Reflection Magnitude as a Predictor of Mortality

The Multi-Ethnic Study of Atherosclerosis


See Editorial Commentary, pp 929–930

Abstract—Arterial wave reflections have been associated with mortality in an ethnically homogenous Asian population. It is unknown whether this association is present in a multiethnic population or whether it is independent of subclinical atherosclerosis. We hypothesized that reflection magnitude (defined as the ratio of the amplitude of the backward wave \([P_b]\) to that of the forward wave \([P_f]\)) is associated with all-cause mortality in a large multiethnic adult community-based sample. We studied 5984 participants enrolled in the Multi-Ethnic Study of Atherosclerosis who had analyzable arterial tonometry waveforms. During 9.8±1.7 years of follow-up, 617 deaths occurred, of which 134 (22%) were adjudicated cardiovascular deaths. In Cox proportional hazards models, each 10% increase in reflection magnitude was associated with a 31% increased risk for all-cause mortality (hazard ratio [HR]=1.31; 95% confidence interval [CI]=1.11–1.55; \(P=0.001\)). This relationship persisted after adjustment for various confounders and for markers of subclinical atherosclerosis (HR=1.23; 95% CI=1.01–1.51; \(P=0.04\)), including the coronary calcium score, ankle–brachial index, common carotid intima–media thickness, and ascending thoracic aortic Agatston score. \(P_b\) was independently associated with all-cause mortality in a similarly adjusted model (HR per 10 mm Hg increase in \(P_b\)=2.18; 95% CI=1.21–3.92; \(P=0.009\)). Reflection magnitude (HR=1.71; 95% CI=1.06–2.77; \(P=0.03\)) and \(P_b\) (HR=5.02; 95% CI=1.29–19.42; \(P=0.02\)) were mainly associated with cardiovascular mortality. In conclusion, reflection magnitude is independently associated with all-cause mortality in a multiethnic population initially free of clinically evident cardiovascular disease. This relationship persists after adjustment for a comprehensive set of markers of subclinical atherosclerosis. (Hypertension. 2014;64:958-964.) ● Online Data Supplement

Key Words: arteries ■ atherosclerosis ■ mortality

As the pulse wave generated by the left ventricle travels away from the heart, it is partially reflected because of interactions with the elastic and muscular arteries, generating multiple reflected waves that travel back toward the heart. These waves arise at multiple sites in the arterial tree, where changes in geometry and stiffness occur, thus being influenced by arterial properties. Reflected waves summate in transit and form a composite wave. When this wave arrives back at the left ventricle during late systole, it increases ventricular afterload and has been shown to adversely impact left ventricular remodeling, as well as systolic and diastolic function. We have recently shown that reflection magnitude (RM), defined as the ratio of the amplitude of the backward wave to that of the forward wave, is strongly predictive of incident heart failure and is also predictive of a combined end point of cardiovascular events.

Wang et al recently used a triangular-flow approach in a homogeneous population and demonstrated that the amplitude of the backward wave (\(P_b\)) was predictive of both cardiovascular and all-cause mortality in men and women. However, it is unknown whether this relationship is independent of atherosclerotic disease at baseline or the occurrence of incident heart failure. Furthermore, the study by Wang et al enrolled only Asian participants.
In this study, we tested the hypothesis that RM is a predictor of all-cause mortality in a multiethnic sample free of clinically evident cardiovascular disease at baseline and that such a relationship is independent of subclinical atherosclerosis or clinical manifestations of heart failure in a multiethnic sample.

Methods

Study Population
The Multi-Ethnic Study of Atherosclerosis (MESA) enrolled 6814 men and women aged 45 to 84 years from 6 centers across the United States to ensure inclusion of subjects from diverse ethnic backgrounds. Subjects self-reported their ethnicity as black, Asian American (predominantly Chinese), white, or Hispanic. All subjects were free of cardiovascular disease by self-report at the time of inclusion. Subjects were enrolled between 2000 and 2002 and contacted every 9 to 12 months for assessment of clinical end points. All subjects were followed through December 31, 2011. Information was collected from death certificates, hospital medical records, and autopsy reports. In the case of out-of-hospital deaths, interviews or questionnaires were administered to physicians, relatives, or friends.17 Follow-up telephone interviews were completed in 92% of living participants, and medical records were obtained for 98% of hospital admissions.18 The study was approved by the institutional review boards of participating centers, and all participants signed informed consent.

