# REVIEW ARTICLE

Richard P. Cambria, MD, Section Editor

# A systematic review and meta-analysis of the association between markers of hemostasis and abdominal aortic aneurysm presence and size

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***Objective:*** **The purpose of this study was to summarize the current evidence of the association between markers of hemostasis and both the presence and size of abdominal aortic aneurysms (AAAs).**

***Methods:*** **A systematic review and meta-analysis was performed according to Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines by use of the search terms "aneurysm AND abdominal AND aortic AND coagulation" NOT "thoracic." Outcome data including concentration of hemostatic marker, number of patients, and significance level were recorded.**

***Results:*** **A total of 22 nonrandomized studies were included in the analysis, with a total of 9862 patients. Fibrinogen mean difference (MD) (0.43 g/L; 95% confidence interval [CI], 0.28-0.58 g/L; $P \leq .00001$), D-dimer MD (325.82 ng/mL; 95% CI, 199.74-451.89 ng/mL; $P \leq .00001$), and thrombin-antithrombin III complex MD (5.58 g/L; 95% CI, 3.34-7.83 g/L; $P \leq .0001$) were significantly elevated in the presence of AAAs. Tissue plasminogen activator, prothrombin fragments F1+F2, and platelet count were not shown to be significantly different between patients with and those without AAAs. Meta-regression of studies reporting plasma D-dimer concentration and aneurysm diameter suggests a strong and significant association ($r^2 = 0.94$; $P \leq .0001$).**

***Conclusions:*** **This study suggests that the presence of AAAs is associated with increased fibrin turnover, fibrinolysis, and thrombin generation, as shown by increased levels of fibrinogen, D-dimer, and thrombin-antithrombin III complex. This is clinically relevant because markers of hemostasis are independent risk factors for cardiovascular events, highlighting the necessity of addressing all modifiable cardiovascular risk factors in patients with AAAs. Furthermore, the finding that plasma D-dimer concentration appears to have a linear relationship with aneurysm diameter may be useful as a future biomarker of AAAs. (J Vasc Surg 2014;59:528-35.)**

Abdominal aortic aneurysms (AAAs) are a substantial burden on health care in most developed countries and an important cause of years of life lost in the United Kingdom. Efforts to reduce mortality rates from AAAs depend largely on the early detection and elective repair of the AAA, and, in the United Kingdom, the NHS AAA Screening Programme (NAAASP) is due to be fully rolled out on the basis of evidence that ultrasound screening for AAAs is safe, cost-effective, and has a high sensitivity and specificity.[1] The presence of an AAA is, however, strongly associated with cardiovascular disease; for example, the United Kingdom Small Aneurysm Trial observed a 28% incidence of cardiovascular mortality over an 8-year period.[2] Several studies have shown that this risk progressively increases with aortic diameter,[3] and, although much of this association is thought to be secondary to shared risk factors, several studies have shown that circulating markers of hemostasis are elevated in patients with aortic dilatation and that they are independently associated with cardiovascular events.[4]

The nearly consistent presence of a nonocclusive mural thrombus[5] in patients with AAAs, characterized by erythrocyte hemagglutination and neutrophil trapping (a process that releases free hemoglobin, leading to platelet activation, fibrin formation, and binding of plasminogen causing oxidative and proteolytic injury of the arterial wall[6]), may drive this coagulopathy. This activity is mainly orchestrated at the intraluminal thrombus-blood interface,[7] and thus circulating markers of this activity could be measured peripherally.

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Comparing circulating markers of hemostasis in patients with and those without AAAs adds to our understanding of the pathophysiology of the disease, and several studies have investigated their usefulness as possible biomarkers of aneurysm presence and size; therefore, the purpose of this study is to summarize the current evidence. We performed a systematic review and meta-analysis of case-control studies comparing markers of hemostasis in patients with and those without AAAs and of the association between markers of hemostasis and aneurysm diameter.

## METHODS

Standard reporting guidelines set by the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA)[8] were followed to identify case-control studies comparing plasma concentrations of markers of hemostasis in patients with and those without AAAs and studies testing the association between markers of hemostasis and aneurysm size. Study titles and abstracts were searched through the use of Medline and Embase databases, with the use of Ovid Online (Version: OvidSP_UI03.04.02.112; Ovid Technologies, Inc) on December 28, 2013, separately by D.S. and P.S. No language restrictions or filters used to restrict study designs were applied. Reference lists were searched for further studies to be included.

