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ORIGINAL ARTICLE

Noninvasive Voice Biomarker Is Associated With Incident Coronary Artery Disease Events at Follow-up

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Abstract

Objective: To evaluate the association between a preidentified voice biomarker and incident coronary artery disease (CAD) events.

Methods: Patients referred for clinically indicated coronary angiography underwent a total of three 30-second voice recordings using the *Vocalis* Health smartphone application between January 1, 2015, and February 28, 2017. A pre-established voice biomarker was derived from each individual recording, and the mean biomarker value was calculated for each patient. Individuals were clinically observed through December 31, 2019. The prespecified primary outcome was a composite of presenting to the emergency department with chest pain, being admitted to the hospital with chest pain, or having an acute coronary syndrome; the prespecified secondary outcome was a composite of a positive stress test result at follow-up or the presence of CAD at follow-up coronary angiography.

Results: In the final analysis, 108 patients were included (mean age, 59.47±11.44 years; male, 59 [54.6%]). The median follow-up time was 24 months (range, 1 to 60 months). In multivariable Cox proportional hazards models adjusting for CAD grade on baseline angiography, a high baseline mean voice biomarker was significantly associated with both the primary (hazard ratio, 2.61; 95% CI, 1.42 to 4.80; P=.002) and secondary (hazard ratio, 3.13; 95% CI, 1.13 to 8.68; P=.03) composite outcomes.

Conclusion: This study found a significant association between a noninvasive voice biomarker and incident CAD events at follow-up. These results may have important clinical implications for the remote and noninvasive screening of patients to identify those at risk of coronary disease and its complications.

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Globally, approximately 18 million deaths were attributed to cardiovascular disease (CVD) in 2017, which amounted to an increase of 21.1% from 2007.[1] Between 2013 and 2030, medical costs of coronary artery disease (CAD) are projected to increase by approximately 100%,[2] highlighting an increasing health and socioeconomic problem. Nevertheless, CAD may be preventable,[3] and preventive strategies are cost-effective.[4] Identifying at-risk groups and managing their risk factors form the cornerstone of successful preventive strategies. To date, this has been achieved using multivariable risk prediction algorithms,[5-8] such as the Framingham-based models. These have important shortfalls, however, including the incorporation of only a limited number of so-called traditional CVD risk factors that account for less than 70% of all incident cases of CAD.[9] Whereas alternative nonconventional risk factors, such as computed tomography calcium scoring and measures of endothelial function, account for some of this gap and can provide useful information for risk stratification,[10-12] these tests require additional in-person, often lengthy and costly evaluations. Thus, simple, inexpensive, and noninvasive methods to identify individuals at risk that can be undertaken remotely from health care providers as adjuncts to existing approaches would be of great value.

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Furthermore, non—face-to-face clinical assessments reduce risk of transmission of diseases between patients and providers and are more cost-effective and time-efficient alternatives to face-to-face visits, offering important advantages in resource-poor settings and overburdened health care systems.

Voice signal analysis has been used to derive noninvasive biomarkers that are associated with a variety of different conditions.[13,14] We previously identified a significant association between specific voice characteristics, using feature extraction, and CAD in individuals undergoing clinically indicated coronary angiography,[15] highlighting the potential value of voice analysis in detecting CVD. We extended these observations by demonstrating that a "prespecified voice biomarker" derived using artificial intelligence was associated with increased mortality and rehospitalization in patients with heart failure.[16] Most recently, we reported that the same voice biomarker was associated with hemodynamic indices of pulmonary hypertension obtained invasively during clinically indicated cardiac catheterization.[17] In this study, we aimed to investigate the association of the same voice biomarker used in the aforementioned studies with incident CAD events, hypothesizing that this voice biomarker is associated with future CAD events.

