

## Circulating Markers of Abdominal Aortic Aneurysm Presence and Progression

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Over the last decade, abdominal aortic aneurysm (AAA) has increasingly been recognized as an important cause of mortality in older persons. In 1999, for example, AAA was noted to be the 15th leading cause of mortality in the United States.<sup>1</sup> Exact estimates of AAA-related fatalities are hampered by the low rate of postmortems when sudden death occurs in elderly subjects; however, recent figures suggest that AAA accounts for  $\approx$ 15 000 deaths annually in the United States despite the increasing number of elective AAA repairs.<sup>2,3</sup> Approximately 25 000 endovascular and open AAA repairs are performed annually in the United States.<sup>3</sup>

Ultrasound screening of men  $>65$  years of age has been demonstrated to reduce AAA-related mortality, and selective screening (of men  $\geq 65$  of age who have ever smoked) has been introduced in the United States.<sup>4</sup> Most screen-detected AAAs are small ( $<55$  mm), and surgery for these AAAs has not been demonstrated to improve outcome.<sup>5-7</sup> In a screening study of 12 203 men  $\geq 65$  years of age performed in Australia, for example, 814 (6.7%) had a small AAA measuring 30 to 54 mm, but only 61 (0.5%) had a large AAA ( $\geq 55$  mm).<sup>8</sup> The increase in identification of small AAAs resulting from screening programs, in association with an ageing population, highlights the number of deficiencies in the current diagnosis and management of this condition.

First, there are no accurate nonimaging methods of diagnosing small AAAs, with clinical examination being inaccurate.<sup>9</sup> Second, prognostic determinants for AAA are relatively poorly defined.<sup>10</sup> Approximately 70% of 40- to 55-mm AAAs expand within 10 years to a size requiring treatment.<sup>6,7</sup> There are, however, large inpatient and outpatient variations in rates of expansion of small AAAs during follow-up.<sup>10</sup> To date, only initial aortic diameter has consistently been shown to predict a subsequent increase in aortic diameter.<sup>10-13</sup> Smoking has been associated with increased and diabetes with decreased AAA expansion in some but not all studies.<sup>10-13</sup> More accurate prognostic predictors would offer the possibility of selecting patients for different management pathways rather than relying on aortic diameter alone.<sup>10</sup> Finally, the management of small AAAs remains controversial despite randomized controlled trials indicating that open

surgical repair of 40- to 55-mm AAAs does not reduce mortality.<sup>6,7</sup> Many centers manage all AAAs  $\leq 55$  mm conservatively. Estimates based on the UK Small Aneurysm Trial support repeat imaging for 30- to 40-, 41- to 45-, 46- to 50-, and 51- to 55-mm AAAs at 24-, 12-, 6-, and 3-month intervals, respectively.<sup>10</sup> The increasing use of endovascular repair of AAA, with its lower perioperative mortality, has been suggested as more appropriate management for small AAAs, particularly those in the 50- to 55-mm range.<sup>14,15</sup> At present, however, no randomized controlled trial examining the outcome of endovascular repair of small AAAs has been completed, although 1 such study is expected to report soon.<sup>16</sup> The lack of any proven medical therapy for prevention of the progression and rupture of AAAs represents an important challenge.<sup>17</sup> Only 1 randomized trial has examined the value of a medication (propranolol) for small AAAs in a cohort of a reasonable size ( $>500$  subjects).<sup>18</sup>

### Potential Value of Circulating Biomarkers

Associating concentrations of a range of circulating proteins with AAA has been of interest for a number of reasons in keeping with the currently accepted deficiencies in the management of this condition outlined earlier. Most commonly, investigators have measured circulating concentrations of a marker to assess its possible role in the pathogenesis or progression of AAA. When identified, such biomarkers may thus suggest possible targets for new medical treatments to slow AAA progression.<sup>19</sup> With increasing interest in identifying AAAs at an early stage, circulating markers also could play a role in the diagnosis of small AAAs. Furthermore, biomarkers may have a role in predicting subsequent progression of AAA and therefore ultimately tailoring the management of the condition. The complications of AAAs are not completely reflected by aortic diameter alone. For example, some small AAAs rupture and some large AAAs remain stable for prolonged periods.<sup>20,21</sup> Circulating markers that accurately reflect aortic wall destruction or inflammatory activity could potentially aid substantially in the identification of appropriate patients for different monitoring protocols and intervention (both drug based when developed and

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surgery) rather than the use of aortic diameter alone. Given these potential values of circulating biomarkers in the management of AAA, we carried out a literature review to summarize the present evidence for an association between different markers and AAA presence or progression.

