Association of serum phosphate with efficacy of statin therapy in hemodialysis patients

Supplemental Material

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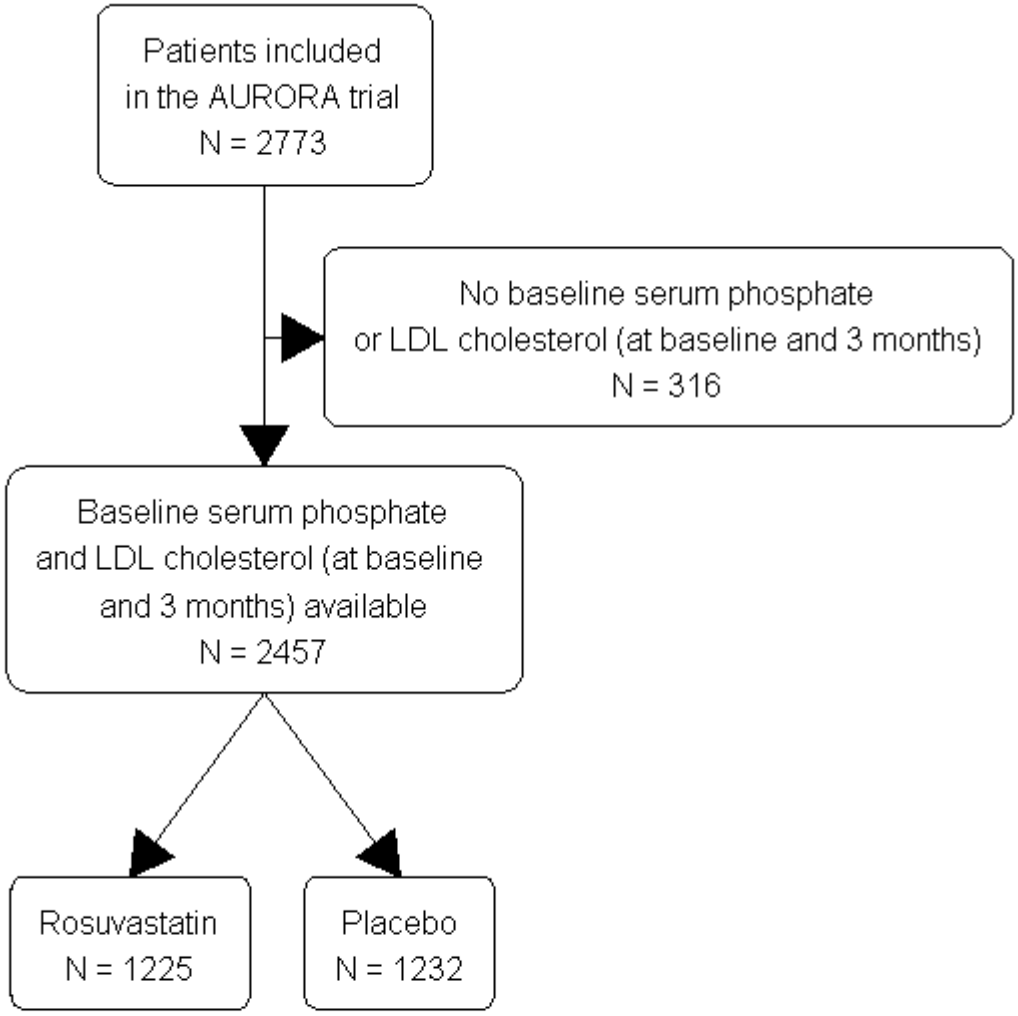
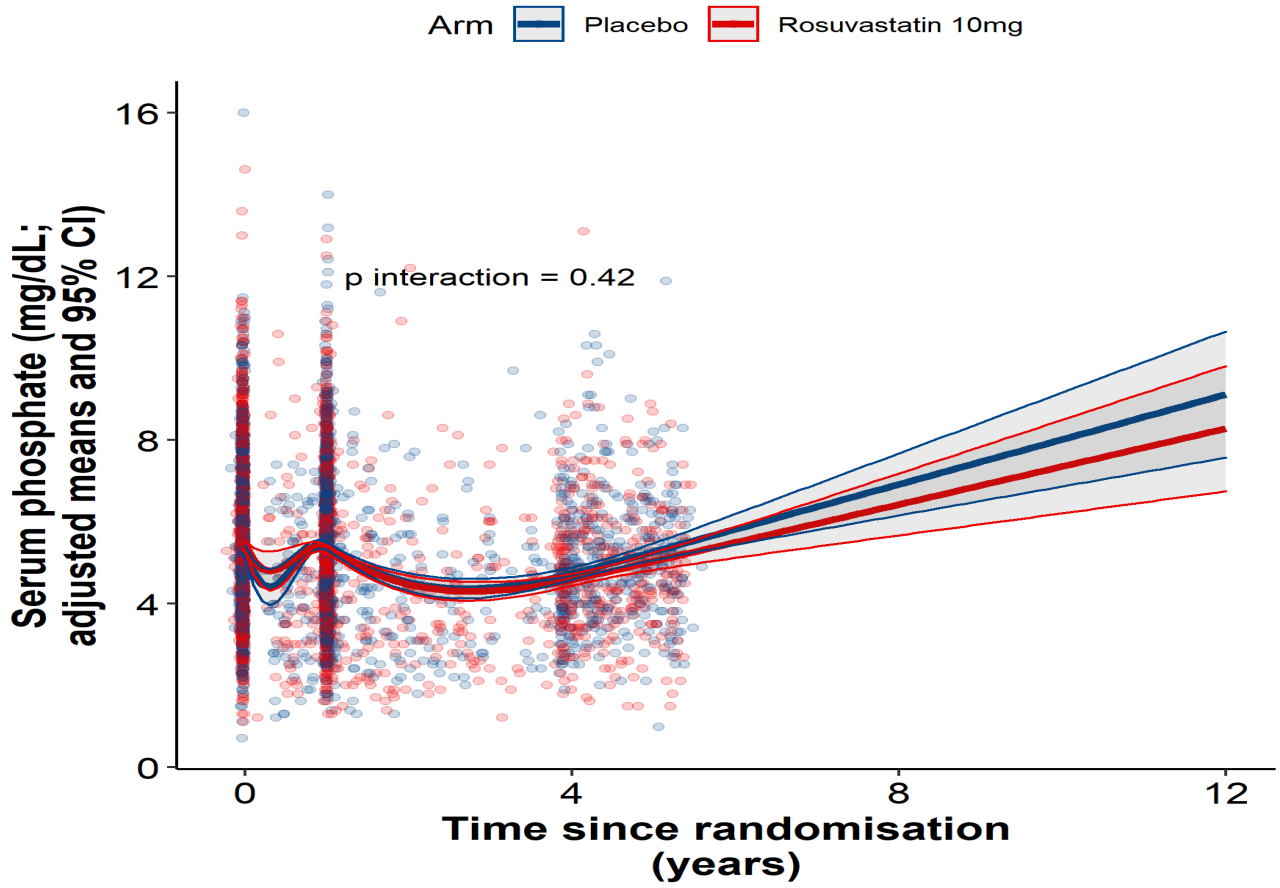
Table of contents of supplemental material

