Prospective evaluation of postimplantation syndrome evolution on patient outcomes after endovascular aneurysm repair for abdominal aortic aneurysm

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Objective: **This study prospectively investigated the association of postimplantation syndrome (PIS) with the clinical outcome during the first year after endovascular aneurysm repair (EVAR) for abdominal aortic aneurysm and assessed the evolution of the inflammatory response as outlined from specific inflammatory markers.**

Methods: **The study prospectively included 182 consecutive patients treated electively by EVAR for abdominal aortic aneurysm from January 2010 to January 2013. PIS was defined according to systemic inflammatory response syndrome criteria. Patients were monitored for 1 year. Adverse events included any major adverse cardiovascular events (MACE), acute renal failure, readmission, and death from any cause.**

Results: **PIS was diagnosed in 65 patients (35.7%). White blood cell count, high-sensitivity C-reactive protein, and interleukin 6 were significantly higher in the PIS group during the postoperative period ($P < .001$). At the 1-year follow-up, high-sensitivity C-reactive protein ($P = .99$) and interleukin 6 ($P = .17$) were attenuated toward the values of the non-PIS group. The white blood cell count ($P = .02$) remained higher in the PIS group, although within the normal reference range. During the follow-up period, MACE and adverse events occurred, respectively, in 17.2% and in 18.8% of patients in the PIS group and in 4.3% and 5.1% of the non-PIS group. The occurrence of PIS was the only independent predictor of a MACE ($P = .007$) or an adverse event ($P = .005$) during the follow-up period.**

Conclusions: **The inflammatory response after EVAR is attenuated after the first postoperative month, as shown 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. (J Vasc Surg 2016;63:1248-55.)**

Endovascular aneurysm repair (EVAR) of abdominal aortic aneurysm (AAA) may raise a systemic inflammatory response occurring in an early phase after endograft implantation.[1] This so-called postimplantation syndrome (PIS) has been observed in nearly one-third of EVAR patients and is characterized by fever and leukocytosis, fulfilling two of the systemic inflammatory response syndrome criteria.[2,3] Although this systemic inflammatory response syndrome response may be responsible for prolonged hospitalization, its effect on patient's outcome has not been adequately defined nor confirmed in several large EVAR reports.[2]

Data on the association of PIS and patient outcomes are scarce. In most studies, PIS is considered a well-tolerated, benign state; however, most of these reports did not prospectively study patient outcomes. Nano et al,[4] by retrospectively reviewing nearly 120 EVAR patients, found a worse quality of life in PIS patients during a mean follow-up of 4 years. Our group recently published the results of a prospective study investigating the relation of PIS with clinical outcome during the first month after EVAR.[5] We found that the intensity of inflammation, as assessed mainly by the high-sensitivity C-reactive protein (hs-CRP) levels, correlated with the occurrence of a cardiovascular or any other adverse event during the first month.[5] We also confirmed the results of two previous studies reporting that endografts made of polyester correlated with a stronger inflammatory response.[6,7]

In continuance to our previous report, the present study prospectively investigated the association of PIS with the clinical outcome of the patients during the first

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year after EVAR and assessed the evolution of the inflammatory response as outlined from the kinetics of specific inflammatory markers during that interval.

METHODS

All consecutive patients with AAA undergoing elective EVAR in our department from January 2010 to January 2013 were prospectively enrolled in this study protocol. The Institutional Review Committee approved the study. Exclusion criteria and the endovascular procedure were previously described in detail.[5]

The stent grafts implanted in the study patients were Endurant (Medtronic Inc, Santa Rosa, Calif), Anaconda (Vascutek, a Terumo company, Inchinnan, Scotland, United Kingdom), Zenith (Cook Inc, Indianapolis, Ind), Aorfix (Lombard Medical Technologies, Oxfordshire, United Kingdom), Powerlink (Endologix, Irvine, Calif), and Excluder (W. L. Gore & Assoc, Flagstaff, Ariz). The first four devices are made of polyester material, and the last two devices are made from expanded polytetrafluoroethylene (ePTFE). All patients were treated by the same surgical and anesthesiology team in a fully equipped operating room, with the patient under general anesthesia. Small transverse incisions were used for access to both femoral arteries.