### Literature Search

Given the potentially large number of markers that may have been investigated, we carried out a staged search strategy. First, we performed a general search to identify biomarkers that have been investigated for association with AAA. The search terms *biomarker* and *abdominal aortic aneurysm* (articles identified, 185), *plasma* and *abdominal aortic aneurysm* (limits, human; articles identified, 245), and *serum* and *abdominal aortic aneurysm* (limits, human; articles identified, 332) were used to search the PUBMED database. These terms were selected because we wanted to concentrate on factors measurable in serum and plasma, rather than cell-associated markers, because we thought these markers would be more easily applicable to measurement in the average diagnostic laboratory. Publications with at least 50 patients (cases and controls combined) were selected for further examination. Markers for which  $\geq 2$  studies were identified from this initial search were assessed in more individualized searches using focused terms. Thus, searches for *fibrinogen* and *abdominal aortic aneurysm*, for example, were carried out, along with other identified markers. In general, 3 types of studies were identified from these searches. The most common study type involved a comparison of the circulating biomarker concentrations in cases with AAA and controls who were aged matched and healthy or had other cardiovascular disease. Other studies related the biomarker concentration to AAA expansion. Finally, a small number of studies related biomarkers to clinical outcomes such as the likelihood of presentation with aortic rupture or a successful aortic surgery. In the following sections, we describe the findings of these studies, concentrating most on association studies with AAA presence because they make up the commonest study type.

## Circulating Biomarkers and Their Association With AAA Presence in Case-Control Studies

### Rationale for Biomarker Selection

A number of approaches are possible in the identification of possible biomarkers for AAA. Most studies have chosen biomarkers on the basis of the present understanding of the pathogenesis of AAA. Examination of aortic biopsies from patients undergoing open repair demonstrates medial destruction associated with a paucity of vascular smooth muscle cells, an accumulation of macrophages and lymphocytes, elastin fragmentation, high concentrations of proteolytic enzymes and cytokines, and laminated thrombus.<sup>19,22–25</sup> On the basis of these pathological features, investigators have examined circulating lipids, thrombosis-related proteins, markers of extracellular matrix turnover and degradation, and proinflammatory and related cytokines.

A potential alternative approach to biomarker selection is based on screening patients with AAA compared with control subjects. A range of proteomic screening techniques are now

available, including those based on gel electrophoresis, mass spectrometry, and multiplex antibody arrays.<sup>26</sup> These and related techniques have been used to compare aortic wall, but not blood, samples from patients with AAA and control subjects.<sup>27–30</sup> These studies have suggested the upregulation of proinflammatory cytokines such as interleukin (IL)-1 $\beta$ , IL-6, IL-8, and tumor necrosis factor- $\alpha$ <sup>27,30</sup>; chemokines such as chemokine CC motif ligand 227; matrix-degrading enzymes, particularly matrix metalloproteinase (MMP)-9<sup>28,30</sup>; and expression of genes involved in immune function in general.<sup>29</sup> With the results of such analyses, it would be possible to select potential circulating biomarkers for AAA. It should be noted, however, that all these tissue biomarker studies have involved very small numbers ( $n \leq 10$ ) of patients with AAA and similar numbers of control subjects. The selection of suitably matched controls also is problematic in these studies, especially because the availability of normal-aged aorta is often limited to postmortem samples, which are usually collected in a very different way from operative AAA biopsies.

### Circulating Extracellular Matrix Markers

Three markers of extracellular matrix remodeling have been associated with AAA in case-control studies: the carboxyterminal propeptide of type I procollagen, the aminoterminal propeptide of type III procollagen, and tenascin-X.<sup>31–36</sup> Both type I collagen and type III collagen are important components of the aortic media, and fragmentation and synthesis of new type I and III collagen are typically found in biopsies of AAAs.<sup>37</sup> Parts from both the carboxyterminal and aminoterminal ends of the precursor molecule are split off and released during collagen synthesis. Hence, it might be assumed that type I and III procollagen fragments would be found at increased concentrations in the circulation of patients with AAA. Measurement of these fragments is not straightforward with investigators using radioimmunoassays.<sup>31–35</sup>

Circulating concentrations of the aminoterminal propeptide of type III procollagen were reported to be significantly increased in patients with AAA compared with control subjects in 2 studies (Table 1).<sup>31,33</sup> However, the most recent and the largest studies showed no association of serum type III procollagen peptides with AAA.<sup>34,35</sup> The circulating concentration of the carboxyterminal propeptide of type I procollagen has been compared between patients with AAA and control subjects in 3 small studies of only 190 cases.<sup>31–33</sup> None of these studies demonstrated higher concentrations of this peptide in patients with AAA. Nakamura and colleagues<sup>32</sup> reported lower concentrations in the plasma of patients with AAA ( $n=17$ ) compared with healthy control subjects ( $n=22$ ) but not those with peripheral artery disease ( $n=14$ ).

