

D-dimer measurement: a useful prognostic marker in surveillance of patients with abdominal aortic aneurysm?

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This editorial refers to ‘Evaluation of the diagnostic and prognostic value of plasma D-dimer for abdominal aortic aneurysm’[†], by J. Golledge *et al.* on page 354

Over the last decade, abdominal aortic aneurysm (AAA), defined as an aortic diameter ≥ 30 mm, has increasingly been recognized as an important cause of mortality, accounting for 2.1% of deaths in men aged >65 years. Large screening studies have suggested a prevalence of 5.1–7.7% in men over the age of 64. Despite advances in surgical and anaesthesiological techniques, mortality remains high in patients with a ruptured AAA. Thus, elective repair in appropriately selected individuals is advantageous, prevents rupture, and thereby improves life expectancy. Simplified abdominal ultrasound is recognized for its accuracy in identifying AAA, with a reported sensitivity of 95% and specificity of 99%. Evidence suggests that a single screening in the highest risk group is sufficient to exclude risk from this disease for >10 years with $<2\%$ of examinations insufficient to measure aortic diameters.¹

Based on these data, ultrasound screening programmes have been evaluated in an attempt to reduce AAA-related mortality in the general population. The largest of these trials, the Multicentre Aneurysm Screening Study, randomized a population-based sample of 67 800 men aged 65–74 years in the UK. After 4 years of follow-up, relative risk reduction of AAA-related deaths was 42% [95% confidence interval (CI) 22–58%].² A meta-analysis of further randomized controlled trials subsequently confirmed these results [odds ratio (OR) in AAA-related mortality, 0.56; 95% CI 0.44–0.72]. Moreover, long-term results showed a significant reduction in emergency operations (OR 0.48; 95% CI 0.28–0.83), while the number of elective operations increased significantly (OR 2.81; 95% CI 2.40–3.30).³ Thus, a single ultrasound examination reduces AAA-related mortality by facilitating elective surgical intervention before rupture.⁴ In addition to evidence of a mortality benefit and feasibility of implementation, relevant cost-effectiveness studies of population-based AAA screening have

shown it to be in the same range as other cost-effective preventive services such as screening for arterial hypertension or breast cancer.

Ultrasound screening for AAA is cost-effective, and single screening excludes risk from this disease for >10 years. Do we need more diagnostic parameters than that?

National ultrasound screening programmes for AAA in men between the ages of 65 and 75 who have ever smoked have recently been implemented in England, Scotland, and in the USA as part of Medicare.⁵ Ultrasound screening is a quick, inexpensive, and non-invasive procedure that enables early detection of AAAs. Once detected, an AAA can be monitored for size and surgical or endovascular repair offered at a size threshold of ≥ 55 mm where the risk of rupture is considered high.

As a matter of fact, most screening-detected AAAs are small (<55 mm). In a screening study of 12 203 men ≥ 65 years of age performed in Australia, 814 (6.7%) had a small AAA measuring 30–54 mm, but only 61 (0.5%) had a large AAA (≥ 55 mm). The policy of early elective surgery for small AAAs (40–55 mm) has not been demonstrated to save lives as it is associated with a low rate of rupture of $\sim 1\%$ per annum.⁶ However, risk of rupture still exists in small AAAs (Table 1) with considerable inter-patient variation, i.e. some small AAAs rapidly progress to rupture and some large AAAs remain stable for prolonged periods.

The increase in identification of small AAAs resulting from screening programmes, in association with an ageing population, therefore creates a problem with surveillance offered to these patients.⁶ Prognostic determinants for AAA progression in patients with a small AAA <55 mm are poorly defined, although $\sim 70\%$ of

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small AAAs expand to a size requiring treatment within 10 years. As ultrasound surveillance alone is incapable of detecting biological activity it becomes apparent that not all patients with small AAAs are protected, and rapid progression to rupture can occur unnoticed between scanning intervals.

Is there an incremental value of D-dimer measurement?

