Advanced Journal of Vascular Medicine

Review Article

# Abdominal Aortic Aneurysm by Hyperhomocysteinemia -Role of Matrix Metalloproteinases -

**Federico Cacciapuoti***

*Department of Internal Medicine, "L. Vanvitelli" University, Piazza L. Miraglia, 2 Naples, Italy*

***Address for Correspondence:** Federico Cacciapuoti, Department of Internal Medicine, "L. Vanvitelli" University, Piazza L. Miraglia, 2 Naples, Italy, Tel: +39-081-566-6022;
E-mail: fulvio.cacciapuoti@gmail.com

**Submitted:** 05 July 2019; **Approved:** 29 July 2019; **Published:** 02 August 2019

**Cite this article:** Cacciapuoti F. Abdominal Aortic Aneurysm by Hyperhomocysteinemia -Role of Matrix Metalloproteinases. Adv J Vasc Med. 2019; 4(1): 004-008.



ISSN: 2640-5601

ISSN: 2640-5601


## ABSTRACT

The aim of this review was to better define pathogenesis of Abdominal Aortic Aneurysm (AAA) in patients with increased homocysteine plasma levels.

AAA is a non-frequent clinical condition that could evolve towards death for its rupture. It has traditionally been regarded as a consequence of atherosclerosis. That is induced by several risk factors, such as age, family history, smoking, hypertension, diabetes, dyslipidemia and others. Among these risk-factors, elevated plasma levels of homocysteine is also found. Hyperhomocysteinemia (HHcy) can cause breakdown in the elastic fibers of the aortic wall, through degradation of Extracellular Matrix (ECM). That causes the activation of Matrix Metalloproteinases (MMPs) contrarily acting to their Tissue Inhibitors (TIMPs). The imbalance of TIMPs/MMPs ratio with the MMPs prevalence, in turn, induces a proteolytic effect (elastolysis) of the aortic wall and AAA formation. Subsequently, the activation of coagulative process may cause intraluminal thrombus formation that can accelerate or delay the aneurysmatic rupture. But, numerous doubts exist around the role of HHcy in the dilatation of abdominal aortic tract, the importance of intraluminal thrombus for AAA rupture or protection, and the slowing down effect of TIMPs in the AAA formation. Thus, other researches are needed to definitively solve these uncertainties.


**Keywords:** Abdominal aortic aneurysm; Hyperhomocysteinemia; Matrix metalloproteinases; Tissue inhibitors of metalloproteinases.

## INTRODUCTION

Abdominal Aortic Aneurysm (AAA) is a rather rare, but irreversible, dilatation of abdominal aortic tract, usually classified by their size in two types: small aneurysms (diameter less than 5.5 cm.) and large aneurysms (diameter greater than 5.5 cm.) [1]. Large aneurysm is much more likely to rupture than small. The 5-year survival rate is 48% in patients with small aneurysms, whereas it is only 6% in those with large aneurysms. The incidence of AAA ranges from 1.3% to 12.5% and clearly prevails in aged individuals and in male gender [2]. Its rupture is a dramatic event that may result in abdominal and/or back pain, low blood pressure, or low consciousness, and often in death. It is responsible of approximately 8000 annual deaths in the United Kingdom and up 15,000 in the United States. In Italy, the annual mortality is about 6000 cases [3,4].Although several studies indicate that AAA incidence may be declining, AAA mortality has not declined globally [5].

The pathogenesis of AAA is multifactorial and includes advanced age, smoking, positive family history, atherosclerosis, systemic hypertension, diabetes, dyslipidemia, obesity and male sex [6]. But, several studies have demonstrated that Hyperhomocysteinemia (HHcy) is also associated with the formation, size and expansion rate of AAA [7-10].

## HOMOCYSTEINE

Homocysteine is an intermediate amino acid of methionine metabolism that can be further metabolized via two alternative pathways:

A) Homocysteine irreversibly degrades to cysteine, through the transsulfuration pathway.