Deficiency of the extracellular matrix protein tenascin-X has been implicated in some cases of Ehlers-Danlos syndrome, a condition prone to aortic dissection and aneurysm formation.<sup>38</sup> Zweers and colleagues<sup>36</sup> reported higher serum concentrations of tenascin-X in 87 patients with AAA compared with 86 control subjects. Unlike most studies, these investigators adjusted their analyses for potential confounding factors and reported that tenascin-X serum concentrations in the highest quartile were associated with a 5-fold increased

**Table 1. Association of Circulating Biomarkers and AAA**

Marker/Reference	Cases, n	Controls, n	Concentration, Cases	Concentration, Controls
PIIINP, $\mu\text{g/L}$				
34*	95	83†	324 $\pm$ 127	312 $\pm$ 101
35*	201	246†	3.73 (3.53–3.93)	3.65 (3.49–3.81)
31‡	86	20†	4.6 $\pm$ 1.5§	2.8 $\pm$ 0.9
33*	87	90	3.47 (3.2–3.7)§	2.73 (2.5–3.0)
MMP-9, ng/mL				
41‡	53	9†/17	622.0 $\pm$ 400.2§	280.8 $\pm$ 165.5/284.3 $\pm$ 151.4
34‡	95	83†	353 $\pm$ 252	455 $\pm$ 499
42*	22	12	61 $\pm$ 49	51 $\pm$ 28
43*	45	10†	30.9 $\pm$ 17.1§	8.9 $\pm$ 2.5
44*	25	5†/15	99.4 $\pm$ 17.4§	36.1 $\pm$ 7.7/54.7 $\pm$ 10.5
45*	22	8†/9	85.6 $\pm$ 11.64§	13.16 $\pm$ 1.94/25.75 $\pm$ 4.16
Fibrinogen, g/L				
49*	110	110	2.89 (2.45–3.40)§	2.53 (2.1–3.07)
50*	89	98†	3.5 (2.9–4.1)§	3.1 (2.7–3.6)
51*	36	37†/31	3.80 (3.22–4.20)	2.95 (2.64–3.22)/4.05 (3.30–4.39)
52*				
Men	263	2699†	3.72 $\pm$ 0.91§	3.32 $\pm$ 0.88
Women	74	3350†	3.77 $\pm$ 0.68§	3.43 $\pm$ 0.80
53*	23	20†	3.6 (1.9–6.3)§	2.2 (1.3–3.0)
54*	21	42†/42	3.6 $\pm$ 1.2	3.3 $\pm$ 0.9/3.8 $\pm$ 0.6
55*	40	200†	3.05 (2.61–3.57)§	2.62 (2.21–3.08)
56*	22	244†	5.65 (4.81–6.68)	5.40 (4.78–6.31)
D-dimer, ng/mL				
59*	40	41†	625 (460–1437)§	86 (38–176)
50*	89	98†	441.5 (198.8–771.0)§	93.0 (57.8–158.8)
60*	18	10†	421 $\pm$ 400§	238 $\pm$ 180
61*	36	25†	7700 $\pm$ 6700§	1000 $\pm$ 1200
55*	40	200†	142 (84–210)§	83 (68–129)
62*	41	30	8400 $\pm$ 10 800§	2100 $\pm$ 2700
tPA, $\mu\text{g/L}$				
59*	40	41†	10.5 (8.6–14.8)	11.1 (8.5–15.2)
72*	42	100†	13.6 $\pm$ 4.7§	11.4 $\pm$ 4.3
50*	89	98†	7.9 (6.0–11.1)	8.6 (6.8–11.5)
53*	23	20†	10.2 (4.9–24.2)†	9.4 (2.9–19.0)†
55*	40	200†	8.5 (7.0–10.5)	7.9 (5.8–10.1)

PIIINP indicates aminoterminal propeptide of type III procollagen; tPA, tissue plasminogen activator. Numbers are mean $\pm$ SD, mean (95% CI), or median (interquartile range or range) as appropriate.

\*Measured in plasma.

†Healthy controls.

‡Measured in serum.

§Significantly higher concentration in cases ( $P<0.05$ ).

||Controls with atherosclerosis and no AAA.

risk of AAA (odds ratio, 5.3; 95% CI, 2.0 to 13.8).<sup>36</sup> At present, this association has not been confirmed in another cohort.

### Matrix-Degrading Enzymes

Fragmentation of the extracellular matrix of the aortic media is perhaps the most specific histological hallmark of AAA.<sup>22</sup> Matrix-degrading enzymes implicated in AAA include the MMP and cathepsin groups.<sup>22,30,39,40</sup> Surprisingly, relatively

few and small studies have compared the circulating concentrations of these enzymes or their inhibitors in patients with AAA and control subjects.<sup>34,41–46</sup> Circulating MMP-9 concentrations have been investigated most frequently, but the findings have not been completely consistent (Table 1).<sup>34,41–45</sup> Four of 6 studies reported higher concentrations of circulating MMP-9 in patients with AAA compared with healthy control subjects or subjects with atherosclerosis but not AAA.<sup>41,43–45</sup> Two studies,

including the largest, found no association of MMP-9 with AAA.<sup>34,42</sup> Concentrations of MMP-9 are several-fold higher in serum than plasma (because of platelet degranulation), and this may have contributed to the disparate findings.<sup>47</sup> The studies reporting no association between MMP-9 and AAA involved assessments of plasma in 1 instance and serum in the other example, suggesting that the inconsistent findings are not explained by differences in sampling alone.<sup>34,42</sup> All studies assessing plasma MMP-9 concentrations, however, did report higher mean concentrations in subjects with AAA, although this difference reached significance in only 3 of 4 studies.<sup>42–45</sup> Single studies have investigated the association of circulating concentrations of MMP-1, MMP-2, MMP-3, tissue inhibitor of MMP-1, and  $\alpha$ 1-antitrypsin with AAA.<sup>32,34,43,46</sup> These studies reported higher concentrations of MMP-3 and tissue inhibitor of MMP-1 in patients with AAA, but the sample sizes ( $n=55$  and  $53$ ) and the absence of replication make any firm conclusions impossible.<sup>32,43</sup>