All patients received antiplatelet therapy with aspirin (100 mg, once daily) for at least 3 weeks before 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 taking a statin, atorvastatin (20 mg, once daily) was initiated at the screening visit.

We defined PIS as the presence of fever (persisting body temperature >38°C lasting for >1 day during hospitalization) and leukocytosis (white blood cell [WBC] count >12,000/μL), with negative blood culture results. Outpatient follow-up was performed at 1, 6, and 12 months after surgery. All patients continued their medical treatment with statins and antiplatelets during the follow-up period.

Variables of interest. Demographics, risk factors, preprocedural and postprocedural medication, type of endograft, the occurrence of PIS, maximum temperature, perioperative complications, and hospital duration of stay were recorded for each patient. Adverse events included any major adverse 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 (MI; ST and non-ST), worsening of cardiac status needing intervention, ischemic stroke, and transient ischemic attack. 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 electrocardiogram changes, including development of new Q waves or new persistent ST-T segment or T wave changes.[8] Unstable angina was defined as severe chest pain lasting for at least 30 minutes, unresponsive to standard therapeutic intervention, and associated with transient ST segment deviation of ≥0.05 mV, new or T wave inversion of ≥0.3 mV, without development of Q waves, or creatinine kinase-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 >24 hours or leading to death, with no apparent cause other than that of a vascular origin.[9] Transient ischemic attack included brief episodes of neurologic dysfunction resulting from focal cerebral ischemia, not associated with a permanent cerebral infarction, lasting <24 hours.[10] Acute kidney failure was defined as impaired renal function according to the Kidney Disease Improving Global Outcomes clinical practice guidelines.[11]

Blood samples and laboratory markers. Venous blood was collected without a tourniquet preoperatively, at days 1 and 3 postoperatively, and at 1, 6, and 12 months after the procedure. Patients at the 1-, 6-, and 12-month visits with a history of a recently developed (<15 days) inflammatory disease were rescheduled for an appointment 2 weeks afterward. Besides the traditional inflammatory markers (WBC, hs-CRP, and fibrinogen) we also measured interleukin 6 (IL-6) because it was the only marker significantly altered in PIS patients in our preliminary study.[2] Details on measurement methods of the biomarkers have been previously described.[2,5]

Statistical analysis. Considering the lack of adequate data on the effect of PIS on the occurrence of events during the first year after EVAR, no reliable sample size calculation was feasible. On the basis of the PIS rates (nearly one-third of EVAR patients) as reported in the preliminary study of this group 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 to 70 patients) should have a relatively adequate size for estimation in events differences. Data are expressed as mean ± standard deviation or as median (range) for non-Gaussian parameters. Comparisons of continuous variables were performed by the Student *t*-test for normally distributed variables and by the Mann-Whitney *U* test for non-normally distributed variables. The χ^2 test was used for categoric 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 $P_1 = .25$ were identified. These were used in a binary logistic regression model. The formerly nonsignificant factors were then considered again at level $P_2 = .10$. Interactions between the main effects of the final model were examined. The enter method with significance level $P_3 = .05$ was used to obtain *P* values and odds ratios for the main effects and interactions. All analyses were performed with SPSS 20.0 software (IBM Corp, Armonk, NY).

RESULTS

The study included 182 patients (96% men) who were aged 72.4 ± 7.8 years. Stent deployment was technically