Supplemental Figure 1: Flow chart of the study in AURORA Trial



Supplemental Figure 2: Evolution of serum phosphate over time in relation to treatment



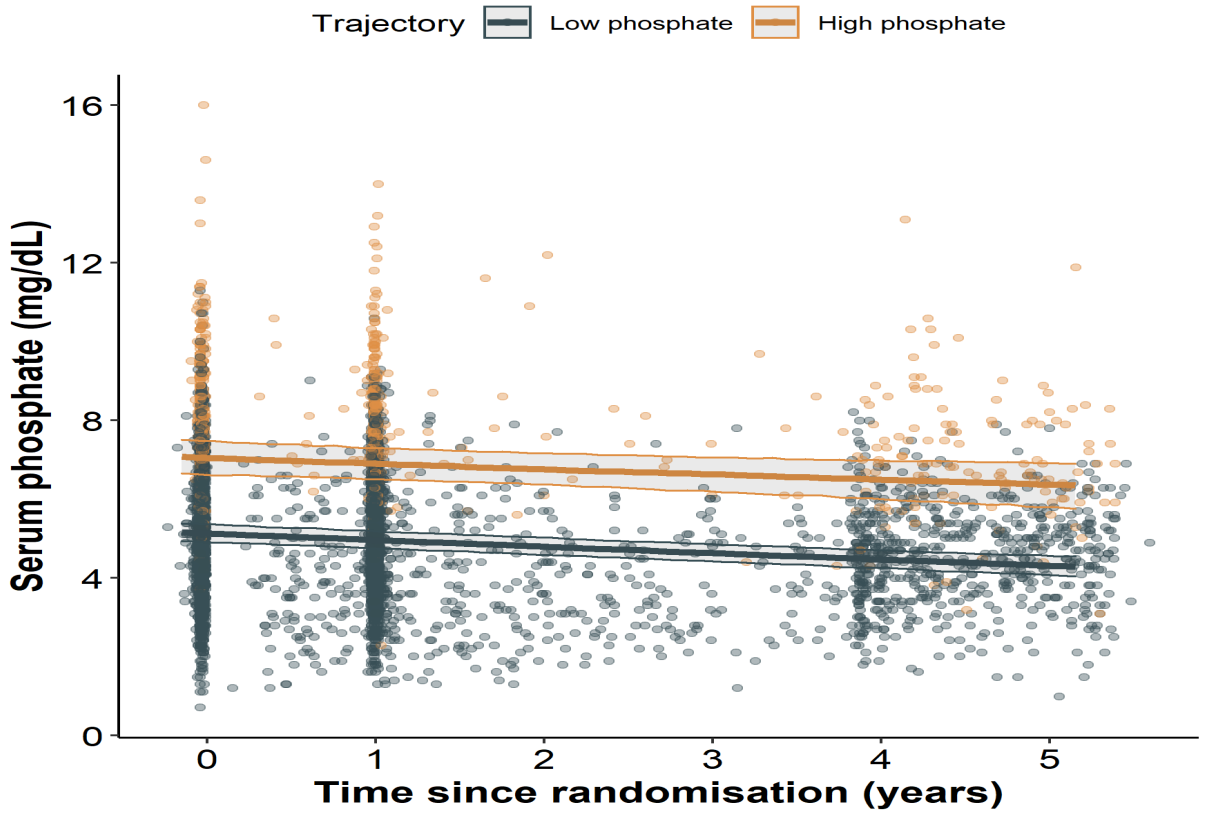
Supplemental Table 1: Comparison of different grouping models for serum phosphate trajectories