### Proteins Associated With Thrombosis

Most AAAs contain significant quantities of intraluminal thrombus, and the volume is correlated with the severity of aortic dilatation.<sup>25</sup> The content of such thrombus includes a number of proteases and has been implicated in AAA progression.<sup>47,48</sup> In vitro aortic thrombus is capable of releasing a range of thrombus-associated products.<sup>48</sup> Proteins involved in, stimulated by, or associated with thrombosis have been the biomarkers most commonly assessed in AAA. Markers evaluated include fibrinogen, D-dimer, homocysteine, tissue plasminogen activator, von Willebrand factor, soluble thrombomodulin, plasminogen activator inhibitor-1, activated protein C–protein C inhibitor complexes, plasmin-antiplasmin complexes, P-selectin, thrombin–antithrombin III complex, and fibrinogen degradation products.<sup>49–72</sup> The association between plasma fibrinogen and AAA has been studied extensively, with 5 of 10 investigations reporting higher concentrations in patients with AAA (Table 1).<sup>49–58</sup> The studies showing no association generally included very small numbers of patients,<sup>51,54,57,58</sup> except for 1 investigation carried out exclusively in smokers.<sup>56</sup> Unlike other studies listed in Table 1, controls in the study by Franks et al<sup>56</sup> did not have an AAA excluded by imaging. Plasma fibrinogen is increased by smoking; thus, the association of fibrinogen with AAA could simply reflect the well-established link between smoking and AAA.<sup>19,73</sup> The association of fibrinogen with AAA was present after adjustment for other risk factors in 2 studies, supporting the independent link between fibrinogen and AAA.<sup>52,55</sup> The odds ratios for an increase in fibrinogen of 1 SD were 1.5 (95% CI, 1.1 to 2.2) and 1.4 (95% CI, 1.2 to 1.7). One of these studies, a population screening investigation, reported an independent association between fibrinogen and AAA in men but not women.<sup>52</sup>

Plasma concentrations of D-dimer reflect the extent of fibrin turnover in the circulation because this antigen is present in several products from the degradation of cross-linked fibrin by plasmin.<sup>74</sup> The circulating concentrations of D-dimer have been compared in patients with AAA and control subjects in 7 studies.<sup>50,55,57,59–62</sup> Six of the 7 studies, including a total of 264 cases and 404 controls, demonstrated

significantly higher D-dimer concentrations in subjects with AAA (Table 1). The 2 largest studies also reported an independent association between plasma D-dimer concentrations and AAA after adjustment for other risk factors.<sup>50,55</sup> The odds ratios for an increase in D-dimer of 1 SD were 4.6 (95% CI, 2.3 to 9.5) and 3.8 (95% CI, 1.8 to 7.8). Only 1 study incorporating just 23 cases and 16 controls reported no significant difference in plasma D-dimer concentrations, although the actual values were not reported.<sup>57</sup>

The circulating concentration of the complex between activated protein C and protein C inhibitor is related to thrombin generation and has been associated with AAA in 1 study.<sup>63</sup> Kölbl and colleagues<sup>64</sup> reported median plasma concentrations of activated protein C–protein C inhibitor complexes to be 0.45 (95% CI, 0.24 to 1.47) and 0.22 (95% CI, 0.15 to 0.48;  $P<0.01$ ) in 78 patients with AAA and 73 with carotid artery disease, respectively ( $P<0.001$ ). The investigators later extended this finding to a larger group of patients with AAA (total, 232) and reported a correlation between activated protein C–protein C inhibitor levels and aortic diameter ( $r=0.22$ ). This marker has not yet been reported in other cohorts.

Studies comparing the plasma concentration of homocysteine in subjects with AAA and control subjects have recently been reviewed.<sup>65</sup> This review identified 5 case-control studies, with all investigators reporting higher circulating homocysteine in subjects with AAA.<sup>66–70</sup> One of these studies, which was much larger (438 cases and 438 controls) than all the others ( $<100$  cases and controls), reported an independent association between raised plasma homocysteine ( $>19$   $\mu\text{mol/L}$  in men and  $15$   $\mu\text{mol/L}$  in women) and AAA after adjustment for other risk factors (odds ratio, 7.8; 95% CI, 4.6 to 13.2).<sup>66</sup> A more recent study failed to show any independent association between homocysteine and AAA after adjustment for serum creatinine.<sup>71</sup> These authors instead found a negative association between circulating vitamin B<sub>6</sub> concentrations and AAA.<sup>71</sup> Given the varying policies on folate and B vitamin supplementation throughout the world, any association between homocysteine and AAA is likely to vary in different populations.