B) Homocysteine can be remethylated to methionine. Defects in remethylation or in transsulfuration result in increased homocysteine plasma levels [11]. In the remethylation pathway, a methyl group ($CH_3$) can be transferred from methionine to some substrates (trans-methylation), such as DNA, neurotransmitters, different proteins, lipids and a variety of small molecules. Particularly, DNA methylation is a process by which a methyl group is added to DNA molecule at CpG (cytosine-phosphate-guanine) site. HHcy causes DNA-hypomethylation by DNA-Methyl Transferases (DNAMTs) inhibition, because the prevalence of S-Adenosyl-Homocysteine (SAH) on S-Adenosyl-Methionine (SAM). A reduced DNA methylation is responsible for some, common human diseases [12] and, among these, degradation of Extra Cellular Matrix (ECM).

It is known that HHcy has correlated with several vascular insults, such as Coronary Artery Disease (CAD), brain vessels disease (stroke) or peripheral diseases (arterial and/or venous thrombosis, and others [13]. But, HHcy may also associated with the formation, size, and expansion of AAA [14,15], particularly in older men [16]. Referring to AAA formation in hyperhomocysteinemic patients, Giusti et al. also reported an increase in total plasma homocysteine levels in patients with aortic dissection or AAA [17]. Too, a large meta-analysis recently performed by Cao and colleagues provided evidence that homocysteine was a predictor of increased risk of AAA [18]. Several experiences indicate that, the main cause of AAA formation induced by HHcy is DNA hypomethylation acting on ECM [19].

## PATHOGENESIS OF AAA BY HHCY

Several mechanisms can be responsible for vascular dysfunction [20,21]. Referring to the patients with HHcy, it is known that the sulfur amino acid triggers the expression and release of pro-inflammatory cytokines able to induce chemokine-expression [22,23]. Concerning that, multiple evidences suggest an increase of pro-inflammatory cytokines, such as IL6, TNF-alfa, IL1-beta. IFN-gamma, IL17A in either plasma or tissue extract from AAA [24]. On the other hand in experimental models, Liu et al. demonstrated that HHcy can amplify Angiotensin II-induced adventitial inflammation. The event, started in the adventitial layer, subsequently progresses toward the intima. Concordantly, inflammatory cells (macrophages, T-lymphocytes, and B-lymphocytes) are before observed in the tunica adventitia of aneurysmal tissue and subsequently are found in the intima. The process happens via activation of the adventitial fibroblasts NADP oxidase. Specifically, angiotensin II-enhanced NADPH oxidase activity contributes to Adhesion Molecule (ICAM) expression, leukocyte infiltration, and vascular growth [25]. Increased homocysteine levels can also induce intracellular calcium mobilization, causing platelets' activation. The consequent intraluminal thrombus formation has potential implications to aneurysm growth and rupture [26]. Other mechanisms coming in AAA formation are: altered lipid metabolism with enhancement of LDL oxidation and lipid peroxidation [27], and smooth muscle cells proliferation [28]. Impaired fibrinolysis by reduction of Tissue-Type Plasminogen Activator (t-PA) is another pathogenetic factor of vascular impairment [29-31] (Table 1).

ISSN: 2640-5601

| Table 1: Factors HHcy-derived, responsible for vascular wall impairment. |
|---|
| **HHcy-factors inducing vascular impairment** |
| *Endothelial dysfunction |
| *Pro-inflammatory cytokines |
| *Platelets' activation |
| *LDL oxidation |
| *Smooth muscle cells' proliferation |
| * ECM activation |

