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Markers of vascular disease do not differ in black and white hemodialysis patients despite a different risk profile

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Abstract

Increased aortic stiffness, as measured by pulse wave velocity (PWV) and augmentation index (Aix), and vascular calcification have been associated with an unfavourable cardiovascular outcome in hemodialysis patients. However, the majority of data have been published in white patients and epidemiological data are discordant on the fate of patients of different races. In this cross sectional study we measured PWV and Aix by applanation tonometry and coronary artery and thoracic aorta calcium score (CAC and AoC) by electron beam tomography (EBT) in 81 Blacks and 61 Whites on maintenance hemodialysis. Vascular stiffness measurements and EBT scans were performed within a week of each other. There was no difference between races in age, systolic blood pressure or gender distribution. Blacks had a more frequent history of hypertension (100% versus 89%; $P = 0.002$), lower prevalence of dyslipidemia (30% versus 66%; $P < 0.001$), higher PTH levels (geometric mean 607 pg/ml versus 245 pg/ml; $P = 0.039$), received calcium based phosphate binders less frequently (37% versus 60%, $P = 0.007$) and calcium antagonists more frequently than Whites (54% versus 28%; $P = 0.003$). Nonetheless, the unadjusted and risk adjusted PWV and Aix, as well as CAC and AoC were not statistically different between races. In this dialysis cohort there was no difference in markers of vasculopathy between black and white patients despite differences in baseline clinical characteristics. Epidemiological data from the general population indicate that Blacks have lower calcium scores and stiffer vessels than Whites. Some studies in the renal populations suggest a better and others a similar survival of Blacks and Whites on hemodialysis. Our findings raise the important question of the prognostic significance of markers of vasculopathy in patients of different races and with different risk profiles.

Keywords: Pulse wave velocity; Coronary calcium; Aorta calcium; Hemodialysis; Vascular stiffness; Arteriosclerosis

1. Introduction

The incidence of cardiovascular disease is several fold-higher in end stage renal disease (chronic kidney disease stage (CKD)-5) as compared with age-matched populations [1,2]. To help assess cardiovascular risk in CKD-5 patients, numerous new markes of cardiovascular risk have been introduced and utilized in outcome studies. Among others, measures of arterial stiffness and vascular calcification have emerged as helpful markers of risk and have been linked with an unfavorable prognosis [3–6]. However, the majority of data on arterial stiffness and vascular calcification in CKD-5 patients have been collected in white patients and little is known of their applicability to the black hemodialysis population.

This information may be particularly relevant in countries like the US where a large number of patients on dialysis is black. Indeed, recent publications from large databases have revealed conflicting information on the effect of race on survival. Several studies that utilized the *United States Renal Data System* (USRDS) information supported a better

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survival and a lower incidence of atherosclerotic non-fatal events for Blacks than Whites on maintenance hemodialysis [7–12]. On the contrary, a report from the American arm of the *Dialysis Outcome and Practice Patterns Study* (DOPPS-1) questioned the existence of a survival advantage for black patients attributing the prior noted differences to insufficient adjustment for confounders [13]. Hence, the question of whether markers of vasculopathy differ in Blacks and Whites undergoing dialysis appears of interest. Accordingly, the purpose of the present study was to compare indexes of vascular stiffness and compliance such as pulse wave velocity (PWV) and augmentation index (Aix) and presence and severity of vascular calcification of the aorta and coronary arteries, in a cross sectional sample of prevalent black and white hemodialysis patients.

2. Methods

2.1. Subjects and design

We included men and women older than 18 years of age on maintenance dialysis for >3 months in two centers (New Orleans, LA and Denver, CO), able to provide an informed consent prior to study enrollment. We excluded pregnant or lactating women or women planning to become pregnant in the following 6 months. In total, we enrolled 81 black and 61 white patients. Demographic data (including race) were collected by means of questionnaires or direct interview and historical clinical data were collected from questionnaires and patient charts. The clinical data collected included time on hemodialysis (vintage), body mass index (BMI), history of diabetes mellitus, hypertension, dyslipidemia, smoking, and atherosclerotic cardiovascular disease (ASCVD: cerebrovascular disease, peripheral vascular disease, angina pectoris, myocardial infarction and revascularization) and heart failure. Systolic and diastolic blood pressure were measured at the time of PWV assessment and current medications were recorded at the same time. The study protocol was approved by the internal review board at each institution and performed in adherence with the Declaration of Helsinki guidelines on ethical principles for medical research involving human subjects [14].

