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RESEARCH LETTER

Atorvastatin Does Not Attenuate Aortic Stiffening After Doxorubicin for Breast Cancer and Lymphoma (PREVENT-WF-98213)

Ascending (AAD) and descending (DAD) thoracic aorta distensibility, and thoracic aorta pulse wave velocity (PWV) reflect vascular stiffening that associates independently with subsequent cardiovascular (CV) events.[1] Four to 6 months following cardiotoxic chemotherapy, AAD decreases and PWV increases.[2,3] The goal of this prespecified secondary analysis of a previously published[4] randomized trial, conducted in collaboration with the Wake Forest NCI Community Oncology Research Program (NCORP) Research Base (PREVENT WF-98213), is to determine the effect of 40 mg/d of atorvastatin or placebo on aortic stiffness among 279 patients who received anthracycline-based chemotherapy and who were without indication to receive a statin. AAD, DAD, and PWV were assessed before (T0) and then 6 months (T1) and 24 months (T2) after treatment initiation. All participants provided informed consent; the study was approved by the institutional review board of the Wake Forest School of Medicine and registered with clinicaltrials.gov (Preventing Anthracycline Cardiovascular Toxicity With Statins [PREVENT]; NCT01988571).

Longitudinal linear mixed-effects models were fit with nonimputed data to assess changes in AAD, DAD, and PWV (model 1). A mixed-effects modeling approach is considered robust for data considered to be missing at random. Models were also fit with data from participants compliant with the study drug (placebo/statin) ≥80% of the time (model 2) or compliant ≥80% and with ≥20 months of follow-up data (model 3). Subgroup analyses examined moderating effects of chest radiation, smoking, and hypertension, whereas body mass index (BMI) was included in all models due to an imbalance between treatment groups.[4] Separate models were also fit with data from fully compliant participants to examine associations between serum lipoproteins (cholesterol, triglycerides, low-density lipoproteins [LDL], high-density lipoproteins) and inflammatory markers (C-reactive protein [CRP], interleukin-[IL] 6, tumor necrosis factor[TNF]-alpha) with aortic stiffness.

Pre-doxorubicin treatment, among the statin and placebo groups, respectively, the age averaged 48.5 ± 12.5 years and 49.4 ± 11.5 years, 11.5% and 15.7% self-reported as Black, BMI was 29.0 ± 6.5 kg/m^2 and 31.0 ± 7.4 kg/m^2, 13.7% and 10.0% were current smokers, 56.1% and 58.6% received chest radiation, and 30.9% and 45.0% were hypertensive. Across the trial, 75.5% and 75% of participants were ≥80% compliant with statins and placebo, respectively, whereas 54.7% and 50% were 80% compliant and with ≥20 months of follow-up data. **Table 1** shows results of models 1 to 3 indicating a significant T0 to T1 (1.6 to 1.3 × 10^{-3} mm Hg; $P = 0.044$) and T0 to T2 decrease in mean AAD (1.6 to 1.1 × 10^{-3} mm Hg; $P = 0.003$) averaged over treatment groups after initiating doxorubicin. For DAD, there was no significant T0 to T1 change; however, a decrease in mean distensibility from T0 to T2 (1.7 to 1.2 × 10^{-3} mm Hg; $P < 0.023$) was significant (model 1). There were no differences by treatment. There was no significant change in PWV at T1 (5.9 to 6.0 m/s; $P < 0.622$); however, a significant cross-over interaction indicated PWV was higher in the statin vs placebo group at T2 (6.6. vs 5.6 m/s; $P < 0.01$).

Subgroup analyses revealed that participants with hypertension vs without hypertension at T0 had a significantly lower AAD at T2 (1.0 vs 1.5 × 10^{-3} mm Hg; $P = 0.020$), a significantly lower DAD at T1 (1.1 vs 1.6 × 10^{-3} mm Hg; $P < 0.010$), and higher PWV at T1 and T2 (7.3 and 7.3 m/s; both $P < 0.001$), respectively.

Among fully compliant participants, having higher levels of cholesterol and LDL at T0 was associated with a small but significant decrease in DAD, but not in AAD or PWV. Higher levels of IL-6 at T0 were associated with small but significantly higher AAD and DAD, whereas higher baseline CRP was only associated with higher AAD. TNF-α was not associated with any aortic stiffness parameters. Notably, associations between group (statin vs placebo) and differences in time-dependent change in aortic stiffness and receipt of doxorubicin were not impacted by

serum measures of cholesterol, LDL, IL-6, TNF-α, nor CRP.