Tissue plasminogen activator activates plasmin, an important fibrinolytic enzyme, which has been implicated in AAA development in experimental models.<sup>75</sup> Plasma tissue plasminogen activator has been compared in subjects with and without AAA in 5 studies.<sup>50,53,55,59,72</sup> Only one of the studies reported significantly higher concentrations in patients with AAA (Table 1). Overexpression of plasminogen activator inhibitor-1, an inhibitor of plasmin activation, inhibits AAA formation in mice.<sup>75</sup> The association of AAA and plasma plasminogen activator inhibitor-1 concentrations was assessed in 3 studies.<sup>59,66,72</sup> The largest of these studies reported mean plasma plasminogen activator inhibitor-1 concentrations of  $28.6\pm 21.6$  and  $17.8\pm 12.6$  mg/dL in 431 patients with AAA and 431 healthy control subjects, respectively.<sup>66</sup> Plasminogen activator inhibitor-1 concentrations  $>42.6$  mg/dL were independently associated with AAA after adjustment for other risk factors (odds ratio, 3.2; 95% CI, 1.7 to 6.1). Two small studies found no association between plasminogen activator inhibitor-1 and AAA but included a total



**Table 2. Association of Serum HDL and LDL With AAA**

Reference	Cases	Controls	HDL, Cases, mmol/L	HDL, Controls, mmol/L	LDL, Cases, mmol/L	LDL, Controls, mmol/L
79	30	26*	0.83±0.18†	1.21±0.18	2.84±0.77	2.49±0.54
80	35	140*	1.2 (1.1–1.2)†	1.3 (1.3–1.4)	3.5 (3.2–3.7)	3.3 (3.2–3.5)
81	206	252*	1.13 (1.07–1.20)	1.16 (1.11–1.22)	4.05 (3.92–4.19)‡	3.71 (3.59–3.83)
52						
Men	263	2699*	1.28±0.37†	1.42±0.37	NS	NS
Women	74	3350*	1.46±0.42†	1.68±0.43		
82	25	266*	1.27§	1.39§	4.24§‡	3.52§
54	21	42*/42	1.1±0.5†	1.5±0.3/1.3±0.3	3.9±0.7	3.4±1.1/4.0±1.1
83	69	1460*	1.32±0.31†	1.57±0.40	3.96±1.06	3.74±1.01
84	114	57	1.22 (1.07–1.50)‡	1.08 (0.95–1.44)	4.50 (3.70–5.40)	4.88 (3.83–5.70)

NS indicates not stated. To convert mmol/L to mg/dL, multiply by 38.67. Numbers are median (interquartile range) or mean±SD as appropriate.

\*Healthy controls.

†Significantly lower concentration in cases ( $P<0.05$ ).

‡Significantly higher concentration in cases ( $P<0.05$ ).

§Only mean, no SD, is stated.

||Controls with atherosclerosis and no AAA.

of only 82 cases and 141 controls.<sup>59,72</sup> The fibrinolytic effects of plasmin are inactivated in the circulation by antiplasmin, leading to the formation of plasmin-antiplasmin complexes. Fowkes and colleagues<sup>50</sup> reported higher median plasma concentrations of plasmin-antiplasmin complex in 89 patients with AAA (596  $\mu\text{g/L}$ ; interquartile range, 432 to 878  $\mu\text{g/L}$ ) compared with 98 healthy control subjects (384  $\mu\text{g/L}$ ; interquartile range, 274 to 486  $\mu\text{g/L}$ ;  $P=0.01$ ). The investigators did not comment on whether this association was maintained in models adjusted for other risk factors.

Endothelial von Willebrand factor mediates platelet adhesion, and circulating concentrations of von Willebrand factor are a marker of endothelial injury and dysfunction.<sup>76</sup> None of the 4 studies identified comparing the concentrations of circulating von Willebrand factor in cases and controls have reported any significant association with AAA.<sup>50,54,55,63</sup> Thrombomodulin is an endothelium-bound protein that plays an important role in the protein C anticoagulant pathway. Circulating levels of thrombomodulin also have been correlated to endothelial dysfunction.<sup>77</sup> Two small studies involving a total of 79 cases and 144 controls investigated the association of circulating thrombomodulin with AAA and reported disparate findings.<sup>54,70</sup> One study reported an association of thrombomodulin with AAA, but this association was not apparent in the other study. One small study reported an association between circulating concentrations of the activated platelet marker P-selectin and AAA, although this finding has not yet been replicated.<sup>54</sup>

