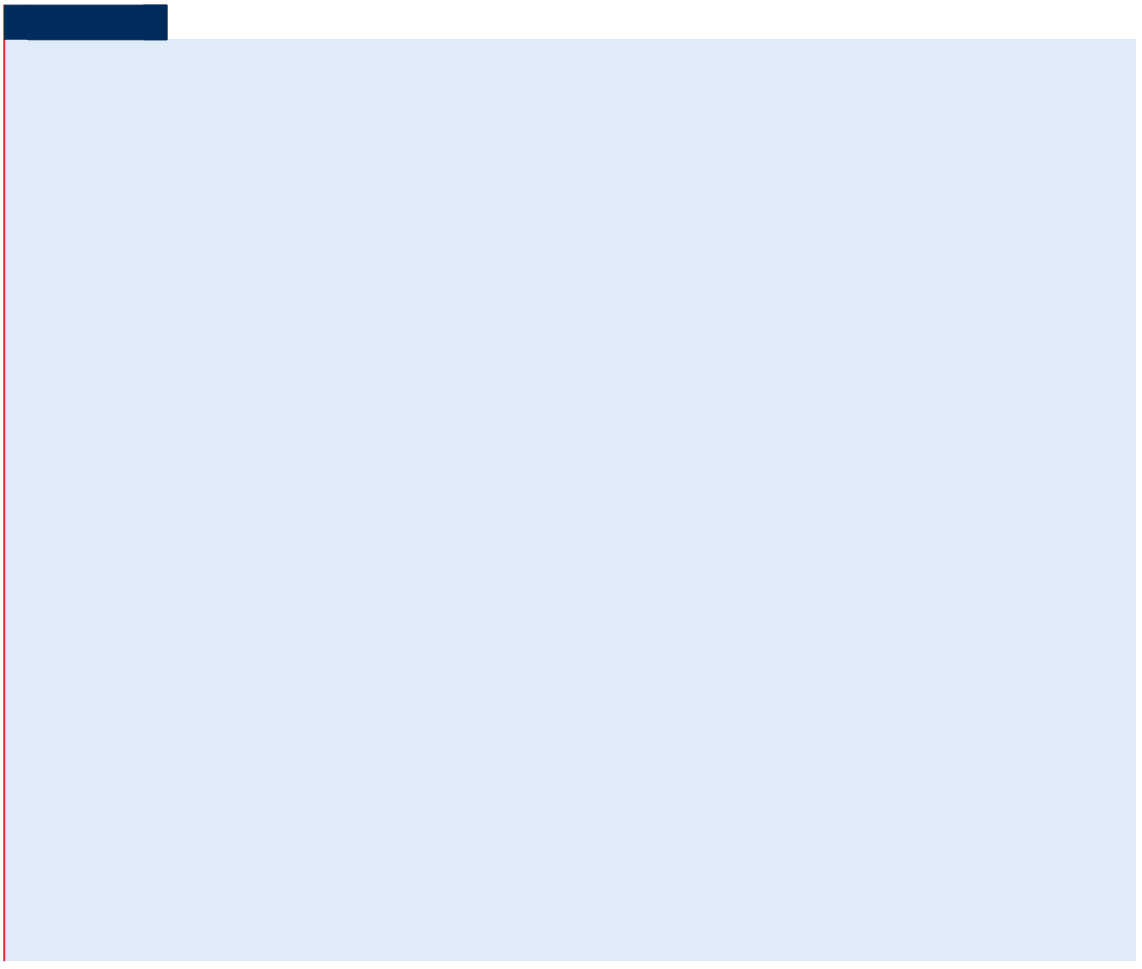
Influence of Subclinical Atherosclerosis Burden and Progression on Mortality



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diagnosis. Hypertension was defined as systolic blood

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FIGURE 2

ASSOCIATION BETWEEN SUBCLINICAL ATHEROSCLEROSIS AND ALL-CAUSE MORTALITY. Over a median follow-up of 12.4 years (Q1-Q3: 12.2-12.9 years), 901 (11.7%) participants died. Higher mortality rates were observed with increasing tertiles of cPB (log-rank $P < 0.001$) (**Figure 3A**, **Table 1**) and CAC score (log-rank $P < 0.001$) (**Figure 3B**, **Table 2**). Baseline cPB and CAC score both remained significantly associated with higher all-cause mortality after adjustment for the variables in model 1 (age, sex, and race) and model 2 (model 1 plus risk factors and medications; see Methods), with trend fully adjusted HRs of 1.23

subclinical atherosclerosis at baseline detected with either imaging modality was significantly associated with all-cause mortality, and these associations remained after multivariate adjustment. While both imaging modalities provided additional predictive value beyond CVRFs alone, carotid VUS performed significantly better than CAC. Moreover, VUS-detected cPB progression independently predicted all-cause mortality even after adjustment for CVRFs, background medication, and baseline cPB.

