Factors Associated With Small Abdominal Aortic Aneurysm Expansion Rate

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IMPORTANCE Because of the high mortality rate after rupture of small abdominal aortic aneurysms (AAAs), surveillance is recommended to detect aneurysm expansion; however, the effects of clinical risk factors on long-term patterns of AAA expansion are poorly characterized.

OBJECTIVE To identify significant clinical risk factors associated with the AAA expansion rate for both constant and accelerated expansion trajectories.

DESIGN, SETTING, AND PARTICIPANTS A multivariate mixed-effects model was established to identify clinical risk factors associated with the AAA expansion rate. Separate shape factor analysis was used to characterize steady vs accelerated expansion over time. Five hundred sixty-seven patients hospitalized at Veterans Affairs medical centers were randomized to the surveillance arm of the Aneurysm Detection and Management (ADAM) study conducted by the Veterans Affairs Cooperative Studies Program from 1992 to 2000. The patients had an AAA with a maximum diameter from 3.0 to 5.4 cm, which was monitored until a 5.5-cm maximum diameter was reached or the aneurysm became symptomatic. Thirty-three participants were not included in this analysis owing to missing or extraneous values in key predictor variables. The mean (SD) follow-up time was 3.7 (2.0) years.

MAIN OUTCOMES AND MEASURES The primary outcome measure was the AAA expansion rate, determined by measurement of the maximum diameter by ultrasonography at regular intervals. The objective to assess the association of clinical variables with the expansion of the AAA was formulated after data collection.

RESULTS The mean (SD) linear expansion rate of AAAs was 0.26 (0.01) cm/y. Current smoking was associated with a 0.05 (0.01)–cm/y increase in the linear expansion rate (95% CI, 0.25-0.28; P < .001), diastolic blood pressure with a 0.02 (0.01)–cm/y increase per 10 mm Hg (95% CI, 0.01-0.04; P = .001), and diabetes mellitus with a 0.11 (0.02)–cm/y decrease (95% CI, 0.07-0.16; P < .001). Diastolic blood pressure and baseline AAA diameter were associated with accelerated AAA expansion (P = .001 and P < .001, respectively).

CONCLUSIONS AND RELEVANCE Smoking cessation and control of diastolic blood pressure are direct actions that should be taken to reduce the rate of AAA expansion. Other clinical risk factors, except for diabetes, were not associated with the AAA expansion rate. This study also provides evidence of differing trajectories in AAA expansion over time, a finding that merits further investigation.
Abdominal aortic aneurysms (AAAs) require careful surveillance: rupture has a mortality rate of up to 90%.4 Because the risk of rupture is well understood to be proportional to the AAA maximum diameter, the elucidation of risk factors for aneurysm enlargement is perhaps the most effective strategy to understand the natural history of AAA. It is incumbent not only to identify the factors broadly associated with AAA enlargement but also to clarify the nature of that enlargement, including analyses that are sensitive to the possibility that the expansion rate may not be constant but rather may increase over time.

Currently, little consensus exists as to which factors are associated with AAA expansion. For instance, findings from a meta-analysis and systematic review5,6 are inconclusive with regard to the ability of pharmacologic interventions to inhibit AAA enlargement (eg, statins and β-blockers). A separate meta-analysis7 of patient-level data from 1983 to 2003 collected from 18 studies with a mean patient follow-up of 4.0 years found that smoking increased the AAA expansion rate, though the presence of diabetes mellitus predicted a slower rate of expansion; pulse pressure and body mass index had no effect on the rate of AAA expansion. Elsewhere, a completely different set of factors—advanced age, severe cardiac disease, and a history of stroke—were significantly associated with rapid expansion.8 The lack of compelling evidence that pharmacotherapy or clinical variables other than maximum diameter could reduce the rate of AAA expansion speaks strongly to the need for further investigation into the identification of risk factors that would enhance our ability to predict rupture.

The purpose of this study was to use a large clinical database from the Aneurysm Detection and Management (ADAM) study to search for factors that predict the rate of AAA expansion. The novelty of this work is in our accounting for 2 potentially independent aspects of AAA enlargement: rate of expansion and character of expansion (ie, constant vs accelerated growth). This information may further illuminate a matter of ongoing research that is of urgent importance to a high-risk patient population.