G	npm	AIC	BIC	SABIC	entropy	%class1	%class 2	%class3	%class 4
1	8	21,696.4	21,742.9	21,717.4	1.0	100.0			
2	11	21,672.0	21,735.9	21,700.9	0.5	87.0	13.0		
3	14	21,678.0	21,759.3	21,714.8	0.2	19.6	80.4	0.0	
4	17	21,675.9	21,774.7	21,720.6	0.5	13.5	86.0	0.5	0.0

All models were run with a beta link function, which was the best trade-off to model the data. G is the number groups of modeled; npm the number of parameters; entropy is a measure of classification accuracy.

All statistics agree on the fact that the 2-group model is the best.

Supplemental Figure 3: Serum phosphate trajectories over time using latent class mixed models. Data were mostly available at baseline (N = 2457), one-year (N = 1939) and close-out (N = 1314).



Supplemental Figure 4: Effect of time-dependent serum phosphate levels changes (non-linear) on outcomes in relation to treatment in the AURORA trial. A) MACE. B) All-cause death. C) HR for specific phosphate values. Models contained the interaction between statin treatment and non-linear time-dependent serum phosphate levels and were adjusted for age, sex, smoking status, diabetes, cardiovascular history, mean blood pressure, C reactive protein and time-dependent LDL, and phosphate was modeled using a restricted cubic spline with the median value of 5.29 mg/dL as reference.

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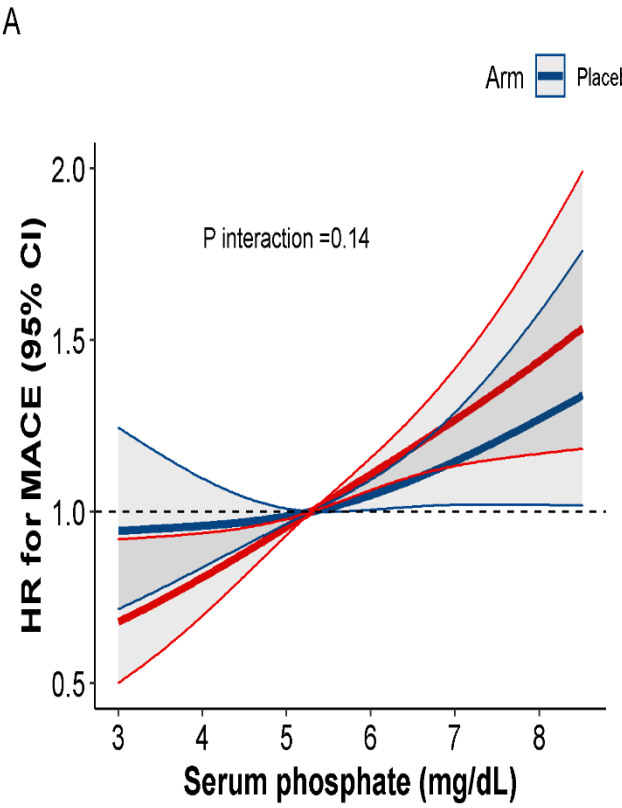

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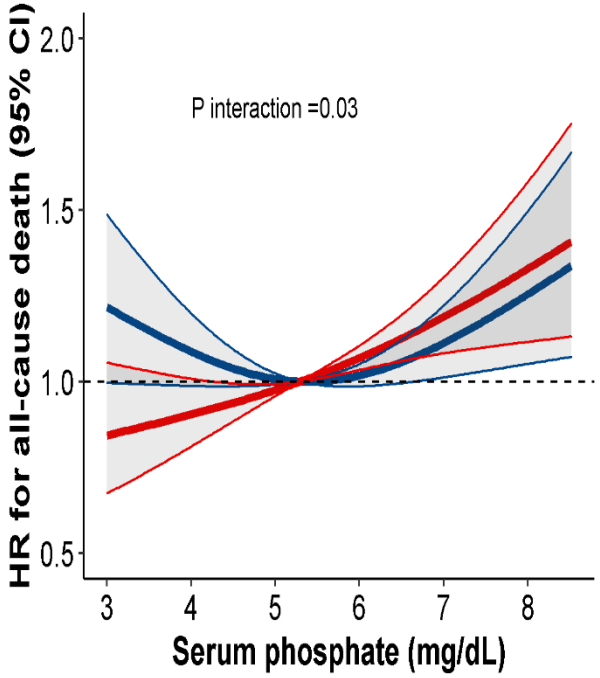