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

Variable[a]	*No PIS (n = 117)*	*PIS (n = 65)*	P
Age, years	72.2 ± 7.8	72.9 ± 7.8	.561
Male gender	112 (95.7)	62 (95.4)	.592
Body mass index, kg/m^2	28 ± 4.9	28.5 ± 5.5	.549
AAA maximum diameter, cm	5.8 ± 1	5.9 ± 1.2	.546
Risk factors			
Hypertension	111 (94.8)	60 (92.3)	.347
Coronary artery disease	57 (48.7)	39 (60)	.144
COPD	52 (44.4)	39 (60)	.07
Smoking	74 (63.2)	43 (66.2)	.411
Congestive heart failure	18 (15.4)	17 (26.2)	.08
Diabetes mellitus	24 (20.5)	15 (23.1)	.686
Hyperlipidemia	97 (82.9)	53 (81.2)	.483
Procedure characteristics			
Duration, min	111.2 ± 49.4	115.3 ± 52.6	.599
Contrast media, mL	166.3 ± 88.4	159.4 ± 116.5	.656
Radiation exposure, mGy	79.9 (67.1-116.5)	86.4 (67.5-141)	.884
Length of stay, days			
Hospital	3 (3-4.5)	6 (5-7)	<.001
Intensive care unit	0.2 ± 0.63	0.5 ± 1.3	.02
PIS characteristics			
Temperature max, °C	37.7 ± 0.7	38.5 ± 0.4	<.001
Temperature duration, days	0.7 ± 1.4	2.7 ± 1.3	<.001
WBC count max postoperative, $\times 10^3$/mL	10.1 ± 2.6	16 ± 3.9	<.001
hs-CRP max postoperative, mg/L	76.4 (41-122)	125 (96-181)	<.001

AAA, Abdominal aortic aneurysm; *COPD,* chronic obstructive pulmonary disease; *hs-CRP,* high-sensitivity C-reactive protein; *PIS,* postimplantation syndrome; *WBC,* white blood cell.
[a]Continuous data are presented as the mean ± standard deviation or median (range) and categoric data as number (%).

successful in all patients, with no intraoperative complications. PIS was diagnosed in 65 patients (35.7%). Baseline characteristics in patients with and without PIS are summarized in Table I. Traditional risk factors were equally distributed between the two groups. Five patients did not attend the 1-year follow-up visit but were reached by telephone.

Limb thrombosis occurred after EVAR in five patients, three in the PIS group and two in the non-PIS group, during the first month in four patients and during the fifth month in one. Endograft migration and type I endoleak occurred in one patient and was treated with an aortic cuff at 6 months after the initial procedure. A type II endoleak occurred at some point during the follow-up period in 26 patients (14.3%), 14 in the non-PIS group and 12 in the PIS group. The endoleak in 22 disappeared during follow-up. The type II endoleak in four patients remained at the 1 year visit but without any sac enlargement. There was no correlation of the endoleak or any complication rates with the occurrence of PIS (all $P > .05$).

Variables

WBC count. Baseline WBC levels were similar between the two groups ($P = .102$). There was a significant increase in WBC count in favor of PIS group at the postoperative period ($P < .001$). This difference remained statistically significant during the 1-year follow-up period at all time points until the end of the follow-up-period (Table II; Fig 1).

Platelet count. Baseline and postoperative platelet count levels were similar between the two groups ($P = .65$ and $P = 1$, respectively). The PIS patients had higher platelet count levels at 1 month after the procedure ($P < .001$); however, no significant difference was evident at 6 ($P = .22$) and 12 ($P = .99$) months between the two groups (Table II; Fig 1).

Fibrinogen. Concentration of fibrinogen did not differ significantly between the two groups at baseline ($P = .98$), postoperatively ($P = .12$), at 1 month ($P = .99$) and at 6 months ($P = .96$) after the procedure. Patients of the PIS group had significantly higher levels of fibrinogen at the first year than patients of the non-PIS group ($P = .006$; Fig 1).

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 ($P < .001$) and at 1 month ($P = .04$). These values returned to nearly baseline levels at 6 ($P = .99$) and 12 ($P = .99$) months (Table II and Fig 1).

IL-6. Baseline IL-6 levels were similar between the two groups ($P = 1$). At the postoperative period, the PIS patients had significantly higher levels of IL-6 than the non-PIS patients ($P < .001$). These levels were attenuated quite quickly, being similar between the two groups at 1 ($P = .43$), 6 ($P = .46$), and 12 months ($P = .17$) after the procedure (Table II; Fig 1).