METHODS

Study Population

The study comprises the same population as in our previous study, in which we evaluated the association between voice characteristics, using feature extraction, and CAD at baseline angiography in individuals without previously known CAD.[15] Enrolled participants were referred for coronary angiography for the following indications: elective angiography to evaluate chest pain suggestive of stable ischemic heart disease or a positive stress test result, patients hospitalized with acute coronary syndrome, and patients undergoing clinically indicated preoperative coronary angiography.[15] All participants underwent angiography between January 1, 2015, and February 28, 2017, at Mayo Clinic, Rochester, Minnesota. Exclusion criteria were as follows, as outlined in our previous study: individuals with a known history of CAD or previous coronary intervention, cardiac transplant patients undergoing annual routine coronary angiography, individuals with a current or known history of voice disorder either primary or secondary to neuromuscular disorders or other disease, age younger than 18 years, and pregnancy.[15] The study protocol was approved by the Institutional Review Board at Mayo Clinic, and all patients provided informed consent for participation.[15]

Voice Characteristics

The methods for the evaluation of voice signal characteristics have been described previously.[13,15-17]

Patient Information

An outline and description of baseline characteristics of patients collected for this study have been described previously.[15,17]

Study End Point

Study participants were observed for clinical events through December 31, 2019. The primary study outcome was the composite incidence of the following: presenting to the emergency department with chest pain; admission to the hospital due to chest pain; and diagnosis of unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI), or ST-segment elevation myocardial infarction (STEMI) at follow-up. Presentation to the emergency department with chest pain was defined as patients presenting to the emergency department with chest pain as the principal presenting complaint; admission to the hospital due to chest pain was defined as patients being admitted to the hospital for either at least 24 hours or at least 1 overnight stay in the hospital with chest pain as the principal reason for admission; and UA, NSTEMI, and STEMI were each defined by clinical criteria in accordance with the Fourth Universal Definition of Myocardial Infarction

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(2018).[18] The secondary end point was the composite of objective evidence of stable coronary disease, defined as a positive stress test result for ischemia at follow-up, which included stress electrocardiography, stress echocardiography, and nuclear stress testing, or the presence of CAD as described previously.[15] All stress tests and coronary angiography studies were clinically indicated at the discretion of each study participant's evaluating physician, and the results of each were reported by the operating physician of each test, who was blinded to patient voice data. Both composite outcomes were prespecified before any analyses.

Statistical Analyses

Poor-quality recordings were removed, as were individuals who therefore did not have at least 1 value of the prespecified voice biomarker available for analysis. In a previous study, we reported that there were no significant differences in the association between the voice biomarker and heart failure–related outcomes when the biomarker was derived from individuals asked to read predefined text out loud or when they were asked to describe a positive or a negative experience.[16] Furthermore, we have also found very good agreement, using intraclass correlation coefficient, across distinct voice biomarker values (when each biomarker was derived from the same individual reading predefined text out loud, describing a positive experience, and describing a negative experience) among the entire study population.[17] Thus, in that study, we decided to use the mean voice biomarker value for each patient.[17] We therefore elected to use the same method in this study, and after calculating the intraclass correlation coefficient for the voice biomarkers across all patients, we computed the "mean voice biomarker value" for each patient and used these numbers in our final analyses.

Patients were separated into 3 tertiles, according to the distribution of the mean voice biomarker: T1, corresponding to the lowest tertile of biomarker values; T2, the middle tertile; and T3, the tertile with the highest biomarker values. Patients were then separated into 2 groups, high biomarker (T3) vs low biomarker (T1 and T2) values. Clinical characteristics, including the incidence of the primary and secondary composite outcomes, were then compared across groups. As previously described, data are presented as a mean ± standard deviation for normally distributed continuous variables and as frequency (percentage) for categorical variables.[15,17] Normal distribution and equal variance were checked by the Shapiro-Wilk test and Levene test, respectively, for each variable. Continuous variables were compared between the groups using Student *t*-test, and categorical variables were compared using the χ^2 test. The probability of each of the 2 composite outcomes according to the 2 voice biomarker groups was graphically displayed using the Kaplan-Meier method, and the cumulative event-free survival was compared between groups using the log-rank test. Cox proportional hazards regression modeling was used to determine the hazard ratio (HR) separately for each of the 2 composite outcomes using the voice biomarker as a dichotomous variable (T3 vs T1 and T2) with the low biomarker group as the reference and as a continuous variable. The multivariable Cox proportional hazards model was adjusted for the grade of CAD on the baseline coronary angiogram. For all analyses, the type I error rate was .05 in a 2-sided test, and *P* values and CIs were calculated and presented at the 95% CI. The statistical analyses were performed using JMP 9 software[15,17] (SAS Institute).