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Outcome	Arm	HR for 3.5 mg/dL	HR for 5 mg/dL	HR for 6.5 mg/dL	HR for 8 mg/dL
MACE	Placebo	0.95 [0.77;1.17]	0.99 [0.96;1.01]	1.09 [1.01;1.18]	1.27 [1.02;1.58]
MACE	Rosuvastatin	0.74 [0.59;0.93]	0.95 [0.93;0.98]	1.19 [1.1;1.28]	1.44 [1.17;1.77]
All-cause death	Placebo	1.15 [0.99;1.33]	1.01 [0.99;1.02]	1.06 [0.99;1.12]	1.25 [1.05;1.49]
All-cause death	Rosuvastatin	0.87 [0.74;1.03]	0.98 [0.96;0.99]	1.12 [1.06;1.19]	1.33 [1.12;1.58]

Supplemental Figure 5: Effect of time-dependent serum phosphate levels changes (non-linear) on outcomes in relation to treatment. A) cardiovascular death (N = 558); B) non-cardiovascular death (N = 452); C) HR for specific phosphate values. Models contained the interaction between statin treatment and non-linear time-dependent serum phosphate levels and were adjusted for age, sex, smoking status, diabetes, cardiovascular history, mean BP, CRP and time-dependent LDL, and phosphate was modeled using a restricted cubic spline with the median value of 5.29 mg/dl as reference.

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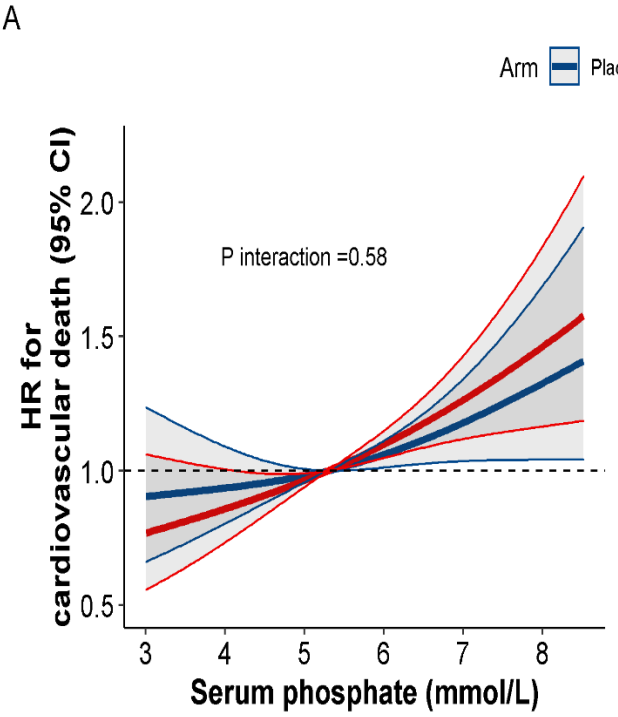

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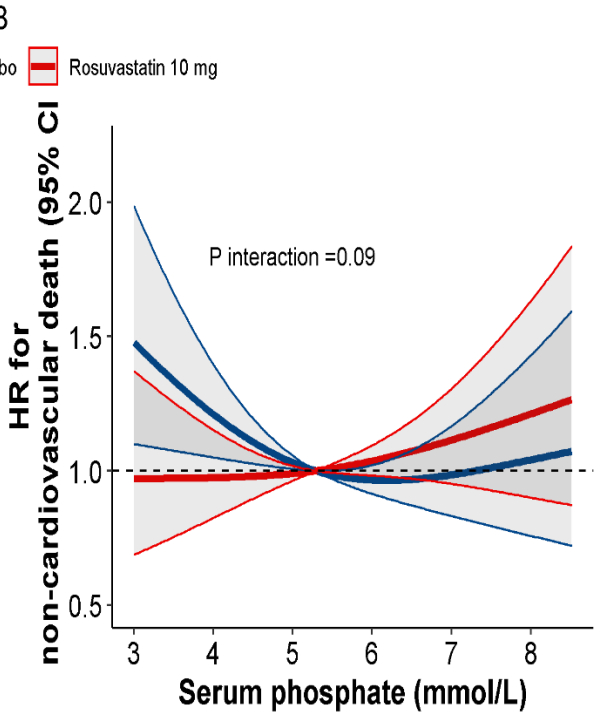

