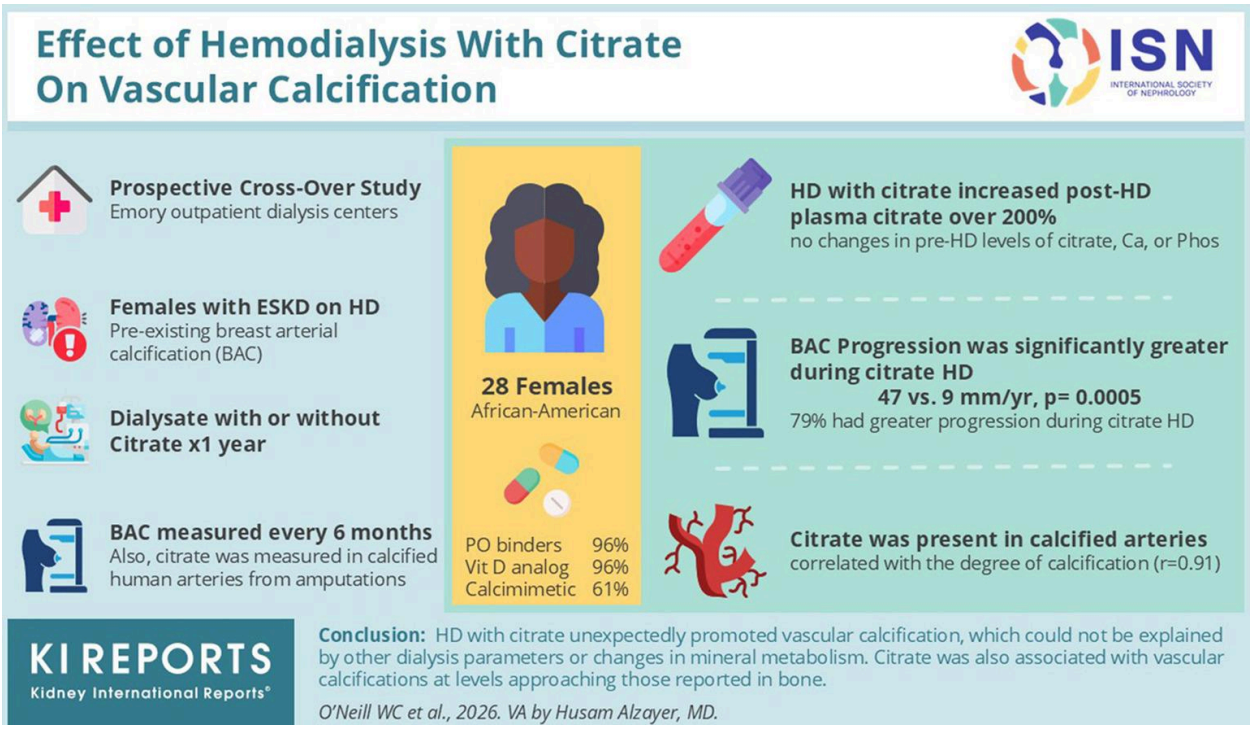
1/ Hey #NephX! 👋
We're back with a fresh #Xtorial from KIReports

Citrate dialysate is often viewed as a friend in dialysis : it chelates Ca, and inhibits Ca/Phos crystallization, But what if the effect on the vessel wall is not so simple?



2/ A new KI Reports study asks a provocative question : does citrate-containing dialysate affect vascular calcification in HD?

https://www.sciencedirect.com/science/article/pii/S2468024926028536

The answer was unexpected. Let's look at the study, the signal, and what we should make of it.

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CLINICAL RESEARCH

Effect of Hemodialysis With Citrate on Vascular Calcification

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Introduction: Vascular calcification, specifically medial calcification, is prevalent in patients undergoing hemodialysis (HD) and leads to poor outcomes. Citrate is present in some HD solutions and could potentially inhibit vascular calcification. This was examined by comparing the progression of medial arterial calcification, as measured using mammography, in female patients with end-stage renal disease (ESRD) undergoing HD with and without citrate.