**Eligibility criteria and study selection.** A comprehensive literature search was performed through the use of the search terms "aneurysm AND abdominal AND aortic AND coagulation" NOT "thoracic." Two reviewers, DS and PWS, individually reviewed potential studies according to a set of eligibility criteria, with discrepancies discussed. Inclusion criteria were that the study must either (a) be an original publication with either a case-control design comparing markers of hemostasis in patients with AAAs and control subjects, or (b) test the association between markers of hemostasis and aneurysm size. The following articles were excluded: review articles, studies in which duplicated data was published, and those pertaining to thoracic aortic aneurysms. The quality of the nonrandomized controlled studies was evaluated by use of the Newcastle-Ottawa Scale.[9] The potential for publication and reporting bias was assessed through the use of funnel plots.

**Data collection.** Data were extracted independently by two reviewers, DS and PWS, with any discrepancies discussed. The following outcomes were recorded: year of publication; author; journal; concentration of marker in AAA; concentration of marker in control; number of patients; mean; median; standard deviation (SD); interquartile range (IQR); significance level; mean aneurysm size; and SD of aneurysm size.

**Statistical analysis.** The data were analyzed with the use of Review Manager 5.2.[10] Separate analyses were performed for each individual outcome, with all possible papers included in which they had published results on the outcome under analysis. For each study, data were extracted on mean concentrations SDs. In articles reporting the median and IQR, we took the median to be representative of the mean and converted the IQR into an SD.[10] To assess heterogeneity between studies, the $I^2$ statistic was used.

Meta-analysis was performed by means of a random-effects model in which significant statistical heterogeneity was identified and a fixed-effects model in which it was not identified. An $\alpha$ level of $\leq .05$ was used to determine statistical significance, with outcomes reported as mean differences and confidence intervals. To determine whether biomarker concentrations were associated with AAA size, meta-regression was performed by means of inverse variance weighted linear regression. Biomarker concentrations were compared with the reported mean/median aneurysm size from each study. In cases in which biomarker concentrations were reported stratified by AAA size, each size subgroup was entered into the regression as a separate outcome. Sensitivity analyses were performed by excluding studies with less than 100 patients and recalculating the pooled mean difference (MD) estimates for the remaining studies.

## RESULTS

**Literature search.** A total of 309 abstracts were identified through literature search, with three studies identified through manual searching of reference lists from these articles. After removal of duplicates, review of the titles and abstracts of 254 papers was performed. A total of 27 papers were obtained and read in full. Five studies were excluded for the following reasons: Two studies were excluded because they were review articles,[6,11] two studies were excluded because they compared markers of coagulation in patients with ruptured vs nonruptured AAAs,[12,13] and one was excluded because it contained duplicate data.[14]

A total of 22 nonrandomized studies were included in the analysis. Three studies[15-17] reported on both a control group of age-matched individuals and a control group with peripheral arterial disease. For the purpose of this analysis, the peripheral arterial disease group was excluded. Seven studies specifically investigated the association between AAA diameter and markers of hemostasis (Supplementary Table I, online only).[18-24] The PRISMA diagram is shown in Fig 1.

**Study quality and publication bias.** The Newcastle-Ottawa scale was used to assess the quality of nonrandomized studies, with all studies scoring 7 or more of 9. Funnel plots were performed for all outcomes. All funnel plots suggested minimal publication bias (Supplementary Fig 1, *a-f*, online only).

### Studies comparing patients with and those without AAAs

**Fibrinogen.** A total of 12 studies[16-18,20,25-31] reported on concentrations of plasma fibrinogen in patients with and those without AAAs. The largest of these studies included 3424 patients,[32] whereas the smallest contained 34 patients.[29] Methods were similar between studies, with the majority comparing AAAs diagnosed on USS against healthy age-matched control subjects; however, two studies used control groups including healthy age-matched individuals and patients with peripheral arterial disease.[16,17] Ten of the 12 studies[31] reported fibrinogen concentrations in men and