The short and medium term effects of Endovascular Aneurysm Repair (EVAR) on coagulation, fibrinolysis and renal function in patients with Abdominal Aortic Aneurysms

By

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Abstract

Background:

Previous reports described activation of the haemostatic mechanism in patients with abdominal aortic aneurysm (AAA). Both open and endovascular repair of AAA have been found to affect the haemostatic markers. Cystatin C is an endogenous marker of renal function that may be more sensitive for detecting mild to moderate reduction in glomerular filtration rate (GFR). High cystatin C has been shown to be strongly associated with cardiovascular outcomes in different clinical scenarios.

Aim:

To establish the medium term effects of endovascular and open aneurysm repair on coagulation and fibrinolysis. In addition to that, to explore the effect of endovascular repair on renal function using Cystatin C.

Patients and Methods:

Twenty-nine patients completed the twelve months follow up after endovascular aneurysm repair (EVAR), eleven patients were recruited after they had open aneurysm repair (OAR) and eight age-matched control (AMC) without AAA, as documented by CT scan, were recruited. Patients were tested for markers of coagulation, fibrinolysis and renal function pre-operatively and at 1, 6 and 12 months post-operatively.

Results:

Pre-operatively, PF1+2 levels were significantly higher in patients with AAA than in AMC. PF1+2 levels post-EVAR and post-OAR were significantly lower than pre-operative values and similar to AMC. There was no significant difference in TAT, PAI, or t-PA between AMC, AAA preoperatively, and post-EVAR. Post-OAR, PAI activity was significantly higher than in pre-operative patients.

At 24 hours after procedure, a significant increase in Cystatin C and serum creatinine (sCr) and significant decrease in eGFR were seen. Cystatin C continued to increase and was significantly higher at 1, 6 and 12 months. Cystatin C increased significantly post-operatively regardless of the baseline renal function. None of the patients required renal replacement therapy.

Conclusion:

AAA is associated with increased thrombin generation without up-regulation of fibrinolysis. The pro-thrombotic, hypo-fibrinolytic diathesis observed in patients with AAA returns toward normal in the medium term after EVAR and OAR.

EVAR is associated with a significant increase in Cystatin C starting 24 hours after the procedure and is maintained for 12 months. sCr and eGFR only show significant change at 24 hours and therefore may underestimate long-term renal damage after EVAR.

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Dedication

To my wife, Heba, and my children; Farida, Jana and Noor, for their unlimited love, support and patience.

To my parents for their continuous love and endless support.

Declaration

I carried out the work in this research while working as Clinical research fellow at the vascular units at University Hospital Birmingham and Heartland Hospital. I was a research fellow at University of Birmingham as well during the same time. The work described in this thesis is my own. I was deeply involved in the design of the research work and writing the protocol. I carried out patient recruitment, data collection, sample handling, processing and storage. The laboratory work using the ELISA machine was performed in the Haematology department at Heartland Hospital. I did the statistical analysis of the data and results after seeking advice from Dr Peter Nightingale. The thesis has not been submitted in candidature for any other degree, diploma or professional qualification.

I have presented the finding of this research in four national conferences, one international conference and several regional meetings. I have published three papers as first author and two as second author in high impact vascular journals.

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List of Abbreviations:

AAA	Abdominal Aortic Aneurysm
AAAQIP	Abdominal Aortic Aneurysm Quality Improvement Programme
AKI	Acute kidney injury
AMC	Age-matched controls
APC	Activated protein C
APC-PCI	Activated Protein C-protein C Inhibitor complex
ATIII	Antithrombin III
B-EVAR	Branched EVAR
CEUS	Contrast enhanced ultrasound
CKD	Chronic kidney disease
CKD-Epi	Chronic Kidney Disease Epidemiology
COPD	Chronic obstructive airway disease
CrC	Creatinine clearance
CT	Computerised Tomography
CVD	Cardiovascular disease
Cyst C	Cystatin C
DIC	Disseminated Intravascular Coagulation
EC	Endothelial cell

eGFR	Estimated glomerular filtration rate
EUROSTAR	European Collaborators on Stent–graft Techniques for Aortic Aneurysm Repair
EVAR	Endovascular Aneurysm Repair
F-EVAR	Fenestrated EVAR
FM-F	Fibrin Monomer-Fibrinogen complex
GFR	Glomerular filtration rate
HF	Heart Failure
HMWK	High-molecular-weight kininogen
hr	Hour
hs-CRP	highly sensitive C-reactive protein
HT	Hypertension
IHD	Ischaemic heart disease
IL	Interleukin
IMA	Inferior mesenteric artery
IQR	Inter-quartile range
IR	Infra-renal fixation
LV	Left ventricular
MDRD	Modification of Diet in Renal Disease
MI	Myocardial infarction

OAR	Open aneurysm repair
PAI	Plasminogen activator inhibitor
PF1+2	Prothrombin Fragments 1+2
Plt	Platelets
Pre-op	Pre-operative
PS	Proteins
PVD	Peripheral vascular disease
RBC	Red blood cell
RF	Renal function
sCr	Serum Creatinine
SD	Standard Deviation
sE-selec	Soluble E-selectin
sP-selec	soluble P-selectin
SR	Supra-renal fixation
t-PA	tissue plasminogen activator
TAFI	Thrombin activatable fibrinolysis inhibitor
TAT	Thrombin-antithrombin III-complex
TF	Tissue Factor
TFPI	Tissue factor pathway inhibitor
TM-IIa	Thrombo-modulin-thrombin complex
UK	United Kingdom

US	United States
vWF	Von-Willebrand factor

Chapter 1

General background 1

1.1 Abdominal Aortic Aneurysm: Prevalence and risk of rupture:

Abdominal Aortic Aneurysm (AAA) is a leading cause of death worldwide. In the United States (US), AAA occurs in an estimated 5%–7% of the population older than 60 years of age, often as an unrecognized disease.(1) The prevalence of AAA may be falling in the United Kingdom (UK); however, the condition remains relatively common in patients over the age of 65 years.(2) AAA often remain asymptomatic and undetected until rupture occurs and, despite advances in surgical and anaesthetic techniques, most patients with ruptured AAA die of the condition, often before they reach hospital.(3)

The risk of aneurysm rupture is related to AAA diameter and repair is indicated in aneurysms measuring 5.5 cm or more.(2) This is because the risk of aneurysm rupture is higher for AAA more than 5.5 cm in diameter.(4) Aneurysm rupture accounts for 4000 deaths every year in England and Wales.(5) AAA is the 15th leading cause of death overall in the United States and the 10th leading cause of death in men older than age 55, with approximately 9,000 AAA-related deaths occurring annually.(1, 6)

The presence of an AAA is strongly associated with atherosclerotic cardiovascular disease (CVD).(7) The latter is primarily responsible for the annual mortality rate of 5% in men with a small AAA.(4) The cardiovascular risk is both proportional to aortic diameter and independent of baseline CVD and conventional atherosclerotic risk

factors.(8-10) The risk of death in men with a small AAA principally relates to CVD, not aortic rupture. The nature of this risk is currently unexplained.

There is an association between deranged haemostatic markers and cardiovascular morbidity. Activated coagulation leads to the development of micro-vascular and macro-vascular thrombosis resulting in myocardial infarction, multiple organ failure and thrombo-embolism.(11-13) The level of coagulation dysfunction is related to old age, smoking and the presence of peripheral atherosclerosis.(14-16)

Previous studies found activation of the haemostatic mechanism in patients with AAA.(17-19) This has been found to correlate with aneurysm size.(20) However, high fibrin turnover was found in patients with small abdominal aortic aneurysm as well. The intra-mural thrombus plays an important role in maintaining the coagulation activity through fibrin generation and turnover in the thrombotic mass.(21) Positive correlation was found between the thickness of the thrombus in AAA and activation of blood coagulation and fibrinolysis activity.(12, 13, 22)

Major surgery results in a peri-operative pro-thrombotic diathesis as well as deranged fibrinolysis and platelet hyperactivity. This results in elevated levels of factor VIII, fibrinogen, thrombin-antithrombin III-complex (TAT) and Von-Willebrand factor (vWF).(23-28) Patients undergoing elective open infra-renal AAA repair have an associated operative mortality rate of 3-10%.(29-33) The majority is probably secondary to micro- and macro- vascular thrombosis causing myocardial injury, thrombo-embolism and multiple organ failure.(34)

The Abdominal Aortic Aneurysm Quality Improvement Programme (AAAQIP) was initiated after the UK was found to have a high outlying mortality rate for AAA surgery

at 7.9%, compared to the rest of Europe at 3.5%. The aim was reducing elective AAA mortality in the U.K to 3.5% by 2013.

1.2 Endovascular Aneurysm Repair:

EVAR was first performed by the Ukrainian surgeon Nicholas Volodos in 1987. However, it was the publication by Juan Parodi in 1990 (35) that EVAR had been widely promoted as providing a less invasive and safer alternative treatment option to conventional open repair of AAA, especially in the high risk patients. It is now well established, following the publications of EVAR-1, EVAR-2, DREAM, OVER and ACE trials, that endovascular repair of AAA reduces operative mortality by approximately 60% compared with open surgical repair in the fit and anatomically suitable patient.(36-41)

However, EVAR have been found to promote a systemic inflammatory response and pro-thrombotic coagulopathy equal if not greater than that witnessed after open surgical repair. It has been suggested that this could be secondary to cytokine release from thrombus within the aneurysm sac either as a result of the introducer and catheter manipulation or, possibly, ischaemia after AAA exclusion.(42-44)

Exponents have argued that the initial operative mortality benefits encountered with EVAR are offset by the long term economic cost due to secondary technical complications.(45)

1.3 Endoleak:

Endoleak is the outflow and leak of blood outside the endovascular stent graft but still within the aneurysm sac.(46) It is a specific complication to EVAR and results in restoring blood flow within the aneurysm sac resulting in perfusion of the aneurysm sac with the subsequent risk of rupture. The majority of cases are caused by the back flow from the IMA and/or lumbar arteries leading to incomplete exclusion of the sac form the systemic circulation. The long term outcome and durability of EVAR are dependent on the incidence and type of endoleak as well as graft migration. Both complications are the most common complications after EVAR and could represent an obstacle to establish EVAR as a durable alternative treatment option to open surgical aneurysm repair.(47) The EVAR-1 trial reported 22% (118 cases) of EVARs were complicated by endoleak and 35% required a secondary procedure to maintain complete aneurysm exclusion within 3 years of the procedure. A systemic review by Drury et al reported 17.5% and 21.3% of all EVAR procedures demonstrated endoleak at 30 days and 12 months respectively.(48)

1.3.1 Types of Endoleak:

Endoleak is classified into five types according to the source of blood leak inside the aneurysm sac that causes continued perfusion of the aneurysm sac.

1.3.1.1 Type I endoleak

This occurs due to inadequate seal at the top and/or the bottom of the stent graft to the aortic or iliac artery wall. If there is inadequate fixation at the proximal end, this represents type IA and if the leak occurs at the distal end of the stent graft, this indicates type IB. This leads to continued sac perfusion as a result of the inadequate

fixation and seal resulting in increasing the pressure inside the aneurysm sac. This type of endoleak is dangerous and inevitably requires further intervention as it carries high risk of aneurysm sac rupture as it seldom resolves spontaneously. In the majority of cases, endovascular intervention is usually enough to correct the problem. However, if endovascular treatment is not feasible, open surgical intervention may be necessary.

1.3.1.2 Type II endoleak

This is the most common type and it is considered a benign condition. The continuous perfusion of the residual AAA sac occurs due to leak from one or more patent vessels that normally arise from the abdominal aorta. Lumbar arteries are the most common source of type II endoleak. However, inferior mesenteric artery (IMA) is identified as another source of this kind of endoleak. Back flow of arterial blood through a patent artery inside the aneurysm sac provides the inflow to the residual AAA sac. If there is another patent artery, it serves as the outflow vessel. The majority of type II endoleak do not require intervention as they do not result in increase in the sac pressure or size and they usually resolve spontaneously. Sildof et al has concluded that rupture secondary to an isolated type II endoleak is rare (< 1%), but over a third occur in the absence of sac expansion. Translumbar embolization has a high success rate in treating this type of endoleak.(49, 50)

1.3.1.3 Type III endoleak

It occurs when there is disarticulation or separation of one or more modular components of the stent-graft. It also happens due to fracture of the stent graft resulting in significant reperfusion of the residual aneurysm sac. This could be due to

a functional fault of the graft or insufficient seal between the different stent grafts used to exclude the aneurysm sac. This type does require urgent treatment due to the high risk of aneurysm rupture associated. It does not resolve spontaneously and endovascular intervention is the usual and most successful treatment option.

1.3.1.4 Type IV endoleak

This type is significantly less common than it has been in the past as a result of manufacturer improvements in fabric composition. It results from high porosity of the graft fabric that causes leak of blood through the fabric resulting in perfusion of the residual sac. This type usually occurs once the stent graft is inserted and it usually settles within days and seldom requires further intervention.

1.3.1.5 Type V endoleak

This type is also known as endotension. It happens when there is continuous expansion of the residual aneurysm sac in absence of an identifiable source of endoleak. In this type, no endoleak is identified through the available imaging modalities. Despite that, the aneurysm sac continues to increase in size. Some believe this type is actually one of the previous four types while there is failure in demonstrating the type and source of the endoleak.(47) Failure of the detection of the endoleak by the available imaging tools with the continuous perfusion of the sac result in high pressure within the sac with the increase in size.(51, 52) Other explanations include filtration of serous fluid ultra-filtrate through the graft fabric back into the aneurysm sac.(53, 54) The treatment of type V endoleak depends on the cause and it is individualized.

1.4 Surveillance after EVAR:

Long term surveillance of patients following EVAR is essential for (i) detection and characterization of endoleak; (ii) detection of increase or decrease of the residual aneurysm sac by measuring the aneurysm sac size and detection of significant alteration in aneurysm sac dimensions; (iii) detection of mechanical complications of the stent-graft, such as migration, kinking, or fracture; and (iv) assessment of the long-term outcome and performance of the stent grafts.

At present contrast-enhanced spiral Computerised Tomography angiography (CTA) scan with specialized 3D reconstruction is considered as the gold-standard for endoleak surveillance.(55) CTA is efficient in defining the anatomy of aneurysm sac, detection of endoleak and its classification. However, factors such as a high dose of radiation with risk of malignancy (56), administration of nephrotoxic contrast (57) and high cost (58) are the main limitations of its use as a lifelong surveillance tool. For these reasons the short term peri-operative mortality/morbidity benefits of EVAR may be outweighed by its long term economic and resource burden to the institution, in addition to the increased risk of malignancy associated with frequent x-ray exposure.

Duplex ultrasound is being investigated as an alternative to CT for the follow-up of EVAR patients. This modality is less expensive and does not carry the risks associated with ionizing radiation or contrast induced nephrotoxicity. Duplex ultrasound with non-nephrotoxic contrast agents have been used to detect post-EVAR endoleak.(59, 60) In their meta-analysis, Mirza et al found that the unenhanced duplex ultrasound has poor sensitivity for endoleak detection; however contrast enhanced ultrasound (CEUS) is a highly sensitive modality.(61)

Despite the advancement in imaging modalities to follow up EVAR, plain radiography continues to be used in basic post-EVAR surveillance. Some still believe that plan X-ray is superior to CT for demonstrating the conformation of thoracic stent-grafts (62) and for detection of kinks in abdominal stent-grafts.(63) Plain X-ray usually requires four views to cover all the angles of the stent grafts. Antero-posterior and lateral pictures can identify stent-graft migration and component separation and oblique radiographs may detect of stent fracture. However, plain radiography does not have any role in diagnosis or identification of endoleak or sac expansion.

1.5 Supra-renal Fixation of EVAR:

Successful EVAR requires proximal seal of the endograft to prevent stent migration and Type 1a endoleak. Unfavourable features of the infra-renal aortic neck, e.g. severe angulation, short neck length, cone shaped neck, presence of thrombus or calcification, may adversely affect the long term outcome of EVAR.(64) To overcome the unfavourable morphological anatomy of infra-renal neck, supra-renal (SR) fixation has been proposed as an option to provide safe and more secure form of proximal fixation which will lead to increase the number of patients eligible for standard EVAR. SR-EVAR shows bare stents crosses the renal arteries in comparison to infra-renal (IR) fixation in which no stents crosses the renal arteries.(65)

Dilatation of the infra-renal neck, which could lead to endograft migration, has been reported following EVAR.(66-73) The advantage of SR-EVAR is providing more durable fixation in the supra-renal portion of the aorta. This part of the aorta is less susceptible to aneurysm disease.(74, 75) Although several studies have reported the effectiveness of SR-EVAR (76-79), concern persists regarding the long term effect on renal function and the patency of renal arteries when the renal artery origins are crossed by the bare stents. Miller et al conducted a systematic review and meta-analysis of 21 studies representing more than 4000 patients to determine the effect of SR-EVAR and IR-EVAR on renal function. They concluded that there is no risk of post-operative following both modalities especially with the newer devices. They suggested long term studies to look at the long term effect of supra-renal fixation on renal function. (80)

1.6 Fenestrated EVAR:

Juxta-renal AAAs are those with either a very short or no infra-renal neck. A suprarenal cross-clamp would be needed to enable open repair of the AAA with or without implantation of one or more renal arteries. Data from the European Collaborators on Stent–graft Techniques for Aortic Aneurysm Repair (EUROSTAR) registry indicate that EVAR for aneurysms with an infra-renal neck length of less than 15 mm are associated with a significantly increased risk of proximal endoleak.(81) The minimum length of good-quality infra-renal aortic neck necessary to secure a safe and durable seal is 10 mm. Therefore, in the endovascular era, a juxta-renal aortic aneurysm could be redefined as an aneurysm with an infra-renal neck of less than 10 mm. In order to achieve endovascular proximal seal in juxta-renal AAAs, the use of a customized stent-graft design including fenestrations for the aortic side branches above such a short neck (i.e. the renal arteries and the superior mesenteric artery) is necessary. This enables the first sealing portion of the stent-graft to be positioned in a more stable part of the aorta with the customized fenestrations at the exact origin of the targeted vessels. This approach, Fenestrated EVAR (F-EVAR), makes it possible to treat patients with short necks and perhaps patients with juxta-renal aneurysms.(82-84) A number of published series have demonstrated excellent early and mid-term results of the technique and confirmed the potential lower peri-operative mortality of the technique in comparison with open repair. However, these studies acknowledge the lack of longer-term data.(85-91)

Another group of patients, who benefit from F-EVAR, are the patients who develop complications following open aneurysm repair (OAR) or EVAR. These complications include true juxta-anastomotic aneurysms and pseudo-aneurysms following open

repair and type I endoleak following EVAR.(92-94) These complications carry significant risk of rupture and subsequent mortality if left untreated.(93) In one series of patients with para-anastomotic aneurysms (PAA), emergency repair resulted in a 24% mortality, repair after rupture in 67% mortality, and elective repair carried an 11% mortality.(95) The utilization of F-EVAR and branched EVAR (B-EVAR) has increased the percentage of patients with PAAs after open surgery that could be offered an endovascular treatment option. However, the unique difficulties of increased graft on graft friction hindering placement, short working distance, and increased patient co-morbidities should be recognized.(96, 97)

One series reported their 8-year experience of F-EVAR with one hundred patients treated during the study period with median follow-up 24 months. This included 16 patients after previous open surgery or EVAR. Thirty-day mortality and intra-operative conversion to open repair was 1% for each. Operative visceral vessel perfusion rate was 98.9%. Twenty-two patients died during follow-up, all aneurysm unrelated. No aneurysm ruptured. Cumulative visceral branch patency was 93.3 ± 1.9% at 5 years. Visceral artery stent occlusions all occurred within the first 2 postoperative years. Four renal artery stent fractures were observed, of which three were associated with occlusion. Twenty-five patients had an increase of serum creatinine (sCr) of more than 30%; two of them required dialysis.(98)

Chapter 2

General Background 2

2.1 Normal Haemostasis:

Haemostasis enables an organism to (i) close off damaged blood vessels, (ii) keep the blood in a fluid state, and (iii) remove blood clots after restoration of vascular integrity. The haemostatic system is highly conserved machinery in which blood clotting, also referred to as coagulation, has a prominent role.(99)

Normal circulation requires the blood to flow in a fluid state in equilibrium not to be very thin with the risk of spontaneous bleeding and not thick to develop blood clot. The normal haemostatic response to vascular injury is the development of clot to seal the site of injury and stop the bleeding. With vascular injury, there is damage to the endothelium that activates the coagulation cascade. First, there is adhesion of the platelets to the endothelium leading to the formation of platelet plug, at the site of injury, and the formation of fibrin mesh on top of that plug. The migration of leukocytes to the site of vascular injury is facilitated by chemokines to protect the wound from infection and aides in the healing process. The fine line between formation of clot to seal the vascular injury in normal healthy individuals and the excessive formation of clot causing thrombo-embolic complications should be continuously regulated.

The normal endothelium is anti-thrombotic. However, at the site of injury, tissue factor is released causing activation of the coagulation cascade resulting in the formation of fibrin. At the same time, the fibrinolytic mechanism is activated to limit

the deposition of fibrin to the site of injury, blocking excessive activation of the coagulation cascade.

Dys-regulation of the haemostatic mechanism is the main drive of thrombus formation. There are many factors that can contribute to the over expression of the coagulation enzymes including genetic and environmental factors.(100)

2.2 The Blood Coagulation Cascade:

The coagulation cascade is formed of two main pathways. The intrinsic pathway which is also known as the contact pathway and the extrinsic pathway which is called the tissue factor (TF) pathway (Figure 1). Recent evidence has disputed the formerly believed idea of equal importance of the two pathways. The main function of the intrinsic (contact) pathway is to augment the coagulation cascade stimulated by the TF pathway. The activation of factor IX can be achieved by both pathways.

