



Review

Biomarkers and therapeutic strategies for abdominal aortic aneurysm: a contemporary update

Actualización de biomarcadores y terapias en pacientes con aneurisma aórtico abdominal

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Abstract

Abdominal aortic aneurysm (AAA) is a condition characterized by the progressive dilation of the aortic wall, which can result in rupture, a fatal event in over 80 % of cases. The prevalence of AAA in men over 65 years old can reach up to 8 %. Management of asymptomatic patients with aneurysms measuring less than 55 mm in maximum diameter includes periodic follow-up with imaging studies, control of cardiovascular risk factors, and treatment with antiplatelet and lipid-lowering therapy. However, there is currently no effective pharmacological treatment to limit its progression or prevent rupture. At present, aortic diameter is the sole marker for the risk of rupture and determines the need for surgical repair. This review highlights the challenges in identifying effective biomarkers for this disease, updates on the potential biomarkers identified to date, and explores strategies for identifying new therapeutic targets.

Keywords:

Abdominal aortic aneurysm. Risk factors. Biomarker. Pathophysiology. Medical treatment.

Resumen

El aneurisma de aorta abdominal (AAA) es una patología en la que se produce la dilatación progresiva de la pared aórtica, lo que puede llevar a su rotura, un fenómeno mortal en más del 80 % de los casos. Presenta una prevalencia que, en varones de más de 65 años, puede alcanzar el 8 %. El manejo de los pacientes asintomáticos, con aneurismas por debajo de 55 mm de diámetro máximo, consiste en un seguimiento periódico con pruebas de imagen, en el control de los factores de riesgo cardiovascular y en el tratamiento con terapia antiagregante e hipolipemiente. Sin embargo, actualmente no existe ningún tratamiento farmacológico efectivo capaz de limitar su progresión o evitar su rotura. En la actualidad, el diámetro aórtico es el único marcador de riesgo de rotura, y es lo que determina la necesidad de reparación quirúrgica. En esta revisión se exponen las dificultades para disponer de biomarcadores efectivos para esta enfermedad, se actualizan los potenciales biomarcadores descritos hasta ahora y se plantean las estrategias para la identificación de nuevas dianas terapéuticas.

Palabras clave:

Aneurisma de aorta abdominal. Factores de riesgo. Biomarcador. Fisiopatología. Tratamiento médico.

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INTRODUCTION AND OBJECTIVE

Abdominal aortic aneurysm (AAA) is a condition consisting of a localized and permanent dilation of the aorta, generally in its infrarenal portion, > 50% of the vessel diameter in adjacent areas (1,2).

This review aims to address and update the main aspects related to the epidemiology, diagnosis, therapeutic management, and, primarily, the possibility of obtaining useful biomarkers for the disease.

DEVELOPMENT

Epidemiology and management

AAA affects men 6 times more frequently than women (1). The mean annual incidence rate of new-onset AAA diagnoses in Western populations goes from 0.4% to 0.67% (3).

Since AAA usually proceeds silently, the diagnosis typically occurs as an incidental finding. However, in some countries, screening programs using ultrasonography (US) are performed in risk groups, which has proven to be useful from a cost-effective point of view (4,5).

Currently, the management of AAA, when its diameter remains between 30 mm and 55 mm, is conservative. It is based on monitoring with imaging tests and adequate control of cardiovascular risk, although currently there is no effective pharmacological treatment capable of limiting its progression and rupture. This type of management should be conducted as long as the AAA does not reach 55 mm of maximum diameter. From that moment, surgical treatment will be necessary, as well as in the event of an aneurysmal growth > 5 mm at the 12-month follow-up or in the case of symptomatic aneurysms (6).

Abdominal aortic aneurysm physiopathology

The physiopathology of AAA is complex and involves multiple factors, such as inflammation, proteolysis, and oxidative stress. These are key processes underlying the pathogenesis and expansion of AAAs (7) and occur both at the level of the media and the

adventitia, as well as the intraluminal thrombus (ILT), which plays a key role in aneurysmal development. The presence of ILT is associated with a thinner arterial wall, greater elastolysis, less smooth muscle cell density in the media, and a higher level of immunoinflammation in the adventitia (8).