2.2. Blood samples

Blood samples were drawn in the morning of the midweek dialysis session, after an overnight fast of at least 12 h. We measured serum albumin, calcium, phosphate, intact-PTH (iPTH), alkaline phosphatase, fetuin-A, uric acid and C-reactive protein. Whole blood was used to measure hemoglobin, and ethylenediaminetetraacetic acid (EDTA)-plasma was used to measure lipoproteins (total cholesterol, HDL-cholesterol, and triglycerides). LDL-cholesterol was calculated. All blood samples were shipped in ice and analyzed in a central laboratory (Quest Diagnotics, Los Angeles, CA). Women of childbearing potential were required to have a negative pregnancy test to enter the study.

2.3. Hemodynamic parameters and arterial stiffness assessment

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured before the midweek hemodialyis session, with the patient in a seated position and after 5-min rest.

PWV and Aix were successfully recorded in all but five Blacks and six Whites. Aortic PWV and Aix were determined by applanation tonometry (SphygmoCor, AtCor Medical, Sydney, Australia) according to a well standardized protocol [15]. Aortic PWV was recorded within 24 h from the midweek hemodialyis session after 5 min of bed rest. PWV was calculated as the ratio of the distance between two recording sites (carotid artery and femoral artery) and the pulse transit time (PWV = distance (m)/transit time (s)). The length of the carotid-femoral arterial segment was estimated by measuring the distance from the carotid pulse and the sternal notch and the distance between the sternal notch and the femoral pulse. The pulse transit time was estimated as the delay in arrival of the pulse wave at the carotid site and at the femoral site gated to the peak of the R-wave on a simultaneously recorded surface ECG. Data were then converted into aortic pressure waveforms using a validated algorithm (SphymoCor, AtCor, Sydney, Australia) and central hemodynamic parameters were derived. Aortic pulse pressure was calculated as the difference between aortic systolic and diastolic pressure. Finally, Aix was defined as the difference between early and late systolic blood pressure peaks divided by the pulse pressure amplitude. The SphymoCor device (AtCor, Sydney, Australia) has an internal quality control that guarantees the quality of the recording and measurement. In fact, the computer does not compute either PWV or Aix until 10 consecutive pressure waves are clearly interpretable. With this approach the reproducibility of the measurements ranges from 5 to 8%.

2.4. Vascular calcification asssessment

All subjects except one white and three black patients underwent electron beam tomography (EBT) whithin 1 week of measuring PWV and Aix. Imaging was performed in both centers using a C-150 scanner (GE-Imatron, San Francisco, CA, USA) according to a standard protocol [16,17]. Briefly, 40–60 contiguous tomographic slices were obtained at end-expiration and at 60% of the R-to-R interval (recorded on the simultanoeusly acquired surface electrocardiogram). Tomographic imaging extended from above the aortic arch to the diaphragm. Slice thickness and acquisition time were set at 3 mm and 100 ms, respectively. A coronary artery calcium score (CAC) and aorta calcium score (AoC) was calculated for each area of interest identified along the course of the coronary arteries and thoracic aorta according to the Agat-

ston et al. method [18]. This score takes into consideration the size and attenuation (i.e density) of a calcific focus, therefore incorporating information about the volume as well as the concentration of calcium into the plaque. To avoid errors, all areas containing intravascular stents, metal clips or other hardware were carefully excluded from the score calculation. The reported interscan variability of the calcium score is 8–10% [19], similar to our in-house results previously published.

