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Associations of cardiac injury biomarkers with risk of peripheral artery disease: The Multi-Ethnic Study of Atherosclerosis

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Abstract

INTRODUCTION: We investigated the associations of high-sensitivity cardiac Troponin T (hs-cTnT) and N-terminal pro B-type natriuretic peptide (NT-proBNP) levels with risk of developing clinical peripheral artery disease (PAD) or a low ankle–brachial index (ABI).

METHODS: Hs-cTnT and NT-proBNP were measured in 6692 and 5458 participants respectively without baseline PAD between 2000 and 2002 in the Multi-ethnic Study of Atherosclerosis. A significant number also had repeat biomarker measurement between 2004 and 2005. Incident clinical PAD was ascertained through 2017. Incident low ABI, defined as ABI <0.9 and decline of ≥0.15 from baseline, was assessed among 5920 eligible individuals who had an ABI >0.9

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[1]The authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

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Supplementary data

Supplementary material

at baseline and at least one follow-up ABI measurement 3–10 years later. Multivariable Cox proportional hazards and logistic regression modeling were used to determine the association of these biomarkers with clinical PAD and low ABI, respectively.

RESULTS: Overall, 121 clinical PAD and 118 low ABI events occurred. Adjusting for demographic and clinical characteristics, each log unit increment in hs-cTnT and NT-proBNP was associated with a 30% (adjusted hazard ratio (HR) 1.3, 95% confidence interval (CI): 1.1, 1.6) and 50% (HR) 1.5, 95% CI: 1.2, 1.8) higher risk of clinical PAD respectively. No significant associations were observed for incident low ABI. Change in these biomarkers was not associated with either of the PAD outcomes.

CONCLUSIONS: NT-proBNP and hs-cTnT are independently associated with the development of clinical PAD. Further study should determine whether these biomarkers can help to better identify those at higher risk for PAD.

Keywords

Peripheral vascular disease; Biomarkers

Introduction

Lower extremity peripheral artery disease (PAD) is a significant public health problem, affecting over 200 million people worldwide.[1] PAD is associated with significant morbidity, mortality, and health care expenditures.[2] Continued investigation into the discovery of additional risk markers can help improve identification of those at higher risk for PAD and provide an earlier opportunity to initiate preventive measures.

Cardiac troponin T and N-terminal pro B-type natriuretic peptide (NT-proBNP) are clinically established biomarkers for diagnosis of myocardial infarction and acute heart failure (HF), respectively.[3, 4] High sensitivity cardiac troponin T (hs-cTnT) and NT-proBNP levels in asymptomatic populations have also been shown to identify those at increased risk for future cardiovascular disease (CVD) and HF events, suggesting a prognostic utility of these biomarkers for the detection of subclinical cardiac injury in the general population.[5–8]

There is limited evidence to suggest that these cardiac injury biomarkers may also improve risk assessment in PAD.[9–11]Higher hs-cTnT and NT-proBNP levels have both been associated with an increased risk of PAD.[9, 10] These studies were performed in predominantly white cohorts, included individuals with baseline CVD, focused only on hospitalized PAD, and did not evaluate whether changes in these markers also impacted PAD development.[10]

The objective of the present study was to examine the longitudinal association of circulating hs-cTnT and NT-proBNP levels with PAD, including both low ABI and symptomatic PAD, in a well-characterized multi-ethnic cohort without baseline CVD. We also determined whether changes in these cardiac markers over time had an association with the subsequent risk of incident PAD

Materials and Methods

Cohort

The Multi-Ethnic Study of Atherosclerosis (MESA) is a National Heart, Lung, and Blood Institute-funded, multicenter, longitudinal community-based cohort study.[12] The study recruited 6814 adults aged 45 to 84 years and free of clinically recognized CVD from 6 field centers (Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles, California; New York, New York; and St Paul, Minnesota) to undergo baseline examination between 2000 and 2002.[11] The study participants self-identified with 1 of 4 race/ethnic groups: non-Hispanic white (38%), black (28%), Hispanic (22%), and Chinese (12%). Follow-up visits 2, 3, 4, and 5 were done in 2002– 2004, 2004– 2005, 2005– 2007, and 2010– 2012, respectively. Institutional review boards at each site approved the study, and all participants gave informed consent. Participants were not involved in the study design or conduct and did not determine outcome measures. Research questions were determined by investigators based on data collected from the participants and the outcomes assessed.

Exposure variables—hs-cTnT and NT-proBNP

A 250μl ethylenediaminetetraacetic acid plasma sample previously unthawed or only thawed once was used for plasma analysis. Hs-cTnT was measured at Exam 1 (n=6873) and Exam 3 (n=3577). Measurements were performed at the University of Maryland using the Cobas e601 (Roche Diagnostics) and details have been described previously.[13] The interassay coefficients of variation (CVs) observed for the MESA cohort measurements were 3.6% at 28 ng/L and 2.0% at 2154 ng/L. Measurements at the 3 ng/L, defined as the limit of detection (LOD) for this instrument, were well within the reportable range for the hs-cTnT used in this study.

