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DEPARTMENT OF SURGERY
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"OBSERVATIONAL PROSPECTIVE STUDY OF POST IMPLANTATION SYNDROME AFTER ENDOVASCULAR ANURYSM REPAIR OF ABDOMINAL AORTIC ANEURYSM"

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To my parents…

The reason of what I become today.

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To my teachers…

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A. GENERAL SECTION

1 ABDOMINAL AORTIC ANEURYSM

1.1 Overview

Abdominal aortic aneurysm (AAA), defined as a focal dilation 50 percent greater than the normal diameter of the aorta, is a common but potentially lethal condition. The abdominal aorta is the most common site of true arterial aneurysm affecting predominantly the segment of aorta below the renal arteries (infrarenal aorta). Well-defined risk factors are associated with the development of AAA and include older age, male gender, Caucasian race, a positive family history, smoking, the presence of other large vessel aneurysms and atherosclerosis. The natural history of AAA is one of progressive dilation, and although expansion rates vary, large aneurysms generally expand at a faster rate than small aneurysms. Many pathogenic mechanisms have been proposed for the development, expansion, and rupture of AAA, and some have been validated in animal models; however, the relative contribution of these mechanisms to AAA expansion and rupture in humans is unclear. The main risk factors associated with expansion and rupture of AAA include large aneurysm diameter, faster aortic expansion rate, and female gender. AAA can be detected on physical examination or by imaging studies. Abdominal ultrasonography is considered the screening modality of choice for AAAs because of its high sensitivity and specificity, as well as its safety and relatively low cost. For asymptomatic patients, elective repair of the aneurysm is the most effective management to prevent rupture. However, elective aortic surgery is also associated with risks, and thus, elective AAA repair is not recommended until the risk of rupture exceeds the risks associated with repair.

1.2 Historic Background of AAA

The first report of AAA is found in ancient India, from Sushrata (800 ~ 600 BC), in chapter 17 of his great text of medicine “Sushruta Samhita”, where he mentions aneurysm or “Granthi” and was the first to ligate bleeding vessels with hemp fibres.[1] Galen (Greek: Κλαύδιος Γαληνός; AD 129 – c. 200/c. 216) a prominent Greek surgeon in ancient Rome[2] first formally described these “tumours” as localized pulsatile swellings that disappear with pressure.[3] However, Antyllus, a second-century surgeon from ancient Greece, was the first to describe the anatomy and treatment of aneurysms. He described two sorts of aneurysmal

lesions: those originating from a local arterial dilatation, which were cylindrical, and those arising from trauma, which were rounded.[4] Antyllus is also credited with performing the first recorded surgical interventions for the treatment of AAA which involved proximal and distal ligation, and even evacuation of the aneurismal sac.[5] It wasn't until Renaissance when the modern anatomy was born, and with it, a proper understanding of aortic morphology. In 1554 Vesalius (1514-1564) produced the first true anatomical plates based on cadaveric dissection, in 'De Humani Corporis Fabrica'.[6] A year later he provided the first accurate diagnosis and illustrations of AAA pathology and is regarded as the father of modern anatomy.[7] The modern period of AAA surgery began in 1817 when Cooper first ligates the abdominal aorta to treat a ruptured iliac aneurysm.[8] A lot have been improved in the development of treatment and understanding of AAA (Fig. 1) with at least two breakthrough: the Dubost´s[12] operation in 1951, chocking the vascular surgical world, with the first resection and repair of AAA with a preserved arterial homograft and the Parodi's[15]first endovascular repair of abdominal aortic aneurysm in 1991, which undeniably represent the beginning of the new era in vascular surgery.

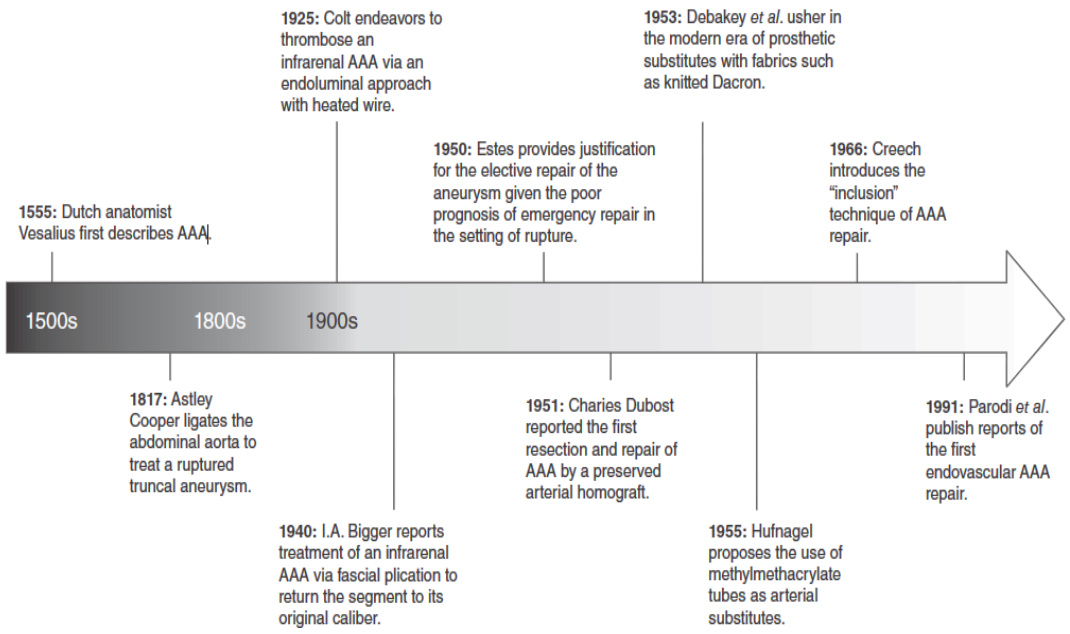


Figure 1. Historical Background. Timeline illustrating the progression of our understanding of the pathophysiology and treatment of abdominal aortic aneurysm from the 16th to the 20th century [9 – 19] By Enrico Ascher, Haimovici's Vascular Surgery, 6th Edition, Blackwell Publishing Ltd, 2012

1.3 Definition

Aneurysm, which is derived from the Ancient Greek word “ανεύρυσμα”, means a permanent dilatation or widening of a body vessel at least 50% larger than its expected normal diameter.[20] Aneurysms occur in various locations including the intra-cranial arteries, iliac and popliteal arteries and the aorta (thoracic and abdominal). The abdominal aorta is the most common site of arterial aneurysm affecting predominantly the segment of aorta below the renal arteries (infrarenal aorta) (Fig. 2). An abdominal aortic aneurysm (AAA) is generally considered to be present when the diameter of the abdominal aorta exceeds 30mm, which represent more than two standard deviation above the mean diameter for both men and women.[21-23] Taking into account the individual variation in the aorta, other researchers have purposed an alternative definition. They define adnominal aorta to be aneurysmal, when its maximum infra-renal aortic diameter is at least 1.5 times larger than the expected normal infra-renal aortic diameter. [24-26]

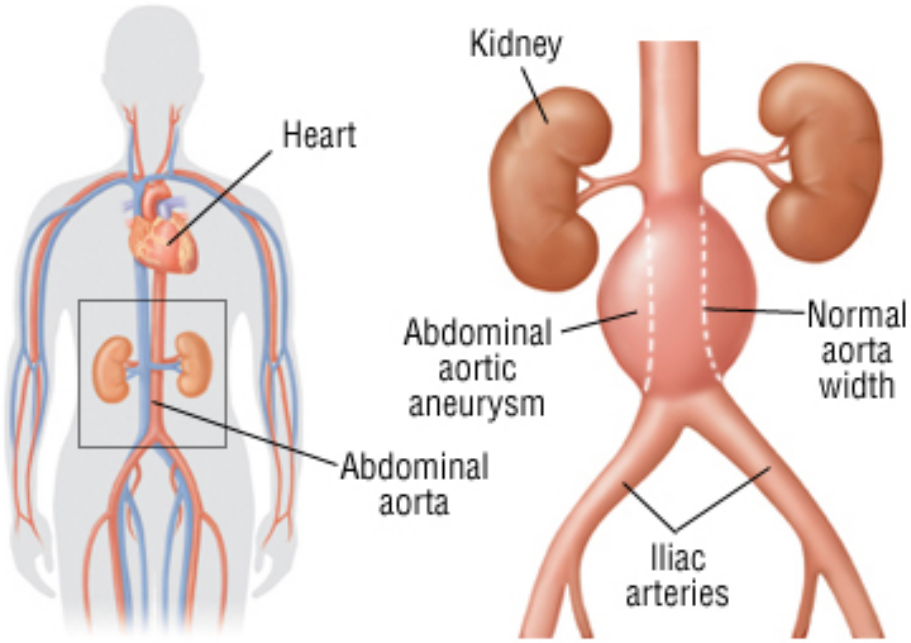


Figure 2. Abdominal Aortic Aneurysm

1.4 Epidemiology

1.4.1 Impact of Rupture

In the United States, ruptured AAAs are the 15th leading cause of death overall and the 10th leading cause of death in men older than 55 years, with the death rate increasing with age[27] (Fig. 2) Overall, the age standardized death rate from ruptured AAAs in the population older 45 years old in the United States between 1999 and 2009 was 5.6 per 100,000 individuals, being significantly higher in males (9.0/100,000) and lower in females (3.2/100,000). In the most at risk groups, the rates are even higher, being 11.3 per 100,000

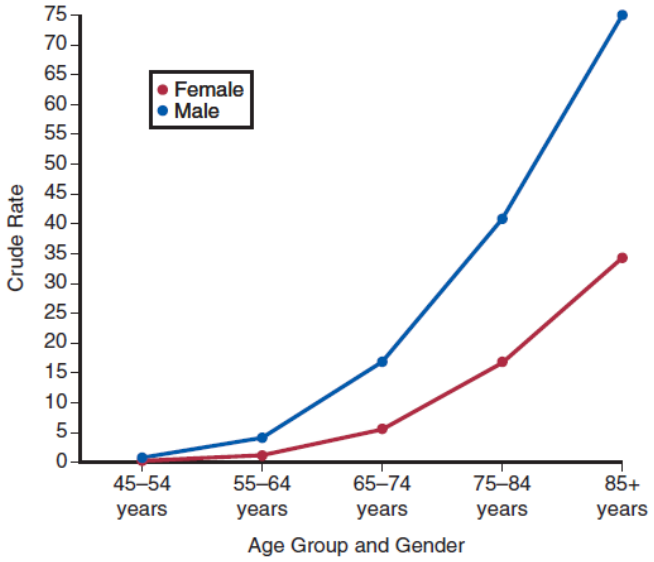


Figure 3. Crude death-rate per 100,000 population in the United States by age and gender from abdominal aortic aneurysms (ruptured and intact). (From the Centers for Disease Control and Prevention, National Center for Health Statistics: Compressed Mortality File 1999-2009. Series 20 No. 2O, 2012. Available at: http://wonder.cdc.gov/cmf-icd10.html. Accessed November 23, 2012.)

in whites, males, and non-Hispanics older than 55 years. The reason for these high death rates is that only half of patients with AAA rupture survive to reach the hospital, many of whom do not have a known diagnosis of AAA before aneurysm rupture. Historically, about a half are offered surgery, although this proportion might now be increasing, and the surgical mortality rate is approximately 50%, with 15% dying intraoperatively.[28] That said, there is mounting evidence from both the United States and the United Kingdom that not only is the prevalence of AAA falling, but the rate of mortality from aneurysm rupture is also decreasing[29-31] (Figs. 4 and 5). This is likely due to a combination of factors, including better

medical management of patients with cardiovascular disease, the advent of population aneurysm screening programs, a greater overall availability of cross-sectional imaging leading to earlier detection of AAAs, and finally, to a reduction in population smoking rates. The advent of endovascular aneurysm repair may also be playing a positive role on aneurysm population rupture rates and deaths. Despite these improvements, aneurysm rupture remains a common cause of death and morbidity, and an entity with a high associated mortality.

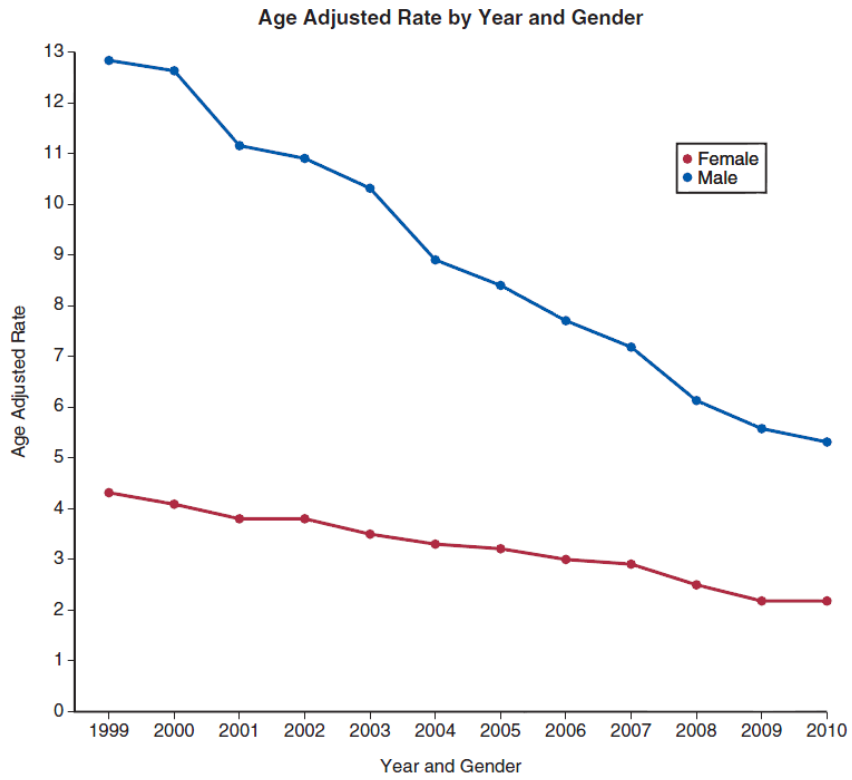


Figure 4. Age-adjusted death rate per 100,000 population by year and gender from ruptured abdominal aortic aneurysms in the United States from 1999 to 2009. (From the Centers for Disease Control and Prevention, National Center for Health Statistics: Compressed Mortality File 1999-2009. CDC WONDER Online Database, compiled from Compressed Mortality File 1999-2009 Series 20 No. 20, 2012. Available at: http://wonder.cdc.gov/cmf-icd10.html. Accessed November 23, 2012.)

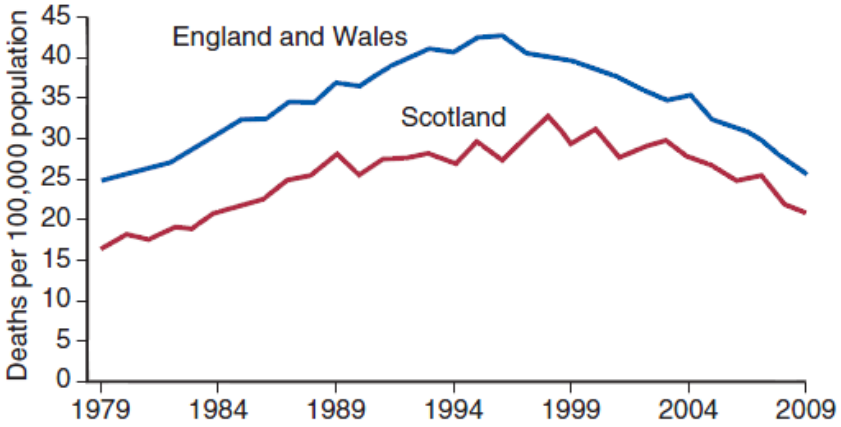


Figure 5. Deaths per 100,000 population in the United Kingdom from ruptured abdominal aortic aneurysm. (From Anjum A, et al: Is the incidence of abdominal aortic aneurysm declining in the 21st century? Mortality and hospital admissions for England & Wales and Scotland. Eur J Vasc Endovasc Surg 43:161-166, 2012.)

1.4.2 Incidence

AAAs primarily affect the population older than 50 years. AAAs are two to six times more common in men than in women, and are two to three times more common in white men than in black men.[32-35] In men, AAAs begin to occur at approximately 50 years of age and reach a peak incidence at approximately 80 years of age.[36-38] In women, AAA onset is delayed, beginning at approximately 60 years, with the incidence continuing to increase thereafter. Screening studies have provided information on both the prevalence and incidence of AAAs.

In the Huntingdon, United Kingdom, screening program for men older than 50 years, the incidence of new AAAs was 3.5 per 1000 person-years.[39] The most recent data from the U.K. National Aneurysm Screening Program showed that of the 107,051 men ages 65 years offered screening in 2011, only 1.5% had aortic diameters more than 3 cm.[40] The difference between the two reports might reflect public health measures to reduce smoking and to improve cardiovascular health. In the United States, a screening study of male veterans found new AAAs in 2.6% of patients 4 years after an initial normal aortic ultrasound study, for an incidence of 6.5 per 1000 person-years.[41] Similarly, in the Huntingdon study, new AAAs were discovered in 2% of patients screened a second time at a mean of 5.5 years after an

initial negative study. These data highlight the relevance of screening and potentially re-screening of the at-risk population to fully detect aneurysms within that population.

Overall, the age-adjusted incidence of both asymptomatic and ruptured AAAs, and of AAA-related death, is twofold to sixfold higher in men than in women (fig. 6)

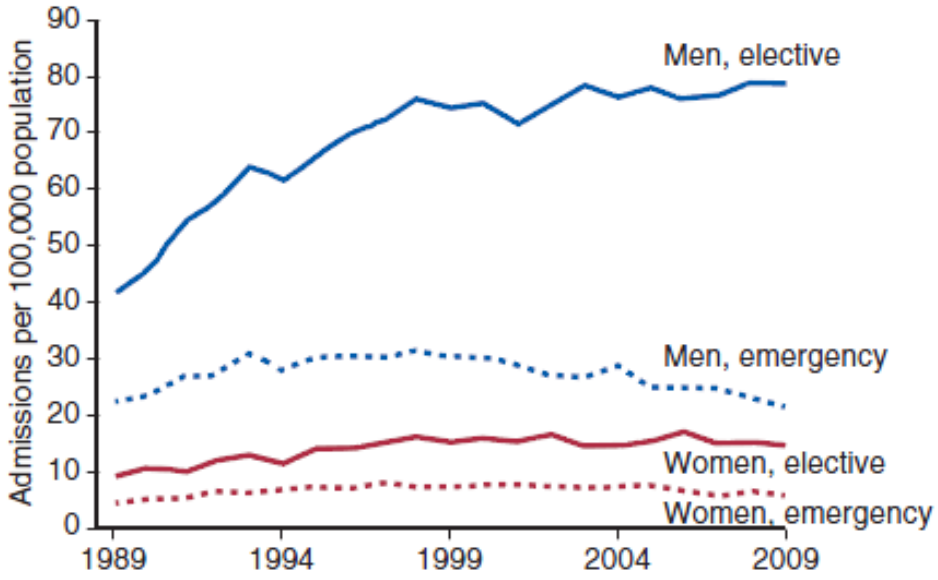


Figure 6. Admissions with aortic-related pathologies per 100,000 population in the United Kingdom by gender and mode of admission. (From Anjum A, et al: Is the incidence of abdominal aortic Scotland. *Eur* aneurysm declining in the 21st century? Mortality and hospital admissions for England & Wales and *J Vasc Endovasc Surg* 43:161- 166, 2012.)

1.4.3 Prevalence

Prevalence estimates for asymptomatic AAAs (likelihood of having an AAA) are more accurate than incidence estimates (likelihood of an AAAs developing) now that ample published data from several large ultrasound populations screening studies are performed. Some of them are randomized trials and try to evaluate the benefit of screening [42-45] and some being epidemiological screening studies. [46, 47] The prevalence rates differ according to age, gender and geographical location (table 1). [48] In a Veterans Affairs (VA) screening study of more than 73,000 patients 50 to 79 years old, the prevalence of AAAs ≥3 cm was 4.6% and that of AAAs ≥4 cm was 1.4%.[49] The prevalence of AAAs reported varied according to both age and gender (Table 2). The highest prevalence of AAA ≥3.0 cm was 5.9% and was found in white male smokers between the ages of 50 and 79 years.

Study location	Chichester, UK[42]	Viborg, Denmark[43]	Western Australia[44]	MASS UK[45]	Rotterdam, Netherlands[46]	Tromsø, Norway[47]
No.	15,775	12,628	41,000	67,800	5,419	6,386
Gender	Men & women	Men	Men	Men	Men & women	Men & women
Age (years)	65-80	65-73	65-79	65-74	>55	55-74
Sampling dates	1988-90	1994-8	1996-8	1997-9	1994-5	1994-5
Date published	1995	2002	2004	2002	1995	2001
Aneurysm prevalence	4.0% (7.6% men, 1.3% women)	4.0%	7.2%	4.9%	4.1% men, 0.7% women	8.9% men, 2.2% women

Table 1. From Moll et al: Management of abdominal aortic aneurysms clinical practice guidelines of the European society for vascular surgery. *Eur J Vasc Endovasc Surg* 41(Suppl 1):S1-S58, 2011. *MASS UK*, Multicentre Aneurysm Screening Study, United Kingdom.

Prevalence Estimates of AAA Based on Race, Sex, and Smoking History			
Race	**Sex**	**Smoking History**	**Prevalence AAA≥ 3cm (%)**
White	Male	Yes	5.9
		No	1.9
	Female	Yes	1.9
		No	0.6
Black	Male	Yes	3.2
		No	1.4
Other	Male	Yes	3.6
		No	1.3

Table 2. Lederle FA, et al: Prevalence and associations of abdominal aortic aneurysm detected through screening. Aneurysm Detection and Management (ADAM) Veterans Affairs Cooperative Study Group. Ann Intern Med 126(6):441–449, 1997. AAA = Abdominal aortic aneurysm

1.5 Risk Factors

Well-defined clinical risk factors are associated with the development of AAA.[50] These include advancing age, male gender Caucasian race, smoking, a family history of AAA, the presence of other large aneurysms, and atherosclerosis.[51] Although these risk factors are associated with increased AAA prevalence, they may not be independent predictors and may be markers rather than causes of AAA disease.

1.5.1 Age, sex and ethnicity

The risk of AAAs increases dramatically after 60 years of age.[47, 52] Clinically relevant aneurysms (more than 4 cm in diameter) are present in approximately 1% of men between 55 and 64 years of age, and the prevalence increases by 2% to 4% per decade thereafter.[47, 52] AAAs are four to six times more common in men than in women[42, 53]. In addition, AAAs develop in women approximately 10 years later than in men[37]. AAAs were found to occur more frequently in white people than in black people. In the ADAM trial, AAA occurred approximately twice as frequently in whites compared with blacks.[54]

1.5.2 Smoking

A history of cigarette smoking is one of the strongest independent risk factors for AAA formation.[55] In the ADAM study[57] found smoking to be the risk factor most strongly associated with AAA. The likelihood of finding AAA was significantly higher in smokers compared with nonsmokers (odds ratio [OR] 2.97 for AAA 3.0 to 3.9 cm, 95% CI 2.65-3.32; OR 5.07 for AAA >4.0 cm, 95% CI 4.13-6.21).The association with smoking was directly related to the number of years of smoking, and the association decreased with the number of years after cessation of smoking.[49] Smoking predicts a larger aortic diameter at presentation,[56] and in screening studies, 18 to 52 percent of patients with small AAAs are current smokers.[47, 49,57] Once an aneurysm has formed, active smoking is associated with the highest risk of aneurysm progression and rupture.[52, 54, 58, 59] A decrease in the prevalence of smoking is likely responsible for a decreasing incidence in AAA reported in some countries.[60-62] With smoking cessation, the risk of AAA slowly declines over time[50, 63], thus, smoking cessation is an essential component of risk reduction in patients with AAA.

1.5.3 Family history

A positive family history is another potential factor that significantly increases the risk of AAA.[64] A family history of surgical intervention for an AAA in a first-degree relative may increase the risk fourfold[65] In a Swedish nationwide survey, the relative risk of developing AAA for a first-degree relative of a person diagnosed with AAA was approximately double that of a person with no family history of AAA.[66] In a study of 238 first-degree relatives of patients who underwent surgery for AAA and 281 controls, a family history increased the risk of having an aneurysm 4.3-fold; the highest risk was among brothers older than 60 years of age, in whom the prevalence was 18 percent.[65]

1.5.4 Other large vessel aneurysm

Patients with a large vessel peripheral aneurysm (e.g. iliac, femoral, popliteal, carotid) have an increased risk for AAA, which, in different studies, has been found in 85 percent of patients with a femoral aneurysm and in about 60 percent of those with a popliteal aneurysm.[67, 68] In a retrospective review of patients with AAA, more than 25 percent were found to have a concomitant thoracic aortic aneurysm (TAA).[69] Significantly more women had combined AAA and TAA compared with men (48 versus 28 percent). The association between AAA and other large vessel aneurysms is likely related to common pathogenic mechanisms.

