Differential Impact of Age, Sex, and Hypertension on Aortic Atherosclerosis
The Framingham Heart Study


Objective—The purpose of this study was to investigate the impact of age, sex, and hypertension (HTN) on aortic atherosclerotic burden using cardiovascular MRI (CMR) in a free-living longitudinally followed cohort.

Methods and Results—1763 participants (829 M and 934 F; 38 to 88 years of age) of the Framingham Heart Study Offspring cohort underwent CMR of the thoracoabdominal aorta using an ECG-gated 2D T2-weighted black-blood sequence. Of these, 1726 subjects (96%) with interpretable CMR were characterized by sex, age-quartile, and presence or absence of HTN and clinical cardiovascular disease (CVD). Aortic plaque prevalence and volume increased with increasing age in both sexes. For the nonhypertensive (no-HTN) group, plaque was identified in 702 (46%) with greater prevalence in women than in men (P<0.006). HTN was associated with greater aortic plaque burden (P<0.02). The 200 subjects with clinical CVD had greater plaque burden than subjects without CVD (P<0.0001).

Conclusions—in this free-living longitudinally followed cohort, subclinical aortic atherosclerosis was seen in nearly half of subjects and increased with advancing age. HTN was associated with increased aortic plaque burden. Among no-HTN subjects, women had greater plaque burden than men. These data suggest that subclinical atherosclerosis is more common in no-HTN women and emphasize the importance of focusing on preventive measures in both sexes.

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Key Words: MRI ■ aortic atherosclerosis ■ hypertension ■ age ■ sex

Atherosclerotic cardiovascular disease (CVD) is the leading cause of morbidity and mortality in the Western world. Hypertension (HTN) is a major modifiable risk factor for atherosclerotic CVD that affects about 65 million adults in the United States.1 Autopsy studies have demonstrated that both aortic and coronary atherosclerosis have long subclinical phases2–6 and in such studies, HTN is associated with greater prevalence and extent of aortic and coronary atherosclerosis.3,5,6 A growing body of evidence has linked subclinical coronary7 and aortic8–10 atherosclerosis to increased risk for clinically overt CVD, suggesting that early diagnosis and treatment of atherosclerosis in the preclinical stage may reduce CVD sequelae such as myocardial infarction and stroke. However, beyond autopsy studies, our understanding of the relationship between age, sex, and HTN with aortic atherosclerotic burden is incomplete.

There are several reports about the relationship between HTN and atherosclerosis. Carotid intima-media thickness (IMT) is greater in persons with HTN than nonhypertensive subjects, and the association between IMT and blood pressure parameters, particularly systolic blood pressure, was found to be independent of age and gender.11–13 However, the influence of HTN on prevalence of aortic plaque burden in an adult population is unknown. Cardiovascular magnetic resonance (CMR) offers unique advantages for assessment of the aorta and quantification of atherosclerotic plaque burden14–17 including the lack of ionizing radiation, while providing highly reproducible measures of aortic anatomy and atherosclerosis.18 We sought to determine the relationship of age, sex, and HTN with aortic atherosclerotic prevalence and burden using CMR in a longitudinally followed free-living community based cohort.

Methods

Study Population and Sample Selection
The design of the Framingham Heart Study (FHS) has been detailed elsewhere.19 Subjects considered for this investigation were participants in the Offspring cohort, which was initiated in 1971 and followed with serial (“Cycle”) examinations every 4 to 5 years.
Cycle 7 (1998 to 2001) included 3799 subjects from which 1794 subjects in sinus rhythm and without contraindication to CMR were recruited.

Two hundred subjects had a history of clinical CVD, defined as coronary heart disease (stable angina, documented coronary stenosis, positive stress test, or myocardial infarction), cerebrovascular disease (stroke or transient ischemic attack), intermittent claudication, or congestive heart failure. The 1526 subjects without clinical CVD (no-CVD) were characterized by sex, age-quartile, and presence or absence of history of HTN, defined by a systolic blood pressure ≥140 mm Hg or a diastolic blood pressure of ≥90 mm Hg or current use of antihypertensive medications. The study was approved by the Institutional Review Boards of the Boston University Medical Center and the Beth Israel Deaconess Medical Center. Written informed consent was obtained from all participants.

