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# Effects of SNF472, a Novel Inhibitor of Hydroxyapatite Crystallization in Patients Receiving Hemodialysis — Subgroup Analyses of the CALIPSO Trial

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**Introduction:** Coronary artery calcium (CAC) is highly prevalent and linked with poor outcomes in patients receiving maintenance hemodialysis, and its reduction may improve patient prognosis. SNF472, a selective inhibitor of hydroxyapatite crystallization, slows CAC progression in patients receiving maintenance hemodialysis. In this analysis, we assessed the efficacy of SNF472 in prespecified patient subgroups.

**Methods:** In a randomized clinical trial SNF472 300 mg, SNF472 600 mg, or placebo were infused thrice weekly in 91, 92, and 91 patients receiving maintenance hemodialysis and with CAC at baseline, respectively. In prespecified subanalyses, the percent change in CAC volume score (CACvs) from baseline to week 52 in modified intention-to-treat (mITT) and per-protocol (PP) populations was calculated in the following subgroups: age, sex, diabetes mellitus, dialysis vintage, prior atherosclerotic cardiovascular disease, baseline use of non-calcium and calcium-based phosphate binders, calcimimetics, activated vitamin D, warfarin, and statins.

**Results:** In the main trial, SNF472 significantly reduced CACvs progression compared with placebo (11% versus 20% mITT analyses; $P = 0.016$; 8% vs. 24% PP analyses; $P < 0.001$). Treatment differences for CACvs progression were similar across all subgroups, and all interaction $P$ values were non-significant in mITT and PP analyses.

**Conclusions:** SNF472 treatment for 52 weeks reduced CACvs progression compared with placebo in a broad range of patients receiving maintenance hemodialysis. Future studies will determine the impact of SNF472 on cardiovascular events in this population.

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CAC is highly prevalent and linked with an increased risk of morbidity and mortality in patients with end-stage kidney disease (ESKD).[1] In these patients, CAC accumulates in the arterial intima within atherosclerotic plaques and in the media layer due to dysregulation of mineral metabolism.[2] CAC is associated with a variety of cardiovascular events such as acute and chronic coronary artery syndromes, heart failure with preserved and reduced ejection fraction, cardiac arrhythmias, and sudden death.[1] Although the initiating stimulus may be different, all calcification processes ultimately depend on the formation of calcium phosphate crystals and, in most cases, they result in the deposition of a

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**Table 1.** Patient characteristics according to prespecified subgroups[a,b]

| Characteristics | Placebo N = 91 | Combined SNF472 doses N = 183 | Overall N = 274 |
|---|---|---|---|
| Age, yr, mean ± SD | 64.1 ± 8.2 | 63.3 ± 9.0 | 63.5 ± 8.9 |
| Female | 33 (36.2) | 74 (40.4) | 107 (39.0) |
| Dialysis vintage, mo, median (range) | 34.5 (6–263) | 44.3 (7–521) | 41 (6–521) |
| Diabetes mellitus | 60 (65.9) | 114 (62.2) | 174 (63.5) |
| Atherosclerotic cardiovascular disease | 45 (49.5) | 70 (38.3) | 11 (40.1) |
| Non-calcium-based phosphate binders | 55 (60.4) | 119 (65.0) | 174 (63.5) |
| Calcium-based phosphate binders | 26 (28.6) | 55 (30.0) | 81 (29.5) |
| Calcimimetics | 26 (28.6) | 60 (32.7) | 86 (31.3) |
| Activated vitamin D | 47 (51.6) | 97 (53.0) | 144 (52.5) |
| Warfarin | 5 (5.5) | 13 (7.1) | 18 (6.5) |
| Statins | 53 (58.2) | 115 (62.8) | 168 (61.3) |

[a]Values shown are n (%) unless otherwise stated.
[b]Patients could take both calcium-based and non–calcium-based phosphate binders simultaneously.

hydroxyapatite solid phase. SNF472 is an intravenous formulation of the hexasodium salt of myo-inositol hexaphosphate with highly effective *in vitro* and *in vivo* inhibition of hydroxyapatite nucleation and crystal formation.[3] In the phase 2b Calcifactant for Acute Lung Injury in Pediatric Stem Cell Transplant and Oncology Patients (CaLIPSO) trial of patients receiving maintenance hemodialysis, SNF472 significantly reduced the progression of CACvs compared with placebo in an mITT population, and the effect was confirmed in a PP population.[4] In this report, we present results of prespecified patient subgroup analyses.