RESULTS

Study Population and Baseline Characteristics

The initial study population included a total of 117 participants who underwent baseline coronary angiography between January 1, 2015, and February 28, 2017. Of these, 8 were excluded for having coronary angiography as part of routine follow-up care after cardiac transplant, and another patient was excluded for not having at least 1

high-quality voice recording available for analysis. Thus, the final study sample consisted of 108 patients, of whom 61 (56.5%) had stable angina, 16 (14.8%) had an acute coronary syndrome, and 31 (28.7% of total) were being evaluated preoperatively as the indication for baseline angiography. Table 1 summarizes the baseline characteristics of the 108 patients in the final study sample. The intracorrelation coefficient value for baseline biomarker values across all available recordings for R1, R2, and R3 among all study participants included in the final analysis was 0.82 (95% CI, 0.75 to 0.88), implying very good agreement. Across all 108 patients, the median (Q1 to Q3) average voice biomarker was 0.0675 (−0.3523 to 0.5217). Patients were divided into those with a high voice biomarker value (T3, biomarker >0.5217) and those with a low biomarker value (T1 and T2, biomarker ≤0.5217).

Follow-up CAD-Related Events

Follow-up information was collected through December 31, 2019, and the median (range) follow-up time was 24 months (1 to 60 months). Overall, 43 (39.8%) patients had the composite primary outcome at follow-up, and 15 (13.8%) patients had the composite secondary outcome. Seventeen patients (15.7%) underwent clinically indicated follow-up coronary angiography. In taking each follow-up clinical outcome individually, 35 (32.4%) participants presented to the emergency department with chest pain, 12 (11.1%) were admitted to the hospital with chest pain, 4 (3.7%) had UA, 1 (1.0%) had NSTEMI, and 0 had STEMI. Thirteen (76.5% of those who underwent follow-up coronary angiography and 12.0% of all study participants) had CAD on follow-up angiography, and 10 (9.3%) had at least 1 positive noninvasive stress test result at follow-up, of which 3 (2.8%) had an abnormality detected on nuclear medicine testing, 5 (4.6%) had an abnormal stress echocardiography recording, and 6 (5.6%) had an abnormal stress electrocardiography recording.

In a post hoc analysis, there were no significant differences in the value or frequency of the following established baseline risk factors and markers for CAD in those who had either the composite primary or secondary outcome: age, male sex, hypertension, diabetes mellitus, hyperlipidemia, smoking status, family history of CAD, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, and 10-year risk of CVD. At baseline coronary angiography, there was a significantly higher proportion of patients with grade 3 disease who had the composite secondary outcome compared with those who did not have the composite secondary outcome. This difference was not observed for the composite primary outcome (Supplemental Table 1, available online at http://www.mayoclinicproceedings.org).

Relationship Between Baseline Voice Biomarker and Follow-up CAD-Related Events

Patients with a high mean voice biomarker value at baseline had a significantly higher frequency of the primary composite end point compared with those with a low mean voice biomarker value at baseline (21 [58.3%] vs 22 [30.6%]; P=.006). However, patients with a high mean voice biomarker value at baseline had a similar frequency of the secondary composite end point compared with those with a low mean voice biomarker value at baseline (8 [22.2%] vs 7 [9.7%]; P=.08). Similarly, the frequency of undergoing clinically indicated follow-up coronary angiography in patients with a high compared with a low voice biomarker value at baseline was not different (8 [22.2%] vs 9 [12.5%]; P=.20).

Figure 1 shows the Kaplan-Meier survival analysis curves for the primary composite end point across the groups, demonstrating that the cumulative probability for development of the primary composite outcome was higher among patients with a high mean voice biomarker value at baseline (log-rank test, P=.001). In a univariable Cox proportional hazards ratio model using the mean voice biomarker as a categorical variable (T3 compared with

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TABLE 1. Baseline Characteristics of the Study Cohort[a,b,c]