Cardiovascular Magnetic Resonance (CMR)

Subjects underwent thoracoabdominal aortic CMR using a 1.5-T whole-body CMR system (Gyroscan ACS-NT, Philips Medical Systems) with a PowerTrak 6000 gradient system (peak gradient 23 mT/m, rise time 219 ms). Thoracic aortic images were obtained with a 5-element cardiac phased-array receiver coil. Abdominal aortic images were obtained using the body coil as a receiver. Total aortic imaging time was <20 minutes. Thirty-six transverse slices encompassing the aorta from the arch to the aortoiliac bifurcation were obtained using a free-breathing, ECG-gated, fat-suppressed, black blood 2D T2-weighted turbo spin-echo sequence with in-plane spatial resolution of 1.03 mm × 0.64 mm and 5-mm slice thickness. A 10-mm slice gap was used for the thoracic aorta, whereas a denser sampling of 24 slices with a 5-mm gap was used for the abdominal aorta.

Aortic and Atherosclerotic Plaque Analysis

CMR images were analyzed using commercial software (MASS v 6.1, QT-MEDIS) by a single expert reviewer (N.O.) blinded to all clinical data. Images were considered suitable for analyses if they (1) were perpendicular to the descending thoracic and abdominal aorta and (2) had visual definition of ≥50% of the inner circumference of the aortic wall. An interactive free-hand manual drawing tool was used for the aortic and plaque contour tracing (Figure 1). Atherosclerotic plaque was defined as characteristic luminal protrusions of ≥1 mm in radial thickness that could be visually distinguished from the minimal residual blood signal of each plaque. Location of plaque was classified as thoracic or abdominal according to location above or below the diaphragm, respectively. For each subject, the cross-sectional area of each plaque (Figure 1) was measured and total plaque volume was calculated. Subject plaque volume was also normalized for calculated body surface area (BSA) based on contemporaneous (Cycle 7) data.

Statistical Analysis

The overall number and overall percentage of participants with plaque in any slice was determined. Plaque volume was summarized using mean and standard error. We used age-quartiles to assess linear trends in both plaque prevalence and plaque volume measures. A 2-sample t test and linear regression model adjusting for age and sex were used to analyze continuous response measures satisfying the normality assumption. Equality of variances F test was used to determine whether a pooled variance 2-sample t test or unequal variance 2-sample t test was appropriate. For continuous response variables, analysis of covariance (ANCOVA) was used to adjust for age, sex, and history of diabetes, hypertension, and hyperlipidemia. For continuous response variables in which the normality or homogeneity of variances assumptions were violated, the response values were first converted to ranks then the ranked response was analyzed using linear regression as described by Quade. Age-quartile differences in categorical measures were assessed using a Chi-square test. All statistical analyses were conducted using SAS/STAT (Release 8.1, SAS Institute Inc). An age-tertile stratified random subsample of 24 men and 24 women was selected for reproducibility analyses. Inter- and intrarater reproducibility were assessed using interclass correlation coefficient (ICC). Interreader reproducibility was assessed using plaque measures obtained by 2 independent readers (N.O.; R.R.J.) blinded to all clinical data. A probability value of <0.05 was considered significant.

Results

Of the 1794 subjects (aged 65±9 years) scanned, 31 had incomplete CMR studies and 32 had poor image quality precluding analyses, leaving 1726 (96%) for analysis. Summary demographics of these 1726 subjects (53% female) are provided in Table 1. Subjects with CVD (n=200) were more likely to be male, older, and to have diabetes, hyperlipidemia, and with higher systolic and diastolic blood pressure than the 1526 subjects without clinical CVD (no-CVD; P<0.0005 for all comparisons).

**Table 1. Study Sample Characteristics and Plaque Burden by Baseline CVD Prevalence Status**

<table>
<thead>
<tr>
<th>n</th>
<th>No-CVD Group</th>
<th>CVD Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender, n (%)</td>
<td>847 (56%)</td>
<td>73 (37%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age, years</td>
<td>64±9</td>
<td>70±8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>125±18</td>
<td>130±18</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>74±10</td>
<td>72±8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hypertension_ever, n (%)</td>
<td>740 (48.5%)</td>
<td>161 (80.5%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>202±35</td>
<td>192±38</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>HDL, mg/dL</td>
<td>55±17</td>
<td>47±15</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cholesterol/HDL</td>
<td>4.01</td>
<td>4.44</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Triglyceride,* mg/dL</td>
<td>107 [76, 160]</td>
<td>142 [95, 190]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>118 (7%)</td>
<td>51 (26%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Any plaque prevalence, n (%)</td>
<td>702 (46%)</td>
<td>129 (64.5%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Thoracic plaque prevalence, n (%)</td>
<td>99 (6.5%)</td>
<td>38 (19%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Abdominal plaque prevalence, n (%)</td>
<td>663 (43.5%)</td>
<td>126 (63%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total plaque volume, cm³</td>
<td>0.44±1.07</td>
<td>1.5±3.12</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Median with 25/75 percentiles; †after adjusting for age, sex, hypertension, hyperlipidemia, and diabetes.