Proteolysis and inflammation resulting in destruction of arterial connective tissue are the pathological hallmarks of AAA. Thus, circulating markers that reflect aortic wall destruction or inflammatory activity could potentially help in the identification of appropriate patients for different surveillance protocols and

Table 1 Correlation between maximum abdominal aortic aneurysm diameter and risk of rupture⁷

Diameter (cm)	1-year risk of rupture (%)	5-year risk of rupture (%)
3–3.9	0.4	1–2
4–4.9	1.1	5–13
5.5–5.9	3.3	25–38
6.6–6.9	9.4	No data
7–7.9	24	No data

intervention. Currently there is no clear consensus on which markers are of most value to predict AAA growth reproducibly or to select subsets of patients with small AAAs at high risk of rupture.⁸ The study by Golledge *et al.*⁹ indeed raises hope towards improved AAA patient management algorithms. In a multiple logistic regression model, plasma D-dimer levels are confirmed to have a powerful association with AAA diameter (OR 12.1 and 24.7 for cut-offs of 400 and 900 ng/mL as compared with D-dimer levels up to 90 ng/mL, respectively). These findings are consistent with previous small studies that assessed the association of D-dimer and presence of an AAA.¹⁰ Importantly, the present series is based on more subjects than all previous studies combined, and results from patients with AAA are compared with disparate patient groups: the diagnostic value of D-dimer was assessed in both a population sample with 1260 subjects identified from population AAA screening, and 132 subjects with symptomatic peripheral artery disease or AAA from a referral clinic. Elevated concentrations of fibrinogen degradation products have been reported in association with atherosclerosis; however, findings from the current study clearly show that plasma D-dimer levels are distinctively higher in AAA patients as compared with those with atherosclerosis, namely peripheral artery disease alone. Finally, and probably most importantly, the authors demonstrate an association between D-dimer and AAA growth independent from baseline AAA diameter at a median of 5.5 years. Moreover, merging the information of initial D-dimer level and AAA diameter, a separation of AAA growth as disparate as 0.4 and 2.5 mm per year was achievable (Figure 1).

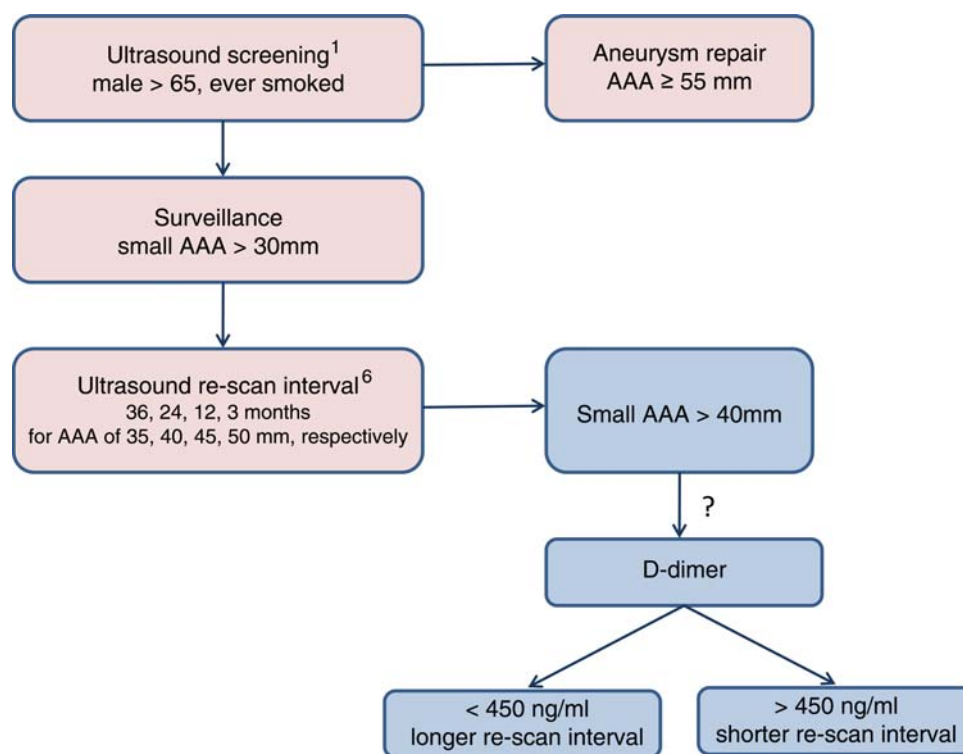


Figure 1 Surveillance of abdominal aortic aneurysm.