Table II. Biomarkers according to postimplantation syndrome (*PIS*) arms

	WBC count, ×10³/mL			*Platelet count, ×10³/mL*		
Variable[a]	*Non-PIS*	*PIS*	P[b]	*Non-PIS*	*PIS*	P[b]
Preoperative	6.6 ± 1.5	7.7 ± 1.4	.102	207.1 ± 58.9	225.4 ± 54.2	.65
Postoperative	10.1 ± 2.6	15.9 ± 3.9	<.001	151.4 ± 52.4	149.7 ± 49.9	1
1 month	7.5 ± 1.6	9 ± 2.1	<.001	226.6 ± 68.1	271.3 ± 98.2	<.001
6 months	7.1 ± 1.4	8.2 ± 1.5	.01	204 ± 56	228.4 ± 58.9	.22
12 months	6.9 ± 1.6	8 ± 1.5	.02	205.7 ± 63.6	214.8 ± 52.8	.99
	Fibrinogen, mg/dL			*hs-CRP, mg/L*		
Preoperative	417 ± 109.4	442 ± 116.7	.98	3.2 (1.6-5.7)	4.6 (2.3-9.5)	1
Postoperative	555 ± 184.2	620 ± 178.8	.12	76.4 (41.3-122.5)	125 (96.2-182)	<.001
1 month	513 ± 144.1	528 ± 162.3	.99	4.8 (2.6-9.8)	12.5 (5.7-26.1)	.04
6 months	413 ± 107.2	438 ± 138.9	.96	3 (1-4.7)	4.4 (2.4-7.4)	.99
12 months	371 ± 106.1	449 ± 137.1	.006	2.1 (1-3.9)	2.9 (1.6-9)	.99
	IL-6, pg/mL					
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)	<.001			
1 month	22.4 (7.1-54.9)	22.8 (7.9-71.2)	.43			
6 months	10 (5.5-35.2)	27.4 (7.5-68.9)	.46			
12 months	8 (4.6-22.9)	21.7 (6.2-64.5)	.17			

hs-CRP, High-sensitivity C-reactive protein; *IL-6,* interleukin 6; *WBC,* white blood cell.
[a]Values are expressed as mean ± standard deviation, except for non-normally distributed parameters, which are shown as median (interquartile range).
[b]*P* values indicate between-group analysis.