## METHODS

The study design has been published in detail before.[5] Briefly, we randomized 274 adult patients (18 to 80 years old) on maintenance hemodialysis for ≥6 months, with diabetes mellitus if younger than 55 years of age, and baseline CAC Agatston score between 100 and 3500 units on a screening noncontrast multidetector computed tomography to placebo, 300 mg, or 600 mg of SNF472 infused thrice weekly during hemodialysis for 52 weeks. The Agatston CAC score is commonly used in clinical practice; however, the CACvs is more reproducible. Therefore, the CACvs was used to measure CAC change.[6] Multidetector computed tomography imaging was performed at enrollment and at week 52, or as soon as feasible after voluntary withdrawal or kidney transplantation. An experienced radiologist blinded to patient data, including treatment assignment, reviewed the quality of all scans for acceptability and measured CACvs. A portion of all scans (~15%) was reviewed by an expert reader blinded to treatment allocation to assess inter-reader agreement. The study was approved by the research ethics committee of each participating institution and the trial was conducted according to the principles of the Declaration of Helsinki.

The primary efficacy analysis model was an analysis of covariance with the change in log score (log[week 52] − log[baseline]) as the dependent variable, and a fixed effect term for randomized treatment group as well as log(baseline) as covariates; the model was stratified by baseline Agatston CAC score. The geometric least square means and 95% confidence intervals were estimated and back-transformed to yield mean percent change from baseline to week 52 for the primary analysis of the combined SNF472 groups compared with placebo. The primary analyses were conducted on an mITT population (patients who received at least 1 dose of SNF472 or placebo and had an evaluable multidetector computed tomography at baseline and 52 weeks, or any time during follow-up if a patient was discontinued prematurely from the study). The PP population included those in the mITT who met all study entry criteria, received at least 80% of study drug, and had a week-52 visit and multidetector computed tomography scan. We report results in predefined subgroups at baseline: age (<65 or ≥65 years), sex, diabetes mellitus, dialysis vintage (<2, 2 to <5, ≥5 years), prior atherosclerotic cardiovascular disease, non-calcium and calcium-based phosphate binders, calcimimetics, activated vitamin D, warfarin, and statins.

## RESULTS

Table 1 shows the patient characteristics of the placebo and pooled SNF472 cohorts. Table 2 shows the baseline and week-52 serum levels of calcium, phosphorus, and intact parathyroid hormone for the placebo and the combined SNF472 treatment groups. In the primary analyses, SNF472 significantly reduced progression of log CACvs compared to placebo

**Table 2.** Serum calcium, phosphorus, and intact parathyroid hormone at baseline and week 52

| Analyte | Mean ± SD, (N) | |
|---|---|---|
| | Placebo (N = 90) | Combined Dose (N = 183) |
| Calcium, mmol/L | | |
| Baseline | 2.18 ± 0.17 (84) | 2.22 ± 0.19 (164) |
| Week 52 | 2.23 ± 0.18 (73) | 2.23 ± 0.18 (183) |
| Phosphorus, mmol/L | | |
| Baseline | 1.42 ± 0.51 (32) | 1.31 ± 0.38 (60) |
| Week 52 | 1.49 ± 0.53 (35) | 1.39 ± 0.51 (70) |
| Intact parathyroid hormone, pmol/L | | |
| Baseline | 48.3 ± 41.0 (84) | 44.6 ± 36.7 (161) |
| Week 52 | 46.0 ± 37.9 (71) | 39.0 ± 32.5 (149) |

