean phosphate, mg/dl	6.6 ± 2.2	5.8 ± 1.7

- Imbalance in enrollment rates between arms

Arm	% Ineligible	Approached	Consented	Consent Rate
Hi	31.2%	625	237	37.9%
Lo	21.2%	502	318	63.3%

- Pivot to individual level randomization

High-level comparison of trial designs

HiLo
A Pragmatic Trial Sponsored by the National Institutes of Health

HiLo

- Pragmatic
- Targets: <5.5 vs >6.5 mg/dl
- Non-study clinicians drive Rx
- Data collected: clinical only
- Outcome: Hierarchical win ratio
  - Death, all cause
  - Hospitalizations, all cause
- No outcome adjudication
- Progress: n=550 (cluster)
  - 200 of 3800 (individual)

PHOSPHATE

- Pragmatic
- Targets: <4.65 vs 6.2–7.75 mg/dl
- Non-study clinicians drive Rx
- Data collected: clinical only
- Outcome: Time to first event
  - CV death, non-fatal MI, coronary revasc, stroke, PAD event
- Outcomes are adjudicated
- Progress: n=1400 of 4000

Potential threat: Calcium vs non-calcium

LANDMARK Trial

JAMA Network

QUESTION Does lanthanum carbonate–based treatment without calcium-based phosphate binders reduce cardiovascular events compared with calcium carbonate–based treatment in patients with hyperphosphatemia undergoing hemodialysis?

CONCLUSION Among patients with chronic kidney disease (CKD) undergoing hemodialysis, treatment of hyperphosphatemia with lanthanum carbonate compared with calcium carbonate did not result in a significant difference in cardiovascular events.

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POPULATION

1271 Men
864 Women

Adults with CKD, hyperphosphatemia, and ≥1 vascular calcification risk factor

Median age: 69 years

LOCATIONS

273 Hemodialysis facilities in Japan

INTERVENTION

2309 Patients randomized
2135 Patients analyzed

1063
Lanthanum carbonate
750 mg/d oral lanthanum carbonate (3 doses, 250 mg each, after meals) or previously prescribed dose

1072
Calcium carbonate
3000 mg/d oral calcium carbonate (3 doses, 1000 mg each, after meals) or previously prescribed dose

PRIMARY OUTCOME

Composite of cardiovascular events: cardiovascular death, nonfatal myocardial infarction or stroke, unstable angina, TIA, or hospitalization for heart failure or ventricular arrhythmia

FINDINGS

Incident rate of composite cardiovascular events

Lanthanum carbonate
4.8 events per 100 person-years
(147 of 1063 patients)

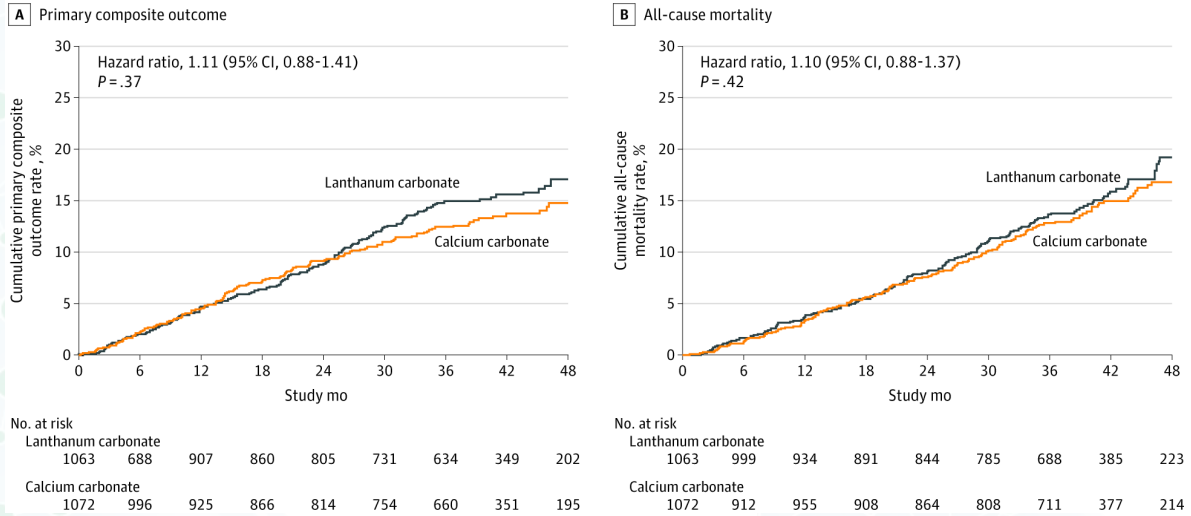
Calcium carbonate
4.3 events per 100 person-years
(134 of 1072 patients)