Could D-dimer be a target for functional imaging in patients with small AAA?

Aneurysms of the abdominal aorta are characterized by a dilated, diseased wall frequently lined by a non-occlusive thrombus. Its morphological characteristics are linked to AAA evolution in that thrombus volume is highly correlated with the severity of aortic dilatation and growth of such a thrombus, possibly predicting aneurysm rupture. The pathogenic role is thought to be mediated by inflammatory cell and proteolytic enzyme sequestration. An active role for the mural thrombus in disease progression is supported by findings showing more degradation within an aneurysmal wall lined by a thrombus compared with an adjacent wall in contact with flowing blood. The thrombus mass itself is biologically active, with fibrin generation demonstrable at the luminal interface, and markers of fibrin turnover correlate with maximum aortic diameter. The tightest association is noted for TAT complex and D-dimer levels.¹¹ This suggests that the predictive values of fibrinolytic components found in AAA patients mirror the proteolytic activity of the mural thrombus, explaining the link between the observed thrombus and the immediate risk of rupture.¹² Thus, the finding that elevated concentrations of D-dimer found in AAA patients might be related to the biological activity of the mural thrombus suggests that measurement of plasma D-dimer could be a target for functional imaging of small AAA in addition to ultrasound surveillance.

Can elevated D-dimer in patients with a small AAA be differentiated from other disease processes?

D-dimer is a fibrin degradation product present in negligible amounts in healthy individuals, but thrombotic–fibrinolytic disease conditions substantially increase D-dimer in plasma. Emerging evidence endorses that D-dimer levels provide an indication for a variety of diseases, including venous thromboembolism, disseminated intravascular coagulation, acute aortic dissection, stroke, acute coronary syndrome, infectious diseases, and cancer. As patients with conditions with potential activation of the thrombotic–fibrinolytic system were not excluded from the study by Golledge *et al.*,⁹ it is difficult to ascertain whether the cause of high D-dimer is the expression of more mural thrombus in patients with AAA or the result of various associated co-morbidities. Most critically, the high prevalence of cardiovascular disease is associated with the presence of AAA. Although elevated concentrations of fibrinogen degradation products have been reported in association with atherosclerosis, Golledge *et al.* demonstrate that plasma D-dimer concentrations are distinctively higher in AAA patients as compared with those with atherosclerosis, namely peripheral artery disease.

Conclusion

Ultrasound screening is not limited to identifying patients with large AAAs (>55 mm) for repair, but includes the identification of patients with small AAAs (30–54 mm) at risk. It is unlikely that D-dimer assessment will replace ultrasound as first-line diagnostic modality to diagnose the presence of AAA. It is postulated, however, that biomarkers such as D-dimer measured at baseline or during follow-up might provide important prognostic information about subsequent aortic behaviour, thereby allowing for more patient-specific management. Data of the present study are important and suggest that the level of D-dimer found in AAA patients mirrors the proteolytic activity of the mural thrombus and allows for a better prediction of disease progression than ultrasound surveillance alone.

Screening for AAA and continued surveillance incur costs to health providers and some anxiety for patients. Both can be minimized by using the maximum interval between surveillance visits that does not compromise patient safety. Further studies are surely required to establish whether D-dimer testing, alone or combined with other prognostic indicators, can be used to better identify patients with high risk of small AAA progression or rupture.

Conflict of interest: none declared.

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