Event Adjudication
Trained personnel abstracted data from the medical record to ascertain cardiovascular events. Cardiovascular and noncardiovascular deaths were then adjudicated by a MESA study committee using standardized definitions (the reader is referred to the web appendix for reference 19). Cardiovascular deaths include death from atherosclerotic coronary heart disease (fatal myocardial infarction), stroke, deaths from vascular aneurysms, death because of valvular heart disease, death because of congestive heart failure resulting in shock or low output states, death after a cardiac procedure such as coronary revascularization, or death because of pulmonary embolism. If none of the above causes were determined, or a strong history of another likely cause of death was present, deaths were coded as noncardiovascular. For noncardiovascular deaths, city or state records were sought to determine the underlying cause.

Data Collection
Standardized questionnaires were administered at the time of enrollment. Resting blood pressure was obtained in the right arm in triplicate after resting for 5 minutes in the seated position. An automated oscillometric device (Dinamap-Pro100, GE Medical Systems, Waukesha, WI) was used to obtain the readings, with the second and third readings averaged to obtain the recorded pressure. Serum cholesterol and C-reactive protein levels were obtained after a 12-hour fast.18 Coronary artery calcium was measured using computed tomography and referenced to a phantom of known calcium concentration that was included in the field of view. Each participant was scanned twice to determine the average phantom-adjusted Agatston score.20 During these scans, calcification within the thoracic aorta was also measured and quantified as coronary artery calcium.21 The ankle–brachial index (ABI) was determined for each lower extremity using a hand-held Doppler probe. The numerator was set as the higher of the 2 pressures between the dorsalis pedis and posterior tibial arteries for each leg. The denominator was the higher brachial artery pressure between both arms. The lower ABI of the 2 lower extremities was recorded for each patient.22,23

Statistical Methods
Baseline characteristics of the cohort are presented as means±SD or as medians with interquartile ranges as appropriate. The cohort was divided into quintiles based on RM and Pf. Kaplan–Meier mortality curves were generated and assessed using the log-rank test. We used Cox proportional hazards modeling to assess the relationship between RM and mortality. Unadjusted Cox proportional hazards models were built to assess the risk increase for all-cause mortality, cardiovascular mortality, and noncardiovascular mortality per 10% change in RM. Additional models were then constructed with increasing adjustments for potential confounders. In addition, we built models that adjusted for the presence of subclinical atherosclerosis, assessed by a combination of atherosclerotic markers in different vascular territories (coronary calcium score, ABI, common carotid IMT, and ascending aortic Agatston score). To assess whether the association between RM and death was independent of incident heart failure, we built models that censored participants at the time of the first heart failure event, thereby predicting only those individuals whose death was not preceded by clinical heart failure. Analogous models were also constructed for the absolute magnitude of the forward (Pf) and backward (Pb) waves. Variables that were not normally distributed were log-transformed before entering the models if a multiplicative relationship with mortality was present. A 2-tailed type I error rate of ≤0.05 was considered to be statistically significant. Statistical analyses were performed using STATA 13 (StataCorp, College Station, TX).

Results
Baseline demographic, laboratory, anthropomorphic, and clinical data of our sample are presented in Table 1. Of 6336 participants who underwent radial tonometry, 5989 cases had reliable data for RM computations. Follow-up information on...
Markers of subclinical atherosclerosis

NT-pro-BNP, pg/mL, median (IQR) 52.64 (23.39, 109.1)
C-reactive protein, mg/L, median (IQR) 1.88 (0.82, 4.19)
Urine albumin, g/creatinine, mg ratio, median (IQR) 5.3 (3.3, 10.9)

Committee; LDL, low-density lipoprotein; and NT-pro-BNP, NT-probrain rate; HDL, high-density lipoprotein; IQR, interquartile range; JNC, Joint National Committee; BMI, body mass index; BP, blood pressure; GFR, glomerular filtration rate; HDL, high-density lipoprotein; IQR, interquartile range; JNC, Joint National Committee; LDL, low-density lipoprotein; and NT-pro-BNP, NT-probrain natriuretic peptide.

vital status was missing in 5 subjects, leaving a final cohort size of 5984 subjects. Subjects were followed for a mean of 9.8±1.7 years (range: 62 days–11.5 years). A total of 617 deaths occurred over the follow-up period, of which 134 (22%) were adjudicated cardiovascular deaths and 460 (75%) were noncardiovascular (n=327); 23 (4%) deaths were of unknown cause. Further information about cause of death can be found in the table in the online-only Data Supplement (Table S1 in the online-only Data Supplement). Four thousand nine hundred forty-six subjects (83% of the subjects included in these analyses) had a baseline determination of NT-pro-BNP.