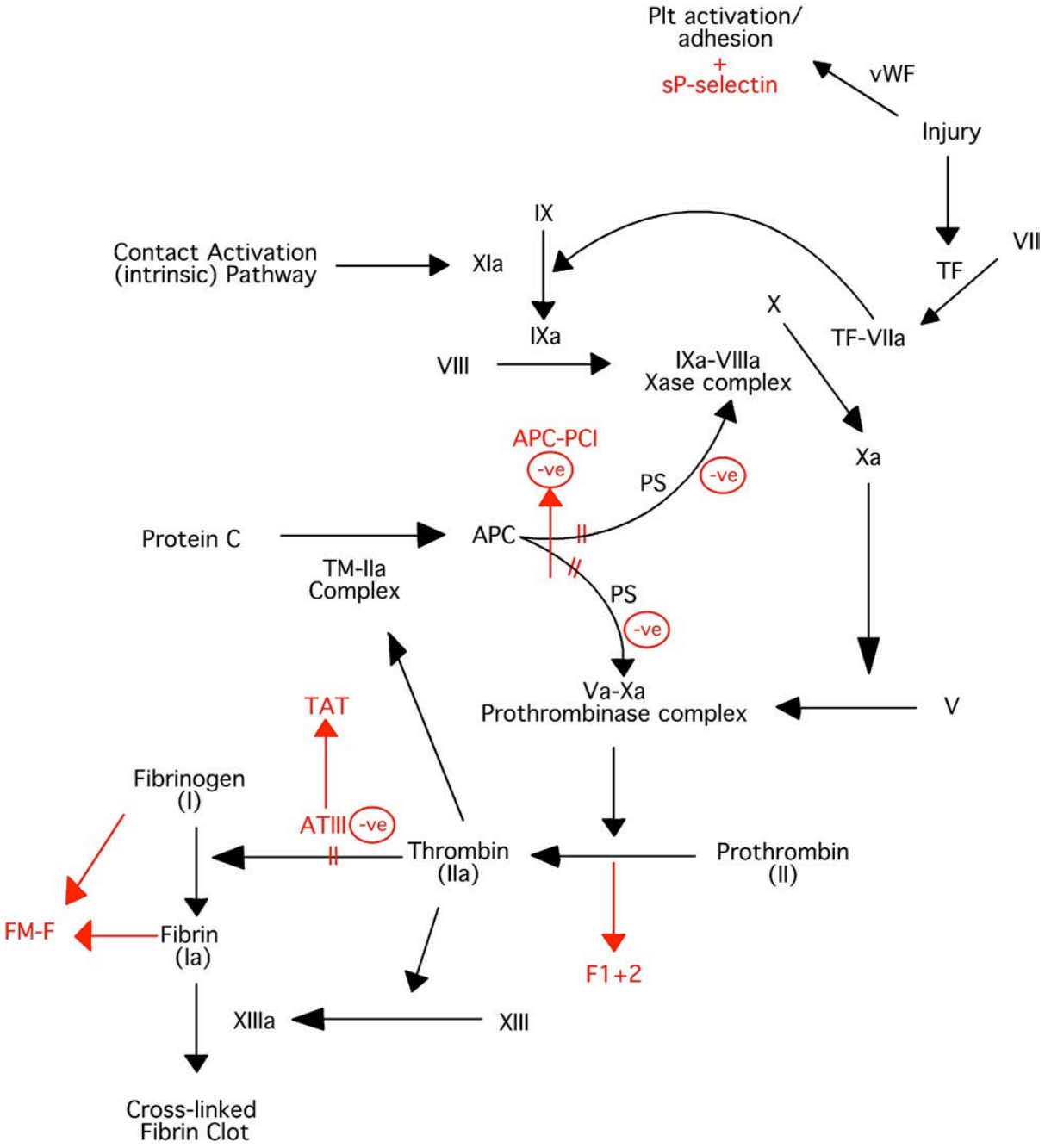


Figure 1: Coagulation cascade.

APC, Activated protein C; APC-PCI, activated protein C-protein C inhibitor complex; ATIII, antithrombin III; F1+2, prothrombin fragments 1+2; FM-F, fibrin monomer-fibrinogen complex; Plt, platelets; PS, proteins; SP-selectin, soluble P-selectin; TF, tissue factor; TM-IIa, thrombo-modulin-thrombin complex; TAT, thrombin-antithrombin complex; vWF, von Willebrand factor.

2.2.1 Extrinsic/tissue factor pathway:

TF, which is an active cofactor, triggers the extrinsic pathway when it comes in contact with plasma containing activated or inactive factor VII.(101) TF is not produced inside cells that come in contact with plasma except at time of vascular injury. Then TF can bind to factor VII resulting in the production of TF-VIIa complex. When attached to the cell membrane, this complex is a powerful activator of the coagulation cascade. Furthermore, TF can produced by monocytes and smooth muscle cells in response to cytokines and inflammatory mediators.(102)

Factor VII is a typical vitamin-K-dependent plasma protein that is produced in the liver. The vast majority of factor VII is inactive with only 1% is present as an activated factor VIIa which is a weak enzyme when not part of the TF-VIIa complex. Factor VII abundance has been linked with thrombotic conditions, while its deficiency is a rare condition in which major bleeding could happen (103-107)

A recombinant activated human factor VII produced by transfection of the human factor VII gene is available (Novo-Seven). Its indication is for promoting haemostasis in individuals with haemophilia who have antibody inhibitors to coagulation factors VIII or IX, patients with acquired haemophilia, patients with congenital factor VII deficiency and for treatment Glanzmann's thrombasthenia.

2.2.2 Intrinsic/Contact pathway:

The intrinsic pathway is activated when blood comes into contact with a negatively charged surface resulting in the activation of factor XII. Despite that, factor XII deficiency is not associated with bleeding and may even be associated with thrombosis.(108) The intrinsic pathway causes activation of factor IX. Activation of factor XII (Hageman factor) is produced secondary to the binding to an artificial or negatively charged surface. XIIa activates prekallikrein and factor XI leading to the formation of kallikrein and XIa.(100) Active factor IX (IXa) is produced due to cleavage of High-molecular-weight kininogen (HMWK).(109)

The manifestations of intrinsic pathway deficiency vary whether in vitro or in vivo. In vitro, it causes prolonged partial thromboplastin time. However, it does not cause bleeding in vivo except for factor XI, which causes mild bleeding following trauma or injury.(110) It is suggested that factor XI is essential for the production of thrombin and down-regulation of fibrinolysis via thrombin activatable fibrinolysis inhibitor (TAFI). The Leiden thrombophilia study showed that increased levels of factor XI is a risk factor for thrombosis.(111), (112)

Recent reports have suggested that the proteins of the intrinsic pathways are biologically active. Prekallikrein and HMWK are involved in the regulation of blood pressure and play a role in fibrinolysis. Factor XII can activate neutrophils and up-regulate the release of cytokines from monocytes and macrophages.(113)

2.2.3 Tenase Complex Formation:

This complex is formed of active factor IX (IXa), active factor VIII (VIIIa), calcium and phospholipids and it leads to activation of factor X to Xa. The tenase complex is the most important activator of factor X and it is necessary for haemostasis. Absence of factor VIII or factor IX produces haemorrhagic disease known as haemophilia, the severity of which is related to the degree of deficiency of these factors.

2.2.4 Conversion of Prothrombin to Thrombin:

The formation of active thrombin is achieved by the production of the prothrombinase complex. This process consists of binding active factor X to active factor V, calcium and phospholipid membrane. Thrombin and TF-VIIa can produce factor Va.(100) The tenase complex and TF-VIIa are essential in activating the vitamin-k dependent factor X. The tenase complex is required as the activation of factor X produced by TF-VIIa gets rapidly down-regulated by the effect of tissue factor pathway inhibitor (TFPI).

Active factor V is required to accelerate the conversion of prothrombin to thrombin. This requires the binding to the phospholipid surface of activated platelets or monocytes.(114) α-thrombin is produced by activation of prothrombin under the effect of the tenase complex. This occurs through various steps, one of which produces the active thrombin and a by-product called Prothrombin Fragment (PF) 1+2.(115) PF1+2 is used as a marker of thrombin production as it is more stable to be measured and thrombin concentration is difficult to assess. PF1+2 is considered an indicator of hyper-coagulability.(116) Functions of the active enzyme thrombin

include the conversion of fibrinogen into fibrin, activating coagulation factors V, VIII and XI; platelets, TAFI and protein C.(117)

2.2.5 Fibrin Formation:

This is the end stage of normal coagulation in order to seal the site of vascular injury and allow wound healing. Fibrin is formed by the conversion of the soluble fibrinogen into an insoluble polymer. This is a multi stage process.

2.3 Regulation of Blood Coagulation:

Normal blood coagulation should act locally for the appropriate period of time to provide enough fibrin at the site of vascular injury to ensure proper seal of the site of injury. If not regulated tightly, this process can cause wide spread fibrin deposition leading to thrombo-embolic complications.

These regulatory mechanisms include:

1) The coagulation system is active where the negatively charged phospholipids co-exist. This occurs on the surface of activated cells and platelets.

2) TF, which is the initiator of the cascade, is abundant on the surface of monocytes and cells that become active in response to vascular injury.

3) The presence of anticoagulant proteins that limit the activity of the active coagulation factors.

4) Fibrinolysis.

The anticoagulant proteins and cofactors include:

1) TFPI which is released from endothelial cells.

2) Anti-thrombin which binds to and neutralizes factors IXa, Xa, TF-VIIa complex and thrombin. Thrombin-antithrombin (TAT) complex is rapidly cleared from the circulation.(118) This complex is also used as a marker of hyper-coagulability because it is an indicator of thrombin production.(119)

3) Protein C pathway which is a essential in preventing thrombosis in the microcirculation.

The activation process of protein C pathway takes two steps as protein C circulates in an inactive form. The first step requires thrombin to produce activated protein C (APC). For APC to become fully active, it has to bind to protein S which is, similar to protein C, a vitamin K dependent plasma protein. Having no enzymatic activity, protein S binds to APC creating the protein S-APC complex that acts as inhibitor of factor Va and factor VIIIa. The full activation of the protein C pathway stops thrombin production by shutting down prothrombinase and tenase activity.(120)

2.4 Fibrinolysis:

The fibrinolytic system controls and limit clot formation. When activated, it changes fibrin into fibrin fragments known as fibrin degradation products (Figure 2). The control of this mechanism is crucial in maintaining a haemostatic balance.

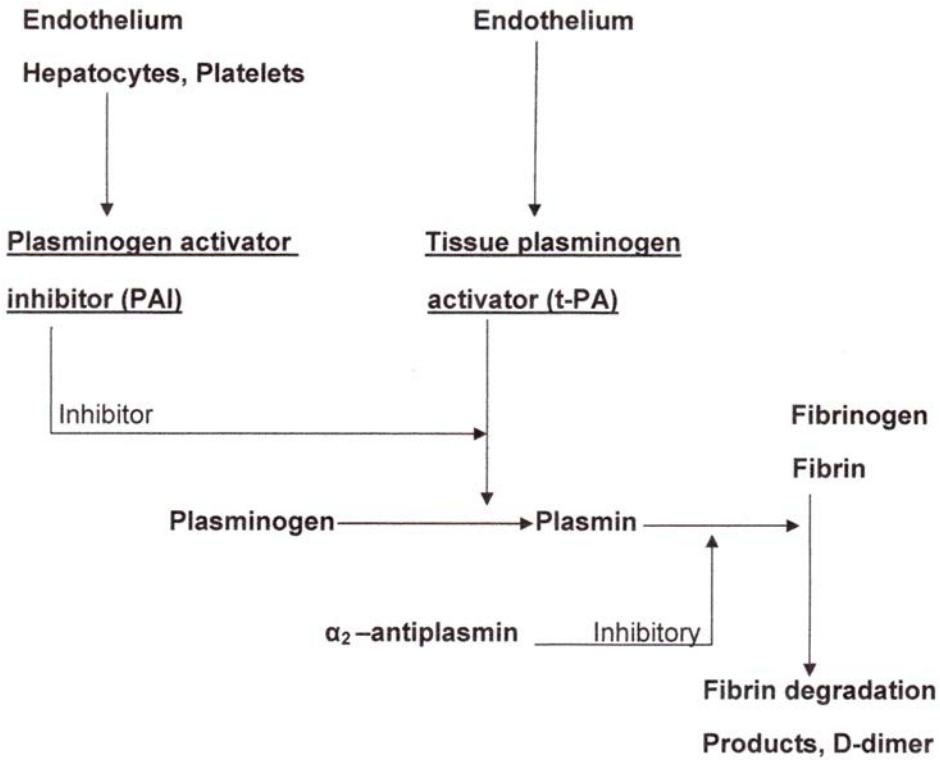


Figure 2: Mechanism of the fibrinolytic system.

Endothelial activation and injury causes the release of tissue plasminogen activator (t-PA) antigen, which converts plasminogen into the active plasmin. This active enzyme leads to the breakdown of fibrinogen, fibrin, and fibrin clot to fibrin degradation products. Plasminogen activator inhibitor (PAI) is released from the endothelium, hepatocytes, and platelets to inhibit t-PA.

2.4.1 Plasminogen and plasmin

The breakdown of the fibrin into fibrin degradation products (FDPs) is carried out through the effect of the plasmin enzyme. Its precursor is the inactive plasminogen. Plasminogen activators lead to the formation of the active protease plasmin. The presence of plasminogen activators and their inhibitors is essential in controlling fibrinolysis.(121)

2.4.2 Plasminogen activators

tissue plasminogen activator (t-PA) is the main plasminogen activator in vivo. It is a serine protease that is produced by the endothelial cells. In the presence of fibrin, it gets bound to fibrin and activation of plasminogen is accelerated to produce plasmin. However, in the absence of fibrin, it is an inefficient activator of plasminogen. The release of t-PA at the site of vascular injury is stimulated by fibrin, thrombin attached to the formed clot, or by the effects of venous occlusion.(122, 123)

2.4.3 Inhibitors of fibrinolysis

α2-antiplasmin inhibits the active plasmin by forming an irreversible plasmin-antiplasmin complex. Plasminogen activator inhibitors (PAI) is another major player in regulating fibrinolysis. There are four different types of PAI: PAI-1, PAI-2, PAI-3 and protease nexin. PAI-1 is the most important in inhibiting t-PA in plasma. PAI-1 is mainly produced in the endothelial cells and it is usually present in excess over t-PA in order to prevent the premature breakdown of fibrin in the forming clot and to inhibit

systemic fibrinolysis. PAI-2 is produced in the placenta and is found only in the plasma of pregnant women. Another fibrinolysis inhibitor is TAFI, which when activated; it directly inhibits plasmin activity and prevents premature lysis.(124-127)

2.5 Abnormal Haemostasis:

Abnormal Haemostasis or coagulopathy occurs due to imbalance between coagulation and fibrinolysis. It happens as a result of excessive activation of the extrinsic and/or intrinsic coagulation pathways. Coagulopathy could be due to acute or chronic causes. TF release is the major cause of acute coagulopathy. Coagulation factors operate within a narrow range of temperature and pH; hence hypothermia and acidosis have a major impact on haemostasis. AAA may precipitate chronic coagulopathy.

2.6 The effect of AAA on haemostasis:

AAA is characterized by chronic inflammation and the presence of mural thrombus. Blood flow is maintained through the mural thrombus of an aortic aneurysm, thereby providing an interface for exchange between the systemic circulation and thrombus.(128) The structure of the thrombus is highly complex with a network of interconnecting canaliculi which contain cellular infiltrates, including neutrophils, macrophages, and platelets, often in a state of de-granulation. This may lead to consumption of platelets and coagulation factors to such an extent that a sub-clinical disseminated intravascular coagulopathy (DIC) may exist.(129) Thus, the mural thrombus represents a biologically active entity with the ability to trap polymorph nuclear leukocytes, absorb circulating plasma components, and aggregate platelets as well as being implicated as a source of proteolysis and fibrinolytic activity thought to be implicit in AAA progression.(130-132) Furthermore, it has been proposed that the luminal part of the thrombus could play a critical role in the evolution of AAA through its ability to act as solid catalyst between substrates transported through the thrombus and proteases originating from the arterial wall.

Several studies have examined the effects of AAA on direct and indirect biomarkers of thrombin generation, fibrinolysis, and platelet activity (Tables 1-3). An elevated level of plasma fibrinogen is an independent risk factor for cerebrovascular events and myocardial infarction as well as cardiovascular mortality.(133, 134) An association between elevated fibrinogen and atherosclerotic peripheral arterial disease has been widely reported, and elevated levels of plasma fibrinogen are found in patients who subsequently develop peripheral arterial disease. The association between AAA and plasma fibrinogen levels has been extensively

investigated (Table 1).(18, 29, 135-141) Seven of 14 studies have reported significantly elevated fibrinogen levels in patients with asymptomatic AAA.

Several studies investigated the association between AAA and fibrinolysis.(5, 18-20, 135, 140-147) (Table 1). Some studies assessed the impact of AAA on plasma D-dimer levels. The degradation of fibrin by plasmin ultimately results in the formation of D-dimer. Thus, the presence of D-dimer in the circulation represents ongoing clot formation and fibrinolysis. All these studies have reported elevated levels of plasma D-dimer in patients with AAA. On multivariate analysis, both Lee et al (143) and Parry et al (5) have reported an independent association between circulating D-dimer levels and AAA. The majority of studies have reported no difference in circulating t-PA antigen levels in patients with or without AAA. The one exception is Wanhainen et al (146) who have reported elevated levels of t-PA antigen in patients with screen-detected AAA. Only three studies have analysed both t-PA antigen and PAI-1 activity levels, and all three studies have reported no significant difference compared to their control populations. Adam et al (34, 142) were the only group to report t-PA activity and PAI-1 activity levels which were comparable to the manufacturer's normal reference in patients with symptomatic, non-ruptured AAA.

Similarly, several studies have reported on the effect of AAA on the levels of TAT and/or PF1+2.(5, 18-20, 141, 142, 144, 145) (Table 2). Elevated levels of both TAT and PF1+2 have been demonstrated in men with AAA <5.5 cm in diameter. Wallinder et al (20) reported elevated levels of TAT, but normal levels of PF1+2. This may be explained by the short half-life of PF1+2 such that elevated TAT levels are more indicative of ongoing thrombosis, whereas PF1+2 may be more reflective of a single acute thrombotic event.

Table 1: Summary of studies investigating the association between AAA and levels of fibrinogen and biomarkers of fibrinolysis

Study	Cases	Controls	Fibrinogen			Fibrinolysis								
						D-Dimer			tPA ag			PAI-1		
			case	Control	P-value	Case	controls	P-value	case	controls	P-value	case	controls	P-value
Adam et al(142)	7	0 **	4.85 (1.61-7.9) g/l	1.5 - 4.0 g/l	0.033	1633 (753-3014) ng/ml	630-850 ng/ml	0.005	1.7 (0.75-3.2) IU/ml ***	0.2-2.0 IU/ml	0.023	6.3 (3.2-15.4) AU/ml	<15 AU/ml	0.005
Adam et al(34)	9	0 **	2.80 (1.59-.02) g/l	1.5 - 4.0 g/l	N/A				0.49 (0.14-3.2) IU/ml ***	0.2-2.0 IU/ml	N/A	8.2 (3.2-21.7)	<15 AU/ml	N/A
Al-Barjas et al(136)	110	110	2.89 (2.45-3.4) g/l	2.53 (2.1-3.07) g/l	<0.01									
Blann et al(138)	21	42	3.6 +/- 1.2 g/l	3.3 +/- 0.9	0.185									
Bradbury et al(29)	23	0 **	5.16 (2.61-4.3) g/l	1.5-4.0 g/l	n/s									
Fowkes et al(135)	89	98	3.5 (2.9-4.1) g/l	3.1 (2.7-3.6) g/l	0.02	441.5 (198.8-771.0) ng/ml	93.0 (57.8-158.8) ng/ml	<0.001	7.9 (6.0-11.1) ng/ml	8.6 (6.8-11.5) ng/ml	0.64			

Holmberg et al(137)	23	o **	3.6 (1.9-6.3) g/l	2.0-3.6 g/l	n/s									
Holmberg et al(19)	23	20				571 (60-1515) µg/L	32 (10-536) µg/L	<0.01	10.2 (4.9-24.2) µg/ml	9.4 (2.9-19.0) µg/ml	>0.05	3.5 (2.0-33.1) IU/ml	4.7 (2.0-30.9) IU/ml	>0.05
Hosaka et al(141)	49	o **	336 +/-85 mg/dl	160-350 mg/dl	N/A	8.5 +/-6.7 µg/ml	<1.0 µg/ml	N/A						
Ihara et al(145)	22	26				732.6 +/-858.6 ng/ml	125.7 +/- 46.1 ng/ml	<0.0001						
Jelenska et al(144)	20	22	4.2 +/-79 mg/dl	313+/-55 mg/dl	<0.001	778 +/-311 ng/ml	362 +/-242 ng/ml	<0.001						
Kolbel et al(148)	78	121												
Lee et al(143)	40	200	3.05 (2.61-3.57) g.l	2.62 (2.21-3.08) g/l	≤0.001	142 (84-209.5) ng/ml	83 (67.5-129) ng/ml	≤0.001	8.5 (7-10.5) ng/ml	7.9 (5.8-10.1) ng/ml	NS			
Milne et al(149)	105	32												
Parry et al(5)	75 males	90	2.92 (0.76) g/l	2.59 (0.65) g/l	0.019	346.7 (288.5-427.5) ng/ml	120.2 (106.9-134.2) ng/ml	<0.001	9.12 (8.03-10.50) ng/ml	8.80 (8.14-9.51) ng/ml	0.719	17.9 (15.4-20.4) ng/ml	16.2 (14.4-17.9) ng/ml	0.619