Understanding the physiopathology of AAA is fundamental when determining possible biomarkers that allow an early diagnosis, as well as for identifying effective and efficient pharmacological therapies capable of preventing its progression (9).

Risk factors

The pathogenesis of AAA is complex and multifactorial. It shares several risk factors associated with atherosclerotic disease (10). It is worth noting that diabetes *mellitus* (DM), a risk factor for atherosclerosis, is a protective factor for AAA (6).

These are some of the risk factors involved: age (11), sex (12,13), family history (14,15), smoking (16), high blood pressure (17), heart disease and peripheral arterial disease (18), lipid levels (19), and diabetes *mellitus* as a protective factor (20).

Potential abdominal aortic aneurysm biomarkers

A biomarker is a protein, peptide, gene, lipid, or metabolic product that represents a relevant biological process, in the body from which it originates, at a given moment (21). The research and discovery of new markers help to understand and better comprehend the physiopathology of certain diseases. An ideal biomarker must meet a series of characteristics, such as presenting a causal relationship with the disease it indicates being specific for that particular disease and involved in the physiopathological pathways of said disease (7).

For decades, potential circulating biomarkers of AAA progression have been studied, with different levels of evidence. However, very few have been introduced into clinical practice, given their low sensitivity and specificity. Knowing the uncertainty that exists around AAA growth, and the difficult management of the disease, the analysis of biomarkers, as well as

their potential validation for clinical application, is a topic of interest (22-25).

The most recent evidence, based on a large prospective study, supports the fact that patients who combine a greater number of AAA-related biomarkers are significantly associated, and adjusted for risk factors, with an increase in AAA incidence. Thus, the presence of several AAA-related biomarkers could be capable of determining a group of high-risk patients for the development of AAA (26) (Fig. 1).

The studies analyzed in this work investigate the correlation of various biomarkers with different parameters. Some of them propose the association with the presence of AAA, others with the diameter as a marker of aneurysmal progression, and others with AAA growth, generally prospectively (Table I).

However, of note, how the association between circulating biomarkers and AAA disease does not allow establishing causality, although it can guide and propose the association between different biomarkers and the presence and/or progression of the disease.

Below, most possible AAA biomarkers known so far are detailed, classifying them based on their relationship with aneurysmal physiopathology. Those that present the greatest interest for future application in clinical practice are indicated.

Extracellular matrix degradation

- *Matrix metalloproteinases (MMPs)*: MMPs are a family of enzymes whose function is to degrade the collagen and elastin of the extracellular matrix of the vascular wall. This function implies that they may be involved in processes where matrix remodeling exists, such as the migration of inflammatory cells or angiogenesis (27-29). Elevated levels of various MMPs have been identified in the AAA wall vs the normal aortic wall, as well as elevated plasma levels of these in patients with AAA vs healthy control individuals or those with atherosclerotic disease (30-32).
- *Matrix metalloproteinase 2 (MMP-2)*: MMP-2 is mainly secreted by vascular smooth muscle cells and fibroblasts. In 1995, it was demonstrated that it is the dominant protease in the wall of small AAAs and that, as aneurysmal growth progresses, MMP-9 acquires a main role (33). Thus, MMP-2 could be more related to the expansion of AAAs and MMP-9, to their rupture (34). Although the role of MMPs in the degradation of the aortic wall is demonstrated, it has not been confirmed that MMP-2 has been significantly elevated in patients with AAA (35,36). Furthermore, in the Flon-