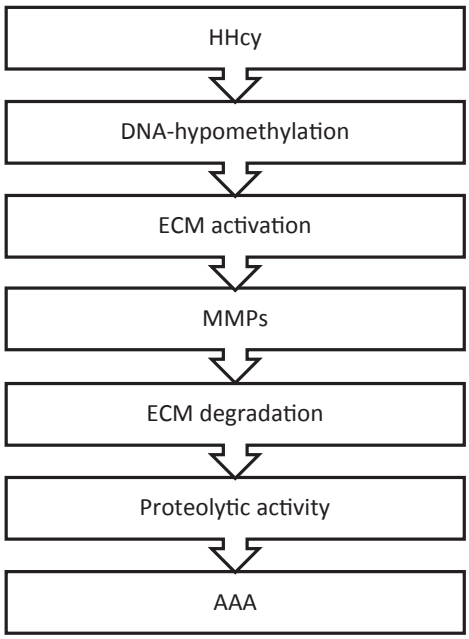


**Table 2:** The sequence of events happening from HHcy to A.A.A. formation.

## EXTRACELLULAR MATRIX

But, the main factor deriving from HHcy is the activation and the degradation of ECM via epigenetic changes (DNA hypomethylation, histone modifications, etc.) [32,33]. ECM is a non-cellular network present within the connective cells composed by macromolecules and glycoproteins, that provide structural and biochemical support to the cells. Enzymes, such as Matrix Metalloproteinases (MMPs or matrixins) and their inhibitors (TIMPs), are also present in the network. But, the basement of ECM is composed by fibrous proteins, such as collagen, laminin, fibronectin, and elastin. These have multiple functions, such as constituents of basal membranes, of cells' adhesion molecules, of structures to maintain tissue architecture or to impart elasticity to tissue.

Summarizing, the essential functions of ECM includes [34]:

A) Formation of an essential support structure for the cells;

B) Control of communications among the cells;

C) Regulation of cells' processes (growth, migration, differentiation, etc.)

## MATRIX METALLOPROTEINASES

As previously affirmed, some enzymatic compounds, called Matrix Metalloproteinases (MMPs), are present in ECM. These are a group of proteases that play an important role in the protein synthetic-lytic equilibrium of connective tissue.

MMPs are secreted in the latent form (pro-MMPs), requiring activation for their proteolytic activity. These enzymes contain a zinc ion and are inhibited by TIMPs. MMPs are divided into subclasses based upon substrate specificity, such as gelatinases, elastases, and collagenases [35]. Specifically, members of the gelatinase subclass, such as MMP2 and MMP9, have demonstrated an ability to degrade denaturated fibrillar collagen (gelatin), elastin and types IV, V, and VII collagen. Referring to AAA formation, some evidences have recognized that elastin degradation contributes to their pathogenesis [36].

Under inflammatory conditions caused by HHcy, infiltrating macrophages, vascular smooth muscle cells, endothelial cells and adventitial fibroblasts of ECM secrete pro-MMPs that activate MMPs [37]. This condition induces a prevalence of MMPs on TIMPs, responsible for abdominal aortic dilation. In fact, contrarily to MMPs, TIMPs prevalence reduces the destruction abdominal aortic wall and, therefore, set oneself against AAA formation [38].

The ECM stimulation (induced by DNA hypomethylation) causes an imbalance of the TIMPs/MMPs ratio, with the prevalence of MMPs, acting such as an independent risk factor for AAA [25]. In fact, this imbalance enhances the proteolytic activity of MMPs on the aortic wall, favoring abdominal aortic dilatation. Referring this, in an *in vitro* study, Siennika et al. observed that MMP2, may favor the AAA formation by its proteolytic activity [39]. In addition, some previously published meta-analyses have confirmed that HHcy is a risk factor of AAA [40]. The proteolytic activity of MMPs is due to the synthesis of serine elastase that, acting on arterial smooth muscle cells, causes elastolysis by degradation of ECM located in the lamina media of abdominal aorta. The release of Reactive Oxygen Species (ROS), is implicated in AAA pathogenesis too [41,42]. However, whether homocysteine plays a direct causal role in the AAA pathogenesis or is merely an innocent bystander remains elusive too. In a Chinese Han population, Liu et al. report HHcy such as an independent risk factor for AAA [10]. In accordance, Brunelli et al. showed that risk increased AAA by up to six times in presence of HHcy, and this association was further observed in a subgroup without evidence of atherosclerosis [9]. In contrast, Naydeck et al. did not find any association between Hcy serum levels and AAA. Perhaps, this discrepancy may stem from the confounding effect of age, other conditions and/or diseases [43]. The succession of events induced by HHcy in the formation AAA are reported in Table II.