The findings were not significant:

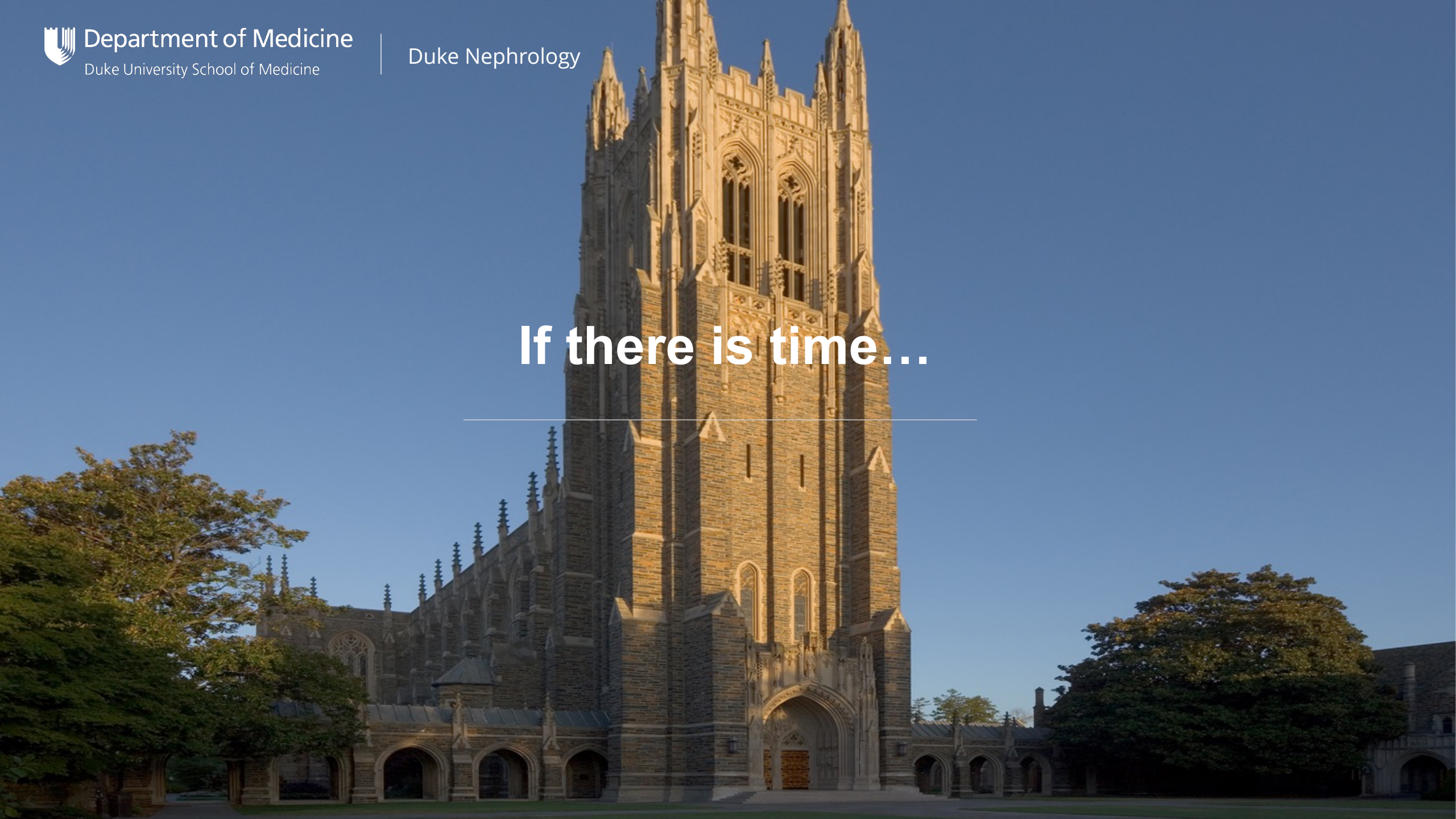
Difference, 0.5 events per 100 person-years
(95% CI, −0.57 to 1.56)