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Outcome	Arm	HR for 3.5 mg/dL	HR for 5 mg/dL	HR for 6.5 mg/dL	HR for 8 mg/dL
cardiovascular death	Placebo	0.92 [0.73;1.16]	0.98 [0.96;1.01]	1.11 [1.03;1.21]	1.32 [1.04;1.68]
cardiovascular death	Rosuvastatin	0.81 [0.64;1.03]	0.96 [0.94;0.99]	1.17 [1.09;1.27]	1.46 [1.16;1.83]
Non-cardiovascular death	Placebo	1.34 [1.07;1.66]	1.03 [1.01;1.06]	0.97 [0.87;1.07]	1.04 [0.76;1.43]
Non-cardiovascular death	Rosuvastatin	0.97 [0.75;1.25]	0.99 [0.96;1.02]	1.07 [0.97;1.18]	1.21 [0.9;1.63]

Supplemental Table 2: Interaction between baseline phosphate and rosuvastatin for both MACE and all-cause death outcomes

		MACE (N = 692 events)			All-cause death (N = 1115 events)		
Model	**Effect**	**N event/N per group**	**HR [95% CI]**	**P-value**	**N event/N per group**	**HR [95% CI]**	**P-value**
Without time-dep. LDL adjustment							
	Treatment effect for T1 baseline phosphate	210/835	0.77 [0.59;1.01]	0.06	373/835	0.81 [0.66;0.99]	0.04
	Treatment effect for T2 baseline phosphate	229/844	1.08 [0.83;1.4]	0.57	367/844	1.04 [0.85;1.28]	0.68
	Treatment effect for T3 baseline phosphate	253/778	0.98 [0.77;1.26]	0.90	375/778	1.06 [0.87;1.3]	0.54
			P for interaction (cat. phosphate) = 0.20			P for interaction (cat. phosphate) = 0.11	
	Effect of baseline phosphate in Placebo group	357/1232	1.09 [1.02;1.16]	0.01	573/1232	1.03 [0.98;1.09]	0.24
	Effect of baseline phosphate in Rosuvastatin group	335/1225	1.12 [1.06;1.19]	<0.001	542/1225	1.09 [1.04;1.14]	<0.001
			P for interaction (cont. phosphate) = 0.49			P for interaction (cont.phosphate) = 0.13	
With time-dep. LDL adjustment							
	Treatment effect for T1 baseline phosphate	210/835	0.71 [0.53;0.94]	0.02	373/835	0.69 [0.56;0.86]	<0.001

		MACE (N = 692 events)			All-cause death (N = 1115 events)		
Model	**Effect**	**N event/N per group**	**HR [95% CI]**	**P-value**	**N event/N per group**	**HR [95% CI]**	**P-value**
	Treatment effect for T2 baseline phosphate	229/844	0.98 [0.75;1.29]	0.91	367/844	0.9 [0.73;1.11]	0.33
	Treatment effect for T3 baseline phosphate	253/778	0.9 [0.69;1.16]	0.40	375/778	0.91 [0.74;1.13]	0.39
			P for interaction (cat. phosphate) = 0.21			P for interaction (cat. phosphate) = 0.11	
	Effect of baseline phosphate in Placebo group	357/1232	1.09 [1.02;1.16]	0.01	573/1232	1.03 [0.98;1.09]	0.24
	Effect of baseline phosphate in Rosuvastatin group	335/1225	1.12 [1.06;1.19]	<0.001	542/1225	1.09 [1.04;1.14]	<0.001
			P for interaction (cont. phosphate) = 0.51			P for interaction (cont. phosphate) = 0.14	

MACE: Major cardiovascular event (nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes); HR: hazard ratio; CI: confidence interval.
Models were adjusted for age, sex, smoking status, diabetes, CV history, mean BP and CRP.

