Risk Profiles for Aortic Dissection and Ruptured or Surgically Treated Aneurysms: A Prospective Cohort Study

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Background—Community screening to guide preventive interventions for acute aortic disease has been recommended in high-risk individuals. We sought to prospectively assess risk factors in the general population for aortic dissection (AD) and severe aneurysmal disease in the thoracic and abdominal aorta.

Methods and Results—We studied the incidence of AD and ruptured or surgically treated aneurysms in the abdominal (AAA) or thoracic aorta (TAA) in 30,412 individuals without diagnosis of aortic disease at baseline from a contemporary, prospective cohort of middle-aged individuals, the Malmö Diet and Cancer study. During up to 20 years of follow-up (median 16 years), the incidence rate per 100,000 patient-years at risk was 15 (95% CI 11.7 to 18.9) for AD, 27 (95% CI 22.5 to 32.1) for AAA, and 9 (95% CI 6.8 to 12.6) for TAA. The acute and in-hospital mortality was 39% for AD, 34% for ruptured AAA, and 41% for ruptured TAA. Hypertension was present in 86% of individuals who subsequently developed AD, was strongly associated with incident AD (hazard ratio [HR] 2.64, 95% CI 1.33 to 5.25), and conferred a population-attributable risk of 54%. Smoking was also a risk factor for AAA with a smaller effect. Smoking (HR 5.07, 95% CI 3.52 to 7.29) and high apolipoprotein B/A1 ratio (HR 2.48, 95% CI 1.73 to 3.54) were strongly associated with AAA and conferred a population-attributable risk of 47% and 25%, respectively. Smoking was also a risk factor for AD and TAA with smaller effects.

Conclusions—This large prospective study identified distinct risk factor profiles for different aortic diseases in the general population. Hypertension accounted for more than half of the population risk for AD, and smoking for half of the population risk of AAA. (J Am Heart Assoc. 2015;4:e001513 doi: 10.1161/JAHA.114.001513)

Key Words: aneurysm • aorta • dissection • epidemiology • risk factor

Upture and dissection of the aorta are critical vascular events that can cause severe internal hemorrhage and have an acute mortality exceeding 20% even with modern treatment.¹ Such acute events can be prevented by surgical or endovascular treatment, and potentially by timely risk factor intervention, in individuals with aortic wall weakening and dilation found on radiological or ultrasound imaging examination. Reports of increasing incidence of aortic rupture, dissection, and surgical treatment of aortic dilation in the second half of the 20th century therefore motivated community screening programs to identify individuals with dilation of the abdominal aorta who might benefit from surgical or endovascular interventions. However, the initial results of such screening programs in broad age- and sex-specific groups have recently been reported, with lower prevalence estimates of aortic dilation than expected observed in several countries.²–⁵ These findings have led to calls for improved cost-effectiveness in screening programs by focusing on high-risk populations.²,³ We were therefore interested in evaluating the population risk for aortic disease attributable to each of the major cardiovascular risk factors.

Gradual aortic dilation precedes the development of aortic aneurysms and, to some extent, aortic dissection (AD). However, in the International Registry of Acute Aortic Dissection (IRAD) >80% of ADs developed in the absence of a preexisting aneurysm, indicating that ruptured aneurysms
and dissection represent distinct pathophysiological states.\textsuperscript{6,7} Furthermore, different mechanisms are thought to drive aortic dilation and rupture at different aortic sites, most importantly for abdominal compared with thoracic aortic aneurysms (AAAs and TAAAs, respectively).\textsuperscript{8} It can therefore be hypothesized that risk profiles differ under these disease states.

Previous studies of risk factors for aortic disease are, with a few exceptions, limited in interpretation by case series design such as the IRAD, by case-control designs, or by focusing on cross-sectional risk factor associations with aortic diameter rather than clinical outcomes.\textsuperscript{9–16} Accurate incidence and population-attributable risks (PARs) cannot be estimated from such study designs. We therefore used a large Swedish population-based cohort study of middle-aged subjects with long-term follow-up to evaluate the population risk attributable to major risk factors for AD and severe aneurysms in the abdominal (AAA) or thoracic aorta (TAA), defined as ruptured or surgically treated aneurysms.