NT-proBNP was measured in 5597 participants at Exam 1 and 4996 participants at Exam 3. Measurements were performed at the Veteran's Affairs San Diego Healthcare System (La Jolla, CA) using the Elecsys platform (Roche Diagnostics). The intra- and inter-assay coefficients of variation were as follows: at 175 pg/ml, 2.7% and 3.2%; at 355 pg/ml, 2.4% and 2.9%; at 1,068 pg/ml, 1.9% and 2.6%; and at 4,962 pg/ml, 1.8% and 2.3%, respectively. Details for NT-proBNP measurement have been previously reported.[8]

Peripheral artery disease – Clinical PAD and Low ABI

During follow-up, clinical PAD was identified by self-report of a PAD diagnosis by the participant via (1) MESA clinic visits, (2) follow-up phone call, or (3) notification to study teams; or by review of medical records. Follow-up for this analysis extended through 2017. Two physician members of the MESA mortality and morbidity review committee independently classified events. The full committee made final classifications if there were disagreements.

Physician adjudicators subclassified "definite" clinical PAD as (1) lower extremity claudication, (2) atherosclerosis of arteries of the lower extremities, or (3) arterial embolism and/or thrombosis of the lower extremities. Criteria for clinical PAD were met by a)

Obstruction or ulcerated plaque (≥50% of the diameter or ≥75% of the cross-sectional area) demonstrated on ultrasound or angiogram of the iliac arteries or below, b) Absence of pulse by Doppler in any major vessel of the lower extremities, c) Exercise test that was positive for lower extremity claudication, d) Surgery, angioplasty, or thrombolysis for peripheral vascular disease, e) Amputation of one or more toes or part of the lower extremity because of ischemia or gangrene, or f) Exertional leg pain relieved by rest in combination with either physician-diagnosed claudication or an ankle-brachial index ≤0.8.

For diagnosis of subclinical PAD, the ABI was performed at baseline examination, as well as clinic exam 3 (September 2002 to February 2004), and clinic exam 5 (April 2010 to December 2011). To obtain the measurements used to calculate the ABI, participants rested supine for 5 minutes, and then systolic blood pressures were measured in both arms and legs with the appropriate-sized cuffs. For each leg, the systolic blood pressure in each posterior tibial and dorsalis pedis artery was measured using a continuous-wave Doppler ultrasound 5-mHz probe. The leg-specific ABI was calculated as the higher systolic blood pressure in the posterior tibial or dorsalis pedis divided by the average of the left and right brachial pressures. In the event that left and right brachial pressures differed by 10 mmHg or more, the higher of the brachial pressures was chosen, since subclavian stenosis could be present. The lower of the two leg-specific ABIs was used for analysis.

Individuals with a history of lower extremity revascularization and those with an ABI ≤0.90 at the baseline visit were excluded from the clinical PAD and low ABI analyses respectively. Participants with evidence of non-compressible vessels (ABI>1.4) at baseline were also excluded from the low ABI analyses. Incident clinical PAD required a physician-adjudicated diagnosis of “definite” PAD as defined above. Incident low ABI was defined as a decline in ABI of at least 0.15 and to 0.90 or less in either leg. This approach for ABI decline was used to limit the impact of regression to the mean and measurement error and avoid small, clinically insignificant changes being included in the incident low ABI definition.[14] If only one follow-up ABI was available, then that was used for the analysis. If both follow-up ABIs were available, then exam 5 was used unless the participant already met criteria for ABI decline at V3.

Measurement of covariates

Standardized questionnaires were used at baseline to obtain age, sex, race/ethnicity, level of physical activity, alcohol consumption, smoking history, and medication usage, including statin, aspirin, anti-hypertensive, and anti-diabetic use. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Three separate systolic and diastolic resting blood pressure measurements were taken in seated participants, with the last two measurements being averaged for analysis. Physical activity was recorded as participant-reported number of intentional exercise metabolic equivalent (MET)-minutes per week. Alcohol consumption was categorized as current, former, or never and also by self-reported number of drinks per week. Cigarette smoking was calculated in pack-years and also defined as current, former, or never. Aspirin use was defined as a self-reported use of at least 3 days per week. Hypertension was defined as a self-report of physician diagnosis

and use of an anti-hypertensive medication, or systolic blood pressure ≥140 mmHg, or diastolic blood pressure ≥90 mmHg.

Coronary artery calcium (CAC) was measured at baseline by cardiac computed tomography (CT) using either cardiac-gated electron-beam CT or multi-detector CT systems, depending on the study site. CAC scores were reported using the Agatston method. Total and high-density lipoprotein (HDL) cholesterol and glucose were measured from fasting blood samples. Diabetes was defined as a fasting glucose >125 mg/dl or use of anti-diabetic medications. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equations.[15]

Statistical analysis

Hs-cTnT levels were categorized as follows: participants with concentrations below the LOD (ie, <3 ng/L)[16] comprised the lowest category and the remaining distribution of measurable hs-cTnT was divided into 3 categories of equal numbers of participants (categories 2–4). Those values <LOD were imputed at 1.5 ng/L (ie, 50% of the lowest detectable value). NT-proBNP was categorized according to quartiles. We examined the distributions of baseline characteristics according to baseline concentrations of predefined hs-cTnT categories and NT-proBNP quartiles.