1.5.5 Association with atherosclerosis

A positive correlation between cardiovascular disease and AAA has been found in numerous studies.[46,47,49-51,54,70-74] Patients with AAA have a significantly higher prevalence of risk factors for atherosclerosis compared with age and gender-matched controls.[55,76] The prevalence of AAA is about 5 percent in patients with known coronary heart disease, and approximately 10 percent in those with peripheral artery disease.[71-74]

In the ADAM trial and Life Line Screening cohorts, coronary heart disease, cerebrovascular disease, hypertension and high cholesterol levels were associated with an increased risk for AAA >4.0 cm in diameter.[50,54] Another cohort study of over 104,000 patients confirmed that major atherosclerotic risk factors (except diabetes and obesity) are related to AAA.[76] Conversely, data from the United Kingdom Small Aneurysm Trial showed

that lipid levels and elevated blood pressure were not significantly associated with aneurysm expansion.[77] These findings led to the traditional view that AAA is caused by atherosclerotic disease; however, the formation of AAA, and AAA expansion and rupture involves multiple intertwined pathogenic processes, and atherosclerosis may be a consequence rather than the cause of this process.

1.5.6 Others Factors

Female gender, non-Caucasian race, and diabetes mellitus are associated with a decreased risk for developing AAA. Although diabetes mellitus is consistently a strong risk factor for atherosclerosis, it is negatively associated with AAA.[54,76] In the Aneurysm Detection and Management (ADAM) trial, for example, the odds ratio in patients with diabetes mellitus relative to non-diabetic patients was 0.52 (95% CI 0.45-0.61) for AAA >4.0 cm in diameter.[54] (Table 3)

Independent Risk Factors for Detecting an Unknown 4-cm-Diameter or Larger Abdominal Aortic Aneurysm during Ultrasound Screening		
Risk Factor	**Odds Ratio***	**95% CI**
INCREASED RISK		
Smoking history	5.1	4.1-6.2
Family history of AAA	1.9	1.6-2.3
Older age(per 7-year interval)	1.7	1.6-1.8
Coronary artery disease	1.5	1.4-1.7
High cholesterol	1.4	1.3-1.6
COPD	1.2	1.1-1.4
Height (per 7-cm interval)	1.2	1.1-1.3
DECREASED RISK		
Abdominal imaging within 5 yr.	0.8	0.7-0.9
Deep venous thrombosis	0.7	0.5-0.8
Diabetes mellitus	0.5	0.5-0.6
Black race	0.5	0.4-0.7
Female gender	0.2	0.1-0.5

Table 3. From Lederle FA, et al: The aneurysm detection and management study screening program: validation cohort and final results. Aneurysm Detection and Management Veterans Affairs Cooperative Study Investigators. *Arch Intern Med* 160:1425, 2000. *AAA*, Abdominal aortic aneurysm; *COPD*, chronic obstructive pulmonary disease.
*Odds ratio indicates relative risk in comparison to patients without that risk factor

1.6 Pathogenesis

Aneurysmal degeneration of the abdominal aorta is a multifactorial, systemic process generally felt to be due to alterations in vascular wall biology leading to a loss of vascular structural proteins and wall strength.[78]

Although atherosclerotic changes frequently coexist with AAA[49,54,71-74] and the risk factors for aneurysmal and atherosclerotic aortic disease overlap to some extent, contemporary research suggests that atherosclerosis is not causal.[79-82] Aneurysmal degeneration of the aortic wall is pathologically distinguished from atherosclerosis. Whereas atherosclerotic changes are limited to inner layers of the aortic wall, AAAs are characterized by transmural inflammatory change, abnormal collagen remodeling and cross-linking, and loss of elastin and smooth muscle cells.[83-84] These changes result in aortic wall thinning and progressive aortic expansion.

A role for inflammation in the pathogenesis of AAA was first speculated because of a clinical entity called an inflammatory aneurysm, which represents approximately 5 percent of patients with AAA.[85,86] Inflammatory aneurysms are characterized by marked aortic wall thickening with increased vascularity and associated with elevated erythrocyte sedimentation (ESR) levels, indicative of inflammation.[87-89] This type of aneurysm has distinct clinical and pathologic characteristics that may represent an extreme manifestation of the inflammatory processes present in all aortic aneurysms.[86]

Aneurysm formation is also associated with other circulating markers of inflammation such as C-reactive protein (CRP), and interleukins. A positive association between serum CRP and aneurysm diameter, and the presence of CRP mRNA in aneurysmal tissue is consistent with a causal hypothesis.[90] Tissue cultures of biopsied aneurysm wall tissue secrete large amounts of cytokines, including interleukin-6 (IL-6), in aneurysm patients. In a study of 466 patients with small aneurysms, high concentrations of circulating IL-6 signaled rapid aneurysm expansion.[91]

Chronic inflammation of the aortic wall likely mediates aortic wall elastin and collagen degradation through proteases, including plasmin (formed from plasminogen by urokinase plasminogen activator and tissue type plasminogen activator), matrix metalloproteinases (MMPs), and cathepsin S and K.[81,92-101] These factors are derived from endothelial and smooth muscle cells and inflammatory cells infiltrating the media and adventitia.

The pathologic factors responsible for aneurysm rupture have been less well studied. In an animal model, aneurysm rupture correlated with an increase in MMP-2 and MMP-9 levels.[97] Local overexpression of tissue inhibitor of MMP-1, produced by retrovirally infected smooth muscle cells, prevented aneurysmal degeneration and rupture. These findings are consistent with a study in humans in which biopsies were taken from the walls of ruptured and nonruptured AAAs.[102] Only MMP-8 (collagenase-2) and MMP-9 were significantly increased at the rupture site compared with the nonruptured anterior wall.

1.7 Natural History

The natural history of AAA is one of progressively increasing diameter; however, expansion rates vary. The main risk factors associated with AAA expansion and rupture include large aneurysm diameter, faster aortic expansion rate, current smoking, and female gender.

1.7.1 Aortic expansion

The rate of aortic expansion is greater for larger compared with smaller diameter AAA.[56,77,103-105] This pattern of differential expansion over time related to baseline AAA diameter was illustrated in an analysis from the United Kingdom Small Aneurysm Trial in which the following annual expansion rates were noted:[77]

- 1.9 mm per year for aneurysms 2.8 to 3.9 cm in baseline diameter
- 2.7 mm per year for those 4.0 to 4.5 cm in baseline diameter
- 3.5 mm per year for those 4.6 to 8.5 cm in baseline diameter

The cumulative evidence from studies that prospectively followed the size of AAAs suggests that small and medium-sized AAAs (<5.5 cm) expand at an average rate of 2 to 3 mm/year, while larger aneurysms expand at about 3 to 4 mm per year. [56,77,103-105] Some aneurysms, for unclear reasons, remain relatively fixed in size for a period of time and then undergo rapid expansion, which is thought to increase the risk for rupture, and is defined as an increase in maximal aortic diameter ≥5 mm over a six-month period of time or >10 mm over a year.[55,106] Aneurysm expansion tends to be more rapid in smokers, and less rapid in patients with diabetes mellitus or peripheral artery disease.[77] Active smoking is associated with the highest

risk of aneurysm expansion and rupture.[52,54,58,59,107-109] It has been estimated that active smoking increases the aneurysm expansion rate by 20 to 25 percent per year.[52,110]

1.7.2 Risk of rupture

Aneurysm diameter is the most important factor predisposing to rupture, with risk increasing markedly at aneurysm diameters greater than 5.5 cm.[52,104,11-116] (Figure 7) In addition to diameter, a faster rate of expansion (highest in smokers), gender, and other factors play a role.[116]

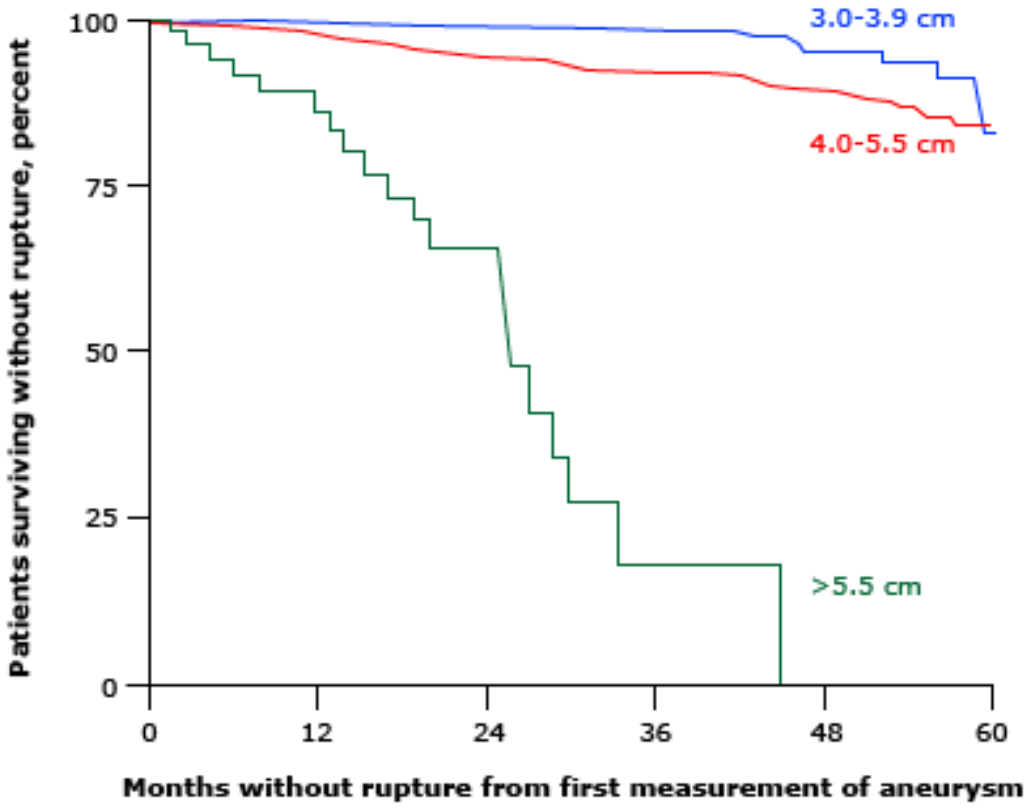


Figure 7. Risk of rupture of an abdominal aortic aneurysm (AAA) over time according to the first measurement of aneurysm diameter in 1792 men and 465 women. The risk of rupture increased markedly in aneurysms larger than 5.5 cm in diameter.
Data from: Powell, JT, Greenhalgh, RM, N Engl J Med 2003; 348:1895.

1.7.2.1 Aneurysm diameter

The relationship of aneurysm diameter to aortic rupture was first demonstrated in a seminal study in which patients with aneurysms >6 cm had a much higher rate of rupture at five years compared with aneurysms <6.0 cm (43% vs 20%), and lower rate of survival (6% vs 48%). Virtually identical differences in survival rates have been noted in other series.[59,111,117] A statement from the Joint Council of the American Association for Vascular Surgery and Society for Vascular Surgery estimated the annual rupture risk according to AAA diameter:[106,116] (Table 4)

Table 4. 12-month AAA Rupture Risk by diameter.

Diameter (cm)	**Rupture Risk** (%)
<4.0	0
4.0 - 4.9	0.5 - 5
5.0 - 5.9	3 - 15
6.0 - 6.9	10 - 20
7.0 -7.9	20 - 40
≥ 8.0	30 - 50

AAA, abdominal aortic aneurysm.

1.7.2.2 Rate of expansion

The rate of aneurysm expansion may also be an important determinant of rupture risk.[103,118] A small (<4.0 cm) or medium (4 to 5.5 cm) AAA that expands ≥0.5 cm over six months of follow-up is considered to be at high risk for rupture.[55] One study, for example, found mean expansion rates of ruptured versus non ruptured aneurysms of 0.82 and 0.42 cm/year, respectively.[103] Active smoking is associated with the highest rates of aneurysm

expansion and rupture.[52,54,58,59] In the United Kingdom Small Aneurysm Trial, active smokers were at an increased risk for aneurysm rupture relative to nonsmokers and former smokers (odds ratio [OR] 2.1, 95% CI 0.95-4.67), and had a poorer prognosis related to worse pulmonary function.[59,119] In the women's health initiative that enrolled more than 160,000 women, current smoking was associated with the highest risk of having an AAA event defined as development of AAA requiring intervention (symptomatic or ruptured).[120]

1.7.2.3 Female Gender

The risk of AAA rupture is increased in women compared with men for the same aortic diameter. Although the prevalence of AAA is 4 to 6 times lower for women compared with men, [47, 49, 54, 70,121-123] about a third of admissions for ruptured AAA are women.[123]

- In the United Kingdom Small Aneurysm Trial, the risk for AAA rupture in women relative to men for a given diameter was increased fourfold (odds ratio 4.5, 95% CI 1.98-10.2).[59,124]
- In another review, the rupture rate for AAA ≥5.0 cm was 19 percent for women and 12 percent for men.[131]

These differences may reflect the smaller 'normal' diameter of the female aorta. Thus, a diameter of 5.0 to 5.5 cm represents a greater degree of dilatation in women.[52,131] This concept is supported by the results of a study in which the mean diameter of the aorta at the time of rupture was 5 mm smaller for women compared with men.[125] Mortality rates following repair are also higher for women.[132]

1.7.2.4 Other factors

In addition to the main risk factors for aneurysm rupture discussed above (aneurysm diameter, rate of expansion, female gender), other factors that may influence the risk of rupture include medical factors and recent surgery; the configuration of the aneurysm may also play a role.

- **Medical factors** — In the United Kingdom Small Aneurysm Trial, medical risk factors for AAA rupture included mean arterial blood pressure >110 mmHg (OR

1.04, 95% CI 1.02-1.07) and lower FEV1. Low FEV1 measurements correlated with the presence of severe chronic pulmonary disease.[59,116]

- **Recent surgery** — Rupture rates as high as 33 percent are reported in prospective studies of patients undergoing coronary artery revascularization prior to aneurysm repair.[126,127] AAA rupture has been reported following other types of surgery, but no causal etiology has been proven. One prospective study found a 3 percent rupture rate after unrelated noncardiac surgery in patients with AAA diameter >5 cm.[128]
- **Aneurysm configuration** — Studies using advanced mechanical modeling (e.g. finite element analysis), to more accurately evaluate the stresses on the aortic wall have identified that the highest mechanical stress is located at the transition zone from normal aortic tissue to the dilated region.[129,130] Some have speculated that saccular aneurysms have higher risk for rupture compared with fusiform aneurysms. Although saccular aneurysms have a very abrupt transition zone, saccular aneurysms are not necessarily associated with an increased risk of rupture, particularly if the configuration is concentric.[125] On the other hand, asymmetric saccular aortic aneurysm may be a manifestation of aortic infection, and these do appear to have an increased risk for rupture.

1.7.3 Long-term outcomes

In addition to the risk of rupture, patients with AAA (any diameter) are more likely to have cardiovascular disease and more likely to experience a cardiovascular event. In a screening study of 4734 subjects over the age of 65, 8.8 percent were found to have an aortic aneurysm, of which 88 percent were smaller than 3.5 cm in diameter.[122] During a 4.5-year follow-up, patients with an aneurysm had a higher rate of overall mortality compared with subjects without an aneurysm, an effect that was more pronounced if the aneurysm was >3.5 cm in diameter. After adjusting for age, sex, race, height, weight, smoking, lipid levels, family history, and history of a cardiovascular disease event, mortality risk remained significantly elevated (relative risk [RR] 1.47, 95% CI 1.18 to 1.83). However, further adjustment for disease in other vascular beds by measuring carotid wall thickness, presence of major electrocardiographic abnormalities, or an abnormal ankle–brachial index, reduced the risk (RR 1.32, 95% CI 1.04-1.67). The differences in mortality rates were due predominantly to other associated cardiovascular disease in participants with aneurysm.

1.8 Screening

Asymptomatic abdominal aortic aneurysms (AAAs) can be detected on physical examination or by imaging studies. Abdominal ultrasonography is considered the screening modality of choice for AAAs because of its high sensitivity and specificity, as well as its safety and relatively low cost.

1.8.1 Ultrasonography

Abdominal ultrasonography has been used as the screening modality in the large randomized trials of screening for AAA. With a sensitivity of 95 to 100 percent and a specificity of nearly 100 percent,[133] ultrasonography has superb test characteristics for diagnosing and following an AAA. The four randomized trials of population screening are the Chichester trial in the UK,[42] the Viborg trial in Denmark,[43] the Western Australia trial[44] and the MASS trial in the UK.[45] In each trial, populations were randomized to either an offer of aneurysm screening or to no offer of screening, and in each trial screening, was shown to reduce aneurysm related mortality for men. These results, to 5 years, have been summarized in a Cochrane Review[134] and the odds ratio in favor of screening for men was 0.60 [95%CI 0.47-0.78]. A systematic review for the US Preventive Task Force reported a similar benefit for screening men, odds ratio 0.53 [95%CI 0.42e0.68].[64] The individual characteristics of the trials are summarized in Table 5.

1.8.2 Physical examination

The aorta bifurcates at the umbilicus. Thus, physical examination in a patient with an AAA may reveal a pulsatile mass in the epigastrium. The accuracy of the clinical examination is markedly diminished by obese body habitus and smaller aneurysm size.[135] The reproducibility of physical examination findings between clinicians has not been studied. Use of abdominal palpation for screening purposes has been evaluated in several

Summary of the population-based randomized screening trials.				
Trial characteristics	Chichester, UK[42]	Viborg, Denmark[43]	MASS UK[45, c]	Western Australia[44]
Number randomized	15,775	12,628	67,800	41,000
Gender	Men & women	Men	Men	Men
Age (years)	65-80	65-73	65-74	65-79
Dates recruited	1988-90	1994-8	1997-9	1996-8
Date published	1995	2002	2002	2004
% accepting screening	68%	76%	80%	70%[d]
Aneurysms found	4% (7.6% in men)	4%	4.9%	7.2%
Place of screening	Hospital	Hospital	Community	Community
Intervention policy	At 6 cm	At 5 cm	At 5.5 cm (internal diameter)	None
Mean follow-up (months)	30.5	61	49	43
AAA mortality	0.59 men only	0.31	0.58	0.72
odds ratio screened vs not (95%CI)[a]	(0.27-1.29)	(0.13-0.79)	(0.42-0.78)	(0.39-1.32)
All-cause mortality	Men only 1.07		0.97	0.98
odds ratio Screened vs not (95%CI)[b]	(0.93-1.22)		(0.93-1.02)	(0.91-1.04)
Other outcomes reported	No aneurysm-related mortality benefits in women	Hospital deaths Costs Quality of life	Quality of life Costs Workload	
Extended follow-up available	Yes		Yes	

[a] Pooled odds ratio overall 4 trials strongly in favor of screening, OR 0.57 (0.45-0.74), together with a halving of the incidence of aneurysm rupture in screened populations.

[b] Pooled odds ratio trend in favor of screening, OR 0.98 (0.95-1.02).

[c] The MASS trial recently has published 10-year follow-up, demonstrating the cost-effectiveness of screening and a significant all-cause mortality benefit but a rising incidence of AAA rupture in the screened group.

[d] As percentage of those alive when invitation for screening was sent: randomization predated this invitation by several months in A large sector of subjects.

Table 5. From Moll et al: Management of abdominal aortic aneurysms clinical practice guidelines of the European society for vascular surgery. *Eur J Vasc Endovasc Surg* 41(Suppl 1):S1-S58, 2011. *MASS UK*, Multicentre Aneurysm Screening Study, United Kingdom.

populations. One report of asymptomatic, high-risk internal medicine clinic attendees found an aneurysm prevalence of 9 percent.[136] Using ultrasonography as the gold standard, the sensitivity of abdominal palpation varies from 23 to 68 percent, and specificity from 75 to 91 percent.[136-138] Sensitivity increases with the size of the aneurysm and decreased abdominal girth. In one study, the sensitivity was 61 percent for AAAs 3.0 to 3.9 cm, 69 percent for aneurysms 4.0 to 4.9 cm, and 82 percent for aneurysms 5.0 cm or greater; when girth was less than 100 cm, sensitivity was 100 percent for aneurysms 5.0 cm or larger.[138] The predictive value of palpation declines dramatically below age 70.[139,140]

1.8.3 Other imaging modalities

AAAs may be seen on plain films of the abdomen, abdominal computed tomography (CT), and magnetic resonance imaging (MRI). Both CT and MRI appear to be highly accurate tests for AAAs but are not generally performed for screening as they are more expensive than abdominal ultrasonography. However, nearly two-thirds of aneurysms leading to surgery are detected as incidental findings on imaging studies (most often CT or MRI) that are performed for other indications.[141]

1.9 Management

Elective AAA repair is the most effective management to prevent rupture. However, elective aortic surgery is associated with risks, and thus, elective AAA repair is not recommended until the risk of rupture exceeds the risks associated with repair (anesthetic risk, technique-related risks).[106] For asymptomatic patients, randomized trials comparing observation for medium-sized (4.0 to 5.5 cm AAA) with open or endovascular AAA repair have found that the risk of AAA rupture generally does not exceed the risk associated with elective AAA repair until aneurysm diameter exceeds 5.5 cm.[104,142-145] We agree with 2009 guidelines from the Joint Council of the American Association for Vascular Surgery and Society for Vascular Surgery and recommend observation for asymptomatic AAA <5.5 cm in diameter based upon these trials.[106]

The timing of AAA repair may be affected by other factors such as the presence of coexistent peripheral artery disease or peripheral aneurysm (e.g., iliac aneurysm, femoral aneurysm) and other factors that increase the risk of rupture, including advanced age and

rapid aneurysm expansion. Although repair may not be warranted in patients with AAA diameter <5.5 cm, these patients remain at risk for aneurysm expansion. As such, management consists of ongoing clinical evaluation and AAA surveillance, and risk modification.

Based upon observational studies of the natural history of AAA showing that it was uncommon for asymptomatic AAA smaller than 5 cm to rupture, this was the traditional threshold above which open aneurysm repair was performed.[146,147] Whether this represented optimal management was addressed in randomized trials comparing aneurysm repair with non-operative management plus surveillance imaging for medium-sized aneurysms (4.0 to 5.5 cm), with two trials using open AAA repair[104,142], and three later trials using endovascular aneurysm repair.[143-145,148,149] A meta-analysis of these trials found no advantage to early repair (open or endovascular) for AAA measuring 4.0 to 5.5 cm.[150] In the United Kingdom (UK) Small Aneurysm and Aneurysm Detection and Management (ADAM) trials, which were predominantly composed of men, the risk of death due to rupture during the period of surveillance of medium-sized (4.0 to 4.4 cm) AAA was lower than the risk of death from open AAA repair.[104,142] A subsequent meta-analysis in 2007 of these trials found no significant differences in all-cause mortality between the groups at five to eight years follow-up.[151]The UK Small Aneurysm Trial and the ADAM trial were performed prior to the widespread use of endovascular aneurysm repair (EVAR). Two trials comparing EVAR to observation for AAA <5.5 cm similarly found no significant long-term differences between AAA repair and non-operative management, and these studies lend further support to the 5.5 cm threshold established from earlier randomized trials.[143, 144, 148, 149] In spite of the lower perioperative mortality rate associated with EVAR, there appears to be no advantage to elective EVAR repair for small and medium-sized aneurysms.

2 AAA AND INFLAMMATION

Inflammation is considered a crucial component in the pathogenesis and development of AAA along with proteolytic processes, genetic coding, and alterations in wall tension. AAA has been described as a chronic proinflammatory condition.[152] Preceding reports concerning histological analysis of diseased aortas have all displayed the transmural infiltration of T and B cells, macrophages, dendritic cells neutrophils, and mast cells in the media and adventitia of aneurysmal aortas.[153] These cells generate cytokines in the affected abdominal wall. Although a vast asset of them has been researched, only a few are considered specific to this pathology as compared to normal or atherosclerotic aortas and characterize the inflammatory process in AAA.(Figure 8) In particular, there is an overexpression of interleukin 6 and interleukin 8 and preeminence of their related responses, TNF-1 and interferon gamma (INF-1), which belong to the group of TH1 associated cytokines, IL1B and IL10.[153] Furthermore, messenger RNA and protein analysis on AAA samples have shown a distinct presence of intense activation of inflammatory transcription factors nuclear factor 1 B (NF-1B) and activator- protein 1 (AP-1) in the smooth muscle cells.[154] This induces secretion of matrix metalloproteinases (MMPs) and other proteases leading to wall degradation and to repeated secretion of more cytokines thus perpetuating the inflammatory process. In clinical application, there are several reports concerning measuring of plasma biomarkers in attempt to observe aneurysm progression such as C reactive protein (CRP) and IL. However, either results are conflicting or evidence is weak.[155] Karlsson et al. found no correlation of CRP and IL6 plasma levels with the aneurysm expansion rate, while De Haro et al. reported a statistically significant association of CRP levels with the growth rate of the aneurysm.[156,157] Treska et al. showed a significant correlation of IL-6 levels and AAA diameter and TNF-1 with the symptoms of AAA.[157] Furthermore Jones et al. reported that for patients with small aneurysms a specific IL-6 genotype predicted future cardiovascular mortality without however finding any association between plasma IL-6 or IL-6 genotype and aneurysm growth.[91] AAA is a complex entity and despite the significant advances in surgical and endovascular approaches, no therapies have been established that can effectively retard the progressive inflammation and elastolysis. Concentrating on isolated components of the inflammatory process is unlikely to control aneurysm growth rate due to biological redundancy. Further research of the interactions and relations of the

components of the inflammatory process as a whole assemblage and their clinical implication may have the potential to shift AAA detection and growth control in the future.