Shindo et al(140)	43	o **	300.2 +/- 15.5 mg/dl	150-330 mg/dl	N/A	10.6 +/- 2.0 µg/ml	<0.8 µg/ml	N/A						
Sofi et al(147)	438	438										28.6 +/- 21.6 mg/dl	17.8 +/- 12.6 mg/dl	<0.0001
Singh et al(139)	263 ♂	2699 ♂	3.72 (0.91) mmol/l	3.32 (0.88) mmol/l	<0.001									
	74 ♀	3350 ♀	3.77 (0.68) mmol/l	3.43 (0.80) mmol/l	<0.001									
Wallinder et al(20)	40	41				625 (460-1437) ng/ml	86 (38-176) ng/ml	<0.001	10.5 (8.6 - 14.8) ng/ml	11.1 (8.5-15.2)ng/ml	>0.05	4.0 (1.9-8.7) IU/ml	2.7 (1.9-7.9) IU/ml	>0.05
Wanhainen et al(146)	42	100							13.6 +/- 4.7 µg/ml	11.4 +/- 4.3 µg/ml	0.016			
Yamazumi et al(18)	36	25	326 +/- 77 mg/dl	298 +/- 63 mg/dl	0.21	7.7 +/- 6.7 µg/ml	1.0 +/- 1.2 µg/ml	<0.01						

** Manufacturer's range

Table 2: Summary of studies investigating the association between AAA and biomarkers of thrombin generation

Study	Cases	Controls	Thrombin Generation											
			TAT			F1+2			FDP			APC-PCI		
			Case	controls	P-value	Case	Controls	P-value	case	controls	P-value	case	controls	P-value
Adam et al(142)	7	0**				2.1(1.1-5.2) nmol/l	0.4-1.1 nmol/l	0.001						
Adam et al(34)	9	0**	21.6 (6.6-180.4) µg/L	1.0-4.0 µg/L	N/A	2.2 (0.7-7.1) nmol/l	0.4-1.1 nmol/l	N/A						
Holmberg et al(19)	23	20	11.5 (2.6-30.3) µg/L	2.6 (2.0-5.6) µg/L	<0.01	2.2 (0.9-4.6) nM	1.2 (0.5-3.1) nM	>0.05						
Hosaka et al(141)	49	0**	11.5 +/- 11.3 ng/ml	<3.5 ng/ml	N/A									
Ihara et al(145)	22	26	16.4 +/- 16/9 ng/ml	2.6 +/- 1.3 ng/ml	<0.001									
Jelenska et al(144)	20	22				1.17 +/- 0.36nM	0.99 +/- 0.28 nM	<0.001						
Kolbel et al(148)	78	121										0.45 (0.24-1.47) µg/l	0.15 (0.10-0.23) µg/l	<0.0001
Parry et al(5)	75 males	90	4.57 (2.68-8.7) ng/ml	1.89 (1.48-2.49) ng/ml	<0.001	1.33 (0.98-1.79) ng/ml	0.82 (0.75-0.90) ng/ml	0.004						

Shindo et al(140)	43	0**							718.6 +/- 138.2 ng/ml	<100 ng/ml	N/A			
Wallinder et al(20)	40	41	6.0 (3.8-9.1) µg/ml	2.9 (2.1-3.9) µg/ml	<0.001	0.8 (0.6-1.1) nmol/l	0.8 (0.6-1.0) nmol/l	>0.05						
Yamazumi et al(18)	36	25	17.4 +/- 13.6 ng/ml	3.8 +/- 2.2 ng/ml	<0.01				11.6 +/- 12.0 µg/ml	3.6 +/- 2.0 µg/ml	<0.01			

** Manufacturer's range

Table 3: Summary of studies investigating the association between AAA and vWF, platelet count, and sP-selec

Study	Cases	Controls	vWF			Platelet count			sP-selec		
			case	Controls	P-value	case	controls	P-value	case	controls	P-value
Adam et al(142)	7	0 **				183 (75-292) $x10^9$/l	150-350 $x10^9$/l	<0.05			
Blann et al(138)	21	42	123 +/- 37 IU/dl	113 +/- 32 IU/dl	<0.001				325 (155-4253) ng/ml	202 (80-440) ng/ml	<0.001
Bradbury et al(29)	23	0 **				204 (140-293) $x10^9$/l	150-350 $x10^9$/l	>0.05			
Fowkes et al(135)	89	98	122.5 (98.0-150.2) IU/dl	123.0 (101.0-152.0) IU/dl	0.55						
Holmberg et al(19)	23	20									
Ihara et al(145)	22	26									
Milne et al(149)	105	32				215+/- 47.5 x 10^9/l	269+/- 57 x 10^9/l	<0.0001			

Shindo et al(140)	43	0 **				17.9 +/- 5.7 x 10^3/mm3	15.7-34.2 x 10^3/mm3	N/A			
Wallinder et al(20)	40	41	154 (138-176) %	150 (125-165) %	>0.05	216 (176-242) x10^9/l	207 (177-238) x10^9/l	>0.05			
Yamazumi et al(18)	36	25				19.6 +/- 5.4 x 10^4/µL	23.7 +/- 6.1 x 10^4/µL	<0.05			

** Manufacturer's range

2.7 Association between AAA morphology and haemostasis:

Seven studies have reported on the correlation between AAA maximum diameter, thrombus volume, and markers of haemostasis (18, 20, 22, 136, 140, 141, 150, 151) (Table 4). Some authors have demonstrated a correlation between AAA size and total volume/maximum thrombus thickness and the changes in thrombin generation and fibrinolysis. By contrast, Kölbel et al (148) have failed to show a correlation between APC-PCI levels and thrombus volume or thrombus intra-luminal surface area. Yamazumi et al (18) have reported a correlation between AAA tortuosity and markers of thrombosis which may represent the association between blood flow velocity changes, particularly turbulent flow, and red blood cell (RBC) activation. Shindo et al (140) have reported a correlation between RBC counts and the AAA lumen volume. Activated RBCs release adenosine di-phosphate resulting in platelet aggregation and activation.(152) The consumptive coagulopathy, resulting from the thrombus mass and the abnormal flow field in a tortuous lumen may both contribute to the haemostatic derangement in patients with AAA.

Table 4: Summary of studies investigating the association between AAA morphology and biomarkers of haemostasis

Biomarker	Study	Maximum diameter of AAA	Worst angle along length of AAA	Max thickness of intra-luminal AAA thrombus	Total Intra-luminal AAA thrombus volume
APC-PCI	Kolbel et al(148)	r=0.22, p=0.001			r=0.123, p=0.142
D-Dimer	Shindo et al(140)	r=0.208, p=NS			r=0.208, p=NS
	Wallinder et al(20)	r=0.427, p<0.001			
	Yamazumi et al(18)	r=0.644, p=0.0001	r=-0.411, p=0.009	r=0.650, p=0.0001	
F-TFPI	Yamazumi et al(18)	r=0.408, p=0.016	r=-0.583, p=0.0006		
FDP	Shindo et al(140)	r=0.208, p=NS			r=0.171, p=NS
	Yamazumi et al(18)	r=0.561, p=0.0009		r=0.513, p=0.0024	
Fibrinogen	Al-Barjas et al(136)	r-0.323, p<0.01			r=0.323, p<0.05
FM-FC	Hosaka et al(141)	r=0.128, p=0.381		r=0.233, p=0.125	
PAI-ag	Aho et al(22)				r=0.51, p<0.007
PIC	Yamazumi et al(18)	r=0.413, p=0.0146		r=0.484, p=0.042	
TAT	Wallinder et al(20)	r=0.28, p=0.018			
	Yamazumi et al(18)	r=0.566, p=0.001	r=-0.366, p=0.0305	r=0.677, p=<0.0001	

2.8 The effect of open surgical repair on biomarkers of haemostasis:

Major surgery is known to produce a pro-thrombotic derangement with raised levels of factor VIII, fibrinogen, TAT, vWF, platelet hyperactivity, and evidence of deranged fibrinolysis.(23-28) Studies reporting the effect of open surgical AAA repair on haemostasis are summarized in (Table 5). Aho et al (22) have reported significantly elevated levels of PF1+2 at 72 hours postoperatively compared to pre-operative levels. There was a non-significant trend toward elevated levels of TAT, D-dimer, t-PA antigen, and PAI antigen within the first 72 hours postoperatively. These biomarkers returned to pre-operative levels by 3 months after the operation, but remained elevated when compared to healthy individuals suggestive of ongoing up-regulation of thrombin generation and fibrinolysis. Yamazumi et al (18) have reported significantly lower levels of TAT and D-dimer at 3 months following open repair when compared to pre-operative levels. Holmberg et al (153) have reported similar findings with elevated peri-operative levels of TAT and PF1+2 which returned to pre-operative levels by 1-week postoperatively, but remaining elevated compared to age-matched controls (AMC). In a separate study, the same group has reported that open surgical repair reduced the pre-operative thrombotic derangement in the long-term with a reduction in TAT and D-dimer levels at a median follow-up of 26 months (19). However, the values remained slightly higher than the normal healthy reference ranges suggesting ongoing haemostatic derangement despite thrombus volume reduction.

Table 5: Summary of studies investigating the effects of open surgery on biomarkers of haemostasis

Biomarker	Study	Controls (units)	Pre-operative	24 hours		72 hours		1 week		3 months		>12 months	
			Value	Value	p-value	Value	p-value	Value	p-value	Value	p-value	Value	p-value
D-dimer	Holmberg et al(19)	32 (10-536) µg/L	511 (60-1275)									*39 (23-326)*	*<0.05*
	Yamazumi et al(18)	1.0 +/- 1.2 µg/ml	7.7+/-6.7							*4.6+/-3.5*	*<0.01*		
PF1+2	Aho et al(22)	0.4-1.1 nmol/ml	1.6+/-0.6	1.5+/-1.2	NS	*2.0+/-0.9*	*<0.05*	1.9+/-0.8	NS	1.4+/-0.6	NS		
	Holmberg et al(153)	1.2 (0.5-3.1) nM	2.2 (0.9-4.6)					2.7 (1.5-5.7)	NS				
	Holmberg et al(19)	1.2 (0.5-3.1) nM	1.4 (0.0-4.6)									1.2 (0.8-3.0) **	NS
FDP	Yamazumi et al(18)	3.6 +/- 2.0 µg/ml	11.6 +/-12.0							7.6+/-4.6	0.17		
Fibrinogen	Aho et al(22)	1.7-4 g/l *	3.9+/-0.8	3.5+/-0.7	NS	*7.1+/-2.0*	*<0.05*	5.9+/-1.3	NS	3.8+/-0.4	NS		
	Holmberg et al(137)	2.0-3.6 g/l *	3.6 (1.9-6.3)					*5.6 (3.3-8.4)*	*<0.001*				
	Yamazumi et al(18)	298 +/- 63 mg/dl	326 +/- 77							331+/-55	0.75		

PAI Ag	Aho et al(22) Holmberg et al(19)	4-43 ng/ml 4.7 (2.0-30.9) IU/ml	18.8+/-6.0 5.6 (2.0-29.3)	*32.4+/-13.3*	*<0.05*	27.9+/-6.2	NS	25.9+/-10.7	NS	15.4+/-6.0	NS	9.9 (2.0-54.5)	NS
Platelet Count	Bradbury et al(29) Yamazumi et al(18)	150-350 $x10^9$/l * 23.7 +/-6.1 x 10^4/µL	292 (179-51) x 10^9/L 19.6 +/- 5.4 x 10^4	187 (103-364) $x10^9$/l	<0.001					*21.2+/-5.0 x 10^4*	*<0.05*		
TAT	Holmberg et al(153) Holmberg et al(19) Yamazumi et al(18)	2.6 (2.0-5.6) µg/L 2.6 (2.0-5.6) µg/L 3.8+/-2.2 ng/ml	11.5 (2.6-30.3) 11.5 (2.6-26.1) 17.4 +/-13.6					11.8 (4.4+/-31.3)	NS	*10.4+/-4.5*	*<0.01*	*3.8 (2.7-16.2)***	*<0.05*
tPA Ag	Aho et al(22) Holmberg et al(19)	1-20 ng/ml 9.4 (2.9-19.0) µg/ml	9.7+/-2.6 10.3 (7.6-15.3)	*14.3+/-4.9*	*<0.05*	13.6+/-4.3	NS	11.2+/-4.6	NS	9.1+/-2.8	NS	12.5(6.6-14.9)	NS

2.9 The effect of EVAR on biomarkers of haemostasis:

Five studies have reported the effects of EVAR on haemostasis (22, 43, 154-156) (Table 6). Serino et al (156) have reported the short-term effects of EVAR on circulating D-dimer levels in nine patients assessed pre-operatively and day 4 postoperatively. D-dimer levels were elevated in seven patients and decreased in two patients. The median level for the entire patient cohort did not demonstrate a statistically significant difference. This lack of statistical significance may represent a type II error. Monaco et al (154) have reported a significant decrease in levels of platelets, fibrinogen, plasminogen, and prothrombin activity in patients undergoing EVAR during the first 10 days after the operation. This was associated with increased D-dimer and fibrin degradation product (FDP) levels suggestive of coagulation factor/platelet consumption coupled with hyper-fibrinolysis during the peri-operative period in patients undergoing EVAR. By 1-month post-EVAR, all biomarkers returned to pre-operative levels with the exception of fibrinogen, which peaked at 1-month and remained significantly elevated at 6-months post-operatively. Three studies have compared open surgical repair with EVAR on haemostasis. Engleberger et al (43) have reported elevated levels of markers of thrombin activity (fibrinopeptide A and FM), thrombin formation (TAT) and fibrinolysis (D-dimer) in both groups during the peri-operative period with return to pre-operative values by post-operative day 5. During this period, inter group comparison revealed significantly elevated levels of thrombin activity and formation in the EVAR group. Aho et al (22) have reported similar changes in the peri-operative period with elevated levels of markers for thrombin formation (TAT, PF1+2) and fibrinolysis (D-dimer, t-PA antigen). The post-operative increase in TAT levels was found to be

earlier and more pronounced in the EVAR group compared to the open group (day 1 vs day 3). All markers of haemostasis returned to pre-operative levels by 1 week post-operatively with the exception of D-dimer. D-dimer increased in both groups after surgery and remained above normal values for 3 months. However, compared to pre-operative levels, only the EVAR group demonstrated a significant increase in D-dimer at 3 months. Fibrinogen decreased in both groups during the first 24 hours post-operatively, but thereafter increased such that at 72 hours it was significantly elevated compared to pre-operative values, but no inter group difference was found. Odegård et al (155) have reported similar findings in the peri-operative period for both EVAR and open repair. These changes in fibrinogen can be explained by consumption and/or depletion due to operative blood loss during the first 24 hours, followed by an increase in levels due to ongoing inflammation associated with the endoprosthesis/graft as indicated by elevated levels of C-reactive protein and interleukin (IL)-6.

Table 6: Summary of studies investigating the effects of EVAR on biomarkers of haemostasis and comparing them to open repair

Biomarker	Study	Type of repair	Controls (units)	Pre-op Value		24 hours			72 hours		
					Inter-group P-value	Value	Intra-group p-value	Inter-group P-value	Value	Intra-group P-value	Inter-group P-value
D-dimer	Monaco et al(154)	Endo	<450ng/ml*	278+/-93.3		428.44+/-147.3	<0.01				
PF1+2	Aho et al(22)	Open	0.4-1.1 nmol/ml *	1.6+/-0.6	NS	1.5+/-1.2	NS	NS	*2.0+/-0.9*	*<0.05*	NS
		Endo		1.4+/-0.4		2.0+/-1.0	NS		2.3+/-0.9	<0.05	
FDP	Monaco et al(154)	Endo	<100ng/ml *	6.3 +/- 1.3		11.2 +/- 3.8	<0.01				
Fibrinogen	Aho et al(22)	Open	1.7-4 g/l *	3.9+/-0.8	NS	3.5+/-0.7	NS	NS	*7.1+/-2.0*	*<0.05*	NS
		Endo		3.7+/-0.6		3.5+/-0.8	NS		*6.1+/-1.6*	*<0.05*	
	Odegard et al(155)	Open	N/A g/l								
		Endo									
	Monaco et al(154)	Endo	160-350 mg/dl *	309.6+/-50.6		159.4+/-44.9	<0.01				
PAI Ag	Aho et al(22)	Open	4-43 ng/ml *	18.8+/-6.0	NS	*32.4+/-13.3*	*<0.05*	NS	27.9+/-6.2	NS	NS
		Endo		16.5+/-6.4		24.5+/-8.5	<0.05		21.3+/-8.2	NS	

Platelet Count	Englberger et al(43)	Open	N/a x 10^9/l	232+/-52	0.82	143+/-52		0.41			
		Endo		226+/-46		165+/-56					
	Monaco et al(154)	Endo	130-340 x10^3/dl *	233.2+/-52.9		190.9+/-48.4	<0.05				
tPA Ag	Aho et al(22)	Open	1-20 ng/ml *	9.7+/-2.6	NS	*14.3+/-4.9*	*<0.05*	NS	13.6+/-4.3	NS	NS
		Endo		8.5+/-3.1		11.4+/-4.1	<0.05		9.9+/-4.3	NS	

Table 6 (continue):

5-7 days Post-op			3 months			6 months		
Value	**Intra-group p-value**	**Inter-group P-value**	**Value**	**Intra-group p-value**	**Inter-group P-value**	**value**	**Intra-group P-value**	**Inter-group P-value**
420.5+/-149.8	<0.05					265.9+/-86.9	>0.05	
1.9+/-0.8	NS	NS	1.4+/-0.6	NS				
2.0+/-0.7	NS		1.7+/-0.6	NS				
12.0+/-3.4	<0.01					6.0 +/- 1.0	>0.05	
5.9+/-1.3	NS	NS	3.8+/-0.4	NS	NS			
6.1+/-2.1	*NS*		3.6+/-0.7	NS				
5.8 (4.9-6.9)	*P<0.001*	NS						
5.8 (5.0-6.7)	p<0.001							
187.3+/-44.7	<0.01					348.8+/-79.7	<0.01	
25.9+/-10.7	NS	NS	15.4+/-6.0	NS	NS			
25.3+/-8.0	NS	NS	18.6+/-6.4	NS				

229+/-75		0.98						
229+/-74								
170.6+/-34.7	<0.001					*237.8+/-60.3*	*>0.05*	
11.2+/-4.6	NS	NS	9.1+/-2.8	NS	NS			
10.3+/-4.9	NS		8.7+/-3.2	NS				

Chapter 3

General Background 3

3.1 Effect of EVAR on Renal function:

The effect of EVAR on renal function remains uncertain. Early reports showed a significant increase in sCr and reduction in creatinine clearance (CrC) following EVAR.(157-159) The incidence of renal impairment following EVAR has been reported to be 6-29% depending on the presence of pre-operative renal impairment.(160, 161) Other studies have failed to demonstrate a significant change in renal function following EVAR.(162, 163) Deterioration in renal function following fenestrated EVAR has been reported to be as high as 10-30% (16% in those without renal dysfunction and 39% for patients with pre-operative renal dysfunction).(91, 98, 164, 165)

In clinical practice, sCr is the most commonly used marker to assess renal function (RF). However, sCr appears to be a rather unreliable marker of RF because sCr concentrations are affected by tubular secretion, age, sex, muscle mass, physical activity, and diet, and therefore it does not have a direct relationship with the glomerular filtration rate (GFR).(166) The Cockcroft-Gault (167) and the Modification of Diet in Renal Disease (MDRD) (168) equations, both based on sCr, are being used increasingly because they overcome, at least in part, some of the limitations of sCr measurements. Both equations are currently recommended for the estimation of GFR, which is an established method for detection and classification of Chronic kidney disease (CKD) in clinical practice.(169) However, these creatinine-based equations, which have been validated in patients with CKD, have several limitations,

particularly among CKD patients with multiple co-morbidities, elderly individuals, obese patients, and patients with only mild impairment of RF.(170-172)

sCr is considered relatively specific, but not very sensitive since its levels significantly increase when more than 50% of the GFR is reduced.(173) Its concentration may be significantly influenced by several extra-renal factors (muscle mass, changes in tubular secretion, dietary intake). Especially in elderly female patients with reduced muscle mass, measurement of sCr may grossly underestimate the reduction in the GFR. Finally, numerous drugs and endogenous substances also interfere with the measurement of sCr, leading to falsely high or low values.

3.2 Cystatin C:

Cystatin C (cyst C) is an endogenous marker of renal function that is believed to be more sensitive in detecting mild to moderate reduction in GFR. It is produced by all nucleated cells and it is related to the cysteine proteinase inhibitors. Cyst C is filtered freely across the glomerular membrane and is metabolized in the proximal tubules.

Several studies have suggested that its level is not affected by age, sex, or muscle mass and it is more accurate than sCr for detection of early renal impairment.(174)

In the Chronic Kidney Disease Epidemiology (CKD-Epi) Study, although both sCr and cyst C were associated with demographic factors independent of direct measures of GFR, this was to a larger extent for sCr.(175) Increased weight and height, current smoking, higher C-reactive protein (CRP) levels, hyperthyroidism and glucocorticoid use have also been associated with higher cyst C levels (176-178) and more recent studies have noted associations with obesity and waist circumference, (179, 180) as well as secretion of cyst C by adiposities.(181) In the MDRD Study, cyst C was however highly correlated with GFR suggesting that kidney function is the primary determinant of cyst C in CKD.(182)

Multiple studies have compared cyst C and sCr as predictors of GFR. Most studies have found cyst C to be a better predictor, although others have found no difference. However, there is still some evidence that it has more clinical importance than sCr alone or Estimated GFR (eGFR). Cyst C may be used to detect and diagnose acute kidney injury (AKI) in critically ill patients one or two days earlier when compared to sCr measurements. Serum Cyst C is an indicator of impaired glomerular filtration(183), whereas, the urinary cyst C to creatinine ratio is a good indicator of

renal tubular dysfunction. Moreover, urinary cyst C has been used in cases of AKI to anticipate the requirement for renal replacement therapy earlier than urinary creatinine.