SBP indicates systolic blood pressure; DBP, diastolic blood pressure obtained at Cycle 7; CVD, cardiovascular disease.

Hypertension_ever = defined by a SBP ≥140 mm Hg or a DBP of ≥90 mm Hg or current use of antihypertensive medication.
Aortic Atherosclerosis and CVD
Aortic plaque was identified in 702 (46%) of the 1526 no-CVD subjects. Aortic plaque was far more prevalent in the abdomen than in the thorax (plaque prevalence ratio, 7:1, Table 1). The CVD group had higher plaque prevalence than the no-CVD group (P<0.0001, Table 1). Thoracic plaque prevalence in the CVD group was 3-fold higher than that in the no-CVD group (P<0.0001). In addition, the CVD group had more than 3-fold greater total plaque volume than the no-CVD group; this difference remained significant after adjusting for sex, age, hypertension, diabetes, and hyperlipidemia (P<0.0001).

Subjects Without CVD
Summary demographics of the 1526 no-CVD subjects (56% female), including 740 subjects with a history of HTN, are shown in Table 2. As expected, subjects with HTN had greater systolic and diastolic blood pressures than subjects without HTN (no-HTN) (P<0.001). They were also older than no-HTN subjects (P<0.001). Within each subgroup (HTN and no-HTN), there were no sex differences with respect to age, history of diabetes, total cholesterol, and blood pressure.

Impact of Sex on Plaque Burden
Among the no-HTN group, prevalence of abdominal aortic plaque, and prevalence of any aortic plaque, was higher in women than in men (P<0.02 for both; Table 2). Total plaque volume, both absolute and normalized to BSA, was larger in women than men (P<0.05) in the no-HTN group. In the HTN group there was no sex difference in plaque prevalence or plaque volume.

Impact of Age on Plaque Burden
The prevalence of both abdominal and thoracic atherosclerosis increased across age-quartile (trend for age-quartile, P<0.001 for all, Figure 2). This age relationship was noted in both the no-HTN and HTN groups (Figure 2). The impact of age on thoracic plaque prevalence was greater than that for abdominal plaque, especially in the HTN group (Figure 2). Total plaque volume also increased across age-quartiles (trend for age-quartile, P<0.001, Figure 2).

Impact of Hypertension on Plaque Burden
Aortic plaque prevalence in the HTN group (n=740) was greater than in no-HTN subjects (P<0.005, Figure 3). HTN was associated with an increase in both thoracic and abdominal plaque prevalence among men (P<0.01), but only thoracic plaque prevalence in women (P<0.007, Figure 3). Aortic plaque volume in the HTN group was greater than in no-HTN subjects (0.56±0.05 cm$^3$ versus 0.33±0.03 cm$^3$, P=0.0186), a difference that persisted after adjustments of age, sex, hypertension, hyperlipidemia, and diabetes. However, this difference was significant only for men (P<0.006).

Reproducibility
Intrareader differences in aortic plaque volume were small (0.0 to 0.2 cm$^3$) as were interreader differences (range: −0.2 to 0.8 cm$^3$). ICC for interreader comparisons was 0.94 for plaque volume. High correlations (ICC=0.99) were also noted for intrareader comparisons.

Discussion
To our knowledge, the present report represents the first CMR study of a free-living longitudinally followed cohort assessing the differential impact of HTN on aortic atherosclerosis burden between sexes and across age. We found that nearly half of all subjects had CMR evidence of subclinical aortic atherosclerosis. As with our pilot study of 200 no-CVD subjects, both thoracic and abdominal aortic plaque burden

### Table 2: Study Sample Characteristics and Plaque Burden in Participants Without CVD (n=1526) by Sex and Hypertension Status