Methods

Participants and Data Selection
The study was approved by the human subjects research committees of the Cooperative Studies Program Coordinating Center and each participating medical center. Written informed consent was obtained prior to randomization. No compensation was provided other than locally determined mileage payments for patient travel. This analysis used data selected from the patients who were randomized to the surveillance arm of the ADAM study, conducted by the Department of Veterans Affairs Cooperative Studies Group from July 20, 1992, to July 31, 2000; the study design and results of the primary analysis are described elsewhere.9,10 The patients of the surveillance arm were evaluated with a scheduled imaging visit at least every 6 months to monitor the diameter of their AAA by means of ultrasonography or computed tomography (CT), and surveillance was maintained until the diameter reached 5.5 cm, began to grow rapidly (defined as a 0.7-cm expansion in 6 months or a 1-cm expansion in 12 months), or until symptoms developed that were attributed to the AAA. If any of these criteria were met, the patient was scheduled for open repair within 6 weeks, provided he or she remained a candidate for surgery.7

Measurements
This study sought to characterize expansion prior to intervention; therefore, only participants with 2 or more preoperative measurements of the AAA dimensions were studied, and data collected after an operation were not analyzed. In instances of multiple measurements (eg, using both CT and ultrasonography or readings by multiple radiologists), a representative measurement was chosen based on assumptions of precision and consistency.8 For CT scans, the diameter of the AAA was defined as the maximal external cross-sectional measurement in any plane but perpendicular to any curvature in the aorta.7 Ultrasonographic measurements were made by a study ultrasonographer who determined the maximum external AAA diameter in at least 2 planes.7

Expansion Rate Analysis
All statistical analyses were performed using SAS, version 9.3 (SAS Institute Inc). Exploratory analysis was conducted by examining all potential predictors of expansion under individual linear mixed-effects models. These predictors were factors obtained from the physical examination and medical history, including medications taken at baseline or during follow-up.

A multivariate mixed-effects model was built with the variables that showed significance to the expansion rate in their respective models, based on the t test and defining a significance level of .05, using 2-tailed, unpaired P values. Significance of the association with expansion was demonstrated by a significant interaction with time of a given predictor. Random effects were included for intercept and time to accommodate between-patient variability for individual deviation from the population's mean baseline size and slope. This model allowed for varying lengths of follow-up time across patients and unevenly spaced visits within individual patients. Accordingly, within-patient errors were assumed to be independent and normally distributed, and the variance-covariance structure of the random-effects matrix was assumed to be unstructured with a multivariate normal distribution. The final model structure was chosen according to the smallest Akaike information criterion. An indicator variable was included in the model to adjust for systematic bias in measurements from CT scans vs ultrasonography scans. Baseline AAA diameter was included as a concomitant predictor variable to provide a better fit and a more accurate prediction of size. A mean expansion rate was estimated using the mixed-effects model, and t tests were used to identify differences in expansion rates among the predictors as well as among factors that had a presumed association with aneurysm enlargement a priori: baseline size, smoking factors, and medical history.
Accelerating Expansion Rate Analysis
In addition to the mixed-effects model, a separate “shape-factor” analysis was performed wherein the same predictive factors were assessed for association with a constant or accelerating AAA expansion rate. Although this analysis was predicated on characterization of the growth profile, it was not possible to integrate both CT and ultrasonographic measurement modalities. Parsimony was sought in excluding the less-rich data set, and ultrasonographic measurements outnumbered CT measurements at an approximately 2:1 ratio; consequently, CT measurements were excluded.

Data sets were assigned to modules with similar growth profiles using the weighted gene coexpression network analysis package, which clusters data according to the shape of a 1-dimensional profile (ie, AAA size over time). Individual growth profiles were temporally normalized and compared against all other profiles via standard correlation. These profiles were then clustered by shape similarity in up to 50 modules (arbitrarily set to approximately 10% of our sample size). To facilitate clustering, we rescaled the correlation matrix by raising it to a large positive exponent ($\beta \approx 10$), effectively increasing the contrast within the matrix by a factor of $10^\beta$. A threshold goodness-of-fit ($R^2 = 0.95$) was reached. These were subsequently aggregated into one of 3 final modules: linear increasing, quadratic increasing, or other (uncategorized).

