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Modeling the implications of changes in vascular calcification in patients on hemodialysis

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Modeling the implications of changes in vascular calcification in patients on hemodialysis.

Background. The Treat-to-Goal Study found that sevelamer slowed the progression of coronary calcification in patients on hemodialysis compared to calcium-based phosphate binders. To understand the implications of this effect for cardiovascular events, risk equations are needed.

Methods. Data on 179 patients on hemodialysis treated at one center in France included biochemical values during the year prior to study entry, patient characteristics, and cardiovascular events over an average of 4 years. As arterial calcification was evaluated ultrasonographically and quantified using a 0 to 4 score, an equation relating this to the electron-beam tomography (EBT)-based calcification score used in the trial was developed and applied to all patients. The estimated scores were then used in survival and Cox proportional hazards analyses of cardiovascular events in relation to the degree of calcification, controlling for other characteristics.

Results. Mean age at inclusion was 54 years, dialysis vintage 70 months, average follow-up 49 months; 32% suffered an event. The calcification score, diabetes, C-reactive protein (CRP), diastolic blood pressure, gender, smoking and hypertension are independent predictors of cardiovascular risk. The resulting equation indicates that, relative to a calcification score below 400, the risk of an initial event increases 44% for a score of 600, and more than doubles for a score of 1000.

Conclusion. In the absence of long-term follow-up studies, these equations permit quantification of the expected long-term clinical consequences of the impact of various phosphate binders on vascular calcification. Together with resource use and cost information, these equations are key inputs for formal cost-effectiveness analyses.

Patients with end-stage renal disease (ESRD) are at high risk for cardiovascular disease, particularly coronary and sudden cardiac death. Epidemiologic and clinical studies have shown that damage to large arteries is a major contributory factor to this high cardiovascular morbidity and mortality. These effects are attributable to both occlusive lesions, mainly atherosclerotic plaques, and stiffening of arterial walls [1]. The detection and quantification of calcium are being used in contemporary coronary imaging practice as a marker for the presence and extent of atherosclerosis. Although controversy still exists, evidence supporting the independent predictive value of imaging on the basis of electron-beam tomography (EBT) has been accumulating in the general population [2–8].

Calcification develops at two sites in the arterial wall: the intima and the media. Arterial intima calcification represents an advanced stage of atherosclerosis and is associated with the development of plaques and occlusive lesions. Arterial media calcification is observed with predilection in muscle-type conduit arteries, such as femoral, tibial, and uterine arteries [9, 10]. While the precise pathogenesis remains unclear, several factors likely contribute to the predisposition to widespread calcification in ESRD. Some of the risk factors are the classic ones associated with coronary artery disease in the general population (e.g., hypertension, diabetes, dyslipidemia), whereas others are specific to ESRD patients [10]. Loss of kidney function, possibly complicated by metabolic abnormalities associated with the underlying disease, produces a myriad of physiologic disturbances, among which is an increasingly disordered calcium and phosphate metabolism. Calcium homeostasis is regulated mainly by the parathyroid gland and the kidney, which removes any excess. With deteriorating renal function, patients lack the normal route of excretion and excess calcium is transported into cellular and interstitial compartments. Although this process helps serum calcium levels stay near normal, it predisposes the patient to extraosseous calcification of soft tissues, including vascular [11]. The net positive imbalance is exacerbated in those on hemodialysis by calcium absorption from dialysate, abnormalities in bone buffering and turnover, and ingestion of calcium-based phosphate binders to treat hyperphosphatemia [12].

Key words: arterial calcification, cardiovascular risk, end-stage renal disease, hemodialysis.

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In 1998, sevelamer hydrochloride (Renagel™), a nonmetal, noncalcium polymer that binds preferentially to phosphate through ion exchange and hydrogen bonding in the duodenum, was shown to be safe and effective in patients on hemodialysis [13]. More recently, sevelamer has also been shown to attenuate the progression of coronary and aortic calcification, evaluated using EBT, over 1 year relative to calcium-based binders (Treat-to-Goal Study) [14, 15].