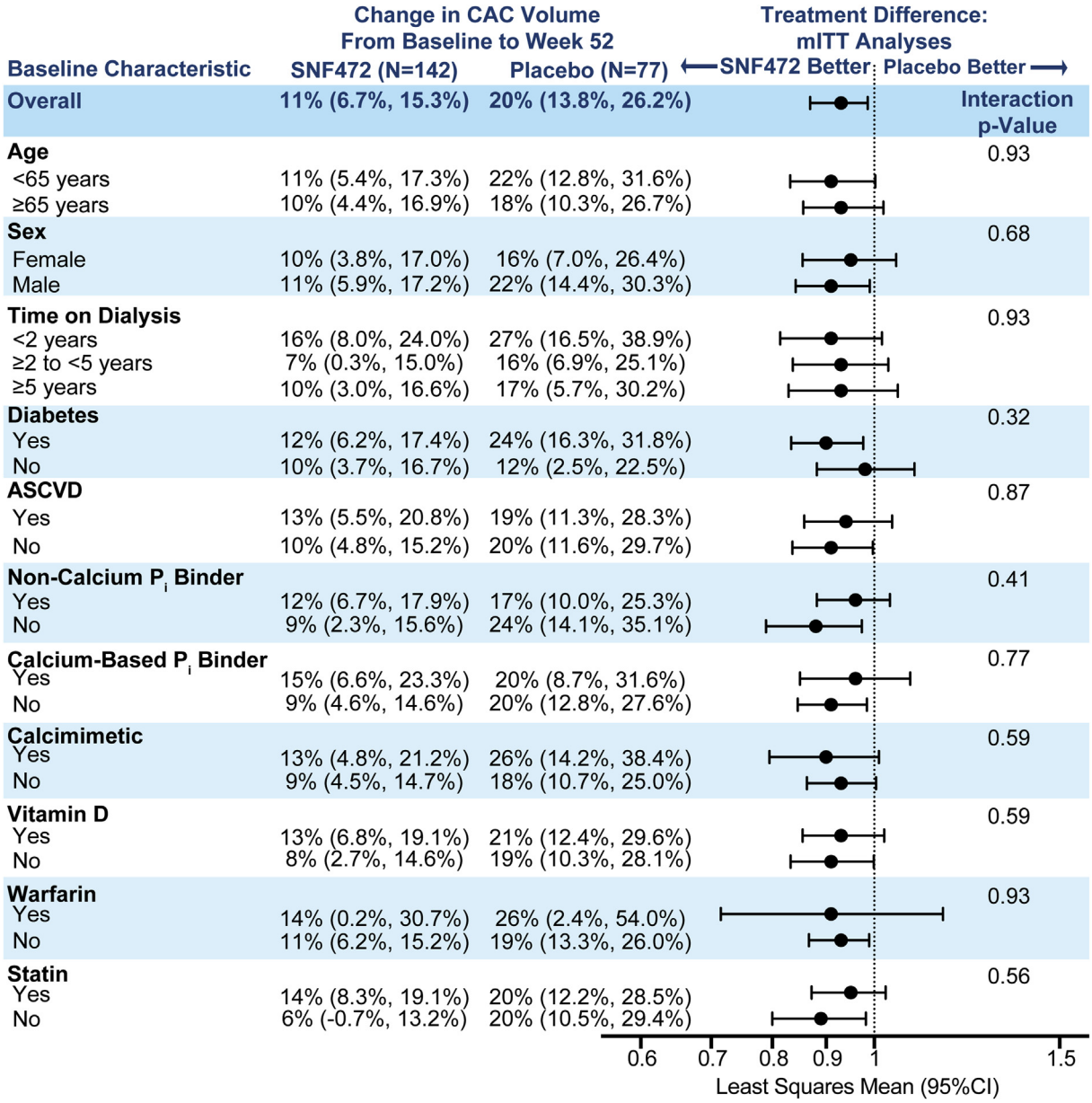


**Figure 1.** Progression of coronary artery calcium volume score in patient subgroups (modified intention-to-treat analyses). CAC, coronary artery calcium; CI, confidence interval; mITT, modified intention to treat; Pi, phosphate.