3.2.1 Cystatin C as a measure of GFR

Investigators from CKD-EPI developed three GFR estimating equations for cyst C: using cyst C alone, cyst C with demographic coefficients, and cyst C with sCr and demographic coefficients. Cyst C alone provided GFR estimates that were nearly as accurate as the MDRD equation; however, an equation including cyst C, sCr and demographic coefficients provided the most accurate estimates. Among patients with known CKD, defined as creatinine-based eGFR< 60 ml/min 1.73m2, cyst C offered only a moderate gain over sCr for approximating GFR;(175) however, in patients with early kidney disease, for example diabetics, changes in GFR over time have a stronger correlation with cyst C than sCr.(184, 185) Cyst C may also have advantages over sCr in conditions of decreased mass including older adults, those with chronic diseases (such as heart failure, cirrhosis, AIDS) and those without established CKD; however since studies in these populations lack direct GFR measurements, validated equations incorporating cyst C have not been developed.(186)

3.2.2 Association between cyst C and cardiovascular disease

High concentrations of circulating cyst C have been consistently and strongly associated with cardiovascular outcomes. Furthermore, Cyst C is superior over other renal markers through providing prognostic information in some cardiovascular conditions. In one study, the prognostic value of serum cyst C has been investigated in cases of acute Heart Failure (HF) in comparison with other renal markers.(187) The mortality rate in acute HF has been found to be significantly high with high cyst C. Moreover, the mortality rate in patients with high cyst C was significantly higher at 12 months when compared to patients with normal sCr levels: 40.4% vs 12.6%. Manzano-Fernandez et al produced similar findings in their study.(188) Another study showed that cyst C has been used to predict cardiovascular mortality in elderly patients with chronic HF.(189)

Cyst C has been shown to be a risk factor for HF and cardiovascular disease mortality in the general population.(190) Higher levels of cyst C have been associated with left ventricular (LV) hypertrophy.(191) Being an inhibitor of elastolytic proteases, cyst C was found to be involved in atherosclerosis. The increased plasma concentrations of cystatin C may indicate an attempt to counter-balance the potentially damaging increased elastolytic activity.(192) Several studies have reported increased risk of death, myocardial infarction (MI), or HF in patients with cardiovascular disease and high levels of cyst C.(193, 194)

3.2.3 Association between cyst C and AAA

AAA involved extensive extracellular matrix degradation and remodelling of the aortic wall. Several matrix metallo-proteases and serine proteases have been reported to be involved.(195, 196) Two elastolytic cysteine proteases, cathepsin S and K, have been isolated and are over-expressed in atherosclerotic lesion compared to normal arteries.(197) Macrophages and smooth muscle cells are present in the aneurysm wall and are capable of releasing cathepsins.(198) Cyst C is the most available extra-cellular inhibitor of the cysteine proteases. In one study, cyst C correlated negatively with AAA size and annual expansion rate. Cyst C level was found to be predictor of size expansion to >5 cm at the time of AAA repair. They concluded that cyst C deficiency is associated with increase aneurysm size and expansion rate.(199)

In summary, AAA is a leading cause of death worldwide, with strong association with atherosclerotic cardiovascular disease. There is a strong association between deranged haemostatic markers and cardiovascular morbidity. AAA is characterized by chronic inflammation and the presence of mural thrombus. Blood flow is maintained through the mural thrombus providing an interface for exchange between the systemic circulation and thrombus. This may lead to consumption of platelets and coagulation factors.

Major surgery results in a peri-operative pro-thrombotic diathesis as well as deranged fibrinolysis and platelet hyperactivity. However, the effect of open and endovascular aneurysm repair on coagulation, fibrinolysis and renal function remains uncertain. Several studies have reported conflicting results.

Chapter 4

Aims

Due to the uncertainty of the effect of OAR and EVAR on haemostasis and renal function, we aim to explore, investigate and answer the following key points:

1. To determine the difference in coagulation and fibrinolysis between patients with asymptomatic AAA and AMC.
2. To determine the changes that occur in the coagulation and fibrinolytic systems in the peri-operative period and up to 12 months following endovascular aneurysm repair.
3. To investigate the medium term effects of EVAR and OAR on coagulation and fibrinolysis and compare these changes between the two groups of patients.
4. To compare the utility of Cyst C, sCr, and eGFR as markers of renal function following standard and fenestrated EVAR.
5. To look into the impact of EVAR and F-EVAR on renal function using Cyst C, sCr and eGFR and compare the changes in these markers.
6. To determine the sensitivity of Cyst C in detecting minor renal damage following EVAR.

Chapter 5

Study Design

5.1 Ethics:

Ethical approval was obtained from Birmingham East, North and Solihull and Birmingham South Research Ethics committees.

5.2 Patients: Patients were included in the research unless they have one or more of the exclusion criteria.

5.2.1 Exclusion criteria

1. Recent (vascular and non-vascular) surgical or endovascular procedure within 3 months previous to recruitment.
2. Presence of hereditary or acquired conditions that alter coagulation, fibrinolysis or platelet function.
3. Patients presenting with symptomatic AAA.
4. Patients on anticoagulation therapy with vitamin K antagonist.
5. Patients unable or unwilling to give fully informed consent.

5.2.2 Patients

5.2.2.1 Group 1:

Patients presenting to the Vascular Surgery Units of the Heart of England NHS Foundation Trust and University Hospital Birmingham NHS Trust and underwent elective endovascular AAA repair. Patients who were willing and able to give fully

informed written consent were prospectively recruited. It was estimated that a minimum of 25 (sample size + an estimated 30% drop-out rate) patients will be recruited in a 12-month period and these patients will be followed-up for a minimum of 12 months.

Recruitment started in July 2008 and continued till April 2009. The study was discussed with patients who potentially fulfilled the inclusion and exclusion criteria and they were given a copy of the patient information sheet by their responsible consultant or one of the team. Patients were then approached by a member of the research team after they had sufficient time (at least 24 hours) to study the patient information sheet. The member of the research team discussed the research project, determined if the patients met the inclusion or exclusion criteria and invited the patient to be included in the study. Patients who agreed to participate in the study were asked to give fully informed written consent.

During the recruitment period, 35 patients were approached for recruitment before they had elective EVAR. Two patients refused to participate in the study, and two were on anticoagulation and were excluded. The remaining 31 patients were recruited. One patient withdrew from the study on the first post-operative day and one died of massive myocardial infarction 3 months after the operation.

Twenty-nine patients (27 men and 2 females) completed the twelve months follow up period as per protocol of the research. The mean age of these patients was 77 years (range, 55-89 years). The mean diameter of the AAA sac was 6.9 cm (range, 5.5-10 cm). 19 patients underwent standard EVAR for infra-renal AAA and 10 patients had F-EVAR for juxta or supra-renal AAA. General anaesthesia was used in 12 patients, whereas 17 patients had the procedure under epidural anaesthesia. All patients

received bolus injection of intravenous heparin (3000 units for standard and 5000 units for F-EVAR) prior to inserting the stent graft. Twenty-two patients were taking antiplatelet (aspirin 75 mg daily), 14 were being treated for hypertension, 16 had a history of ischemic heart disease, 14 had renal impairment, 3 were diabetics, 22 had hypercholesterolaemia, 3 had peripheral vascular disease (PVD) and 5 had chronic obstructive airway disease (COPD). (Table 7)

Table 7: Group 1 patients' demographics and significance of co-variables

		Significance
Mean Age (range)	76.9 yrs (55.2-88.5)	N/A
>75 yrs (%) <75 yrs (%)	18 (62.1%) 11 (3.9%)	* on pre-operative TAT & t-PA antigen
Sex (M:F)	27:2 (93.1%:6.9%)	N/A
HT (%)	14 (48.3%)	* on hsCRP at one mth
IHD (%)	16 (55.2%)	* on sP-selec pre-op & 24 hrs
CKD (%)	14 (48.3%)	No significance
Mean aneurysm size (range)	6.9 cm (5.5-10)	N/A
Aneurysm Anatomy (%) - Infra-renal	 19 (65.5%)	 * on pre-op hsCRP
EVAR (%) - Standard - Fenestrated	 19 (65.5%) 10 (34.5%)	* on hsCRP at 1,6 & 12 mths
Anaesthesia - General - Epidural	 12 17	N/A
Make of Stent (%) - Zenith - Excluder	 23 6	* on TAT & hsCRP at 1, 6 & 12 mths and t-PA antigen at 1 mth
Patients on anti-platelets (aspirin) (%)	22 (75.9%)	* on sP-selec pre-op & 24 hrs

HT: hypertension; IHD: ischaemic heart disease; *: significant (p,0.05); mths: months

5.2.2.2 Group 2:

Eleven patients (nine men and two women) were recruited after they had OAR. The mean age at the time of surgery was 70.2 years (range 55-83). Median time between OAR and collecting the blood samples was 16 months post-operatively (range 7-21 months). They were all unsuitable to have EVAR at the time of the initial aneurysm repair due to anatomical variations of the aneurysm. These patients could have been suitable for FEVAR, however, this option was not available at the time of the operation. (Table 8)

Table 8: Reason for unsuitability for EVAR among the OAR group

Patient's number	Reason
1	Angulated (65 degrees) short neck
2	Conical neck with large accessory renal artery arising of the lower part of the neck
3	Calcified and stenosed iliac arteries
4	Angulated (90 degrees) short neck
5	Angulated (70 degrees) conical neck
6	Irregular neck containing thrombus
7	Juxta-renal AAA
8	Young age
9	Juxta-renal AAA
10	Severe conical neck
11	Angulated (80 degrees) neck

5.2.2.3 Group 3:

Eight AMC without AAA (four men and four women), as documented by CT scan, were recruited. The mean age was 73.1 years (range 65-90). The CT scans were performed for various reasons. Five patients had CT scan as 2-years post-operative follow up following colon resection for colon cancer and three patients had the scan for non-specific abdominal pain.

Table 9: Demographics of patients in the three groups

	AMC group (n=8)	EVAR group (n=29)	OAR group (n=11)	P-value (Fisher's Exact test)
Age (mean ± SD)	73.1 ± 8	76.9 ± 7.4	70.2 ± 8.7	0.024
Sex (% men)	4 (50)	27 (93.1)	9 (81.8)	0.014
HT (%)	3 (37.5)	14 (48.3)	6 (54.5)	NS
IHD (%)	1 (12.5)	16 (55.2)	5 (45.5)	NS
CVA (%)	0	3 (10.3)	1 (9.1)	NS
CKD (%)	1 (12.5)	14 (48.3)	1 (9.1)	0.026
Anti-platelet (%)	2 (25)	21 (72.4)	10 (90.9)	0.009

HT; hypertension, IHD; ischemic heart disease, CVA; cerebral-vascular accidents, CKD; chronic kidney disease, NS; not significant

(The significance in age is between the EVAR and open groups)

5.3 Data collection:

The following clinico-pathological data have been collected prospectively: Patients' demographics - age and sex; co-morbidity and medications; diameter of the aneurysm measured by pre-operative CT scan; peri-operative bloods results; procedural details; post-operative data including imaging investigations, re-interventions, complications and mortality; cardiovascular morbidity and mortality.

5.4 Blood sample collection:

A resting venous blood sample was drawn from an ante-cubital fossa vein without tourniquet at the following time points for haemostatic assays: pre-procedure, days 1 and 1, 6 and 12 months post-procedure. Blood was sampled into a standard syringe without the application of suction, and then transferred to specific tubes. A 2.7ml sample was collected into EDTA anticoagulant, a 3ml sample into sodium citrate anticoagulant, a 9ml sample into a tube containing clot activator and a 4.5 ml sample into strong acid citrate. Samples were immediately transferred to the laboratory where they were centrifuged within 30 minutes of collection at 3,500 revolutions per minute for 15 minutes at a temperature of 4 C. Plasma and serum were separated and stored at -80 C for later batch analysis.

5.5 Assay Methods:

Tests were performed using the fully automated, multi-batch and multi-test Triturus® EIA Analyzer (Grifols USA, LLC, Los Angeles, CA) according to the manufacturer's

instructions. The following markers have been tested for all patients at all time points.

5.5.1 Markers of Coagulation:

PF 1+2 (normal range 0.4-1.1 nmol/l) (USCN Life Science Inc, Wuhan, China) and **TAT** (normal range 1-4.1 µg/l) (Enzygnost TAT Micro, Siemens Healthcare Diagnostics Inc, Deerfield, Ill) were measured.

5.5.2 Markers of fibrinolysis:

PAI activity (normal range 1-7 U/ml) (Technozym PAI-1 Actibind; Technoclone Ltd, Surrey, United Kingdom) and **t-PA antigen** (normal range 2-8 ng/ml) and **activity** (0 U/ml) (t-PA Combi Actibind; Technoclone Ltd) were measured.

5.5.3 Markers of platelet and endothelial activation and inflammation:

sP-selec (normal range 92-212 ng/ml) was measured as a marker of platelet activation, **sE-selectin** (normal range 17.5-88.1 ng/ml) as a marker of endothelial cell (EC) activation (IBL International GMBH, Hamburg, Germany), and **highly sensitive C-reactive protein (hs-CRP)** was measured as a marker of the inflammatory response.

5.5.4 Markers of renal function:

Cyst c (normal range 0.53-1.05 mg/l) was measured using the Turbidimetric Human Cyst C Kit for the Roche Modular P unit (manufactured by The Binding Site Ltd., Bham, UK), whereas **sCr** (normal range 60-110 µmol/l) was analysed using Kinetic colorimetric assay (Jaffe) performed on a Roche Modular P Unit. **eGFR** (ml/min/1.73m^2) was calculated at the same time points using the validated MDRD formula.

5.6 Power Calculation:

Statistical advice has been sought from the chief statistician at University Hospital Birmingham regarding study sample size calculation. Based upon previously published data by this institution, a minimum sample size of 17 patients was required to demonstrate a similar degree of haemostatic improvement following EVAR as was found after open surgical repair with a power of 80% (β-error =0.8) and a significance of <0.05 (α-error=0.05).

5.7 Statistical Analysis:

As for previous studies from this institution, statistical assistance was sought from the Department of Public Health and Epidemiology at the University of Birmingham. The calculations were performed using SPSS for Windows (version 16.0; SPSS Inc., Chicago, III) and GraphPad Prism 5 for Windows (Version 5.03; GraphPad Software Inc., CA). A *p* value of less than 0.05 was considered statistically significant. Unless

indicated, median values with inter-quartile range (IQR) were used for continuous variables.

The groups were compared using Friedman test. The change over time was analysed using Dunn's multiple comparison test and Wilcoxon signed rank paired test. In order to determine the effects of co-variables on the results, data were log transformed in order to follow normal distribution and analysis was performed using the parametric independent-sample *t*-test. Correlation between co-factors was performed using the log transformed data using Pearson correlation coefficient.

Chapter 6

Changes in coagulation and fibrinolytic system following EVAR

6.1 Introduction:

Abdominal aortic aneurysm (AAA) is associated with deranged haemostasis, endothelial cell (EC) and platelet activation, and cardiovascular morbidity and mortality.(5, 7, 9-20) We have shown recently that patients with AAA exhibit increased thrombin generation and activity as well as increased fibrin turnover.(200) Although these derangements appear to be correlated with aneurysm size,(20) increased fibrin turnover is also found in patients with small AAA.(5) This may show that haemostatic derangement is related to the size of intra-sac thrombus than aneurysm size.(21)

Both open surgical (OR) and endovascular (EVAR) repair of AAA are associated with increased thrombin generation and relative hypo-fibrinolysis in the immediate peri-operative period.(19, 22, 34, 43, 154, 200, 201) The resultant pro-thrombotic diathesis after OR and EVAR may account for the high level of peri-operative thrombotic complications. It was found that the haemostatic response is significantly reduced in the long term following OR but not normalized.(153) However, it remains unclear what happens in the long term following EVAR and what the clinical consequences of these haemostatic abnormalities might be for patients.

The aim of this study, therefore, was to examine thrombin generation, fibrinolysis, and EC, platelet activation and inflammatory response for up to 12 months following elective EVAR.

6.2 Methods:

Twenty-nine patients (27 men and 2 females) of mean age 77 years (range, 55-89 years) and with AAA of mean diameter 6.9 cm (range, 5.5-10 cm) underwent 19 standard and 10 fenestrated EVARs under general (n=12) or epidural (n=17) anaesthesia. Patients' demographics are shown in (Table 7).

All patients received bolus injection of intravenous heparin (3000 units for standard and 5000 units for fenestrated EVAR) prior to inserting the stent graft. Further boluses of heparin were given during the operation to maintain the activated clotting time above 200. Twenty-two patients were taking aspirin (75 mg daily), 14 were being treated for hypertension, 16 had a history of ischemic heart disease, and 14 had renal impairment.

Venous blood was collected from the ante-cubital fossa without tourniquet into sodium citrate tubes before induction of anaesthesia and at 1 day and 1, 6, and 12 months post-operatively. Samples were centrifuged for 15 minutes at 3500 revolutions per minute within 30 minutes of collection; plasma was isolated, aliquot, and stored in the freezer at -80°C for later batch analysis.

Markers of thrombin generation and neutralization.

Prothrombin fragment (PF) 1+ 2 (USCN Life Science Inc, Wuhan, China) and thrombin-antithrombin complexes (TAT; Enzygnost TAT Micro, Siemens Healthcare Diagnostics Inc, Deerfield, Ill) were measured.

Markers of fibrinolysis.

Plasminogen activator inhibitor (PAI) activity (Technozym PAI-1 Actibind; Technoclone Ltd, Surrey, United Kingdom) and tissue plasminogen activator (t-PA) antigen and activity (t-PA Combi Actibind; Technoclone Ltd) were measured.

Markers of platelet and endothelial activation and inflammation.

Soluble (s)P-selectin was measured as a marker of platelet activation, sE-selectin as a marker of EC activation (202) (IBL International GMBH, Hamburg, Germany), and highly sensitive C-reactive protein (hs-CRP) was measured as a marker of the inflammatory response.

Tests were performed using the fully automated, multibatch and multi-test Triturus EIA Analyzer (Grifols USA, LLC, Los Angeles, Calif) according to the manufacturer's instructions.

6.3 Results:

6.3.1 Patients and stent grafts

Twenty-three patients had a Zenith (Cook Inc., Bloomington, Ind.) and six had an Excluder (WL Gore Inc., Flagstaff, AZ). Standard EVAR was used for patients with infra-renal AAA (19 patients) and F-EVAR was used to treat juxta-renal, supra-renal and thoraco-abdominal AAA (10 patients). All the grafts were implanted successfully with no graft failure or graft related mortality encountered during the 12-month period.

Three patients required re-intervention at six months post-operatively. They developed claudication-type symptoms due to stenosis in one limb of the graft. This was diagnosed clinically and confirmed using duplex scanning. Two patients required angioplasty and the third patient required combined common femoral artery endarterectomy and angioplasty. Two other patients developed type II endoleak. This was detected by duplex and confirmed by CT scan at 6 months follow up visit with no intervention required. Changes in different markers are shown in table 10.

Table 10: Changes in different markers over time (median and IQR)

	Pre-operative	24 hours	1 month	6 months	12 months
PF1+2 (0.4-1.1 nmol/l)	2.1 (1.5-3.7)	2 (1.4-2.9)	2.1 (1.6-3.4)	1.9 (1.2-2.5)*	1 (0.7-2)*
TAT (1-4.1 µg/l)	6.2 (4.4-15.6)	14 (11-24.6)*	8.1 (5.4-14.3)	8.9 (5.1-11.6)	7 (5.1-11)
PAI activity (1-7 U/ml)	4.9 (0.3-6.8)	8.5 (0.3-10.6)*	0.3 (0.3-3)*	0.3 (0.3-4)*	5.7 (3.8-7.7)
t-PA antigen (2-8 ng/ml)	3.4 (2.6-4.4)	5.1 (3.1-6.4)*	3.5 (2.4-5.4)	1.2 (1-2.2)*	3.4 (2.4-4.5)
t-PA activity (0 U/ml) Mean(SD)	0 (0)	0 (0)	0.046 (0.09)*	0.023 (0.06)*	0 (0)
sP-selec (92-212 ng/ml)	71 (61-86)	80 (61-93)	113 (80-141.5)*	110 (73.5-139.5)*	87 (61-116)*
E-selec (17.5-88.1 ng/ml)	14 (9-18)	24.5 (12.5-42.5)*	15 (9-22)	52 (23.5-59.5)*	38 (24-42)*
hsCRP (mg/l)	4.3 (1.5-12.75)	82.2 (53-105.5)*	7 (3.3-19)	4.3 (2.1-16.3)	2.7 (1.2-11.6)

*p<0.05 against pre-operative values. IQR: inter-quartile range. SD: standard deviation.

The groups were compared using Friedman test. The change over time was analysed using Dunn's multiple comparison test and Wilcoxon signed rank paired test. In order to determine the effects of co-variables on the results, data were log transformed in order to follow normal distribution and analysis was performed using the parametric independent-sample *t*-test.