## INTRALUMINAL THROMBUS

Some studies suggest that HHcy leads an alteration in coagulation and fibrinolysis. Specifically, it has been reported that homocysteine exhibits antifibrinolytic properties, by the reduction of tissue-type Plasminogen Activator (PA-1) gene expression. These observations indicate that HHcy modifies endothelial function in a pro-thrombotic manner and favors thrombogenesis. Intraluminal thrombus can either be eccentrically located or occupying the entire internal wall of the AAA (figure 1). It must be added that thrombus also works as a site of protease release and is correlated to the further dilation of AAA [44,45]. But, its role in the aneurysmatic rupture appears controversial. In fact, some authors supposed that thrombus accelerates AAA rupture [46], others suggest that intraluminal thrombus in AAA provides biomechanical advantage by decreasing

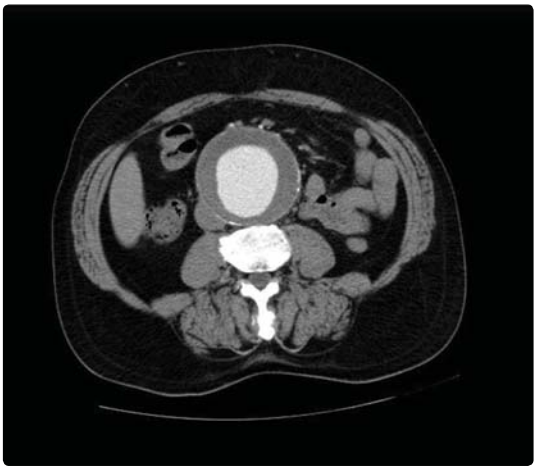

**Figure 1:** Abdominal aortic aneurysm seen at angio-TC, fully bounded by a parietal thrombus.

wall stress [47]. We can reasonably conclude that a thrombus in AAA is associated with a higher AAA growth rate, but also a lower wall stress, with reduced probability of rupture [47].

## CONCLUSIVE REMARKS

AAA consists in an abnormal dilatation of abdominal aorta, often associated with intraluminal thrombus, aortic wall rupture and elevated mortality. Its pathogenesis is multifactorial, but HHcy seems to be an independent risk factor for AAA formation. Enhancement of proteolytic effects induced by protease's release, consequent to the activity of MMPs in ECM are the main mechanisms carried out by HHcy in the pathogenesis of AAA.

Intraluminal thrombus frequently complicates AAA HHcy acts by Tissue Factor (TF) and Plasminogen Activator Inhibitor-1 (PAI-1), that favor thrombogenesis and modifies endothelial function in a pro-thrombotic manner. But at present, whether intraluminal thrombus accelerates the AAA rupture or reduces the probability of that is debated. Concordantly, whether homocysteine levels play a role or is simply a marker in the AAA pathogenesis remains elusive. Finally, in consideration of the reduced expansion of AAA induced by TIMPs nanoparticles, treatment with these could represent an option for preventing a further expansion of small AAA [48]. Therefore, a wide range investigations are requested to clarify these dilemmas.