	All (N=108)	Lower voice biomarker, T1 and T2 (n=72)	Higher voice biomarker, T3 (n=36)	*P* value
Age (y)	59.47±11.44	61.38±9.89	55.71±13.41	.03[d]
Male	59 (54.6)	47 (65.3)	12 (33.3)	.002[d]
Hypertension	48 (44.4)	36 (50.0)	12 (33.3)	>.99
Diabetes mellitus	15 (13.9)	10 (13.9)	5 (13.9)	>.99
Hyperlipidemia	45 (41.7)	31 (43.1)	14 (38.9)	.68
BMI (kg/m^2)	29.94 (26.40-33.76)	29.91 (27.16-33.66)	30.77 (25.03-35.69)	.68
Current smoker	13 (12.2)	10 (13.89)	3 (8.57)	.42
Obstructive sleep apnea	28 (25.9)	17 (23.61)	11 (30.56)	.44
Family history of coronary artery disease	76 (70.4)	49 (68.06)	27 (75.00)	.45
Hemoglobin (g/dL)	13.46±1.99	13.96±1.55	12.45±2.38	.001[d]
Creatinine (mg/dL)	1.09±1.10	1.16±1.33	0.97±0.31	.27
Total cholesterol (mg/dL)	180.31±41.14	184.28±41.66	172.61±39.59	.18
HDL cholesterol (mg/dL)	53.71±22.07	53.92±22.09	53.30±22.35	.99
LDL cholesterol (mg/dL)	100.92±34.0	102.59±34.05	97.96±34.38	.61
Triglycerides (mg/dL)	130.75±86.21	145.02±94.93	104.70±61.07	.04[d]
10-year risk of cardiovascular disease (%)	11.45±11.51	12.57±10.77	9.17±12.77	.21
Unstable angina	6 (5.6)	5 (6.94)	1 (2.78)	.35
NSTEMI	3 (2.8)	2 (2.78)	1 (2.78)	>.99
CAD on baseline coronary angiography				.07
Normal	34 (31.5)	17 (23.61)	17 (47.22)	
Mild	33 (30.5)	25 (34.72)	8 (22.22)	
Moderate	12 (11.1)	10 (13.89)	2 (5.56)	
Severe	29 (26.9)	20 (27.78)	9 (25.00)	
Individuals who had PCI	20 (18.5)	13 (18.06)	7 (19.44)	.86
No. of coronary vessels with disease				.51
0	58 (53.7)	35 (48.61)	23 (63.89)	
1	20 (18.5)	15 (30.83)	5 (13.89)	
2	19 (17.6)	14 (19.44)	5 (13.89)	
3	11 (10.2)	8 (11.11)	3 (8.33)	
Grade of CAD				.08
0	34 (31.5)	17 (23.61)	17 (47.22)	
1	34 (31.5)	26 (36.11)	8 (22.22)	
2	11 (10.2)	9 (12.50)	2 (5.56)	
3	29 (26.9)	20 (27.78)	9 (25.00)	

[a]BMI, body mass index; CAD, coronary artery disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention.

[b]SI conversion factors: To convert hemoglobin values to g/L, multiply by 10; to convert creatinine values to μmol/L, multiply by 88.4; to convert LDL, HDL, and total cholesterol values to mmol/L, multiply by 0.0259; to convert triglyceride values to mmol/L, multiply by 0.0113.

[c]Categorical variables are presented as number (percentage). Continuous variables are presented as mean ± standard deviation or median (Q1-Q3).

[d]Statistically significant.

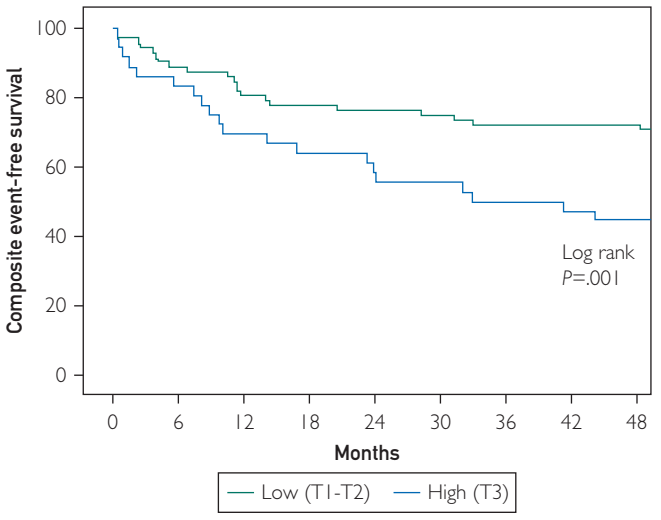

FIGURE 1. Kaplan-Meier survival analysis curves showing the composite event-free survival for the primary composite outcome of patients with a high (T3) compared with a low (T1 and T2) baseline mean voice biomarker value.