Recently, Suddala et al[5] showed that before chemotherapy, women with breast cancer (BC) had reduced AAD in comparison to women without hypertension or BC ($P = 0.0047$) and that women with BC had aortic stiffness similar to women with hypertension, despite controlling for age and BMI. Our findings extend this work, indicating that whereas a moderate-to-high daily dose of atorvastatin decreased LDL and cholesterol, unlike prior studies in noncancer patients, it did not: 1) impact changes in thoracic aortic distensibility or PWV; or 2) markedly influence systemic inflammation (CRP, IL-6, or TNF-α). Additionally, although we did not observe an overall change in the association between statin administration and AAD, DAD, or PWV after accounting for these biomarkers, we did find that higher baseline levels of cholesterol and LDL were significantly associated with increases in aortic stiffness, despite receipt of statins. In those with higher baseline levels of other inflammatory markers (IL-6, CRP), we observed modest associations with AAD and DAD, and although there seemed to be a potential benefit from statins clinical interpretation is limited by a lack of data on major adverse cardiac events. Together, these findings suggest that the impact of doxorubicin on aortic stiffness may entail mechanisms beyond those involving lipoprotein metabolism or reflected in conventional measures of systemic inflammation and highlight the importance of managing pre-existing CV risk factors.

In summary, in patients without an indication to receive a statin for primary or secondary prevention of future CV events, our results indicate a persistent increase in arterial stiffness up to 24 months post-initiation of doxorubicin for BC or lymphoma regardless of the receipt of 40 mg per day of atorvastatin.

TABLE 1 Mixed-Effects Linear Regression Models Examining Aortic Distensibility and PWV by Visit and Treatment

		Model 1	Model 2	Model 3
AAD, $\times 10^{-3}$ mm Hg^{-1}				
Patient-level variables				
Visit	Baseline, T0[a]	1.6 (1.4-1.8)	1.5 (1.3-1.7)	1.5 (1.2-1.7)
	6 mo, T1	1.3 (1.1-1.5)[b]	1.2 (1.0-1.4)	1.3 (1.1-1.5)
	24 mo, T2	1.1 (1.0-1.3)[c]	1.1 (0.9-1.3)	1.2 (1.0-1.4)
Treatment	Placebo	1.3 (1.2-1.5)	1.3 (1.1-1.4)	1.3 (1.1-1.5)
	Statin	1.4 (1.2-1.5)	1.3 (1.2-1.5)	1.4 (1.2-1.5)
DAD, $\times 10^{-3}$ mm Hg^{-1}				
Patient-level variables				
Visit	Baseline[a]	1.7 (1.6-1.9)	1.7 (1.6-1.9)	1.7 (1.4-1.9)
	6 mo	1.7 (1.5-1.9)	1.7 (1.4-1.9)	1.5 (1.3-1.8)
	24 mo	1.2 (1.0-1.4)[b]	1.2 (1.0-1.4)	1.2 (1.0-1.4)
Treatment	Placebo	1.5 (1.3-1.6)	1.4 (1.3-1.6)	1.4 (1.2-1.6)
	Statin	1.6 (1.4-1.8)	1.6 (1.4-1.8)	1.5 (1.3-1.7)
PWV, m/s				
Patient-level variables				
Baseline[a]	Placebo	6.0 (5.7-6.4)	6.2 (5.7-6.6)	6.1 (5.6-6.5)
	Statin	5.8 (5.4-6.1)	6.0 (5.5-6.4)	6.0 (5.6-6.4)
6 mo	Placebo	6.0 (5.6-6.5)	6.2(5.6-6.6)	6.0 (5.5-6.5)
	Statin	5.9 (5.5-6.4)	6.2 (5.7-6.8)	6.2 (5.7-6.7)
24 mo	Placebo	5.6 (5.2-6.1)[c]	5.6 (5.2-6.1)[c]	5.9 (5.4-6.4)
	Statin	6.6 (6.1-7.1)[c]	6.9 (6.3-7.4)[c]	6.6 (6.1-7.1)

Values are mean (95% CI). Means are adjusted for all model covariates. Model 1: full dataset; model 2: participants ≥80% compliant with statin/placebo; model 3: participants ≥80% compliant and ≥20 months follow-up. All models are adjusted for baseline values of outcomes, body mass index, and group × time interactions. For pulse wave velocity (PWV), a significant treatment × time interaction at T2 (crossover interaction) was found in models 1 and 2, therefore adjusted means are shown for each treatment group by time. [a]Pre-treatment. [b]$P < 0.05$. [c]$P < 0.01$.

AAD = ascending aortic distensibility; DAD = descending aortic distensibility.

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