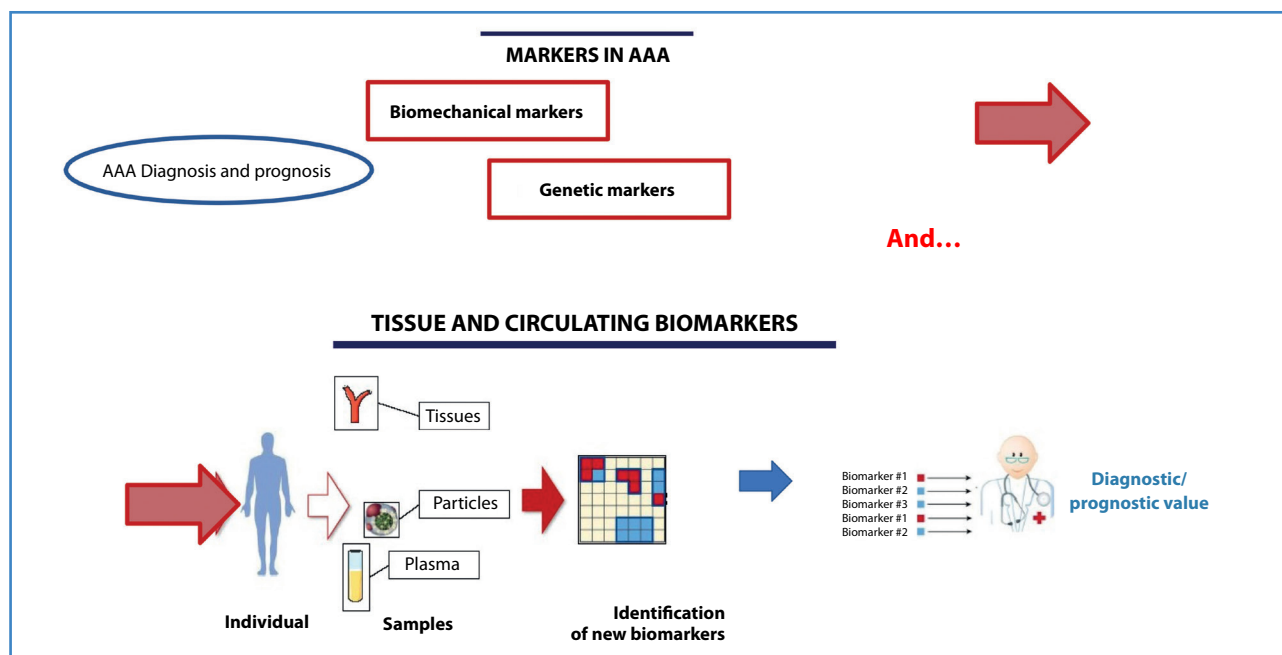


Figure 1. AAA markers and acquisition of tissue and circulating biomarkers.

Table I.

Biomarker	<i>n</i>	Correlation biomarker–presence	Correlation biomarker–diameter	Correlation biomarker–growth	Author and year of publication
Related to extracellular matrix degradation					
MMP-2	353	Negative correlation	Negative correlation		Flondell-Sité D, 2010
	44		Weak positive correlation		Hackmann AE, 2008
	31		No correlation		Eugster T, 2005
MMP-9	580	Positive correlation	Weak positive correlation		Takagi H, 2009
	25	Strong positive correlation	Weak positive correlation	No correlation	Hovsepian DM, 2000
	37			Positive correlation	Speelman L, 2010
CSTB	270			Positive correlation	Memon AA, 2020
CTSC	142			Negative correlation	Lindholt JS, 2001
Tryptase	Experimental model			Positive correlation	Zhang J, 2011
Homocysteine	89	Positive correlation			Arapoglou V, 2009
	423		Positive correlation		Giusti B, 2008
	74		Negative correlation		Warsi AA, 2004
Alpha 1-AT	12639	Weak positive correlation			Lindholt JS, 2010
			No studies		
Related to immune-inflammatory response and oxidative stress					
MPO	29	Positive correlation	Negative correlation		Houard X, 2009
	270			Positive correlation	Memon AA, 2020
NGAL	278			Positive correlation	Ramos-Mozo P, 2012
	54			No correlation	Groeneveld ME, 2019
PCR	1392	Positive correlation	Positive correlation		Golledge J, 2011
	435		Positive correlation	Positive correlation	De Haro J, 2012
Cistatina C	151	Positive correlation			Lindholt JS, 2001

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Table I (cont.).