T1 and T2), a high mean voice biomarker value at baseline was significantly associated with the primary composite outcome (Table 2). This association remained significant after adjustment for CAD grade at baseline coronary angiography (HR, 2.61; 95% CI, 1.42 to 4.80; *P*=.002; Table 2). Similarly, the mean voice biomarker as a continuous variable was significantly associated with the primary composite outcome both in a univariable model (Table 2) and after adjustment for CAD grade at baseline coronary angiography (HR, 1.73; 95% CI, 1.18 to 2.52; *P*=.005; Table 2).

Figure 2 shows the Kaplan-Meier survival curves for the secondary composite end point across the 2 groups (log-rank test, *P*=.08). In a univariable Cox proportional hazards ratio

TABLE 2. Univariable and Multivariable Cox Proportional Hazards Ratios for the Associations Between the Mean Voice Biomarker as a Categorical Variable and as a Continuous Variable and the Primary Composite Outcome[a]

	Hazard ratio	95% CI	*P* value
Univariable, as categorical variable			
High mean voice biomarker (T3 vs T1 and T2)	2.29	1.26-4.17	.007[b]
Multivariable, as categorical variable			
High mean voice biomarker (T3 vs T1 and T2)	2.61	1.42-4.80	.002[b]
CAD grade on baseline angiography (0-3)	1.36	1.06-1.74	.02[b]
Univariable, as continuous variable			
Mean voice biomarker	1.68	1.14-2.49	.01[b]
Multivariable, as continuous variable			
Mean voice biomarker	1.73	1.18-2.52	.005[b]
CAD grade on baseline angiography (0-3)	1.33	1.03-1.71	.03[b]

[a]CAD, coronary artery disease.
[b]Statistically significant.

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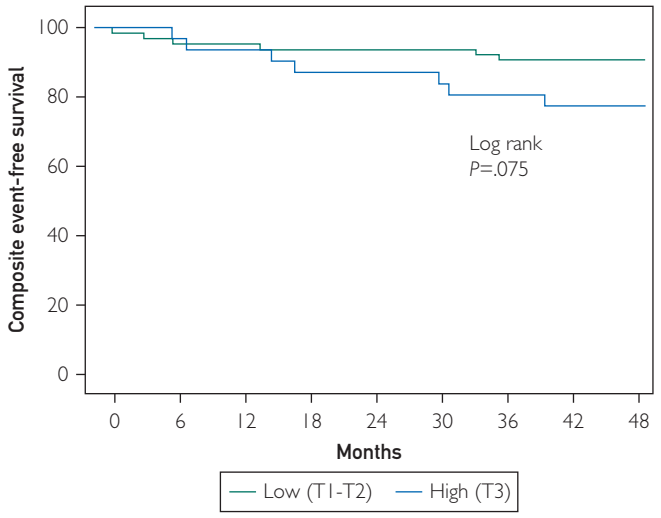

FIGURE 2. Kaplan-Meier survival analysis curves showing the composite event-free survival for the secondary composite outcome of patients with a high (T3) compared with a low (T1 and T2) baseline mean voice biomarker value.

model using the mean voice biomarker as a categorical variable (T3 compared with T1 and T2), a high mean voice biomarker value at baseline was not associated with the secondary composite outcome (Table 3). However, after adjustment for CAD grade at baseline coronary angiography, there was a significant association between a high mean voice biomarker value at baseline and the secondary composite outcome (HR, 3.13; 95% CI, 1.13 to 8.68; *P*=.03; Table 3). The mean voice biomarker as a continuous variable was not associated with the secondary composite outcome in a univariable model (Table 3). After adjustment for CAD grade at baseline coronary angiography, the mean voice biomarker was not associated with the secondary composite outcome (HR, 1.66; 95% CI, 0.96 to 2.90; *P*=.07; Table 3).