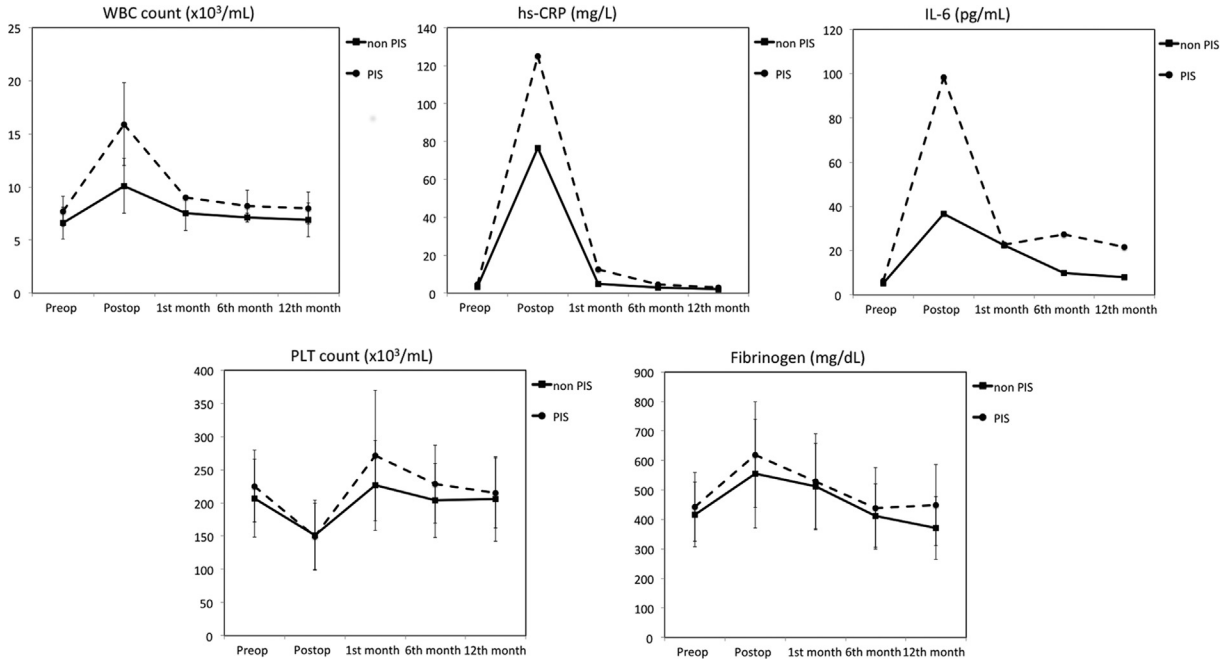

Fig 1. Graphic representation of the mean measures of white blood cell (*WBC*) count, platelets (*PLT*) count, fibrinogen, and median values of high-sensitivity C-reactive protein (*hs-CRP*) and interleukin 6 (*IL-6*) in the group with (*solid line*) and without (*dashed line*) postimplantation syndrome (*PIS*). The *error bars* show the standard deviation.

Graft material and inflammation

A total of 108 endografts (59.3%) were made of polyester, and 74 (40.7%) were made of ePTFE. Endografts made of polyester had significantly higher rates of PIS development compared with endografts made from ePTFE (52.7% vs 10.8%; $P < .001$). Inflammation, as determined by the WBC count, hs-CRP levels, and IL-6 concentration, was significantly higher at the postoperative period

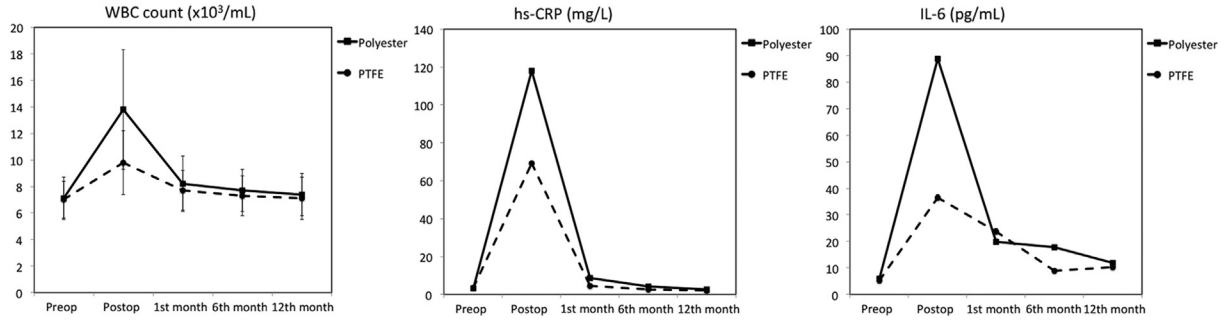

Fig 2. Graphic representation of the mean (*error bars* show the standard deviation) measures of white blood cell (*WBC*) count and median values of high-sensitivity C-reactive protein (*hs-CRP*) and interleukin 6 (*IL-6*) according to polyester (*solid line*) and expanded polytetrafluoroethylene (ePTFE; *dashed line*) material.

in patients receiving an endograft made of polyester (WBC count, $P < .001$; hs-CRP, $P < .001$; IL-6, $P = .009$). All of these inflammation markers attenuated, with no differences observed between the two groups of different graft material at 1, 6, and 12 months after the procedure (Fig 2).