**Methods**

**Study Sample**

The population-based Malmö Diet and Cancer Study (MDCS) includes 30,447 men born 1923–1945 and women born in 1923–1950 from the general population of Malmö, Sweden. Participants attended baseline examinations between 1991 and 1996 with sampling of peripheral venous blood and ascertainment of clinical characteristics as previously described.\textsuperscript{17} Participants underwent anthropometric measurements and blood pressure measurement using a mercury-column sphygmomanometer in the supine position after 10 minutes of rest, and they completed a questionnaire that included questions about smoking and medication use. Apolipoproteins A1 (apoA1) and B (apoB) were measured at Quest Diagnostics (San Juan Capistrano, CA), blinded to case-control status, by using an immunonephelometric assay run on the Siemens BNII. The interassay variability was <4.0% for both apoA1 and apoB. Traditional low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol fractions were available in a random subset of 5,444 patients.\textsuperscript{18} The Pearson correlation coefficients between apolipoproteins and the corresponding traditional cholesterol fractions were 0.72 (apoA1-HDL), 0.73 (apoB-LDL), and 0.86 (apoB/apoA1-LDL/HDL). Smoking was defined as self-reported regular smoking or smoking cessation within the past year. Hypertension was defined as use of antihypertensive medication or blood pressure ≥140/90 mm Hg. Obesity was defined as body mass index (BMI) >30 kg/m\textsuperscript{2}. Diabetes mellitus was defined as a (1) self-reported physician’s diagnosis or use of antidiabetic medications or from 1 of 5 nationwide or regional registers—a diagnosis of diabetes in the nationwide Swedish Diabetes Register, the nationwide Inpatient Register with coverage of all hospital discharges and outpatient care at Swedish hospitals, the regional Diabetes 2000 register of the Scania region in southern Sweden in which Malmö is the largest city, or (2) a prescription of antidiabetic medication in the nationwide Swedish Prescribed Drug Register, or (3) if at least 2 glycated hemoglobin recordings were ≥6.0% according to the Swedish Mono-S standardization system (corresponding to 7.0% according to the US National Glycohemoglobin Standardization Program [NGSP]) in the Malmö HbA1c register, which includes all glycated hemoglobin samples measured since 1988 at the Department of Clinical Chemistry, which receives samples from the entire greater Malmö area. Informed consent was obtained from all participants, and the study was approved by the ethics committee of Lund University, Sweden.

**End Point Ascertainment and Validation**

Individuals from the MDCS with a first registered diagnosis of AD, AAA, TAA, ruptured AAA, or ruptured TAA or who underwent a surgical procedure for AAA or TAA were identified from Swedish national registers (the Inpatient Register and the Cause of Death Register) by linkage of the 10-digit personal identification number unique to each Swedish resident.\textsuperscript{19} These registers have complete coverage of Swedish hospitals through the tax-financed health care system, and reimbursement to hospital departments is dependent on correct diagnostic coding. Both registers were established in the 1950s–1960s and are administered by the National Board of Health and Welfare (http://www.socialstyrelsen.se/english).\textsuperscript{20,21} The Inpatient Register includes information on dates of admission and discharge as well as diagnostic and procedural codes from all hospitalizations in Sweden. The Cause of Death Register includes diagnoses of underlying and contributing causes of death from death certificates. In both registers, diagnoses are coded using a Swedish revision of the International Classification of Disease (ICD). The eighth edition (ICD-8) was used until the end of 1986, the ninth edition (ICD-9) was used between 1987 and 1996, and the 10th edition (ICD-10) has been used since 1997. Before 1997, the Swedish classification Op6 was used for surgical procedures, and since 1997, the KKÄ97 classification has been used, a Swedish revision of the Classification of Surgical Procedures from the Nordic Medico-Statistical Committee (1996). End points were defined from diagnosis codes as shown in Table 1 and from codes for surgical procedures as shown in Table 2. The acute mortality in ruptured aneurysms and in AD, defined as death before reaching a hospital or during the first admission, was determined from the Inpatient Register and the Cause of Death Register.
Table 1. Diagnosis Codes for Aortic Disease