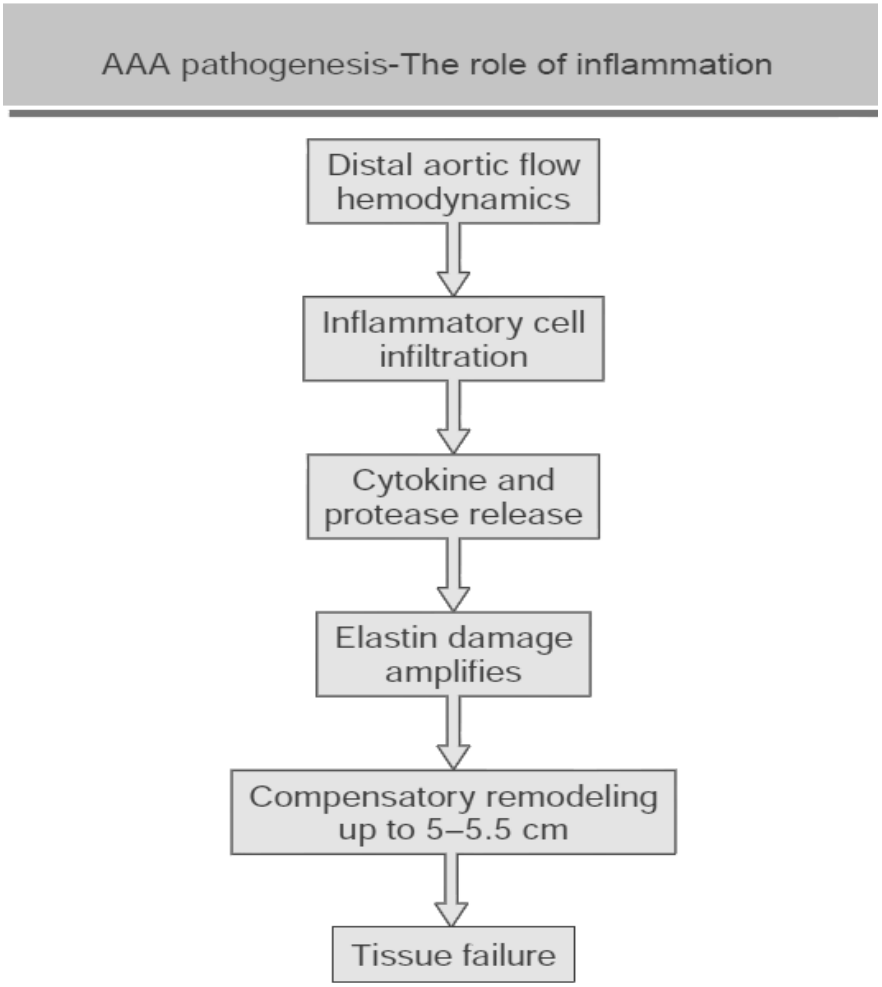


Figure (8) The role of inflammation in the AAA pathogenesis.

AAA = Abdominal Aortic Aneurysm

3 ENDOVACULAR AORTIC ANEURYSM REPAIR (EVAR)

3.1 General

Open AAA repair (OAR) consists of prosthetic graft interposition through laparotomy, associated with an overall mortality rate of approximately 5%.[48] Severe comorbidities could further increase the perioperative risk and consequently the mortality rate. Cardiac events, respiratory dysfunction, renal impairment and multiple organ failure are adverse events that may develop following open AAA repair, as a result of a severe inflammatory response.[158,159] Intraoperative tissue damage, ischemia and reperfusion injury caused by aortic clamping, and biochemical injury at cellular level are possibly triggering the above-mentioned severe inflammatory response.[160,161]

The indication for aneurysm treatment is the elimination of the risk of rupture and death. For asymptomatic patients elective repair of the aneurysm constitutes the most effective management to prevent rupture. However elective aortic surgery has been also associated with considerable risks and therefore elective AAA repair is not recommended until the risk of rupture exceeds the risks associated with the repair. For asymptomatic patients the risk of rupture exceeds the risk of repair when the AAA diameter is larger than 5-5.5cm.[48,106] Endovascular repair of AAA involves the placement of an expandable stent graft within the aorta to treat aortic disease without operating directly on the aorta through laparotomy.

Endovascular aortic aneurysm repair (EVAR) has rapidly expanded since Parodi's first report and is progressively replacing OSR for the treatment of infrarenal abdominal aortic aneurysms (AAAs).[15,162] According to nationwide hospital databases, there has been a 600% increase in the annual number of EVAR procedures performed in the United States since 2000.[163] Although long-term durability and associated costs have not been completely established, EVAR now accounts for more than half of all AAA repairs. Moreover, since the introduction of EVAR, the annual number of deaths from intact and ruptured AAA has significantly decreased in the United States. This has coincided with an increase in elective AAA repair after the introduction of EVAR and a decrease in the diagnosis and repair of ruptured AAA.[63]

3.2 30-day and in-hospital outcome

It would seem to be axiomatic that EVAR, as a minimally invasive technology would be associated with lower inhospital and 30-day mortality rates as compared to OSR. Indeed, among nonrandomized but controlled trials, 30- day mortality rates of less than 2% were reported among all FDA pivotal study populations (AneuRx [n = 416] 1.7%; Excluder [n = 235] 1.3%; Zenith [n =352] 1.1%; Powerlink [n =192] 1%).[106] In an analysis of pooled trial data for patients considered at high risk for OSR, 30-day mortality for patients treated by EVAR or OSR was comparable (2.9% EVAR vs 5.1% OSR, p=0.32).[164] Among randomized, prospective trials, lower mortality was observed among those patients treated by EVAR. Specifically, in-hospital mortality rates in the EVAR-1 trial and the DREAM trial were 1.7% and 1.2% for EVAR and 6% and 4.6% for OSR, respectively.[165,166] These differences, however, did not achieve statistical significance (p=0.1). Moreover, only 23% of screened patients in the EVAR-1 trial were eligible for randomization with more than half of all patients excluded from the trial due to the presence of anatomic unsuitability for EVAR (54%).

It is noteworthy that with rapid adoption of this technology in the United States, much lower mortality rates have been reported for EVAR in analyses of large statewide and multi-state population-based databases.[167] These trends were noted early after initial FDA approval of first generation devices. In-hospital mortality of 4.2% for OSR and 0.8% for EVAR was observed among approximately 1,600 patients treated in New York State treated in 2002.[168] Lee at al analyzed 4,607 patients who underwent OSR and 2,565 treated by EVAR that were enrolled in the Nationwide Inpatient Sample (NIS) database in 2002.[169] In-hospital mortality was significantly lower following EVAR (1.3% vs 3.8%), despite the presence of greater cardiovascular co-morbidity. In a review of 65,502 patients entered into the NIS database who underwent elective EVAR between 2001 and 2004, Timaran et al noted an in- hospital mortality of 2.2%.[170] Stratified analyses, including only elective EVAR procedures, revealed that in-hospital mortality was 1.7% in patients with the most severe comorbidities and 0.4% among those with lower comorbidity. In this regard, analysis of a high risk cohort from the from the Veteran Affairs (VA) National Surgical Quality Improvement Program (NSQIP) revealed those patients who underwent elective EVAR (n=788) had a significantly lower 30- day

mortality than those treated by OSR (n=1,580) (3.4% vs 5.2%,p=0.047).[171] In a recent analysis of 45,000 propensity score- matched Medicare beneficiaries treated by EVAR and OSR, mortality was significantly lower after EVAR (1.2% vs 4.8%; p=0.001), with reduction in mortality most pronounced for those of advanced age (80 to 84 years: 1.6% vs 7.2%; 85 years: 2.7% vs 11.2%; p=0.001).[172]

3.3 Mid-term outcomes

The DREAM and EVAR-1 trials have provided mid-term follow-up data at two and four years, respectively.[165,166] Although a 3% reduction in aneurysm-related mortality persisted throughout the follow-up period, in both trials, the initial reduction in all-cause mortality was eliminated within one to two years with equivalent overall survival in both treatment groups. Moreover, EVAR was associated with a greater number of late complications and secondary reinterventions. In the EVAR-1 trial, reinterventions occurred three times as often, exceeding 20% at four years, whereas for OSR the reintervention rate was approximately 6%. The DREAM trial showed a similar pattern in the first nine months after randomization (hazard ratio, 2.9; 95% confidence interval. (CI), 1.1 to 6.2), with roughly parallel rates for reintervention for EVAR and OSR, thereafter (hazard ratio, 1.1; 95% CI, 0.1 to 9.3). A population-based study of 45,660 Medicare beneficiaries undergoing either EVAR or OSR demonstrates similar findings.[172] Survival curves converged three years after initial repair and by four years, AAA rupture (1.8% vs 0.5%) and AAA-related reinterventions (9.0% vs 1.7%) were more likely after EVAR than after OSR. In contrast, laparotomy-related complications that required surgical repair were more likely among patients who had undergone OSR (9.7%, vs 4.1%), as were hospitalizations for bowel obstruction or abdominal-wall hernia. Although the DREAM trial reported that quality of life scores were greater for those patients treated by EVAR, within six months, differences were no longer apparent and sexual function scores were similar or better for those patients who underwent OSR.[173] Likewise, in the EVAR-1 trial, SF-36 mental component scores were similar for both treatment groups throughout the postoperative and follow-up periods, with differences only observed for the physical component scores, which were lower during the first three postoperative months for those treated by OSR.[174]

4 POST IMPLANTATION SYNDROME

4.1 Incidence-Definition

Several reports have mentioned that endovascular procedures may initiate a systemic inflammatory response, known as post-implantation syndrome (PIS).[175,176] This inflammatory process may be triggered by manipulations with sheaths and catheters within the aortic lumen and the intramural thrombus, leading to the release of inflammatory mediators such as tumor necrosis factor α (TNFα), interleukin-6 (IL-6) and other cytokines.[177,178] Endothelial dysfunction may also prompt this inflammatory reaction, reflecting a synergic role between the material of the graft and the endovascular surgical technique.[175,176] Despite the fact that PIS is frequently well-tolerated by patients, its impact on the outcome of patients is still unknown, especially in patients at high risk, including the elderly with several comorbidities.[179] According to the reporting standards for endovascular aneurysm repair (EVAR), PIS could be considered a moderate complication of the procedure.[162]

Post implantation syndrome is the clinical and biochemical expression of an inflammatory response following endovascular repair of an aortic aneurysm. The reported incidence of PIS in the literature has been varying widely from 14 to 60%.[180-183]

The underestimation of this syndrome, which is not systematically reported, and the relatively small number of patients involved in most studies may account for this variation. Additionally, the lack of a universally accepted definition should also be acknowledged. Velazquez et al first described PIS in 1999 as the presence of fever and leukocytosis with a white blood cell (WBC) count >11,000/ml.[184] Thereafter Gorich et al reported a 45% incidence of PIS by defining leukocytosis as WBC count >10,000/ml.[185] Blum et al reported a raised incidence of PIS (100%) in 154 consecutive EVAR patients, taking into account leukocytosis of WBC count >9800/ml and elevated CRP, but not the presence of fever.[186]

A definition of the syndrome according to the systemic inflammatory response (SIRS) seems logical. This definition seems to be more reasonable because there is

evidence supporting a systemic inflammatory response induced by the implantation of the endoprosthesis. PIS seems to constitute a SIRS state as it actually fulfills at least two of the SIRS criteria (fever and leukocytosis).[187]

PIS is mainly a clinical condition associated with the implantation of an endograft and is diagnosed by the presence of fever accompanied by elevated WBC count above normal without any evidence of an infection. All patients presenting with fever during the postoperative period, whether or not fulfilling the PIS criteria, are undergoing a thorough work up for possible infection. If any of these tests reveal evidence of an early pulmonary, urinary tract or any other kind of infection, the patient is not considered to suffer from PIS.

4.2 Causes

Multiple factors have been proposed as causes of the inflammatory response after EVAR. Some authors suggest that manipulation of the aneurysm may activate white blood cells and lead to release of various cytokines, while others speculate that injury to the endothelium may cause protein C activation and subsequent coagulopathy.[178,180,188] None of these theories have been proved. Furthermore, an experimental study showed that iodide-containing contrast agent that is used during EVAR for vessel visualization induced neutrophil granulocyte degranulation.[189] A PIS-induced effect due to contrast media has not been observed in either clinical study so far.[175,176,190]

***Thrombus*:** Aneurysm thrombus has also been proposed to incur a role on the inflammatory response. Norgren et al in the early years of EVAR proposed that this endovascular procedure may induce an inflammatory response mainly involving TNF-a release from cell activation arising from intra-aneurysmal device manipulation.[182] The theory was based on the finding that mural thrombus of an aortic aneurysm contains high amounts of IL-6 and that manipulations with endovascular instruments inside the mural thrombus might release IL-6.[177] Gabriel et al supported this hypothesis 10 years later, though neither of these studies performed any quantitative evaluation of thrombus manipulation during the procedure.[51] Future large studies should focus on the effect of

sac thrombosis after AAA exclusion from the circulation on the inflammatory biomarkers and its relation with PIS development.

***Role of material*:** Differences between the type of the stent graft deployed and the development of PIS might indicate that different materials and maybe configurations of the grafts, can interfere with an inflammatory response. Stent grafts are a collapsible hybrid product composed of either woven Dacron or ePTFE with stents providing for radial support. Gerasimidis et al in a relatively underpowered study found for the first time in 2005 that fever was more common in a group of patients who received polyester endovascular grafts that in those that received PTFE graft.[180] The type of endograft's material may incur a principle role in PIS development and may have a predictive role for a significant portion of EVAR patients.

Furthermore there are other differences between stent grafts, unrelated to graft material, which theoretically might also influence PIS occurrence. The vast majority of the stent grafts have an exoskeleton made of nitinol. Since the presentation of nitinol for medical application, it has been extensively used in coronary and peripheral arterial stents. No inflammatory response is reported in these applications, despite frequent treatment of multiple and lengthy lesions, requiring large quantities of the material. It is, therefore, doubtful that variances in the application of nitinol between stent grafts to have any effect on PIS.

4.3 Role of C-reactive protein

One easily measurable factor for the determination of PIS is C-reactive protein (CRP). This is an acute phase protein, that apart from reflecting the degree of systematic inflammation, might be considered as a surrogate of atherosclerotic burden that may also have a direct role in atherosclerotic plaque rupture and thrombosis.[191,192] In a surgical setting Choi et al. reported that high-preoperative CRP represents a strong and independent predictor of perioperative major cardiovascular event in noncardiac surgery, while our group in a previous report suggested that hs-CRP may predict the occurrence of cardiovascular event during the first postoperative year after vascular surgery.[193,194] CRP has been used as PIS indicator in many studies. CRP levels increase

rapidly, usually 6 hours after an inflammatory trigger, reaches a peak in 1-2 days and return to baseline in 4 to 10 days.[195] Although CRP seems to be able to serve as an indicator in the diagnosis of PIS, more studies are needed to confirm its real value.

4.4 Role of cytokines

Cytokines seem to play an important role on the inflammatory response after EVAR. Cytokines constitutes components of a complex signaling network. They can broadly get classified as growth factors. chemotactic factors (IL-4, IL-8), modulators of lymphocyte function (IL-2, IL-4) and modulators of the inflammatory response (IL-1b, TNFa, IL-6).[196,197] Swartbol et al in an in-vitro study of 10 mural thrombus specimens obtained from 10 different aortic aneurysms reported elevated levels of IL-6 from the aneurysmal thrombus, causing WBC stimulation and production of TNF-a.[177] This finding has been confirmed in a clinical study by Dawson et al.[198] They found that circulating IL-6 was elevated within the aorta in patients with aneurysms and also correlated with the aneurysm surface area. In EVAR the endograft material is exposed to the bloodstream and its surface activates inflammatory mediators. Plasma levels of IL-6 after endoluminal graft placement in the abdominal aorta have been shown to increase in all patients on the first postoperative day.[199] Gabriel et al. in a relatively small study (25 patients) evaluated the inflammatory reactions following endovascular abdominal and thoracic aortic aneurysm repair and showed that in all patients there was an elevation of IL-6 which culminated at 24 hours and triggered both an elevation of CRP and the development of fever 24 hours later.[51] However it is not a readily available assay in normal hospital laboratories and cannot be easily applied outside of research use.

4.5 Outcome

The relation of PIS with patient's outcome has not been adequately established. In most studies PIS is considered a benign condition. Seldom, the inflammatory process has been reported to lead to the development of serious complications such as pulmonary dysfunction, cardiovascular events, renal insufficiency, even multi-system organ

failure.[70,200,201] However, PIS has not been reported as an outcome measure in none of the large EVAR trials. Our group has reported a few years ago 5 EVAR and 1 TEVAR patients that needed readmission during the first 30 days after the procedure due to a systemic inflammatory response syndrome (SIRS).[202] All these patients had PIS postoperatively and were discharged home after PIS had been attenuated. Several days later, they returned because of continuous fever and a generalized inflammatory response, including dyspnea, tachycardia, leg edema, weakness, anorexia, even renal insufficiency and pleural infusions, which eventually led to readmission. All patients underwent several examinations and were assessed by experienced doctors within different specialties, but no other diagnosis founded by clinical evaluation and laboratory tests could be made, except that all patients were developing SIRS. It is important future studies to assess whether PIS patients remain at a greater risk of suffering from an adverse event when compared to non-PIS patients even after the first month and might require closer surveillance after the procedure.

B. MAIN SECTION

1 Objectives

Endovascular procedures have been proposed as minimally invasive alternative treatment, allowing safe and effective aortic aneurysm repair. Despite the potential benefits, it has been demonstrated that endovascular stent grafting may elicit an unexpected systemic inflammatory response, which has been named post-implantation syndrome (PIS), first described by Velazquez et al. in 1999. [54]

The main features of PIS include continuous pyrexia despite antibiotic therapy, negative culture results, leukocytosis and/or coagulation disturbances.[160,188,2003-205] The incidence of the syndrome has been reported to vary widely between 3% and 60% for abdominal aortic aneurysms (AAAs).[206] Although, there are many laboratory and clinical data suggesting a systemic inflammatory response syndrome (SIRS) state,[181,182,188,] from the pathophysiological and clinical point of view there is no clear definition of the syndrome and its potential significance so far. It seems that PIS manifests clinically as a systemic inflammatory response syndrome (SIRS), meeting two of the four criteria according to the definition of SIRS, fever and leukocytosis.[187,207] This response is primarily attributed to endothelial dysfunction reflecting a synergic role between the material of the graft and the endovascular surgical technique; the acute formation of a large amount of thrombus within the aneurysmal sac may also play a role.[208] The clinical importance of PIS is unclear and the impact of the syndrome on the outcome of the patients is still unknown. However, postoperative inflammatory response raises concerns of postoperative morbidity, especially in patients at high risk, including the elderly with several comorbidities.[179,209] In most cases, PIS is generally well tolerated, but even then it may result in a more demanding post-operative recovery leading to prolonged hospitalization, and thus it might be considered a moderate complication of the procedure.

The present study was designed to prospectively evaluate PIS after elective endovascular aneurysm repair of abdominal aortic aneurysm (AAA) and to investigate its association with various clinical and laboratory parameters, as well as the clinical outcome of the patients during the first year after EVAR.

2 Patients and Methods

2.1 Definition

PIS fulfills at least two of the SIRS criteria (i.e., fever and leukocytosis).[187] Therefore, PIS was defined as the presence of fever (persisting body temperature >38 ^{o}C lasting for more than 1 day during hospitalization) and leukocytosis (white blood cell count > 12.000/mL) despite antibiotic therapy and negative blood culture results.

2.2 Study sample

From May 2007 to July 2008, 40 consecutive patients undergoing elective EVAR repair in our department were enrolled in a pilot study to prospectively evaluate whether EVAR is associated with PIS as well as the relationship of clinical and biochemical relation of PIS with several acute phase inflammation markers.

Subsequently, from January 2010 to June 2013, 214 consecutive patients with AAA undergoing elective EVAR in our department were prospectively enrolled in a full scale study protocol (30-day and 1-year follow up). All patients gave written informed consent, and the study protocols was approved by the institutional Ethics Committee. During this time, endovascular repair was offered to all suitable patients according to the ESVS practice guidelines for the management of AAA.[211] Exclusion criteria included:

- Clinical and/or laboratory evidence of infection preoperatively, including leukocytosis (white blood cell count [WBC] > 10.000/mL) and elevated body temperature.
- Signs of gangrene.
- Previous trauma or surgery two months prior to enrollment.
- Previous implantation of endoprosthesis.
- Any autoimmune disease or systemic inflammatory condition.
- Any malignancy.

- Use of anti-inflammatory drugs, chemotherapeutic agents, immunosuppressants, or anticoagulants.

2.3 Procedure

All patients were treated by the same surgical and anesthesiology team in a fully equipped operating room with the patient under general anesthesia. Every effort was made to follow the selection criteria recommended by the manufacturer of the stent graft, however, the surgeon's decision as to which device to use was based on the anatomical characteristics of the proximal neck, the iliac artery configuration, and the presence of thrombus or calcification. Open surgical access through small transverse incisions for both femoral arteries was used and systemic heparinization was achieved with 5,000 IU of heparin. Every effort was made to deploy the endovascular device just below the level of the lowest renal artery. The stent grafts implanted were Endurant (Medtronic Inc, Santa Rosa, CA, USA), Anaconda (Vascutek, a Terumo company, Inchinnan, UK), Zenith (Cook Inc., Indianapolis, IN, USA), Aorfix (Lombard Medical Technologies, Oxfordshire, UK), Powerlink (Endologix, Irvine, California), and Excluder (W.L. Gore & Associates, Flagstaff, AZ, USA). The material of the first four devices is polyester, while the last two devices are made from ePTFE. All the devices were bifurcated systems. All patients received antibiotic prophylaxis (teicoplanin 400 mg, and ceftriaxone 1 g) half an hour pre-operatively and for the day of operation, as well as 3500 IU of low molecular weight heparin (tinzaparin) from the first postoperative day until discharge. In all patients, demographics, intra-operative and post-operative complications, the incidence of PIS, the diameter of the aneurysm, the type of the graft deployed, the operation time, the amount of contrast media administered (Optiray 320, Mallinckrodt Inc, St. Louis, MO, USA), and length of postoperative stay, were recorded. Temperature was recorded eight times daily for the duration of hospitalization. Blood tests including troponin levels were measured on the first and third post-operative day and the day before discharge. Post-operative pain was controlled with intravenous tramadol, while in cases of fever >38.5°C lasting more than 2 hours intravenous paracetamol (1 g) was administered. According to the protocol no anti-inflammatory drugs (steroids or non-

steroids) were used during the post-operative period. All patients presenting with fever during the post-operative period, whether or not fulfilling the PIS criteria, underwent a thorough work up for possible infection. If any of these tests revealed evidence of an early pulmonary, urinary tract or any other kind of infection, the patient was not considered to suffer from PIS. Patients were discharged in the absence of any complications, with a body temperature <37.5 ^{O}C for at least 24 hours and a WBC <12.000/mL. Outpatient follow-up was performed at the 1st, 6th, and 12th month after surgery. All patients continued their medical treatment with statins and antiplatelets during the follow-up period.

2.4 Variables of interest

Demographics, risk factors, pre- and post-operative medication, maximum aneurysm diameter, contrast media used, duration of the procedure, type of endograft, the occurrence of PIS, maximum temperature, peri-operative complications, and duration of hospital stay were recorded for each patient. Aneurysm volume was calculated from the computed tomography using a workstation with dedicated reconstruction software (3Mensio, Medical imaging B.V., Bilthoven, The Netherlands) by the same operator. At first the total AAA volume from pre-operative computed tomography angiography (CTA) was calculated. Furthermore, from CTA in the first month, the amount of newly formed thrombus was calculated by subtracting the endograft volume and the pre-operative thrombus volume from the total AAA volume. Adverse events included any major cardiovascular event (MACE), acute renal failure, readmission and death of any cause. MACE was defined as a composite of death from cardiac causes, nonfatal acute myocardial infarction (ST and non-ST), worsening of cardiac status needing intervention, ischemic stroke and transient ischemic attack (TIA). Death was considered due to cardiac causes if the patient died of MI, cardiac arrhythmia, or congestive heart failure caused primarily by a cardiac condition. The diagnosis of MI required elevated troponin concentration with at least one of two 12-lead ECG changes, including development of new Q waves or new persistent ST–T segment or T-wave changes.[212] Unstable angina was defined as severe chest pain lasting for at least 30 min, unresponsive

to standard therapeutic intervention, and associated with transient ST- segment deviation of 0.05mV or greater, new or T-wave inversion of 0.3 mV or greater without development of Q waves, or CK-MB elevation. Stroke was defined according to the current World Health Organization definition as rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin.[213] TIAs included brief episodes of neurological dysfunction resulting from focal cerebral ischemia not associated with permanent cerebral infarction, lasting less than 24 hours.[214] Acute kidney failure was defined as impaired renal function according to KDIGO clinical practice guidelines.[27]

2.5 Medication

All patients were on antiplatelet therapy (aspirin 100 mg once daily) for at least 3 weeks prior to the procedure. Preoperative medications were continued immediately after surgery. Patients who were enrolled and were already receiving a statin continued their medication. For patients not already on statin, atorvastatin (20 mg once daily) was initiated at the screening visit.