Cox proportional hazards models were performed separately to calculate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations of baseline hs-cTnT and NT-proBNP with incident clinical PAD. Biomarkers were entered as (1) continuous variables (per log-transformed standard deviation increase) and (2) according to categories described above (referent=category with lowest levels). Models were adjusted for age, sex, race/ethnicity, study site (Model 1). Additional adjustments were made for BMI, diabetes, hypertension, total cholesterol, HDL cholesterol, lipid lowering therapy, smoking, and eGFR (Model 2). We repeated this analysis for development of low ABI using logistic regression modeling instead and additionally adjusting for the difference in time between the baseline and follow-up ABI measures (depending on which exam was used for the participants). To determine effects of coronary artery disease on observed associations, exploratory analyses were performed additionally adjusting for subclinical coronary atherosclerosis (CAC) and interim MI (those that occurring after a PAD event were censored).

We also determined whether changes in hs-cTnT and NT-proBNP levels between exams 1 & 3 were associated with incident clinical PAD occurring after exam 3. Changes in hs-cTnT and NT-proBNP levels were modeled as a categorical variable in separate approaches as described previously.[17, 18]. Briefly, cTnT was stratified based on whether hs-cTnT was detectable at follow-up as well as, for those with detectable baseline cTnT only, according to percent change. NT-proBNP change was modeled according to percentage change only but separate analyses were performed based on their exam 1 level (<190 pg/mL vs. ≥190 pg/ml). Covariates were taken from exam 1. Participants developing clinical PAD prior to exam 3 were censored from this analysis.

Results

A total of 6692 participants were included in the prospective incident clinical PAD analysis (mean age 62 years; 53% female; 40% white, 25% African-American, 23% Hispanic, and 12% Chinese). Baseline characteristics according to hs-cTnT and NT-proBNP levels are presented in Tables 1 and 2 respectively. Participants with higher hs-cTnT and NT-proBNP levels were older, were more likely to be male, less likely to currently smoke, had a higher SBP, had a lower eGFR, and reported more use of anti-hypertensive, lipid lowering, and aspirin therapy. Participants with higher hs-cTnT levels also were more likely to be black, were more likely to have had a higher DBP, had a higher prevalence of diabetes, and had a lower HDL-c. With the exception of race, opposite trends were observed for each of these clinical characteristics for participants with higher NT-proBNP levels.

The Kaplan Meier clinical PAD cumulative hazard estimates according to baseline hs-cTnT and NT-proBNP levels are shown in Supplemental Figures 1 and 2 respectively. The log rank test p-values were <0.01 for both hs-cTnT and NT-proBNP, suggesting that the survival distribution differed by category for both biomarkers. In adjusted analyses, while no interquartile associations were observed for hs-cTnT, each natural log-transformed SD increase in hs-cTnT levels was associated with a 30% higher risk of clinical PAD (adjusted HR 1.3; 95% CI: 1.1, 1.6; Model 2, Table 3). Compared to participants in the 1st quartile of NT-proBNP levels those in the 2nd and 4th quartiles were at a higher risk of developing clinical PAD in adjusted analyses (2nd quartile HR 2.2 (95% CI: 1.2, 4.3) and 4th quartile HR 2.6 (95% CI: 1.3, 5.2); Model 2, Table 3). Each log-transformed SD increase in NT-proBNP levels was also associated with a 50% higher risk of clinical PAD (95% adjusted HR 1.5; 95% CI: 1.2, 1.8). NT-proBNP associations remained significant after additional adjustment for CAC and interim MI (Supplemental Table 1). There was no significant improvement in clinical PAD risk prediction after incorporating either hs-cTnT or NT-proBNP compared to Model 2 covariates alone (minimal change in Harrel's c-statistic from 0.81 to 0.82 with adding either hs-cTnT or NT-proBNP and to 0.825 by adding both).

Baseline associations of hs-cTnT and NT-proBNP levels with incident low ABI are reported in Table 4. There were 118 cases of incident low ABI that occurred over 44,639 person-years of follow-up. In adjusted analyses neither NT-proBNP nor hs-cTnT was associated with the development of a low ABI (odds ratio (OR) per log-transformed SD increase in hs-cTnT 0.9 (95% CI: 0.7, 1.2); OR per log-transformed SD increase in NT-proBNP 1.2 (95% CI: 0.9, 1.6)).

Associations of changes in hs-cTnT and NT-proBNP levels with risk of clinical PAD are presented in Supplemental Tables 2 and 3 respectively. No significant associations with clinical PAD were observed according to changes in either hs-cTnT or NT-proBNP levels.

Discussion

In this large, multiethnic cohort of individuals without symptomatic CVD at baseline, both NT-proBNP and hs-cTnT levels were associated with a higher risk of developing clinical PAD.

Our results are consistent with the few prior prospective studies examining these associations. In an analysis of over 12,000 in the Atherosclerosis Risk in Communities (ARIC) study participants followed for over 20 years, those in the highest category of hs-cTnT and NT-proBNP levels were at an approximately threefold increased adjusted risk of hospitalized PAD compared with the lowest category.[10] The hazard ratios associated with the highest categories for both of these biomarkers were even greater when the PAD outcome was further restricted to the critical limb ischemia (HR=7.74 for hs-cTnT and HR=4.63 for NT-proBNP).[10] In a study of over 5000 individuals from the Malmo Diet and Cancer Study (MDCS), each SD increment in NT-proBNP was associated with a 28% higher risk of clinical PAD.