PREVALENCE OF SUBCLINICAL ATHEROSCLEROSIS DETECTED BY CAC AND VUS AND ITS ASSOCIATION WITH FRS. The prevalence of subclinical atherosclerosis detected with either modality at enrollment in this population was very high (near 80%), as previously reported by Baber et al.[4] This prevalence is substantially higher than described in other cohorts,[5,25] likely reflecting the older age and higher risk profile of the BioImage study population, as well as the greater sensitivity of the modalities used to detect atherosclerosis. Most of the BioImage participants, particularly those with an intermediate or high FRS, already had multiterritorial subclinical atherosclerosis at baseline affecting the carotid and coronary arteries. VUS detected disease in 72%, 83%, and 91% of participants with a low, intermediate, and high FRS, respectively, whereas CAC scoring detected disease in 58%, 80%, and 87% of participants in these categories. Interestingly, although the percentage of patients with isolated CAC was similar in each FRS category (~10%), the percentage of patients with isolated carotid disease was substantially higher in the low-FRS group (25%) and decreased with increasing FRS category. This suggests that VUS is a more sensitive detector of subclinical atherosclerosis in individuals assigned a low cardiovascular risk based on CVRFs (in whom conventional scores may underestimate risk) and before the onset of calcification of coronary lesions.

ASSOCIATION BETWEEN IMAGING-DETECTED SUBCLINICAL ATHEROSCLEROSIS AND ALL-CAUSE MORTALITY. Subclinical atherosclerosis detected by carotid VUS or CAC scoring was positively associated with all-cause

mortality at a median follow-up of 12.4 years. The positive association between increasing cPB or CAC score tertile and all-cause mortality was also observed when atherosclerosis burden was considered as a continuous variable. In the multivariate analysis, the association between atherosclerosis burden detected with either modality and all-cause mortality remained statistically significant after adjustment for CVRFs and background medication, highlighting the incremental prognostic value of direct atherosclerosis imaging in asymptomatic individuals. In our cohort, from the fully adjusted model we know that only age and cigarette smoking had a stronger prediction of mortality risk than carotid plaque burden. Moreover, while both imaging modalities improved the performance of the multivariate model incorporating CVRFs and background medication (model 2), carotid VUS

progression of >20 U/y independently predicted all-cause mortality. In addition, Sabeti et al[30] demonstrated that progression of carotid stenosis within a 6- to 9-month interval by VUS predicted the occurrence of major adverse cardiovascular events. Our study supports these previous works that have demonstrated the prognostic relevance of the progression of atherosclerosis and adds that cPB progression (even without causing stenosis) is associated with greater all-cause mortality. These results suggest that noninvasive atherosclerosis monitoring has potential to improve primary prevention by reinforcing lifestyle recommendations, establishing finer control of CVRFs, and facilitating closer follow-up of patients showing disease progression with the ultimate goal of improving their survival. However, selecting the best imaging modality is not straightforward because plaque characteristics can change in response to lipid-lowering therapy. Several imaging studies have demonstrated that intensive statin therapy reduces total plaque burden and progression by decreasing necrotic core volume but typically increases fibrous cap thickness and the degree of calcification.[31-33] The consistent increase in plaque calcification observed with statin therapy[33,34] makes plaque volume a more useful prognostic indicator than parameters that record calcium volume, such as CAC scoring. In addition, VUS is an ideal method for this purpose due to its wide availability, patient safety, and low cost. Currently, it requires some training, but it might change in the future with the use of automatic AI measurements.[35] Further research comparing the predictive accuracy of cPB and CAC progression would be needed to confirm which technique may provide more clinically useful information.

STUDY LIMITATIONS. First, all-cause mortality was identified from Social Security and National Death

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event in all studies of mortality risk and has unquestionable relevance to the study of predictive factors and the evaluation of potential preventive measures. Second, the BioImage study participants were mostly White and about half were women, and the study population was older than others examined in previous primary prevention cohorts, so the results may not be fully generalizable. Third, baseline characteristics of the 385 (6.3%) participants excluded due to missing values signifi

absence of plaque improves prediction of coronary heart disease risk: the ARIC (Atherosclerosis Risk In Communities) study. *J Am Coll Cardiol*