RM and Mortality

Kaplan–Meier mortality curves for participants in each of the RM quintiles are shown in Figure 1. Mortality was significantly different among the 5 groups (Figure 1; log-rank test P=0.01).

Results of proportional hazards models for RM are shown in Table 2. In unadjusted analysis (model 1), each 10% increase in RM was associated with a 31% increase in the risk of all-cause mortality (hazard ratio [HR]=1.31; 95% confidence interval [CI]=1.11–1.55; P=0.001). This was not affected by adjustment for heart rate (model 2). Similarly, after additional adjustment for demographic, clinical, laboratory data, and markers of subclinical atherosclerosis (model 4), including ABI, maximum common carotid IMT, coronary calcium Agatston score, ascending aortic Agatston calcium score, RM remained independently associated with all-cause mortality (HR=1.23; 95% CI=1.01–1.51; P=0.04). Finally, adjustment was made for NT-pro-BNP in the subset of subjects who had levels drawn at baseline (model 5). In this model, which included only 4005 subjects, the HR for RM did not change appreciably, although the P value was not nominally significant (HR=1.22; 95% CI=0.98–1.52; P=0.07).

Associations between RM and cardiovascular and noncardiovascular deaths are also shown in Table 2. Although the number of events was small (134 cardiovascular deaths, 460 noncardiovascular deaths), RM was independently associated with cardiovascular mortality in the adjusted models. No significant relationship between RM and noncardiovascular mortality persisted after adjustments.

Pb Versus Pf and Mortality

Table 3 presents various models in which the backward (Pb) and forward (Pf) waves were included as separate terms as predictors of all-cause mortality. HR are expressed for each 10 mm Hg increase in the amplitude of Pb and Pf. In unadjusted analyses, each 10 mm Hg increase in Pb amplitude resulted in more than a doubling of the risk for all-cause mortality (model 1, HR=2.02; 95% CI=1.27–3.22; P=0.003). Pb was independently predictive of all-cause death when subsequent adjustments were performed for heart rate (model 2, HR=2.42; 95% CI=1.51–3.87; P<0.001), clinical, demographic, and laboratory data (model 3, HR=1.81; 95% CI=1.03–3.16; P=0.04), and markers of subclinical atherosclerosis (model 4, HR=2.18; 95% CI=1.21–3.92; P=0.009). In the subgroup of subjects who had NT-pro-BNP drawn, Pb continued to be independently predictive of all-cause mortality in the fully adjusted model (model 5, HR=2.03, 95% CI=1.08–3.81; P=0.03). Importantly, in this model, Pf demonstrated a negative relationship with mortality risk (HR=0.55; 95% CI=0.32–0.93; P=0.03), indicating that it is the difference between Pb and Pf that is primarily related to mortality. Figure 2 shows mortality curves based on quintiles of Pb; mortality rates were significantly different between groups (P<0.0001).

Models were also created for cardiovascular and noncardiovascular mortality (Table 3). Each 10 mm Hg increase
in $P_b$ amplitude was associated with an increased risk for cardiovascular mortality (model 5, HR=5.02; 95% CI=1.29–19.42; $P=0.02$). Interestingly, a relationship between $P_b$ and noncardiovascular mortality was also evident, although nonsignificant in some of the adjusted models.