(mITT: 11% vs. 20%, $P = 0.016$; PP: 8% vs. 24%, $P < 0.001$). Figure 1 shows the difference in progression of CACvs in the prespecified subgroups in mITT analyses. Figure 2 shows the difference in progression of CACvs in the prespecified subgroups in the PP analyses. All interactions were nonsignificant and SNF472 consistently reduced progression of CACvs in all prespecified subgroups.

## DISCUSSION

Vascular calcification is a complex phenomenon involving numerous active and passive mechanisms. The final step requires nucleation of calcium phosphate crystals that lead to the formation of a hydroxyapatite solid phase. SNF472 is a first-in-class inhibitor of crystallization of calcium and phosphorus, whose metabolism is highly dysregulated in ESKD. Several factors have been associated with CAC progression. Age is most influential, as atherosclerosis is almost universal among adult individuals. In the general population, men show an earlier onset and larger accumulation of CAC compared to women,[7] although this difference may be attenuated in ESKD. Diabetes mellitus is a strong predictor of progression of CAC in the general population and in ESKD where it is often associated with low turnover bone disease and accelerated vascular calcification.[8] Prior atherosclerotic cardiovascular disease is an obvious risk factor for the progression of CAC, whereas time on dialysis

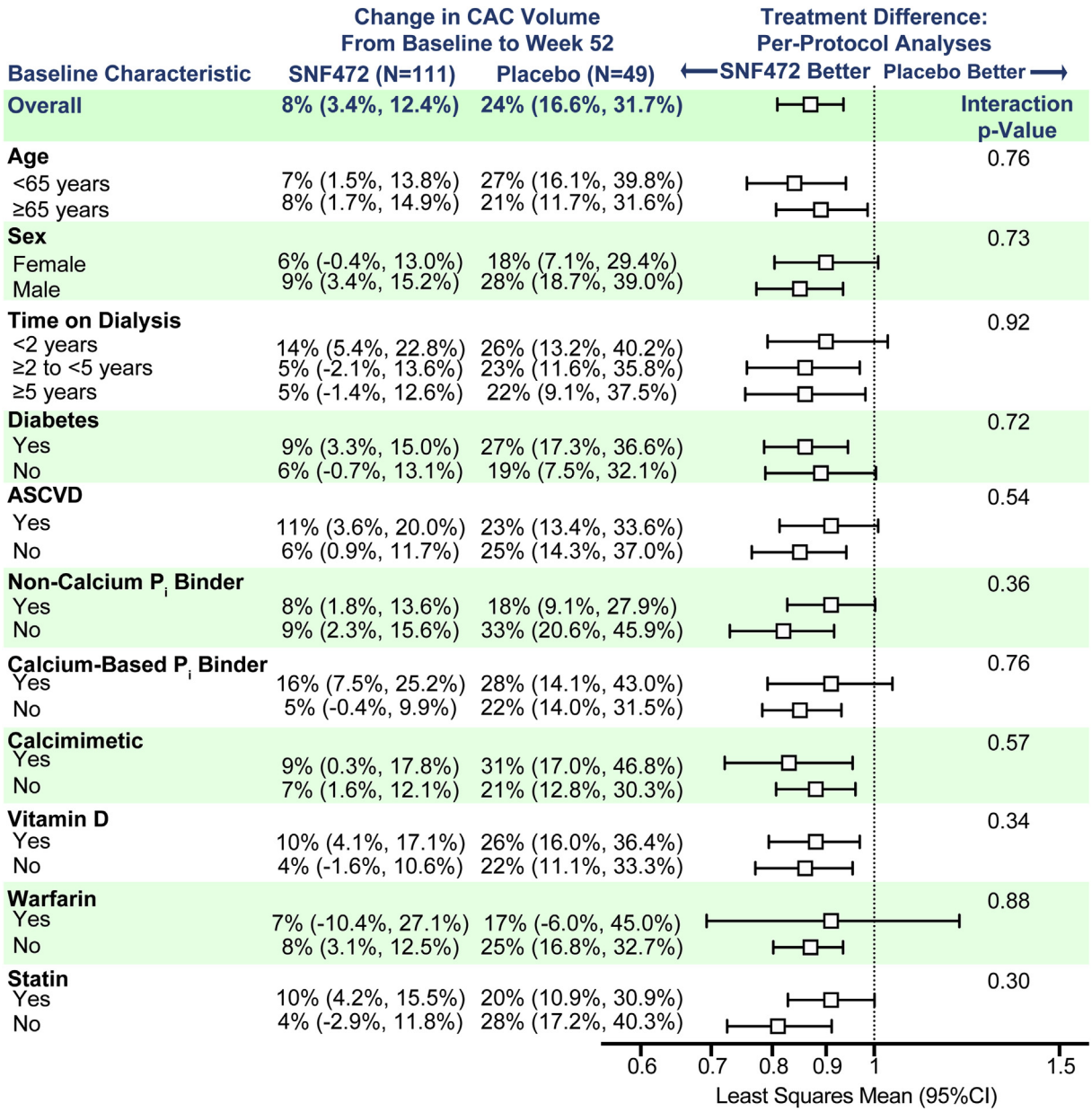


**Figure 2.** Progression of coronary artery calcium volume score in patient subgroups (per-protocol analyses). CAC, coronary artery calcium; CI, confidence interval; Pi, phosphate.

predisposes to CAC accumulation through continuing exposure to dysregulated mineral and bone metabolism, as well as chronic inflammation and oxidative stress.[9] Some medical interventions appear to affect CAC progression. Warfarin and statins, through a probable interference with natural inhibitors of calcification, have been associated with progression of CAC.[10] Large doses of active vitamin D may accelerate and calcimimetics may reduce CAC progression.[11,12] The non–calcium-based phosphate binders are the only class of drugs that have been shown in open-label randomized clinical trials to reduce progression of CAC when compared to calcium-based binders.[13,14] SNF472 demonstrated similar efficacy in all subgroups, showing that inhibition of hydroxyapatite crystallization with this agent can reduce progression of CAC independently of comorbidities or concomitant treatments.