Findings reported here also build upon the established literature in several important ways. First, we extend findings to a multi-ethnic cohort that was free of clinical CVD at baseline. The MDCS and ARIC cohorts were predominantly white cohorts with a significant number of participants having some form of baseline CVD, including heart failure, stroke, atrial fibrillation, and CHD. Second, we report a wide spectrum of PAD outcomes that included milder forms of clinical PAD as well as a low ABI. Findings in ARIC were limited to hospitalized PAD and no prior studies included the low ABI outcome. The smaller magnitude of associations observed here for both hs-cTNT and NT-proBNP with risk of clinical PAD may have been due to these differences in patient and study characteristics described above. Finally, our study is the first to evaluate the relationship of longitudinal changes in hs-cTnT and NT-proBNP with risk of PAD.

The reasons by which subclinical elevations of these cardiac markers contribute to an increased PAD risk over time need further elucidation. NT-proBNP and hs-cTnT are both associated with heart failure and atrial fibrillation, clinical conditions that increase risk for systemic embolism which can cause acute PAD events.[19, 20] High levels of NT-proBNP have been associated with vulnerable plaque components while higher hs-cTnT levels have been associated microvascular damage.[21–23] Elevated hs-cTNT and NT-proBNP levels have both been directly associated with increased arterial stiffness.[24–29] Additionally, PAD and CHD share several common risk factors, such as hypertension and diabetes mellitus. When present, these risk factors may promote cardiac remodeling, leading to higher hs-cTnT and NT-proBNP in blood before clinical CVD is evident.[30–32] In parallel, these risk factors may similarly promote changes in the lower extremity that eventually lead to the development of PAD. NT-proBNP and hs-cTnT have already been shown to be independently associated with subclinical cerebral injury, defined by the presence of silent MRI-defined brain infarcts and white matter lesions.[23]

Troponin is largely released as a consequence of myocardial injury, which can occur under a variety of ischemic and non-ischemic cardiac conditions.[33] The attenuation of the relationship between hs-cTnT and incident PAD after adjustment for subclinical CAD and interim CHD raises the possibility that the previously described associations of troponin with PAD may in part reflect associations of CAD with PAD which have been well documented. NT-proBNP, on the other hand, is largely released in the ventricle in response to increased mechanical stretch, which is due, in part, to increased peripheral vascular resistance and hypertension, both of which are mechanistically linked to PAD. Elevations in

these biomarkers likely reflect a cumulative burden of subclinical cardiac injury and cardiac stretch, which indirectly reflects risk for LE atherosclerosis. It is also possible that direct effects of NT-proBNP itself may have some importance as it relates to the risk of developing PAD in asymptomatic populations.

Clinical PAD directly has direct implications on medical management for secondary CVD prevention compared to an incident low ABI, which can be largely asymptomatic, and clinically these are recognized as different entities. However, both are a result of atherosclerotic progression, and it was not expected that hs-cTnT and NT-proBNP would only be associated with incident clinical PAD. One possibility is that hs-cTnT and NT-proBNP may more closely reflect clinically active atherosclerotic disease rather than the actual lower extremity atherosclerotic burden. Both biomarkers, as mentioned above, are associated with clinical conditions (heart failure and atrial fibrillation) which can increase risk of systemic embolism. Additionally, they are associated with higher levels of systemic inflammation, which is known to correlate more strongly with active disease.[34, 35] Finally, also mentioned above, higher NT-proBNP levels been directly associated with the presence of vulnerable plaque characteristics.[21]

Increases in hs-cTnT and NT-proBNP levels were not associated with incident clinical, which was unexpected. We think a few factors may explain the lack of association with change in biomarkers and clinical PAD. First, since a notable proportion of participants who had a baseline measurement of biomarkers did not have follow up measurements (18% for NT- BNP and 33% for cTNT), our study had lower power to detect the associations of changes in biomarkers with the outcomes. Another possible explanation is that like some other risk factors, the higher baseline values carry a more important contribution to the risk and pathophysiology of the disease than the change. However, that would be the topic of a more detailed subsequent investigations, ideally with more frequent measurements done at different time intervals and further analyses done to explore if for some subsets of the population, this change in biomarkers have stronger association with outcomes.

Important strengths of this study include the recruitment of a racially/ethnically diverse population spread across 6 U.S. cities who were without prior clinical CVD at the time of enrollment, measurement of cardiac biomarkers by a core laboratory, careful assessment of each participant’s medical history and risk factors, and rigorous adjudication of clinical outcomes. Our study also has some limitations. Although the diagnosis of clinical PAD involved a comprehensive adjudication process, the number of events was low (3%) and reported confidence intervals of associations were wide. We were unable to determine whether associations differed by race/ethnicity or perform fully adjusted analyses for associations of cardiac biomarker change with incident PAD due to insufficient power. While hazard ratios increased across higher quartiles of baseline hs-cTnT, we did not observe any significant interquartile associations for hs-cTnT levels and clinical PAD, which may have been a result of reduced power as well. Incident low ABI may have been inadequately assessed due to the exclusion of participants with an ABI >1.4 at baseline and lack of toe-brachial index testing. Additionally, ABI measurements did not include a post-exercise value and, therefore, may not have detected PAD in some individuals. Lastly, this is an observational study, and we cannot exclude the possibility of residual confounding.