### Table 2. Hazard Ratios and Confidence Intervals for Each 10% Increase in Reflection Magnitude and Death in Unadjusted and Adjusted Models

<table>
<thead>
<tr>
<th>Model</th>
<th>All-Cause Mortality (617 Deaths)</th>
<th>Cardiovascular Mortality (134 Deaths)</th>
<th>Noncardiovascular Mortality (460 Deaths)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio</td>
<td>Confidence Interval</td>
<td>$P$ Value</td>
</tr>
<tr>
<td>Model 1*</td>
<td>1.31</td>
<td>1.11–1.55</td>
<td>0.001</td>
</tr>
<tr>
<td>Model 2†</td>
<td>1.32</td>
<td>1.12–1.56</td>
<td>0.001</td>
</tr>
<tr>
<td>Model 3‡</td>
<td>1.18</td>
<td>0.97–1.44</td>
<td>0.09</td>
</tr>
<tr>
<td>Model 4§</td>
<td>1.23</td>
<td>1.01–1.51</td>
<td>0.04</td>
</tr>
<tr>
<td>Model 5║</td>
<td>1.22</td>
<td>0.98–1.52</td>
<td>0.07</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; HDL, high-density lipoprotein; and LDL, low-density lipoprotein.

*Model 1–unadjusted (n=5984, 617 total deaths).
†Model 2–adjusted for heart rate (n=5984, 617 total deaths).
‡Model 3–model 2+adjustment for age, sex, ethnicity, systolic and diastolic blood pressure, estimated glomerular filtration rate, urinary albumin/creatinine ratio, total cholesterol, LDL cholesterol, HDL cholesterol, treatment with antihypertensive medications, treatment with statins, current smoking status, BMI, family history of myocardial infarction, diabetes mellitus, C-reactive protein, highest level of education, family income, alcohol use, total calories per day, percent of calories from fat, and physical activity (n=4825, total 473 deaths).
§Model 4–model 3+adjustment for ankle–brachial index, maximum common carotid intima–media thickness, mean phantom-adjusted Agatston coronary calcium score, and ascending thoracic aortic Agatston calcium score (n=4762, 464 deaths).
║Model 5–model 4+NT-pro-BNP (n=4005, total 394 deaths).

### Table 3. Hazard Ratios and Confidence Intervals for Each 10 mm Hg Increase in the Magnitude of the Forward ($P_f$) and Backward ($P_b$) Wave and Death in Unadjusted and Adjusted Models

<table>
<thead>
<tr>
<th>Model</th>
<th>All-Cause Mortality (617 Deaths)</th>
<th>Cardiovascular Mortality (134 Deaths)</th>
<th>Noncardiovascular Mortality (460 Deaths)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio</td>
<td>Confidence Interval</td>
<td>$P$ Value</td>
</tr>
<tr>
<td>Model 1*</td>
<td>$P_b$ 2.02</td>
<td>1.27–3.22</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>$P_f$ 0.84</td>
<td>0.56–1.25</td>
<td>0.38</td>
</tr>
<tr>
<td>Model 2†</td>
<td>$P_b$ 2.42</td>
<td>1.51–3.87</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>$P_f$ 0.78</td>
<td>0.52–1.16</td>
<td>0.22</td>
</tr>
<tr>
<td>Model 3‡</td>
<td>$P_b$ 1.81</td>
<td>1.03–3.16</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>$P_f$ 0.71</td>
<td>0.45–1.14</td>
<td>0.16</td>
</tr>
<tr>
<td>Model 4§</td>
<td>$P_b$ 2.18</td>
<td>1.21–3.92</td>
<td>0.009</td>
</tr>
<tr>
<td></td>
<td>$P_f$ 0.56</td>
<td>0.35–0.92</td>
<td>0.02</td>
</tr>
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<td>Model 5║</td>
<td>$P_b$ 2.03</td>
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BMI indicates body mass index; HDL, high-density lipoprotein; and LDL, low-density lipoprotein.

*Model 1–unadjusted (n=5984, 617 total deaths).
†Model 2–adjusted for heart rate (n=5984, 617 total deaths).
‡Model 3–model 2+adjustment for age, sex, ethnicity, systolic blood pressure, eGFR, urinary albumin/creatinine ratio, total cholesterol, LDL cholesterol, HDL cholesterol, treatment with antihypertensive medications, treatment with statins, current smoking status, BMI, family history of myocardial infarction, diabetes mellitus, C-reactive protein, highest level of education, family income, alcohol use, total calories per day, percent of calories from fat, and physical activity (n=4825, total 473 deaths).
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║Model 5–model 4+NT-pro-BNP (n=4005, total 394 deaths).
Heart Failure