Hazard ratio, 1.11
(95% CI, 0.88 to 1.41) *P* = .37

Ogata H, Fukagawa M, Hirakata H, et al. Effect of treating hyperphosphatemia with lanthanum carbonate vs calcium carbonate on cardiovascular events in patients with chronic kidney disease on hemodialysis: the LANDMARK randomized clinical trial. *JAMA*. Published May 18, 2021. doi:10.1001/jama.2021.4807

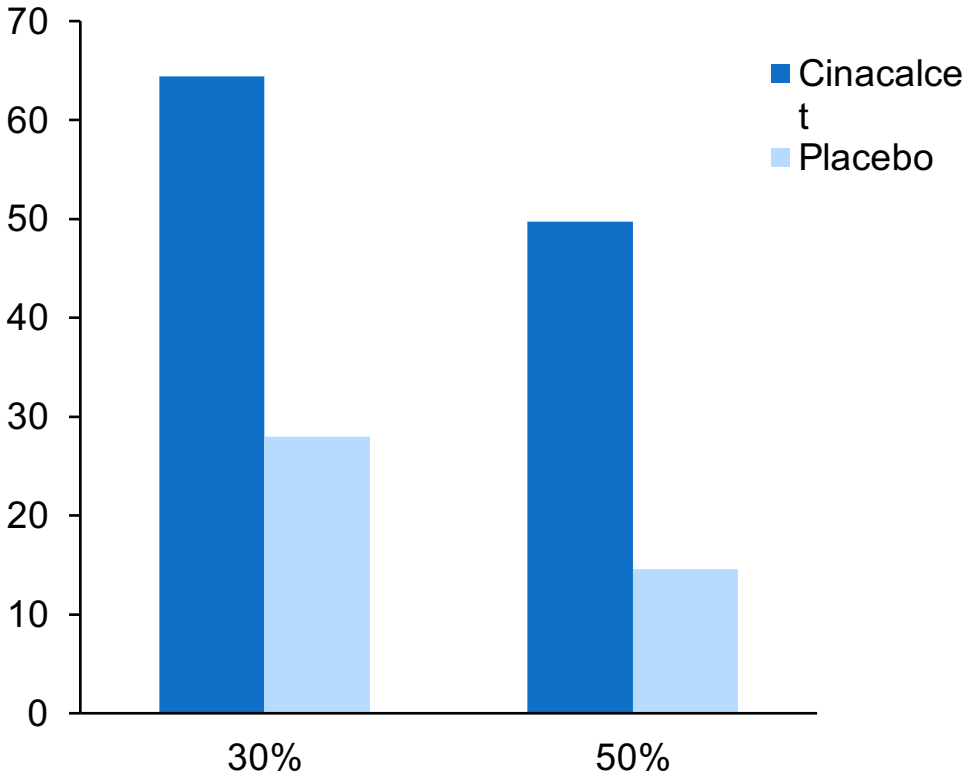


Ogata H. JAMA 2021



If there is time…

FGF23 reduction & outcomes: EVOLVE Study



	No. Events ≥30% N = 832	No. Events <30% N = 458	HR (95% CI)	p-value
Primary composite endpoint	376	235	0.82 (0.69, 0.98)	0.03
All-cause mortality	290	171	0.86 (0.70, 1.05)	0.14
Cardiovascular mortality	136	102	0.66 (0.50, 0.87)	<0.01
Sudden death	54	49	0.57 (0.37, 0.86)	<0.01
Heart failure	74	59	0.69 (0.48, 0.99)	0.04
Tertiary cardiovascular composite	228	170	0.67 (0.54, 0.83)	<0.001