2.6 Blood samples and laboratory markers

For our preliminary study blood test were obtained without tourniquet 24 hours prior to, and after the surgery. In contrast, in our main study venous blood was collected without tourniquet preoperatively, at day 1 and 3 postoperatively, at the 1st, 6th and 12th month after the procedure. Patients at the 1st, 6th and 12th month visits with a history of a recently developed (<15 days) inflammatory disease were rescheduled for an appointment two weeks afterwards.

For the determination of WBC and PLT counts, 2 ml blood was transferred into an evacuate tube containing 3.6 mg K ethylenediaminetetraacetic acid (EDTA) dry salt (Becton–Dickinson Vacutainer, Plymouth, UK). The blood was mixed with the anticoagulant by repeated inversions of the tube. Complete blood cell counts were measured in the SE- 9500 model of Automated Haematology Analyzer (Sysmex

Corporation, Kobe, Japan). For the determination of Fib plasma levels (mg/dl) 4.5 ml of blood transferred into an evacuated tube containing 0.5 ml (0.105 M) sodium citrate (Becton–Dickinson Vacutainer, Plymouth, UK). The blood was mixed with the anticoagulant by repeated inversions of the tube. The tube was centrifuged in 2000 g for 10 min twice, and the separated plasma collected in plastic tubes. The Fib plasma levels were measured according the Clauss method in the BCS model of Behring Coagulation Analyzer (Dade–Behring, Marburg, Germany). A high-sensitivity assay was used for the determination of serum CRP levels (hs-CRP Beckman Coulter, Miami, FL, USA). The serum CRP levels were determined via the scatter of light produced by the formation of immune complexes in the test solution (Beckman Coulter, Immage Immunochemistry System). For serum collection a 5-ml blood sample was transferred into a sterile evacuated tube (Becton–Dickinson Vacutainer, Plymouth, UK). The blood allowed clotting at room temperature. After the clot formation, the tube was centrifuged at 3000 g for 15 min and the separated serum was collected in plastic tubes. Serum samples were frozen at –70 °C until analysis.

Besides the traditional inflammatory markers (WBC, hs-CRP and fibrinogen) we also measured IL-1β, IL-6 and TNF-α. From these markers IL-6 was the only marker significantly altered in PIS patients in our preliminary study.[210] Thus we measured only the IL-6 in the patients not included in preliminary data. IL-1β, IL-6 and TNF-α, serum levels were determined by immunosorbent assays in duplicated samples according to the manufacturer's instructions (Bender MedSystems, Vienna, Austria). In brief, serum and standard samples were incubated into the micro wells of an enzyme linked immunosorbent assay (ELISA) plate, coated with a mouse monoclonal antibody against the corresponding human molecule (e.g.anti-IL-6). During the incubation a bound complex of antigen- antibody was formed (e.g. anti-IL-6 –IL-6). After the removal of the unbound material, a mixture of streptavidine-horseradish peroxidase (HRP) and a biotin-conjugated detector monoclonal antibody against the complex was added. Following the incubation step, the excess unbound material was removed and a substrate solution reactive with the HRP was added. During a new incubation step, a colored product was formed in proportion to the serum amount of IL-6. The enzymatic reaction was stopped and the absorbance of the colored product

was measured at 450 nm. A standard curve of various IL-6 concentrations is used for the determination of IL-6 concentration in the tested sample. Troponin concentrations were measured by Immunolite 2000 troponin I, a solid phase, two site chemiluminescent assay (Diagnostic Products Corporation, Corporate Offices, Louisiana, USA).

2.7 Statistical analysis

2.7.1 Preliminary Study

Preliminary analysis was performed to ensure no violation of the assumptions of linearity and normality. The Shapiro– Wilk test was used to evaluate whether each parameter followed by a Gaussian distribution. Data are expressed as mean"S.D., except for non-Gaussian parameters, which are presented as median (range). Comparisons of continuous variables between groups was performed by an unpaired two-tailed Student's t-test for normally distributed variables and a Mann–Whitney U-test for non-normally distributed variables, whilst x2-tests were used for categorical variables. Differences of study parameters between baseline and postoperative values within the same group were evaluated by paired-samples t-test or Wilcoxon's rank test for normally distributed or non-normally distributed variables, respectively. Relationships between variables were explored by determining Pearson's or Spearman's rank correlation coefficients as appropriate. Statistical analysis was performed using SPSS for Windows Release 15.0 (SPSS Inc, Chicago, IL, USA). A P-value of <0.05 was considered as statistically significant.

2.7.2 Main Study

Considering the lack of adequate data on the effect of PIS on the events occurrence during the first year after EVAR no reliable sample size calculation was feasible. Based on PIS rates (nearly 1/3 of EVAR patients) as reported in the preliminary study of this group[210] and considering certain financial restrictions, this prospective study was designed

to include nearly 180 patients for the 1-year follow-up, so that the PIS group (≈ 60-70 patients) should have a relatively adequate size for estimation in events differences. Data were expressed as mean ± standard deviation (SD) as appropriate, except for non-Gaussian parameters that are presented as median (range). Comparisons of continuous variables were performed by Student t test for normally distributed variables and Mann-Whitney U test for non-normally distributed variables, while the chi-square test was used for categorical variables. To assess the effect of the independent variables observed within the study context, each one was initially examined separately and the significant predictors at level p_1=0.25 were identified. These were used in a binary logistic regression model. The formerly non-significant factors were then considered again at level p_2=0.10. Interactions between the main effects of the final model were examined. The enter method with significance level p_3=0.05 was used to obtain p –values and odds ratios for the main effects and interactions. All analyses were carried out with SPSS 20.0 statistical package for Windows (IBM Corporation, Armonk, New York).

3 Results

Between May 2007 and July 2008, elective EVAR for asymptomatic infrarenal AAA was performed in 43 consecutive patients aged between 53 and 87 years (median age 74.2 years). Three patients were excluded from the study due to previous use of anti-inflammatory drugs (n=2) and to signs of gangrene in the toes (n=1). A total of 40 patients aged between 53 and 87 years (median age 74.2 years, 100% males) were included in the study.

From January 2010 to June 2013 a total of 242 consecutive patients assessed for eligibility criteria, 28 patients were excluded: eight of these patient had diagnosed with a malignancy (3 with lung cancer, 2 with Leukemia, 2 with large bowel Cancer, 1 with prostate cancer), five patients had taken anti-inflammatory drugs, four patients had undergone previous surgical procedure within the previous two month, four patients was under anticoagulant, two patients had Chronic Kidney Failure and was under hemodialysis, two patients were diagnosed with infection, two patients had peripheral vessel disease and sighs of gangrene and one patient had liver failure. A total of 214 patients (72.3 ±8.1 years, 97% males) were included in the 30 day follow up, with 182 patients (72.4±7.8 years, 96% males) being available for analysis after a year follow up. Five did not attend the 1-year follow up but were reached via phone. Stent deployment was technically successful in all patients, with no intra-operative complications.

3.1 PIS Preliminary data

From May 207 to July 2008, 40 consecutive patients aged between 53 and 87 years (median age 74.2 years) were evaluated to preliminary report our data on whether the endovascular treatment of AAAs is associated with early inflammatory response as well as the relationship of clinical and biochemical expression of PIS with several acute phase inflammation markers.

The patients' characteristics are presented in Table 1. PIS was recorded in 14 (35%, PIS group) of the 40 patients. There were no significant differences in patients' characteristics between the two groups (PIS group and no PIS group, Table 1). Pre- and postoperative laboratory data are shown in Table 2. Peak postoperative temperature

correlated with the postoperative values of WBC (Spearman p=0.506, p=0.002), hs-CRP (Spearman p=0.451, p=0.05) and IL-6 (Spearman p=0.532, p=0.005). Patients (n=26) without PIS postoperatively showed a significant increase in the values of hs-CRP (p=0.005) and fibrinogen (P=0.015), while the PLT count decreased (P=0.005). No significant differences regarding the pre- and postoperative values of IL-1, IL-6 and TNF-a, were noted. In patients with PIS (n=14), the changes in the values of hs-CRP, PLT, IL-1, and TNF-a, were similar to those in patients without PIS. There were no significant differences in laboratory data between PIS and no PIS groups preoperatively, while postoperatively there was a pronounced significant increase in WBC count and IL-6 values in the PIS group of patients (Table 3). Of note, a significant increase in IL-6 levels was observed only in the PIS group (median difference value 82.5 vs. 11.5, p=0.001) postoperatively (Table 2 and Fig.1). The decrease in PLT count was greater in the PIS group compared with the non-PIS group (median difference value 70 vs. 49, p=0.005) and the increase in hs-CRP was also greater in the same group (median difference value 110.46 vs. 71.93, p=0.002), (Fig. 1).

The grafts that were deployed for the successful exclusion of the aneurysm included: 16 Talent grafts (Medtronic Vascular AVE, Medtronic Europe SA, Route du Molliau, Switzerland), 17 Excluder grafts (W.L. Gore & Associates, Inc, Flagstaff, AZ, USA), five Anaconda grafts (Vaskutek-Terumo Cardiovascular System Corp, Ann Arbor, MI, USA) and two Zenith grafts (Cook Medical Inc, Bloomington, IN, USA). The incidence of PIS according to the type of the graft deployed was 6/16 (37.5%) for the Talent group, 5/5 (100%) for the Anaconda group and 1/2 (50%) for the Zenith group compared with 2/17 (11.7%) for the Excluder group (x^2=15.03, p=0.002). There was not any significant correlation of PIS with the patient's age, the maximum diameter of the aneurysm, the amount of contrast media used, and the duration of the operation.

The median stay in hospital after the procedure was five days (range 2–9). Postoperative hospitalization was significantly prolonged in the PIS group compared to PIS- free group [median value, (range) 5.5 (5–9) vs. 3 (2–7) days, p=0.002], (Fig. 2). Two patients who developed PIS suffered a mild myocardial infarction on the first postoperative day. Both patients were admitted in the cardiac intensive care unit (ICU) and were

eventually discharged home on the eighth and ninth postoperative day, respectively. All other patients were discharged from hospital after uncomplicated recoveries.

3.2 PIS and 30-day outcome

A total of 214 patients (72.3±8.1 years, 97% males) were included in the study. PIS was diagnosed in 77 (36%) patients. Baseline and peri-operative characteristics in patients with and without PIS are shown in Table 4. In terms of baseline characteristics, traditional cardiac risk factors were equally distributed among the groups (Table 4). Sixteen patients (7.5%) had MACE within 30 days of surgery, resulting in one death. More specifically, 11 patients sustained a non-fatal acute myocardial infarction, three a transient ischemic attack, and one patient had a stroke. Four patients suffered from acute renal failure, and four patients were readmitted due to symptoms of severe inflammation.

3.2.1 Predictors of PIS

Pre-operative WBC count values ($p < .001$), endograft material (polyester) ($p < .001$), and heart failure ($p = .03$) were independent predictors of PIS, as shown by multiple logistic regression analysis. For every 1,000 units increase in pre- operative WBC count the chance of PIS increased by 95.5% (95% CI 50-255%). The use of polyester raised (95% CI 5, 3-29, 5 times) the possibility of PIS 12 times compared with the use of ePTFE. Patients suffering from heart failure were three times (95% CI: 1.1-8.5 times) more likely to have PIS than those who did not. The endografts that were deployed are shown in Table 5. The relationship between the different endografts deployed and the occurrence of PIS is shown in Fig 3. 127 grafts were made of polyester, and 87 were ePTFE. Endografts made of polyester had significantly higher rates of PIS development than endografts made from ePTFE (polyester group 52.8% vs. PTFE group 11.5%, $p < .001$) (Fig. 3B). There were no differences recorded either in total preoperative AAA volume, pre-operative endoluminal thrombus, or in the amount of newly formed thrombus between the two groups (Fig. 4).

3.2.2 PIS qualitative and quantitative characteristics.

PIS characteristics are shown in Table 4. Mean postoperative temperature ($p < .001$), length of hospital ($p < .001$) and ICU ($p = .008$) stay, as well as maximum post-operative WBC count ($p < .001$), IL-6 ($p < .001$), and hs-CRP values ($p < .001$) were significantly higher in the PIS group. In the vast majority (73/77, 94.8%) of patients in the PIS group, the syndrome was evident from the first postoperative day. In all patients who sustained an adverse event, PIS occurred before that event.

3.2.3 Influence on 30-days outcome

3.2.3.1 Major adverse cardiovascular events.

None of the patients was lost to follow up. During the first 30 days, three of 137 patients (2.2%) in the non-PIS group had MACE, compared with 13 out of 77 patients (16.8%) in the PIS group ($p < .001$). More specifically, multiple logistic regression analysis showed that the presence of coronary artery disease ($p = .01$), post-operative hs-CRP ($p = .001$), and duration of fever ($p = .02$) independently predicted the occurrence of MACE. Patients suffering from CAD were 7.9 times (95% CI 1.6-38.6 times, $p = .011$) more likely to sustain MACE during the first 30 days after the procedure. For every additional day of post-operative fever after the first, the chance of MACE increased by 67.9% (95% CI 9.8-260%, $p = .017$), while for every 10 unit increase in the post-operative hs-CRP the chance for MACE increased by 15% (95% CI 6-24%, $p = .001$). The ROC curve analysis showed that post-operative hs-CRP is an important value in predicting the occurrence of MACE during the first 30 days after the procedure (area under the curve [AUC] 0.804; $p < .001$; Fig. 5). A threshold value of 125 mg/L was highly associated with the occurrence of MACE, with a sensitivity of 82% and specificity of 75%.

3.2.3.2 Adverse events.

During the first 30 days, four of 137 patients (2.9%) in the non-PIS group had an adverse event, compared with 20 of 77 patients (25.9%) in the PIS group ($p < .001$). Multiple logistic regression analysis showed that hs-CRP post-operative values ($p = .004$),

post-implantation syndrome (p = .01), maximum temperature (p = .02), and history of smoking (p = .02) were independent predictors of an adverse event during the first 30 days after the procedure. For every 10 unit rise in the value of post-operative hs-CRP the chance of an adverse event increased by 12% (95% CI 4-19%, p = .004), while for every 1 degree rise in maximum temperature the risk increased 3.1 times (95% CI 1.15-8.5 times higher, p = .03). Patients diagnosed with PIS after implantation were about five times (95% CI 1.5- 17.6, p = .011) more likely to suffer an adverse event than non-PIS patients, while smokers were about 4.3 times (95% CI 1.25-15.1, p = .02) more likely than non-smokers. The ROC curve analysis showed that post-operative hs-CRP is an important value in predicting the occurrence of an adverse event during the first 30 days after the procedure (area under the curve [AUC] 0.79; p < .001, Fig. 6). A threshold value of 125 mg/L was highly associated with the occurrence of an adverse event, with a sensitivity of 72% and specificity of 75%.

3.3 PIS and 1-year outcome

From January 2010 to January 2013, a total of 182 patients (72.4±7.8 years, 96% males) were included in the study. PIS was diagnosed in 65 (35.7%) patients. Baseline characteristics in patients with and without PIS are shown in Table 6. Traditional risk factors were equally distributed between the two groups. Five patients did not attend the 1-year follow-up visit but were reached via phone. Five patients, 3 in the PIS and 2 in the non-PIS group, suffered from limb thrombosis occurred at the 1st month in four of them and at the 5th month post-EVAR in one of them. One patient had a migration of the endograft and a type I endoleak and was treated with an aortic cuff at the 6th month after the initial procedure. 26 (14.3%) patients, 14 in the non- PIS and 12 in the PIS group, had a type II endoleak at some point during the follow-up period. In 22 patients the endoleak disappeared during follow-up. In 4 patients endoleak type II remained at the 1 year visit, without however any sac enlargement. There was no correlation of the endoleak or any complication rates with the occurrence of PIS (all p>0.05).

3.3.1 Variables

White blood cell count*:* Baseline WBC levels were similar between the two groups (p=0.102). There was a significant increase in WBC count in favor of PIS-group at the postoperative period (p<0.001). This difference remained statistically significant during the 1st year follow-up period at all time points until the end of the follow-up-period. (Table 7), (Figure 7).

Platelet count: Baseline and postoperative platelet count levels were similar between the two groups (p=0.65 and p=1 respectively). Patients of the PIS group had higher platelet count levels at the first month after the procedure (p<0.001). However no significant difference was evident at 6 (p=0.22) and 12 (p=0.99) months between the two groups (Table 7), (Figure 7).

Fibrinogen: Concentration of fibrinogen did not differ significantly between the two groups at baseline (p=0.98), postoperatively (p=0.12) and at the first (p=0.99) and sixth (p=0.96) month after the procedure. Patients of the PIS group had significantly higher levels of fibrinogen at the first year when compared to patients of the non-PIS group (p=0.006), (Figure 7).

hs-CRP: The median baseline hs-CRP level was 3.2 mg/L in the non-PIS group and 4.6 mg/L in the PIS group (p=1). Patients of the PIS group had significantly higher levels of hs-CRP at the immediate postoperative period (p<0.001) and at the first month after the procedure (p=0.04). These values returned to near baseline levels at the 6^{th} (p=0.99) and 12^{th} (p=0.99) month (Table 7), (Figure 7).

Interleukin-6: Baseline IL-6 levels were similar between the two groups (p=1). At the postoperative period patients of the PIS group had significantly higher levels of IL-6 when compared to non-PIS group (p<0.001). These levels were attenuated quite quickly, being similar between the two groups at the 1^{st} (p=0.43), 6^{th} (p=0.46) and 12^{th} (p=0.17) after the procedure (Table 7), (Figure 7).

3.3.2 Graft material and inflammation

108 (59.3%) endografts were made of polyester, while 74 (40.7%) were from ePTFE. Endografts made of polyester had significantly higher rates of PIS

development when compared to endografts made from ePTFE (Polyester group: 52.7% vs PTFE group: 10.8%, p<0.001). Inflammation as depicted from WBC count, hs-CRP levels and IL-6 concentration was significantly higher at the postoperative period in patients receiving an endograft made of polyester (WBC count, p<0.001; hs-CRP, p<0.001; IL-6, p=0.009). All these inflammation markers attenuated, with no differences observed between the two groups of different graft material at the 1st, 6th and 12th month after the procedure (Figure 8).

3.3.3 Influence on one-year outcome

3.3.3.1 Major adverse cardiovascular events (MACE)

During the first 30 days, 3 out of 117 patients (2.6%) in the non-PIS group had a MACE, comparing with 12 out of 65 patients (18.4%) in the PIS group (p<0.001). One patient of the PIS group died at the 20th day in the cardiac unit after a severe acute myocardial infarction. During 1 to 12 months of follow-up period, a MACE was recorded in 16 (8.8%) of the remaining 181 patients: 11/64 (17.2%) patients in the PIS group and 5/117 (4.3%) patients in the non-PIS group (p<0.001). In the PIS group, 3 patients died of a cardiac-related cause (2 patients sustained a fatal acute MI and 1 patient had severe heart failure) on month 5, 10 and 10 following surgery respectively; 4 patients had a nonfatal acute MI; 2 patients sustained an ischemic stroke (one fatal), while in 2 patients, unstable angina and worsening of their cardiac status needing a cardiac intervention was developed during the follow-up period. In the non-PIS group, 3 patients had an AMI (one fatal), while 2 patients experienced new-onset unstable angina and worsening of their cardiac status and underwent a cardiac intervention. Multiple logistic regression analysis showed that the occurrence of PIS was the only independent predictor of a MACE during the follow-up period. More specifically, patients diagnosed with PIS after the implantation were about 4.5 times (95% CI: 1.5-13.8, p=0.007) more likely to suffer a MACE compared to non-PIS patients.

3.3.3.2 Adverse events

During the first 30 days, 4 out of 117 patients (3.4%) in the non-PIS group had an adverse event, comparing with 17 out of 65 patients (26.2%) in the PIS group ($p<0.001$). During 1 to 12 months of follow-up period, an AE was recorded in 18 (9.8%) of the 181 patients: 12/64 (18.8%) patients in the PIS group and 6/117 (5.1%) patients in the non-PIS group ($p<0.001$). In the PIS group 11 patients suffered a MACE and 1 patient presented with acute renal failure 10 months after the procedure. In the non-PIS group 5 patients presented with a MACE and 1 with acute renal failure at 6 months. Multiple logistic regression analysis showed that the occurrence of PIS was the only independent predictor of an AE during the follow-up period. More specifically, patients diagnosed with PIS after the implantation were about 4.51 times (95% CI: 1.5-11.7, $p=0.005$) more likely to suffer an AE compared to non-PIS patients.

4 Discussion

Endovascular aneurysm repair has been proposed as a minimally invasive alternative to conventional aneurysm resection.[145,216,] Open aneurysm repair has been associated with elevated inflammatory biomarkers, probably as a result of the extensive surgical trauma and the ischemia reperfusion response associated with the aortic cross clamping.[160,161]However the risk of a severe inflammatory response of the endovascular aortic repair was thought to be lower than that of an open repair.[160,161] Recent reports have mentioned that endovascular procedures may initiate a systemic inflammatory response, known as post-implantation syndrome (PIS).

In our study PIS affects nearly one third of patients after EVAR for AAA. The reported incidence of PIS in the literature varies widely from 14% to 60%.[180-183,217] The lack of a universally accepted definition may account for this variation. Some authors described PIS as the presence of fever coinciding with an elevated serum CRP level, whereas others regard it as the presence of fever combined with a leukocytosis of different cut off values.[175,176,180-183,217] This group has proposed a definition of the syndrome according to SIRS, as PIS actually fulfills at least two of the SIRS criteria (fever and leukocytosis).[217] In this study PIS was defined as the presence of fever (>38 °C) and leukocytosis (>12.000/mL). However, hs-CRP values were strongly related to the presence of PIS and also emerged as an important predictor of the 30 day outcome. Thus hs-CRP probably expresses the intensity of the inflammatory response to endograft deployment more consistently and reliably. It is likely that this biomarker is more appropriate in defining PIS than WBC count and the definition of the syndrome might be based mainly on hs-CRP values. Voûte et al.[175] in their report included CRP in the PIS definition and described PIS as fever >38 °C coinciding with an elevated serum CRP level above 10 mg/L. In any case, a universally accepted definition is needed for use in everyday clinical practice and for reporting standards when comparing different studies.

The cause of the inflammatory response after EVAR has not been clearly defined. It is important to identify the primary event causing the inflammatory reaction. In open AAA repair, a more pronounced elevated systemic inflammatory response has been observed than in EVAR, probably due to the more significant invasiveness of the

procedure.[218] The magnitude of this response may cover any effect of other co-factors such as the type of the graft, although this has not been studied so far. In EVAR cases, the amount of contrast media, the endograft material, or the amount of mural thrombus within the aneurysm sac have all been implied as possible causative factors.[175,176,178,189,] The type of anesthesia may also have a role by influencing the inflammatory cytokine response.[219] As most of the patients worldwide are operated on under general anesthesia, to avoid any possible bias all patients in this study were operated on under general anesthesia. In the present study the contrast media used as well as the aneurysm's thrombus load were not correlated with PIS. This finding is in accordance with the recent publication of Voûte et al.[175]

However, in the same report the authors showed that the implantation of stent grafts based on polyester was independently associated with a stronger inflammatory response.[175] Moulakakis et al.,[176] observing a milder inflammatory activation in patients with a PTFE endograft, have confirmed this finding in a later report. In accordance with these reports it was found that the use of polyester endograft independently predicted PIS and was correlated with a greater than 10 times higher risk for an inflammatory response. Although other endograft parameters such as the exoskeleton material (nitinol vs. stainless steel) have not been investigated in the present study, the wide application of these materials in cardiac and peripheral arterial stenting with no reports of a remarkable inflammatory response show that differences in the application of nitinol among stent grafts is unlikely to influence PIS. Based on the three studies mentioned above (450 patients overall), it is quite obvious that the polyester fabric of the endograft can predict the occurrence of PIS in more than 50% of patients. Although the inflammatory response, as depicted from the levels of certain biomarkers, was initially more severe in the polyester group during the postoperative period, it became quite similar between the two groups of different graft materials after the first month and through the 1-year follow-up period. Nevertheless, as shown in the multivariate analysis, some other parameters seem to influence PIS occurrence and perhaps the primary event causing the inflammatory reaction is still unidentified and further study is therefore required.