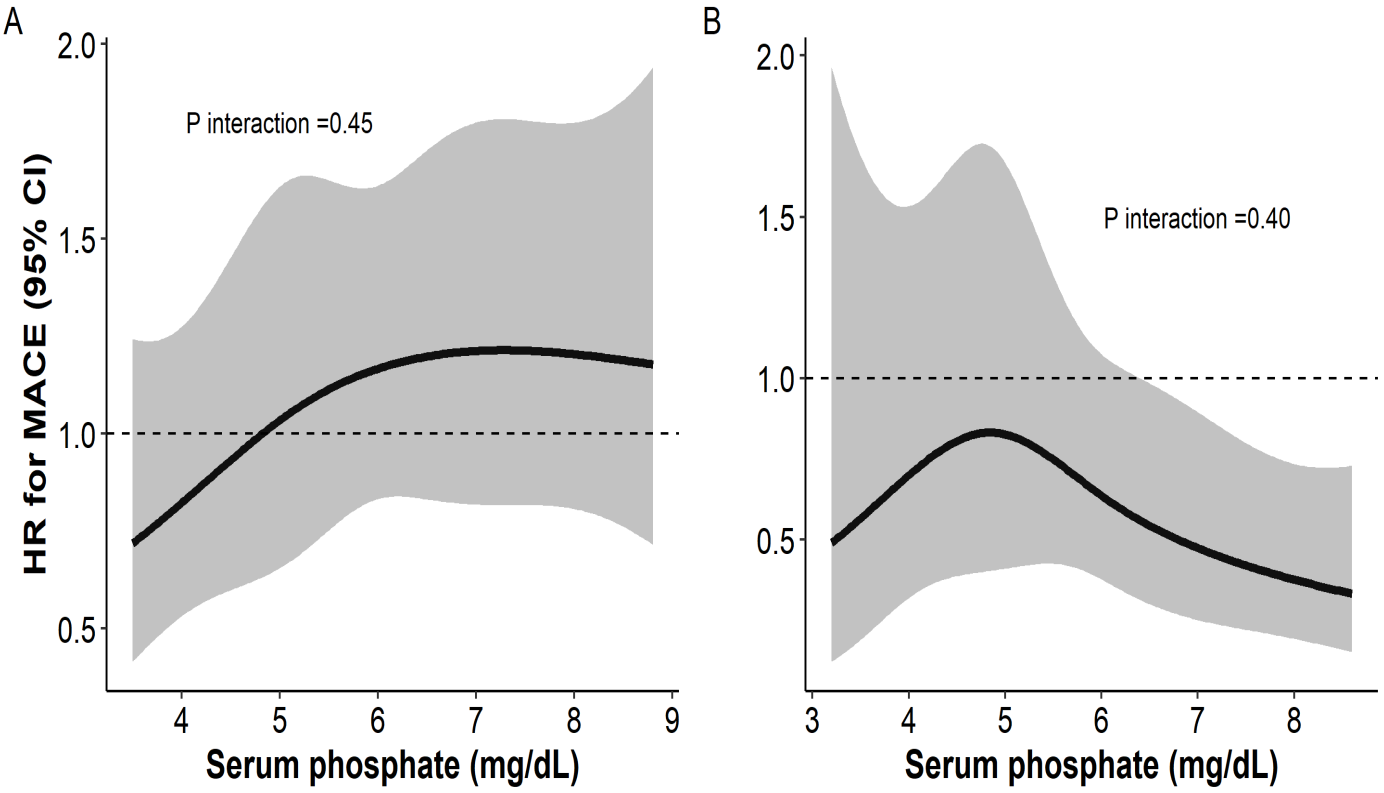
Supplemental Table 3: Interaction between linear time-dependent phosphate and atorvastatin for both MACE (by time period) and all-cause death outcomes in the 4D study

		MACE (before 2.5 years) (N = 318 events)			MACE (after 2.5 years) (N = 119 events)			All-cause death (N = 617 events)		
Model	**Effect**	**N event per group**	**HR [95% CI]**	**P-value**	**N event per group**	**HR [95% CI]**	**P-value**	**N event per group**	**HR [95% CI]**	**P-value**
Without time-dep. LDL adjustment										
	Treatment effect for T1 time-dep. phosphate	95	0.79 [0.51;1.2]	0.27	25	1.13 [0.47;2.73]	0.79	200	0.91 [0.68;1.23]	0.53
	Treatment effect for T2 time-dep. phosphate	97	1.22 [0.79;1.89]	0.36	36	0.71 [0.36;1.37]	0.30	174	1.04 [0.76;1.42]	0.82
	Treatment effect for T3 time-dep. phosphate	126	1.08 [0.76;1.54]	0.68	58	0.51 [0.29;0.91]	0.02	243	0.93 [0.71;1.2]	0.56
			P for interaction (cat. phosphate) = 0.33			P for interaction (cat. phosphate) = 0.33			P for interaction (cat. phosphate) = 0.81	
	Effect of time-dep. phosphate in Placebo group	164	1.08 [0.98;1.18]	0.13	71	1.28 [1.14;1.45]	<0.001	320	1.09 [1.02;1.17]	0.01
	Effect of time-dep. phosphate in Rosuvastatin group	154	1.17 [1.06;1.28]	0.001	48	1.13 [0.97;1.32]	0.11	297	1.13 [1.05;1.21]	<0.001
			P for interaction (cont. phosphate) = 0.22			P for interaction (cont. phosphate) = 0.20			P for interaction (cont.phosphate) = 0.52	