A number of other thrombosis-associated products, including thrombin-antithrombin III complexes and fibrinogen degradation products, have been assessed in small studies. Two studies involving a total of 77 cases and 55 controls reported increased concentrations of fibrinogen degradation products in those with AAA.<sup>61,62</sup> One of these studies also reported higher thrombin-antithrombin III complex concentrations in 36 patients with AAA and 25 healthy control subjects.<sup>61</sup>

## Lipids

Circulating lipids are normally considered a risk factor for, rather than a biomarker of, atherothrombosis. Low-density lipoprotein (LDL) and high-density lipoprotein (HDL) are independent risk factors for cardiovascular events such as myocardial infarction and stroke, so it would be expected that these lipids would be the primary ones assessed in case-control studies for AAA.<sup>78</sup> We identified 10 studies that compared HDL between patients with and without AAA, including 3 population screening studies.<sup>52,54,79–86</sup> The 8 studies in which average HDL concentrations were stated are listed in Table 2. Five of these studies, including the 2 largest studies, reported lower concentrations of HDL in subjects with AAA compared with healthy control subjects. Additionally, Alcorn and colleagues,<sup>85</sup> in a population study of 4741 subjects, reported a negative association between HDL and AAA, whereas in a smaller study of only 200 subjects, Blanchard et al<sup>86</sup> reported no association between HDL and AAA. It may be important that neither of the 2 small studies comparing HDL concentrations in subjects with AAA and control subjects with atherothrombosis reported lower concentrations in those with AAA.<sup>54,84</sup> This finding may indicate the lack of specificity of HDL to AAA as opposed to atherothrombosis; other larger studies incorporating subjects with peripheral artery disease are required. We identified 7 studies that compared LDL concentrations in patients with and without AAA. In general, these studies found a less consistent association of LDL with AAA than seen for HDL (Table 2). Three studies reported higher concentrations in subjects with AAA.<sup>81,82,85</sup> The increasing use of statins in subjects as a result of concurrent atherothrombosis makes it unlikely that LDL is a practical marker of AAA.

Some of the studies discussed above also assessed the relationship between AAA and triglycerides or apolipoprotein A and B. A number of studies,<sup>52,79,83</sup> but not all,<sup>46,81,84</sup> have shown slightly higher concentrations of serum triglycerides in patients with AAA. This association has not

**Table 3. Association of Lipoprotein(a) and IL-6 With AAA**

Marker/Reference	Cases, n	Controls, n	Concentration, Cases	Concentration, Controls
Lp(a), nmol/L				
87*	425	230†/262‡	29.9 (<2–583)	17.0 (<2–285)§/28.8 (<2–539)
66	438	438†	728 (7–9646)§	352 (32–2481)
88	75	43†	674 (<342–1445)§	<342 (<342–582)
89*	29	274†	382§¶	228¶
56*	22	244†	750 (417–1267)	742 (262–2099)
83	69	1460†	453±511	414±453
IL-6, pg/mL				
92*	27	15‡	4.94±0.48§	2.65±0.51
50*	89	98†	2.8 (2.0–4.2)§	1.8 (1.3–2.7)
90*	74	30†	64.2±157.3§	6.7±5.1
91	50	38†/42‡	0.24§	0.014/0.086

Lp(a) indicates lipoprotein(a). To convert nmol/L to mg/dL, divide by 35.7. To convert pg/mL to pmol/L, multiply by 0.037. Numbers are median (interquartile range) or mean±SD as appropriate.

\*Measured in plasma.

†Healthy controls.

‡Controls with atherosclerosis and no AAA.

§Significantly higher concentration in cases ( $P<0.05$ ).

||Measured in serum.

¶Only mean or median is stated; no SD or interquartile range is given.

generally been maintained after adjustment for other risk factors such as atherothrombosis.<sup>52</sup> Three studies that reported apolipoprotein concentrations in relation to AAA were identified.<sup>56,82,83</sup> Two of these studies reported higher concentrations of apolipoprotein B in subjects with AAA, but no adjusted analyses were presented.<sup>82,83</sup> A greater number of studies assessing the association of lipoprotein(a) with AAA were identified (Table 3). These studies demonstrate higher concentrations of lipoprotein(a) in subjects with AAA compared with healthy control subjects but no difference compared with patients with atherothrombosis.<sup>56,66,83,87–89</sup>

### Markers of Inflammation

A large number of circulating markers of inflammation have been assessed for association with AAA; however, this has mostly involved measuring the different biomarkers in single populations usually involving small numbers of subjects. Examples of markers assessed are IL-1 $\beta$ , IL-2, IL-6, IL-8, tumor necrosis factor- $\alpha$ , interferon- $\gamma$ , C-reactive protein, osteopontin, resistin, leptin, adiponectin, sCD28, sCD86, sCTLA-4, sVCAM-1, sICAM-1, endothelin 1/2, and antibodies to *Chlamydia pneumoniae*.<sup>50,54,90–98</sup> The most consistently associated with AAA is IL-6.<sup>50,90–92</sup> Increased concentrations of IL-6 have been demonstrated in biopsies of AAA compared with control biopsies.<sup>99</sup> Plasma concentrations of IL-6 have been shown to increase distal to an AAA, suggesting that the aneurysm itself is the source of this cytokine.<sup>92</sup> Plasma IL-6 also has been correlated to aortic diameter in subjects without AAA.<sup>100</sup> Furthermore, 4 small studies have demonstrated increased circulating concentrations of IL-6 in patients with AAA compared with control subjects (Table 3). Two of these studies also reported higher concentrations of plasma IL-1 in a total of 124 subjects with AAA and 110