## REFERENCES


1. Upchurch GR. Schaub TA. Abdominal aortic aneurysms. New Engl J Med. 2006; 73: 1198-1204. http://bit.ly/2ymf3vu
2. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, et al. Executive summary: heart disease and stroke statistics-2013 update: a report from American Heart Association (AAA). Circulation. 2013; 127: 143-152. http://bit.ly/2MmuLPp
3. Gillum RF. Epidemiology of aortic aneurysm in the United States. J Clin Epidemiol. 1995; 48: 1289-1298. http://bit.ly/2Ywnu6i
4. Thompson MM. Controlling the expansion of abdominal aortic aneurysms. Br J Surg. 2003; 90: 897-898. http://bit.ly/2yhKbwi
5. Sidloff D, Stather P, Dattani N, Bown M, Thompson J, Sayers R, et al. Aneurysm global epidemiology study: public health measures can further reduce abdominal aortic aneurysm mortality. Circulation. 2014; 129: 747-753. http://bit.ly/2LNvgTl
6. Forsdahl SH. Singh K. Solberg S, Bjarne K. Jacobsen. Risk factors for abdominal aortic aneurysms. Circulation. 2009; 119: 2202-2208. http://bit.ly/32XhFhn
7. Warsi AA, Davies B, Morris Stiff G, Hullin D, Lewis MH. Abdominal aortic aneurysm and its correlation to plasma homocysteine, and vitamins. Eur J Vasc Endovasc Surg. 2004; 27: 75-79. http://bit.ly/30YXe1S
8. S Caldwell, P Burns, P Haggart, AW Bradbury, DA Mosquera. Association between hyperhomocysteinemia and abdominal aortic aneurysm. Br J Surg. 2001; 88: 609. http://bit.ly/2YCEzvu
9. Brunelli T, Prisco D, Fedi S, Rogolino A, Farsi A, Marcucci R, et al. High prevalence of mild hyperhomocysteinemia in patients with abdominal aortic aneurysm. J Vasc Surg. 2000; 32: 531-536. http://bit.ly/2GygsDS
10. Liu J, Zuo SW, Yue Li, Xin Jia, , Sen Hao Jia, , Tao Zhang, et al. Hyperhomocysteinemia is an independent risk factor of abdominal aortic aneurysm in a Chinese Han population. Scientific Reports. 2016; 6: 17966. https://go.nature.com/2OoaYSt
11. Selhub J. Homocysteine metabolism. Annu Rev Nutr. 1999; 19: 217-246. http://bit.ly/2Yc2C4E
12. Cacciapuoti F. DNA hypomethylation by hyperhomocysteinemia: a biochemical mechanism responsible for some human diseases, explained to the Internist. Ann Clin Exper Metabol. 2018; 3: 1028-1032.
13. Ganguly P. Alam SF. Role of homocysteine in the development of cardiovascular disease. Nutr J. 2015; 10: 14-16. http://bit.ly/2Yqi1d1
14. Moroz P. Le TQ, Norman PE. Homocysteine and abdominal aortic aneurysm. ANZ J Surg. 2007; 77: 329-332. http://bit.ly/2YcVW6m
15. Halazun KJ, Bofkin KA, Asthana S, Evans C, Henderson M, Spark JI. Hyperhomocysteinemia is associated with the rate of abdominal aortic aneurysm expansion. Eur J Vasc Endovasc Surg. 2007; 45: 863. http://bit.ly/2OpCzTr
16. Wong YY, Golledge J, Flicker L, McCaul KA, Hankey GJ, van Bockxmeer FM, et al. Plasma total homocysteine is associated with abdominal aortic aneurysm and aortic diameter in older men. J Vasc Surg. 2013; 58: 364-370. http://bit.ly/2SRgPOH
17. Giusti B, Marcucci R, Lapini I, Sestini I, Lenti M, Yacoub M, et al. Role of hyperhomocysteinemia in aortic disease. Cell Mol Biol. 2004; 50: 945-952. http://bit.ly/2Yr9kiO
18. Cao H, Hu X, Zhang Q, Li J, Wang J, Shao Y, et al. Homocysteine level and risk of abdominal aortic aneurysm: a meta-analysis. PloS ONE. 2014; 9: 85831. http://bit.ly/2Yc82Nn
19. Krishna SM, Dear A, Craig JM, Norman PE, Golledge J. The potential role of homocysteine mediated DNA methylation and associated epigenetic changes in abdominal aortic aneurysm formation. Atherosclerosis. 2013; 228: 295-305. http://bit.ly/2YpmcFT
20. Kent KC. Clinical practice: abdominal aortic aneurysms. NEJM. 2014; 371: 2101-2108. http://bit.ly/30VNFRg
21. Kuivaniemi H, Ryer EJ, Elmore JR, Tromp G. Understanding the pathogenesis of abdominal aortic aneurysm. Expert Rev Cardiovasc Ther. 2015; 13: 775-787. http://bit.ly/2LNw6PY
22. Radomki MW, Salas E. Nitric oxide-biological mediator, modulator and factor of injury: its role in the pathogenesis of atherosclerosis. Atherosclerosis. 1995; 118: 869-880. http://bit.ly/2YyqCOM
23. Desai A. Lamkhord HA, Warren JS. Homocysteine augments cytokine-induced chemokine expression in human vascular smooth muscle cells: implication for atherogenesis. Inflammation. 2001; 25: 179-186. http://bit.ly/2OFWcXx
24. Dawson J, Cockerill GW, Choke E, Belli AM, Loftus I, Thompson MM. Aortic aneurysms secrete interleukin-6 into the circulation. J Vasc Surg. 2007; 45: 350-356. http://bit.ly/2SWtlN7
25. Liu Z, Luo H, Zhang L, Huang Y, Liu B, Ma K, et al. Hyperhomocysteinemia