Because data sets with 3 or fewer observations would be uniquely determined in this process, profiles with fewer than 4 observations were excluded from this analysis.

Restricting focus to the monotonically increasing AAAs (ie, those with linear or quadratic expansion), a logistic regression analysis was performed on each predictor variable to assess its association with growth trajectory. A subanalysis of the expansion rate was then performed to determine the factors associated with linear and/or accelerated growth with this filtered data set using mixed-effects models with the method described above.

Results
Patient Characteristics
Of the 1136 patients recruited for the ADAM study, 567 were randomly assigned, with equal probability, to the surveillance arm. Of these, 534 patients were used in this analysis owing to missing or extraneous values for significant predictors of the chosen model observed in 33 participants. More than 99% of the analysis group were men with a mean (SD) age of 67.6 (6.1) years, and all patients analyzed were either current smokers or ex-smokers. The mean AAA diameter at baseline was 4.2 (0.6) cm, and the mean follow-up time was 3.7 (2.0) years. Of the 534 patients analyzed, 327 (61.2%) eventually underwent surgical repair. Additional baseline characteristics are reported in Table 1.

Among the 534 patients retained in the analysis, 330 (61.8%) met the strict requirements for inclusion in the shape factor analysis. Following aggregation by polynomial fit, 3 clusters emerged from an original 9 distinct clusterings: linear growth ($n = 184$), accelerating growth ($n = 69$), and other (ie, not monotonically increasing) ($n = 77$) (Figure). Expansion Rate Analysis
The multivariate mixed-effects model determined by this analysis included time interactions with current smoking, diabetes mellitus, and diastolic blood pressure, because these were found to be significant predictors of AAA expansion ($P < .001$, $P < .001$, and $P = .001$, respectively). Two-way interactions among these predictors were evaluated but were not significant, and, although a quadratic time variable showed significance, it was not included because it increased the Akaike information criterion, reducing the model fit. The mean (SD) expansion rate from this model was 0.26 (0.01)
Current smokers had an expansion rate increased by 0.05 (0.02) cm/y (95% CI, 0.02-0.08) compared with ex-smokers, and patients with diabetes showed an expansion rate decreased by 0.11 (0.02) cm/y (95% CI, 0.07-0.16) compared with those who did not have diabetes. A 10–mm Hg increase in diastolic blood pressure was associated with a 0.02 (0.01)-cm/y increase (95% CI, 0.01-0.04) in the AAA expansion rate. Additional details are reported in Table 2. Inclusion of these predictors provided a far better fit for the model to the data compared with the null model that considered only the time slope according to the reduction in the Akaike information criterion.

The baseline AAA diameter was not significantly associated with the expansion rate after adjustment for the other predictors (P = .82). After stratification by 1-cm increments (3.0–3.9, 4.0–4.9, and 5.0–6.0 cm), there was a 0.4-cm increase in expansion rate per year for the 5.0–6.0-cm group compared with the 3.0–3.9-cm and 4.0–4.9-cm groups, but this was not a significant trend (P = .24 and P = .18, respectively).

Medications that were suspected of decreasing the AAA expansion rate were also examined, and β-blockers, cholesterol-lowering medications, antihypertensives, daily aspirin, antiarrhythmics, and anticoagulants were not associated with the expansion rate. Additional factors expected to show an association (ie, smoking, hypertension, atherosclerosis, and other medical history items) also were not significantly associated with the expansion rate (Table 3).

Accelerating Expansion-Rate Analysis
Baseline AAA size was among the factors presumed to be associated with enlargement a priori. However, where we expected, but did not find, an association between the baseline AAA size and expansion rate in the multivariate mixed-effects model (as either a continuous or stratified predictor), we tested the relationship between the expansion trajectory shape (ie, linear vs quadratic expansion profile over time) and baseline diameter. By testing this association in a more homogeneous data set, we anticipated that we would increase our power to identify any latent relationship between baseline size and AAA expansion. We found that the association between increased initial AAA diameter and the patient’s membership in the quadratic growth module was significant (P < .001).