As long-term follow-up data are not yet available, understanding the implications of this physiologic effect from a clinical and economic perspective requires predictive equations. Development of such model cannot wait for the accumulation of follow-up data because treatment decisions are made today based on current evidence. In this paper, we present the approach taken to estimate the clinical impact, specifically, the cardiovascular risk implications, of the changes in vascular calcification observed with sevelamer.

METHODS

As no single data source contained all the necessary data elements, two steps were necessary to build the link between the extent of vascular calcification on EBT and cardiovascular risk. Using data from the Treat-To-Goal Study, an equation was developed to estimate the EBT score on the basis of readily available patient and disease characteristics. Next, this equation was applied to patients in a separate cohort study of cardiovascular events to predict their EBT score and this value was included in regression analyses of the cardiovascular risk.

Estimating EBT score

The Treat-To-Goal Study was a 1-year, open-label, randomized clinical trial comparing sevelamer with calcium-based phosphate binders in 200 patients on hemodialysis. Apart from the targeted concentrations of serum phosphorus, calcium, and intact parathyroid hormone (iPTH), outcomes also included calcification of the coronary arteries and thoracic aorta using an EBT score. The study has been described in detail elsewhere [14, 15].

Data on baseline characteristics of all patients enrolled in the Treat-to-Goal Study were obtained. Multivariate regression analyses were carried out with the logarithmically transformed EBT score for coronary arteries as the dependent variable (because the distribution of the EBT scores was quite skewed, the values were logarithmically transformed to achieve a normal distribution and permit use of standard parametric statistical tests). All other baseline variables were considered, including clinical characteristics, blood chemistries, blood pressure parameters, and medical history. Since the model was for prediction, the subset of variables retained in the final equation was not selected based solely on statistical significance, but rather on the overall predictive quality of the equation, assessed with the Press statistic [16]. Thus, in addition to variables of clinical significance and those with a strong effect on EBT scores in univariate analyses, "weaker" variables and interaction terms that did not necessarily achieve statistical significance were retained if they improved the Press statistic.

Estimating cardiovascular disease risk

The determinants of cardiovascular risk were examined in a dataset of patients on hemodialysis treated at one center in France. It has previously been demonstrated in a subset of this population that arterial calcification, measured using a semiquantitative 0 to 4 score, predicts cardiovascular and all-cause mortality [17]. Here, we expand on that study in several ways: an additional 69 patients are included, cardiovascular morbidity is considered, and calcium burden is quantified using the predicted calcification score derived using the Treat-to-Goal equation.

Study population. All patients treated at the Hôpital F.H. Manhès in Fleury-Mérogis, France, were eligible for inclusion in the dataset if they had been on hemodialysis for at least 3 months, and had no clinical cardiovascular disease during the 6 months preceding entry. The first of 179 patients entered in May 1990; recruitment closed December 2000; and follow-up ended April 30, 2002. Patients who underwent renal transplantation or moved were censored at the day of transplantation or departure ($N = 34$). During follow-up, all patients were dialyzed by the same standardized technique, as previously detailed [18].

Data collection. Information compiled from a questionnaire filled out at entry into the dialysis unit and from patients' files included, among others, age, gender, race, dialysis vintage, body mass index, diabetes, smoking habits, history of cardiovascular disease (i.e., coronary artery disease, angina pectoris, congestive heart failure, peripheral vascular disease, or cerebrovascular disease), use of antihypertensive drugs and calcitriol, and dose of calcium carbonate expressed in grams of elemental calcium prescribed.