Biomarker	<i>n</i>	Correlation biomarker–presence	Correlation biomarker–diameter	Correlation biomarker–growth	Author and year of publication
Related to immune-inflammatory response and oxidative stress					
Cystatin C	12639		Negative correlation		Lindholt JS, 2010
IGF-1	115		Positive correlation	Positive correlation	Lindholt JS, 2011
TSP-1	276			Negative correlation	Krishna SM, 2017
APL	144			Positive correlation	Duftner C, 2014
sTWEAK	79		Negative correlation	Negative correlation	Martin-Ventura JL, 2011
PRX-1	116			Positive correlation	Martinez-Pinna R, 2011
Related to prothrombotic activity					
D-dimer	580		Positive correlation	Positive correlation	Takagi H, 2009
	352	Positive correlation			Sundermann AC, 2018
	96	Positive correlation			DeCeniga MV, 2014
	1392		Positive correlation		Golledge J, 2011
TAT	352			Positive correlation	Sundermann AC, 2018
PAP	580		Positive correlation		Takagi H, 2009
	96			Weak positive correlation	DeCeniga MV, 2014
t-PA	115			Positive correlation	Lindholt JS, 2011
Related to hematology and lipid metabolism					
HbA1c	319			Negative correlation	Kristensen KL, 2017
Total bilirubin and leukocytes	219			Positive correlation	Vuruskan E, 2017
HDLc	122			Positive correlation	Burillo E, 2015

MMP-2: matrix metalloproteinase 2; MMP-9: matrix metalloproteinase 9; CSTB: cystatin B; CTSC: cystatin C; Alpha1-AT: alpha-1 antitrypsin; MPO: myeloperoxidase; NGAL: neutrophil gelatinase-associated lipocalin; CRP: C-reactive protein; IGF-1: insulin-like growth factor 1; TSP-1: thrombospondin 1; APL: antiphospholipid antibodies; sTWEAK: soluble TNF-like weak inducer of apoptosis; PRX-1: peroxiredoxin 1; TAT: thrombin-antithrombin complexes; PAP: plasmin-antiplasmin complexes; t-PA: tissue plasminogen activator; HbA1c: glycated hemoglobin; HDLc: high-density lipoprotein cholesterol.

dell-Sité series, circulating levels of MMP-2 were decreased in patients vs controls. One of the explanations the authors gave for this decrease was the consumption of circulating MMP by the aortic wall. The results regarding MMP-2 concentrations and aortic diameter are very similar. Of note, aneurysmal growth is usually discontinuous (37), which means that AAAs with the same diameter can present very different activity levels, depending on whether they are in a period of growth or latency, which seems to affect the peripheral concentrations of the biomarker under study. Hackmann found a very weak relationship between MMP-2 levels and aneurysmal diameter (38). And in the above-mentioned work conducted by Flondell-Sité, there was a negative correlation between MMP-2 and the diameter of AAA. Other authors, however, have not found a relationship between MMP-2 levels and the diameter of AAAs (24,36,39).

- *Matrix metalloproteinase 9 (MMP-9)*: MMP-9 is one of the most widely studied matrix metalloproteinases. Its levels are increased in aneurysmal walls, mainly in the adventitial zone (40). A correlation has been confirmed between its tissue concentration and the diameter of AAAs (39). Moreover, although various published studies suggest that it may be the most useful marker, a broader study of this topic is needed (9,41). A large part of the analyzed works have found an elevation of MMP-9 in peripheral blood in patients with AAA vs controls (42); also in the meta-analyses conducted by Takagi et al. in 2009 (24,38). According to Hovsepian, given its high specificity and high positive predictive value (PPV), the determination of MMP-9 would be an acceptably good indicator of the presence of AAA, while normal levels are insufficient to rule it out. Similarly, these and other studies describe an association between plasma concentrations of MMP-9 and the diameter of AAAs (32,36,39). A positive relationship has also been demonstrated between MMP-9 levels and the rate of aneurysmal growth (43,44). However, other studies have failed to confirm this (42). The hypotheses given for the-

se results are, on the one hand, that large AAAs with lower MMP-9 concentrations are those that remain asymptomatic, while those with higher concentrations are those that rupture and, for this reason, are not included in the studied series. The second possibility is that the marked growth of AAAs could generate a massive destruction of the elastic network and, for this reason, the tissue MMPs responsible for its degradation would decrease. In turn, a change in tissue MMPs causes changes in circulating MMP levels (45).