control subjects.<sup>90,91</sup> Circulating IL-2 and tumor necrosis factor- $\alpha$ , but not IL-8 and interferon- $\gamma$ , were associated with AAA in one of these studies.<sup>90,91</sup> Two independent but small studies have associated circulating endothelin-1 concentrations with AAA.<sup>96,97</sup> In another study involving 100 cases and 214 controls, plasma concentrations of the T-cell costimulatory molecules sCD28, sCD86, and ligand sCD86 were associated with AAA.<sup>95</sup> Osteopontin has been implicated in AAA because mice deficient in this protein are protected from aortic dilatation.<sup>101</sup> A recent study involving 2 cohorts totaling 365 cases and 300 controls found significantly higher concentrations of serum osteopontin in patients with AAA.<sup>93</sup> An osteopontin concentration in the highest tertile was independently associated with AAA (odds ratio, 2.23; 95% CI, 1.29 to 3.85). One cohort was population based and the other was referral generated, suggesting the potential value of this biomarker in varied subjects. Another study incorporating a subgroup of 952 elderly men screened for AAA in Western Australia investigated the association of 3 serum adipokines with AAA.<sup>94</sup> Serum resistin, which has been implicated in macrophage-based inflammation, was independently associated with AAA (odds ratio, 1.53 per 10 ng/mL; 95% CI, 1.32 to 1.76).<sup>94</sup>

C-reactive protein is the most commonly investigated biomarker in cardiovascular disease.<sup>102</sup> Two studies including a total of 127 cases and 229 controls reported no association between C-reactive protein and AAA.<sup>92,95</sup> Three other studies incorporating a total of 373 cases and 794 controls reported higher concentrations in patients with AAA.<sup>80,94,103</sup> On the basis of an infective theory for AAA, Blanchard and colleagues<sup>98</sup> reported an association between circulating IgG antibodies to *C pneumoniae* and AAA. Subsequently, other investigations have been unable to confirm this finding and noted significant variation in the findings of different serological tests for chlamydia.<sup>104</sup>

## Circulating Biomarkers in Relation to AAA Progression and Outcome

### Assessment of AAA Progression and Biomarkers

Because most small AAAs currently are treated conservatively and followed up by repeated imaging, change in maximum aortic diameter usually is used to monitor AAA progression.<sup>105</sup> It is postulated that biomarkers measured at diagnosis or during follow-up might provide important prognostic information about subsequent aortic behavior, allowing more patient-specific management compared with relying on aortic diameter alone. A number of investigators have related circulating biomarker concentrations to subsequent change in maximum aortic diameter of small AAAs. As highlighted in previous reviews, there are a number of challenges in studying AAA growth, including imaging measurement error, loss to follow-up, and interpatient and inpatient variation in the rate of progression.<sup>17,19,105</sup> Complex modeling approaches have been developed to try to allow for some of these issues, although they have yet to be fully adopted in biomarker studies.

### Biomarkers Assessed for Association With AAA Growth

Table 4 summarizes biomarkers that have been assessed for association with AAA expansion.<sup>10,11,24,91,93,106–115</sup> Review of these studies shows that a large number of markers have been assessed in relatively few and small cohorts. The 22 biomarkers referred to in Table 4 were assessed by just 6 groups of independent investigators: 3 in the United Kingdom,<sup>10,112,114,115</sup> 1 in Finland,<sup>91,107</sup> 1 in Australia,<sup>11,24,93</sup> and 1 in Denmark.<sup>106,108–111,113</sup> The aminoterminal propeptide of type III procollagen is the only marker to have been associated with AAA in 2 distinct cohorts.<sup>106,107</sup> Serum type III procollagen peptide concentrations were correlated with

AAA growth ( $r=0.37$ ) in 139 patients followed up for a mean of 24 months in Finland.<sup>107</sup> Serum type III procollagen peptide concentration also was associated ( $r=0.24$ ) with AAA growth in 99 patients followed up for a similar time in Denmark.<sup>106</sup> A large number of other biomarkers were reported to be associated with aneurysmal expansion in the Danish cohort, although this has yet to be replicated.<sup>106,108–111,113</sup> Most of the other positive studies listed in Table 4 included <200 patients; the 2 largest cohorts both reported negative findings for lipids ( $n\approx 1500$ )<sup>10</sup> and C-reactive protein ( $n=545$ ).<sup>11</sup> Thus, at present, we are unable to confidently support any of these biomarkers as reproducible predictors of AAA growth.