During follow-up, predialysis serum calcium and phosphate were determined twice monthly. Serum albumin, plasma fibrinogen, and C-reactive protein (CRP) were measured every 3 months, blood lipids and PTH were measured every 4 months. In this analysis, averages over up to 1-year preceding study entry were used. Diastolic

Table 1. Multiple linear regression analysis predicting the logarithmically transformed electron-beam tomography (EBT) score

Variable	β	(SE)	*P*	Variable definition (units)	
Age	0.02	(0.01)	0.013	C	Years
Dialysis vintage	0.35	(0.11)	0.002	D	>36 months = 1; ≤36 months = −1
Serum calcium	1.42	(0.73)	0.053	C	mmol/L
Serum phosphate	0.39	(0.21)	0.061	C	mmol/L
Total cholesterol	−0.16	(0.10)	0.117	C	mmol/L
High-density lipoprotein cholesterol	−0.54	(0.30)	0.077	C	mmol/L
Cardiovascular disease history	−0.70	(0.12)	<0.0001	D	no = 1; yes = −1
Cardiovascular disease history × age	0.01	(0.01)	0.139	Interaction term	

Abbreviations are: C, continuous; D, dichotomous. The model F is 12 (8 df) ($P < 0.0001$). The R^2 equals 0.40

and systolic blood pressure, pulse pressure, heart rate, and aortic pulse wave velocity (PWV), determined with transcutaneous Doppler flow recordings and the foot-to-foot method, were obtained as described previously [18, 19].

Arterial calcification was evaluated ultrasonographically in the common carotid artery, the abdominal aorta, the iliofemoral axis, and the legs. Calcification in each region was quantified as absent (0) or present (1). A score, ranging from 0 (absence of calcium deposits) to 4 (calcification present in all segments), was obtained by summing the studied zones, and independently checked by two observers, with good reproducibility [19]. For each patient, the EBT calcification score was estimated using the regression equation derived from the Treat-to-Goal Study.

The number, timing, and type of all nonfatal cardiovascular events suffered during follow-up were abstracted from hospital archives of the nephrology, cardiology, and vascular surgery departments and intensive care unit. The time and cause of death were obtained from death certificates, hospital records, and autopsy data reviewed by one of the authors (G.M.L.).

Statistical analysis. Cardiovascular events were categorized into congestive heart failure, coronary artery, cerebrovascular, aortic and peripheral arterial disease. Kaplan-Meier survival analysis of first events was done and the association of cardiovascular risk to the calcification score and other known risk factors was assessed using Cox proportional hazards analysis. Stepwise forward selection identified additional determinants (at $P < 0.05$). Where necessary, variables were logarithmically transformed to normalize their distribution. Known cardiovascular risk factors that were not automatically retained were reentered into the equation. The proportionality assumption was checked for all variables in the final model. Kaplan-Meier survival analysis of time to next (fatal or nonfatal) cardiovascular event was done in sufferers of a first nonfatal event.

Analyses were performed using SAS System (version 8.0) and JMP (version 4.0.4) (SAS Institute Inc., Cary, NC, USA).

RESULTS

Estimated EBT calcification scores

The final regression model for the calcification score is presented in Table 1. Since the aim is to predict EBT scores, rather than log EBT scores, the predicted scores need to be transformed back. The appropriate retransformed estimates are obtained by multiplying the exponential of the individual patients' predicted log EBT score with a smearing estimator, defined as the average of the exponentiated residuals, which equals 1.847 [20, 21].

Estimating cardiovascular risk

Study population. The mean age of the 179 patients at the time of inclusion was 54 years (SD ±17 years) and dialysis vintage was 70 months (±71 months). Mean follow-up was 49 months (range 2 to 111 months); 60% were male, 51% were past or present smokers, 13% had insulin-dependent diabetes mellitus, 73% received antihypertensive drugs, and 36% had prior cardiovascular disease (Table 2). A breakdown of the various etiologies of ESRD in the study population is provided in Table 3.

Thirty-two percent suffered one or more cardiovascular events during follow-up. Of 58 initial events, 45 were nonfatal. An additional 47 events occurred subsequently, 19 of which were fatal. Thus, 32 patients died from cardiovascular causes and 20 from other causes. The majority of the 73 nonfatal events were of the coronary or peripheral arteries (30 and 29, respectively); there were eight cases of congestive heart failure, four of aortic disease, and two cerebrovascular events.

Occurrence of cardiovascular events was associated with age, body mass index, smoking, dialysis vintage, diabetes, prior cardiovascular events, pulse pressure, triglycerides, serum phosphate, fibrinogen, CRP, aortic PWV, and calcification index. A negative association was noted with diastolic blood pressure, albumin, and PTH.