0.1 1.0 10

Favors ≥30% Reduction *Favors < 30% Reduction*

	No. Events ≥50% N = 642	No. Events <50% N = 648	HR (95% CI)	p-value
Primary composite endpoint	290	321	0.81 (0.68, 0.96)	0.01
All-cause mortality	224	237	0.84 (0.69, 1.02)	0.08
Cardiovascular mortality	104	134	0.68 (0.52, 0.90)	<0.01
Sudden death	39	64	0.56 (0.36, 0.86)	<0.01
Heart failure	50	83	0.56 (0.39, 0.82)	<0.01
Tertiary cardiovascular composite	172	226	0.68 (0.55, 0.84)	<0.001

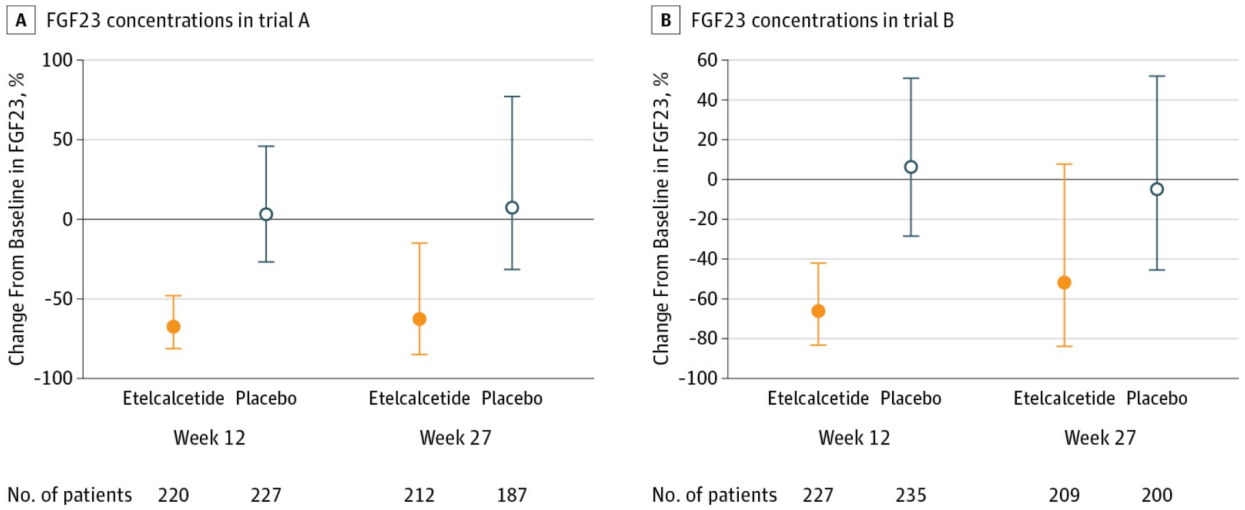
0.1 1.0 10

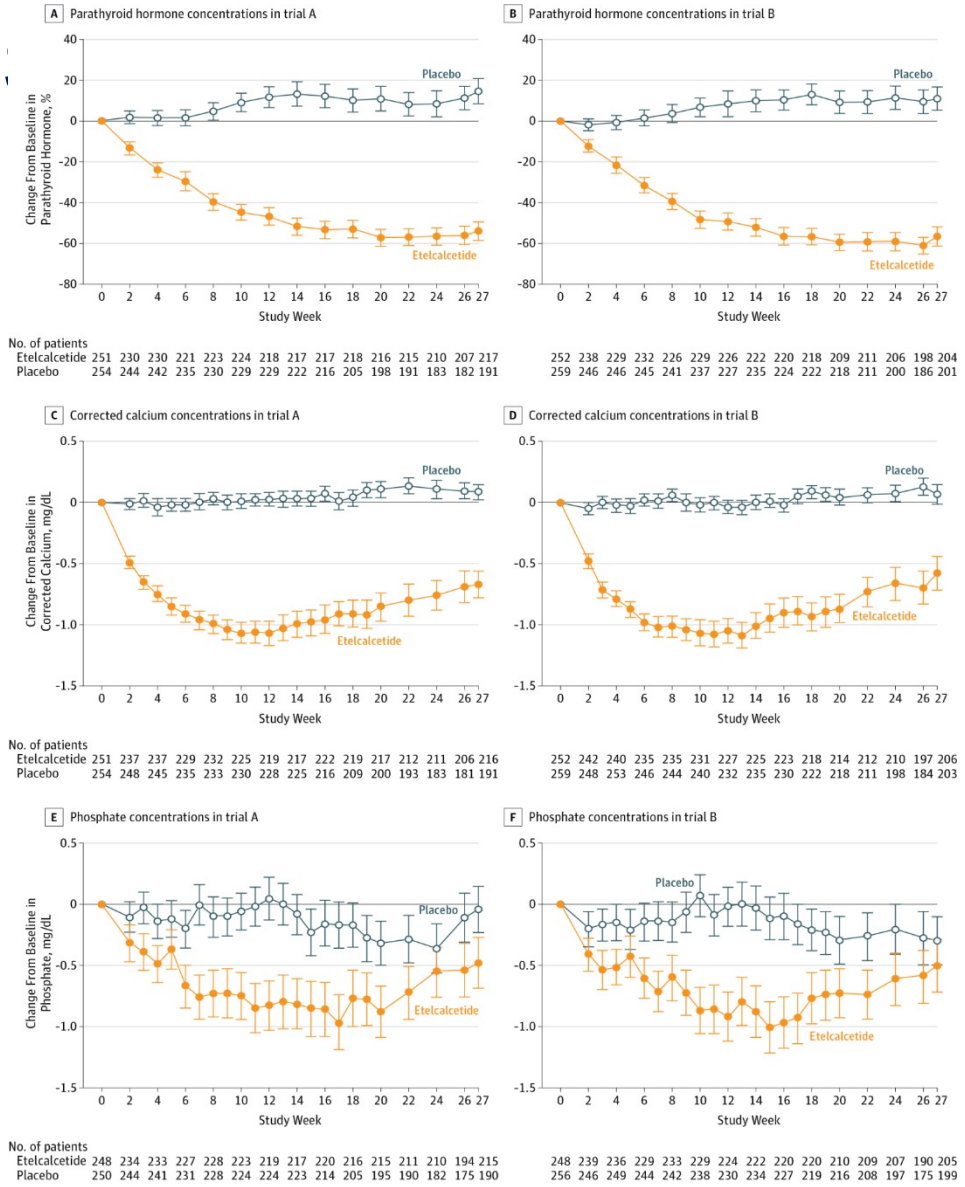
Favors ≥50% Reduction *Favors <50% Reduction*