### Biomarkers Associated With Clinical Presentation of AAA

Not surprisingly, biomarkers for subsequent AAA rupture have been relatively little investigated. A few case-control studies have compared circulating markers in patients presenting with ruptured and elective AAAs.<sup>59,116</sup> The design of these types of studies cannot exclude the possibility that the changes seen in biomarkers are a consequence, rather than a predictor, of aortic rupture. However, 2 population-based studies have examined the risk factors for subsequent AAA rupture or presentation for AAA repair.<sup>117,118</sup> Because not all subjects are imaged in these studies, it is unclear what proportion of the control group have undetected AAAs. These studies suggest the importance of inflammation-sensitive plasma proteins such as fibrinogen and  $\alpha 1$ -antitrypsin in predicting AAA development or rupture and HDL in protecting against AAA.<sup>117,118</sup> Because AAA rupture is a rare event for small AAAs, few ultrasound surveillance studies have assessed the relationship between biomarkers and AAA rupture. An exception is the UK Small Aneurysm Trial.<sup>119</sup> The investigators reported the association of the smoking marker cotinine with subsequent AAA rupture.

### Biomarkers of AAA Repair Success

The durability of endovascular repair is not as good as that for open surgery, with  $\approx 20\%$  of patients requiring repeat intervention within 5 years because of continued aortic sac expansion.<sup>120</sup> Most of these graft failures appear to be secondary to continued pressurization of the aortic sac from patent aortic branches, known as type II endoleak. There has been interest in detecting such endoleaks by the changes in circulating biomarkers during follow-up. Decreases in MMP-3 and MMP-9 concentrations after successful open or endovascular AAA repair have been noted.<sup>121,122</sup> Patients with endoleak have been noted to maintain higher plasma concentrations of these proteolytic enzymes. Larger studies with repeated sampling and longer follow-up are required to confirm the association of such biomarkers.

### Summary and Future Directions

A number of biomarkers associated with AAA presence such as plasma fibrinogen, D-dimer, and IL-6 have now been identified in cross-sectional case-control studies (Tables 1 and 3). Most studies have not assessed the value of these markers as diagnostic tests for AAA or in selecting subsets of

**Table 4. Circulating Biomarkers Assessed for Association With AAA Growth**

Marker Related to	Associated With AAA Growth	Not Associated With AAA Growth
Extracellular matrix turnover	Elastin peptides, <sup>106</sup> PIIINP <sup>106,107</sup>	
Matrix-degrading enzymes	Elastase- $\alpha 1$ -antitrypsin, <sup>108</sup> cystatin c (-ve) <sup>109</sup>	
Thrombosis-associated proteins	Plasmin-antiplasmin complexes, <sup>110</sup> tPA, <sup>111</sup> hcy <sup>112</sup>	PAI-1, <sup>111</sup> uPA, <sup>111</sup> plasminogen, <sup>110</sup> hcy <sup>111</sup>
Lipids		Triglycerides, <sup>10</sup> LDL, <sup>10</sup> HDL <sup>10</sup>
Inflammation	OPN, <sup>93</sup> INF- $\gamma$ , <sup>91</sup> OPG, <sup>24</sup> MIF, <sup>113</sup> Ig A to Cpn <sup>111</sup>	TGF $\beta 1$ , <sup>111</sup> MIF, <sup>111</sup> CRP, <sup>11</sup> IL-6, <sup>114</sup>
Other	Cotinine <sup>111</sup>	Cotinine <sup>10,115</sup>

PIIINP indicates aminoterminal propeptide of type III procollagen; tPA, tissue plasminogen activator; hcy, homocysteine; PAI-1, plasminogen activator inhibitor-1; uPA, urokinase plasminogen activator; OPN, osteopontin; INF- $\gamma$ , interferon- $\gamma$ ; OPG, osteoprotegerin; MIF, macrophage migratory inhibitor factor; Cpn, *Chlamydia pneumoniae*; TGF $\beta 1$ , transforming growth factor- $\beta 1$ ; and CRP, C-reactive protein.



patients for imaging. When this has been done, the sensitivity and specificity appear inadequate for the use of single biomarkers alone in diagnosis. For example, we recently assessed the value of the cytokine resistin and reported an area under the curve, sensitivity, and specificity of 0.69, 69%, and 60%, respectively.<sup>94</sup> The effect of using multiple biomarkers combined with clinical factors requires investigation in large, carefully designed population-based studies and allied referral populations to thoroughly assess the diagnostic value. Such studies need to clearly define the control subjects included. Control subjects used in past studies include those with no evidence of cardiovascular disease or atherothrombosis and those identified from screening studies. Although all these different control groups may have no AAA on imaging, their risk factors and circulating biomarker profiles will be quite different. The association of biomarkers with AAA progression is currently unclear, with larger studies showing negative results to date. Clearer identification of such markers is needed, possibly using proteomic techniques to screen for new candidates, as well as more thorough assessment of markers previously highlighted in small cohorts to date.<sup>26</sup> When identified, such biomarkers will require prospective assessment in large multicenter cohorts.

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### Disclosures

None.

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