<table>
<thead>
<tr>
<th></th>
<th>ICD-8</th>
<th>ICD-9</th>
<th>ICD-10</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAA</td>
<td>441.2</td>
<td>441D, 441E</td>
<td>I713, I714, I715, I716</td>
</tr>
<tr>
<td>Ruptured AAA</td>
<td>441D</td>
<td>441D</td>
<td>I713, I715</td>
</tr>
<tr>
<td>AD</td>
<td>441.0</td>
<td>441A</td>
<td>I710</td>
</tr>
<tr>
<td>TAA</td>
<td>441.1</td>
<td>441B, 441C</td>
<td>I711, I712, I715, I716</td>
</tr>
<tr>
<td>Ruptured TAA</td>
<td>441B</td>
<td>441B</td>
<td>I711, I715</td>
</tr>
</tbody>
</table>

ICD indicates International Classification of Disease; AAA, abdominal aortic aneurysm; AD, aortic dissection; TAA, thoracic aortic aneurysm.

High validity of the diagnosis and surgical procedure codes for AAA used in the present study have been described previously in nationwide Swedish registers.\textsuperscript{20,22,23} We verified all diagnoses or surgical procedures for AD and TAA through a review of patient records and radiological images. Information on diagnostic modalities used was retrieved along with information about the location of aortic disease. Diagnostic definitions were in accordance with guideline recommendations.\textsuperscript{24} Patient records were also reviewed for individuals with a procedural code indicating surgery for AAA but without a diagnostic code to verify that the procedure was performed for AAA.

Statistical Analysis

Individuals with a diagnosis of AAA, AD, or TAA at baseline (n=35; 28 with AAA, 4 with TAA, 2 with AD, and 1 with both AAA and TAA) or with missing information on risk factors were excluded from the current study. For these exclusions, we identified subjects with any occurrence of such diagnoses rather than only ruptured or surgically treated cases. End points studied in subsequent prospective analyses were defined as to reflect severe, clinically relevant disease and included AD, AAA defined as ruptured or surgically treated AAA, and TAA defined as ruptured or surgically treated TAA. Risk factors for these 3 end points were assessed by using Cox proportional hazards regression models. Each risk factor was tested in age- and sex-adjusted models, and significant risk factors were included in a multivariable model. The proportionality of hazards assumption was confirmed through visual inspection of log-negative log survival curves. Age- and sex-standardized incidence rates were calculated as the number of events per 100 000 person-years at risk, with CIs calculated under the assumption of a Poisson distribution. The PAR estimates were calculated for each risk factor by using the standard formula,\textsuperscript{25} adjusting for age and sex by stratification as previously described.\textsuperscript{17,26} Analyses were performed by using SAS 9.2 (SAS Institute).

Results

End Point Validation

Of 103 subjects with a diagnosis of TAA before or after baseline and 81 with AD, patient records were retrieved for all except 4 (4%) subjects with TAA and 10 (12%) with AD whose records were unavailable as shown in Figures 1 and 2. The diagnosis was confirmed in 92 subjects with TAA and 63 with AD, resulting in positive predictive values of 93% and 89% for the corresponding diagnosis codes in national registers, respectively. A majority of patients with AD (62%) and TAA (88%) had radiological evidence of aortic disease. A large proportion of AD cases (29%) and a smaller proportion of TAA cases (5%) were diagnosed on autopsy. A smaller number were diagnosed through echocardiography with TAA (n=5) or AD (n=1), and 2 individuals with TAA and 5 with AD were diagnosed via visual inspection during surgery. Intramural hematoma on computed tomography (n=1) was considered equivalent to AD.

Individuals determined to be miscoded most commonly had aneurysms without evidence of dissection but were miscoded as such (n=5), vice versa (n=2), or had AAAs without evidence of thoracic aortic involvement but were miscoded as such (n=3), highlighting some level of confusion in the medical community about differentiating aortic diseases. The remainder of miscoded diagnoses stemmed from clinical suspicion at time points when patients were transferred across medical units before completion of diagnostic examinations.