6.3.2 Markers of coagulation

PF1+2: The median (IQR) pre-operatively was significantly higher than the normal range 2.1 nmol/l (1.5-3.7). At 24 hours and one month, it stayed significantly higher than normal, but, there was no significant change from the baseline level (2 nmol/l (1.4-2.9) and 2.1 nmol/l (1.6-3.4) respectively). This was followed by significant drop in PF1+2 at six months (1.9 nmol/l (1.2-2.5), p=0.035), however, still significantly higher than the normal range. At 12 months, it dropped further to within the normal range (1 nmol/l (0.7-2), p<0.001) and was significantly lower than the baseline. (Figures 3)

TAT: The median (IQR) pre-operatively was significantly higher than the normal range 6.2 µg/l (4.4-15.6). It increased significantly at 24 hours in response to the operation (14 µg/l (11-24.6), p<0.005). This was followed by return to the pre-operative level at one (8.1 µg/l (5.4-14.3)), six (8.9 µg/l (5.1-11.6)) and 12 months (7 µg/l (5.1-11)) post-operatively. TAT remained higher than the normal range through the whole length of the study. (Figures 4)

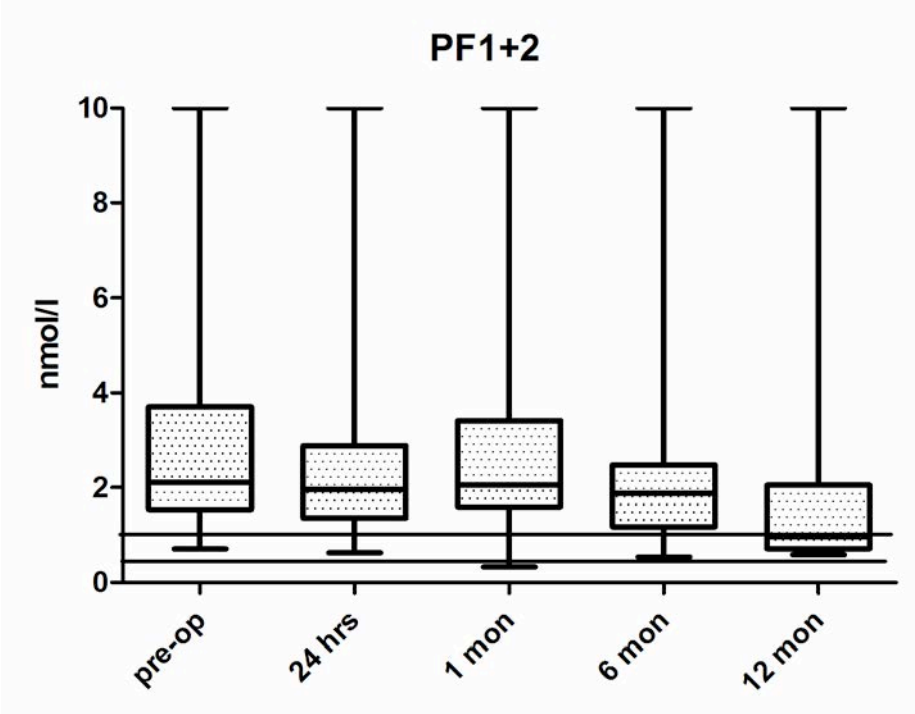


Figure 3: Changes in PF 1+2, horizontal lines represent the normal range

The median (IQR) pre-operatively was significantly higher than the normal range 2.1 nmol/l (1.5-3.7). At 24 hours and one month, it stayed significantly higher than normal, but, there was no significant change from the baseline level (2 nmol/l (1.4-2.9) and 2.1 nmol/l (1.6-3.4) respectively). This was followed by significant drop in PF1+2 at six months (1.9 nmol/l (1.2-2.5), p=0.035), however, still significantly higher than the normal range. At 12 months, it dropped further to within the normal range (1 nmol/l (0.7-2), p<0.001) and was significantly lower than the baseline.

	Pre-operative	24 hours	1 month	6 months	12 months
PF1+2 (0.4-1.1 nmol/l)	2.1 (1.5-3.7)	2 (1.4-2.9)	2.1 (1.6-3.4)	1.9 (1.2-2.5)*	1 (0.7-2)*

*p<0.05 against pre-operative values.

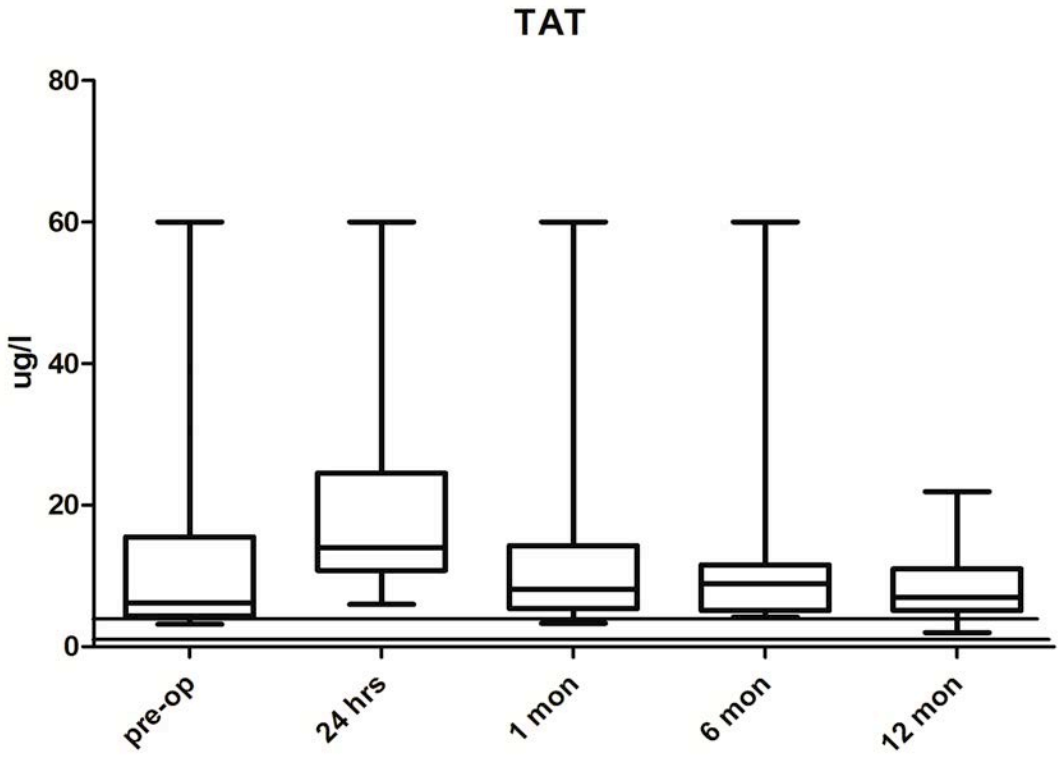


Figure 4: Changes in TAT

The median (IQR) pre-operatively was significantly higher than the normal range 6.2 µg/l (4.4-15.6). It increased significantly at 24 hours in response to the operation (14 µg/l (11-24.6), $p<0.005$). This was followed by return to the pre-operative level at one (8.1 µg/l (5.4-14.3)), six (8.9 µg/l (5.1-11.6)) and 12 months (7 µg/l (5.1-11)) post-operatively. TAT remained higher than the normal range through the whole length of the study.

	Pre-operative	24 hours	1 month	6 months	12 months
TAT (1-4.1 µg/l)	6.2 (4.4-15.6)	14 (11-24.6)*	8.1 (5.4-14.3)	8.9 (5.1-11.6)	7 (5.1-11)

*$p<0.05$ against pre-operative values.

6.3.3 Markers of fibrinolysis

PAI: The median (IQR) of PAI was within the normal range 4.9 U/ml (0.3-6.8). It increased significantly at 24 hours to above the normal level (8.5 U/ml (0.3-10.6), p=0.001). This was followed by significant drop at one (0.3 U/ml (0.3-3), p<0.001) and six months (0.3 U/ml (0.3-4), p=0.002) with the median below the normal range. At 12 months, there was a significant increase in PAI to return to the baseline level 5.7 U/ml (3.8-7.7) (p=0.008) to stay within the normal range. (Figures 5)

t-PA antigen: The median (IQR) of t-PA antigen was within the normal range 3.4 ng/ml (2.6-4.4). t-PA antigen increased significantly at 24 hours (5.1 ng/ml (3.1-6.4), p<0.001) and then returned to the baseline level at one month. This was followed by significant reduction at six months (1.2 ng/ml (1-2.2), p<0.001) and return back to pre-operative values at 12 months. t-PA antigen stayed within the normal range during the whole period of the study. (Figures 6)

t-PA activity: t-PA activity was 0 U/ml pre-operatively. There was no change at 24 hours post-operatively. This was followed by significant increase at one (p<0.005) and six months (p=0.03) and return to pre-operative level at 12 months. (Figures 7)

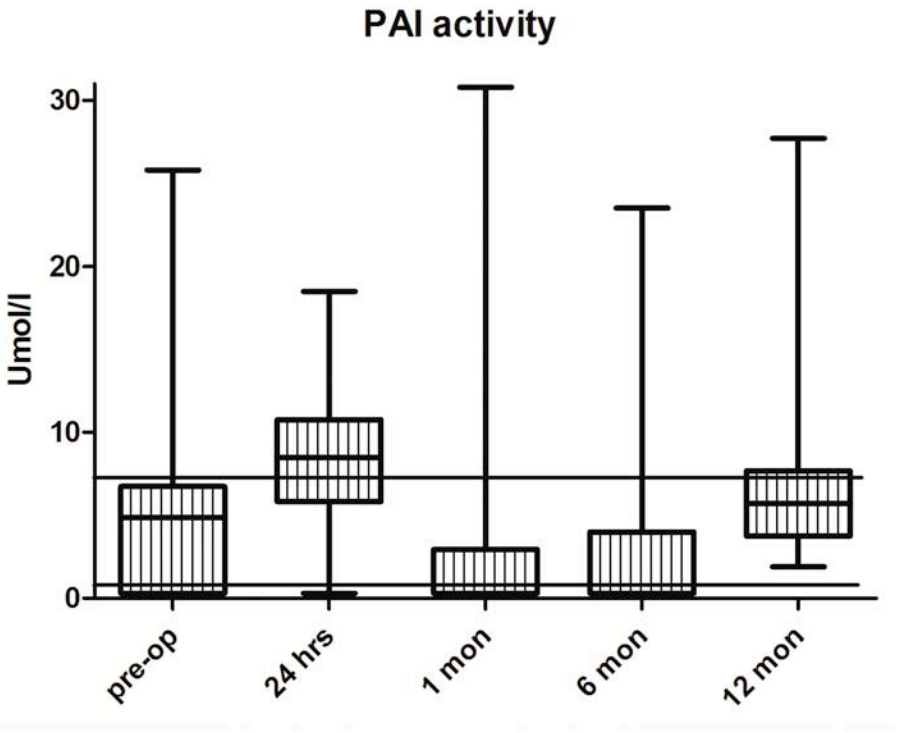


Figure 5: Changes in PAI activity

The median (IQR) of PAI was within the normal range 4.9 U/ml (0.3-6.8). It increased significantly at 24 hours to above the normal level (8.5 U/ml (0.3-10.6), p=0.001). This was followed by significant drop at one (0.3 U/ml (0.3-3), p<0.001) and six months (0.3 U/ml (0.3-4), p=0.002) with the median below the normal range. At 12 months, there was a significant increase in PAI to return to the baseline level 5.7 U/ml (3.8-7.7) (p=0.008) to stay within the normal range.

	Pre-operative	24 hours	1 month	6 months	12 months
PAI activity (1-7 U/ml)	4.9 (0.3-6.8)	8.5 (0.3-10.6)*	0.3 (0.3-3)*	0.3 (0.3-4)*	5.7 (3.8-7.7)

*p<0.05 against pre-operative values.

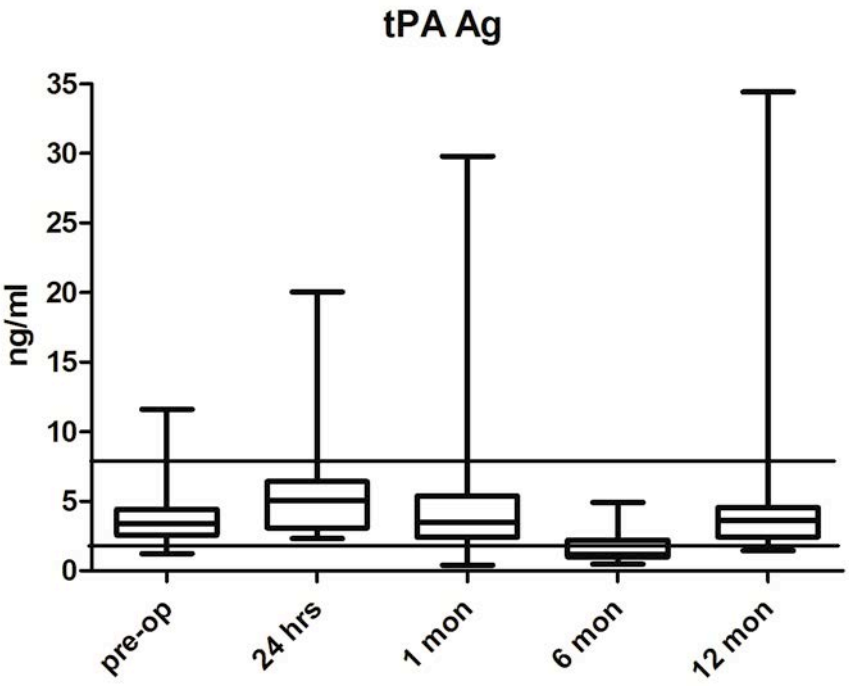


Figure 6: Changes in T-PA antigen

The median (IQR) of t-PA antigen was within the normal range 3.4 ng/ml (2.6-4.4). t-PA antigen increased significantly at 24 hours (5.1 ng/ml (3.1-6.4), $p<0.001$) and then returned to the baseline level at one month. This was followed by significant reduction at six months (1.2 ng/ml (1-2.2), $p<0.001$) and return back to pre-operative values at 12 months. t-PA antigen stayed within the normal range during the whole period of the study.

	Pre-operative	24 hours	1 month	6 months	12 months
t-PA antigen (2-8 ng/ml)	3.4 (2.6-4.4)	5.1 (3.1-6.4)*	3.5 (2.4-5.4)	1.2 (1-2.2)*	3.4 (2.4-4.5)

*$p<0.05$ against pre-operative values.

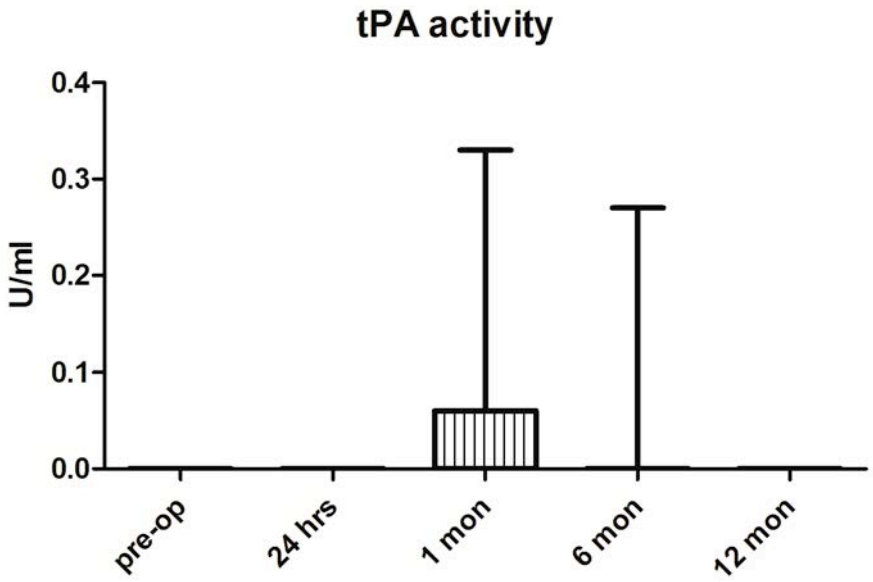


Figure 7: Changes in t-PA activity

t-PA activity was 0 U/ml pre-operatively. There was no change at 24 hours post-operatively. This was followed by significant increase at one ($p<0.005$) and six months ($p=0.03$) and return to pre-operative level at 12 months.

	Pre-operative	24 hours	1 month	6 months	12 months
t-PA activity (0 U/ml) Mean(SD)	0 (0)	0 (0)	0.046 (0.09)*	0.023 (0.06)*	0 (0)

*$p<0.05$ against pre-operative values.

6.3.4 Platelet activation

Pre-operative level of sP-selec was significantly lower than the normal range at 71 ng/ml (61-86). It stayed below the lower limit of the normal range with no significant change at 24 hours post-operatively (80 ng/ml (61-93)). At one month, there was significant elevation (113 ng/ml (80-141.5), p<0.001) which remained high at six months (110 ng/ml (73.5-139.5), p<0.001). Both levels were within the normal levels. There was a significant drop at 12 months from the level of six months (87 vs 110 ng/ml, p<0.005). The median value at 12 months was down to below the normal range, however, higher than the pre-operative level (p=0.008). (Figure 8)

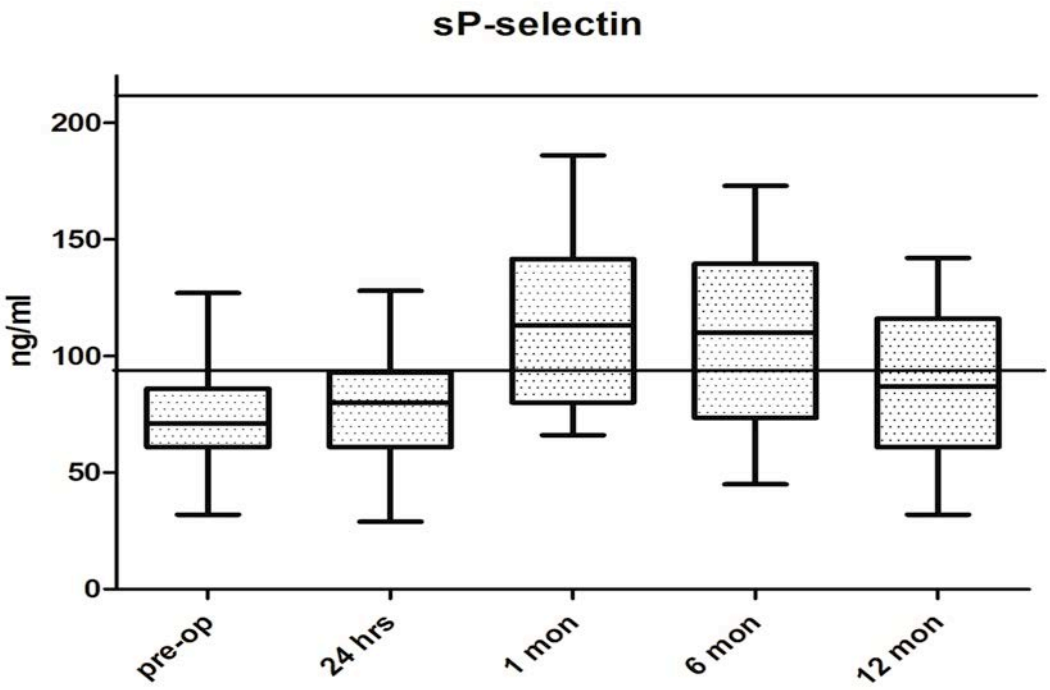


Figure 8: Changes in sP-selectin activity

	Pre-operative	24 hours	1 month	6 months	12 months
sP-selec (92-212 ng/ml)	71 (61-86)	80 (61-93)	113 (80-141.5)*	110 (73.5-139.5)*	87 (61-116)*

*p<0.05 against pre-operative values.

6.3.4 Endothelial activation

sE-selec pre-operatively was found to be lower than the normal level 14 ng/ml (9-18). There was a significant increase at 24 hours when compared with baseline level (24.5 ng/ml (12.5-42.5) vs 14 ng/ml (9-18), p<0.001). This was followed by return to pre-operative value at one month (15 ng/ml (9-22)) and significant increase at six (52 ng/ml (23.5-59.5), p<0.001) and 12 months (38 ng/ml (24-42), p<0.001). (Figure 9)

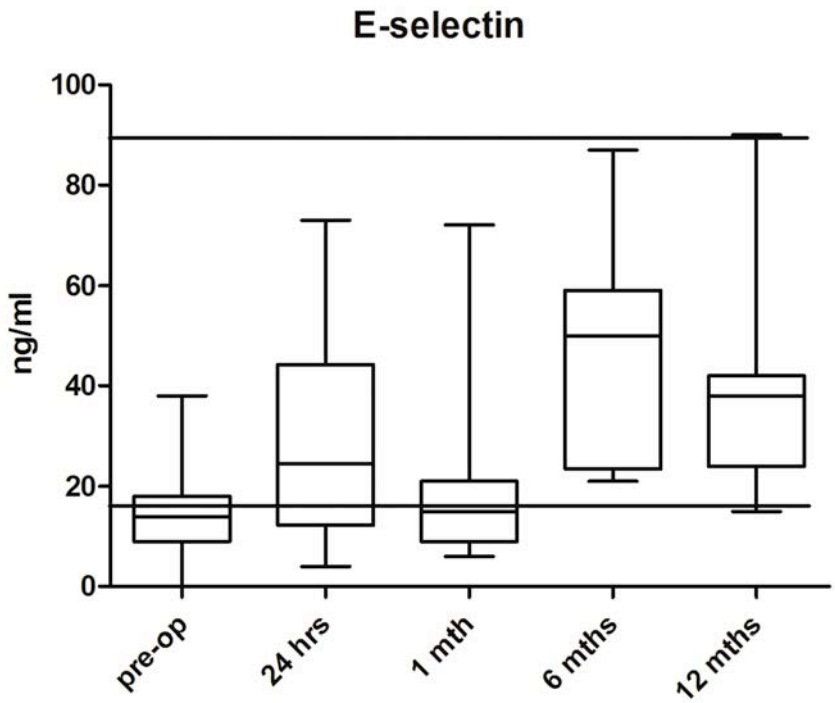


Figure 9: Changes in sE-selectin activity

	Pre-operative	24 hours	1 month	6 months	12 months
E-selec (17.5-88.1 ng/ml)	14 (9-18)	24.5 (12.5-42.5)*	15 (9-22)	52 (23.5-59.5)*	38 (24-42)*

*p<0.05 against pre-operative values.