Methods: In a cross-over study, 28 female chronic in-center HD patients with preexisting breast arterial calcification (BAC) underwent HD using dialysate with or without citrate, each for 1 year with BAC measured at 6-month intervals. In addition, citrate was measured in calcified human arteries.

Results: HD with citrate increased post-HD plasma citrate over 200% with no changes in pre-HD levels of citrate, calcium (Ca), or phosphate. Progression of BAC was significantly greater during citrate HD (47, interquartile range [IQR]:10–124 vs. 9 , IQR: −4 to 34 mm/yr, $P = 0.0005$), with 79% of subjects having greater progression during citrate HD. Citrate was present in calcified human arteries and correlated with the degree of calcification ($r = 0.91$).

Conclusion: HD with citrate unexpectedly promoted vascular calcification, which could not be explained by other dialysis parameters or changes in mineral metabolism. In addition, citrate was associated with vascular calcifications at levels approaching those reported in bone. The results are consistent with known effects of citrate to promote biomineralization and bone formation. Further studies are needed to determine whether this effect of citrate leads to adverse clinical outcomes in patients undergoing HD and occurs with other therapeutic uses of citrate.

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KEYWORDS: citrate; hemodialysis; vascular calcification

3/ Our #Xtorial is by Akshaya J @DrAkshayaJ, adult nephrologist from @CMCNephrology - No COI

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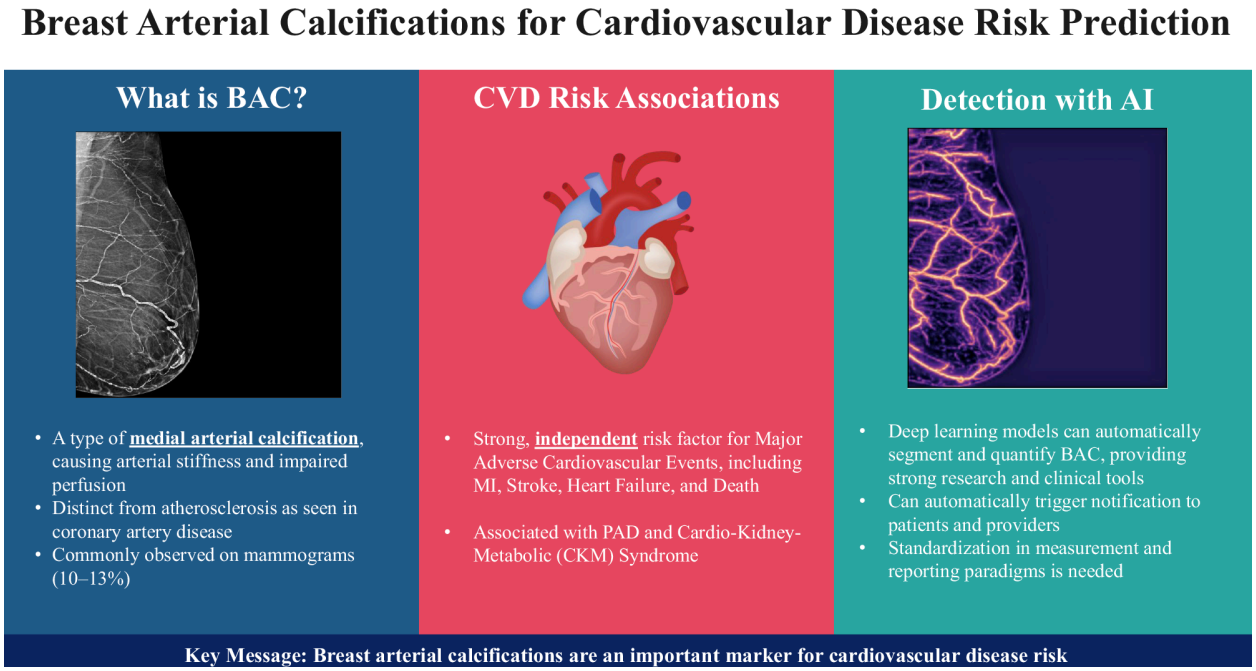
4/ POLL

What is breast arterial calcification (BAC) most reflective of?