This study had several limitations: we did not record or analyze calcium and phosphate balance during or between dialysis sessions and we did not mandate a single dialysate calcium concentration in the CALIPSO study. However, it is unlikely that variability in these parameters could explain the treatment effect in a randomized double-blind controlled study where patient cohorts had similar baseline clinical characteristics. We did not measure serological markers of bone metabolism.

A meta-analysis of several randomized controlled trials comparing non–calcium-based to calcium-based phosphate binders suggested that the former reduce

CAC progression and might reduce mortality in ESKD.[15] Larger and longer-term studies of SNF472 will be required to determine whether SNF472 can reduce the frequency of heart failure, stroke, sudden cardiac death, and other complications associated with coronary, cerebrovascular, and peripheral arterial calcification in ESKD.

## DISCLOSURES

PharmaScribe, LLC, provided medical writing assistance with financial support from Sanifit Therapeutics, S.A. PR has served as a consultant to Sanifit. AB has served as a consultant to Sanifit and received lecture fees from Sanofi-Genzyme, Vifor-Fresenius-Renal Pharma, Abbvie, and Amgen. JB has served as a consultant to and received lecture fees from Sanifit, Sanofi-Genzyme, Vifor-Fresenius-Renal Pharma, Abbvie, and Amgen; and received lecture fees from SHIRE. MR has received lecture fees from Amgen, Kyowa-Kirin, Sanofi, and Vifor. MK has served as a consultant to Sanifit, Amgen, Medice, Sanofi, and Vifor. SS has served as a consultant to Sanifit, Vifor Fresenius, and Napp. DAB has served as a consultant to Sanifit, Tricida, Relypsa/Vifor/Fresenius, Sanofi/Genzyme, and Amgen; has stocks or options in Tricida and Amgen; and currently receives grants from the National Institutes of Health and the Renal Research Institute. RG is a former employee of Sanifit Therapeutics. JP is an employee of Sanifit Therapeutics; has stocks or options in Sanifit Therapeutics; and has patents related to SNF472. AG is an employee of Sanifit Therapeutics and has stocks or options in Sanifit Therapeutics. GMC has served as a consultant to Akebia, AMAG, Amgen, Ardelyx, AstraZeneca, Gilead, Reata, Sanifit, and Vertex; has stocks or options in Ardelyx, CloudCath, Cricket, Durect, Outset, and Physiowave; and has received research funding from Amgen and Janssen.