- *Cystatin B (CSTB)*: can inhibit cathepsin L. Memon (46), in a work of 133 patients, identified that CSTB is significantly associated with the aneurysmal growth rate in linear regression analysis ($p = 0.007$).
- *Cystatin C (CTSC)*: also a cysteine protease inhibitor. There seems to be a negative correlation between CTSC serum levels and the annual aneurysmal expansion rate ($r = -0.24$; 95% CI, $-0.75-0.05$), a correlation that remains significant in multivariate analysis (47).
- *Tryptase*: Is a serine protease that is mainly related to mast cells in allergic reactions. The Zhang group (48) confirmed a significant correlation between serum tryptase levels and the annual growth of AAA, which remained after adjustment for risk factors ($r = 0.29$, $p = 0.005$).
- *Homocysteine*: Hyperhomocysteinemia has been associated, in various studies, independently, with the presence of AAA, with an odds ratio (OR) of 7.8 and after adjustment for traditional cardiovascular risk factors (49). Although it is true that there is an elevation of homocysteine in 5%-7% of the general population, this elevation clearly increases up to 60% in patients with AAA (49,50). Only one study observed how the association between plasma homocysteine levels and the presence of AAA that appeared in the univariate analysis did not exist after adjusting the analysis for creatinine and vitamin B₆ concentrations (51). Works such as those of Brunelli (52) and Giusti (49) found elevated homocysteine levels in patients with large-bore AAA. However, other studies, such as the one conducted by Warsi (53) ruled out this type of correlation.

- *Alpha1-antitrypsin (alfa1-AT)*: The study by Engstrom associated elevated circulating alfa1-AT concentrations with the future development of AAA (54). Furthermore, Lindholt described an elevation in plasma concentration (139 mg/dL) (5). However, in the Lamblin study, protein levels were reduced vs patients with peripheral arterial disease (55).

Oxidative stress and immunoinflammatory response

- *Myeloperoxidase (MPO)*: MPO concentrations seem to be significantly high in patients with AAA in studies such as that conducted by Houard (56). These results support the fact of neutrophil participation in the degradation of the aortic wall through, among others, the release of MPO in degranulation. However, they did not find a correlation with aortic diameter (56), or between plasma and tissue concentrations of the enzyme. Certain works (46) have confirmed that there is a positive correlation between MPO and aneurysmal expansion before and after adjustment for risk factors (RF) ($p = 0.013$). In the ROC curve, the prognostic value of MPO was promising, with a sensitivity of 80%, a specificity of 59%, and an area under the curve of 0.71 (95% CI, 0.61-0.81).
- *Neutrophil Gelatinase-Associated Lipocalin (NGAL)*: Is a neutrophil-derived protein. The correlation between NGAL and aneurysmal expansion was analyzed by Ramos-Mozo et al. (25), who confirmed that there is a positive correlation between the 2 ($n = 40$, $r = 0.4$ and $p = 0.01$), which remained in the multivariate analysis. However, in other cohorts (57), no significant association has ever been reported.
- *C-reactive protein (CRP)*: Increased levels of CRP have been observed in patients with AAA in several studies (23,59). They were first described in 1987 (58). Subsequently, authors such as Parry (59) and Golledge (23) also demonstrated the association between the presence of AAA and the elevation of CRP levels.

Most studies have identified the presence of a correlation between circulating CRP levels and aneurysmal diameter (60). Although Lindholt did not observe this correlation, it is true that he did not use the ultrasensitive technique for the quantification of the protein. Although the study by Parry did confirm that there is correlation, significance was lost in the multivariate analysis (59).

In addition, it has been determined how variations in CRP levels have correlated significantly with aneurysmal expansion rates (OR, 3.4; 95% CI, 2.1-5.6) in multivariate analysis (60).