6.3.6 Inflammatory response

hs-CRP increased significantly 24 hours post-operatively in response to the operation (82.2 mg/l (53-105.5) vs 4.3 mg/l (1.5-12.75), p<0.001). This was followed by a fall down to the baseline levels at one month (7 mg/l (3.3-19)). There was not significant change in the level of hsCRP at six (4.3 mg/l (2.1-16.3)) and 12 months (2.7 mg/l (1.2-11.6)). (Figure 10)

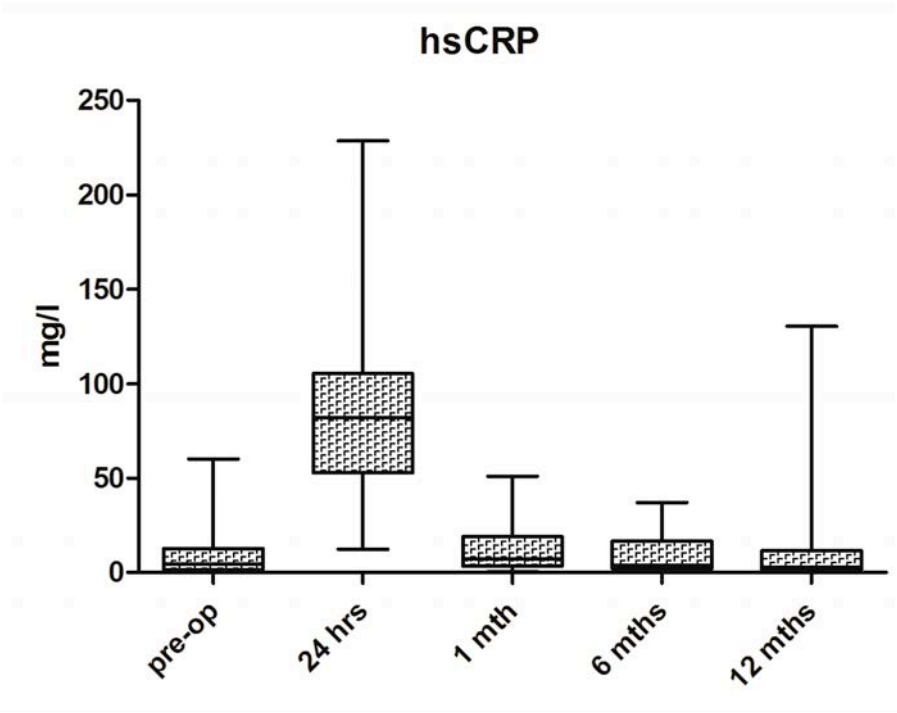


Figure 10: Changes in hsCRP activity

	Pre-operative	24 hours	1 month	6 months	12 months
hsCRP (mg/l)	4.3 (1.5-12.75)	82.2 (53-105.5)*	7 (3.3-19)	4.3 (2.1-16.3)	2.7 (1.2-11.6)

*p<0.05 against pre-operative values.

6.3.7 Correlation of different markers, aneurysm size and demographics

Aneurysm size did not correlate with coagulation, fibrinolytic or inflammatory markers pre or post-operatively. TAT and PF1+2 did not correlate at any time point. PAI activity correlated significantly with t-PA antigen at all time points ($p<0.001$). sP-selec and E-selec did not correlate at any time point. Correlation with other co-variables is shown in table 7.

6.4 Discussion:

There has been a concern of developing coagulation disorders following EVAR especially the fatal complication of consumptive coagulopathy. Ohara et al (203) described fatal DIC in one patient with severe liver disease following EVAR. Cross et al (204) reported another case of fatal consumptive coagulopathy following technically difficult EVAR. It was believed that leaving the thrombus in the isolated aneurysm sac may be the trigger factor for this coagulation derangement. Hollier et al (205) described a non-resective technique for high risk patients with AAA. They ligated the proximal and distal sides of the aneurysm, leaving the contained thrombus behind, and performed an axillo-bifemoral bypass to exclude the aneurysm. Schwartz et al (206) reported that DIC may complicate non-resective treatment of AAA.

The results in this study show that patients with asymptomatic AAA have pre-operative hyper-coagulable state as demonstrated by higher than normal PF1+2 and TAT. (Figures 3 & 4) This result is similar to previous studies which found activated coagulation pre-operatively in patients with AAA.(5, 18, 20, 22, 34, 43, 201) Our results show that pre-operative TAT level was significantly higher in patients >75 years ($p=0.001$). Unlike previous studies, we did not find correlation between pre-operative TAT and PF1+2 with aneurysm size.

The different behaviour of PF1+2 and TAT in response to EVAR and the lack of correlation between these two markers before and after the operation suggest they represent different responses. High levels of PF1+2 and TAT indicate excess thrombin production and neutralization respectively. PF1+2 remained unchanged from baseline at 24 hours and one month post-operatively indicating no increase in

thrombin generation in response to EVAR. At 6 months, it decreased significantly; however, it was higher than normal values. At 12 months, PF1+2 dropped significantly below the pre-operative level to reach the normal range suggesting normalization of thrombin generation at one year post EVAR. This means that the presence of the thrombus in the isolated aneurysm sac does not induce thrombin production as previously thought.

The significant increase in TAT at 24 hours post-operatively may be explained by increased binding with anti-thrombin III in response to manipulation during insertion of the stent graft. Shimazaki et al (201) and Monaco et al (154) showed significant reduction in anti-thrombin III and significant increase in TAT on the first post-operative day. They showed return of anti-thrombin III to baseline on the first week after the operation and then remained unchanged. Results similar to ours were observed at short term in previous studies.(22, 43, 201) However, this is the first report to describe normalization of thrombin generation following EVAR which is detected one year following the operation. This may be due to lack of reports looking at these changes at the long term. The combination of no increase in thrombin generation and increased thrombin neutralization following EVAR may be protective against cardiovascular complications and thrombo-embolic disorders in this group of patients.

Similar to previous studies, we found pre-operative PAI activity, t-PA antigen and activity within normal range suggestive of normal fibrinolysis in patients with AAA.(20, 22, 34) We found t-PA antigen significantly low in older patients ($p=0.025$). This, together with higher TAT, agrees with earlier report that old age is associated with activation of the coagulation and fibrinolytic activity.(14) Following EVAR, PAI

activity increased significantly on the first post-operative day higher than normal range indicating hypo-fibrinolysis. There was significant drop to less than normal values noticed at one and six months suggestive of hyper-fibrinolysis. At 12 months, PAI activity returned to the baseline level within the normal range. Aho et al (22) described significant increase in PAI activity at day one post-operatively, temporary decrease at day three, increase again at day seven and return to pre-operative level at three months.

t-PA antigen increased significantly at 24 hours, though within the normal range. There was significant drop below normal range at six months and return to baseline at 12 months. t-PA activity was undetected pre-operatively and 24 hours following EVAR. It increased significantly at one month, remained high at six months and was undetectable again at 12 months post-operatively. The post-operative fibrinolytic response showed low fibrinolytic activity on the first post-operative day which may be due to the surgical trauma, high fibrinolytic activity at one and six months and return to the normal fibrinolytic activity 12 months following EVAR. The expected correlation between PAI activity and t-PA antigen at all time points indicate the validity of the analysis.

Platelet activity, as represented by sP-selec, was subnormal pre-operatively and 24 hours after the operation. Patients with IHD and those who were on anti-platelet treatment before the operation had significantly lower sP-selec at these two time points. There was significant increase at one and six months followed by significant drop at 12 months. However, one year after EVAR, sP-selec was significantly higher than the baseline level. The significant increase in platelet activity may justify giving dual anti-platelet therapy to patients following EVAR especially during the first year

after the operation. Aho et al described significant reduction in sP-selec on third post-operative day with increase above the baseline three months following EVAR. The significant increase in sE-selec that was observed on the first post-operative day could be due to the manipulation during inserting the stent graft. The absence of correlation between sP-selec and sE-selec at all time points and their different responses to EVAR indicated that they did not arise from the same source.

The increase in hs-CRP experienced on day one, occurred in response to the surgical trauma. However, there was no significant difference in the inflammatory response, from the baseline level, at one, six and 12 months post-operatively. Previous studies showed detected maximum increase in CRP on the second and third days following EVAR.(22, 43)

Patients with infra-renal AAA had significantly lower pre-operative hs-CRP ($p<0.003$). When the inflammatory response to EVAR was compared between patients, those who had F-EVAR had significantly higher response at one ($p=0.012$), six (0.009) and 12 (0.021) months than patients who had standard EVAR. This may indicate that the inflammatory response is related to the extent of the aneurysm rather than the size. It has been confirmed before that CRP correlated with the volume of the intra-mural thrombus.

We found that type of the stent graft affected the coagulation response following EVAR. Patients who had Zenith graft had significantly higher TAT than patients who had Excluder stents at one ($p<0.001$), six ($p=0.03$) and 12 ($p=0.008$) months suggesting more thrombin neutralization. This may be related to the porosity of the graft material. They also had higher hs-CRP at one, six and 12 months ($p<0.05$, 0.005 and 0.003 respectively). However, after adjustment to patients with infra-renal

AAA, there was no statistical difference in the inflammatory response between patients who had Zenith from those who had Excluder grafts.

6.5 Conclusion:

This report shows for the first time normalization of coagulation mechanism one year following EVAR. The unchanged thrombin production and increased thrombin neutralization experienced on the first post-operative day may be protective at the early stages following EVAR. The normalization of thrombin generation and fibrinolytic response one year after the operation may represent a decrease in the incidence of thrombo-embolic events that is high in patients with AAA. Following EVAR, dual anti-platelet therapy may be advisable to counteract the increase in platelet activity experienced during the first post-operative year.

Chapter 7

Effect of EVAR and OAR on thrombin generation, fibrinolysis and inflammatory response

7.1 Introduction:

Abdominal aortic aneurysm (AAA) is a chronic inflammatory condition associated with activation of coagulation.(17-19, 149) The aetiology of these changes is poorly understood but may be related to smoking, the presence of peripheral arterial disease leading to repeated lower limb ischemia and reperfusion, and the biological activity of the aortic wall and/or intra-luminal thrombus.(14-16) Previous studies have suggested an association between the observed haemostatic derangements, micro-vascular and macro-vascular thrombosis, and the development of complications such as myocardial infarction, multiple organ failure, and venous and arterial thromboembolism.(11-13) Open aneurysm repair (OAR) and endovascular aneurysm repair (EVAR) of AAAs have been shown to be associated with an exacerbation of these haemostatic derangements in the immediate peri-operative period.(18, 34, 200) By contrast, the medium- and long term changes in coagulation and fibrinolysis after OAR and EVAR are poorly defined.(153)

The purpose of this study, therefore, was to investigate, we believe for the first time, the medium-term effects of EVAR and OAR on thrombin generation, neutralization, and fibrinolysis.

7.2 Patients and Methods:

7.2.1 Group 1:

Twenty-nine patients (27 men) of mean age 77 years (range, 55-89 years) were studied before (pre-operative) and after EVAR (post-EVAR) for asymptomatic AAA of mean diameter 6.9 cm (range, 5.5-10 cm) between July 2008 and April 2009.

7.2.2 Group 2:

Eleven patients (nine men) were studied at mean of 16 months (range, 7-21 months) after OAR (post-OAR). Mean age at the time of blood sampling was 72 years (range, 58-85 years). All patients who underwent OAR were anatomically unsuitable for standard EVAR.

7.2.3 Group 3:

Eight age-matched controls (AMC) (four men) of mean age 73 years (range, 65-90 years) without AAA as documented by computed tomography (CT) scan, performed for the investigation of a nonvascular condition, were recruited. Specifically, five patients had normal follow-up CT scans 2 years after resection for colon cancer, and three patients had normal CT scans for nonspecific abdominal pain. None of these patients was found to have any significant pathology.

Exclusion criteria included vascular or nonvascular surgical or endovascular procedure within the 3 months before EVAR or blood sampling; known inherited or acquired thrombophilia; known disorders of fibrinolysis or platelet function; and anticoagulation with vitamin K antagonists. Blood sampling and assays. Venous

blood samples were taken from an antecubital fossa vein without tourniquet immediately before and 12 months after EVAR. Patients who underwent OAR and AMC had a single sample taken. Samples were centrifuged for 15 minutes at 3500 rpm within 30 minutes of collection; plasma was isolated, aliquoted, and stored at -80°C for later batch analysis. Levels of prothrombin fragment (PF)1+2, a marker of thrombin generation, (USCN Life Science, Wuhan, China) and thrombin-antithrombin (TAT) complex, a marker of thrombin neutralization (Enzygnost TAT micro, Siemens Healthcare Diagnostics, Deerfield, Ill) were measured using enzyme-linked immunosorbent assays. Tissue-plasminogen activator (t-PA) antigen (t-PA Combi Actibind, Technoclone Ltd, Surrey, UK) and plasminogen activator inhibitor (PAI) activity (Technozym PAI-1 Actibind, Technoclone Ltd, Surrey, UK) were assayed as measures of fibrinolysis.

PF1+2, TAT, t-PA antigen, and PAI activity enzyme linked immuno-sorbent assays were performed using the Triturus EIA Analyzer (Grifols, USA, LLC, Los Angeles, Calif) according to the manufacturer's instructions.

7.2.4 Statistical analysis:

Analyses were performed using SPSS for Windows (version 16.0; SPSS Inc, Chicago, Ill) and GraphPad Prism 5 for Windows (version 5.03; GraphPad Software, San Diego, Calif). Data were log transformed, as they were not normally distributed. Median and Inter-quartile range values were calculated for continuous variables and categorical data were expressed as absolute numbers with percentages. Differences between study groups were assessed by the Fisher exact test for categorical variables and by Mann-Whitney U tests for continuous variables. Correlation was

assessed by the Pearson method. Results were considered statistically significant when P values were < 0.05.

7.3 Results:

All EVAR procedures were undertaken uneventfully with AAA sac exclusion being confirmed by completion angiography and post procedure CT. One patient developed acute coronary syndrome on the day of the operation and showed relatively higher PF1 2 levels. By 6 months, three patients developed unilateral graft limb stenosis and had required re-intervention for claudication; two underwent balloon angioplasty and a third had common femoral artery endarterectomy and patch angioplasty. Two other patients developed asymptomatic type II endoleak, which were treated conservatively. None of the patients who required intervention or those who developed endoleak showed significant pro-coagulant results. None of the patients developed deep vein thrombosis, pulmonary embolism, or post-implantation inflammation syndrome. All OARs were undertaken uneventfully without major complications and none of the patients required re-intervention in the period between surgery and blood sampling. In group 3, one patient who had CT scan for abdominal pain was found to have gall bladder stones and no other significant pathology was found in the remaining seven patients. Laboratory results of different markers are shown in Table 11.

Table 11: Laboratory results of different markers in the three groups (median and IQR). Normal range is according to the manufacture's guidelines.

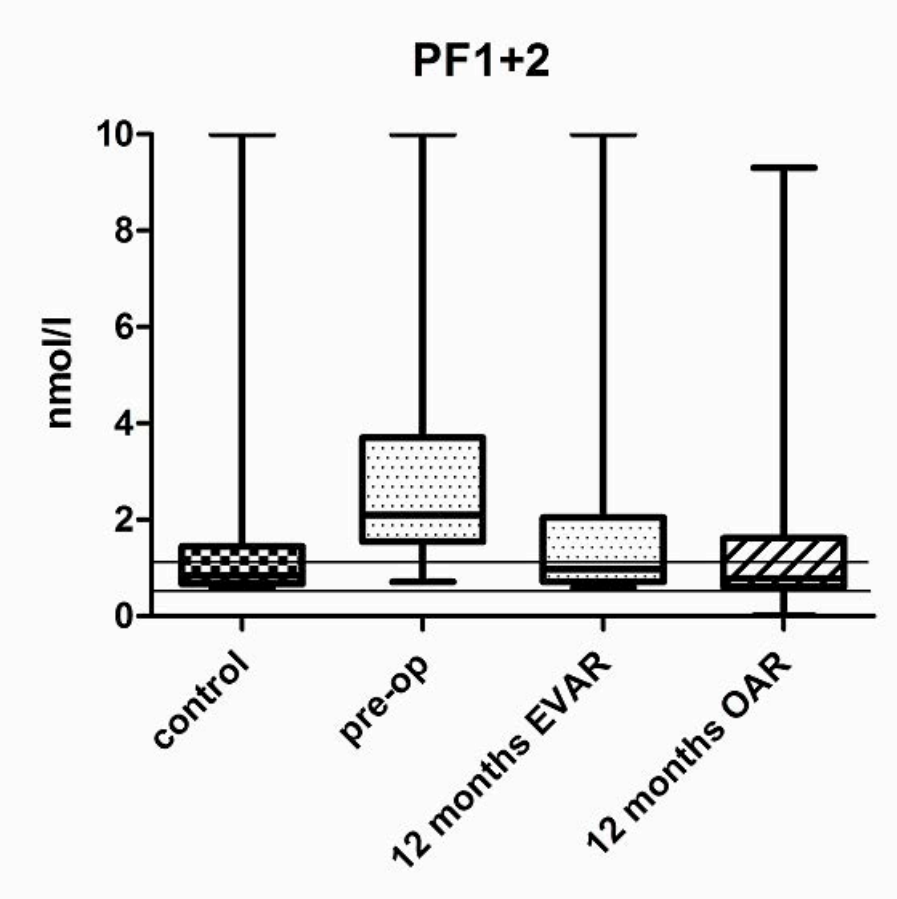
Marker (Normal range)	AMC (n=8)	EVAR (n=29)		OAR (n=11)
		Pre-op	Post-EVAR	
PF1+2 (0.4-1.1 nmol/l)	0.8 (0.7-1.4)	2.2 (1.6-3.5)*	1 (0.7-1.9)	0.8 (0.6-1.6)
TAT (1-4.1 µg/l)	4.6 (2.9-11.3)	6.2 (4.4-15.6)	7 (5.1-11)	5.6 (5-13.3)
PAI activity (1-7 U/ml)	6.4 (3.4-8.7)	4.9 (0.3-6.7)	5.7 (3.8-7.7)	7.5 (5.7-8.3)*
t-PA antigen (2-8 ng/ml)	4.4 (3-4.8)	3.4 (2.6-4.4)	3.6 (2.4-4.5)	4 (3-5)
hs-CRP (mg/l)	1.5 (0.63-4.8)	4.3 (1.5-12.8)*	2.7 (1.2-11.6)	3.8 (1.2-6.7)

* *p*-value <0.05

7.3.1 Markers of coagulation

PF1+2 The median and IQR of PF1+2 was within the normal range in AMC (0.8 (0.7-1.4)). It was significantly higher in patients with AAA pre-operatively than in the AMC group (0.8 (0.7-1.4) vs 2.2 (1.6-3.5), *p value* = 0.0078). Post-EVAR and post-OAR results were significantly lower than pre-operative level (2.2 (1.6-3.5) vs 1 (0.7-1.9) and 0.8 (0.6-1.6), *p value* <0.001 and 0.0046 respectively). The level of PF1+2 post-EVAR was not significantly different from post-OAR. PF1+2 results in both groups were not statistically significantly different from the level in AMC. (Figure 11)

TAT The median levels of TAT in the four groups were higher than the normal range. However, there was no statistical significance between the four groups. (Figure 12)



Figrue11: Changes in PF1+2 among the groups.

The median and IQR of PF1+2 was within the normal range in AMC (0.8 (0.7-1.4)). It was significantly higher in patients with AAA pre-operatively than in the AMC group (0.8 (0.7-1.4) vs 2.2 (1.6-3.5), *p value* = 0.0078). Post-EVAR and post-OAR results were significantly lower than pre-operative level (2.2 (1.6-3.5) vs 1 (0.7-1.9) and 0.8 (0.6-1.6), *p value* <0.001 and 0.0046 respectively). The level of PF1+2 post-EVAR was not significantly different from post-OAR. PF1+2 results in both groups were not statistically significantly different from the level in AMC.

Marker (Normal range)	AMC (n=8)	EVAR (n=29)		OAR (n=11)
		Pre-op	Post-EVAR	
PF1+2 (0.4-1.1 nmol/l)	0.8 (0.7-1.4)	2.2 (1.6-3.5)*	1 (0.7-1.9)	0.8 (0.6-1.6)

* *p*-value <0.05

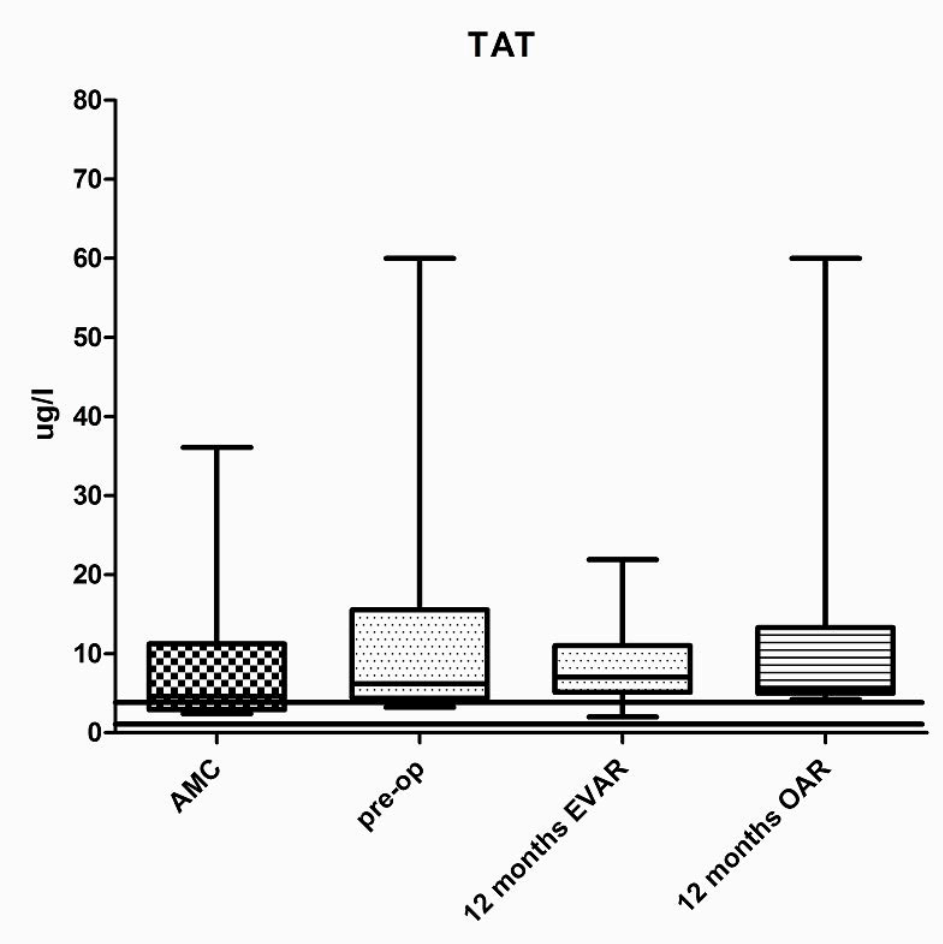


Figure 12: Changes in TAT among the groups.

The median levels of TAT in the four groups were higher than the normal range. However, there was no statistical significance between the four groups.