Moe SM et al. Circulation. 2015;132:27-39

Etelcalcetide versus placebo in E

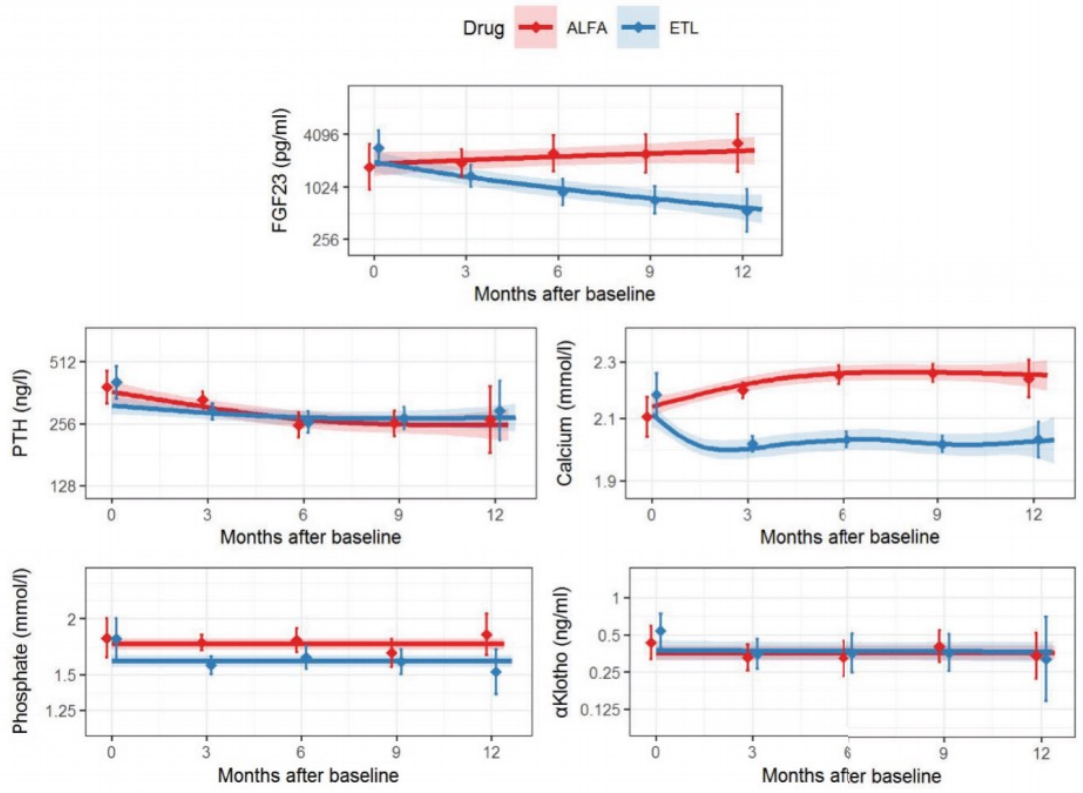
2 separate trials, total:
IV etelcalcetide: n = 503
versus placebo: n = 513
3x weekly for 26 weeks