		MACE (before 2.5 years) (N = 318 events)			MACE (after 2.5 years) (N = 119 events)			All-cause death (N = 617 events)		
Model	**Effect**	**N event per group**	**HR [95% CI]**	**P-value**	**N event per group**	**HR [95% CI]**	**P-value**	**N event per group**	**HR [95% CI]**	**P-value**
With time-dep. LDL adjustment										
	Treatment effect for T1 time-dep. phosphate	95	0.82 [0.52;1.3]	0.40	25	0.98 [0.4;2.44]	0.97	200	0.88 [0.64;1.21]	0.43
	Treatment effect for T2 time-dep. phosphate	97	1.31 [0.83;2.07]	0.25	36	0.61 [0.3;1.22]	0.16	174	1 [0.72;1.39]	0.99
	Treatment effect for T3 time-dep. phosphate	126	1.1 [0.75;1.61]	0.63	58	0.46 [0.25;0.84]	0.01	243	0.9 [0.68;1.19]	0.45
			P for interaction (cat. phosphate) = 0.32			P for interaction (cat. phosphate) = 0.36			P for interaction (cat. phosphate) = 0.83	
	Effect of time-dep. phosphate in Placebo group	164	1.08 [0.98;1.18]	0.14	71	1.28 [1.14;1.45]	<0.001	320	1.09 [1.02;1.17]	0.01
	Effect of time-dep. phosphate in Rosuvastatin group	154	1.16 [1.06;1.28]	0.001	48	1.13 [0.97;1.32]	0.11	297	1.13 [1.05;1.21]	<0.001
			P for interaction (cont. phosphate) = 0.26			P for interaction (cont. phosphate) = 0.19			P for interaction (cont. phosphate) = 0.50	

MACE: Major cardiovascular event (nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes); HR: hazard ratio; CI: confidence interval.
Models were adjusted for age, sex, smoking status, diabetes duration, CV history, mean BP and CRP.

Supplemental Figure 6: Treatment effect on MACE for different values of time-dependent serum phosphate levels (non-linear) and in relation to time period in the 4D study. A) Before 2.5 years. B) After 2.5 years. C) HR for specific phosphate values. Models contained the interaction between statin treatment and non-linear time-dependent serum phosphate levels and were adjusted for age, sex, smoking status, diabetes duration, cardiovascular history, mean BP, CRP and time-dependent LDL. Phosphate was modeled using a restricted cubic spline with the median value of 5.7 and 5.5 mg/dl, respectively.



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Outcome	Period	HR for 3.5 mg/dL	HR for 5 mg/dL	HR for 6.5 mg/dL	HR for 8 mg/dL
MACE	Before 2.5 years	0.72 [0.42;1.24]	1.03 [0.65;1.63]	1.2 [0.83;1.73]	1.2 [0.81;1.8]
MACE	After 2.5 years	0.57 [0.19;1.69]	0.83 [0.41;1.67]	0.54 [0.3;0.98]	0.38 [0.19;0.74]

Supplemental Figure 7: Treatment effect on all-cause death for different values of time-dependent serum phosphate levels (non-linear) in the 4D study. A) Treatment effect for different phosphate values B) HR for specific phosphate values. Model contained the interaction between statin treatment and non-linear time-dependent serum phosphate levels and was adjusted for age, sex, smoking status, diabetes duration, cardiovascular history, mean BP, CRP and time-dependent LDL. Phosphate was modeled using a restricted cubic spline with the median value of 5.6 mg/dl.

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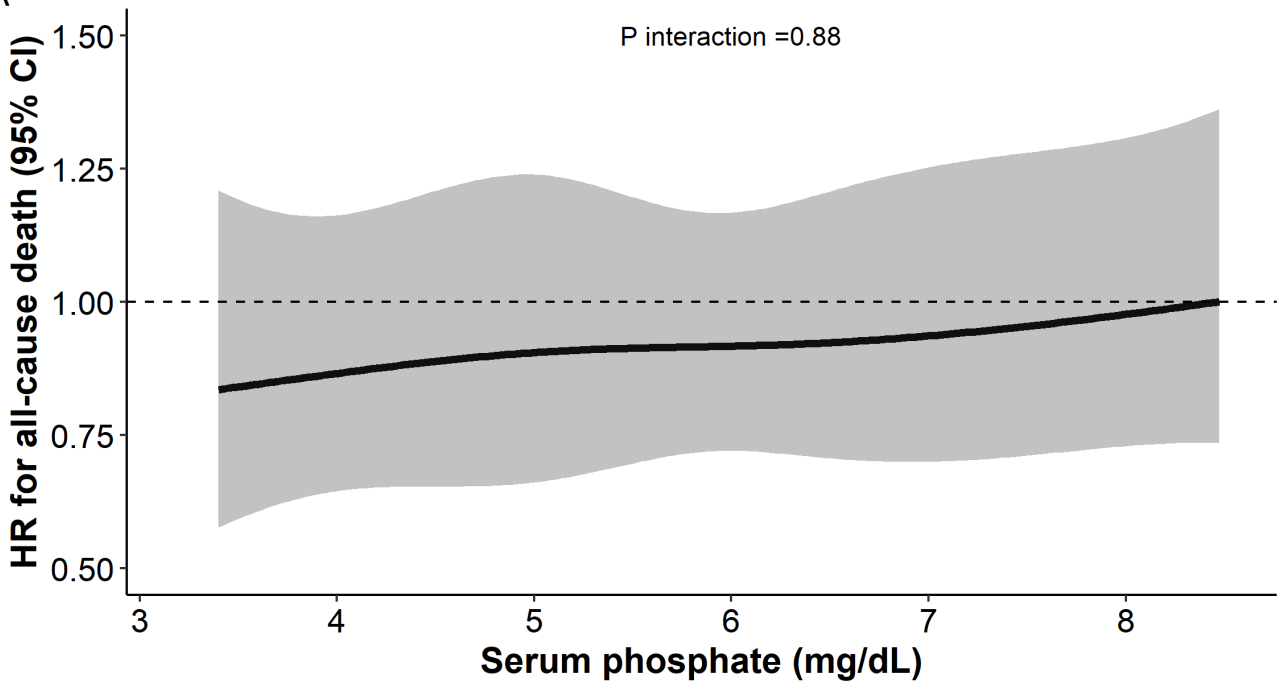