Coagulation disturbances after EVAR occur either as a result of aneurysm sac thrombosis or by direct platelet stimulation by the endograft material.[220] A significant

decrease in platelet count, an indirect index of platelet activation and consumption, during the postoperative period after EVAR has been reported in many studies.[176,221,] Nano et al found that this decrease was significantly more pronounced in patients experienced PIS.[222] However, in this study the incidence of PIS was associated with a longer duration of the procedure and a greater preoperative thrombus thickness.[222] On the contrary, in the present study no statistical differences in PLT count between the two groups was evident at the immediate postoperative or at the conclusion of the follow-up period. On the other hand, elevated levels of fibrinogen, a biomarker playing a crucial role in both inflammation and coagulation, have been reported in patients with AAA.[223] Aho et al by comparing hemostatic mechanisms in AAA patients after open surgery and EVAR found a significant raise in fibrinogen levels at the third postoperative day post-EVAR.[205] These levels however diminished at the 7th postoperative day, while they returned at the baseline levels at the 3rd month. We found that at the postoperative period fibrinogen increase was not related to the occurrence of PIS. However PIS patients at the end of the first year presented with significantly higher levels of fibrinogen when compared with patients of the non-PIS group. This finding may have some clinical implication since fibrinogen have been considered an independent risk marker for the prediction of the first cardiovascular event.[224] A larger study with more patients and events is needed to clarify the exact value of this marker in stratifying patients according to cardiovascular risk assessment after EVAR.

The amount of mural thrombus has also been proposed to incur a role in the inflammatory response, as PIS initially was linked with the release of inflammatory mediators from the aneurysm thrombus.[181,182] Kakisis et al.[190] recently evaluated nearly 85 patients after EVAR and reported an association between new onset thrombus and PIS. However, Voûte et al.[175] by investigating the relation of PIS with new onset thrombus formation in 136 patients after EVAR did not find any correlation. This finding is in accordance with the results here, as there was no difference either in total pre-operative AAA volume and pre-operative endoluminal thrombus, or in the amount of newly formed thrombus between the two groups.

The effect of the syndrome on the outcome of the patients has not been well defined. In most studies PIS is generally well tolerated, showing a benign course during the

post- operative period.[176] Moulakakis et al reported no perioperative clinical adverse events in 87 patients after EVAR without however providing any clear definition on the events or detailed description regarding the duration of hospitalization, monitoring and follow-up of the patients during the first month.[176] Nano et al by retrospectively studying 118 patients after the use of AnacondaTM endograft (Sulzer Vascutek, Bad Soden, Germany) did not find any correlation between the presence of PIS and the occurrence of long-term complications, though the definition of the events was too "wide" including endoleaks, renal failure, limb thrombosis and death of any cause, while oddly only one of the patients sustained a MACE during a 4 year follow-up period.[222] In the same study the analysis of quality of life surveys showed that patients who had PIS after surgery felt significantly more limited in carrying out their daily physical activities and were more emotionally discouraged and depressed/anxious about their state of health than the group that did not have developed PIS.[222]

Although most series have failed to demonstrate any connection between PIS and postoperative complications[180, 209,] no study so far has focused on cardiovascular and other adverse events, by prospectively evaluating the treated patients during the 1-year post- operative period. In many vascular centers, EVAR is considered to be a quite simple procedure and most patients are discharged home the day after the procedure. This could lead to non-awareness of some cardiovascular or other adverse events that might happen during the postoperative period, as patients might be referred to other medical specialties or even hospitals. There is some evidence that in some patients the initial inflammatory response following EVAR is not always spontaneously attenuated and could lead to the development of serious complications even several days after the operation.[202] For example Chang et al.[1201] evaluated the effect of the inflammatory response on post-operative renal function after endovascular repair of thoracoabdominal aneurysms and found that the severity of the inflammation correlated with post-operative renal dysfunction. In a previous publication by our group, five EVAR patients and one TEVAR patient who needed re- admission during the first 30 days after the procedure due to intense SIRS were reported.[202] In the present prospective study patients of the PIS group had significantly more adverse events during the first month after the procedure (9.3% vs. 1.8%). The intensity of the inflammatory process,

as shown from the post-operative values of hs-CRP and the characteristics of fever, independently predicted the occurrence of a cardiovascular or any other adverse event during the first month after EVAR. Based on these results, it seems reasonable that patients who develop an excessive inflammatory response postoperatively might be better kept under surveillance for the first post-operative month. A cut off value of hs-CRP of 125 mg/dL in the immediate post-operative period could probably distinguish those patients that need the extended surveillance. Such a policy could lead to early identification of any cardiovascular or other adverse event that would then be adequately treated.

Also, PIS was found to be the only independent predictor of a cardiovascular or any other adverse event after the first month and during the first year of follow-up. These findings imply that patients with PIS remain at a greater risk of suffering from an adverse event when compared to non-PIS patients even after the first month and may require closer surveillance during the first year. Additionally, these findings have to be considered together with the fact that the benefit from EVAR regarding lower short-term mortality compared to open surgical repair did not persist at the intermediate- and long-term follow up period as both EVAR and DREAM trials have shown.[145,216] In fact, even meta-analyses have shown that both EVAR and open surgical repair were associated with similar incidences of cardiac deaths and fatal stroke rate in the long term despite the minimal invasiveness of EVAR.[225,226] It is well known so far that inflammation could lead to serious cardiovascular events.[227] Could this inflammatory process seen after EVAR have led to more cardiovascular events and deaths in the long term postoperative period, and thus contributed somehow to the loss of survival benefit EVAR has shown over open repair at 30-days? It is difficult to conclude from the findings of this study, but for the first time there is a finding showing that EVAR through a systemic inflammatory patient response could result in increased cardiovascular morbidity in the long term, despite considered a minimal invasive operation.

The kinetics of several inflammatory markers during the 1-year follow-up period is of great interest. These markers describe different aspects of the inflammatory cascade, including products of the hepatic stimulation (hs-CRP), inflammatory stimuli with hepatic effects (IL-6) and cellular response (WBC count).[228] The alterations of

these markers after the postoperative period has not been reported adequately so far. In the present study, all inflammatory markers were significantly higher in the PIS group at the postoperative period when compared to the non-PIS group. However, hs-CRP and IL-6 were attenuated towards the values of non-PIS group at the end of the follow-up period, while only WBC count remained different, although within the normal range. WBC count represents a simple marker of inflammation that has been related to prediction of future cardiovascular events in several different populations.[229,230,] The raise of WBC count even within the normal range is of particular concern. A recent retrospective study found a strong correlation between an increased preoperative WBC within the normal range and the risk of major adverse events and death following endovascular interventions.[231] In the present study at the end of the follow-up period the count for both groups was within normal range with the values in the PIS group being at the upper normal threshold. Overall, it seems that the inflammatory process associated with the endograft implantation is attenuated after the first month and the severity of the inflammatory activation as depicted from several inflammatory biomarkers shows a decline towards the normal levels at the end of first year.

The results of the present study certainly raise the question about the need for PIS- specific treatment, focusing on reducing the post-deployment inflammatory response. Current literature provides scarce evidence and no established algorithm concerning the type and duration of such treatment. Some authors recommended aggressive routine use of anti- inflammatory drugs while most others prefer a more conservative approach.[181,188,] Akin et al.[232] did not observe any clinical benefit of prolonging antibiotic treatment beyond the day of endovascular intervention in PIS patients. Bischoff et al.[183] in a recent survey of vascular surgery departments in Germany reported that 71% of the vascular centers treated PIS with non-steroidal anti-inflammatory agents (NSAIDs). Motte et al published recently a prospective trial of 150 EVAR patients that were randomized to receive a single preoperative dose of methylprednisolone or placebo.[233] The inflammatory response as assessed by the inflammatory biomarkers levels was reduced in the methylprednisolone group, though no differences were noted in patient's outcome between the two groups during a 3 months follow-up period. Data on postoperative use of anti-inflammatory drugs are

absent. However, the routine administration of drugs like steroids or NSAIDs is of serious concern because of their side effects, especially in patients with several comorbidities, including renal failure, heart failure, or coronary artery disease.[202] and therefore cannot be easily provided.[234] It is reasonable that some patients presenting with an intense inflammatory response, leading to prolonged hospitalization or even a readmission, might benefit from anti-inflammatory therapy. Nevertheless as it is shown from the present study the inflammatory response is attenuated after the first month post-EVAR and perhaps a therapeutic strategy focusing on inflammation reduction in the long-term may not have a rational goal. The anti-inflammatory properties of statins may be useful, though all EVAR patients including those in the present report are usually under statin treatment at the time of operation. Based on the fact that PIS was the only independent predictor of an adverse event during the first year after EVAR, it seems that even a strong inflammatory stimulus at the immediate post-operative period could probably affect the cardiovascular health of these patients at the long term. The sustained levels of WBC count in the PIS patients towards the upper normal threshold during the 1st year follow-up might have something to do with that.[176] Thus it seems reasonable that therapeutic measurements might focus on PIS acute treatment or even prevention. Future studies should emphasize on better understanding of the causes of the inflammatory response as well as in evaluating the prompt treatment of patients with PIS with anti-inflammatory drugs from the first post-operative day.

5 Limitations

Several limitations of this study should be considered when interpreting the results. We admit that the sample size and the subsequent small number of cardiovascular events and mortality and the effect of this on the statistical analysis should be acknowledged. This was not a randomized trial, though graft selection was based strictly on anatomical criteria and not on any characteristic of the inflammatory response. Furthermore, the recording of detailed data on AAA anatomy such as the length or angulation of the neck was not part of the present protocol. Although their potential effect on PIS cannot be excluded, it was not considered that these parameters were related to

the inflammatory response after EVAR and they have not been included in any PIS study so far. The lack of a control group to better quantify the inflammatory response should also be acknowledged. However, the creation of a control group with AAA patients undergoing bilateral femoral cut down alone without graft deployment would be unethical. Inflammatory markers were only measured on the first and third post-operative day. Therefore, although PIS is usually evident in the first three post-operative days, any rises in inflammatory markers occurring later may have been missed by the study protocol. During the 1-year follow-up, the blood samples for five patients were not obtained at some time point, though the primary end-point was recorded via phone. Missing values represent a small proportion of the study sample (<2.5%) and therefore could not have influenced the analysis. Despite statistical significance our results need to be confirmed in studies with a larger number of enrolled patients. However the study was performed prospectively in unselected consecutive patients and may therefore have general implications for the overall EVAR population.

6 Conclusions

A systematic inflammatory response is observed in almost one third of patients after EVAR for AAA. The type of endograft material (polyester) seems to play a significant role in this inflammatory process. Although PIS is well tolerated in the majority of patients, the intensity of the inflammation, as assessed mainly by post-operative hs-CRP values, seems to correlate with the presence of a cardiovascular or any other adverse event during the first 30 days after the procedure. The inflammatory response after EVAR is attenuated after the first postoperative month, as showed by the kinetics of several inflammatory biomarkers. However, PIS seems to correlate with the presence of a cardiovascular or any other adverse event during the first year after EVAR. Further studies should focus on whether a change in care is needed to ameliorate the higher cardiovascular risk of PIS patients.

Table 1. Patients' characteristics as well intraoperative and postoperative variables, presented according to the presence or not of the post implantation syndrome (PIS).

Variable	No PIS	PIS (n=	p valu
Age [years,(range)]	72 (53-84)	74 (64-87)	**NS**
Female/male	0/26	2/12	**NS**
Weight [kg, (range)]	74 (61-98)	77 (60-95)	**NS**
ASA II	10 (38.5%)	5 (35.7%)	**NS**
ASA III	16 (61.5%)	9 (64.3%)	**NS**
Aneurysm diameter [cm, (range)]	5.5 (4.8-8.4)	5.35 (4.9-9.8)	**NS**
Procedure duration [min, (range)]	105 (80-150)	102.5 (80-160)	**NS**
Contrast media [ml, (range)]	260 (55-720)	240 (80-340)	**NS**
Post-operative hospitalization [days, (range)]	**3 (2-7)**	**5.5 (5-9)**	**0.002**

All values are expressed as medians, NS= non-significant, ASA= American Society of Anaesthesiologists Physical Status Classification System.

Table 2. Patients' laboratory data presented according to the presence or not of the post implantation syndrome. Correlation between pre- and postoperative values is also shown in each of the two groups.

Laboratory data of patients without PIS (n=26)			
	Preoperatively	**Postoperatively**	**p**
WBC (x10³/μL)	6.7 (4.61-11.58)	8.7 (5.92-14.22)	0.001
hs-CRP (mg/l)	3.2 (1.13-14.7)	76.4 (9.9-180)	0.005
PLT (x10³/μL)	211 (109-253)	152 (75-201)	0.005
Fib (mg/dL)	426 (265-717)	483 (353-685)	0.015
IL-1 (pg/ml)	11.7 (7.76-103.3)	11.5 (8.48-93.6)	0.394
IL-6 (pg/ml)	4.6 (2.78-65.8)	13.5 (4.6-76.74)	0.102
TNF-a (pg/ml)	9.1 (7.4-53.8)	9.9 (7.02-102.48)	0.523
Laboratory data of patients with PIS (n=14)			
	Preoperatively	**Postoperatively**	**p**
WBC (x10³/μL)	7.3 (5.7-8.1)	14.6 (12.12-31.89)	0.001
hs-CRP (mg/l)	4.9 (0.87-13.9)	115 (21.4-229)	0.004
PLT (x10³/μL)	219.5 (155-313)	147.3 (112-209)	0.001
Fib (mg/dL)	492 (332-660)	564.5 (436-776)	0.014
IL-1 (pg/ml)	12.2 (10.72-254.62)	12.1 (8.62-17.72)	1
IL-6 (pg/ml)	4.9 (1.92-12.2)	98.9 (12.72-168)	0.001
TNF-a (pg/ml)	8.2 (6.84-11.26)	10.9 (8.44-18.5)	0.065

All values are expressed as medians, WBC, white blood cell count; hs-CRP, high-sensitivity C-reactive protein; PLT, platelet count; Fib, fibrinogen; IL, interleukin; TNF-a, tumour necrosis factor- alpha

Table 3. Laboratory data of the study population according to the presence of post implantation syndrome

	No PIS	PIS	P-value
Preoperatively			
WBC ($x10^3/\mu L$)	6.7 (4.61-11.58)	7.3 (5.7-8.1)	0.925
hs-CRP (mg/l)	3.2 (1.13-14.7)	4.9 (0.87-13.9)	0.276
PLT ($x10^3/\mu L$)	211 (109-253)	219.5 (155-313)	0.041
Fib (mg/dL)	426 (265-717)	492 (332-660)	0.217
IL-1 (pg/ml)	11.7 (7.76-103.3)	12.2 (10.72-254.62)	0.026
IL-6 (pg/ml)	4.6 (2.78-65.8)	4.9 (1.92-12.2)	0.270
TNF-a (pg/ml)	9.1 (7.4-53.8)	8.2 (6.84-11.26)	0.175
Postoperatively			
WBC ($x10^3/\mu L$)	8.7 (5.92-14.22)	14.6 (12.12-31.89)	0.001
hs-CRP (mg/l)	76.4 (9.9-180)	115 (21.4-229)	0.060
PLT ($x10^3/\mu L$)	152 (75-201)	147.3 (112-209)	0.526
Fib (mg/dL)	483 (353-685)	564.5 (436-776)	0.035
IL-1 (pg/ml)	11.5 (8.48-93.6)	12.1 (8.62-17.72)	0.626
IL-6 (pg/ml)	13.5 (4.6-76.74)	98.9 (12.72-168)	0.000
TNF-a (pg/ml)	9.9 (7.02-102.48)	10.9 (8.44-18.5)	0.764

All values are expressed as medians, WBC, white blood cell count; hs-CRP, high-sensitivity C-reactive protein; PLT, platelet count; Fib, fibrinogen; IL, interleukin; TNF-a, tumour necrosis factor- alpha

Table 4. Baseline characteristics and peri-operative clinical data of the study population.

	No PIS N=137	**PISN =77**	**p**
Age, years	72 ± 8.1	72.9 ± 8	.440
Male gender, n (%)	132 (96.4)	74 (96.1)	.927
BMI, kg/m2	27.7 ± 5	28.5 ± 5.5	.283
AAA diameter, cm	5.8 ± 1.1	5.9 ± 1.3	.558
AAA volume preop	195.4 ± 178.7	204.5 ± 99.6	.767
Endoluminal thrombus pre-op	104.3 ± 73.3	123.3 ± 73.7	.190
Patent IMA	99 (72.3)	53 (68.8)	.639
Inflammatory AAA	10 (7.3)	6 (7.8)	.895
Risk factors			
Hypertension, n (%)	118 (86.1)	69 (89.6)	.462
CAD, n (%)	66 (47.8)	45 (58.4)	.149
COPD, n (%)	58 (42.3)	42 (54.5)	.086
Smoking, n (%)	82 (59.9)	47 (61)	.865
CHF, n (%)	17 (12.4)	15 (19.5)	.164
Diabetes mellitus, n (%)	27 (19.7)	18 (23.4)	.527
Hyperlipidemia, n (%)	106 (77.4)	62 (80.5)	.591
Peri-operative characteristics			
WBC count pre-op (x 103/mL)	6.6 ± 1.4	7.7 ± 1.3	.101
WBC post-op (max, x 103/mL)	10 ± 2.5	15.9 ± 3.8	<.001
hs-CRP preop (mg/L)	3.2 (0.2-49)	4.3 (0.1-49)	.374
hs-CRP post-op (max, mg/L)	88 ± 61.6	132 ± 63.3	<.001
IL-6 pre-op (pg/mL)	5.2 (3.5-9.1)	6.4 (4.5-9.2)	.640
IL-6 post-op (max, pg/mL)	36.9 (21.3-66.8)	98.4 (63.6-126.8)	<.001
PLT pre-op	196.8 ± 51.5	217.5 ± 53.9	.006
PLT post-op (max)	151.4 ± 54	149.7 ± 49.9	0.834
Duration of operation (min)	108 ± 49.2	112.9 ± 53	.521
Media contrast (mL)	151.6 ± 88.4	149 ± 111.3	.852
Radiation Burden (mGym2)	2.1 (0.75-312)	2.1 (0.89-15.7)	.351
Radiation time (min)	21 ± 16.2	23.2 ± 15.2	.318
ICU stay (days)	0 (0-5)	0 (0-7)	.008
Temperature maximum (°C)	37.8 ± .7	38.6 ± 0.5	<.001
Temperature duration (days)	0.78 ± 0.3	2.8 ± 1.3	<.001
Days of stay (days)	3 (2-29)	6 (3-26)	<.001
Accessory renal artery covered	5 (3.6)	3 (3.9)	.954
Newly formed thrombus at first month	64.6 ± 119.7	54.5 ± 59	.620

BMI = body mass index; AAA = abdominal aortic aneurysm; IMA = inferior mesenteric artery; CAD = coronary artery disease; COPD = chronic obstructive pulmonarydisease; CHF =congestive heart failure; hs-CRP: high sensitivity C reactive protein; IL- 6 = interleukin 6; PLT = platelets

Table 5. The stent grafts deployed in the two groups.

	Total N=214	**No PIS n=137**	**PIS n=77**
Endurant	108	52	56
Excluder	86	76	10
Anaconda	11	2	9
Zenith	7	6	1
Powerlink	1	1	0
Aorfix	1	0	1

Table 6. Baseline characteristics and perioperative clinical data of the study population

	no PIS	PIS n=6	p
Age, years	72.2±7.8	72.9±7.8	0.561
Male gender, n	112 (95.7)	62 (95.4)	0.592
(%) BMI, kg/m^2	28±4.9	28.5±5.5	0.549
AAA maximum diameter, cm	5.8±1	5.9±1.2	0.546
Risk factors			
Hypertension, n	111 (94.8)	60 (92.3)	0.347
(%) CAD, n (%)	57 (48.7)	39 (60)	0.144
COPD, n (%)	52 (44.4)	39 (60)	0.07
Smoking, n	74 (63.2)	43 (66.2)	0.411
(%) CHF, n	18 (15.4)	17 (26.2)	0.08
(%)	24 (20.5)	15 (23.1)	0.686
Diabetes mellitus, n (%)	97 (82.9)	53 (81.2)	0.483
Hyperlipidemia, n (%)			
Procedure characteristics			
Duration, minutes	111.2±49.4	115.3±52.6	0.599
Contrast media,	166.3±88.4	159.4±116.5	0.656
ml Radiation,	79.9 (67.1-116.5)	86.4 (67.5-141)	0.884
mGy	3 (3-4.5)	6 (5-7)	<0.001
Days of in-hospital	0.2±0.63	0.5±1.3	0.02
stay ICU stay, days			
PIS characteristics		38.5±0.4	<0.001
Temperature maximum (^{0}C)	37.7±0.7	2.7±1.3	<0.001
Temperature duration (days)	0.7±1.4	16±3.9	<0.001
	10.1±2.6	125 (96-181)	<0.001

BMI: body mass index, AAA: abdominal aortic aneurysm, CAD: coronary artery disease, COPD: chronic obstructive pulmonary disease, CHF: congestive heart failure, hs-CRP: high sensitivity C reactive protein, IL-6:

Table 7. Biomarkers according to PIS arms

	WBC count (x10³/mL)			**PLT count (x10³/mL)**		
	non-PIS	PIS	p*	non-PIS	PIS	p*
Preoperative	6.6±1.5	7.7±1.4	0.102	207.1±58.9	225.4±54.2	0.65
Postoperative	10.1±2.6	15.9±3.9	<0.001	151.4±52.4	149.7±49.9	1
1st month	7.5±1.6	9±2.1	<0.001	226.6±68.1	271.3±98.2	<0.001
6th month	7.1±1.4	8.2±1.5	0.01	204±56	228.4±58.9	0.22
12th month	6.9±1.6	8±1.5	0.02	205.7±63.6	214.8±52.8	0.99
	Fibrinogen (mg/dL)			**hs-CRP (mg/L)**		
	non-PIS	PIS	p*	non-PIS	PIS	p*
Preoperative	417±109.4	442±116.7	0.98	3.2 (1.6-5.7)	4.6 (2.3-9.5)	1
Postoperative	555±184.2	620±178.8	0.12	76.4 (41.3-122.5)	125 (96.2-182)	<0.001
1st month	513±144.1	528±162.3	0.99	4.8 (2.6-9.8)	12.5 (5.7-26.1)	0.04
6th month	413±107.2	438±138.9	0.96	3 (1-4.7)	4.4 (2.4-7.4)	0.99
12th month	371±106.1	449±137.1	0.006	2.1 (1-3.9)	2.9 (1.6-9)	0.99
	IL-6 (pg/mL)					
	non-PIS	PIS	p*			
Preoperative	5.2 (3.5-9.1)	6.4 (4.6-9)	1			
Postoperative	36.7 (21.7-66.5)	98.5 (66.9-126.9)	<0.001			
1st month	22.4 (7.1-54.9)	22.8 (7.9-71.2)	0.43			
6th month	10 (5.5-35.2)	27.4 (7.5-68.9)	0.46			
12th month	8 (4.6-22.9)	21.7 (6.2-64.5)	0.17			

Values are expressed as mean ± SD, except for non-normally distributed parameters, which are shown as median (interquartile range). p* value refers to between group analysis

PIS: post implantation syndrome, WBC: white blood cell, PLT: platelets, hs-CRP: high sensitivity C reactive protein, IL: interleukin

Figure 1. Differences in **A.** platelet counts, **B.** serum high-sensitivity C-reactive protein, and **C.** interleukin-6 plasma levels, between patients with and without PIS. All numbers in y-axis represent difference values.