2.5. Statistical analysis

Data were analyzed with SAS version 9.1 software (SAS Institute. 2003. Cary, NC) and S-Plus6.2 software (2003 Insightful Corp, Seattle, WA). Continuous variables are expressed as mean ± 1 or 2S.D. as specified. Differences in categorical variables were compared using the Chi-square test. Comparison of means was done using ANOVA with Bonferoni post hoc correction and medians were compared using Wilcoxon tests. A P-value <0.05 was considered significant, and all tests were two tailed. General linear regression analyses were conducted to identify factors independently associated with PWV, Aix, CAC and AoC. The following variables were considered in the models: age, gender, race, dialysis vintage, Framingham 10-year risk (http://hp2010.nhlbihin.net/atpiii/calculator.asp?usertype=prof), diabetes mellitus, dyslipidemia, hypertension, smoking, body mass index, history of atherosclerotic cardiovascular disease (ASCVD), diastolic blood pressure, systolic blood pressure, use of ACE-inhibitors or angiotensin receptor blockers, calcium based phosphate binders, sevelamer, statins, calcitriol or vitamin D analogues use. Since each measure of vasculopathy (the outcome) was measured in approximately 140 patients the use of 18 variables did not overload the models. Power calculations were conducted to verify whether our patient sample size was sufficient to demonstrate that the measured Aix and PWV in Blacks and Whites were not different. Assuming a power of

Table 1
Demographic and clinical characteristics of the study population.

	Blacks ($n=81$)	Whites ($n=61$)	P-value
Demographics			
Age (years)	54.4 ± 13.1	56.2 ± 16.9	NS
Men (%)	54%	47%	NS
Dialysis vintage (years)	3.8 ± 3.4	4.5 ± 4.9	NS
Diastolic blood pressure (mm Hg)	79.9 ± 13.9	78.4 ± 14.4	NS
Systolic blood pressure (mm Hg)	143.4 ± 25.6	145.9 ± 25.4	NS
Hypertension	100%	89%	0.002
Dyslipidemia	30%	66%	$P<0.001$
Diabetes mellitus	47%	45%	NS
ASCVD*	39%	38%	NS
Body mass index (kg/m^2)	26 ± 5.6	26.4 ± 5.2	NS
Framingham (10 year risk)	10.5 (2–27.5)	11 (1.5–20)	NS
Main medications			
Calcium based phosphate binders	37%	60%	0.007
Sevelamer (non-calcium phosphate binder)	53%	62%	NS
Vitamin D3 and analogs	58%	52%	NS
ACE inhibitors/ARB	51%	43%	NS
Beta-blockers	58%	43%	NS
Calcium antagonists	54%	28%	0.003
Serological values			
Calcium (mg/dl)	8.9 ± 0.7	9.0 ± 0.8	NS
Phosphorus (mg/dl)	4.8 ± 1.4	5.2 ± 1.5	NS
CaxP (mg^2/dl^2)	45.5 ± 13.6	46.8 ± 13.5	NS
Intact PTH (pg/ml)*	607 (497–741)	245 (181–330)	0.039
Albumin (g/dl)	3.8 ± 0.4	3.8 ± 0.3	NS
Hemoglobin (g/dl)	12.2 ± 2.5	12.7 ± 1.2	NS
Total cholesterol (mg/dl)	157.6 ± 39.3	149.3 ± 37.4	NS
HDL cholesterol (mg/dl)	47.9 ± 14.5	45.8 ± 13.4	NS
LDL cholesterol (mg/dl)	74.3 ± 27.7	68.8 ± 28.4	NS
Triglycerides (mg/dl)	167.6 ± 105.1	175 ± 97.1	NS
hsCRP (mg/dl)*	0.9 (0.71–1.08)	0.7 (0.57–0.86)	NS
Fetuin-A	0.30 ± 0.07	0.29 ± 0.08	NS

ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker; ASCVD: atherosclerotic cardiovascular disease (cerebrovascular disease, peripheral vascular disease, angina pectoris, myocardial infarction and revascularization); HsCRP: high sensitivity C-reactive protein; PTH: parathyroid hormone.
Continuous and normally distributed variables are expressed as mean ± 1S.D.; non-normally distributed variables are expressed as median (interquartile range). Categorical variables are expressed as percent.