<table>
<thead>
<tr>
<th>Hypertension Status</th>
<th>No Hypertension, n=786</th>
<th>Hypertension, n=740</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>n (%)</td>
<td>305 (39%)</td>
<td>481 (61%)</td>
</tr>
<tr>
<td>Age, years</td>
<td>61±8</td>
<td>62±9</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>117±10</td>
<td>114±12</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>73±7</td>
<td>70±8</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>194±32</td>
<td>206±37</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>47±13</td>
<td>63±16</td>
</tr>
<tr>
<td>Cholesterol/HDL</td>
<td>4.4±1.3</td>
<td>3.5±1.1</td>
</tr>
<tr>
<td>Triglyceride, mg/dL</td>
<td>96 [69, 151]</td>
<td>96 [69, 138]</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>3.9%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>2.03±0.16</td>
<td>1.74±0.18</td>
</tr>
<tr>
<td>Total plaque prevalence, n (%)</td>
<td>111 (36.4%)</td>
<td>223 (46.4%)</td>
</tr>
<tr>
<td>Thoracic plaque prevalence, n (%)</td>
<td>6 (2%)</td>
<td>19 (4%)</td>
</tr>
<tr>
<td>Abdominal plaque prevalence, n (%)</td>
<td>108 (35.4%)</td>
<td>214 (44.5%)</td>
</tr>
<tr>
<td>Total plaque volume, cm³</td>
<td>0.20±0.54</td>
<td>0.41±0.86</td>
</tr>
<tr>
<td>Total plaque volume/BSA, 10⁻⁴ cm²</td>
<td>0.10±0.26</td>
<td>0.24±0.52</td>
</tr>
</tbody>
</table>

Data are n (%) or means±SD. *Median with 25/75 percentiles.
increase with age-quartile, and abdominal aortic plaque is markedly more common than thoracic aortic plaque. In this larger study, we were able to compare the impact of age, sex, and HTN on plaque prevalence between asymptomatic (no-CVD) subjects and those with clinically overt CVD. Subjects with overt CVD had higher plaque prevalence and larger plaque volume than subjects in the no-CVD group. The larger plaque volume remained significant even after adjusting for sex, age, hypertension, diabetes, and hyperlipidemia.

HTN was associated with increased prevalence of both thoracic and abdominal plaque among men. Surprisingly, we found that only thoracic plaque prevalence significantly increased with HTN in women. Aortic plaque volume was also related to HTN only in men. Autopsy data have shown that HTN is strongly associated with the extent of fatty streaks and fibrous plaque lesions in the aorta and the effect of HTN increased with age. Our data are consistent with those data. However, the underlying pathophysiology for differential responses to HTN on aortic plaque between sexes and at different anatomic locations remains to be explored. Using ultrasound of the aorta and the iliac arteries, Paivansalo et al found HTN subjects had a larger plaque extent than controls. In a transesophageal echocardiographic study of thoracic plaque, increased plaque was found in older subjects and those with HTN. Fayad et al reported that CMR compares well with measures of atherosclerotic plaque size and extent in the thoracic aorta as determined by transesophageal echocardiography (TEE). CMR offers advantages over TEE, which is seminvasive and requires sedation, because it allows more extensive coverage of the aorta, especially the abdominal aorta. CMR may also be preferable to computed tomography (CT) for the detection and quantification of aortic atherosclerotic plaques, as it does not expose subjects to either ionizing radiation or iodinated, nephrotoxic contrast media.

We found that abdominal plaque prevalence was greater in women than men across all age categories in the no-HTN group. This is consistent with autopsy data showing that women have more fatty streaks in the abdominal aorta than men at all ages. The present work extends these findings to include measurable plaque burden in a free-living population. Although rates of clinically apparent CVD are more frequent in younger men than in younger women, our data suggest that the prevalence and burden of preclinical atherosclerosis in women is greater than in men among community-dwelling adults. This emphasizes the importance of focusing preventive measures on women as well as men.

**Study Limitations**

The present study was not designed to characterize atherosclerotic plaque components. Such characterization would have required additional CMR imaging using T1-weighted and proton-density weighted sequences. Our study protocol did not include these investigations because of external time constraints. Also, because of limitations on total imaging time available per subject, we obtained 12 slices with a 10-mm interslice gap in the thoracic aorta; a denser sampling of 24 slices with a 5-mm gap was used in the abdominal aorta based on previous work from our group showing greater plaque prevalence and plaque burden in the abdominal aorta than the thoracic aorta. Finally the FHS Offspring cohort is predominantly White, and the present study comprises participants.
ranging in age from 35 to 90 years. Our results may not be applicable to other racial or age subgroups.

Conclusions
In this population-based CMR study of the differential impact of age, sex, and HTN on aortic atherosclerosis in a free-living population, subclinical aortic atherosclerosis was seen in nearly half of subjects, with a predominance of abdominal plaque. HTN was associated with an increase in both thoracic and abdominal plaque prevalence among men, but only thoracic plaque in women. HTN was associated with increased plaque volume for only men. Subjects with clinically overt CVD had greater plaque burden than asymptomatic subjects without clinical CVD. Among normotensive subjects CVD had greater plaque burden than asymptomatic subjects with CVD. Among normotensive subjects without CVD, women had greater plaque burden than men across all age-quantiles. These data emphasize the importance of focusing on women as well as men with regard to prevention of subclinical atherosclerosis.

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Disclosures
None.

References
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