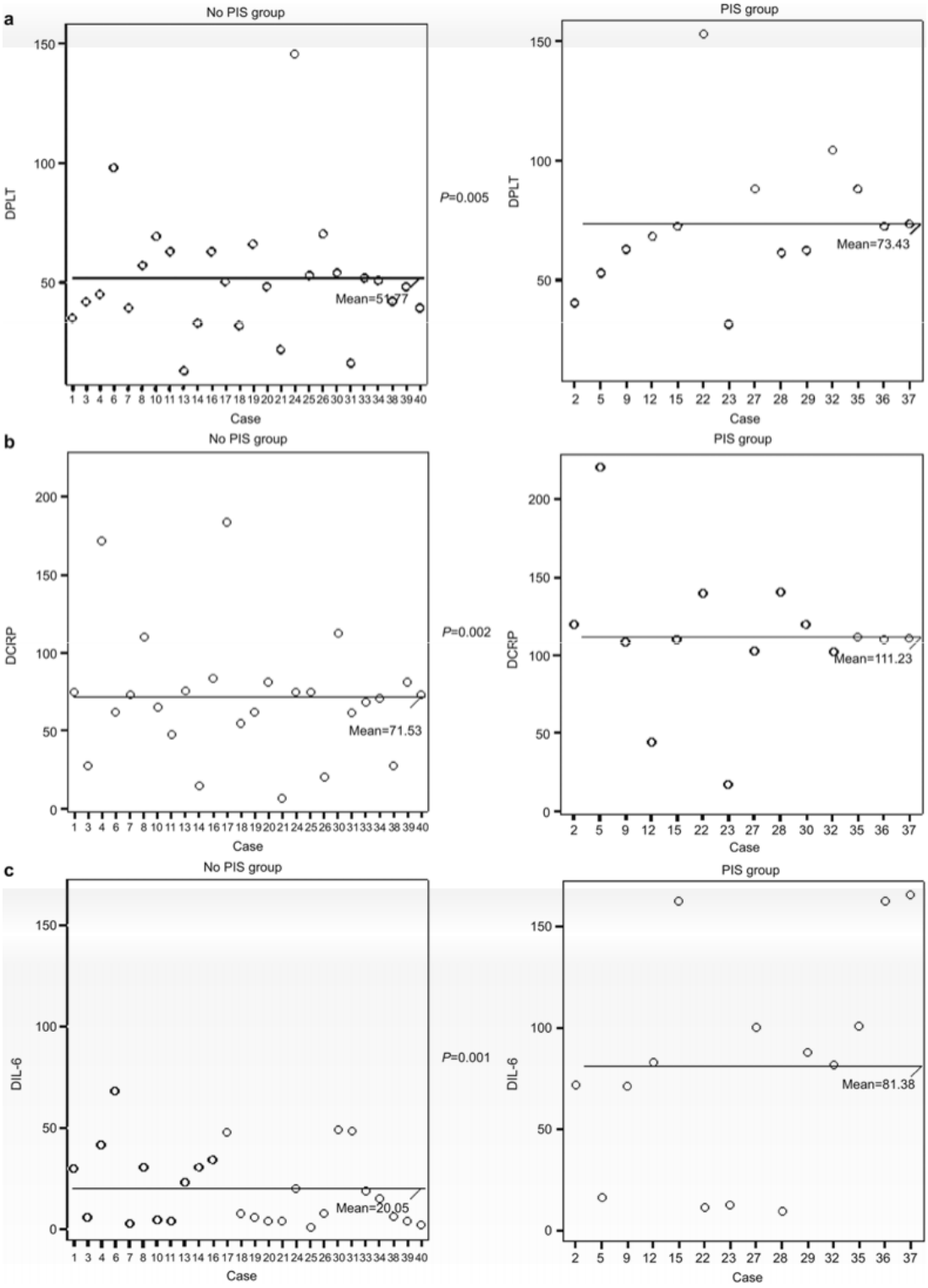


Figure 2. Impact of PIS on the length of post-operative hospitalization

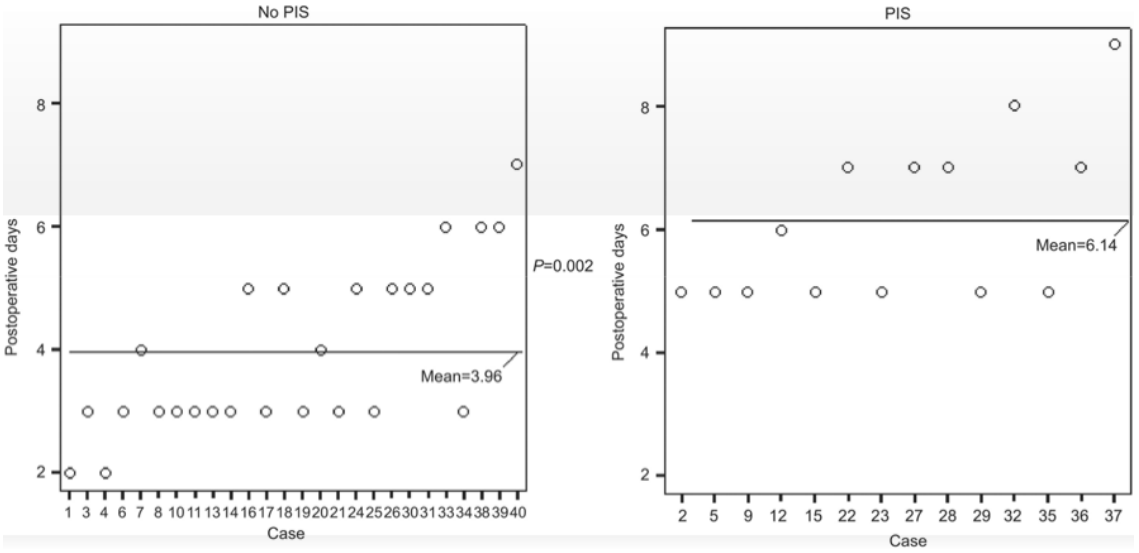


Figure 3. (A) The relation between the different endografts deployed and the occurrence of post-implantation syndrome (PIS). (B) The material the endografts made and its relation to PIS.

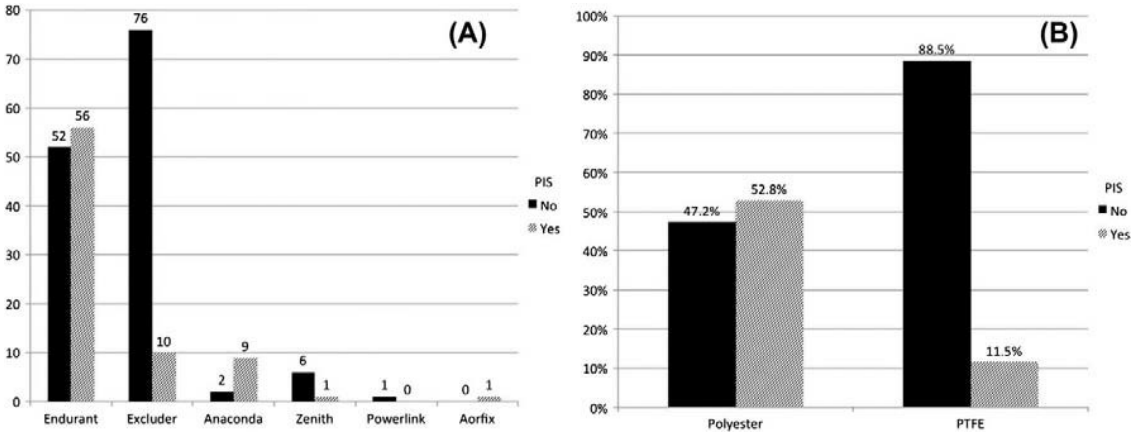


Figure 4. Scatterplot showing (A) total abdominal aortic aneurysm volume in the two groups, (B) the volume of thrombus pre-operatively, and (C) the newly formed thrombus after the first post-operative month.

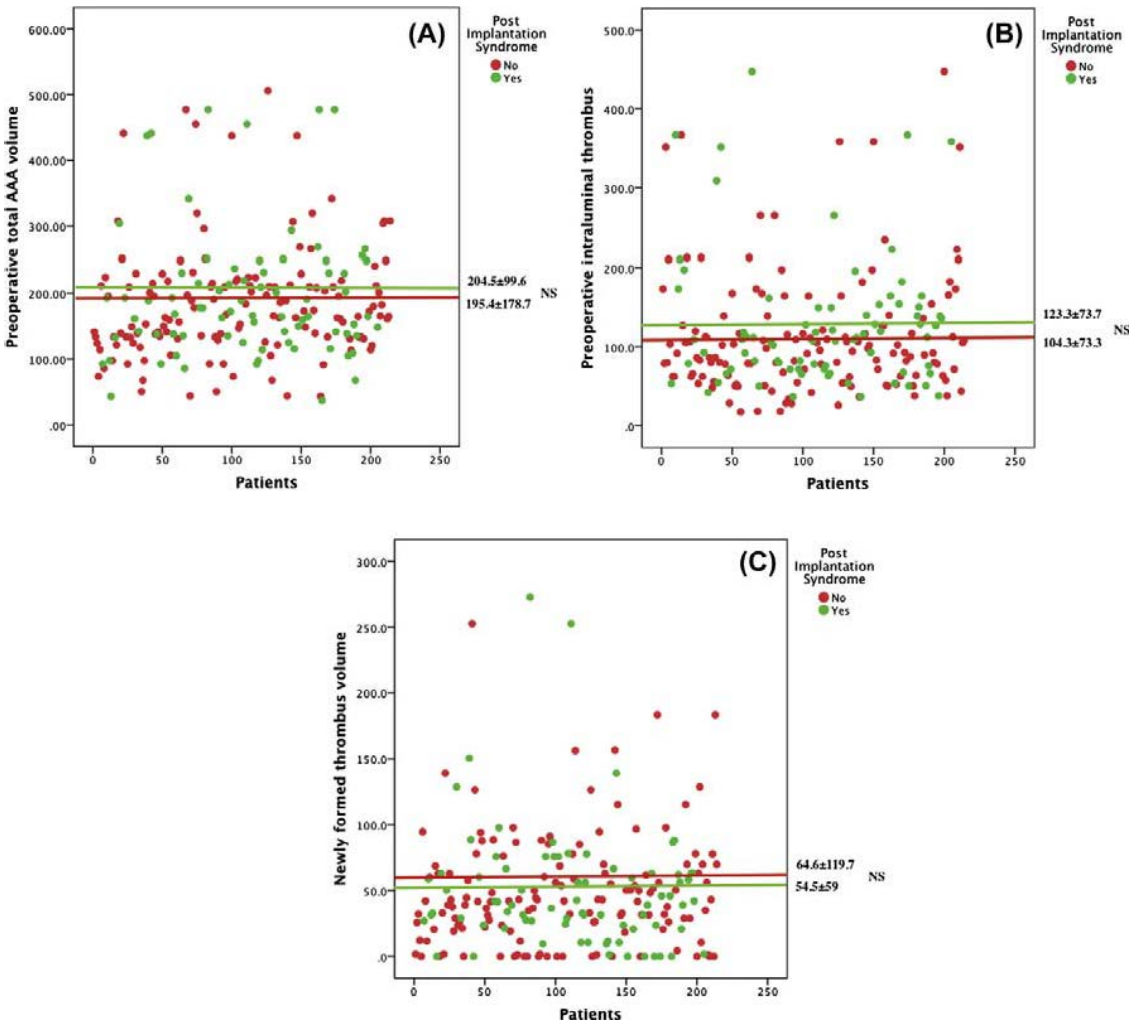


Figure 5. Major adverse cardiac event (MACE) plot of receiver operating characteristic (ROC) curve for high sensitivity C-reactive protein (hs-CRP) measured post-operatively, as well as for fever duration. Diagonal segments are produced by ties.

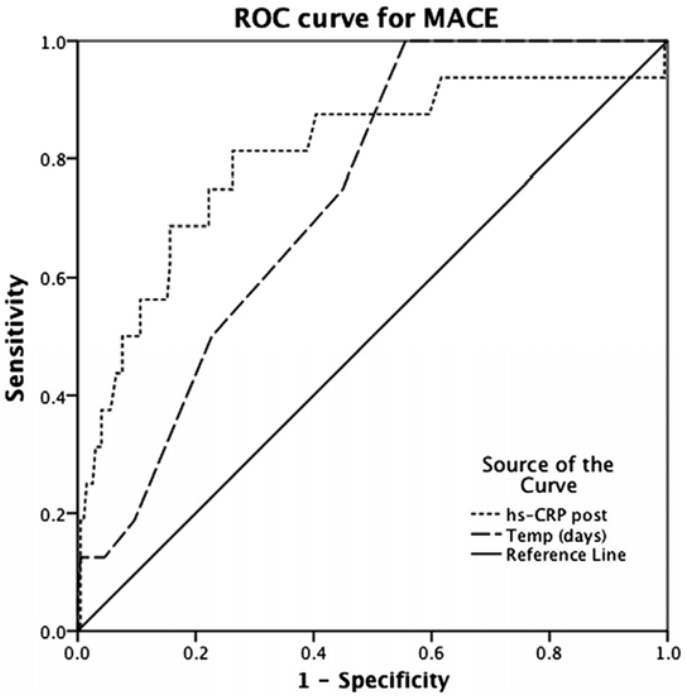


Figure 6. Adverse event plot of receiver operating characteristic (ROC) curve for high sensitivity C-reactive protein (hs-CRP) measured post-operatively, as well as maximum post-operative temperature. Diagonal segments are produced by ties.

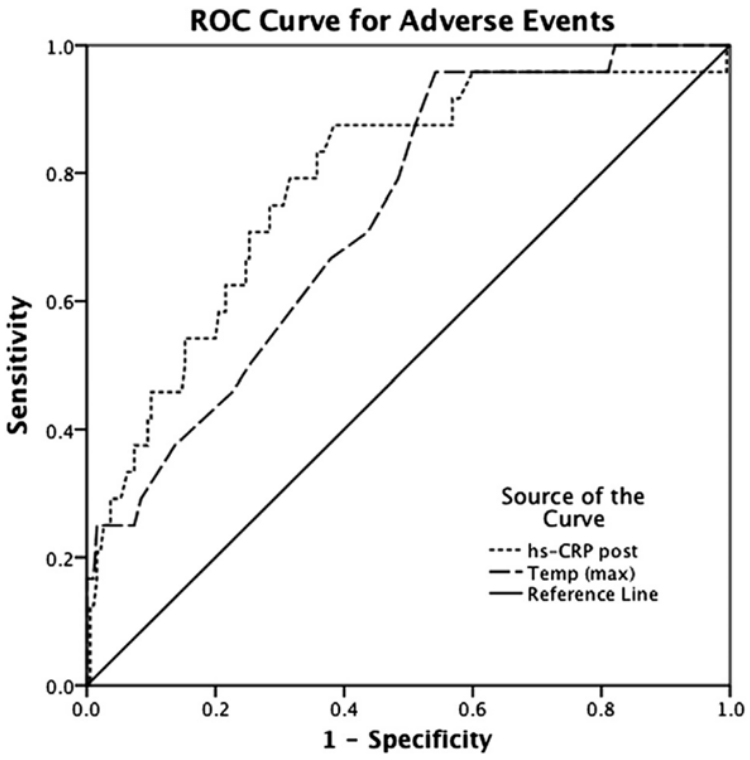


Figure 7. Graphical representation of the mean measures of white blood cell count (WBC), platelets (PLT) count, fibrinogen and median values of hs-CRP and IL-6.

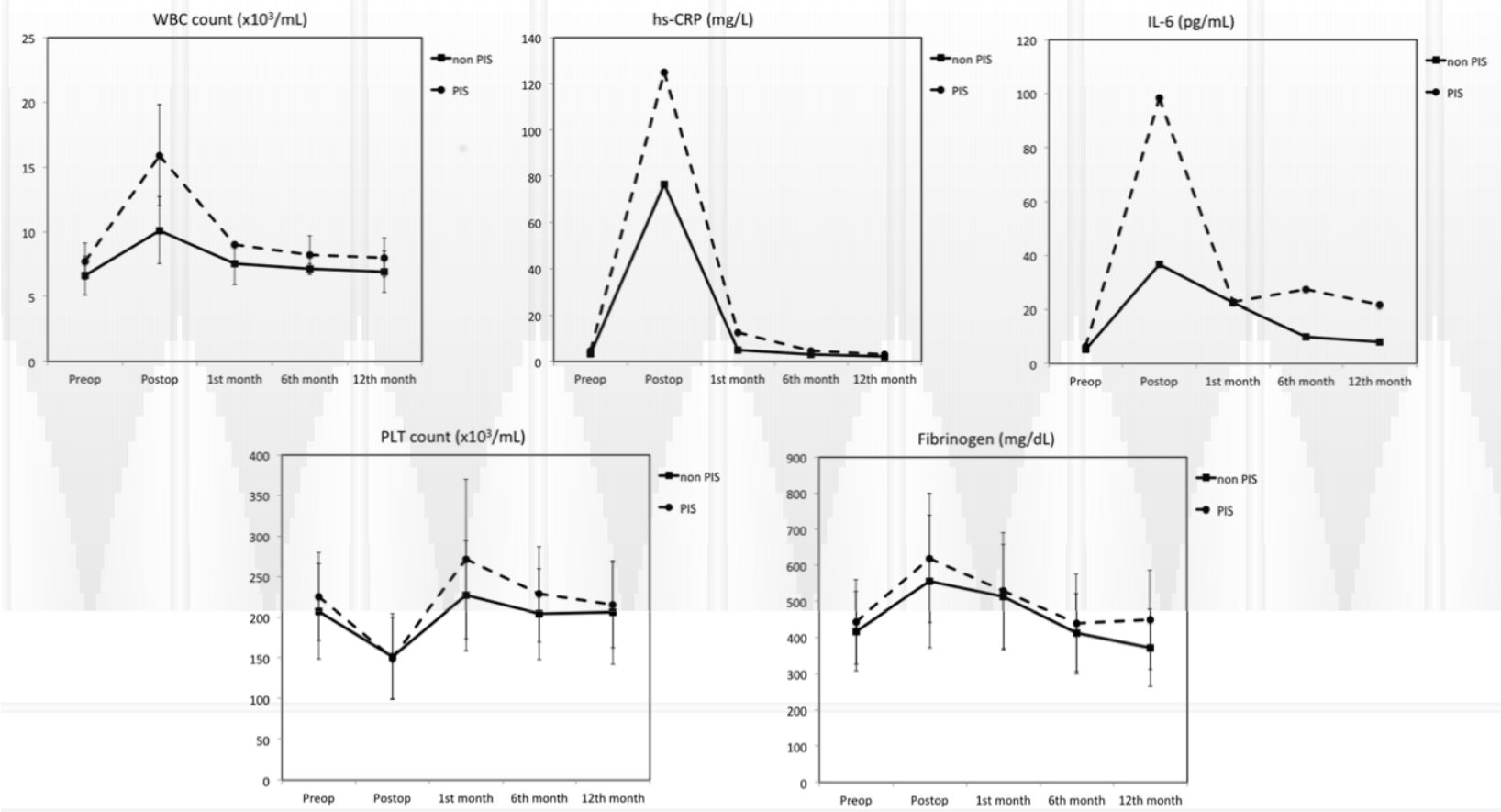
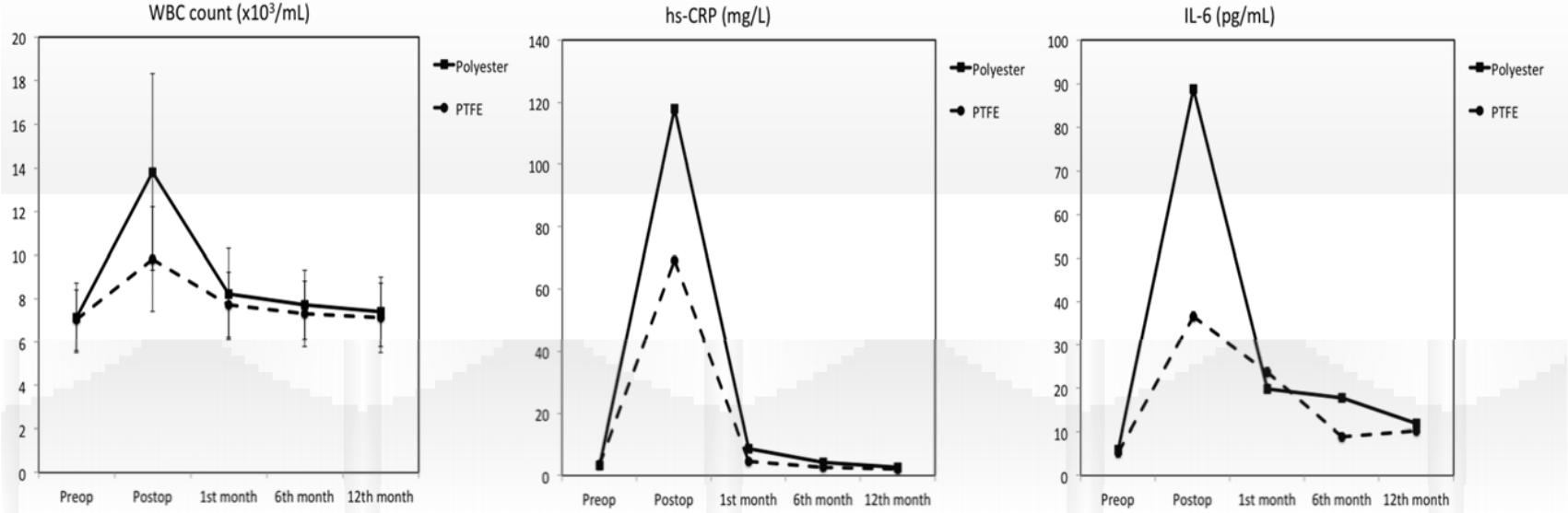


Figure 8. Graphical representation of the mean measures of white blood cell count (WBC) and median values of hs-CRP and IL-6 according to different endograft material.



7 Abstract

Objectives. Endovascular procedures have been proposed as minimally invasive alternative treatment to conventional open surgical repair, allowing safe and effective aortic aneurysm repair. It has been shown to reduce mortality (at least in the early phase), morbidity, time of hospital stay and overall health care cost. Despite these potential benefits, it has been demonstrated that the Endovascular aneurysm repair (EVAR), may elicit an unexpected systemic inflammatory response, which has been named post implantation syndrome (PIS).The main features of PIS include continuous pyrexia (even under antibiotic therapy) and negative culture results, leukocytosis and/or coagulation disturbances. The incidence of the syndrome has been reported to vary widely, from 3 to 70 per cent. It seems that PIS displays clinical features of systemic inflammatory response syndrome (SIRS), fulfilling two out of four criteria according to the definition of SIRS, fever and leukocytosis. The impact of post-implantation syndrome (PIS) on the outcome of patients after elective endovascular aneurysm repair (EVAR) is still unknown. The aim was to prospectively investigate the association of post implantation syndrome (PIS) with the clinical outcome during the first 30 days and during the first year after EVAR for abdominal aortic aneurysm (AAA) and to assess the evolution of the inflammatory response as outlined from specific inflammatory markers.

Methods. From May 2007 to July 2008, 40 consecutive patients undergoing elective EVAR in our department were enrolled in a pilot study to prospectively evaluate whether EVAR is associated with PIS as well as the relationship of clinical and biochemical relation of PIS with several acute phase inflammation markers. The impact of PIS on the length of hospitalization and its correlation with procedure parameters, such as the aneurysm diameter and the type of endograft deployed were also examined. Blood test were obtained 24 hours prior to, and after the surgery and several inflammation markers were evaluated, such as white blood cells (WBC), platelets counts (PLT), high sensitivity C-reactive protein (hs-CRP), interleukin-1 plasma levels (IL-1), IL-6 plasma levels (IL-6) and tumor necrosis factor alpha (TNF-a).

Subsequently, based on the preliminary data from our pilot study on PIS, from

January 2010 till June 2013, we designed a prospective study by including 214 consecutive patients treated electively by EVAR for AAA with a follow up duration of one year. Demographics, risk factors, pre- and post-operative medication, maximum aneurysm diameter, contrast media used, duration of the procedure, type of endograft, the occurrence of PIS, maximum temperature, peri-operative complications, and duration of hospital stay were recorded for each patient. Aneurysm volume and the amount of newly formed thrombus was also calculated.

Adverse events included any major cardiovascular event (MACE), acute renal failure, readmission and death of any cause were recorded. MACE was defined as a composite of death from cardiac causes, nonfatal acute myocardial infarction (ST and non-ST), worsening of cardiac status needing intervention, ischemic stroke and transient ischemic attack (TIA). Venous blood was collected preoperatively, at day 1 and 3 postoperatively, at the 1st, 6th and 12th month after the procedure. The same inflammation markers with our pilot study were determined, except IL-1and TNF-a, that was found to have non-significant changes. No patient was lost during the 30-day follow up. In contrast, only the data of 182 patents where available for the one year follow up. PIS was defined according to SIRS criteria.

Results.

In the preliminary data from the pilot study, 14 patients (35%) out of 40 developed PIS. There were no significant differences in laboratory data between PIS and no PIS groups preoperatively, while postoperatively there was a pronounced significant increase in WBC count and IL-6 values in the PIS group of patients. The decrease in PLT count was greater in the PIS group compared with the non-PIS group (median difference value 70 vs. 49, P= 0.005) and the increase in hs-CRP was also greater in the same group (median difference value 110.46 vs. 71.93, P=0.002). The incidence of PIS according to the type of the graft deployed was 6/16 (37.5%) for the Talent (polyester) group, 5/5 (100%) for the Anaconda (polyester) group and 1/2 (50%) for the Zenith (polyester) group compared with 2/17 (11.7%) for the Excluder (ePTFE) group (x^2=15.03, P=0.002). Postoperative hospitalization was significantly prolonged in the PIS group compared to PIS-free group [median value, (range) 5.5 (5–9) vs. 3 (2–7) days, P=0.002]. There was not any significant

correlation of PIS with the patient's age, the maximum diameter of the aneurysm, the amount of contrast media used, and the duration of the operation.

During the first 30 days, PIS was found in 77 (34%) out of 214 patients. Pre-operative white blood cell (WBC) count values ($p < .001$), endograft material (polyester) ($p < .001$), and heart failure ($p = .03$) were independent predictors of PIS. For every 1,000 units increase in pre-operative WBC count the chance of PIS increased by 95.5% (95% CI 50-255%). The use of polyester raised (95% CI 5, 3-29, 5 times) the possibility of PIS 12 times compared with the use of ePTFE. Patients suffering from heart failure were three times (95% CI: 1.1-8.5 times) more likely to have PIS than those who did not. Mean post-operative temperature ($p < .001$), length of hospital ($p < .001$) and intensive care unit ($p = .008$) stay, as well as maximum post-operative WBC count ($p < .001$) and hs-CRP values ($p < .001$) were significantly higher in the PIS group.

Also, during the first 30 days, three of 137 patients (2.2%) in the non-PIS group had MACE, compared with 13 out of 77 patients (16.8%) in the PIS group ($p < .001$). Post-operative hs-CRP ($p <0.001$), the presence of coronary artery disease ($p = 0.01$) and duration of fever ($p = 0.02$) independently predicted the occurrence of MACE during the first 30 days. Specifically, for every 10 unit increase in hs-CRP the chance for MACE increased by 15% (95% CI: 6-24%, p=0.001). Also, for every additional day of fever after the first one, the chance of MACE increased by 67.9% (95% CI: 9.8-260%, p=0.017). Patients with CAD were 7.9 times (95% CI: 1.6-38.6 times, p=0.011) more likely to sustain a MACE. In addition to, the threshold of post-operative hs-CRP value of 125 mg/L was highly associated with the occurrence of MACE, with a sensitivity of 82% and specificity of 75%.