A. Medial vascular calcification
B. Atherosclerosis
C. Both equally
D. Not sure

5/ The study used breast arterial calcification (BAC) as a marker of medial vascular calcification, answer “A”.

BAC is visible on routine mammography and reflects medial rather than atherosclerotic intimal calcification.



6/ Study design : This was a crossover study. 28 women on chronic HD with pre-existing BAC received citrate or acetate dialysate for ~1 year each, with mammograms at 6-month intervals.

Each patient therefore served as her own control.

Table 1. Patient characteristics

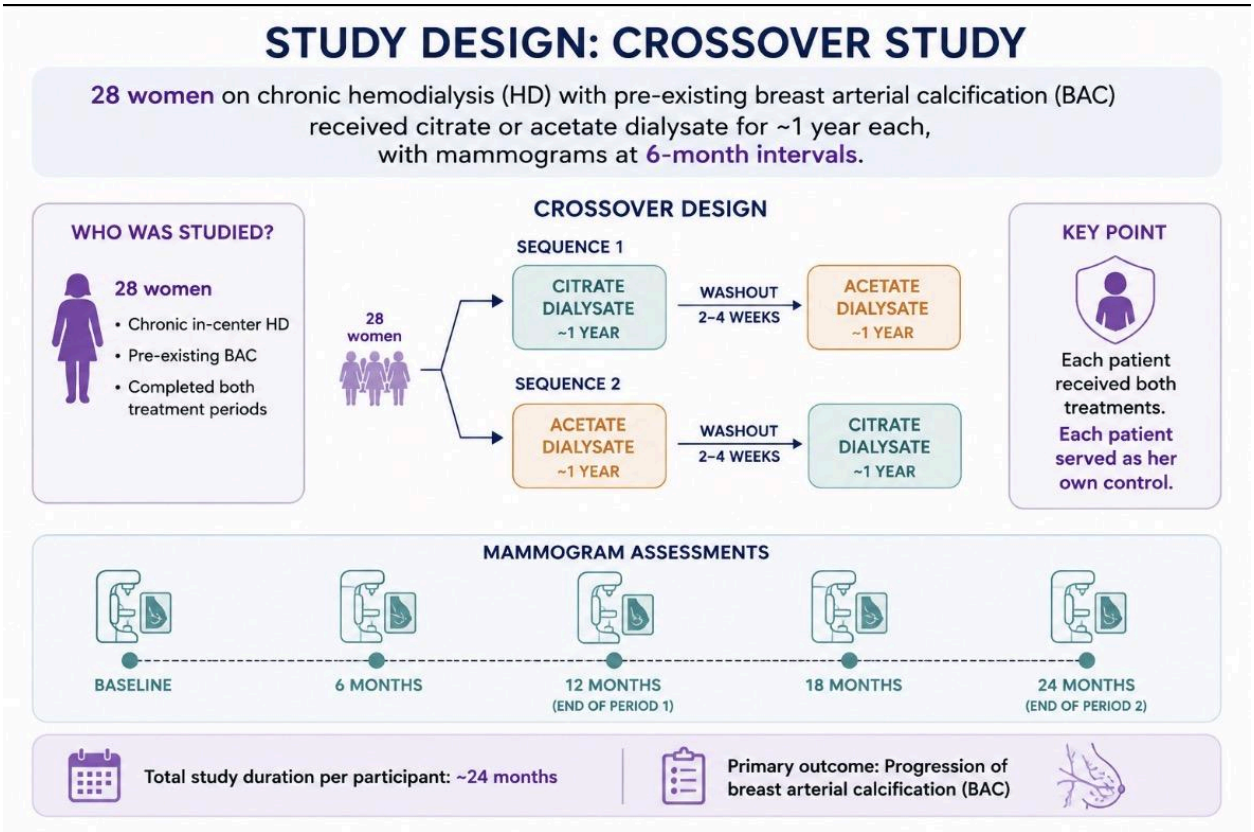
Characteristics	All	Group 1	Group 2
Age (yr)	58.2 ± 2.1	55.7 ± 2.3	60.1 ± 3.1
Race (%AA)	100	100	100
ESRD duration (yr)	6.3 ± 0.8	7.3 ± 1.4	5.6 ± 0.9
Diabetes (%)	54	58	50
Phosphate binder (%)	96	100	94
Sevelamer	54	83	50
Ca acetate	17	17	25
SucroFe oxyhydroxide	14	8	19
Fe citrate	7	8	6
Vitamin D analog (%)	96	92	100
Calcimimetic (%)	61	58	63