The multivariate linear mixed-effects model fitted to the filtered data included significant factors associated with both linear and accelerated expansion rates; diabetes decreased the linear rate of expansion by 0.11 cm/y (95% CI, 0.03-0.20; P = .005), and diastolic blood pressure and baseline size were associated with the rate of change of the expansion, with increased acceleration rates of 0.005 cm/y² per 10 mm Hg (95% CI, 0.002-0.01; P = .001) and 0.02 cm²/y² (95% CI, 0.02-0.03; P < .001), respectively (Table 4).

Discussion

Smoking, Diastolic Blood Pressure, and Diabetes
Our finding of a significant association of current smoking (19% increase) and diabetes (40% decrease) with the linear expansion rate are consistent with the findings of the meta-analysis of factors affecting small AAA expansion reported by Sweeting et al,4 which found a 16% increase and a 25%
decrease, respectively. The counterintuitive finding of apparent mitigation of AAA expansion risk in patients with diabetes may be explained by the significant correlation of diabetes with reduced extensibility as well as increased stiffness of the aorta.\textsuperscript{11,12}

Smoking has been shown\textsuperscript{4,5,13,14} to increase the expansion rate of the aneurysm. The significance of the association that current smoking has on AAA indicates the need for the patient to cease smoking, especially since smoking has been reported\textsuperscript{4} to double the risk of aneurysm rupture. Although current smoking and diabetes have both appeared to be significantly associated with the AAA expansion rate in other studies, diastolic blood pressure has been shown to be associated only with the occurrence of an AAA\textsuperscript{15,16} and not necessarily with its growth. A history of hypertension and use of an antihypertensive medication indicated that it is likely that the persistence of high diastolic blood pressure, despite medication, is associated with the expansion rate.

### Baseline AAA Diameter

Although AAs with a larger baseline diameter were expected to have a faster expansion rate, as has been shown in several other reports,\textsuperscript{4,13,17,18} no significant difference was found in the present study when the comprehensive data set was incorporated into a linear mixed-effects model. However, subgroup analysis was commensurate with our expectation: the expansion rate in the group with the largest baseline AAA diameter (5.0–6.0 cm) was 14% and 15% faster than the expansion rates in the smaller-diameter groups (3.0–3.9 and 4.0–4.9 cm, respectively). Moreover, analysis of the filtered data confirmed that larger baseline AAA size was associated with an accelerating expansion rate in both the logistic regression between linear and quadratic growth modules and the multivariate linear mixed-effects model, suggesting that high-quality data are essential in detecting this pattern.

### Pharmacotherapy

The use of β-blockers had in the past been considered beneficial in slowing AAA enlargement,\textsuperscript{19,20} although a review\textsuperscript{21} of 3 randomized trials examining the effect of propranolol determined that there was not a significant effect. Our analysis supports the conclusion of a lack of effect of β-blockers (the effect on the expansion rate was nonsignificant; \(P = .51\)). The use of cholesterol-lowering medications was associated with a