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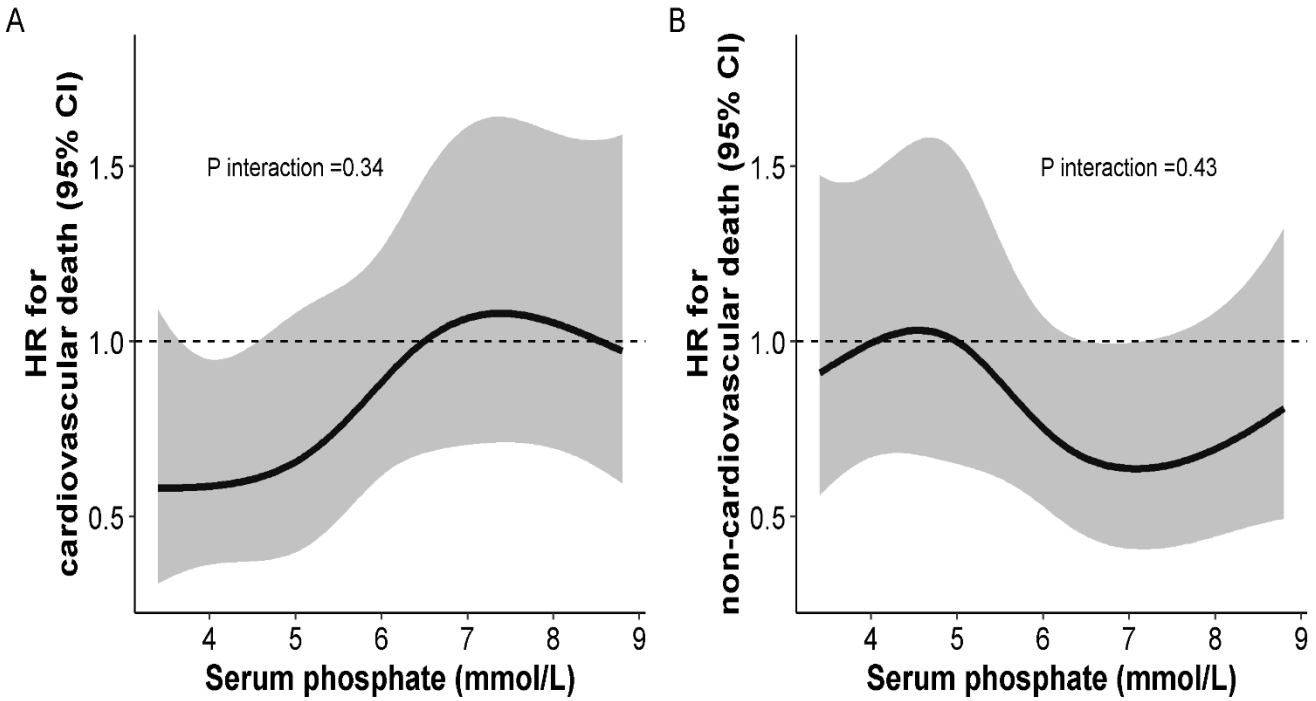
Outcome	HR for 3.5 mg/dL	HR for 5 mg/dL	HR for 6.5 mg/dL	HR for 8 mg/dL
All-cause death	0.84 [0.59;1.19]	0.91 [0.66;1.24]	0.92 [0.71;1.21]	0.98 [0.73;1.31]

Supplemental Figure 8: Treatment effect on outcomes for different values of time-dependent serum phosphate levels (non-linear) in the 4D study. A) cardiovascular death (N = 270); B) non-cardiovascular death (N = 307); C) HR for specific phosphate values. Models were adjusted for age, sex, smoking status, diabetes duration, cardiovascular history, mean BP, CRP and time-dependent LDL, and phosphate was modeled using a restricted cubic spline with the median value of 5.6 mg/dl as reference.



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Outcome	HR for 3.5 mg/dL	HR for 5 mg/dL	HR for 6.5 mg/dL	HR for 8 mg/dL
cardiovascular death	0.58 [0.32;1.05]	0.66 [0.4;1.08]	1 [0.68;1.47]	1.05 [0.69;1.6]
Non-cardiovascular death	0.93 [0.59;1.46]	1 [0.65;1.53]	0.67 [0.45;1]	0.69 [0.44;1.09]