* PTH and hsCRP are presented as geometric mean and 95% confidence interval.

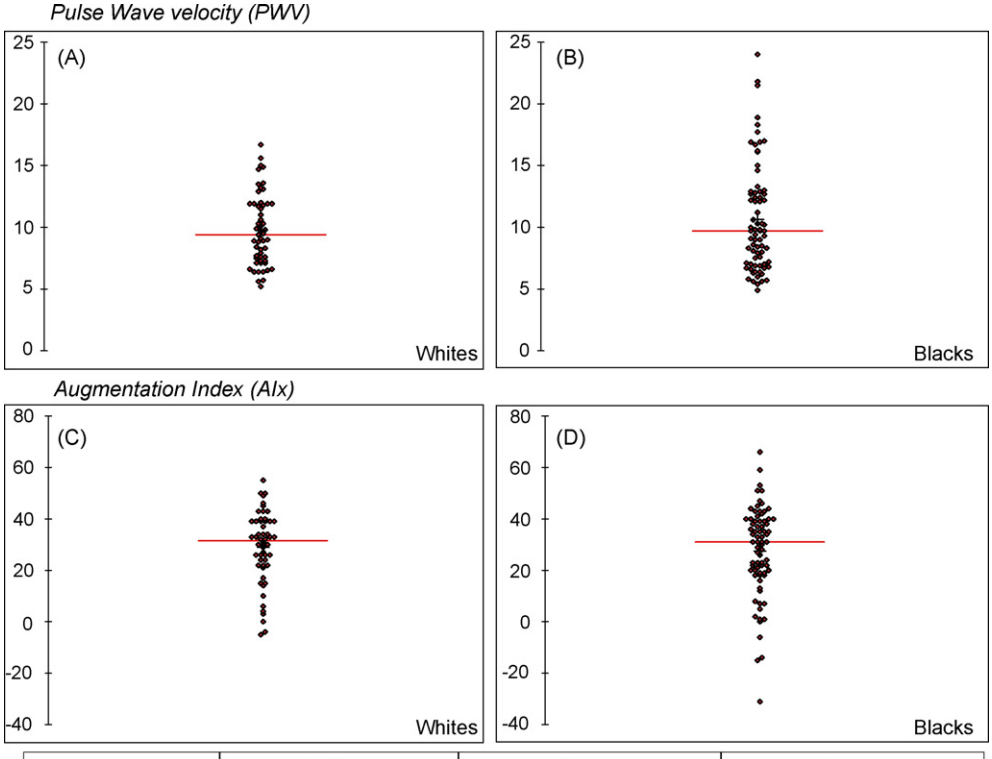
80%, and a *P*-value of 0.05 the absolute difference in Aix between Whites and Blacks should be 18.9% (i.e. Whites' Aix = 29% and Blacks' Aix = 10%) for the present sample size to demonstrate a significant difference. Since our white patients had a Aix of 29% and the black patients had an Aix of 27.5%, it would have required a sample of 12,000 patients per arm to demonstrate that the measurements we report are significantly different. The extremely large sample size, indicates that it is correct to consider our Aix measurements not different between races. Similar considerations can be made for the other measurements performed.

3. Results

The demographic and clinical characteristics of the 142 enrolled patients, identified according to race, are shown in Table 1. There was no difference in age, sex, systolic and diastolic blood pressure, dialysis vintage, history of diabetes, prior ASCVD, body mass index or Framingham risk score between Whites and Blacks. However, black patients were more frequently hypertensive (100% versus 89%; $P = 0.002$), were treated more frequently with calcium antagonists (54% versus 28%, $P = 0.003$) and had higher levels of iPTH (geometric mean (95% CI): 607 (497–741) pg/ml versus 245 (181–330) pg/ml; $P = 0.039$) than Whites. Additionally, Blacks were less likely to have a history of dyslipidemia (30% versus 66%; $P < 0.001$) or to be current users of calcium based phosphate binders (37% versus 60%; $P = 0.007$) than Whites.