- *Cystatin C (CC)*: This epidemiological study (61) showed that elevated serum CC levels (> 1.3 mg/L) independently mark, after adjusting for RF, an increased cardiovascular risk in the general population. However, despite all this, there are few published studies on CC and AAA. According to Lindholt's results published in 2001, CC could independently mark the presence of AAA. Of note, CC is a recognized marker of renal function. Regarding the association of CC and aortic diameter, Lindholt (5) observed a negative correlation, which remained after adjustment for RF; among them, renal function. Shi's group also described that there is a negative correlation between serum CC levels and AAA diameter, which remained after adjustment for serum creatinine and glomerular filtration rate (62).
- *Insulin-like growth factor 1 (IGF-1)*: predictive factor and mediator in cardiovascular disease. Its serum concentrations correlate positively with AAA diameter ($r = 0.23$ and $p = 0.016$) and with its expansion rate ($r = 0.27$ and $p = 0.004$), which is maintained after adjustment for RF (63).
- *Thrombospondin-1 (TSP-1)*: Modulates the phenotype of vascular smooth muscle cells and fibroblasts and preserves the extracellular matrix, inhibiting MMPs. There seems to be a negative correlation between AAA progression and serum TSP-1 concentrations (-0.129 , $p = 0.033$) (64).
- *Antiphospholipid antibodies (APL)*: autoimmune antibodies vs phospholipids and their cofactors. According to groups such as Duftner's (65),

- patients with AAA who show positivity for APL tended to present greater aneurysmal expansion vs those who were APL-negative, which was maintained after adjustment for RF (OR, 9.4; 95% CI, 1.0-86.8, $p = 0.049$).
- *Soluble Tumor Necrosis Factor-like Weak Inducer of Apoptosis (sTWEAK)*: A negative association has been reported in one of the analyzed cohorts, lasting 5 years and 79 patients, between sTWEAK levels and AAA diameter ($r = -0.4$ and $p = 0.008$), as well as with aneurysmal growth ($r = -0.263$ and $p = 0.031$). This last association was confirmed after multivariate analysis (66).
 - *Peroxiredoxin-1 (PRX-1)*: Has shown correlation with aneurysmal growth ($r = 0.3$ and $p = 0.01$), and acceptable results of sensitivity (63%) and specificity (64%) in the analysis using the ROC curve (67).

Prothrombotic activity

- *D-dimer (DD)*: Is one of the best studied prognostic markers of AAA growth. In 2010, Takagi published a meta-analysis where he confirmed the presence of elevated circulating DD in patients with AAA vs healthy controls or those with non-aneurysmal atherosclerotic disease (30). Afterwards, in 2011, a retrospective study by Golledge (23) of 299 patients, proposed the role of DD in the diagnosis of AAA. In another prospective study of 96 patients [Vega de Céniga (68)] and in a retrospective study of 352 patients, [Sundermann (69)] obtained similar results suggesting the importance of the coagulation-fibrinolysis system and the role of mural thrombus in the physiopathology of AAAs. Circulating DD levels have shown a positive correlation with aneurysmal diameter, as well as with ILT volume (23,30).
- *Thrombin-Antithrombin Complexes (TAT)*: Have been studied by groups, such as Sundermann's (69), who demonstrated that both DD and TAT were independent predictors of aneurysmal expansion in multivariate analysis.

- *Plasmin-antiplasmin complexes (PAP)*: PAP presents the same associations regarding aneurysmal diameter as those observed with DD. In addition, Vega de Céniga (68) demonstrated a slight association between PAP and aneurysmal growth (OR, 1.01; 95%CI, 1.00-1.02).
- *Tissue plasminogen activator (t-PA)*: Different studies have demonstrated a positive correlation with AAA expansion ($p = 0.002$ and $p = 0.016$) (63).

Hematology and lipid metabolism

- *Glycosylated hemoglobin (HbA1c)*: Kristensesn (70) studied a cohort of 319 patients and concluded that it was significantly and inversely related to the aneurysmal expansion rate (-0.177 , $p = 0.002$). After adjusting for RF, Kristensesn demonstrated that aneurysmal expansion was attenuated in patients with elevated HbA1c levels. The limitation of this marker lies in the fact that only a small part of patients with AAA exhibit an altered glucose metabolism.
- *Total Bilirubin and Leukocytes*: Both were studied by the Vuruskan group (71). A multivariate analysis showed that both parameters were independent predictors of greater aneurysmal growth (> 10 mm/y, $p < 0.001$ and $p = 0.002$, respectively).
- *HDLc*: A multivariate analysis conducted by Buriilo (72) with 122 patients determined that HDLc was an independent predictor of aneurysmal progression ($p = 0.008$).