Baseline Characteristics

In all analyses in the current study, we elected to use strict criteria for severe and clinically relevant aneurysms, defined as ruptured or surgically treated aneurysms. For AD, all diagnosed cases were included. During up to 20 years of follow-up (median 16 years, IQR 14.8 to 17.7 years), the incidence rate per 100 000 patient-years at risk was 27 (95%
CI 22.5 to 32.1) for ruptured or surgically treated aneurysms in the abdominal aorta, 9 (95% CI 6.8 to 12.6) for aneurysms in the thoracic aorta, and 15 (95% CI 11.7 to 18.9) for AD, as outlined in Figure 3. The total cumulative incidence of aortic disease was 0.8% in the MDCS cohort. Of individuals with TAA and AAA, 36.2% and 60.2% of subjects first presented with a ruptured aneurysm, respectively. The acute mortality, defined as death before reaching a hospital or during the first

Figure 1. Validation of aortic dissections. AD indicates aortic dissection; TAA, thoracic aortic aneurysm.

Figure 2. Validation of thoracic aortic aneurysms (TAA). AAA indicates abdominal aortic aneurysm; AD, aortic dissection.
admission, was 39% for AD, 41% for ruptured TAA, and 34% for ruptured AAA. Baseline characteristics for the MDCS cohort and subjects with aortic diseases are shown in Table 3.

Abdominal Aortic Aneurysm

Increasing age and male compared with female sex were strongly associated with increased risk of incident ruptured or surgically treated AAAs \((P<0.05)\). In age- and sex-adjusted models, hypertension, smoking, and high apoB/apoA1 were significantly associated with incident AAA as shown in Table 4, although a trend to increased risk was observed for high apoB \((P=0.09)\). The proportion of AAA risk attributable to smoking was 19%. Diabetes and obesity were nonsignificantly inversely associated with AAA.

Thoracic Aortic Aneurysm

A majority of ruptured or surgically treated TAAs (80%) affected the ascending aorta as shown in Table 3. Increasing age and male sex were associated with increased risk of incident TAA \((P<0.05)\). In age- and sex-adjusted models, only smoking was significantly associated with incident TAA as shown in Table 4, although a trend to increased risk was observed for high apoB \((P=0.09)\). The proportion of TAA risk attributable to smoking was 19%. Diabetes and obesity were nonsignificantly inversely associated with TAA.

Aortic Dissection

A majority of dissections were classified as Stanford type A (58% of individuals with information on subtype), similar to observations in the IRAD (62%).\(^1\) Increasing age and male sex were associated with increased risk of incident AD \((P<0.05)\). In age- and sex-adjusted models, hypertension, smoking, and apoA1 were significantly associated with AD. The incidence of AD per 100 000 patient-years at risk was 21 (95% CI 16.3 to 27.5) in individuals with hypertension and 5 (95% CI 2.6 to 9.8) in normotensive individuals. Diabetes and obesity were not associated with incident AD \((P>0.05)\). The proportions of AD risk attributable to hypertension, smoking, and low apoA1 were 54%, 14%, and 30%, respectively. In multivariable models incorporating age, sex, hypertension, smoking, and apoA1, all remained significantly associated with incident AD as shown in Table 6.

Discussion

Using a large population-based cohort of middle-aged individuals with follow-up from nationwide Swedish registers, we prospectively evaluated the incidence and mortality of different aortic diseases, assessed risk factors, and the population risk of aortic diseases attributable to risk factors. Our results confirmed high acute mortality in acute dissection and rupture, 34% to 41%, and identified hypertension and smoking as predominant risk factors for AD and AAA, respectively, explaining 54% and 47% of population risk. Smoking was also associated with AD and TAA, and apolipoprotein concentrations with AD and AAA, although with smaller contributions to population risk. Overall, our findings add to a small number of previous prospective studies for aortic disease\(^9-16\) and provide support for distinct
Risk profiles for different aortic diseases, with hypertension accounting for more than half of AD risk, smoking for half of AAA risk, and a more complex risk profile present for TAA.