AA, African American; Ca, calcium; ESRD, end-stage renal disease; Fe, iron.
There were no significant differences between groups. Means ± standard errors.

7/ The cohort was small and highly selected: all 28 were women and African American.

Of 54 who started, only 29 completed the protocol, and 28 had usable BAC progression data.

The attrition matters when interpreting the magnitude of the finding.



8/ The headline result: BAC progressed much faster with citrate.

Median progression was 47 mm/yr with citrate vs 9 mm/yr with acetate. (P=0.0005)

22 of 28 patients had greater progression during citrate exposure.

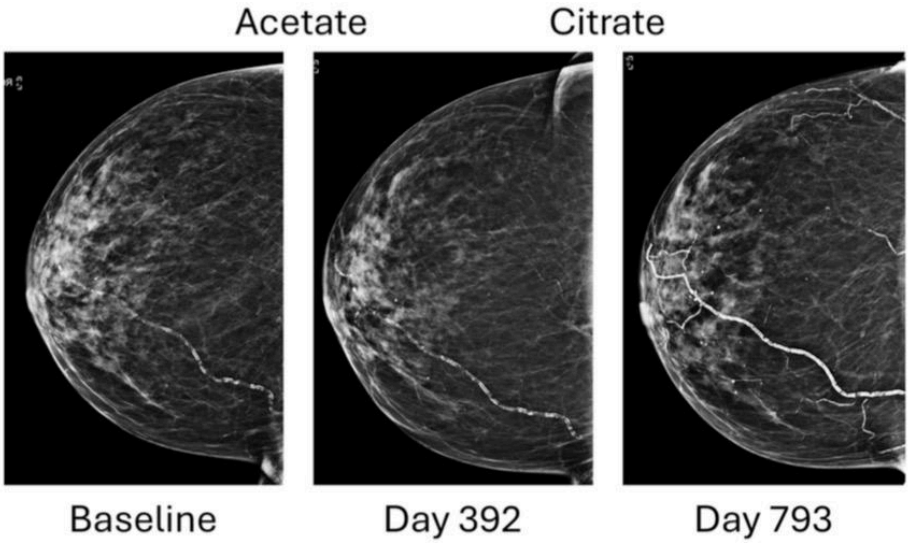


Figure 1. Breast arterial calcification. First, third, and fifth mammogram from 1 subject who started on the acetate arm and finished on the citrate arm.

9/ The finding was also seen as % change from baseline: 40%/yr with citrate vs 21%/yr with acetate.

The effect was significant whether patients started with citrate or acetate, supporting consistency within the crossover design.

Table 6. Progression of breast arterial calcification

Subjects	Parameter	Citrate	Acetate	Citrate-acetate	*P*-value
All	mm/yr	47 (10–124)	9 (−4 to 34)	27 (5–81)	0.0005
	%/yr	40 (20–98)	21 (−3 to 33)	21 (4–104)	0.0005
Citrate first	mm/yr	52 (15–141)	9.0 (−4 to 24)	51 (2–83)	0.034
Acetate first	mm/yr	47 (9–120)	7 (−6 to 41)	18 (8–81)	0.011

Values are medians and interquartile ranges. Significance was determined by paired testing using the Wilcoxon signed-rank test.