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**Table 3. Adjusted Differences in Expansion Rate by Suspected Predictor**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Adjusted Difference (95% CI), cm/y</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smokers vs nonsmokers</td>
<td>(-0.08 (-0.22 to 0.05))</td>
<td>.24</td>
</tr>
<tr>
<td>Years of smoking, per 1-y increase</td>
<td>(0.00001 (-0.001 to 0.001))</td>
<td>.99</td>
</tr>
<tr>
<td>Pack-years, per 1-pack-year increase</td>
<td>(0.0001 (0.000 to 0.001))</td>
<td>.64</td>
</tr>
<tr>
<td>Years ago quit smoking, per 1-y increase</td>
<td>(-0.0002 (-0.002 to 0.001))</td>
<td>.78</td>
</tr>
<tr>
<td>Hypertension factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of hypertension</td>
<td>(0.02 (-0.05 to 0.01))</td>
<td>.16</td>
</tr>
<tr>
<td>Systolic blood pressure, per 10-mm Hg increase</td>
<td>(-0.002 (-0.01 to 0.001))</td>
<td>.66</td>
</tr>
<tr>
<td>Atherosclerosis factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of high cholesterol</td>
<td>(-0.01 (-0.04 to 0.02))</td>
<td>.34</td>
</tr>
<tr>
<td>Total cholesterol, per 5-mg/dL increase</td>
<td>(0.01 (-0.01 to 0.03))</td>
<td>.27</td>
</tr>
<tr>
<td>HDL-C, per 5-mg/dL increase</td>
<td>(-0.05 (-0.11 to 0.02))</td>
<td>.15</td>
</tr>
<tr>
<td>LDL-C, per 5-mg/dL increase</td>
<td>(0.01 (-0.01 to 0.04))</td>
<td>.20</td>
</tr>
<tr>
<td>BMI, per 1-U increase</td>
<td>(0.000 (-0.003 to 0.004))</td>
<td>.95</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>(0.01 (-0.02 to 0.04))</td>
<td>.65</td>
</tr>
<tr>
<td>Angina or coronary artery disease</td>
<td>(-0.003 (-0.03 to 0.03))</td>
<td>.84</td>
</tr>
<tr>
<td>Emphysema or COPD</td>
<td>(0.005 (-0.03 to 0.04))</td>
<td>.79</td>
</tr>
<tr>
<td>Stroke or TIA</td>
<td>(0.04 (-0.004 to 0.08))</td>
<td>.08</td>
</tr>
<tr>
<td>Deep-vein thrombosis</td>
<td>(0.004 (-0.06 to 0.06))</td>
<td>.88</td>
</tr>
<tr>
<td>Claudication</td>
<td>(-0.01 (-0.06 to 0.03))</td>
<td>.52</td>
</tr>
<tr>
<td>CABG or PTCA</td>
<td>(0.002 (-0.03 to 0.03))</td>
<td>.92</td>
</tr>
<tr>
<td>Cancer</td>
<td>(0.02 (-0.02 to 0.05))</td>
<td>.40</td>
</tr>
<tr>
<td>Pulmonary emboli</td>
<td>(0.02 (-0.08 to 0.12))</td>
<td>.69</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-blocker</td>
<td>(0.009 (-0.02 to 0.04))</td>
<td>.51</td>
</tr>
<tr>
<td>Cholesterol-lowering medication</td>
<td>(-0.02 (-0.05 to 0.01))</td>
<td>.18</td>
</tr>
<tr>
<td>Antihypertensive</td>
<td>(-0.001 (-0.04 to 0.03))</td>
<td>.78</td>
</tr>
<tr>
<td>Daily aspirin</td>
<td>(-0.01 (-0.05 to 0.02))</td>
<td>.48</td>
</tr>
<tr>
<td>Antiarrhythmic</td>
<td>(0.000 (-0.03 to 0.03))</td>
<td>.98</td>
</tr>
<tr>
<td>Anticoagulant</td>
<td>(0.001 (-0.03 to 0.03))</td>
<td>.94</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PTCA, percutaneous transluminal coronary angioplasty; TIA, transient ischemic attack.
slower expansion rate by 0.02 cm/y in the present analysis; however, this difference was not statistically significant \( P = .18 \), in contrast to reports\(^{22-24} \) that patients not receiving statins had a significantly larger AAA size after 2 years of follow-up.

**Study Limitations**

The full set of measurement data could not be analyzed simultaneously in a portion of our analysis, since both ultrasonography and CT scans were used and there is no known transfer function to adjust one measurement to the scale of the other. Ultrasonography is limited in terms of its accuracy and variability of measurement, particularly in comparison with CT measurement. However, the study ultrasonographers followed a standardized procedure and were instructed to measure the maximum external cross-sectional measurement of the AAA.\(^7 \) Ultrasonography was the measurement modality used throughout the monitoring stage (CT scans were required only at enrollment, when there was evidence that the AAA had grown to the threshold for repair, and at the end of follow-up), and provided the best support for an analysis of the enlargement of the aneurysm over time.