In conclusion, higher levels of both NT-proBNP and hs-cTnT were associated with an increased risk of incident clinical PAD. Further study is needed to better understand mechanisms linking these biomarkers with risk of PAD, and to determine whether these biomarkers can improve risk prediction for developing PAD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Fowkes FG, Rudan D, Rudan I, Aboyans V, Denenberg JO, Mcdermott MM, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. The Lancet 2013; 382: 1329–1340.
2. Scully RE, Arnaoutakis DJ, DeBord Smith A, Semel M, Nguyen LL. Estimated annual health care expenditures in individuals with peripheral arterial disease. J Vasc Surg 2018; 67: 558–567. [PubMed: 28847660]
3. Thygesen K, Alpert JS, White HD, Jaffe AS, Apple FS, Galvani M, et al. ; Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. Circulation 2007; 116: 2634–2653. [PubMed: 17951284]
4. Januzzi JL, van Kimmenade R, Lainchbury J, Bayes-Genis A, Ordonez-Llanos J, Santalo-Bel M, et al. NT-proBNP testing for diagnosis and short-term prognosis in acute destabilized heart failure: an international pooled analysis of 1256 patients: the International Collaborative of NT-proBNP Study. Eur Heart J 2006; 27: 330–337. [PubMed: 16293638]
5. Daniels LB, Clopton P, deFilippi CR, Sanchez OA, Bahrami H, Lima JA, et al. Serial measurement of N-terminal pro-B-type natriuretic peptide and cardiac troponin T for cardiovascular disease risk assessment in the Multi-Ethnic Study of Atherosclerosis (MESA). Am. Heart J 2016; 170: 1170–1183.
6. Saunders JT, Nambi V, de Lemos JA, Chambless LE, Virani SS, Boerwinkle E, et al. Cardiac troponin T measured by a highly sensitive assay predicts coronary heart disease, heart failure, and mortality in the Atherosclerosis Risk in Communities Study. Circulation 2011; 123: 1367–1376. [PubMed: 21422391]
7. deFilippi CR, de Lemos JA, Christenson RH, Gottdiener JS, Kop WJ, Zhan M, et al. Association of serial measures of cardiac troponin T using a sensitive assay with incident heart failure and cardiovascular mortality in older adults. JAMA 2010;304:2494–2502. [PubMed: 21078811]
8. Choi EY, Bahrami H, Wu CO, Greenland P, Cushman M, Daniels LB, et al. N-terminal pro-B-type natriuretic peptide, left ventricular mass, and incident heart failure: Multi-Ethnic Study of Atherosclerosis. Circ Heart Fail 2012; 5: 727–734. [PubMed: 23032197]
9. Fatemi S, Acosta S, Gottsater A, Melander O, Engstrom G, Dakhel A, et al. Copeptin, B-type natriuretic peptide and cystatin C are associated with incident symptomatic PAD. Biomarkers 2019; 6: 615–621.
10. Matsushita K, Kwak L, Yang C, Pang Y, Ballew SW, Sang Y, et al. High-sensitivity cardiac troponin and natriuretic peptide with risk of lower-extremity peripheral artery disease: the Atherosclerosis Risk in Communities (ARIC) Study. Eur Heart J 2018; ePub ahead of print
11. Kremers B, Wubbeke L, Mees B, Cate HT, Spronk H, Cate-Hoek AT. Plasma biomarkers to predict cardiovascular outcome in patients with peripheral artery disease. Arterioscler Thromb Vasc Biol 2020; 40: 2018–2032. [PubMed: 32640905]