TABLE 3. Univariable and Multivariable Cox Proportional Hazards Ratios for the Associations Between the Mean Voice Biomarker as a Categorical Variable and as a Continuous Variable and the Secondary Composite Outcome[a]

	Hazard ratio	95% CI	*P* value
Univariable, as categorical variable			
High mean voice biomarker (T3 vs T1 and T2)	2.44	0.89-6.74	.08
Multivariable, as categorical variable			
High mean voice biomarker (T3 vs T1 and T2)	3.13	1.13-8.68	.03[b]
CAD grade on baseline angiography (0-3)	2.79	1.62-4.81	<.001[b]
Univariable, as continuous variable			
Mean voice biomarker	1.58	0.83-3.00	.17
Multivariable, as continuous variable			
Mean voice biomarker	1.66	0.96-2.90	.07
CAD grade on baseline angiography (0-3)	2.83	1.61-4.97	<.001[b]

[a]CAD, coronary artery disease.
[b]Statistically significant.

Given that age and sex varied significantly for individuals with a high compared with a low mean voice biomarker value, we undertook additional post hoc multivariable analyses as follows. With regard to the primary composite outcome (n=43), after adjustment for age, sex, and grade of CAD at baseline, having a high mean voice biomarker was associated with a significantly increased risk for development of the primary composite outcome (HR, 2.49; 95% CI, 1.28 to 4.86; *P*=.007). Grade of CAD was also associated with the primary composite outcome (HR, 1.36; 95% CI, 1.05 to 1.76; *P*=.02). Neither age nor sex was significantly associated with the primary composite outcome in this model. With regard to the secondary composite (n=15), we were underpowered to adjust for both age and sex as well as for grade of CAD. Thus, instead we elected to adjust for the 10-year predicted risk as it integrates age and sex as well as other conventional CVD risk factors, such as blood pressure, cholesterol concentration, and smoking status, into a single score. However, we were able to undertake this analysis only in 94 patients as the remaining 14 did not have complete data available to calculate the complete 10-year predicted score. In this analysis, a high mean voice biomarker was not significantly associated with the composite secondary outcome (HR, 3.09; 95% CI, 0.92 to 10.4; *P*=.07). Grade of CAD was associated with the secondary composite outcome (HR, 3.02; 95% CI, 1.61 to 5.65; *P*=.001). The 10-year predicted risk was not significantly associated with the composite secondary outcome.

Changes in Vocal Biomarker at Follow-up

In a post hoc exploratory analysis, we evaluated whether the mean biomarker values changed significantly from baseline to follow-up in a variety of clinical scenarios associated with changes in test results over time or with a clinical intervention such as percutaneous coronary intervention. All included study participants underwent follow-up voice recordings at 6 months ± 2 weeks from the time of baseline angiography in the same manner as for the baseline recordings, and if a patient had 1 or more values recorded, the mean of all values was used. This resulted in a maximum of 1 follow-up value per patient, which was not considered time dependent. For patients who had percutaneous coronary intervention at baseline coronary angiography (n=20), the mean biomarker did not change significantly from baseline to follow-up (0.383±1.26 vs −0.152±0.917; *P*=.10). Among patients who had baseline CAD on coronary angiography but who did not have CAD at follow-up angiography (n=25), the mean biomarker did not change significantly from baseline to follow-up (−0.069±0.55 vs −0.080±0.64; *P*=.94). Among patients who had a baseline negative result of a noninvasive stress test and a positive result of a follow-up stress test (n=4), the mean biomarker did not change significantly across time from baseline to follow-up (1.200±0.947 vs 0.622±0.864; *P*=.25). Last, among patients who had a positive result of a noninvasive stress test at baseline and a negative result of a stress test at follow-up (n=17), the biomarker did not change across time (−0.284±0.443 vs −0.266±0.435; *P*=.88).

DISCUSSION

Summary of Findings

In this study, we report, for the first time, a significant association between a noninvasive voice biomarker and incident CAD events. Specifically, we found that a high compared with a low mean voice biomarker value at baseline was significantly associated with our primary composite outcome of presentation to the emergency department with chest pain, admission to the hospital with chest pain, or a diagnosis of acute coronary syndrome at follow-up. In addition, we found that a high mean voice biomarker value at baseline was significantly associated with our secondary composite outcome of CAD at follow-up established by clinically indicated coronary angiography or a positive stress test result at follow-up. These associations were significant after adjustment for CAD grade at baseline angiography and

when using the mean voice biomarker at baseline as a continuous variable, albeit with borderline significance with the secondary outcome. Thus, the study supports the potential role for voice signal analysis to identify patients at risk of incident coronary disease—related events.