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## REFERENCES

1. Nelson AJ, Raggi P, Wolf M, et al. Targeting vascular calcification in chronic kidney disease. *J Am Coll Cardiol Basic Transl Sci*. 2020;5:398–412.
2. Raggi P, Giachelli C, Bellasi A. Interaction of vascular and bone disease in patients with normal renal function and patients undergoing dialysis. *Nat Clin Pract Cardiovasc Med*. 2007;4:26–33.
3. Ferrer MD, Ketteler M, Tur F, et al. Characterization of SNF472 pharmacokinetics and efficacy in uremic and non-uremic rats models of cardiovascular calcification. *PLoS ONE*. 2018;13:e0197061.
4. Raggi P, Bellasi A, Bushinsky D, et al. Slowing progression of cardiovascular calcification with SNF472 in patients on hemodialysis: results of a randomized phase 2b study. *Circulation*. 2020;141:728–739.
5. Bellasi A, Raggi P, Bover J, et al. Trial design and baseline characteristics of CaLIPSO: a randomized, double-blind placebo-controlled trial of SNF472 in patients receiving hemodialysis with cardiovascular calcification [e-pub ahead of print] *Clin Kidney J*. 2019. https://doi.org/10.1093/ckj/sfz144.
6. Callister TQ, Cooil B, Raya SP, et al. Coronary artery disease: improved reproducibility of calcium scoring with an electron-beam CT volumetric method. *Radiology*. 1998;208:807–814.
7. McClelland RL, Chung H, Detrano R, et al. Distribution of coronary artery calcium by race, gender, and age: results from the Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation*. 2006;113:30–37.
8. Galassi A, Spiegel DM, Bellasi A, et al. Accelerated vascular calcification and relative hypoparathyroidism in incident haemodialysis diabetic patients receiving calcium binders. *Nephrol Dial Transplant*. 2006;21:3215–3222.
9. Kooman JP, Kotanko P, Schols AM, et al. Chronic kidney disease and premature ageing. *Nat Rev Nephrol*. 2014;10:732–742.
10. Chen Z, Qureshi AR, Parini P, et al. Does statins promote vascular calcification in chronic kidney disease? *Eur J Clin Invest*. 2017;47:137–148.
11. Raggi P, Chertow GM, Torres PU, et al. The ADVANCE study: a randomized study to evaluate the effects of cinacalcet plus low-dose vitamin D on vascular calcification in patients on hemodialysis. *Nephrol Dial Transplant*. 2011;26:1327–1339.
12. Urena-Torres PA, Floege J, Hawley CM, et al. Protocol adherence and the progression of cardiovascular calcification in the ADVANCE study. *Nephrol Dial Transplant*. 2013;28:146–152.
13. Chertow GM, Burke SK, Raggi P. Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. *Kidney Int*. 2002;62:245–252.
14. Block GA, Spiegel DM, Ehrlich J, et al. Effects of sevelamer and calcium on coronary artery calcification in patients new to hemodialysis. *Kidney Int*. 2005;68:1815–1824.
15. Jamal SA, Vandermeer B, Raggi P, et al. Effect of calcium-based versus non–calcium-based phosphate binders on mortality in patients with chronic kidney disease: an updated systematic review and meta-analysis. *Lancet*. 2013;382:1268–1277.