Influence on 1-year outcome

MACE. A MACE occurred during the first 30 days in three of 117 patients (2.6%) in the non-PIS group and in 12 of 65 patients (18.4%) in the PIS group ($P < .001$). One patient of the PIS group died at day 20 in the cardiac unit after a severe acute MI. During 1 to 12 months of follow-up, a MACE was recorded in 16 (8.8%) of the remaining 181 patients: 11 of 64 patients (17.2%) in the PIS group and five of 117 (4.3%) in the non-PIS group ($P < .001$). Three patients in the PIS group died of a cardiac-related cause (2 patients sustained a fatal acute MI and 1 patient had severe heart failure) at 5, 10, and 10 months after surgery, respectively; four patients had a nonfatal acute MI, and two patients sustained an ischemic stroke (one fatal). Two patients required a cardiac intervention for unstable angina and worsening of their cardiac status. In the non-PIS group, three patients had an acute MI (one fatal), and two 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% confidence interval, 1.5-13.8; $P = .007$) more likely to suffer a MACE than non-PIS patients.

Adverse events. During the first 30 days, four of 117 patients (3.4%) in the non-PIS group had an adverse event compared with 17 of 65 patients (26.2%) in the PIS group ($P < .001$). During 1 to 12 months of follow-up, an adverse event was recorded in 18 of the 181 patients (9.8%): 12 of 64 patients (18.8%) in the PIS group and six of 117 patients (5.1%) in the non-PIS group ($P < .001$). In the PIS group, a MACE occurred in 11 patients, and one patient presented with acute renal failure 10 months after the procedure. In the non-PIS group, five patients presented with a MACE and one with acute renal failure at 6 months. Multiple logistic regression analysis showed that the occurrence of PIS was the only independent predictor of an adverse event during the follow-up period. More specifically, patients diagnosed with PIS after the implantation were about 4.51-times (95% confidence interval, 1.5-11.7, $P = .005$) more likely to suffer an adverse event than non-PIS patients.

DISCUSSION

EVAR has been proposed as a minimally invasive alternative to conventional aneurysm resection.[12,13] 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.[14,15] However the risk of a severe inflammatory response of the endovascular aortic repair was thought to be lower than that of an open repair.[14,15]

Recent reports have mentioned that endovascular procedures may initiate PIS, a systemic inflammatory response. The relation of PIS with patient outcomes has not been well established. Moulakakis et al[7] reported no perioperative clinical adverse events in 87 patients after EVAR without, however, providing any clear definition on the events or a detailed description regarding the duration of hospitalization, monitoring, and follow-up of the patients during the first month.[7] Nano et al,[4] by retrospectively studying 118 patients after the use of Anaconda endograft (Sulzer Vascutek, Bad Soden, Germany), did not find any correlation between the presence of PIS and the occurrence of long-term complications, although the definition of the events was too "wide," including endoleaks, renal failure, limb thrombosis, and death of any cause, while, oddly, only one patient sustained a MACE during a 4-year follow-up period. In the same study, the analysis of quality of life surveys showed that patients who had PIS after surgery felt significantly more limited in performing their daily physical activities and were more emotionally discouraged and depressed/anxious about their state of health than the group that did not develop PIS.[4]

In a previous prospective study, our group found that patients with PIS were more likely to sustain an adverse event during the 30 days after the procedure, while the intensity of inflammation, as assessed mainly by the postoperative hs-CRP values, correlated with the presence of such events.[5] The present study found PIS was 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 sustaining an adverse event than non-PIS patients, even after the first month, and may require closer surveillance during the first year.

In addition, these findings have to be considered together with the fact that the benefit from EVAR regarding lower short-term mortality compared with open surgical repair did not persist at the intermediate- and long-term follow-up period as the Comparison of Endovascular Aneurysm Repair with Open Repair in Patients with Abdominal Aortic Aneurysm (EVAR) and Dutch Randomised Endovascular Aneurysm Management (DREAM) trials have shown.[12,13] In fact, even meta-analyses have shown that EVAR and open surgical repair were both associated with similar incidences of cardiac deaths and fatal stroke rate in the long-term despite the minimal invasiveness of EVAR.[16,17]

That inflammation can lead to serious cardiovascular events is well known.[18] 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? Concluding this from the findings of this study is difficult, 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 being considered a minimally 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).[19] 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 compared with 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, whereas only the WBC count remained different, although within the normal reference range.