Potential Mechanism Underlying the Relationship Between Voice Signal Analysis and Coronary Disease Events

Voice signal analysis has been used to derive noninvasive biomarkers that are associated with a variety of different conditions, including Parkinson disease.[13,14] We previously identified a significant association between specific vocal features and CAD in a sample of individuals referred for coronary angiography.[15] We also found that a voice biomarker derived using artificial intelligence was associated with increased mortality and rehospitalization in patients with heart failure.[16] We then extended these findings in a recent study reporting that the same prespecified voice biomarker was associated with invasively derived hemodynamic indices of pulmonary hypertension.[17] In this study, we further develop our findings in this area by showing that the same prespecified voice biomarker is also associated with CAD events at follow-up. These coronary disease—related events included both "unstable" events, characterized by the composite of presentation to the emergency department at follow-up with chest pain, admission to the hospital with chest pain, or a diagnosis of acute coronary syndrome, as well as "stable" events, characterized by the composite of coronary disease at follow-up coronary angiography or a positive noninvasive stress test result at follow-up.

Coronary artery disease and its complications are underpinned by systemic inflammatory processes such as endothelial dysfunction and atherosclerosis.[19] Consequently, CAD often coexists with systemic atherosclerotic disease in other vascular beds, leading to macrovascular disease, such as stroke and peripheral vascular disease, or microvascular disease, such as retinopathy, chronic kidney disease, and neuropathy. Thus, our previous findings that voice signal characteristics are associated with CAD[15] and our current findings of the association between a voice biomarker and incident CAD-related events could relate to the systemic nature of atherosclerosis and inflammation, with concomitant (and well-known) effects on the blood vessels of the heart as well as (less well known) effects on the blood vessels perfusing organs of phonation. Interestingly, in post hoc analyses evaluating for temporal changes in the voice biomarker from baseline to follow-up in subsets of patients, there was no significant change in the biomarker across time. This finding suggests that CAD or aberrations in the vascular biology of the coronary bed may not be the sole mechanism accounting for the observed associations seen in this study. Rather, it could be speculated that the voice biomarker instead portends a more global and integrated index of health and well-being, which in turn provides insight into the presence and effects of systemic pathologic processes, such as heightened inflammation or vascular disease.

Moreover, the vagus nerve plays an important role in voice production while also forming a central part of cardiac autonomic regulation. In fact, vagal activity is tightly coupled with heart rate control and variability, which are in turn associated with CAD[20] and CVD events.[21] It is conceivable, therefore, that the joining of voice signal characteristics with CVD could be neurally mediated either directly or indirectly through the risk and manifestation of CAD and its related events. Indeed, ischemia is associated with a constellation of local cardiac and circulatory pathophysiologic changes that are influenced by the upregulation of the autonomic nervous system and manifested as changes in heart rate and blood pressure as well as symptoms of diaphoresis, nausea, and shortness of breath. Thus, alterations in the functioning of the adrenergic nervous system are anticipated in patients presenting with CAD and its complications. The various manifestations of CAD, including occlusive coronary disease on angiography, ischemia on stress

testing, significant chest pain, and acute coronary syndromes, may therefore correspond with vocal changes captured using voice signal analysis as both are underpinned, at least in part, by alterations in the adrenergic nervous system. In this way, it is possible that our voice analysis technology indirectly interrogates the "state" of the autonomic nervous system while providing a means of identifying those at increased risk of CVD. This hypothesis will require further investigation. Indeed, we did not assess the potential mechanisms underpinning the observed associations seen in this study, and further studies that more precisely characterize the biologic link between voice signal and CVD would be of great value.