12. Bild DE, Bluemke DA, Burke GL, Detrano R, Diez-Roux AV Folsom AR, et al. Multi-ethnic study of atherosclerosis: objectives and design. Am J Epidemiol 2002; 156: 871–881. [PubMed: 12397006]
13. Seliger SL, Hong SN, Christenson RH, Kronmal R, Daniels LB, Lima JA, et al. High-sensitive cardiac troponin T as an early biochemical signature for clinical and subclinical heart failure: the Multi-Ethnic Study of Atherosclerosis. Circulation 2017; 135: 1494–1505. [PubMed: 28159799]
14. Kennedy M, Solomon C, Manolio TA, Criqui MH, Newman AB, Polak JF, et al. Risk factors for declining ankle-brachial index in men and women 65 years or older: The Cardiovascular Health Study. Arch Intern Med 2005; 165: 1896–1902. [PubMed: 16157835]
15. Rifkin DE, Shlipak MG, Katz R, Fried LF, Siscovick D, Chonchol M, et al. Rapid Kidney Function Decline and Mortality Risk in Older Adults. Arch Int Med 2008; 168: 2212–2218. [PubMed: 19001197]
16. Fitgerald RL, Hollander JE, Peacock WF, Limkakeng AT, Breitenbeck N, Blechschmidt K, et al. Analytical performance evaluation of the Elecsys® Troponin T Gen 5 STAT assay. Clin Chim Acta 2019; 495: 522–528. [PubMed: 31152695]
17. Daniels LB, Clopton P, deFilippi CR, Sanchez OA, Bahrami H, Lima JA, et al. Serial measurement of N-terminal pro-B-type natriuretic peptide and cardiac troponin T for cardiovascular disease risk assessment in the Multi-Ethnic Study of Atherosclerosis (MESA). Am Heart J 2015; 170: 1170–1183. [PubMed: 26678639]
18. Wu AH, Lu QA, Todd J, Moecks J, Wians F. Short- and long-term biological variation in cardiac troponin I measured with a high-sensitivity assay: implications for clinical practice. Clin Chem 2009; 55: 52–58. [PubMed: 18988755]
19. Kociol RD, Pang PS, Gheorghiade M, Fonarow GC, O'Connor CM, Felker GM. Troponin elevation in heart failure prevalence, mechanisms, and clinical implications. J Am Coll Cardiol 2010;56:1071–1078. [PubMed: 20863950]
20. Kumral E, Balkır K, Uzuner N, Evyapan D, Nalbantgil S. Microembolic signal detection in patients with symptomatic and asymptomatic lone atrial fibrillation. Cerebrovasc Dis 2001;12:192–196. [PubMed: 11641583]
21. Hong YJ, Ahn Y, Sim DS, Yoon NS, Yoon HJ, Kim KH, et al. Relation between N-terminal pro-B-type natriuretic peptide and coronary plaque components in patients with acute coronary syndrome: virtual histology-intravascular ultrasound analysis. Coron Artery Dis. 2009;20:518–524 [PubMed: 19838110]
22. Rubin J, Matsushita K, Ballantyne CM, Hoogeveen R, Coresh J, Selvin E. Chronic hyperglycemia and subclinical myocardial injury. J Am Coll Cardiol 2012;59:484–489. [PubMed: 22281251]
23. Dadu RT, Fornage M, Virani SS, Nambi V, Hoogeveen RC, Boerwinkle E, et al. Cardiovascular biomarkers and subclinical brain disease in the atherosclerosis risk in communities study. Stroke 2013;44:1803–1808 [PubMed: 23660848]
24. Park KC, Gaze DC, Collinson PO, Marber MS. Cardiac troponins: from myocardial infarction to chronic disease. Cardiovasc Res 2017;113:1708–1718. [PubMed: 29016754]
25. Desai AS, Mitchell GF, Fang JC, Creager MA. Central aortic stiffness is increased in patients with heart failure and preserved ejection fraction. J Card Fail 2009;15:658–664. [PubMed: 19786254]
26. Rutten JH, Mattace-Raso FU, Verwoert GC, Lindemans J, Hofman A, Witteman JC, et al. Arterial stiffness as determinant of increased amino terminal pro-B-type natriuretic peptide levels in individuals with and without cardiovascular disease–the Rotterdam Study. J Hypertens 2010;28:2061–2067. [PubMed: 20844371]
27. Qi W, Mathisen P, Kjekshus J, Simonsen S, Bjornerheim R, Endresen K, et al. Natriuretic peptides in patients with aortic stenosis. Am Heart J 2001;142:725–732. [PubMed: 11579366]
28. Haug C, Metzele A, Kochs M, Hombach V, Grunert A. Plasma brain natriuretic peptide and atrial natriuretic peptide concentrations correlate with left ventricular end-diastolic pressure. Clin Cardiol 1993;16:553–557. [PubMed: 8348764]
29. Bai Y, Ye P, Luo L, Xiao W, Xu R, Wu H, et al. Arterial stiffness is associated with minimally elevated high-sensitivity cardiac, troponin T levels in a community-dwelling population. Atherosclerosis 2011;218: 493–498. [PubMed: 21784424]

30. Schwartzkopff B, Mundhenke M, Strauer BE. Remodelling of intramyocardial arterioles and extracellular matrix in patients with arterial hypertension and impaired coronary reserve. Eur Heart J 1995;16(S1):82–86. [PubMed: 8829962]

31. Zheng J, Ye P, Luo L, Xiao W, Xu R, Wu H. Association between blood glucose levels and high-sensitivity cardiac troponin T in an overt cardiovascular disease-free community-based study. Diabetes Res Clin Pract 2012;97:139–145. [PubMed: 22579531]

32. Jeremias A, Gibson CM. Narrative review: alternative causes for elevated cardiac troponin levels when acute coronary syndromes are excluded Ann Intern Med 2005;142:786–791. [PubMed: 15867411]

33. Marti CN, Gheorghiade M, Kalogeropoulos AP, Georgiopoulou VV, Quyyumi AA, Butler J. Endothelial dysfunction, arterial stiffness, and heart failure. J Am Coll Cardiol 2012;60:1455–1469. [PubMed: 22999723]

34. Saunders JT, Nambi V, de Lemos JA, Chambless LE, Virani SS, Boerwinkle E, et al. Cardiac troponin Tmeasured by a highly sensitive assay predicts coronary heart disease, heart failure, and mortality in the ARIC Study. Circulation 2011;123:137–1376. [PubMed: 21200008]

35. Fish-Trotter H, Ferguson JF, Patel N, Aroro P, Allen NB, Bachmann KN, et al. Inflammation and circulating natriuretic peptide levels. Circ Heart Fail 2020;13:e006570 [PubMed: 32507024]

Highlights

- High-sensitivity cardiac Troponin T (hs-cTnT) and N-terminal pro B-type natriuretic peptide (NT-proBNP) levels are associated with an increased risk of developing clinical peripheral artery disease (PAD) in predominantly white populations.
- We expanded these findings to a multi-ethnic cohort without baseline cardiovascular disease. We also observed no significant associations for either of these biomarkers with incident low ankle-brachial index. In addition, change in these biomarkers were not associated with either of the PAD outcomes.
- Future studies are needed to corroborate our findings and determine whether these biomarkers can actually improve PAD risk prediction.