The WBC count represents a simple marker of inflammation that has been related to prediction of future cardiovascular events in several different populations.[20,21] The rise in the WBC count, even within the normal range, is of particular concern. A recent retrospective study found a strong correlation between an increased preoperative WBC count within the normal range and the risk of major adverse events and death after endovascular interventions.[22] In the present study at the end of the follow-up period, the count for both groups was within the normal range, with the values in the PIS group being at the upper limit of normal threshold. Overall, the inflammatory process associated with the endograft implantation seem to be attenuated after the first month and that the severity of the inflammatory activation as depicted from several inflammatory biomarkers shows a decline toward the normal levels at the end of first year.

EVAR has been related to coagulation disturbances due to aneurysm sac thrombosis or to direct platelet stimulation by the endograft material.[23] Many studies have reported a significant decrease in the platelet count, an indirect index of platelet activation and consumption during the postoperative period after EVAR.[7,24] Nano et al[4] found that this decrease was significantly more pronounced in patients who experienced PIS. However, the incidence of PIS in this study was associated with a longer duration of the procedure and a greater preoperative thrombus thickness.[4] On the one hand, no statistical differences in platelet count between the two groups was evident in the present study at the immediate postoperative or at the conclusion of the follow-up period. On the other hand, elevated levels of fibrinogen, a biomarker that has a crucial role in inflammation and coagulation, have been reported in patients with AAA.[25] Aho et al,[26] by comparing hemostatic mechanisms in AAA patients after open surgery and EVAR, found a significant rise in fibrinogen levels at the third postoperative day after EVAR. These levels, however, diminished at postoperative day 7 and returned at the baseline levels at the third 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 than non-PIS patients. This finding may have some clinical implication, because fibrinogen has been considered an independent risk marker for the prediction of the first cardiovascular event.[27] 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.

In our previous report, the use of polyester endografts was associated with a >10-times higher risk for an inflammatory response.[5] Similar findings have also been confirmed by other two studies.[6,7] In the present report 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.

The results of the present study certainly raise the question of whether we should alter our approach and treat patients with PIS by focusing on the reduction of the inflammatory response. Published pertinent data are scarce. Motte et al[28] published recently a prospective trial of 150

EVAR patients who were randomized to receive a single preoperative dose of methylprednisolone or placebo. The inflammatory response, as assessed by the inflammatory biomarkers levels, was reduced in the methylprednisolone group, although no differences were noted in patient outcomes between the two groups during a 3-month follow-up period. Data on postoperative use of anti-inflammatory drugs are absent. Still, nonsteroidal anti-inflammatory drugs have been associated with increased cardiovascular morbidity and mortality and therefore cannot be easily provided.[29] Nevertheless the present study has shown that 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, although all EVAR patients, including those in the present report, are usually under statin treatment at the time of operation. Because 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 postoperative period could probably affect the cardiovascular health of these patients at the long term. The sustained levels of WBC count in the PIS patients toward the upper limit of the normal threshold during the first year follow-up might have something to do with that.[22] That therapeutic measurements might thus focus on PIS acute treatment or even prevention seems reasonable. Future studies should emphasize a better understanding of the causes of the inflammatory response as well as evaluating the prompt treatment of patients with PIS with anti-inflammatory drugs from the first postoperative day.

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 should be acknowledged. Blood samples for five patients were not obtained at some time point, although 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.

This was not a randomized trial, although graft selection was based strictly on anatomic criteria and not on any characteristic of the inflammatory response. 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.

CONCLUSIONS

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.

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AUTHOR CONTRIBUTIONS

Conception and design: EA, GK, NP, HM, VK, MM
Analysis and interpretation: EA, GK, NP, KG, MM
Data collection: GK, NP
Writing the article: EA, GK, NP, MM
Critical revision of the article: EA, GK, HM, VK, MM
Final approval of the article: EA, GK, KG, HM, VK, MM
Statistical analysis: GK
Obtained funding: MM
Overall responsibility: MM

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