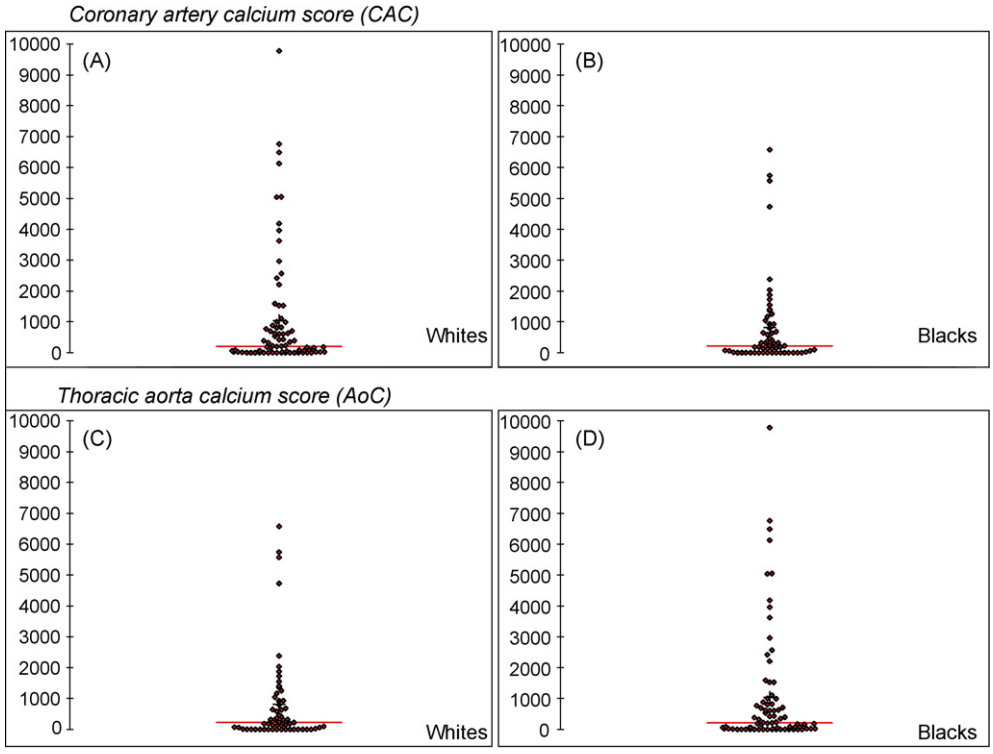
The mean PWV and Aix (Fig. 1) were not different between races (9.7 ± 2.8 m/s Whites versus 10.6 ± 4.3 m/s Blacks; $P = 0.58$ and 29 ± 13.9% Whites versus 27.5 ± 17.4% Blacks; $P = 0.58$, respectively). Additionally, the prevalence and extent of CAC and AoC were similar in Whites and Blacks. CAC was present in 82% of the white and 83% of the black patients ($P = 0.82$). The CAC score was similar in the two groups (median 228 (interquartile range (IQR): 5–934) Whites versus 207 (IQR: 21–882) Blacks; $P = 0.49$) (Fig. 2). Additionally, prevalence and severity of calcification of the thoracic aorta were similar among Whites and Blacks (94% versus 91%; $P = 0.75$, median AoC sore 819 (IQR: 71–4232) versus 576 (IQR: 46–2141), respectively; $P = 0.73$) (Fig. 2).

Table 2 shows the result of the regression analyses investigating factors independently associated (with a $P < 0.10$) with the markers of vasculopathy we studied. The model explained 29–37% of the variability and in no case was race an independent predictor of outcome. In all four models, race was one of the first variables to exit the analyses, confirming our univariate finding that race did not influence the four measures of vasculopathy we considered.