Hypertension and AD

Hypertension is often considered the most important risk factor for AD, with reference to the IRAD study, in which 80% of AD cases were diagnosed with hypertension. However, only 1 previous prospective study of AD has been reported, comprising the population from Oxfordshire, England. That recent study and the current prospective study consistently observed hypertension to be the most important risk factor. In the current study, hypertension was present in 86% of individuals who subsequently developed AD during follow-up. More important, hypertension at baseline translated into a PAR of 54% for AD, with an incidence rate of 21 per 100 000 person-years at risk in hypertensive individuals compared with 5 in normotensive individuals. Our study in combination with the study from Oxfordshire provides strong support for the contention that half of AD events could be prevented by pharmacological intervention in hypertensive subjects, similar to what has been shown in randomized controlled trials for stroke, heart failure, myocardial infarction, renal failure, and mortality. Whether targeted interventions for aortic outcomes with specific therapeutic alternatives such as inhibitors of the renin-angiotensin-aldosterone system or β-blockers could be useful remains to be seen.

Smoking and AAAs

Smoking has been reported to be the major risk factor for AAAs in several studies of both prospective and case-control design. Our results confirm these findings in a large prospective cohort with long-term follow-up and a strict, validated end point. Smoking contributed 47% of population risk for rupture or surgically treated AAA, and the incidence rate of AAA was 58 per 100 000 person-years at risk.
Risk Profiles for Aortic Diseases

Table 4. Risk Factors and Population-Attributable Risk for Aortic Diseases

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>AAA (n=127)</th>
<th>AD (n=70)</th>
<th>TAA (n=45)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P Value</td>
<td>PAR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.03 (1.27 to 3.26)</td>
<td>0.003</td>
<td>34%</td>
</tr>
<tr>
<td>Smoking</td>
<td>5.07 (3.52 to 7.29)</td>
<td>P=0.0001</td>
<td>47%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.76 (0.31 to 1.87)</td>
<td>0.55</td>
<td>—</td>
</tr>
<tr>
<td>Obesity</td>
<td>0.85 (0.50 to 1.46)</td>
<td>0.56</td>
<td>—</td>
</tr>
<tr>
<td>apoB/apoA1</td>
<td>2.48 (1.73 to 3.54)</td>
<td>P=0.0001</td>
<td>25%</td>
</tr>
<tr>
<td>apoA1</td>
<td>1.95 (1.36 to 2.79)</td>
<td>P=0.0001</td>
<td>26%</td>
</tr>
<tr>
<td>apoB</td>
<td>1.59 (1.08 to 2.33)</td>
<td>0.02</td>
<td>8%</td>
</tr>
</tbody>
</table>

Table 5. Incidence of Aortic Diseases Across Risk Groups

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>AAA</th>
<th>AD</th>
<th>TAA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unexposed</td>
<td>Exposed</td>
<td>Unexposed</td>
</tr>
<tr>
<td>Hypertension</td>
<td>11.8 (7.4 to 17.8)</td>
<td>37.1 (30.3 to 45.0)</td>
<td>5.4 (2.6 to 9.8)</td>
</tr>
<tr>
<td>Smoking</td>
<td>14.6 (10.8 to 19.3)</td>
<td>58.4 (46.1 to 73.0)</td>
<td>12.8 (9.3 to 17.3)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>27.0 (22.4 to 32.2)</td>
<td>27.9 (9.0 to 65.0)</td>
<td>14.9 (11.6 to 18.9)</td>
</tr>
<tr>
<td>Obesity</td>
<td>27.5 (22.6 to 33.1)</td>
<td>23.6 (13.2 to 39.0)</td>
<td>14.9 (11.3 to 19.1)</td>
</tr>
<tr>
<td>apoB/apoA1</td>
<td>18.8 (14.7 to 23.6)</td>
<td>65.2 (48.9 to 85.0)</td>
<td>14.6 (11.0 to 18.9)</td>
</tr>
<tr>
<td>apoA1</td>
<td>19.2 (14.8 to 24.4)</td>
<td>49.1 (37.5 to 63.2)</td>
<td>11.0 (7.8 to 15.1)</td>
</tr>
<tr>
<td>apoB</td>
<td>23.3 (18.7 to 28.7)</td>
<td>43.3 (30.5 to 59.7)</td>
<td>15.2 (11.5 to 19.7)</td>
</tr>
</tbody>
</table>