Given the known association between reflected waves and heart failure, additional models were created that censored individuals at the time of the development of incident heart failure (n=208). In the adjusted model, RM was no longer predictive of total mortality (HR=1.16; 95% CI=0.94–1.44; P=0.17). Pb, however, remained significantly predictive of all-cause mortality (HR=1.91; 95% CI=1.02–3.57; P=0.04). This relationship was attenuated when NT-pro-BNP levels were added to the model (each 10 mm Hg increase in Pb; HR=1.72; 95% CI=0.88–3.38; P=0.11), although the power for this analysis was markedly decreased because of the number of subjects who had NT-pro-BNP levels drawn (Table 4).

Discussion

In this study, we demonstrate that in a large multiethnic population of adults free of clinically evident cardiovascular disease at baseline, RM independently predicts all-cause mortality. Furthermore, this association is independent of the presence of subclinical atherosclerosis at baseline. We also demonstrate that when the forward and backward (reflected) waves are assessed as predictors of death, Pb and Pf demonstrate opposite HRs, indicating that it is their difference (ie, magnitude of reflected versus forward waves) that is primarily related to mortality. On further analyses, the relationships between RM, Pb, and Pf were most clear in their impact on cardiovascular mortality. Finally, when subjects who developed heart failure were censored, Pb remained predictive of all-cause mortality.

With each cardiac cycle, blood is ejected from the left ventricle into the arterial tree where complex hemodynamic parameters regulate the rise in arterial pressure in response to the stroke volume. As the pulse wave travels further from the heart, it encounters points of impedance mismatch (ie, points where the opposition to pulsatile blood flow changes). When the forward-traveling pulse wave encounters such a site, a portion of the wave is reflected back toward the central aorta. Reflected waves summate during transit to form a relatively discrete composite wave arriving at the proximal aorta. Reflection sites along the arterial tree include arterial segments where the arterial diameter decreases, branching points, points of turn, or tortuous geometry in conduit vessels, as well as the interfaces between large conduit vessels and the more distal muscular arteries. Although the literature often describes the bifurcation with the iliac arteries as the main reflection site, in reality, there are myriad reflection sites along the arterial tree.
sites throughout the circulatory system, generating many discrete waves that merge to form a discrete reflected wave. Therefore, RM is a composite index influenced by both central and peripheral arterial structure and function and may represent a marker of overall arterial health. In this regard, its relevance to human health may extend beyond its well-known effects on left ventricular afterload, remodeling, and function.

Previously, Wang et al studied RM in a cohort of 1272 Taiwanese subjects followed for a median of 15 years. These authors noted significant correlations between the magnitude of the reflected wave and increased left ventricular mass, carotid IMT, and decreased renal function. In this ethnically homogeneous population, the magnitude of the reflected wave was also associated with increased cardiovascular mortality in both men and women. The authors conclude by stating that wave reflections may be a clinically relevant marker of vascular aging. Our study extends this work and is novel for several additional reasons: (1) We studied a large multiethnic population; (2) We assessed whether the association between RM, \( P_b \), and mortality is independent of subclinical atherosclerosis, extensively assessed in multiple vascular territories (carotid IMT, ABI, coronary and aortic calcium); and (3) We assessed whether these associations are independent of the formerly reported association with incident heart failure. We found that every 10% increase in RM, defined as the ratio of the amplitude of the backward pressure wave to the amplitude of the forward pressure wave, was associated with a 18% to 32% increase in all-cause mortality, depending on the adjustments performed. This relationship was independent of relevant baseline characteristics, as well as multiple other confounders. Importantly, we found that comprehensive adjustment for markers of subclinical atherosclerosis in several beds did not appreciably diminish the association between RM and mortality, suggesting that the association between RM and death is not mediated by atherosclerosis to any great extent.

The association between RM and mortality is partially mediated through its known strong association with heart failure risk. This relationship is consistent with the differential impact of late systolic load imposed on the left ventricle by wave reflections, which has been shown to induce left ventricular hypertrophy, fibrosis, and myocardial dysfunction. Given the known association between RM and heart failure, we performed additional analyses that censored individuals who developed incident heart failure. In these models, although the relationship between RM and total mortality was not significant, an association between \( P_b \) and mortality persisted. Overall, these analyses suggest that additional mechanisms, beyond heart failure, may partially underlie the relationship between reflected waves and total mortality. The mechanism of this association remains unknown perhaps because the parameters that govern it remain incompletely understood.