10/ Could Ca, phosphate or dialysis adequacy explain it?

Not really.

Pre-HD Ca and phosphate, dialysis time, Kt/V and dialysate Ca were similar. Citrate did lower post-HD ionized Ca and Mg, while HCO3 and PTH were slightly higher.

Table 4. Blood chemistries on each arm for the entire cohort

Chemistry		Citrate arm	Acetate arm	*P*
Serum Ca (mg/dl)	Pre-HD	9.0 ± 0.1 (28)	9.0 ± 0.1 (28)	
Serum P (mg/dl)	Pre-HD	5.8 ± 0.2 (28)	5.9 ± 0.3 (28)	
Serum HCO3 (mEq/l)	Pre-HD	22.8 ± 0.3 (28)	22.2 ± 0.3 (28)	0.04
Serum PTH (pg/ml)	Pre-HD	651 ± 76 (28)	562 ± 57 (28)	0.028
Serum iCa (mg/dl)	Pre-HD	4.8 ± 0.07 (28)	4.8 ± 0.10 (27)	
	Post-HD	4.6 ± 0.04 (27)	4.9 ± 0.08 (26)	0.002
Serum Mg (mg/dl)	Pre-HD	2.3 ± 0.04 (28)	2.4 ± 0.07 (26)	
	Post-HD	2.0 ± 0.02 (28)	2.1 ± 0.03 (26)	
Plasma citrate (μM)	Pre-HD	134 ± 9 (25)	130 ± 7 (25)	
	Post-HD	383 ± 16 (25)	187 ± 20 (25)	0.0001

Ca, calcium; HCO3, hydrogen carbonate; HD, hemodialysis; iCa, ionized Ca; Mg, magnesium; P, phosphorus; PTH, parathyroid hormone.
Values for serum Ca, P, HCO3, and PTH are averages of monthly measurements during each arm. Other measurements are averages of 2 measurements during each arm. Data are means ± standard errors of the number of subjects in parentheses. Parentheses indicate number of subjects. *P*-values from paired *t* testing.

11/ The striking biochemical difference was citrate itself.

Pre-HD citrate was similar, but post-HD citrate rose to 383 vs 187 μM with citrate vs acetate. That >3-fold rise makes citrate a plausible contributor, but does not prove causality.

Table 2. Relevant parameters on each arm of the study for the entire cohort

Parameter	Citrate arm	Acetate arm
Duration (d)	401 ± 9	413 ± 18
Age at end of arm (yr)	59.9 ± 2.1	59.8 ± 2.1
Dialysis time (min)	198 ± 4	199 ± 4
Mean kT/V	1.54 ± 0.03	1.55 ± 0.03
Mean dialysate Ca (mEq/l)	2.6 ± 0.04	2.6 ± 0.03
Dialysate Mg (mM)	0.5	0.5
Dialysate HCO3 (mM)	34.6	33.0
Dialysate acetate (mM)	0.3	4.0
Dialysate citrate (mM)	2.4	0

Ca, calcium; HCO3, hydrogen carbonate; Mg, magnesium.
There were no significant differences between arms by paired testing. Means ± standard errors.

12/ Then came the intriguing tissue finding. Citrate was detected in calcified human arterial segments. Citrate content correlated strongly with the amount of calcification (r=0.91). Estimated citrate content was ~0.8% of calcified tissue.

13/ Why is this surprising?

Citrate is a calcium chelator and can inhibit calcium phosphate crystallization. But citrate is also abundant in bone and participates in biomineralization. So its biological effect may depend on context, concentration and tissue environment.