Other Risk Factors and Aortic Disease

Smoking was a risk factor across the entire range of aortic diseases, although with different risk magnitudes for different diseases. Hypertension and dyslipidemia were also risk factors for AD and AAA but were not significantly associated with the less common outcome TAA. In addition to more limited statistical power to detect associations with TAA, we suggest that this outcome might be more etiologically heterogeneous, often occurring comitant with connective tissue diseases such as bicuspid aortic valve disease, or Marfan syndrome. Dyslipidemia has not previously been prospectively studied for association with AD. Our results particularly implicate low apoA1 as a risk factor for AD. Additional studies are needed to validate this observation and clarify underlying mechanisms. The apoA1/apoB ratio was most strongly associated with AAA, consistent with findings for coronary disease. Previous studies have suggested apolipoproteins to be slightly more sensitive markers of cardiovascular risk than the traditional lipoprotein fractions LDL and HDL. We observed strong correlation of apolipoproteins with the corresponding traditional lipoprotein fractions (correlation coefficient >0.7) in the random subset where both were available. We did not observe significant association of diabetes and obesity with any aortic disease. Previous studies have surprisingly found lower rates of aneurysmal disease and dissections in diabetic patients and experimental studies have suggested mechanisms with hyperglycemia such as increased stability of collagen fibers.
The prevalence of diabetes was low in our study, and therefore power to detect such associations was low. However, the effect direction and magnitude were similar to those of previous studies and were consistent with a protective effect of diabetes on risk of aneurysm development but not dissection.

**Study Strengths and Limitations**

The major strengths of the present study was the large size of the population sample, which allowed prospective analyses with an adequate number of aortic disease events to compute incidence rates and study risk profiles relevant to the general population. Many previous studies have been limited in interpretation by case series or case-control designs or by focusing on cross-sectional risk factor associations with aortic diameter rather than clinical outcomes. Calls for prospective studies of predictors have been raised, particularly for incident AD and TAA, which have not been well studied, as they are free of many of the biases inherent to case series and case-control studies but are hampered by the need for large cohort studies. The use of a prospective study design with nationwide registers allowed capture of both fatal cases from mortality registers and hospitalized cases from discharge registers. The registers used here have complete coverage of hospitals in the tax-financed nationwide health care system, and reimbursement to hospital departments is dependent on correct diagnostic coding. Furthermore, in contrast to several previous studies of aortic disease, each event of AD and TAA was confirmed by review of individual patient records. The high validity observed in national registers for broadly defined diagnoses of AD and TAA in the present study lends additional credibility to findings from previous register-based studies of these diseases that have also used physician’s ICD coding as outcome variables but not adjudicated end points. In risk factor analyses, we focused on clinically relevant end points including subjects diagnosed with incident AD, aneurysmal rupture, or surgical intervention for AAAs, rather than all subjects diagnosed with aortic dilation.

However, our study also has limitations that merit consideration. First, subjects were followed for as long as 20 years without reassessment of risk factor burden. It is likely that the risk factor status may have changed in some individuals during that time, which would be expected to attenuate the effect of risk factors, termed “regression dilution,” potentially resulting in underestimates of risk factor contributions to population risk. Second, our study design did not allow investigation of the contribution of less common risk factors for aortic disease, such as connective tissue diseases and aortic valvular disease, of which the most common, Marfan syndrome and bicuspid aortic valve, have been reported in 3% to 6% and in less than 2% to 4% of AD patients, respectively. Although such conditions might explain a sizeable proportion of AD cases diagnosed before 40 years of age, the contribution of these conditions to the overall aortic disease burden in the general population is likely to be limited, possibly with the exception of TAA. Additional studies with careful clinical characterization would be required to prospectively study the collective contribution of such less common disease entities.

**Conclusion**

Our results establish distinct clinical risk factor profiles for critical aortic diseases. Hypertension accounts for more than half of the population risk for AD, while smoking accounts for half of population risk for severe aneurysms in the abdominal
aorta. Our findings have important implications for the targeted surveillance and prevention of aortic disease, suggesting that preventive interventions targeting the population burden of AD should focus on hypertension, whereas AAA interventions should focus on smokers.

Acknowledgments

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Disclosures

Measurement of apolipoproteins was performed and supported by Quest Diagnostics. The funding sources had no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the manuscript for publication.

References