Table 1.

Baseline characteristics of MESA participants according to hs-cTnT levels (n=6783)[*†]

Characteristic	hs-cTnT values				*p*- value
	Below LOB <3 ng/L (n=2,156)	Category 2 (n=1,536)	Category 3 (n=1,548)	Category 4 (n=1,542)	
Age, years	57 (9)	61 (10)	64 (10)	68 (9)	<0.01
Male, %	26	44	57	71	<0.01
Race, %					<0.01
White	36	39	43	42	
Chinese	16	14	11	6	
Black	24	22	24	32	
Hispanic	24	25	22	20	
Body mass index, kg/m2	28 (6)	28 (5)	29 (5)	29 (5)	<0.01
Smoking status, %					<0.01
Former	30	37	39	43	
Current	14	13	12	12	
Pack-years smoking	8 (17)	10 (19)	13 (23)	15 (24)	<0.01
Alcohol use, drinks/wk	3 (6)	3 (6)	4 (7)	4 (7)	0.11
Systolic blood pressure, mmHg	120 (19)	125 (20)	130 (21)	135 (22)	<0.01
Diastolic blood pressure, mmHg	70 (10)	72 (10)	74 (10)	74 (11)	<0.01
Total cholesterol, mg/dL	196 (35)	195 (35)	194 (36)	190 (37)	<0.01
HDL cholesterol, mg/dL	53 (15)	52 (15)	50 (14)	49 (14)	<0.01
Glucose, mg/dL	93 (25)	94 (24)	98 (30)	106 (40)	<0.01
Diabetes, %	7	8	13	24	<0.01
Lipid lowering therapy, %	13	15	18	21	<0.01
Antihypertensive use, %	25	33	42	53	<0.01
Aspirin use, %	17	21	27	33	<0.01
Physical activity, MET-min/wk	296 (1011)	323 (1215)	327 (1076)	342 (1189)	0.64
eGFR, mL/min/1.73m^2	84 (14)	80 (15)	76 (15)	70 (18)	<0.01
Ankle-brachial index	1.1 (0.1)	1.1 (0.1)	1.1 (0.1)	1.1 (0.2)	<0.01
Coronary artery calcium score (Log)	3.7 (1.8)	4.0 (1.8)	4.4 (1.8)	4.9 (1.8)	<0.01

HDL=high-density lipoprotein, eGFR=estimated glomerular filtration rate

[*]The lowest category consists of those participants with concentrations below the LOB (ie, <3 ng/L: category 1), and the remaining distribution of measurable hs-cTnT was divided into 3 categories of equal numbers of participants (categories 2–4). The cut-off values for categories 2– 4 are: Category 2: 3–4.83 ng/dL, Category 3: 4.84–7.89 ng/dL, Category 4: >=7.9 ng/dL

[†]Continuous variables are expressed as mean (SD). Categorical variables are expressed as percent.

Table 2.

Baseline characteristics of MESA participants according to quartiles of NT-proBNP (n=5,597)*

Characteristic	NT-proBNP values†				p-value
	1st quartile (n=1,398)	2nd quartile (n=1,400)	3rd quartile (n=1,398)	4th quartile (n=1,401)	
Age, years	56 (8)	60 (9)	64 (10)	69 (9)	<0.01
Male, %	69	52	40	33	<0.01
Race, %					<0.01
White	27	40	43	50	
Chinese	18	13	13	9	
Black	30	23	20	19	
Hispanic	25	23	24	22	
Body mass index, kg/m2	29 (5)	28 (6)	28 (5)	28 (6)	<0.01
Smoking status, %					<0.01
Former	36	36	38	37	
Current	16	13	11	10	
Pack-years smoking	10 (18)	11 (22)	11 (20)	12 (23)	<0.01
Alcohol use, drinks/wk	4 (7)	4 (7)	4 (6)	4 (6)	0.06
Systolic blood pressure, mmHg	120 (16)	124 (18)	127 (21)	136 (25)	<0.01
Diastolic blood pressure, mmHg	74 (9)	73 (10)	71 (11)	71 (11)	<0.01
Total cholesterol, mg/dL	196 (36)	194 (36)	194 (35)	193 (36)	0.16
HDL cholesterol, mg/dL	46 (12)	50 (14)	52 (15)	55 (16)	<0.01
Glucose, mg/dL	102 (36)	97 (30)	95 (27)	96 (28)	<0.01
Diabetes, %	15	12	11	13	0.01
Lipid lowering therapy, %	14	15	16	19	0.01
Antihypertensive use, %	26	33	37	51	<0.01
Aspirin use, %	19	24	24	31	<0.01
Physical activity, MET-min/wk	302 (1273)	259 (901)	339 (1003)	321 (1177)	0.25
eGFR, mL/min/1.73m^2	84 (14)	80 (15)	76 (15)	71 (17)	<0.01
Ankle-brachial index	1.1 (0.1)	1.1 (0.1)	1.1 (0.1)	1.1 (0.1)	<0.01
Coronary artery calcium score (Log)	3.9 (1.8)	4.2 (1.8)	4.4 (1.8)	4.8 (1.8)	<0.01

HDL=high-density lipoprotein, eGFR=estimated glomerular filtration rate

*Continuous variables are expressed as mean (SD). Categorical variables are presented as percent.