Clinical Implications

The study finds an association between a voice biomarker that can be obtained noninvasively and remotely and incident coronary disease events at follow-up. To date, managing risk of CAD in the primary and secondary prevention settings is most effectively achieved by identifying at-risk groups using multivariable risk prediction algorithms,[5-8] such as the Framingham-based models, the American College of Cardiology/American Heart Association atherosclerotic cardiovascular disease (ASCVD) risk equation, and the Systematic Coronary Risk Evaluation (SCORE) model.[22-24] Although these models are well established, they have several limitations. First, such scores have limited utility in specific subsets of individuals, including asymptomatic patients with preclinical atherosclerosis, sedentary patients, and those with inflammatory disorders,[24] and the Framingham-based risk score in particular discriminates risk poorly in the secondary prevention setting.[25] Second, these risk scores incorporate only a few so-called traditional CVD risk factors, such as hypertension and smoking status, that account for less than 70% of all incident cases of CAD.[9] Third, whereas alternative nonconventional risk factors, such as circulating biomarkers, calcium scoring, and measures of endothelial function, may account for some of this gap and provide useful information for risk stratification,[10-12] these tests require additional in-person, often lengthy and costly evaluations. Thus, this study supports the potential role of evaluating patients remotely from health care providers using voice signal analysis to identify those at risk for future CAD events as an adjunct to existing approaches. Non—face-to-face clinical assessments reduce risk of transmission of diseases between patients and providers and offer more cost-effective and time-efficient alternatives to face-to-face visits. Such a strategy could form a simple, inexpensive, noninvasive means of identifying patients at increased risk who may therefore benefit from in-person assessments, preventive counseling, and, where appropriate, preventive pharmacotherapy. More generally, voice signal analysis together with other advances in telecommunication technologies could be used as an adjunct in the medical management of patients with CVD, offering promise to overburdened health care systems.

Supplemental Table 2 (available online at http://www.mayoclinicproceedings.org) shows the clinical profile of all patients in this study who had a high baseline voice biomarker value (in the upper tertile) and who also had a low 10-year predicted risk of ASCVD (<10%), implying potential voice biomarker "false positives." We identified 36 individuals with a high voice biomarker value, of whom 23 also had a low 10-year predicted risk of ASCVD. Among individuals with a high voice biomarker value and a low ASCVD risk score, 6 (26.1%) developed the prespecified primary composite outcome (composite of presenting to the emergency department with chest pain, being admitted to the hospital with chest pain, or having an acute coronary syndrome) and 10 (38.5%) developed the prespecified secondary outcome (composite of a positive stress test result at follow-up or the presence of CAD at follow-up coronary angiography). For CAD at follow-up, only 6 individuals in this group (26.1%) had follow-up coronary angiography, of whom 2 had grade 0 disease, 1 had grade 1 disease, 1 had grade 2 disease, and 2 had grade 3 disease. In addition,

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8 individuals (34.8%) had a stress test at follow-up; 3 had a positive result. Fifteen patients (65.2%) had echocardiography at follow-up that showed a mean ejection fraction of 63.1% (range, 53% to 73%). It is challenging to draw firm conclusions on the frequency of voice biomarker–related false-positive results, given the small sample sizes here, and further studies are required to clarify the predictive accuracy of the voice biomarker.

Study Limitations

This study has a number of limitations. First, the study included a relatively small and largely homogeneous population referred to a tertiary referral center for evaluation. Future studies will therefore be required in larger and more diverse populations who are being evaluated in a variety of different health care settings. Larger studies will also help in determining the incremental value that the voice biomarker may be able to provide in risk stratification. Second, Supplemental Table 2 demonstrates that the risk profiles, based on the 10-year predicted risk of CVD, between patients who developed and those who did not develop the composite primary or secondary outcome were similar. Whereas we may therefore assume that medical therapy and the intensity of risk preventive efforts may be similar between patients who developed incident CAD events and those who did not develop incident CAD events at follow-up, this study is limited by not including and comparing differences in drug treatment across groups. Last, in this study, all recordings were undertaken using a single study iPad, and all were performed in the English language. Future studies making use of recordings performed with different types of devices and with individuals speaking different languages would be valuable to determine whether there are any changes in the accuracy or reliability of the artificial intelligence–derived voice biomarker in predicting incident CAD events.

CONCLUSION

This study found a significant association between a preidentified voice biomarker and incident CAD events at follow-up. These results demonstrate the potential utility of using voice signal analysis as an adjunct to existing approaches to remotely and noninvasively identify patients at risk of CAD events who may benefit from more aggressive screening and risk preventive strategies.

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SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **ASCVD,** atherosclerotic cardiovascular disease; **CAD,** coronary artery disease; **CVD,** cardiovascular disease; **NSTEMI,** non-ST-segment elevation myocardial infarction; **STEMI,** ST-segment elevation myocardial infarction; **UA,** unstable angina

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