Figure 1 provides the distribution of predicted calcification scores. The mean score was 1262 ± 1432 (range 40 to 6758; median 592) and increased with the number of arterial sites calcified: from a mean of 355 (median 274) for patients with 0 sites calcified to a mean score of 2282

Table 2. Characteristics of patients at inclusion, overall and by occurrence of cardiovascular event during follow-up

Parameter	Overall ($N = 179$)	Cardiovascular event during follow-up: No ($N = 121$)	Cardiovascular event during follow-up: Yes ($N = 58$)
Age *years*	54 ± 17	50 ± 17	62 ± 12
Male %	60	61	57
Caucasian %	85	82	91
Body mass index kg/m^2	23.4 ± 4.0	22.9 ± 4.0	24.3 ± 3.7
Smokers %	51	45	64
Dialysis vintage *months*	70 ± 71	61 ± 64	88 ± 79
Diabetes %	13	7	24
Cardiovascular history %	36	19	71
Antihypertensive therapy %	73	71	78
Calcitriol %	38	40	33
Systolic blood pressure *mm Hg*	148 ± 27	146 ± 25	153 ± 31
Diastolic blood pressure *mm Hg*	82 ± 15	84 ± 15	78 ± 14
Mean blood pressure *mm Hg*[a]	104 ± 17	104 ± 17	103 ± 17
Pulse pressure *mm Hg*	67 ± 21	63 ± 17	75 ± 26
Heart rate *bpm*	71 ± 12	70 ± 11	72 ± 13
Total cholesterol *mmol/L*	5.1 ± 1.1	5.0 ± 1.1	5.1 ± 1.1
High-density lipoprotein cholesterol *mmol/L*	1.1 ± 0.4	1.1 ± 0.4	1.1 ± 0.4
Low-density lipoprotein cholesterol *mmol/L*[b]	3.6 ± 1.0	3.6 ± 1.0	3.7 ± 0.9
Triglycerides *mmol/L*	1.8 ± 0.9	1.7 ± 0.8	2.0 ± 1.1
Albumin *g/L*	40 ± 3	40 ± 3	38 ± 3
Calcium *mmol/L*[c]	2.3 ± 0.1	2.3 ± 0.1	2.3 ± 0.1
Phosphate *mmol/L*	1.8 ± 0.5	1.8 ± 0.4	2.0 ± 0.5
Parathyroid hormone *pg/mL*	303 ± 286	338 ± 305	231 ± 227
Fibrinogen *g/L*	4.2 ± 1.0	3.9 ± 0.8	4.9 ± 1.0
C-reactive protein *mg/L*	10.2 ± 10.5	7.6 ± 8.5	15.6 ± 12.2
Aortic pulse wave velocity *m/sec*	11.1 ± 3.1	10.2 ± 2.2	12.9 ± 3.8
Calcification score	1262 ± 1432	735 ± 868	2360 ± 1731

For continuous variables, the mean ± SD is provided.
[a]Calculated as diastolic blood pressure + 1/3 pulse pressure; [b]Derived using the Friedewald formula; [c]Not corrected for albumin.

Table 3. Etiology of end-stage renal disease (ESRD) in the study population

Etiology	Proportion of patients
Primary glomerulonephritis	28%
Interstitial nephropathies	18%
Polycystic kidney disease	9%
Systemic disease (e.g., lupus nephritis, amyloidosis)	6%
Diabetes	12%
Vascular nephropathy and hypertension	20%
Unknown	7%

(median 1633) for patients with calcifications at all four regions. Analysis of variance showed a strong overall association between the calcification score and the number of arterial sites calcified ($P < 0.0001$).