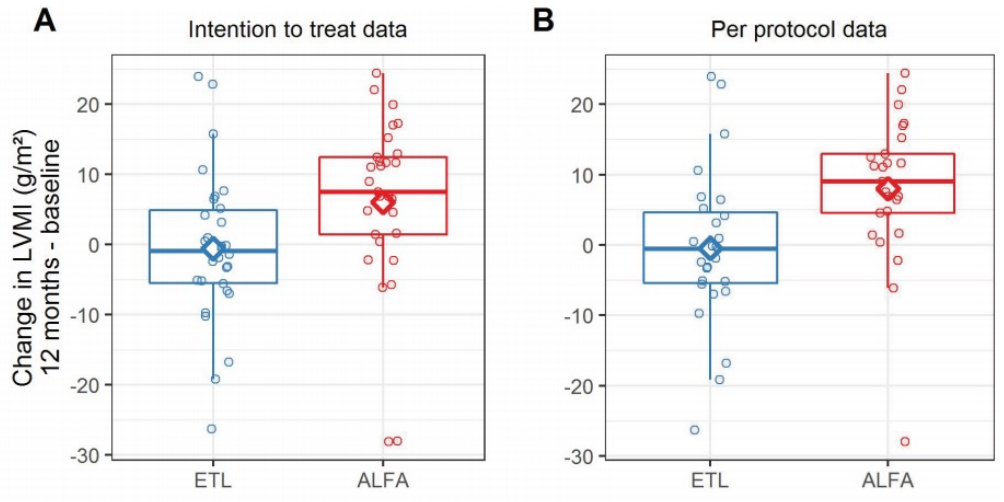


Block GA, et al. JAMA 2017

FGF23 reduction stabilizes LVH in ESRD

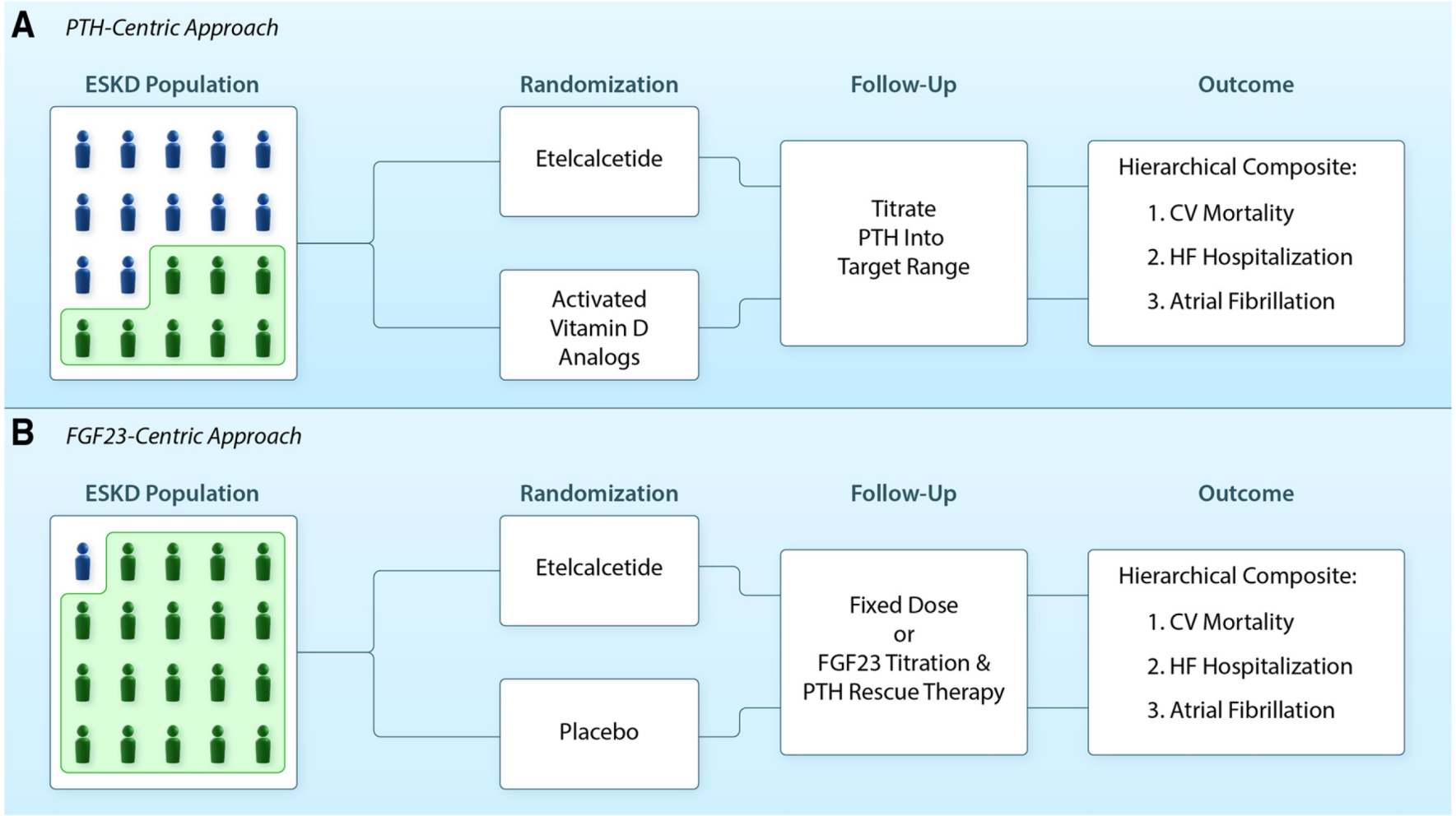


- Pilot RCT in Austria
- 1:1 randomize to etelcalcetide vs alfacalcidol
- N=62
- 1-year follow-up
- LVMI by cardiac MRI



Dörr K, et al. Circ Res. 2021

A different approach?



Murray S, Wolf M. Circ Res. 2021

DISCUSSION