	Whites	Blacks	P value
PWV±2SD (m/sec)	9.7±2.8	10.6 ± 4.3	p=0.58
AIx ±2SD (%)	29 ± 13.9	27.5 ± 17.4	p=0.58

Fig. 1. Distribution and mean ± 2S.D. (solid line) of pulse wave velocity (A and B) and augmentation index (C and D) in white and black hemodialysis patients.



	Whites	Blacks	P value
Median CAC (IQR)	228 (5-934)	207 (21-882)	p=0.49
Median AoC (IQR)	819 (71-4232)	576 (46-2141)	p=0.73

Fig. 2. Distribution and median values (solid line) of coronary artery (A and B) and thoracic aorta (C and D) calcium scores in White and Black hemodialysis patients.

4. Discussion

In this appropriately sampled cross sectional investigation there was no difference in markers of vasculopathy between black and white patients undergoing maintenance hemodialysis in spite of a different risk profile. Indexes of arterial stiffness as well as prevalence and extent of vascular calcification have emerged as indipendent predictors of overall and cardiovascular mortality in the general population [20–23] as well as subjects with CKD-5 [24,6,5]. Furthermore, therapeutic strategies that attenuate PWV and vascular calcification progression have been shown to improve prognosis in CKD-5 [25,6]. However, to date no study has investigated whether race has any influence on the severity of vasculopathy in dialysis patients.

Published data from the general population suggest differences between Blacks and Whites in mechanical properties and composition of large elastic arteries. Indeed, Blacks are more susceptible to hypertension and develop increased systolic blood pressure levels earlier in life compared to Whites [26]. Accordingly, several studies have reported black race to be associated with increased arterial stiffness assessed by applanation tonometry or ultrasonography [27,28]. Furthermore, in the general population Blacks seem to suffer a greater increase in PWV for the same increase in systolic blood pressure than Whites [29]. The rare postmortem studies that investigated structural differences of the large arteries in different racial groups, lend credibility to the hypothesis of a different composition of the arterial wall of the aorta in Blacks and Whites. In a histological study of 110 black and 74 white subjects, Blacks were shown to have a lower collagen/elastin ratio in the wall of the aorta than Whites in young age [30]. The situation was reversed later in life (30–69 years of age), with Blacks showing a greater increase in collagen content [30]. However, interpretation of these cross-sectional post-mortem data is limited by the lack of information about history of hypertension during life in the study subjects. Blacks are also known to have a greater tendency toward excessive collagen deposition in response to skin injury (keloid) [31,32], a higher prevalence of salt sensitivity [33,34], reduced arterial vasodilatory response to nitric oxide and blunted response to beta-adrenergic stimulation [35]. Indeed, while aortic and peripheral PWV slows temporarily in white patients treated with isoproterenol, Blacks do not show the same reactivity [35]. On the contrary, short term smoking causes a marked PWV increase in Blacks but not in Whites from the general population [36]. These findings may justify the observed greater tendency of black individuals compared to white subjects from the general population to develop arterial stiffness. The racial differ-

Table 2
Multivariable models showing factors associated with markers of vasculopathy with a *P*-value <0.10

Pulse wave velocity (*R*-square 0.32)		
Pulse wave velocity	Estimate	*P*-value
ACE inhibitors/ARBs (absence)	1.66	0.0498
Vitamin D3 and analogs (absence)	2.89	0.0326
Warfarin (absence)	2.13	0.0942
Age	0.10	0.0033
Diabetes mellitus (absence)	−3.03	0.0006
Systolic blood pressure	0.05	0.0086
Augmentation index (*R*-square 0.29)		
Augmentation index	Estimate	*P*-value
Calcium based phosphate binders (absence)	7.60	0.0875
Vitamin D3 and analogs (absence)	12.38	0.0415
Hypertension (absence)	23.63	0.0350
Systolic blood pressure	0.05	0.0862
Coronary artery calcium score (*R*-square 0.37)		
Coronary artery calcium score	Estimate	*P*-value
Age	42.54	0.0040
Male gender	735.82	0.0366
Dialysis vintage	76.13	0.0891
Smoking (absence)	−844.65	0.0613
Intact PTH	1.01	0.0003
Thoracic aorta calcium score (*R*-square 0.31)		
Thoracic aorta calcium score	Estimate	*P*-value
Age	200	0.0011

ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker; PTH: parathyroid hormone.

ence, however, seems to disappear after a certain period of hemodialysis treatment.