exaggerates adventitial inflammation and angiotensin II-induced abdominal aortic aneurysm in mice. Circ Res. 2012; 111: 1261-1273. http://bit.ly/2K8uGfy

26. Alexandru N, Jardin I, Popov D, Simionescu M, Garcia-Estan J, Salido GM, et al. Effects of homocysteine on calcium mobilization and platelet function in type 2 diabetes mellitus. J Cell Mol Med. 2008; 12: 2015-2026. http://bit.ly/2Ypauen

27. Voutilainen S, Morrow JD. Roberts LJ. Enhanced in vivo lipid peroxidation at elevated plasma total homocysteine levels. Arterioscler Thromb Vasc Biol. 1999; 19: 1263-1266. http://bit.ly/2OoeTyF

28. Fontaine V, Jacob MP, Houard X, Rossignol P, Plissonnier D, Angles Cano E, et al. Involvement of the mural thrombus as a site of protease release and activation in human aortic aneurysms. Am J Pathol. 2002; 161: 1701-1710. http://bit.ly/32Xryvw

29. Hajjar KA, Mauri L, Jacovina AT, Zhong F, Mirza UA, Padovan JC, et al. Tissue plasminogen activator binding to the annexin II tail domain: direct modulation by homocysteine. J Biol Chem. 1998; 273: 9987- 9993. http://bit.ly/2K0zxAz

30. Midorikawa S, Sanada H, Hashimoto S, Watanabe T. Enhancement by homocysteine of plasminogen activator inhibitor-1 gene expression and secretion from vascular endothelial and smooth muscle cells. Biochem Biophys Res Commun. 2000; 272: 182-185. http://bit.ly/2Yr7cHC

31. Fryer RH, Wilson BD, Gubler DB, Fitzgerald LA, Rodgers GM. Homocysteine, a risk factors for premature vascular disease and thrombosis, induces tissue factor activity in endothelial cells. Arterioscler Thromb. 1993; 13: 1327-1333. http://bit.ly/30VOYj8

32. Robertson KD, Wolffe AP. DNA methylation in health and disease. Nat Rev Genet. 2000; 1: 11-19. http://bit.ly/2K9qITT

33. Fanjul Fernandez M, Folgueras AR, Cabrera S, Lopez Otin C. Matrix metalloproteinases: evolution gene, regulation, and functional analysis in mouse model. Biochim Biophys Acta. 2010; 1083: 3-19. http://bit.ly/30XE7oM

34. Ferrans VJ. New insights into the world of matrix metalloproteinases. Circulation. 2002; 105: 405-407. http://bit.ly/2LMga06