Initial cardiovascular events. The hazard (λ) was shown to be constant over the study period (0.02411 per 100 person-days). The risk (or cumulative incidence) at any given time can thus be estimated as $1 - e^{-\lambda t}$. The probability of surviving without an event was lower with a higher predicted calcification score (Fig. 2). The final predictive equation from the Cox proportional hazards analysis is presented in Table 4. In addition to the calcification score, diabetes, high CRP levels and low diastolic blood pressure were included by the automatic stepwise selection. Gender, smoking, and hypertension (identified by use of antihypertensive therapy) were forced in. The equation suggests that for each unit increase in the logarithmically transformed calcification score, the cardiovascular risk is 2.46 times higher, which roughly corresponds to a 20% higher risk for each 100-unit increase in the calcification score (Fig. 3).

A patient's hazard ratio (HR_i) can be derived directly from the Cox proportional hazards model, and the individual's risk is estimated as $1 - e^{-\lambda \cdot HRi \cdot t}$. The change

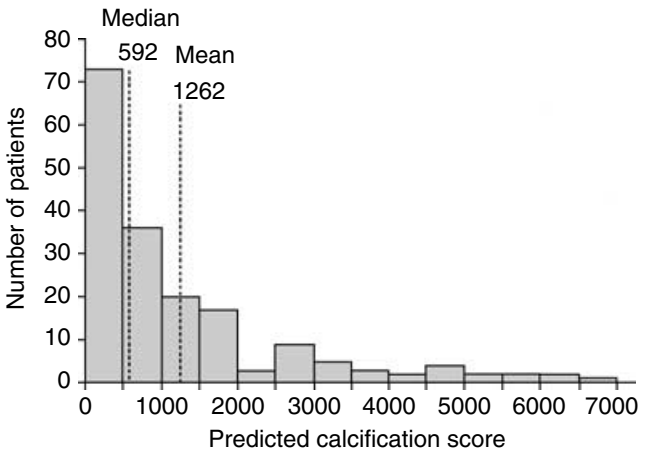

Fig. 1. Predicted calcification score for 179 patients with end-stage renal disease (ESRD) on hemodialysis at the time of inclusion in the dataset.

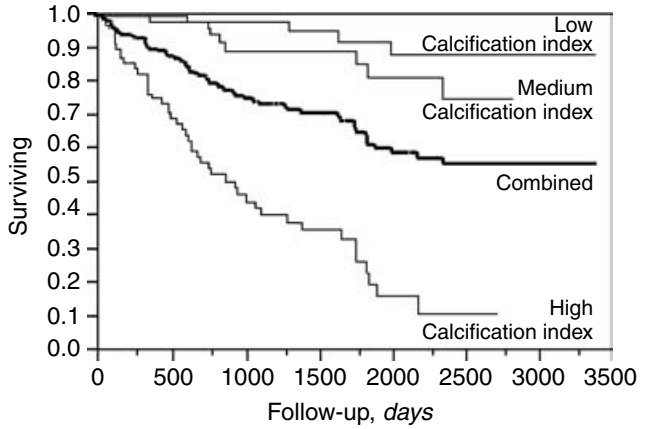

Fig. 2. Kaplan-Meier survival analysis of time to initial cardiovascular event, overall and by categorized calcification index. Comparison between curves was highly significant (log-rank $\chi^2 = 88.04$, $P < 0.0001$) (low calcification score ≤400, medium calcification score 401 to 1000, high calcification score >1000).

Table 4. Cox-proportional hazards analysis for first fatal or nonfatal cardiovascular event

Variable	β	Hazard ratio	*P* value	Variable definition (units)	
Log (calcification score)	0.90	2.46	<0.0001	C	
Diabetes	−0.49	0.61	0.0048	D	No = 1; yes = −1
Log (C-reactive protein)	0.49	1.64	0.0050	C	mg/L
Diastolic blood pressure	−0.03	0.97	0.0058	C	mm Hg
Gender	−0.48	0.62	0.0043	D	Male = 1; female = −1
Smoking	−0.40	0.67	0.0162	D	No = 1; yes = −1
Hypertension	−0.40	0.67	0.0142	D	No = 1; yes = −1

Abbreviations are: C, continuous; D, dichotomous; Model $P < 0.0001$; 18% of variance explained.