Table II illustrates an analysis of the advantages and limitations of the most promising biomarkers to this date either due to their characteristics or the strength of the studies in which they appear.

Drugs used in abdominal aortic aneurysm

Finding an effective optimal medical therapy for AAA is not only important for the benefit of patients but would also mean a significant reduction of health care costs (73).

Table II. Advantages and limitations of the main AAA biomarkers under study

Biomarker	Advantages	Limitations
MMP-9	Association with AAA presence and diameter	Lack of specificity
	Reflects inflammatory activity in the adventitial wall	Interindividual variability due to age, smoking, statins
	Easy detection in plasma and serum	Limited predictive value
		Lack of defined thresholds
Cystatin C	Association with AAA progression	Also related to renal function and cardiovascular disease
	Reflects proteolytic balance in the medial layer near the ILT	Interindividual variability due to age, sex, diabetes, smoking
	Easy detection in plasma and serum	Less evidence than other biomarkers like MMP-9
		Lack of defined thresholds
Homocysteine	Association with AAA presence	Indicator of cardiovascular and renal disease
	Reflects oxidative stress, inflammation, and medial matrix disruption	Interindividual variability due to diet and nutritional status
	Easy detection in plasma and serum	Lack of defined thresholds
Alpha 1-AT	Association with AAA presence	Associated with genetic predisposition (alpha 1-AT deficiency)
	Reflects extracellular matrix degradation in the aortic wall	Acute-phase reactant
	Easy detection in plasma and serum	No established reference values
MPO	Association with AAA presence and diameter	Also elevated in atherosclerosis, coronary disease, or sepsis
	Reflects inflammatory processes in the aortic wall and ILT	Interindividual variability due to autoimmune diseases or drugs
	Easy detection in plasma and serum	Lack of defined thresholds
CRP	Association with AAA presence and diameter	Lack of specificity (infections, chronic inflammatory diseases)
	Reflects inflammatory processes in AAA	Interindividual variability due to age, obesity, or smoking
	Easy detection in plasma and serum	Cannot distinguish stable AAA from rupture-prone AAA
D-dimer	Association with AAA progression	Lack of specificity (VTE, AMI, cancer, infections)
	Prediction of rupture risk	Interindividual variability due to age or comorbidities

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Table II (cont.). Advantages and limitations of the main AAA biomarkers under study

Biomarker	Advantages	Limitations
D-dimer	Reflects thrombotic and fibrinolytic activity in the wall and ILT	Lack of defined thresholds
	Easy detection in plasma and serum	
PAP	Association with AAA diameter	Lack of specificity (DVT, sepsis, or inflammatory diseases)
	Reflects fibrinolysis processes in the AAA wall	Interindividual variability due to age, cardiovascular disease, or anticoagulants
	Prediction of rupture risk	Lack of defined thresholds
	Easy detection in plasma and serum	

MMP-9: metalloproteinase 9; Alpha 1-AT: alpha 1 antitrypsin; MPO: myeloperoxidase; CRP: C-reactive protein; PAP: plasmin-antiplasmin complexes; VTE: venous thromboembolic disease; AMI: acute myocardial infarction; CA: cancer; DVT: deep vein thrombosis.

Therefore, we analyzed different drugs used for other conditions that have had a positive impact when transferred to aneurysmal disease in recent years.