Marker (Normal range)	AMC (n=8)	EVAR (n=29) Pre-op	EVAR (n=29) Post-EVAR	OAR (n=11)
TAT (1-4.1 µg/l)	4.6 (2.9-11.3)	6.2 (4.4-15.6)	7 (5.1-11)	5.6 (5-13.3)

* *p*-value <0.05

7.3.2 Markers of fibrinolysis

PAI activity There was no difference in the level of PAI activity between AMC with patients with AAA pre-operative (6.4 (3.4-8.7) vs 4.9 (0.3-6.7), *p value*>0.5). There was no significant change in PAI activity one year following EVAR (5.7 (3.8-7.7)). However, the level was significantly higher post-OAR than pre-operatively (7.5 (5.7-8.3) vs 4.9 (0.3-6.7), *p value* 0.03). (Figure 13)

t-PA antigen The results were within the normal range with no significant difference between the four groups. (Figure 14)

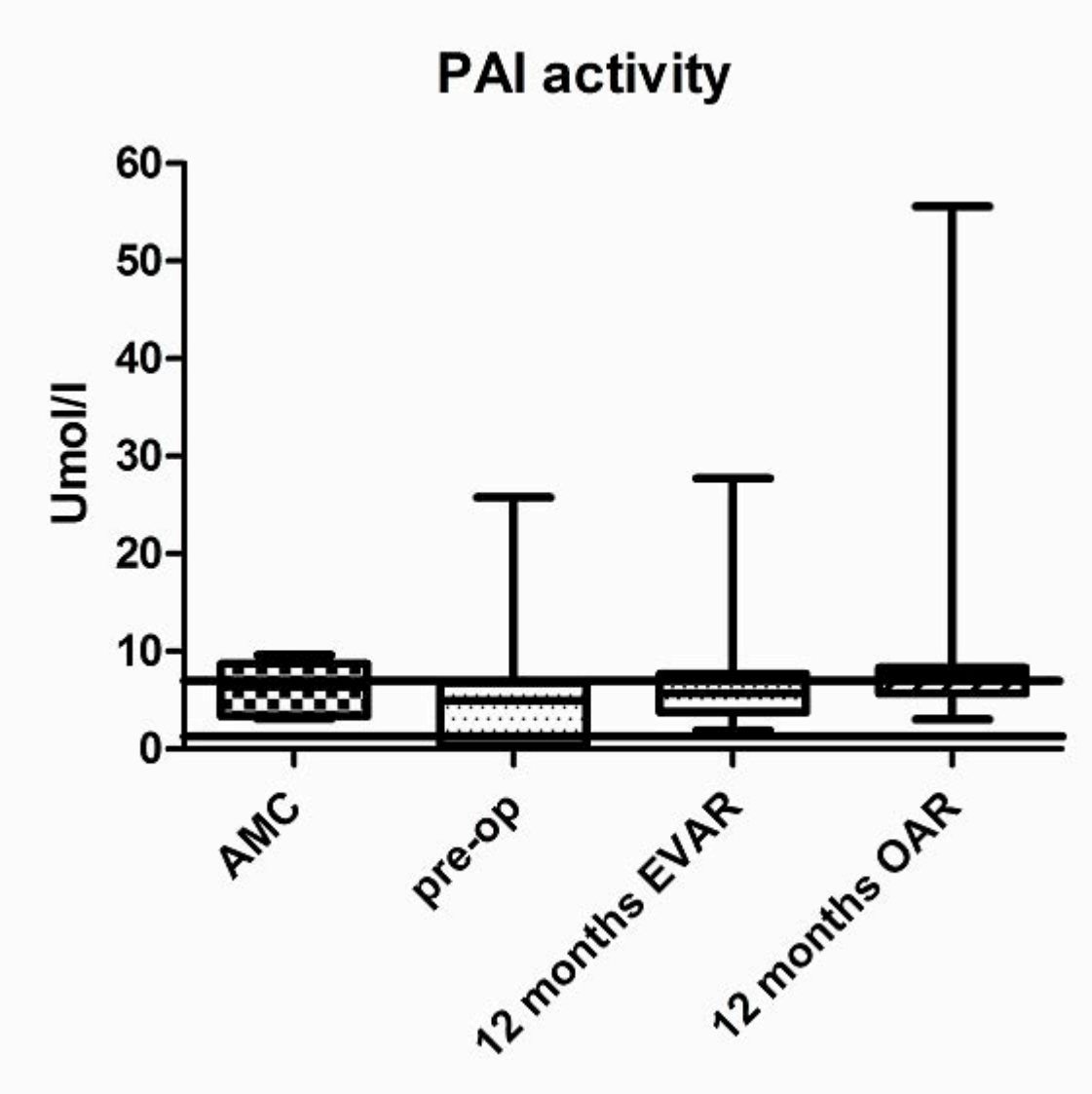


Figure 13: Changes in PAI activity among the groups.

There was no difference in the level of PAI activity between AMC with patients with AAA pre-operative (6.4 (3.4-8.7) vs 4.9 (0.3-6.7), *p value*>0.5). There was no significant change in PAI activity one year following EVAR (5.7 (3.8-7.7)). However, the level was significantly higher post-OAR than pre-operatively (7.5 (5.7-8.3) vs 4.9 (0.3-6.7), *p value* 0.03).

Marker (Normal range)	AMC (n=8)	EVAR (n=29)		OAR (n=11)
		Pre-op	Post-EVAR	
PAI activity (1-7 U/ml)	6.4 (3.4-8.7)	4.9 (0.3-6.7)	5.7 (3.8-7.7)	7.5 (5.7-8.3)*

* *p*-value <0.05

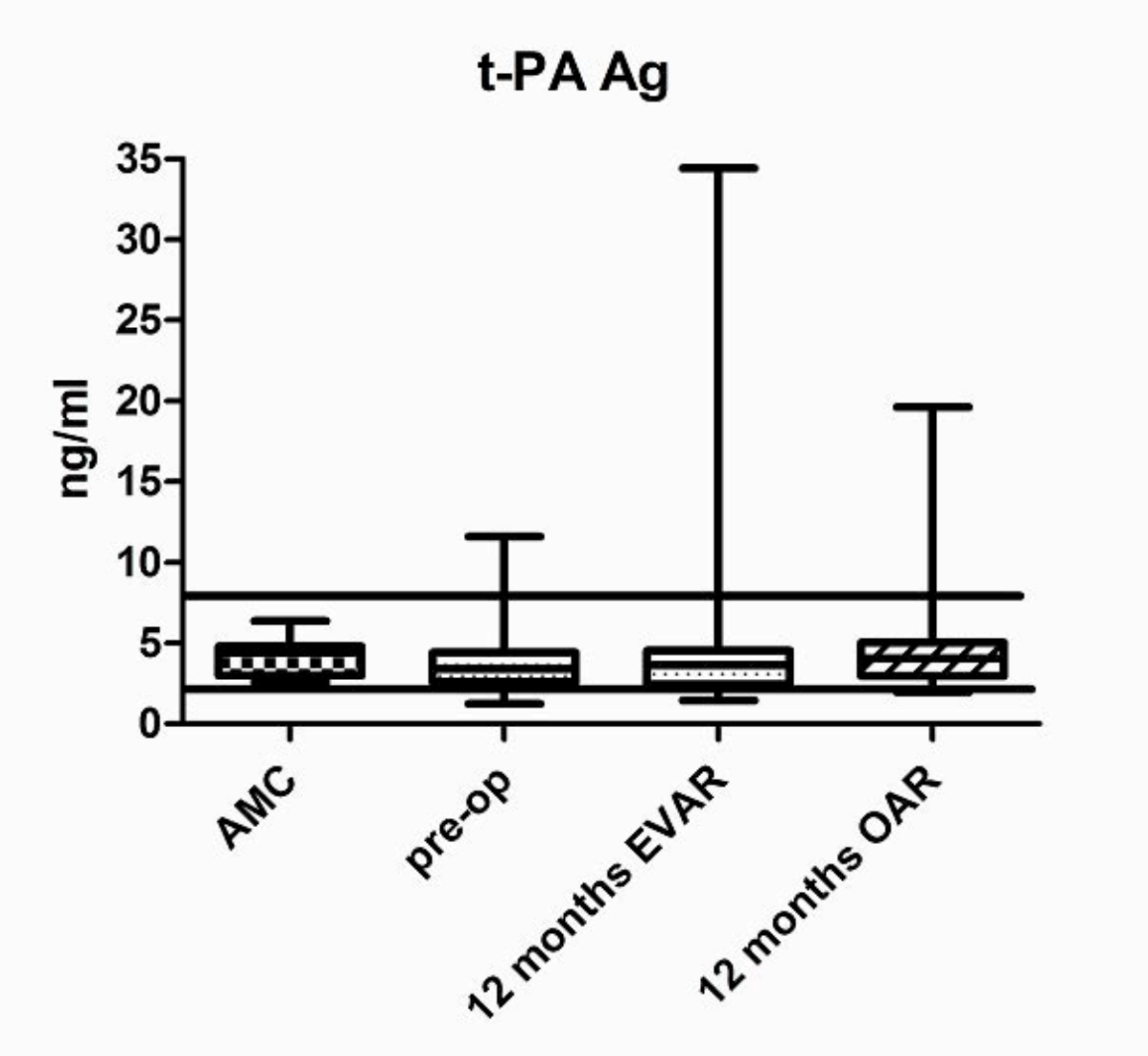


Figure 14: Changes in t-PA antigen among the groups.

The results were within the normal range with no significant difference between the four groups.

Marker (Normal range)	AMC (n=8)	EVAR (n=29) Pre-op	EVAR (n=29) Post-EVAR	OAR (n=11)
t-PA antigen (2-8 ng/ml)	4.4 (3-4.8)	3.4 (2.6-4.4)	3.6 (2.4-4.5)	4 (3-5)

* *p*-value <0.05

7.3.3 Inflammatory Markers

hs-CRP The median and IQR of hs-CRP in patients with AAA pre-operatively was higher than AMC 4.3 (1.5-12.8) vs 1.5 (0.63-4.8), *p value* 0.024). No significant difference was found between post-EVAR and post-OAR groups. (Figure 15)

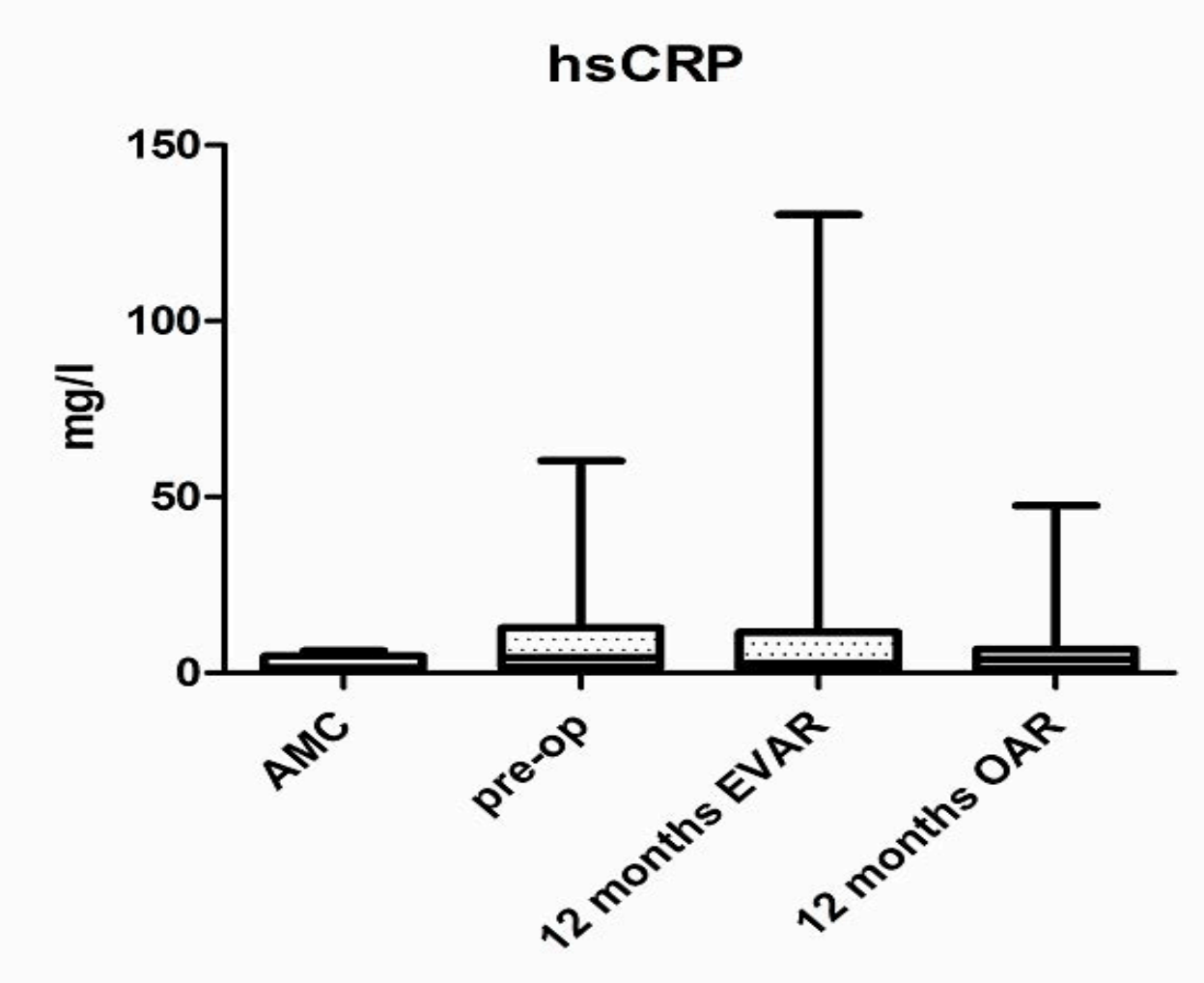


Figure 15: Changes in hsCRP among the groups.

Marker (Normal range)	AMC (n=8)	EVAR (n=29) Pre-op	Post-EVAR	OAR (n=11)
hs-CRP (mg/l)	1.5 (0.63-4.8)	4.3 (1.5-12.8)*	2.7 (1.2-11.6)	3.8 (1.2-6.7)

* *p*-value <0.05

7.4 Discussion:

EVAR is associated with significantly lower peri-operative morbidity and mortality than OAR.(36, 37, 39) However, this benefit is lost six months following the operation.(207, 208) This might be related to continuous coagulopathy at the medium and long term follow up. There is very little information comparing the changes in the haemostatic mechanism at the medium and long term following EVAR and OAR.

The present study confirms that patients with AAA exhibit a hyper-coagulable state compared to AMC. This is confirmed by the significant difference between PF1+2 in pre-operative patients and the control group. The significant drop in PF1+2 one year following EVAR and OAR and the finding that it was not different from AMC group might suggest that the increase in PF1+2 pre-operatively was related to AAA. TAT was not different between the four groups. This might suggest that thrombin neutralization is not related to AAA and is related to other factors like age, atherosclerosis and smoking.(14-16) Our PF1+2 results match the results of Holmberg et al (153), however, TAT results were different. The difference in TAT results may be related to their AMC group constituted of healthy subjects with no history of cardiovascular or peripheral vascular diseases.

PAI activity and t-PA antigen were within the normal range and not different in both AMC and pre-operative groups. This represents relative hypo-fibrinolysis in patients with AAA as you would expect increased fibrinolysis secondary to increased thrombin generation. One year post EVAR, PAI was not different from AMC and pre-operative groups. However, one year post OAR, it was significantly higher than pre-operative group with the median just above the normal range (Figure 13). This might

lead to less fibrinolysis in this group of patients. t-PA antigen was not different post-EVAR and post-OAR from the AMC and pre-operative. These results are similar to Holmberg et al.(153)

Some reports described that EVAR is associated with increased systemic inflammatory response and prothrombotic coagulopathy equal if not greater than that witnessed after OAR at the immediate post-operative period.(42, 154) We found that one year following EVAR and OAR the coagulation mechanism and the inflammatory response are similar and not different from the AMC.

Similar to others (18, 153), we found that removal (as in OAR) or exclusion (as in EVAR) of the intra-aneurysm thrombus from the circulation resulted in correction of the inflammatory and pro-coagulant drive found in patients with AAA. This might confirm the importance of the intra-aneurysm thrombus in the inflammatory and pro-thrombotic diathesis associated with AAA.(21, 22, 128, 153) It has been suggested that the presence of type II endoleak may regain the contact between the circulation and the intra-sac thrombus resulting in deranged haemostasis.(200)

Although the marker of thrombin generation has been normalized one year following EVAR and OAR, thrombin inactivation and fibrinolysis have not had the same response. This may be explained by the presence of atherosclerosis and age.

7.5 Conclusion:

AAA exhibits a significant hyper-coagulable and hypo-fibrinolytic state. This is corrected one year following EVAR and OAR. The increase in thrombin generation reported previously in the immediate peri-operative period after EVAR and OAR does not continue on the medium term. Long follow up is recommended to find out whether the correction of coagulopathy is maintained or lost at the long term and to find the relation of these changes with cardiovascular morbidity and mortality.

Chapter 8

Assessment of Renal Function using Cystatin C

8.1 Introduction:

The effect of EVAR on renal function remains uncertain. Early reports showed a significant increase in serum creatinine (sCr) and reduction in creatinine clearance (CrC) after EVAR.(64, 65, 157-159) sCr levels only increase significantly when glomerular filtration rate (GFR) is reduced by more than 50%,(173) and may be affected by several non-renal factors (e.g., diet, gender, muscle mass, surgical intervention, numerous drugs).

Cystatin C (Cyst C) is a low-molecular-weight plasma protein that is synthesized and secreted by all nucleated human cells and is a more sensitive serum marker of subclinical renal injury than sCr, CrC, or GFR.(209-213) However, Cyst C is not the standard marker used in clinical practice to detect the renal function after EVAR.

Previous studies examining the impact of EVAR on renal function using Cyst C have shown no deterioration in renal function; one report showed no change in Cyst C levels at 3, 6, and 12 months after EVAR, whereas another showed decreased Cyst C levels at 24 hours post-operatively, indicating improved glomerular function. (214, 215)

Deterioration in renal function after fenestrated EVAR has been reported to be as high as 10% to 30%,(91, 98, 165) although this group has never been studied using Cyst C.

Despite the evidence of sensitivity of Cyst C for detecting minor renal damage, as proven in several studies, sCr and estimated GFR are still used as the standard markers of renal function.

The goal of this study, therefore, was to compare the efficacy of Cyst C, sCr, and estimated GFR as markers of renal function after standard and fenestrated EVAR.

8.2 Patients and Methods:

This study included 29 patients (27 men and 2 women) with a mean age of 76.9 years (range, 55-89 years) undergoing standard (n=19) and fenestrated (n=10) EVAR for an abdominal aortic aneurysm (AAA) with a median diameter of 6.2 cm (inter-quartile range [IQR], 5.8-7.5 cm). Patients with elevated pre-operative sCr were included and provided with peri-operative hydration. Surgery was performed under general or epidural anaesthesia. The median contrast load was 75 mL (IQR, 70e90 mL) of VisipaqueTM for patients who had standard EVAR and 110 mL (IQR, 105e130 mL) for those who underwent fenestrated EVAR. No patient required peri-operative blood transfusion.

Venous blood was collected from the ante-cubital fossa without tourniquet to measure serum Cyst C and sCr before induction of anaesthesia, and then again 1 day and 1, 6, and 12 months post-operatively.

Blood samples were collected into Vacuette Z Serum Sep Clot Activator tubes (Greiner Bio One Ltd., Stonehouse, UK). After centrifugation for 15 minutes at 3500 revolutions per minute, serum was isolated, aliquoted, and stored at -80C for later analysis.

Cyst C (mg/L) was measured using the Turbidimetric Human Cystatin C Kit for the Roche Modular P unit (The Binding Site Ltd., Birmingham, UK) and sCr (mmol/L) was analysed using Creatinine Jaffe Kinetic colorimetric test performed on a Roche Modular P unit.

Estimated GFR (mL/min/1.73m2) was calculated for the same time points using the validated Modification of Diet in Renal Disease formula.(168)

Patients were followed up in the outpatient clinic at 1, 6, and 12 months post-operatively. Patients underwent a computed tomography (CT) scan at 1 month and colour flow duplex ultrasound scans at 6 and 12 months.

Statistical Analysis

The groups were compared using the Friedman test. The change over time was analysed using Dunn multiple comparison test and Wilcoxon signed rank test. Data were log transformed to follow normal distribution to determine the effects of co-variables on the results using the parametric independent-sample t test. Calculations were performed using SPSS for Windows (version 16.0; SPSS Inc., Chicago, IL, USA) and GraphPad Prism 5 for Windows (Version 5.03; GraphPad Software

Inc., La Jolla, CA, USA). A P value of less than 0.05 was considered statistically significant.

8.3 RESULTS:

Standard EVAR was used for patients with infra-renal AAA (19 patients) and fenestrated EVAR was used to treat juxta-renal and supra-renal AAA (10 patients). All the endografts were implanted successfully with no deaths or requirement for renal replacement therapy during the 12- month period.

Three patients required re-intervention; two required angioplasty and the third patient required combined common femoral artery endarterectomy and angioplasty.

8.3.1 Pre-EVAR renal function

Prior to EVAR, 14 patients had elevated sCr and 20 had elevated Cyst C. The median (IQR) pre-operative values for Cyst C, sCr and eGFR were 1.25 (1.05-1.5) mg/l (normal range 0.53-1.05), 106 (88.5-149) μmol/l (normal range 60-110), and 62 (41.5-73) ml/min/1.73m2 respectively.

8.3.2 Post-EVAR renal function

Cyst C The median and IQR of Cyst C increased significantly at all time points when compared to the pre-EVAR values: 1.35 (1.24-1.66) mg/l at 24 hours, $p<0.005$; 1.35 (1.17-1.67) mg/l at one month, $p<0.002$; 1.42 (1.24-1.67) mg/l at six months, $p<0.005$; and 1.45 (1.25-1.7) mg/l at twelve months, $p<0.005$.

sCr The level of sCr increased significantly at 24 hours (118 µmol/l (99.5-147.5), p=0.028) when compared with baseline level. There was no significant change at one, six and twelve months after the operation when compared with the pre-operative results.

eGFR There was a significant drop in eGFR 24 hours post-operatively (54 ml/min/1.73m2 (43-66), p=0.04). Following that, there was no significant changesin comparison to pre-operative level.