35. Zervoudaki A, Economou E, Stefanadis C, Pitsavos C, Tsioufis K, Aggeli C, et al. Plasma levels of active extracellular matrix metalloproteinases 2 and 9 in patients with essential hypertension before and after antihypertensive treatment. J Hum Hypertens. 2003; 17: 119-124. http://bit.ly/2K465IE

36. Longo GM, Xiong W, Greiner TC, Zhao Y, Fiotti N, Baxter BT. Matrix metalloproteinases 2 and 9 work in concert to produce aortic aneurysms. J Clin Invest. 2002; 110: 625-632. http://bit.ly/2YsPaZL

37. Wu JT. Circulating homocysteine is an inflammatory marker and a risk factor of life-threatening inflammatory diseases. J Biomed Lab Sci. 2007; 19, 107-112. http://bit.ly/32Q7M58

38. Murphy G. Tissue inhibitors of metalloproteinases. Genome Biol. 2011; 12: 233. http://bit.ly/2YmHIRe

39. Siennika A, Zuchowski M, Chelstowski K, Miloslaw Cnotliwy, Jeremy Simon Clark, Maria Jastrzębska. Homocysteine-enhanced proteolytic and fibrinolytic processes in thin intraluminal thrombus and adjacent wall of abdominal aortic aneurysm: study in vitro. Biomed Res Intern. 2018; 3205324. http://bit.ly/2GuGIPt

40. Takagi H, Umemoto T, Alice Group. A meta-analysis of circulating homocysteine levels is subjects with versus without aortic abdominal aneurysm. Int Angiol. 2015; 34: 229-237. http://bit.ly/2Olht8n

41. Jourdheuil Rahmani D, Rolland PH, Rosset E, Branchereau A, Garçon D. Homocysteine induces synthesis of serine elastase in arterial smooth muscle cells from multi-organ donors. Circ Res. 1997; 34: 597-602. http://bit.ly/2LLF5RG

42. Ke XD, Foucault Bertaud A, Genovesio C, Dignat George F, Lamy E, Charpiot P. Homocysteine modulates the proteolytic potential of human smooth muscle cells through a reactive oxygen species dependant mechanism. Mol Cell Biochem. 2010; 335: 203-210. http://bit.ly/32UuRUx

43. Naydeck BL, Sutton Tyrrell K, Schiller KD, Newman AB, Kuller LH. Prevalence and risk factors for abdominal aortic aneurysms in older adults with or without isolated systolic hypertension. Am J Cardiol. 1999; 83: 759-764. http://bit.ly/2K9Kn6n

44. Kazi M, Thyberg J, Religa P, Roy J, Eriksson P, Hedin U, Swedenborg J. Influence of intraluminal thrombus on structural and cellular composition of abdominal aortic aneurysm wall. J Vasc Surg. 2003; 38: 1283-1292. http://bit.ly/2yiJ2Vj

45. Speelman L, Schurink GW, Bosboom EM, Buth J, Breeuwer M, van de Vosse FN, et al. The mechanical role of thrombus on the growth rate of an abdominal aortic aneurysm. J Vasc Surg. 2010; 51: 19-26. http://bit.ly/2Mp6yZ0

46. Koole D, Zandvoort HJA, Shoneveld A, Vink A, Vos JA, van den Hoogen LL, et al. Intraluminal abdominal aortic aneurysm thrombus is associated with disruption of wall integrity. J Vasc Surg. 2013; 57: 77-83. http://bit.ly/2MpkthA

47. Haller SJ, Crawford JD, Courchaine KM, Bohannan CJ, Landry GJ, Moneta GL, et al. Intraluminal thrombus is associated with early rupture of abdominal aortic aneurysm. J Vasc Surg. 2018; 67: 1051-1058. http://bit.ly/2ModYM8

48. Nosoudi N, Nahar Gohad P, Sinha A, Chowdhury A, Gerard P, Carsten CG, et al. Prevention of abdominal aortic aneurysm progression by targered inhibition of matrix metalloproteinase activity with Batimastat-loaded nanoparticles. Circ Res. 2017; 117: 80-89. http://bit.ly/331XS0D