Antihypertensives

- *Beta-blockers*: Cohort studies and clinical trials have been conducted with these drugs (74). Additionally, clinical trials have been conducted with propranolol which did not obtain statistically significant differences in terms of aneurysmal growth velocity (74,75). Bisoprolol has been shown to reduce the relative risk of morbidity due to adverse cardiac events after AAA surgery. Thus, the AHA guidelines give an AI recommendation for beta-blockers during the AAA perioperative period (76-78).
- *Angiotensin-converting enzyme inhibitors (ACEIs)*: Certain studies have determined an association between ACEI treatment and a reduction in mortality and the risk of surgical intervention in patients with AAA (79). However, regarding clinical trials, the one conducted in 2016 with perindopril did not obtain favorable results (80).
- *Calcium blockers*: The role of these drugs is controversial due to the different results observed across studies. It seems that nifedipine could

generate an inhibition of aneurysmal progression by suppressing the activity of NFκB and MMP-9. However, other drugs of the same family seem to cause an increase in the rigidity of the aortic wall (81). Although the cohort studies conducted have shown differences favorable to the treated group, no statistically significant results have been obtained (17).

Antiplatelet therapy

Based on the fact that ILT plays a significant role in AAA progression and its risk of rupture, it is logical to think that the experimental studies conducted with antiplatelet treatment have generated beneficial effects. However, not all observational studies conducted have supported these results (82). Despite this, it is recommended that patients with AAA be treated with low doses of acetylsalicylic acid.

Statins

The role of statins in reducing AAA growth has not yet been formally evaluated through clinical trials. However, almost all observational and experimental studies support statins as capable of reducing AAA growth (83). Furthermore, given their role in controlling cardiovascular risk, they are drugs that must

be administered to patients with AAA. This means that, currently, it is not possible to conduct a study compared with placebo to evaluate their direct effects on AAA growth.

Reduced levels of MMP-2, MMP-3, and MMP-9 have been demonstrated in the AAA walls of patients on statins. These effects have occurred in 3-week courses only (48). Hurjs, however, did not find this reduction (84). Statins have also been associated with reduced plasma concentrations of MMP-9 in patients with AAA in series such as Gottsater's (85).

Metformin

Several recent experimental and observational studies have suggested the possible effect of metformin, a drug used to treat DM2, in inhibiting growth (86).

There are different clinical trials underway that try to evaluate the effects of metformin on AAA growth, but there are no published data yet (ClinicalTrials.gov).

Doxycycline and nonsteroidal anti-inflammatory drugs (NSAIDs)

MMP-9 is inhibited by doxycycline and NSAIDs. Its specific inhibition reduces AAA development in animal models (40).

The 6-month administration of doxycycline to 36 patients with AAA significantly reduced circulating MMP-9 concentrations, which were elevated at baseline, along with AAA stability during the study period. Patients with higher plasma MMP-9 concentrations experienced the largest decreases in these concentrations with doxycycline treatment (39).

However, subsequent works have dismissed doxycycline as a potential line of research (87).

In conclusion, the current conservative management of AAA consists of:

1. Smoking cessation.
2. Exercise and a healthy diet.
3. Strict control of blood pressure, which should be < 140/90, preferably with beta-blockers or, failing that, ACEIs.
4. Use of statins $\pm$ ezetimibe to maintain LDL levels < 55 mg/dL.

5. Single antiplatelet therapy with acetylsalicylic acid or clopidogrel.

Although this treatment involves reducing the patient's cardiovascular risk, it does not aim to reduce AAA growth rates or stabilization, something that, for the moment, has not been achieved with any of the proposed drugs.

CONCLUSIONS

To predict the risk of aneurysmal expansion in an AAA, numerous biomechanical and circulating markers have been studied, among which aortic diameter is currently the most evident and widely accepted (88,89).

Circulating biomarkers, which are related to AAA pathogenesis processes, such as thrombosis, inflammation, degradation of the extracellular matrix, lipid metabolism, or genetic predisposition, have great potential to improve AAA management, since they allow early detection of high-risk patients and guide personalized therapeutic strategies.

However, the analyzed studies present a series of limitations. On the one hand, the fact that most of them are retrospective studies. On the other hand, the lack of uniformity in the studies regarding the type of biomarker analyzed, population characteristics and cohorts, absence of control groups, discrepancies regarding follow-up intervals, or standardization of quantification methods. All this prevents the results from being completely reliable.

Thus, continuous research into the molecular foundations of AAA and the development of robust biomarker tests are essential steps to reduce AAA-related mortality.

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