14/ Limitations

5 patients may have had dialysate errors, based on unexpectedly ⬆️ citrate levels during the acetate arm

BAC is a surrogate

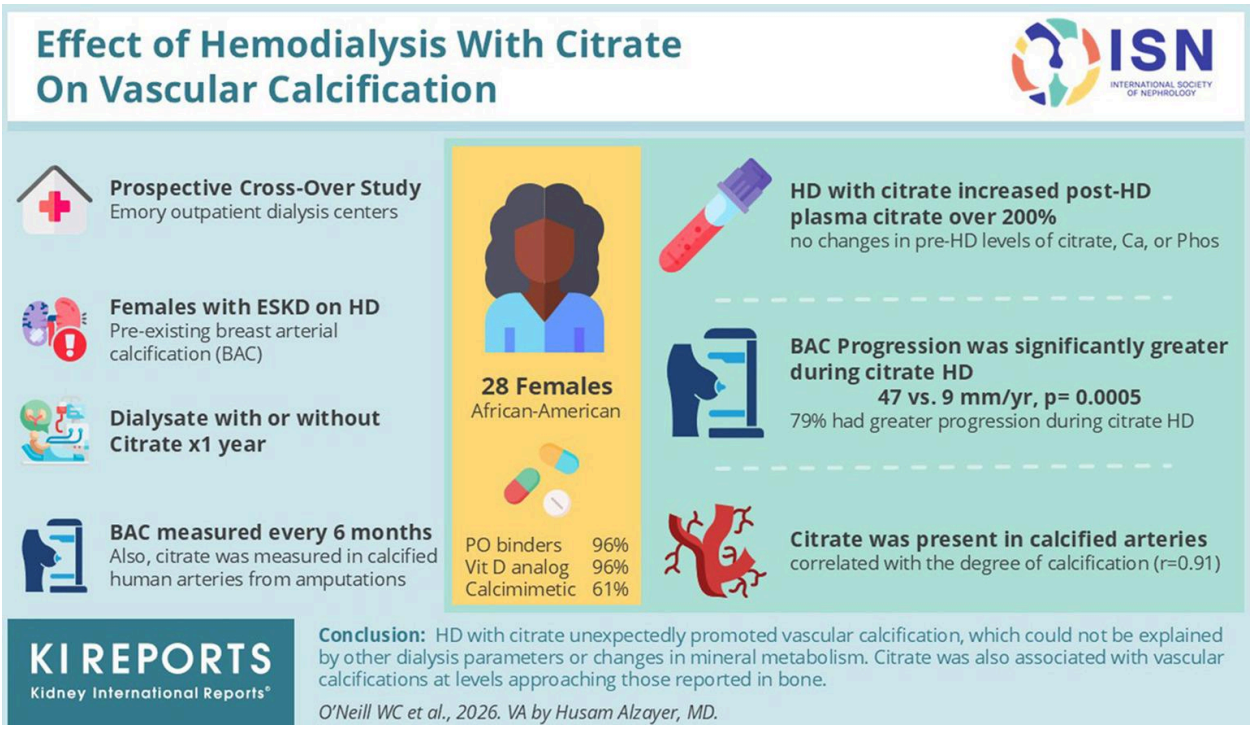
This study did not measure coronary/aortic Ca, calciphylaxis, CV events or mortality. We cannot conclude that citrate dialysate⬆️ CV risk

15/ The study also challenges an interesting disconnect: citrate dialysate can improve short-term serum calcification propensity, yet this study found faster progression of vascular calcification.

A better biomarker does not automatically mean a better tissue-level outcome.

17/ So, should we stop citrate dialysate? No.

This is a small, single-center study with a selected population and surrogate endpoint. But the signal is striking enough to justify larger studies with robust exposure assignment, imaging and clinical outcomes.



18/ Thank you for reading!

This paper is a reminder that dialysis prescriptions can have biological effects we may not predict from short-term biochemical markers.

Read the full KI Reports paper and keep questioning the mechanism. 🧵

https://www.sciencedirect.com/science/article/pii/S2468024926028536