Previous modeling studies suggest that RM is dependent on aortic stiffness, degree of distal aortic reflection, and peripheral resistance rather than arterial tapering. These models, which assume the aorta to be uniform in its properties throughout its length and contain a single reflector at its terminus at the bifurcation, are likely to be oversimplified. Other factors, including alterations in aortic geometry over its length, likely play a significant role in RM. As has been suggested by other authors, RM and \( P_b \) may be markers of arterial health and aging. This notion is supported by our study, which demonstrates an independent association between these parameters measured at baseline and all-cause mortality over the course of approximately a decade, even after adjustment for multiple confounders and a comprehensive assessment of subclinical atherosclerosis in various territories using currently available noninvasive techniques.

Our study must be interpreted in the context of its strengths and limitations. Strengths of this study include its large multiethnic sample, careful follow-up, and detailed event adjudication, as well as the comprehensive assessment of subclinical atherosclerosis. Limitations of this study include the small number of deaths, thus precluding further analysis by subgroups such as sex. In addition, we used a physiological averaged flow waveform for wave separation rather than measured flow. This technique only approximates true RM and likely introduced noise in our computations. This may have underestimated the association between RM and incident risk.

**Perspectives**

In a large multiethnic population of adults free of clinically evident cardiovascular disease at baseline, RM and \( P_b \) independently predicted all-cause mortality. This association was independent of the presence of subclinical atherosclerosis at baseline. The association between \( P_b \) and mortality was also independent of new-onset heart failure. RM and \( P_b \) may thus represent overall markers of arterial health. Further studies are required to assess the precise mechanisms behind their associations with all-cause mortality.

**Acknowledgements**

We thank the other investigators, the staff, and the participants of Multi-Ethnic Study of Atherosclerosis for their valuable contributions.

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**Disclosures**

Dr Chirinos has received minor support (equipment loans) from Atcor Medical, Cardiodynamics, and APC cardiovascular. The other authors report no conflicts.

**References**


**Novelty and Significance**

**What is New?**

- We investigated the impact of reflected waves on all-cause mortality.
- We studied a multiethnic population, free of incident cardiovascular disease.
- We demonstrate that the association between reflected waves and mortality is independent of atherosclerosis.
- The magnitude of the backward wave is likely more important than the overall ratio.

**What is Relevant?**

- Reflected waves represent a novel marker of arterial health.
- The findings help us understand the importance of the arterial system and its function, beyond measuring blood pressure alone.

**Summary**

Reflection waves are independently associated with all-cause mortality. This relationship persisted after adjustment for atherosclerosis. The magnitude of the backward wave is associated with all-cause mortality even after censoring individuals at the time of a first heart failure event, implying that its association with total mortality is at least partially independent of both atherosclerosis and heart failure. Reflected waves represent an important marker of vascular health with adverse prognostic implications.
Reflection Magnitude as a Predictor of Mortality: The Multi-Ethnic Study of Atherosclerosis

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TITLE: Reflection Magnitude as a Predictor of Mortality: The Multi-Ethnic Study of Atherosclerosis

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Table S1 – Cause of Death (n=617) amongst the 5984 participants in the MESA cohort during a mean follow-up of 9.8±1.7 years.

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atherosclerotic Coronary Heart Disease</td>
<td>70 (11.4)</td>
</tr>
<tr>
<td>Stroke</td>
<td>27 (4.4)</td>
</tr>
<tr>
<td>Other Atherosclerotic Disease*</td>
<td>5 (0.8)</td>
</tr>
<tr>
<td>Other Cardiovascular Disease†</td>
<td>32 (5.2)</td>
</tr>
<tr>
<td>Non-Cardiovascular Disease</td>
<td>460 (75)</td>
</tr>
<tr>
<td>Unknown</td>
<td>23 (4)</td>
</tr>
</tbody>
</table>

* Examples of deaths in this category include complications of aneurysms and critical limb ischemia
† Example of deaths in this category include valvular heart disease and pulmonary embolism

For more information regarding death adjudication, the reader is referred to the web appendix from reference 18