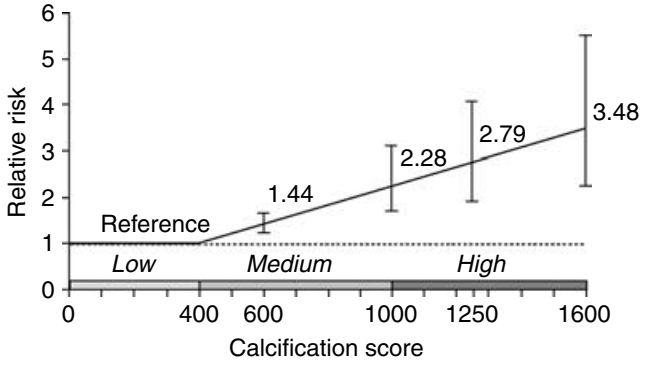

Fig. 3. Relative cardiovascular disease risk by calcification score. The vertical bars indicate the 95% confidence interval. The risk in patients with a calcification score between 0 and 400 is used as the reference. Point estimates are provided for the median (~600), the mean (~1250), and the 75% quartile (~1600) scores estimated for the 179 patients in the dataset

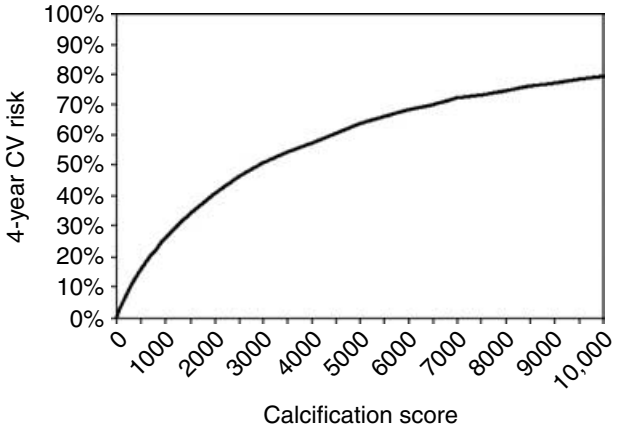

Fig. 4. Four-year cardiovascular disease (CV) risk by calcification score for a sample population defined as 60% males, 12% diabetes, 6% smokers, 73% taking antihypertensive therapy, mean C-reactive protein 7.8 mg/L, mean diastolic blood pressure 81.5 mm Hg. This relationship between calcification score and cardiovascular risk is derived by applying the hazard ratios estimated for this sample population using the Cox proportional hazards equation to the constant base hazard

in cardiovascular risk by calcification score at a population level is further illustrated in Figure 4. For this particular population (60% males, 12% diabetics, 6% smokers, 73% taking antihypertensive therapy, mean CRP 7.8 mg/L, mean diastolic blood pressure 81.5 mm Hg), the 4-year risk equals 4% at a calcification score of 100, and increases to 13% for a score of 400, 26% for a score of 1000, and is as high as 72% for a score of 7000—the maximum calcification score estimated for patients in the source dataset.

Subsequent cardiovascular events. The hazard of subsequent cardiovascular events followed a Weibull distribution given by:

$$\lambda_t = \frac{\gamma}{\alpha}\left(\frac{t}{\alpha}\right)^{\gamma-1}$$

where γ and α, the scale and shape parameters, were 0.658 and 941.553, respectively. The resulting risk of additional events immediately following an event is very high (93% per year), but gradually decreases over time (36% per year after 6 months, 29% per year after 1 year, and 19% per year after 4 years) (Fig. 5).

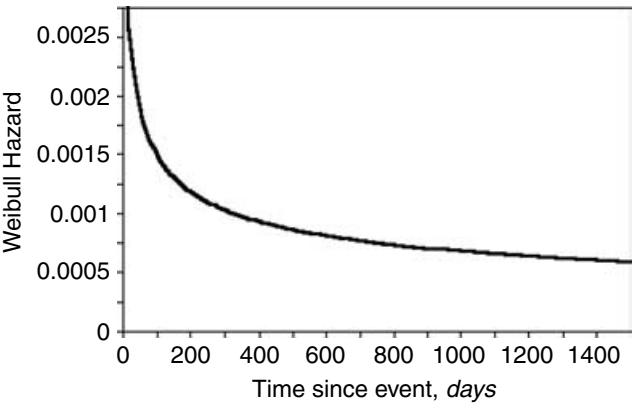

Fig. 5. Change in hazard over time for subsequent cardiovascular disease events.