Another limitation of the present study is that most of these participants were men (99.6%), white (94.2%), and current smokers (99.1%). Although there has been no report indicating a difference in AAA expansion rate associated with race, a distinction has been noted between sexes in that women have a faster rate of expansion,\(^{25} \) in addition to an increased rate of rupture and increased mortality following rupture.\(^{25} \) The results of the present analysis of such a largely homogeneous group may therefore be missing details that are unique to a more heterogeneous population.

In the published results of the ADAM study,\(^7 \) baseline diameter measurement of the AAA and the absence of diabetes were reported as the significant univariate predictors of an increased rate of expansion. This result was identified by calculating expansion rates by taking the difference of the last and first CT measurements, dividing over the difference in time, and testing for association (t test) among potential predictors. In the present study, however, we reported on additional factors owing to the use of a repeated-measures, mixed-effects model, which allowed for expansion rates to be estimated using the follow-up measurements that had been omitted from the aforementioned analysis.\(^7 \) In addition, the methods used here have estimated a mean (SD) expansion rate of the AAAs of 0.26 (0.01) cm/y compared with the previously reported\(^7 \) median value of 0.32 cm/y. Here again, we believe that this difference primarily reflects the variability in approaches to measuring the expansion rate: the present analysis used a more sophisticated approach that takes into account the longitudinal surveillance data; the outcome measures of the ADAM study involved comparison of only the first and last CT scans where AAA measurement for the last CT scan may be positively biased. Nevertheless, the expansion rate reported in the present study is well within the interquartile range reported previously (0.16–0.42 cm/y),\(^7 \) which suggests the viability of these data as a sound comparison data set.

**Shape Factor Analysis**

Inspection of the diameter-vs-time data revealed a spectrum of growth profiles including a substantial proportion of non-linear trends. Because expansion rate is an important factor in the clinical calculus, we set out to ascertain the prevalence of accelerated vs linear growth of the AAA and identify any factors that would predispose an individual to accelerated growth.

To our knowledge, we are the first to report on the prevalence of accelerating AAA growth at approximately 20% (69/330 = 0.209) (Figure) and that only the baseline AAA diameter appears to influence the growth profile shape factor. Otherwise, our results from this analysis may be considered confirmatory of the findings from the multivariate mixed-effects model, with the exception of current smoking. We believe that these findings have important implications for clinical decision making and will have an effect on the AAA research community, both for how AAAs are perceived and how their expansion is studied.

**Conclusions**

The results of this analysis have demonstrated that current smoking and elevated diastolic blood pressure are associated with an increased linear expansion rate of AAAs, diabetes is associated with a decreased linear expansion rate, and larger baseline AAA diameter and elevated diastolic blood pressure are associated with an accelerating expansion rate. These findings suggest that control of diastolic blood pressure and smoking cessation are direct actions that can and should be taken to reduce the rate of AAA enlargement.
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Author Contributions: Ms Bhak and Dr Wininger had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Bhak, Wininger, Johnson, Ballard.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Bhak, Wininger, Messina, Ballard.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Bhak, Wininger, Johnson, Ballard.

Obtained funding: Johnson, Lederele.

Administrative, technical, or material support: Johnson, Lederele.

Study supervision: Wininger, Johnson, Ballard.

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Group Information: The Aneurysm Detection and Management (ADAM) Study investigators include Frank A. Lederle, MD, Samuel E. Wilson, MD, Gary R. Johnson, MD, Donovan B. Reineke, MD, Fred N. Littooy, MD, Charles W. Acher, MD, David J. Ballard, MD, MSPH, PhD, Louis M. Messina, MD, Ian L. Gordon, MD, Edmund P. Chute, MD, William C. Krupski, MD, Steven J. Busuttil, MD, Gary W. Barone, MD, Steven Sparks, MD, Linda M. Graham, MD, Joseph H. Rapp, MD, Michel S. Makaroun, MD, Gregory L. Moneta, MD, Robert A. Cambria, MD, Raymond G. Makhoul, MD, Darwin Eton, MD, Howard J. Ansel, MD, Julie A. Freischlag, MD, and Dennis Bandyk, MD. A complete listing of the members of the ADAM Study group (investigators, ultrasonographers, program site personnel, and monitoring and administrative committees) appears in the eAppendix in the Supplement.

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REFERENCES