†Values for 25th, 50th, and 75th percentile of NT-proBNP were 24.0, 54.5, and 112.5 pg/ml.

Table 3.

Associations of baseline hs-cTnT and NT-proBNP levels with incident clinical PAD among MESA participants [*]

	Incident clinical PAD				
	Events/# at risk	**Model 1 [†] HR (95% CI)**	***p*-value**	**Model 2 [‡] HR (95% CI)**	***p*-value**
hs-cTnT categories					
<LOB	22/2151	1.00		1.00	
Category 2 3–4.83 ng/dL	16/1533	0.8 (0.4, 1.6)	0.55	0.7 (0.4, 1.4)	0.33
Category 3 4.84–7.89 ng/dL	27/1537	1.1 (0.6, 2.1)	0.68	0.9 (0.5, 1.6)	0.64
Category 4 >=7.9 ng/dL	56/1471	2.0 (1.1, 3.6)	0.03	1.3 (0.68, 2.4)	0.45
hs-cTnT continuous					
Per SD change in Log Unit [§]		1.5 (1.2, 1.7)	<0.01	1.3 (1.1, 1.6)	<0.01
NT-proBNP quartiles					
1st quartile ≤24.0 pg/ml	15/1377	1.00		1.00	
2nd quartile 24.1–54.5 pg/ml	30/1365	2.1 (1.1, 3.9)	0.03	2.2 (1.2, 4.3)	0.02
3rd quartile 54.51–112.5 pg/ml	25/1366	1.8 (0.9, 3.5)	0.11	1.9 (0.9, 3.7)	0.08
4th quartile >112.5. pg/ml	39/1350	2.6 (1.3, 5.1)	<0.01	2.6 (1.3, 5.2)	<0.01
NT-proBNP continuous					
Per SD change in Log Unit [§]		1.5 (1.2, 1.9)	<0.01	1.5 (1.2, 1.8)	<0.01

PAD=peripheral artery disease, hs-cTnT=high-sensitivty cardiac Troponin T, NT-proBNP=N-terminal brain natriuretic peptide, HR=hazard ratio, CI=confidence interval

[*] The lowest category consists of those participants with concentrations below the LOB (ie, <3 ng/L: category 1), and the remaining distribution of measurable hs-cTnT was divided into 3 categories of equal numbers of participants (categories 2–4). Results of multivariable Cox proportional hazards models

[†] Model 1 adjusted for age, sex, race, ethnicity, study site

[‡] Model 2 adjusted for Model 1 + body-mass index, diabetes, hypertension, total cholesterol, high-density lipoprotein cholesterol, lipid lowering therapy, smoking, and estimated glomerular filtration rate

[§] The standard deviations (SD) for log units of hs-cTnT and NT-proBNP were 0.6 and 1.2 log units, respectively.

Table 4.

Baseline associations of hs-cTnT and NT-proBNP levels with incident low ABI among MESA participants *

	Incident low ABI				
	Events/ # at risk	**Model 1† OR (95% CI)**	***p*-value**	**Model 2‡ OR (95% CI)**	***p*-value**
hs-cTnT categories					
<LOB	32/1944	1.00		1.00	
Category 2 3–4.83 ng/dL	20/1377	0.7 (0.4, 1.3)	0.22	0.7 (0.4, 1.4)	0.32
Category 3 4.84–7.89 ng/dL	27/1350	0.6 (0.3, 1.1)	0.10	0.6 (0.3, 1.2)	0.15
Category 4 >=7.9 ng/dL	39/1249	0.8 (0.4, 1.5)	0.47	0.8 (0.4, 1.6)	0.55
hs-cTnT continuous					
Per SD change in Log Unit§		0.9 (0.7, 1.2)	0.57	0.9 (0.7, 1.2)	0.58
NT-proBNP quartiles					
1st quartile ≤24.0 pg/ml	17/1265	1.00		1.00	
2nd quartile 24.1–54.5 pg/ml	26/1254	1.0 (0.5, 2.1)	0.93	1.1 (0.53, 2.2)	0.84
3rd quartile 54.51–112.5 pg/ml	25/1246	1.1 (0.5, 2.3)	0.76	1.3 (0.6, 2.6)	0.53
4th quartile >112.5. pg/ml	33/1124	1.4 (0.7, 2.9)	0.39	1.7 (0.8, 3.6)	0.15
NT-proBNP continuous					
Per SD change in Log Unit§		1.1 (0.8, 1.5)	0.45	1.2 (0.9, 1.6)	0.21

ABI=ankle-brachial index, hs-cTnT=high-sensitivty cardiac Troponin T, NT-proBNP=N- terminal brain natriuretic peptide, OR=odds ratio, CI=confidence interval

* The lowest category consists of those participants with concentrations below the LOD (ie, <3 ng/L: category 1), and the remaining distribution of measurable hs-cTnT was divided into 3 categories of equal numbers of participants (categories 2–4). Results of multivariable linear regression models

† Model 1 adjusted for age, sex, race, ethnicity, study site

‡ Model 2 adjusted for Model 1 + body-mass index, diabetes, hypertension, total cholesterol, high-density lipoprotein cholesterol, lipid lowering therapy, smoking, and estimated glomerular filtration rate

§ The standard deviations (SD) for log units of hs-cTnT and NT-proBNP were 0.6 and 1.2 log units, respectively.