Moreover, during the first 30 days, four of 137 patients (2.9%) in the non-PIS group had an adverse event, compared with 20 of 77 patients (25.9%) in the PIS group ($p <.001$). Hs-CRP post-operative values ($p =.004$), post-implantation syndrome ($p = .01$), maximum temperature ($p = .03$), and history of smoking ($p = .02$) were independent predictors of an adverse event during the first 30 days after the procedure. Specifically, for every 10 units rise in hs-CRP the chance of an adverse event increased by 12% (95% CI: 4-19%, p=0.004). Patients diagnosed with PIS after implantation were about five times (95% CI 1.5- 17.6, $p = .011$) more likely to suffer an adverse event than non-PIS patients. For every 1 degree

raise in max temperature, the chance of an adverse event increased 3.1 times (95% CI: 1.15 -8.5 times higher, p=0.03), while smokers were about 4.3 times (95% CI 1.25-15.1, p = .02) more likely than non-smokers.

At the 1-year follow-up in 65 (35.7%) out of 182 patients developed PIS. Hs-CRP (p=0.99) and IL-6 (p=0.17) were attenuated towards the values of non-PIS group, while WBC count (p=0.02) remained higher in the PIS group though within the normal range. Concentration of fibrinogen did not differ significantly between the two groups at baseline (p=0.98), postoperatively (p=0.12) and at the first (p=0.99) and sixth (p=0.96) month after the procedure. Though, patients of the PIS group had significantly higher levels of fibrinogen at the first year when compared to patients of the non-PIS group (p=0.006). On the PIS group platelet count levels was higher at the first month after the procedure (p<0.001). However no significant difference was evident at 6 (p=0.22) and 12 (p=0.99) months between the two groups. During the 1-year follow-up period 17.2% and 18.8% of patients in the PIS group suffered a MACE or an adverse event respectively, in comparison to 4.3% and 5.1% in the non-PIS group. The occurrence of PIS was the only independent predictor of a MACE (p=0.007) or an adverse event (p=0.005) during this one year period. More specifically, patients diagnosed with PIS after the implantation were about 4.5 times (95% CI: 1.5-13.8, p=0.007) more likely to suffer a MACE compared to non-PIS patients and about 4.51 times (95% CI: 1.5-11.7, p=0.005) more likely to suffer an AE compared to non-PIS patients.

Conclusion: A systematic inflammatory response is observed in a significant number of patients after EVAR. The type of endograft material seems to play a significant role in this inflammatory process. The intensity of inflammation, as assessed mainly by the post-operative hs-CRP values, correlates with the presence of a cardiovascular or any other adverse event during the first 30 days after the procedure. After the first postoperative month, the inflammatory response is attenuated as showed by the kinetics of several inflammatory biomarkers. However, PIS seems to correlate with the presence of a cardiovascular or any other adverse event during the first year after EVAR. Further studies should focus on whether a change in care is needed to ameliorate the higher cardiovascular risk of PIS patients.

8 Περίληψη

Σκοπός: Η ενδαγγειακή αντιμετώπιση του ανευρύσματος κοιλιακής αορτής αποτελεί μια ελάχιστα επεμβατική θεραπεία εναλλακτική από την κλασσική ανοικτή χειρουργική αντιμετώπιση , που επιτρέπει την ασφαλή και αποτελεσματική αποκατάσταση των αορτικών ανευρυσμάτων. Η ενδαγγειακή θεραπεία μειώνει τη περιεγχειρητική θνησιμότητα και θνητότητα και τη διάρκεια παραμονής του ασθενούς στο νοσοκομείο. Παρόλα τα ζωτικής σημασίας οφέλη τους, έχει παρατηρηθεί ότι η ενδαγγειακή αποκατάσταση ανευρυσμάτων μπορεί να πυροδοτήσει μια αναπάντεχη συστηματική φλεγμονώδη αντίδραση του οργανισμού, η οποία έχει ονομαστεί σύνδρομο μετά την εμφύτευση ενδαγγειακού μοσχεύματος (ΣΕΕΜ). Τα κύρια χαρακτηριστικά του συνδρόμου περιλαμβάνουν πυρετό, λευκοκυττάρωση και/ή διαταραχές στην πηκτικότητα του αίματος με αρνητικές αιμοκαλλιέργειες. Η επίπτωση του συνδρόμου ποικίλει αρκετά και κυμαίνεται από 3% εως 70%. Φαίνεται πως το ΣΕΕΜ εμφανίζει κλινικά στοιχεία του Σύνδρομο συστηματικής φλεγμονώδους απάντησης (SIRS), εκπληρώνοντας δύο από τα τέσσερα κριτήριά του, τον πύρετο και τη λευκοκυττάρωση. Η επίπτωση του ΣΕΕΜ αναφορικά με την έκβαση των ασθενών, μετά από την ενδαγγειακή αποκατάστασης ΑΚΑ, είναι ακόμα άγνωστη. Στόχος της παρούσας εργασίας αποτέλεσε η προοπτική μελέτη του ΣΕΕΜ και η συσχέτιση του συνδρόμου με την κλινική έκβαση των ασθενών κατά τη διάρκεια του πρώτου έτους μετά την επέμβαση. Επιπρόσθετα, θα διερευνηθεί η εξέλιξη της φλεγμονώδους αντίδρασης μετά την επέμβαση όπως αυτή αποτυπώνεται από ειδικούς δείκτες φλεγμονής.

Μεθοδολογία: Από το Μάιο του 2007 έως και τον Ιούλιο του 2008, 40 συνεχόμενοι ασθενείς που υποβλήθηκαν σε εκλεκτική ενδαγγειακή αποκατάσταση ανευρύσματος κοιλιακής αορτής στο τμήμα μας συμπεριλήφθηκαν σε μια πιλοτική προοπτική μελέτη προκειμένου να αξιολογηθεί το κατά πόσον οι ενδαγγειακές τεχνικές σχετίζονται με την εμφάνιση του συνδρόμου ΣΕΕΜ καθώς και τη συσχέτιση των κλινικών και βιοχημικών παραμέτρων του ΣΕΕΜ με διάφορους δείκτες της οξείας φάσης της φλεγμονής. Επίσης εξετάστηκε η επίπτωση του ΣΕΕΜ στην διάρκεια της νοσηλείας καθώς και η συσχέτισή του με διάφορους ανατομικούς και περιεγχειρητικούς παράγοντες. Δείγματα αίματος ελήφθησαν 24 ώρες πριν και κατά την πρώτη μετεγχειρητική ημέρα. Δείκτες φλεγμονής

που αξιολογήθηκαν ήταν τα λευκά αιμοσφαίρια, τα αιμοπετάλια, η υψηλής ευαισθησίας C-αντιδρώσα πρωτεΐνη καθώς και τα επίπεδα κάποιων μονοκυτταροκινών (IL-1, Il-6, TNF-a).

Στη συνέχεια, έχοντας στη διάθεση μας κάποια από τα αποτελέσματα από την πιλοτική μελέτη 214 ασθενείς που υποβλήθηκαν σε ενδαγγειακή αποκατάσταση ΑΚΑ σε τακτική βάση, συμπεριλήφθηκαν σε μια προοπτική μελέτη με παρακολούθηση των ασθενών έως ένα χρόνο. Καταγράφηκαν αναλυτικά σε κάθε ασθενή τα δημογραφικά στοιχεία, οι παρόντες κίνδυνου, η φαρμακευτική του αγωγή πριν και μετά το χειρουργείο, η μέγιστη διάμετρος του ανευρύσματος, το ποσό του σκιαγραφικού που χρησιμοποιήθηκε, η εμφάνιση ή όχι του ΣΕΕΜ, η μέγιστη τιμή και διάρκεια του πυρετού καθώς και οι περιεγχειρητικές επιπλοκές μαζί με την διάρκεια νοσηλείας. Επίσης υπολογίστηκε ο συνολικός όγκος καθώς και ο νεοσχηματισθείς θρόμβος του ανευρύσματος σε κάθε ασθενή.

Στις ανεπιθύμητες εκβάσεις συμπεριλαμβάνονται τα μείζονα καρδιαγγειακά συμβάματα (ΜΚΣ), η οξεία νεφρική ανεπάρκεια, η επανεισαγωγή του ασθενούς στο νοσοκομείο και τέλος, ο θάνατος από οποιαδήποτε αιτία. Ως ΜΚΣ ορίστηκε ο θάνατος από καρδιακά αίτια, τα μη θανατηφόρα οξύ εμφράγματα του μυοκαρδίου (ST και non-ST), επιδείνωση της καρδιακής λειτουργίας που να χρειάστηκε παρέμβαση, ισχαιμικό εγκεφαλικό επεισόδιο και παροδικό ισχαιμικό επεισόδιο (ΤΙΑ). Δείγματα αίματος ελήφθησαν προεγχειρητικά, την 1^{η} και την 3^{η} μετεγχειρητική ημέρα καθώς και τον 1^{ο}, τον 6^{ο} και τον 12^{ο} μετεγχειρητικό μήνα. Αξιολογήθηκαν οι ίδιοι δείκτες φλεγμονής που μετρήθηκαν και στη πιλοτική μας μελέτη με εξαίρεση των μονοκυτταροκινών IL-1 και TNF-a, οπού είχαν βρεθεί να μην έχουν σημαντική προγνωστική αξία στην αρχική πιλοτική μελέτη. Όλοι οι ασθενείς προσήλθαν για επανέλεγχο στις 30 ημέρες. 182 ασθενείς, ολοκλήρωσαν την παρακολούθηση στον ένα χρόνο μετά την επέμβαση. Το ΣΕΕΜ προσδιορίστηκε σύμφωνα με τα κριτήρια του συνδρόμου συστηματικής φλεγμονώδους αντίδρασης (SIRS).

Αποτελέσματα

Από τα αποτελέσματα της πιλοτικής μελέτης, 14 (35%) από τους συνολικά 40 ασθενείς εμφάνισαν ΣΕΕΜ. Δε διαπιστώθηκαν σημαντικές διάφορες στις προεγχειρητικές εργαστηριακές τιμές μεταξύ των ασθενών που εμφάνισαν και αυτών που δεν εμφάνισαν

ΣΕΕΜ, ενώ μετεγχειρητικά βρέθηκε στατιστικά σημαντική αύξηση των τιμών των λευκών αιμοσφαιρίων (WBC) και της ιντερλευκίνης-6 (IL-6). Επίσης, μετεγχειρητικά, διαπιστώθηκε πως η μείωση των τιμών των αιμοπεταλίων (διαφορά διάμεσης τιμής 70 vs 49, P=0,005) και η αύξηση των τιμών της υψηλής ευαισθησίας C-αντιδρώσα πρωτεΐνη (διαφορά διάμεσης τιμής 110,46 vs 71,93, p=0,005) ήταν στατιστικά σημαντικότερη στην ομάδα που εμφάνισε ΣΕΕΜ συγκριτικά με την ομάδα που δεν εμφάνισε ΣΕΕΜ. Η συχνότητα εμφάνισης του ΣΕΕΜ ανάλογα με τον τύπο του μοσχεύματος που χρησιμοποιήθηκε ήταν 6/16 (37,5%) στην ομάδα που χρησιμοποιήθηκε μόσχευμα Talent (πολυεστέρας), 5/5 (100%) στην ομάδα που χρησιμοποιήθηκε μόσχευμα Anaconda (πολυεστέρας) και 1/2 (50%) στην ομάδα που χρησιμοποιήθηκε μόσχευμα Zenith (πολυεστέρας), ενώ στην ομάδα που χρησιμοποιήθηκε μόσχευμα Excluder (πολυτετραφλουροαιθυλένιο) μόνο 2/17 (11,7%) εμφάνισαν ΣΕΕΜ ($x^2 = 15.03$, $p = 0.002$). Η διάρκεια μετεγχειρητικής νοσηλείας ήταν σημαντικά μεγαλύτερη στην ομάδα που εμφάνισε ΣΕΕΜ σε σύγκριση με την άλλη ομάδα [διάμεση τιμή 5,5 vs 3 ημέρες, p = 0,002]. Δεν υπήρχε στατιστικά σημαντική συσχέτιση του ΣΕΕΜ με την ηλικία του ασθενούς, την μέγιστη διάμετρο του ανευρύσματος, την συνολική ποσότητα σκιαγραφικού που χρησιμοποιήθηκε καθώς και την διάρκεια της επέμβασης.

Κύρια προοπτικη μελέτη/ παρακολούθησης των 30 ημέρων. 77 από τους 214 ασθενείς (34%) εκδήλωσαν ΣΕΕΜ. Οι προεγχειρητικές τιμές των λευκών αιμοσφαιρίων (WBC) ($p < 0.001$), το υλικό (πολυεστέρας) του ενδοαγγειακού μοσχεύματος ($p < 0.001$), και η παρουσία καρδιακής ανεπάρκειας ($p = 0.03$) ήταν ανεξάρτητοι προγνωστικοί παράγοντες για το ΣΕΕΜ. Συγκεκριμένα, για κάθε αύξηση κατά 1000 μονάδων της προεγχειρητικής τιμής των λευκών αιμοσφαιρίων αυξάνει η πιθανότητα εμφάνισης του ΣΕΕΜ κατά 95,5% (95% CI: 50-255%, $p<0.001$). Η χρήση μοσχεύματος από πολυεστέρα αυξάνει την πιθανότητα εμφάνισης ΣΕΕΜ κατά 12 φορές συγκριτικά με την χρήση των ePTFE μοσχευμάτων. Επίσης οι πάσχοντες από καρδιακή ανεπάρκεια είχαν τρεις φορές μεγαλύτερη πιθανότητα να εμφανίσουν ΣΕΕΜ από τους μη πάσχοντες. Η μέση μετεγχειρητική θερμοκρασία ($p<0.001$), η συνολική διάρκεια νοσηλείας ($p<0.001$), η διάρκεια νοσηλείας στη μονάδα εντατικής θεραπείας ($p = 0.008$) καθώς και η μέγιστη μετεγχειρητική τιμή των WBC ($p<0.001$) και hs-CRP ($p < 0.001$) ήταν σημαντικά υψηλότερα στην ομάδα των ασθενών με ΣΕΕΜ.

Επίσης, κατά την διάρκεια του 1ου μήνα, στην ομάδα που δεν εμφάνισαν ΣΕΕΜ τρία από τους 137 ασθενείς (2,2%) εκδήλωσαν ΜΚΣ συγκριτικά με 13 από τους 77 ασθενείς της ομάδας που εμφάνισε ΣΕΕΜ (p<0,001).Οι μετεγχειρητικές τιμές της hs-CRP (p< 0.001), η παρουσία στεφανιαίας νόσου (p=0.01) και η διάρκεια του πυρετού (p = 0.02), αποτέλεσαν ανεξάρτητους προγνωστικούς παράγοντες για την εμφάνιση μείζονα καρδιακών συμβαμάτων κατά τη διάρκεια των πρώτων 30 ημερών. Ειδικότερα, για κάθε αύξηση 10 μονάδων της τιμής της μετεγχειρητικής hs-CRP η πιθανότητα εκδήλωσης ΜΚΣ αυξάνει κατά 15% (95% CI: 6-24%, p=0.001). Επίσης, για κάθε προσθετή ημέρα εμπύρετου πέραν της μιας ημέρας, η πιθανότητα εμφάνισης ΜΚΣ αυξάνει κατά 67.9% (95% CI: 9.8-260%, p=0.017). Οι ασθενείς με στεφανιαία νόσο είχαν 7.9 φορές (95% CI: 1.6-38.6 φορες, p=0.011) μεγαλύτερη πιθανότητα να εκδηλώσουν ΜΚΣ. Επιπλέον, η μετεγχειρητική τιμή hs-CRP ίση με 125 mg/L σχετίζεται σε σημαντικό βαθμό με την εμφάνιση ΜΚΣ, παρουσιάζοντας ευαισθησία 82% και ειδικότητα 75%.

Επιπλέον, κατά τον πρώτο μετεγχειρητικό μήνα, 4 από τους 137 ασθενείς (2.9%) που δεν εμφάνισαν ΣΕΕΜ είχαν κάποιο ανεπιθύμητη έκβαση συγκριτικά με 20 από τους 77 ασθενείς (25.9%) της ομάδας που εμφάνισαν ΣΕΕΜ (p<0.001). Οι μετεγχειρητικές τιμές της hs-CRP (p=0.004), η παρουσία του Σ.Ε.Ε.Μ (p = 0.01), η μέγιστη θερμοκρασία (p = 0.03) και το ιστορικό καπνίσματος (p=0.002) αποτέλεσαν ανεξάρτητους προγνωστικούς παράγοντες για την εμφάνιση ανεπιθύμητων εκβάσεων κατά τη διάρκεια των πρώτων 30 ημερών μετά την επέμβαση. Ειδικότερα, για κάθε αύξηση 10 μονάδων της τιμής της μετεγχειρητικής hs-CRP η πιθανότητα εκδήλωσης ανεπιθύμητης έκβασης αυξάνει κατά 12% (95% CI: 4-19%, p=0.004) ενώ οι ασθενείς που εμφάνισαν ΣΕΕΜ, είχαν περίπου πέντε φορές μεγαλύτερη πιθανότητα να εμφανίσουν ανεπιθύμητη έκβαση. Επίσης, για κάθε αύξηση 1^0 C από την μέγιστη θερμοκρασία, η πιθανότητα εμφάνισης ανεπιθύμητης έκβασης αυξάνεται κατά 3.1 φορές (95% CI: 1,15 -8,5, p=0.03), ενώ στους καπνιστές η πιθανότητα αυξάνεται κατά 4.3 φορές (95% CI 1.25-15.1, p = 0.02) συγκριτικά με τους μη-καπνιστές.

Κατά τη διάρκεια της παρακολούθησης ενός έτους 65 από τους 182 ασθενείς (35.7%) εκδήλωσαν ΣΕΕΜ. Οι τιμές των hs-CRP (p = 0.99) και IL-6 (p = 0.17) των ασθενών με Σ.Ε.Ε.Μ ήταν παρόμοιες με την ομάδα χωρίς Σ.Ε.Ε.Μ, ενώ οι τιμές των WBC (p = 0.02) παρέμειναν υψηλότερες στην ομάδα ασθενών που εμφάνισαν Σ.Ε.Ε.Μ, αν και εντός των φυσιολογικών ορίων. Η συγκέντρωση του ινωδογόνου δεν διέφερε

σημαντικά μεταξύ των δύο ομάδων προεγχειρητικά (p = 0.98), μετεγχειρητικά (p = 0.12), και στον 1ο (p = 0.99) και τον 6ο (p = 0,96) μήνα μετά τη επέμβαση. Ωστόσο, οι ασθενείς της ομάδας που εμφάνισαν ΣΕΕΜ είχαν στατιστικά σημαντικά υψηλότερα επίπεδα του ινωδογόνου τον 12ο μήνα σε σύγκριση με τους ασθενείς της ομάδας που δεν εμφάνισαν ΣΕΕΜ (p = 0.006). Σχετικά με τα επίπεδα του αριθμού των αιμοπεταλίων , ενώ ήταν υψηλότερα κατά τον πρώτο μήνα μετά την επέμβαση στην ομάδα που εμφάνισε ΣΕΕΜ (p <0,001), καμία σημαντική διαφορά ήταν εμφανής στον 6ο (p = 0.22) και τον 12ο (ρ = 0,99) μήνα μεταξύ των δύο ομάδων. Κατά τη διάρκεια της παρακολούθησης στο πρώτο έτος, 17,2% και 18,8% των ασθενών που εμφάνισαν Σ.Ε.Ε.Μ παρουσίασαν κάποιο ΜΚΣ και άλλες ανεπιθύμητες εκβάσεις αντίστοιχα, σε σύγκριση με 4,3% και 5,1% των ασθενών που δεν εμφάνισε Σ.Ε.Ε.Μ. Η παρουσία του Σ.Ε.Ε.Μ ήταν ο μόνος ανεξάρτητος προγνωστικός δείκτης που συνέβαλε στην εμφάνιση ΜΚΣ (p = 0.007) ή κάποιας ανεπιθύμητης έκβασης (p = 0.005) κατά τη διάρκεια της περιόδου του ενός έτους παρακολούθησης. Συγκεκριμένα, ασθενείς που διαγνωστήκαν με ΣΕΕΜ μετά την επέμβαση είχαν περίπου 4,5 φορές (95% CI: 1.5-13.8, p=0.007) μεγαλύτερη πιθανότητα να παρουσιάσουν ΜΚΣ και 4.51% (95% CI: 1.5-11.7, p=0.005) αυξημένη πιθανότητα να παρουσιάσουν ανεπιθύμητες εκβάσεις συγκριτικά με τους ασθενείς χωρίς ΣΕΕΜ.

Συμπέρασμα: Μετά την ενδαγγειακή αποκατάσταση ΑΚΑ, μια συστηματική φλεγμονώδης αντίδραση παρατηρείται στο ένα τρίτο των ασθενών. Το είδος του ενδαγγειακού μοσχεύματος φαίνεται να συσχετίζεται σημαντικά σε αυτή τη φλεγμονώδη αντίδραση. Η ένταση της φλεγμονώδους απάντησης, όπως εκτιμάται με βάση τις μετεγχειρητικές τιμές hs-CRP, συσχετίζεται με την εμφάνιση ΜΚΣ ή οποιουδήποτε ανεπιθύμητου συμβάματος κατά τη διάρκεια των πρώτων 30 ημερών μετά την επέμβαση. Μετά τον πρώτο μετεγχειρητικό μήνα η φλεγμονώδης απόκριση εξασθενεί, όπως αποδεικνύεται από τη κινητικότητα των διαφόρων φλεγμονωδών βιοδεικτών. Ωστόσο, το ΣΕΕΜ. φαίνεται να συσχετίζεται με την εμφάνιση ΜΚΣ ή οποιουδήποτε ανεπιθύμητου συμβάματος κατά τη διάρκεια του πρώτου έτους μετά την ενδαγγειακή αποκατάσταση ΑΚΑ. Οι νέες μελέτες θα πρέπει να διερευνήσουν εάν απαιτείται κάποια αλλαγή στη θεραπευτική αντιμετώπιση των ασθενών για να μειωθεί ο καρδιαγγειακός κίνδυνος των ασθενών που εμφανίζουν ΣΕΕΜ.

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10 Awards-Publications

Awards

Award for best oral presentation- LIVES 2009 Larissa International Vascular Endovascular Symposium. Post implantation Syndrome after endovascular repair of Abdominal Aortic Aneurysm. Preliminary results H.M. Arnaoutoglou, G. Kouvelos, H. Milionis, A. Kostoula, N. Kolaitis, G. Papadopoulos, M. Matsagas

Publications

- Arnaoutoglou E, **Papas N**, Milionis H, Kouvelos G, Koulouras V, Matsagkas MI. Post implantation syndrome after endovascular repair of aortic aneurysms: need for post discharge surveillance. Interact Cardiovasc Thorac Surg. 2010 Oct;11(4):449-54
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- Arnaoutoglou E, Kouvelos G, **Papa N**, Kallinteri A, Milionis H, Koulouras V, Matsagkas M. Prospective Evaluation of Post-implantation Inflammatory Response After EVAR for AAA: Influence on Patients' 30 Day Outcome. Eur J Vasc Endovasc Surg. 2015;49(2):175-83
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INTERACTIVE CARDIOVASCULAR AND THORACIC SURGERY

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Negative results - Aortic and aneurysmal

Post-implantation syndrome after endovascular repair of aortic aneurysms: need for postdischarge surveillance

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Abstract

Objective: To present the consequences and the need for readmission due to a vigorous inflammatory response in six patients who underwent endovascular repair of aortic aneurysms and developed post-implantation syndrome (PIS), during the postoperative period. **Methods:** From January 2007 to December 2009, 162 patients underwent endovascular repair of an aortic aneurysm. PIS was recorded in 49 patients. Among these, we present six patients who developed a systemic inflammatory response syndrome (SIRS) after discharge from hospital, which led to readmission within the first 30 postoperative days. **Results:** Five patients were treated for asymptomatic infrarenal abdominal aortic aneurysm and one for a thoracic one. All patients were discharged from hospital in the absence of any complications, fever or leukocytosis, but several days later they developed features of SIRS leading to readmission, even to the intensive care unit in two of them. After the administration of anti-inflammatory drugs all patients showed a complete recovery and finally left hospital several days later. **Conclusions:** In some patients, the initial inflammatory response following endovascular aortic aneurysm repair is not always spontaneously attenuated and could lead to the development of SIRS even several days after the operation. It seems reasonable that patients developing PIS after endovascular aneurysm repair might be better kept under surveillance for the first postoperative month.