Two other markers of vasculopathy, coronary and aortic calcification were also not different in our black and white subjects, unlike data reported in the general population. The prevelance and extent of calcification of the coronary arteries and aorta in our cohort were remarkably similar to those of a prior randomized, multicenter trial of prevalent hemodialysis patients [4], supporting the notion that ours was a fairly representative sample of the hemodialysis population.

A postmortem study of 777 patients with normal renal function from Lousiana [37] showed a lower prevalence of calcified lesions in the coronary arteries of black subjects compared to Whites. More recently, the Multi-Ethnic Study of Atheroscerosis (MESA) showed that presence and extent of coronary calcium detected by computed tomography were significantly lower in black compared to white men and women free of clinical cardiovascular disease and these differences were unchanged after adjustments for age, education and commorbid conditions [38]. However, in another large population-based study, the Dallas Heart Study, there were no racial related differences in prevalence and extent of CAC [39]. Nonetheless, a greater body mass index of black women and recruitment of subjects with estabished cardiovascular disease in the the Dallas Heart Study might account in part for the discordant results between this study and MESA.

Our findings are of interest in light of discrepant reports on outcome in patients of different races undergoing maintenance hemodialysis. The American arm of the Dialysis Outcome and Practice Patterns Study (DOPPS-1) [13] recently questioned the greater mortality risk attributed to white patients undergoing hemodialysis compared to Blacks as reported in several publications from the USRDS data [7–12]. In the DOPPS-1 report, the unadjusted survival advantage for black patients disappeared after adjustment for comorbidities, concurrent therapies and nutritional variables (hazard ratio: 0.97, 95% CI 0.85–1.11) [13]. The investigators proposed that the apparent survival advantage for Blacks on dialysis might be explained by a selection bias with black patients being healthier than white patients at dialysis onset in spite of a different risk profile. This could be due to the fact that black patients are sicker and die more frequently in the pre-dialysis period which would select healthier subjects to survive till dialysis [40]. Socioeconomical disparities and difference in access to health care may contribute to the racial difference in outcome seen in the years leading to dialysis [41]. Although the DOPPS investigators were unable to distinguish between the relative contribution of biologic and social causes, they concluded that no difference in survival should be expected between black and *identical* white patients on maintenance hemodialysis [13].

The similarity in markers of vascular disease between races suggests, although it does not prove, that these methods may be equally helpful in assessing cardiovascular risk in Blacks and Whites undergoing hemodialysis. This is particularly relevant considering the difference in prevalence of traditional cardiovascular risk factors between black and white patients [42], and their limited predictive value for events [43]. Future studies should focus on the important question of the predictive value of arterial stiffness and vascular calcification in these two prevalent racial groups undergoing dialysis in the US.

Our limitations include the cross-sectional nature of the study that did not allow for an a-priori matching of patient characteristics. The one-time acquisition of imaging data did not allow us to make any inferences as to whether the progression of markers of disease is different in Blacks and Whites. Finally, the Blacks in this study may not be fully representative of the various black ethnicities present in this Country and the world.

In summary, we demonstrated that race was not a predictor of arterial stiffness or severity of coronary artery and aorta calcification in a cohort of prevalent hemodialysis patients, in discordance with evidence noted in the general population. Future studies should investigate the predictive value of markers of vasculopathy in patients of different races undergoing dialysis, and explore whether therapeutic strategies aimed at reducing PWV and attenuate vascular calcification progression will result in a similar improvement in prognosis.

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