Sevelamer versus calcium-based phosphate binders

Given the findings from the Treat-to-Goal Study and using these predictive equations, it can now be estimated that in a population of 100 patients, 33 of those receiving sevelamer are likely to experience an initial cardiovascular event, compared with 37 of those who receive

calcium. A total of 32 subsequent events are expected to occur while on sevelamer treatment, compared with 37 on calcium. Sevelamer use, by slowing or reversing coronary calcification as reflected in EBT, is thus estimated to prevent a total of nine events over the patients' lifetime, which represents a 12% reduction in cardiovascular risk. Therefore, 11 patients would need to be treated for 1 year to prevent one cardiovascular event.

DISCUSSION

The purpose of this study was to translate the findings of the Treat-to-Goal Study to clinically meaningful estimates. This was done by estimating the EBT score on the basis of various patient characteristics and then deriving the association between this vascular calcification index and the occurrence of cardiovascular events in patients on hemodialysis. The equation predicting the EBT was quite strong as were the multivariate risk calculations, which suggest that the degree of vascular calcification provides incremental prognostic information beyond gender, smoking, hypertension, diabetes, CRP, and diastolic blood pressure. It may seem surprising that some known risk factors, such as age, cardiovascular history, and cholesterol, are not included directly in that Cox proportional hazards equation. It should be noted, however, that their effect is conveyed through the derived calcification score since they are included as independent variables in the regression equation used to derive that value. When examined in relative terms, the risk increase observed for scores above 400 (Fig. 3) is more pronounced than those observed above the 5.5 mg/dL cutoff point for serum phosphorus levels [22, 23].

These predictive equations permit quantification of the cardiovascular implications of using sevelamer instead of calcium-based binders to treat hyperphosphatemia in patients on hemodialysis. Indeed, based on the findings of the Treat-To-Goal Study, a 12% decrease in cardiovascular risk is expected to occur over the patients' lifetime.

The association between calcification measured by EBT and clinical coronary artery disease has been documented in initially asymptomatic, low-to-intermediate-risk individuals without ESRD [3–7]. For high-risk individuals, the relationship has been somewhat less clear [2], although the validity of this study's conclusions has been challenged due to the imaging technique used [24]. In patients with ESRD, the association between calcification and mortality was shown in a subset of the patients included in this analysis. In that analysis, both arterial calcification (measured using the semiquantitative 0 to 4 score) and increased common carotid artery incremental elastic modulus (a measure of arterial function) were strongly and independently predictive of mortality [17]. Although the original 0 to 4 score is reproducible, inexpensive, and readily available, it is imprecise because, as discussed in the original paper, it does not quantitate the calcium concentration in the arteries [17], whereas the Agatston score derived from an EBT does so with great sensitivity, which was the rationale for including it as a measure in the Treat-to-Goal Study [14, 15].

These results should be interpreted in view of several limitations. First, in the absence of a dataset with both components (EBT calcification score and cardiovascular events over time), the EBT scores were derived using a regression equation rather than being measured directly. The predicted score adequately discriminated between patients with high and low EBT scores, however, and a significant positive association was found with the number of arterial sites calcified. Second, the risk equation is based on data from only one center in France.

Although it is desirable to have long-term data to confirm the effect of sevelamer on cardiovascular risk, it will take several years for these to be available. In the meantime, administrators must decide whether or not to make this binder available and individual physicians must make treatment decisions based on the available evidence. The predictive equations help inform these decisions by quantifying the expected clinical consequences of the physiologic effects obtained in clinical trials. The results suggest that the choice of phosphate binder has implications for cardiovascular risk in patients on hemodialysis.

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