Keywords: Aortic aneurysm; Endovascular repair; Post-implantation syndrome; Systemic inflammatory response syndrome

Negative Results

1. Introduction

Endovascular procedures have been proposed as minimally invasive alternative treatment, allowing safe and effective aortic aneurysm repair. Despite the potential benefits, it has been demonstrated that endovascular stent grafting may elicit an unexpected systemic inflammatory response, which has been named post-implantation syndrome (PIS) [1]. This is characterized by the presence of fever, leukocytosis and sometimes coagulation disturbances [1–5]. As yet, there is no clear definition of the syndrome from the clinical and pathophysiological point of view [6]. It seems that PIS manifests clinically as a systemic inflammatory response syndrome (SIRS), meeting two of the four criteria according to the definition of SIRS, fever and leukocytosis [7, 8]. The clinical importance of PIS is unclear and the impact of the syndrome on the outcome of the patients is still unknown. In most cases, this transient SIRS state is generally well tolerated, causing no serious consequences. However, it has been reported that a number of patients develop excessive clinical signs of inflammation in the early postoperative period after endovascular aneurysm repair (EVAR) [6, 9–11]. The excessive inflammatory response raises concerns of inducing postoperative morbidity, especially in patients at high risk, including the elderly with several comorbidities, such as activation of inflammatory pathways and the release of inflammatory cytokines might underpin an already established but still subclinical organ dysfunction [12, 13].

Herein, we describe the clinical setting and consequences owing to a vigorous inflammatory response in six patients who underwent endovascular treatment of aortic aneurysms and developed PIS during the postoperative period.

2. Patients and methods

In a three-year period from January 2007 to December 2009, a total of 162 patients underwent an endovascular repair of their aortic aneurysm [148 for an infrarenal abdominal aortic aneurysm (AAA), and 14 for a descending thoracic aorta aneurysm] in the University Hospital of Ioannina. All endovascular procedures were performed under general anesthesia and a standard vascular protocol, by the same anesthesiological and surgical team. All patients were treated with a beta-blocker and a statin for

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Follow-up papers - Aortic and aneurysmal

Post-implantation syndrome following endovascular abdominal aortic aneurysm repair: preliminary data

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Abstract

Objectives: Endovascular aneurysm repair (EVAR), may elicit an unexpected systemic inflammatory response, which has been named post-implantation syndrome (PIS). The aim of this study was to prospectively evaluate the association of PIS with clinical and laboratory parameters in patients who underwent EVAR for abdominal aortic aneurysms (AAA). **Methods:** Forty consecutive patients who underwent EVAR for AAA were studied. Complete blood count, fibrinogen, high sensitivity C-reactive protein (hs-CRP), interleukin (IL)-6, IL-1, tumor necrosis factor-alpha were determined before and after surgery. Several parameters regarding the operation, as well as the hospitalization days were recorded. **Results:** PIS was diagnosed in 35% of the patients. Patients with PIS showed significant greater changes of inflammation marker levels, including hs-CRP and IL-6, as compared with the non-PIS group. PIS was associated with longer hospitalization. **Conclusion:** PIS is a relatively common complication of EVAR used to treat AAAs and it is associated with features of a systemic inflammatory response and prolongation of hospitalization. Further studies are necessary towards understanding the underlying pathophysiology and evaluating effective preventive strategies.

Keywords: Abdominal aortic aneurysm; Endovascular aneurysm repair; Inflammatory markers; Post-implantation syndrome

Follow-up Paper

1. Introduction

Post-implantation syndrome (PIS) has been used to encompass a clinical entity characterized by systemic inflammation after stenting of the abdominal aorta first described by Velazquez et al. in 1999 [1]. The main features of PIS include continuous pyrexia despite antibiotic therapy, negative culture results, leukocytosis and/or coagulation disturbances [2–6]. The incidence of the syndrome has been reported to vary widely between 3% and 60% for abdominal aortic aneurysms (AAAs) [7]. Although, there are many laboratory and clinical data suggesting a systemic inflammatory response syndrome (SIRS) state [5, 8, 9], from the pathophysiological and clinical point of view there is no clear definition of the syndrome and its potential significance so far. This response is primarily attributed to endothelial dysfunction reflecting a synergic role between the material of the graft and the endovascular surgical technique; the acute formation of a large amount of thrombus within the aneurysmal sac may also play a role [10].

The impact of the syndrome on the outcome of patients is still unknown. Postoperative inflammatory response raises concerns of postoperative morbidity, especially in patients at high risk, including the elderly with several comorbidities [11, 12]. In most cases, PIS is generally well-tolerated, but even then it may result in a more demanding postoperative recovery leading to prolonged hospitalization, and thus it might be considered a moderate complication of the procedure, according to the reporting standards for endovascular aneurysm repair (EVAR) [13].

In the present study, we prospectively investigated whether the endovascular treatment of AAAs is associated with early inflammatory response as well as the relationship of clinical and biochemical expression of PIS with several acute phase inflammation markers. We also examined the impact of PIS on the length of hospitalization and its correlation with procedure parameters, such as the aneurysm diameter, and the type of endograft deployed.

2. Patients and methods

This is a pilot study showing preliminary data, since PIS represents a continuous study project of our department. Between May 2007 and July 2008, an endoluminal repair of asymptomatic infrarenal AAA was performed in 43 consecutive patients aged between 53 and 87 years (median age 74.2 years). The patients were allocated to EVAR according

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highlighting the utility of endovascular aneurysm repair in this frail group and the importance of careful patient selection for open repair in patients with any degree of COPD. Furthermore, Cox proportional hazards analysis not only confirmed oxygen dependence was associated with diminished 5-year survival, but also medically managed COPD, again emphasizing the ongoing challenge of selecting patients with COPD for aneurysm repair.

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Regarding "The impact of endograft type on inflammatory response after endovascular treatment of abdominal aortic aneurysm"

We read with great interest the paper recently published by Moulakakis et al.[1] In this prospective study, the authors evaluated the impact of the endograft type on the inflammatory response and concluded that the postimplantation syndrome (PIS) was not associated with perioperative adverse clinical events showing a benign course. However, the effect of the syndrome on the outcome of the patients remains almost unknown. In fact, in most cases, PIS is generally "well-tolerated," but in some patients, it may lead to severe complications, including cardiovascular events, renal function impairment, and multisystem organ failure during the postoperative period.[2] In a previous publication from our team, five patients out of 148 who underwent an endovascular repair for an abdominal aortic aneurysm manifested a vigorous inflammatory response several days after discharge that led to readmission; all these patients developed PIS after the procedure.[2] In another publication, we reported preliminary data and we described two patients out of 14 who developed PIS and experienced a nonfatal myocardial infarction on the first postoperative day.[3] It is also not uncommon for patients suffering from PIS to present with symptoms like fatigue and elevated body temperature, sometimes even weeks after the procedure.[2,4] This discrepancy regarding the impact of PIS on patients' outcome compared with the data reported by Moulakakis et al could be explained by looking into the methodology of the present study.[1] Specifically, the postoperative morbidity was not accordingly defined, and there is a vague statement in the results section that there was no postoperative increase in cardiac troponin levels. Consequently, a major concern would be whether troponin levels were the sole criterion for cardiovascular morbidity. But again, the time intervals of measurements and definitions are missing, as well as a detailed description regarding the duration of hospitalization, monitoring, and follow-up of the patients during the first month.

In our opinion, the most important reason for the different conclusions drawn from several studies involving PIS so far is the lack of a widely accepted definition. For example, some authors describe PIS as the presence of leukocytosis and elevated C-reactive protein,[4] whereas others define PIS as the presence of fever and leukocytosis with different cut-off values.[1] Since we have been studying PIS prospectively and systematically for several years, we have already proposed a definition of the syndrome according to the systemic inflammatory response syndrome.[2,3] This definition seems to be more reasonable because there is evidence supporting a systemic inflammatory response induced by the implantation of the endoprosthesis.[2,5] In fact, PIS fulfills at least two of the systemic inflammatory response syndrome criteria (ie, fever and leukocytosis).[6] Therefore, we propose the definition of PIS as the presence of fever (persisting body temperature >38°C) and leukocytosis (white blood cell count >12,000/μL), despite antibiotic therapy and negative blood culture results.[3,6] We believe that this may represent the best way to compare variables related to the syndrome among different studies and to evaluate its clinical significance. Nonetheless, close surveillance of patients developing an excessive inflammation response postoperatively is mandatory and may favorably affect the outcome.

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http://dx.doi.org/10.1016/j.jvs.2013.04.037

Reply

We read with interest the letter by Arnaoutoglou et al reporting their concerns about the definition of the postimplantation syndrome (PIS) following endovascular aneurysm repair and the methodology used in our study. The PIS, as manifested clinically, has gained the interest of vascular surgeons since the early years of

Eur J Vasc Endovasc Surg (2014) ■, 1–9

Prospective Evaluation of Post-implantation Inflammatory Response After EVAR for AAA: Influence on Patients' 30 Day Outcome

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WHAT THIS PAPER ADDS

The impact of post-implantation syndrome (PIS) on the outcome of patients after elective endovascular aneurysm repair (EVAR) is still unknown. In the present study PIS after EVAR was prospectively evaluated and its association with various clinical and laboratory parameters, as well as the clinical outcome of the patients was investigated. It was found that a systematic inflammatory response is observed in almost one third of the patients after EVAR. For the first time in the literature it has been shown that the intensity of the inflammation, as assessed mainly by the post-operative high sensitivity C-reactive protein values, correlates with the presence of a cardiovascular or any other adverse event during the first 30 days after the procedure.

Objectives: The aim was to prospectively evaluate post-implantation syndrome (PIS) after elective endovascular aneurysm repair (EVAR) of abdominal aortic aneurysms (AAAs) and to investigate its association with clinical and laboratory parameters and the clinical outcome of the patients.

Methods: From January 2010 till June 2013, 214 consecutive patients treated electively by EVAR for AAA were prospectively included. PIS was defined according to systemic inflammatory response syndrome criteria. Adverse events included any major adverse cardiovascular events (MACE), acute renal failure, re-admission and death from any cause.

Results: PIS was diagnosed in 77 (34%) patients. Pre-operative white blood cell (WBC) count values ($p < .001$), endograft material (polyester) ($p < .001$), and heart failure ($p = .03$) were independent predictors of PIS. Mean post-operative temperature ($p < .001$), length of hospital ($p < .001$) and intensive care unit ($p = .008$) stay, as well as maximum post-operative WBC count ($p < .001$) and hs-CRP values ($p < .001$) were significantly higher in the PIS group. Post-operative hs-CRP ($p = .001$) and duration of fever ($p = .02$) independently predicted the occurrence of MACE. Post-operative hs-CRP ($p = .004$), maximum temperature ($p = .03$), and the presence of PIS ($p = .01$) were independent predictors of an adverse event during the first 30 days. A threshold of post-operative hs-CRP value of 125 mg/L was highly associated with the occurrence of MACE, with a sensitivity of 82% and specificity of 75%.

Conclusions: A systematic inflammatory response is observed in a significant number of patients after EVAR. The type of endograft material seems to play a significant role in this inflammatory process. The intensity of inflammation, as assessed mainly by the post-operative hs-CRP values, correlates with the presence of a cardiovascular or any other adverse event during the first 30 days after the procedure.

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Keywords: Post-implantation syndrome, 30 day outcome, Inflammatory response, EVAR, Abdominal aneurysm, Endovascular

INTRODUCTION

Post-implantation syndrome (PIS) has been used to describe a clinical entity characterized by systemic inflammation after endovascular repair of an abdominal aortic aneurysm (EVAR).[1] The impact of the syndrome on patient outcome is still unknown. The post-operative inflammatory response raises concerns of increased morbidity, especially in

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11 CURRICULUM VITAE

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Publications

Greek Journals

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- Λαπαροσκοπικός αποκλεισμός κάτω μεσεντερίου αρτηρίας για την αντιμετώπιση εμμένουσας ενδοδιαφυγής τύπου ΙΙ μετά ενδαγγειακή αποκατάσταση ανευρύσματος κοιλιακής αορτής. Ελληνική Αγγειοχειρουργική 2010;19: 25-30. Γ. Γεωργίου, Χ. Μπαλή, Γ. Κούβελος, **Ν. Παπάς**, Γ. Παπαδόπουλος, Μ. Φατούρος, Μ. Ματσάγκας.

International Journals

- Post-implantation syndrome after endovascular repair of aortic aneurysms: need for post discharge surveillance. *Interact CardioVasc Thorac Surg 2010; 11: 449-454* (Eleni Arnaoutoglou, **Nektarios Papas**, Haralampos Milionis, George Kouvelos, Vasilios Koulouras and Miltiadis I. Matsagkas)
- Post-implantation syndrome following endovascular abdominal aortic aneurysm repair: preliminary data. *Interact CardioVasc Thorac Surg 2011; 12: 609-14* (Eleni Arnaoutoglou, George Kouvelos, Haralampos Milionis, Anestis Mavridis, Nikolaos Kolaitis, **Nektario Papa**, George Papadopoulos and Miltiadis Matsagkas)
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- Prospective Evaluation of Post-implantation Inflammatory Response After EVAR for AAA: Influence on Patients' 30 Day Outcome. Eur J Vasc Endovasc

Surg . 2014 Dec, (E. Arnaoutoglou ,G. Kouvelos **,N. Papa** , A. Kallinteri , H. Milionis , V. Koulouras , M. Matsagkas)

- Standard endovascular treatment of abdominal aortic aneurysms in patients with very shortproximal necks using the Endurant stent graft. J Vasc Surg. 2015 Jan, (Miltiadis Matsagkas, MD,PhD, FEBVS, George Kouvelos, MD, PhD, Michalis Peroulis, MD, PhD, Stavros Avgos, MD, Eleni Arnaoutoglou, MD, PhD, Nektario Papa, MD, and George Papadopoulos, MD, PhD, Ioannina, Greece)

Postgraduate Workshops-Courses

- Canadian Cardiovascular Research Network "Gauging the Guidelines. Cardiovascular. Which road to take?" Mississauga, Ontario, February 28, 2015
- Institute of Vascular Diseases, Greece."Educational Seminar in Thrombosis and Anti-thrombotic therapy" Ioannina, Greece, November 4-5, 2011
- Hands-On Practice "Masterclass on Endovenous Interventions". Leading Innovative Vascular Education 2011, Chalkidiki, Greece, May 6, 2011.
- Medtronic Academia "Basic over the Wire Skills". Cardioskills Simulation Center, Frankfurt, Germany, March 24-25, 2011
- Leading Innovative Vascular Education 2010. Revision Course "Preparation for the European Board of Vascular Surgery Examination". Corfu, Greece, May 29, 2010
- Leading Innovative Vascular Education 2010 "Workshop on Thoracic Endografting". Corfu, Greece, May 29, 2010
- European Resuscitation Council. "ALS provider course" University of Ioannina, Ioannina, Greece, April 4-5, 2009.
- Hellenic Society of Vascular Surgery. "Open Surgery for AAA: Tips and Tricks" Ioannina Cardio-Vascular Education, Ioannina, Greece, December 4, 2008.
- Working Group on Hemodynamic and Interventional Cardiology of the Hellenic Cardiological Society. "Endoscopic vein harvesting in cardiac and

peripheral vascular surgery". Ioannina Cardio-Vascular Education, Ioannina, Greece, December 4, 2008.

- Hellenic Society of Endoscopic Surgery and Other Interventional Techniques "Introduction in Laparoscopic Surgery". 3rd Training Seminar, Ioannina, Greece, June 7, 2008
- Hellenic Society of Vascular Surgery. "How to cope with a scientific work". Ioannina Cardio-Vascular Education, Ioannina, Greece, December 6, 2007.
- Hellenic Society of Vascular Surgery. **"**Radiaton Protection in Fluoroscopy – Guided Medical Interventions" .Ioannina Cardio-Vascular Education, Ioannina, Greece, December 7-8, 2007.
- American College of Surgeons, Hellenic Chapter, "Advanced Trauma Life Support" course, Ioannina, Greece, October 20-21, 2007

AWARDS

- Award for the best scientific presentation in Ioannina Cardio-Vascular Education, ICE 2008 meeting, Ioannina, December 4-6, 2008: Subclavian artery injuries after blunt trauma. Is endovascular repair the management of choice? (Xanthopoulos D, Kouvelos G, Arnaoutoglou H, Lianos G, **Papas N**, Papadopoulos G, Matsagkas M.)
- Award for the best scientific presentation in Leading Innovative Vascular Education, LIVE 2011 meeting, Chalkidiki, May 5-8, 2011: The effect of intensified lipid lowering therapy on one-year prognosis in patients undergoing vascular surgery. (G. Kouvelos,

  H. Milionis, E. Arnaoutoglou, C. Kostara, **N. Papa**, V. Koulouras, M. Peroulis, M. Matsagkas)
- Α' καλύτερη Ελεύθερη Ανακοίνωση- 13ο Πανελλήνιο Συνέδριο Αγγειακής και Ενδαγγειακής Χειρουργικής, Αθήνα, 2012 «Η επίδραση της έντονης υπολιπιδαιμικής αγωγής στη νεφρική λειτουργία σε ασθενείς που υποβάλλονται σε αγγειοχειρουργική επέμβαση». Γ. Κούβελος, Ε. Αρναούτογλου, **Ν. Παπάς**, Χ. Κωστάρα, Α. Καλλιντέρη, Μ. Περούλης, Χ.Μιλιώνης, Μ. Ματσάγκας

- Award for best poster presentation- Leading Innovative Vascular Education, LIVE 2013, Thessaloniki Greece. Normal preoperative white blood cell count is predictive of major adverse events after endovascular repair for abdominal aortic aneurysms. (E. Arnaoutoglou, G Kouvelos, P. Tzimas. **N.Papa**, A. Petrou, E. Laou, N. Kolaitis, M. Matsagkas)

Presentations in Greek and international Conferences

- Πανελλήνιο Αγγειοχειρουργικό 2008- In situ αρτηριακές παρακάμψεις σε ασθενείς με κρίσιμη ισχαιμία των κάτω άκρων Βουρλιωτάκης Γ., Παπακώστας Ι., Αρναούτογλου Ε., Ξανθόπουλος Δ., Παπάς Ν., Κούβελος Γ., Παπαδόπουλος Γ., Ματσάγκας Μ.
- 23rd World Congress of the International Union of Angiology Hybrid operations in the management of patients with critical limb ischemia due to complex multifocal peripheral arterial disease G. Kouvelos 1, D. Xanthopoulos 1, G. Vourliotakis 1, E.Arnaoutoglou 2, N. Papas 1, G. Papadopoulos 2, L. Michalis 3, M. Matsagas 1
- 6ο Πανελλήνιο Συνέδριο Ιατρικής Βιοπαθολογίας Προ και μετεγχειρητικές τιμές της hs-CRP και πρόβλεψη της νοσηρότητας των 30 ημερών σε ασθενείς που υποβάλλονται σε ενδαγγειακή αποκατάσταση ανευρύσματος κοιλιακής αορτής Ε. Αρναούτογλου, Γ. Κούβελος, Α. Καλλιντέρη, Η. Κατσούλα, Ν. Παπάς, Μ. Ματσάγκας, Α.Κ. Μαυρίδης
- Leading Innovative Vascular Education 2010 Corfu The value of postoperative cardiac troponin i level in predicting one-year cardiovascular outcome in patients undergoing vascular surgery G. Kouvelos, 2E. Arnaoutoglou, 3H. Milionis, 4C. Kostara, 1N. Papas, 2P. Tzimas, 1M. Matsagkas
- Leading Innovative Vascular Education 2010 Corfu The impact of the endograft on the development of post implantation syndrome after endovascular repair of abdominal aortic aneurysm N. Papas, 2E. Arnaoutoglou, 1G. Kouvelos, 3H. Milionis, 4N.Kolaitis, 2G. Papadopoulos, 1, M. Matsagkas

- Leading Innovative Vascular Education 2010 Corfu Endovascular grafting for acute isolated abdominal aortic dissection G. Vourliotakis, 1, G.N. Kouvelos, 1N. Papas, 1D. Godevenos, 1I. Gizas, 2G. Papadopoulos, 1M.I. Matsagkas
- Leading Innovative Vascular Education 2011-Chalkidiki The effect of intensified lipid lowering therapy on one-year prognosis in patients undergoing vascular surgery. G. Kouvelos, 2 H. Milionis, 3 E. Arnaoutoglou, 4 C. Kostara, 1 N. Papa, 5 V. Koulouras, 1 M. Peroulis, 1 M. Matsagkas

  60th International Congress of the European Society for Cardiovascular and Endovascular Surgery Moscow 2011 The effect of intensified lipid lowering therapy on one-year prognosis in patients undergoing vascular surgery G. Kouvelos, 2 H. Milionis, 3 E. Arnaoutoglou, 4 C. Kostara, 1 N. Papa, 5 V. Koulouras, 1 M. Peroulis, 1 M. Matsagkas

- Πανελλήνιο Αναισθησιολογικό 2011 Αλεξανδρούπολη Αξιολογηση της προγνωστικης ικανοτητας τησ κλιμακας ASA στη βραχυπροθεσμη θνητοτητα και νοσηροτητα σε ασθενεις που υποβαλλονται σε μειζονες αγγειοχειρουργικες επεμβασεις Καλαντώνης Δ.1, Αρναούτογλου Ε.1, Παππάς Ν.2, Κούβελος Γ.2, Ματσάγκας Μ.2, Παπαδόπουλος Γ.
- Πανελλήνιο Αναισθησιολογικό 2011 Αλεξανδρούπολη Η ικανοτητα των τιμων των λευκων αιμοσφαιριων και της υψηλης ευαισθησιας c-αντιδρωσας πρωτει_νης να προβλεπουν την εκβαση μετα απο ενα χρονο, ασθενων που υποβαλλονται σε ενδαγγειακη αποκατασταση ανευρυσματος κοιλιακης αορτης. Αρναούτογλου Ε.1, Παπαθανάκος Γ.1, Παππάς Ν.2, Κολαΐτης Ν.2, Κούβελος Γ.2, Ματσάγκας Μ.2, Παπαδόπουλος Γ.1
- 61st International Congress of the European Society for Cardiovascular and Endovascular Surgery 2012-Dubrovnick The Effect of Intensified Lipid Lowering Therapy on Renal Function in Patients Undergoing Vascular Surgery George Kouvelos1, Elena Arnaoutoglou2, Nektario Papa1, Christina Kostara3, Michalis Peroulis1, Haralampos Milionis4, Miltiadis Matsagkas1 109
- Leading Innovative Vascular Education 2012 Suprarenal versus infrarenal fixation in endovascular abdominal aneurysm repair: analysis of effects on renal

function George N. Kouvelos1, Ioannis Mpoletis2, Nektario Papa1, Michalis Peroulis1, Stavros Avgos1, Dimitrios Godevenos1, Miltiadis I. Matsagkas1

- 13ο Πανελλήνιο Συνέδριο Αγγειακής και Ενδαγγειακής Χειρουργικής Η επίδραση της έντονης υπολιπιδαιμικής αγωγής στη νεφρική λειτουργία σε ασθενείς που υποβάλλονται σε αγγειοχειρουργική επέμβαση Γ. Κούβελος, Ε. Αρναούτογλου, Ν. Παπάς, Χ. Κωστάρα, Α. Καλλιντέρη, Μ. Περούλης, Χ. Μιλιώνης, Μ. Ματσάγκας
- Leading Innovative Vascular Education 2013, Thessaloniki, Oral Presenattion. Endovascular Treatment for isolated acute abdominal aortic dissection. G Kouvelos, G. Vourliotakis, E. Arnaoutoglou, N. Papa, S. Avgos, M. Peroulis, G. Zilis, G. Papadopoulos, M. Matsagkas
- Leading Innovative Vascular Education 2013. Normal preoperative white blood cell count is predictive of major adverse events after endovascular repair for abdominal aortic aneurysms. E. Arnaoutoglou, G. Kouvelos, P. Tzimas, N. Papa, A. Petrou, E. Laou, N. Kolaitis, M. Matsagkas
- 62nd International Congress of the European Society for Cardiovascular and Endovascular Surgery. Endovascular Treatment for isolated acute abdominal aortic dissection. G Kouvelos, G. Vourliotakis, E. Arnaoutoglou, N. Papa, S. Avgos, M. Matsagkas
- 62nd International Congress of the European Society for Cardiovascular and Endovascular Surgery. Normal preoperative white blood cell count is predictive of 110 major adverse events after endovascular repair for abdominal aortic aneurysms. G. Kouvelos, E. Arnaoutoglou, P. Tzimas, N. Papa, N. Kolaitis, M. Matsagkas
- 62nd International Congress of the European Society for Cardiovascular and Endovascular Surgery. Evaluation of the Endurant stent graft use in patients with short abdominal aortic aneurysm proximal neck. G. Kouvelos, M. Peroulis, S. Avgos, E. Arnaoutoglou, N. Papa, M. Matsagkas
- 23th Mediterranean Congress of Angiology and Vascular Surgery. Changes in platelet count and activity following endovascular abdominal aortic aneurysm

repair. E Arnaoutoglou, E. Laou, G. Kouvelos, N, Papa, A. Karamoutsos, G. Vartholomatos, M. Matsagkas

- 23th Mediterranean Congress of Angiology and Vascular Surgery. EVAR for AAA using off-label the Endurant stent graft in patients with very short proximal neck. G. Kouvelos, M. Peroulis, S. Avgos, E. Arnaoutoglou, N. Papa, G. Papadopoulos, M. Matsagkas