Changes in Cyst C, sCr and eGFR at pre-operatively, 24 hours, 1, 6 and 12 months post-operatively are shown in Figures 16, 17 & 18.

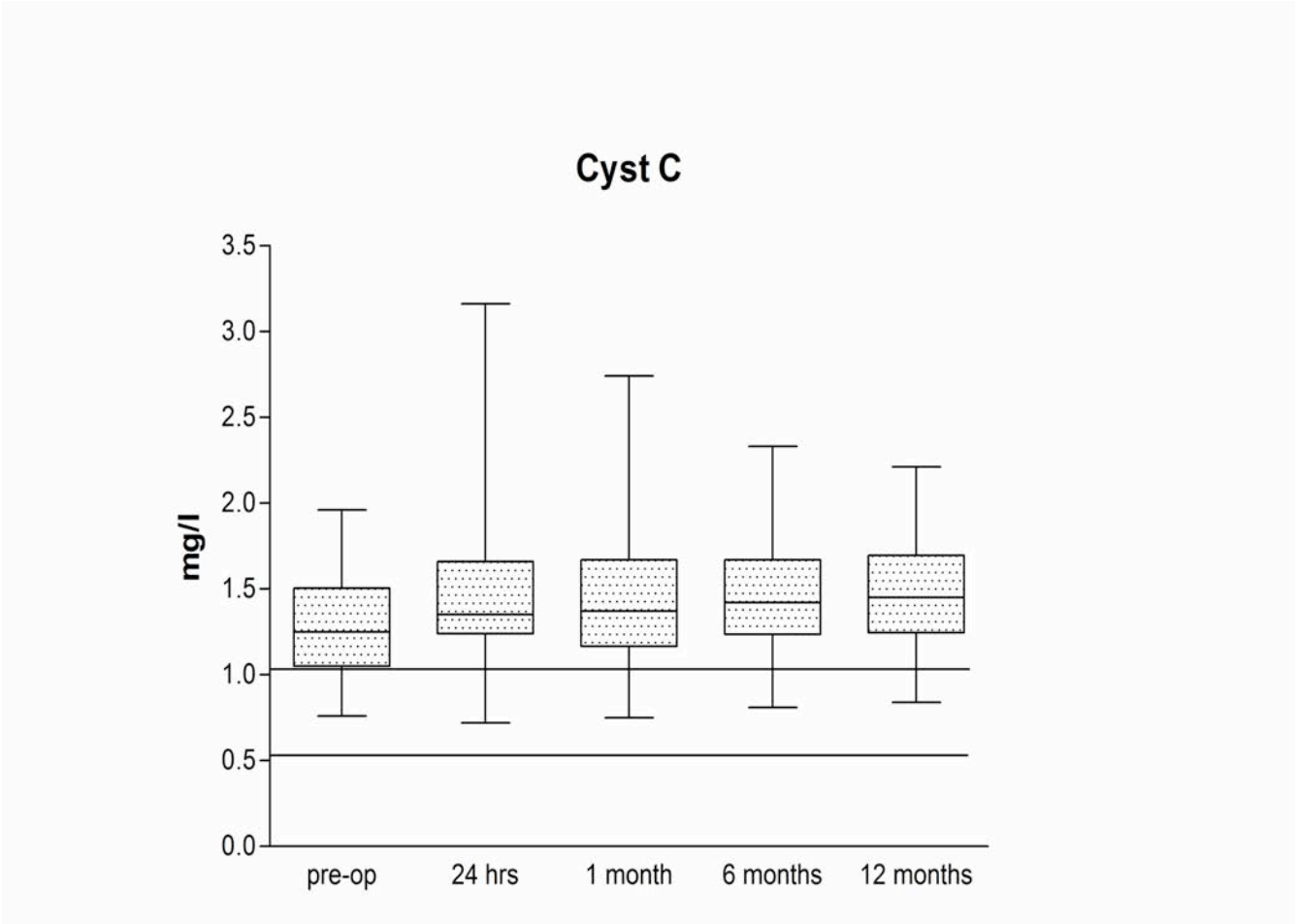


Figure 16: Changes in Cyst C.

The median and IQR of Cyst C increased significantly at all time points when compared to the pre-EVAR values: 1.35 (1.24-1.66) mg/l at 24 hours, $p<0.005$; 1.35 (1.17-1.67) mg/l at one month, $p<0.002$; 1.42 (1.24-1.67) mg/l at six months, $p<0.005$; and 1.45 (1.25-1.7) mg/l at twelve months, $p<0.005$.

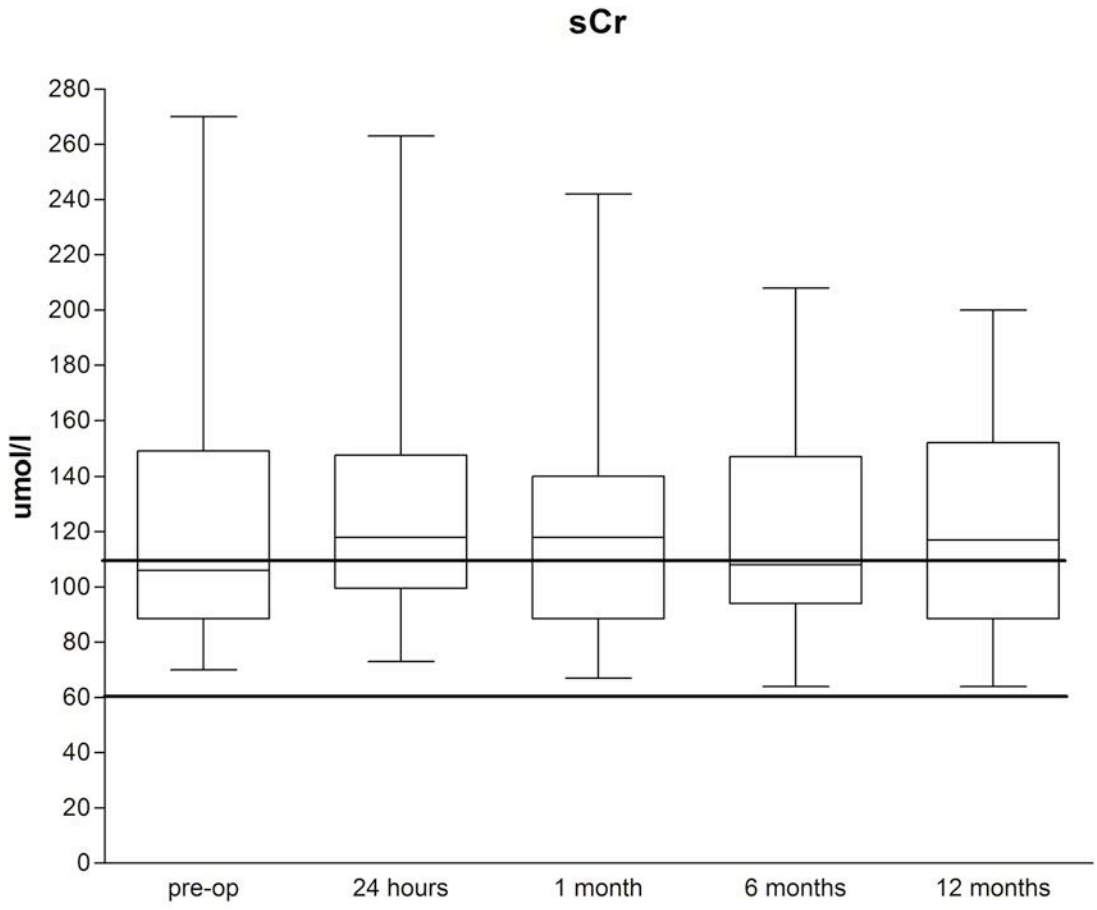


Figure 17: Changes in sCr.

sCr increased significantly at 24 hours (118 µmol/l (99.5-147.5), p=0.028) when compared with baseline level. There was no significant change at one, six and twelve months after the operation when compared with the pre-operative results.

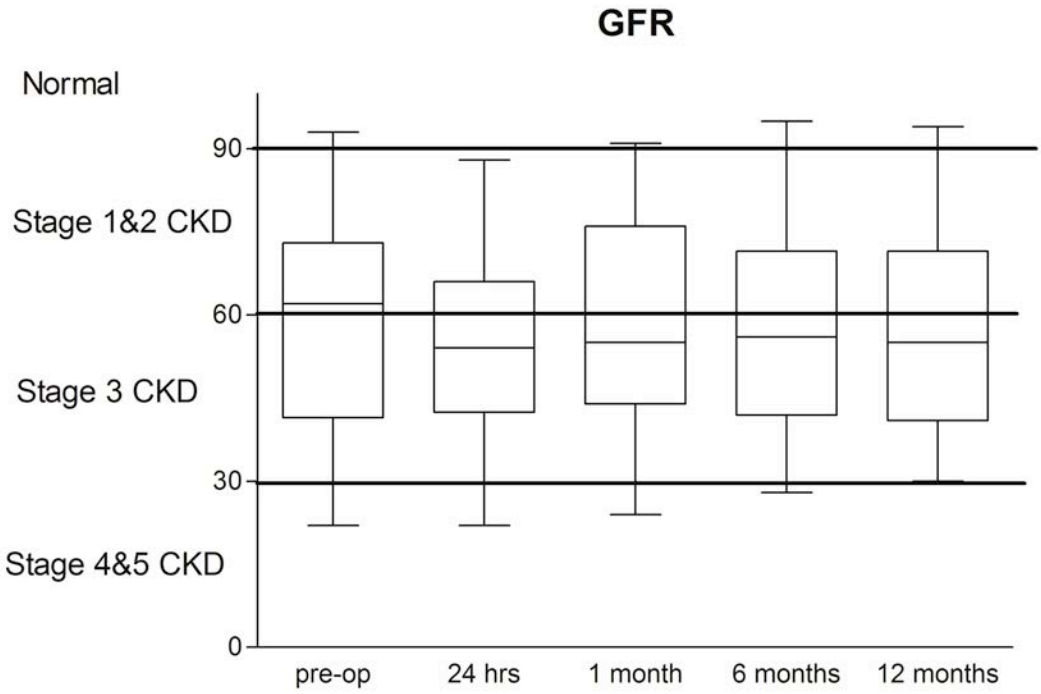


Figure 18: Changes in eGFR.

There was a significant drop in eGFR 24 hours post-operatively (54 ml/min/1.73m2 (43-66), p=0.04). Following that, there was no significant changesin comparison to pre-operative level.

8.3.3 Correlation between renal markers and clinical characteristics

The correlation between the changes in Cyst C and sCr at different time points is shown in Table 12.

Table 12: Correlation between changes in markers of renal function at different time points

Calculation	**Mean (SD)**	**Pearson coefficient**	***p*-value**
Cyst C 24 hrs – Cyst C pre-op	0.05 (0.07)	0.638	<0.001
sCr 24 hrs - sCr pre-op	0.02 (0.08)		
Cyst C 1 month - Cyst C 24 hrs	-0.009 (0.1)	0.896	<0.001
sCr 1 month - sCr 24 hrs	-0.01 (0.1)		
Cyst C 6 moths - Cyst C 1 month	0.02 (0.06)	0.396	0.027
sCr 6 moths - sCr 1 month	-0.009 (0.08)		
Cyst C 12 moths – Cyst C 6 months	0.005 (0.04)	0.263	0.2
sCr 12 moths – sCr 6 months	-0.005 (0.09)		

8.3.4 Pre-existing chronic kidney disease

Patients with pre-existing renal impairment (higher than normal sCr) had significantly higher Cyst C and sCr and lower eGFR at all time points ($p<0.05$). In patients with normal pre-operative sCr, there was a significant increase at 24 hours (100 µmol/l (81-106) vs 89 µmol/l (70-97) p=0.015) and trend toward an increase at 6 months (96 µmol/l (81-108) vs 89 µmol/l (70-97) p=0.053) (Figure 19).

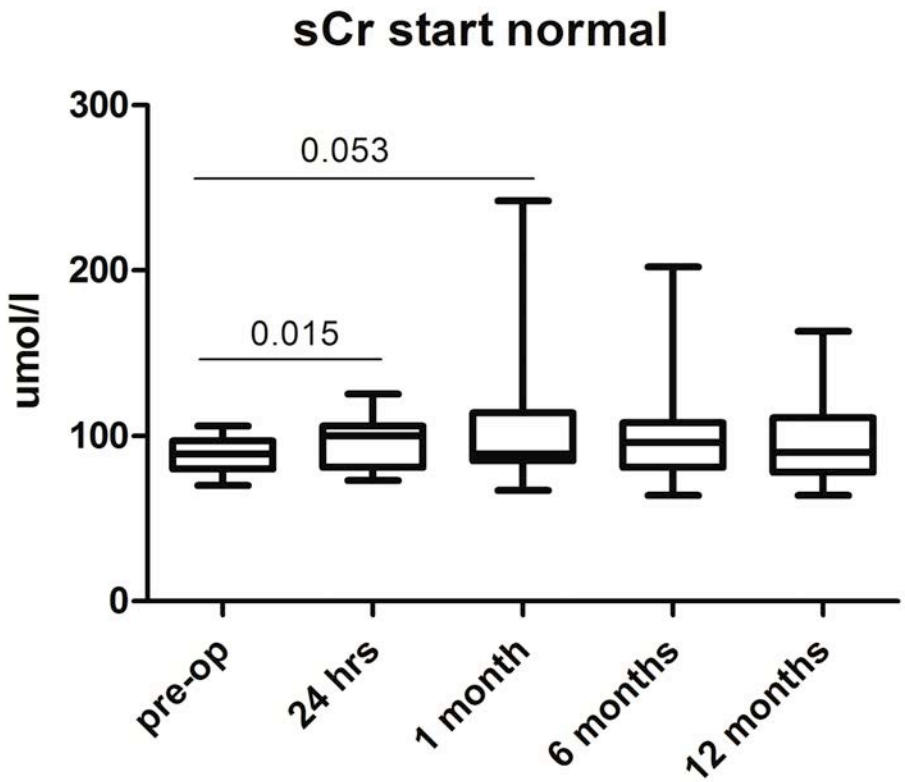


Figure 19: Changes in sCr in patients with no Chronic Kidney Disease.

8.3.5 Normal Cyst C

Patients with normal Cyst C pre-operatively had significant increase in the level of Cyst C at all time points (Figure 20).

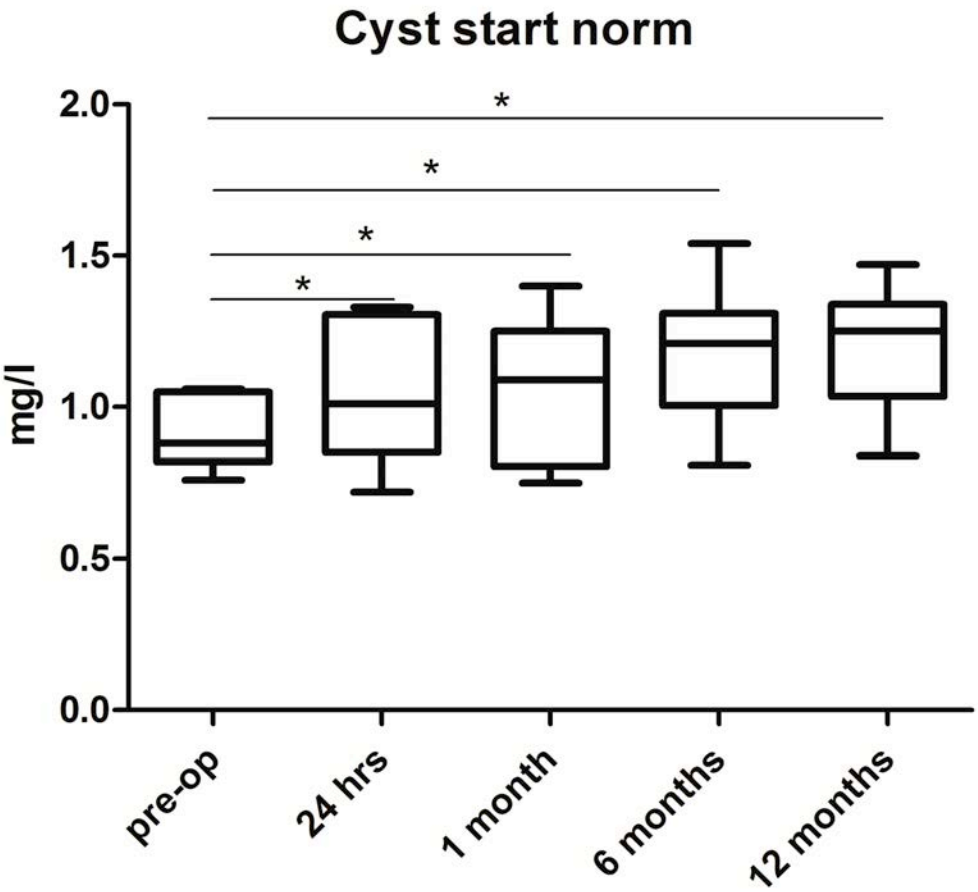


Figure 20: Changes in Cyst C in patients with normal values pre-op.

8.3.6 Cyst C following standard and fenestrated EVAR

Cyst C increased significantly in patients who had standard EVAR at the four time points post-operatively (p value 0.009, 0.008, <0.001 and <0.001 respectively) when compared with pre-operative values.

In patients who had F-EVAR, there was a significant increase in Cyst C at 24 hours, no significant change at one month and a significant increase at 6 and 12 months (p value <0.005, 0.1, 0.01 and <0.005 respectively). (Figure 21)

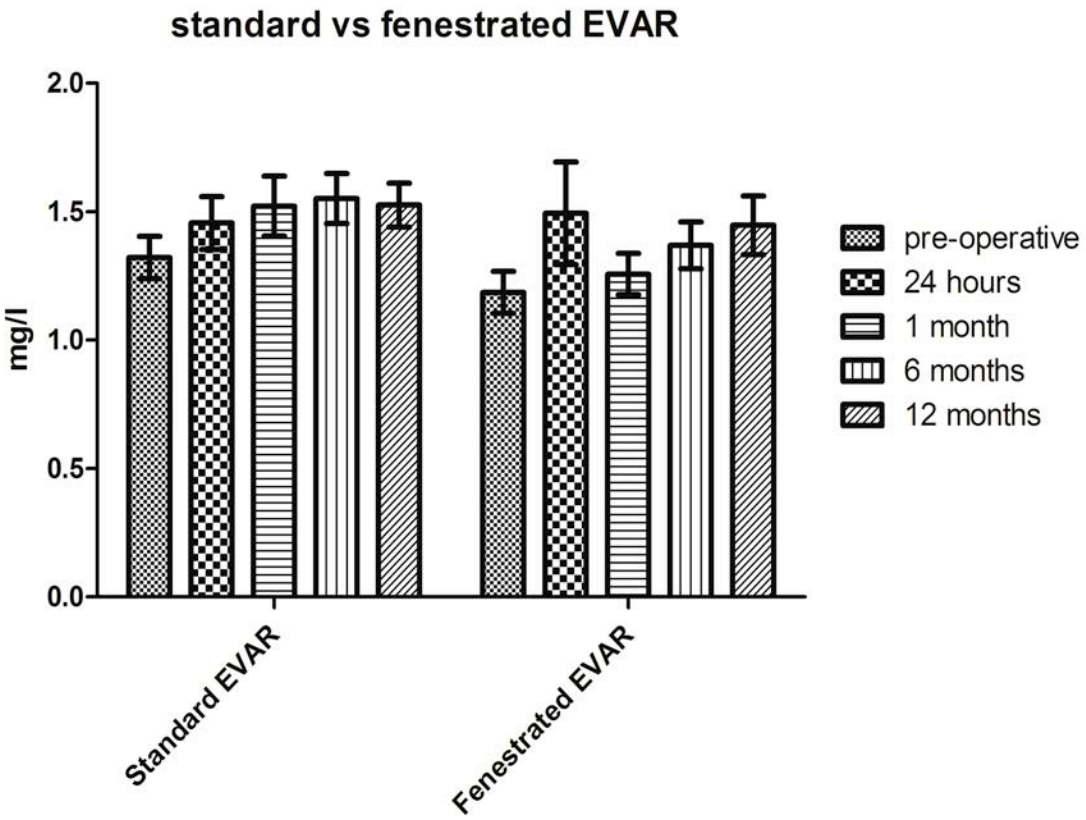


Figure 21: Changes in Cyst C in patients who had standard and Fenestrated EVAR.

8.4 Discussion:

Despite the physiological and analytical limitations of sCr (160, 161), the vast majority of studies used sCr and CrC as markers of renal function. Cyst C has a number of advantages.(209-213) It depends almost completely on the GFR as it is freely filtered in the glomerulus, completely re-absorbed and catabolised in the proximal tubules. It is considered as a potential replacement for serum creatinine as a marker of glomerular filtration as it is more sensitive than sCr in detecting small reductions in GFR (25-30%).(209, 213)

The incidence of renal impairment following EVAR has been reported to be 6-29% depending on the presence of pre-operative renal impairment.(162, 163) Other studies have failed to demonstrate a significant change in renal function following EVAR.(159, 216, 217)

Two studies used Cyst C to check renal function post-EVAR. Aho et al used Cyst C, sCr and CrC as markers of renal glomerular filtration in 24 patients with AAA (15 had EVAR and 9 had open repair). They also used N-acetyl-β-D-glucosaminidase as a marker of proximal tubular damage. A significant decrease in Cyst C and sCr and significant increase in CrC at 24 hours was shown, suggestive of increased glomerular filtration. However they demonstrated a significant increase in N-acetyl-β-D-glucosaminidase at the end of the operation in both groups, suggesting proximal tubular damage.(214) Davey et al (215) measured Cyst C, sCr and CrC following EVAR (using suprarenal fixation), open aneurysm repair and colorectal resection and found no significant difference in Cyst C and CrC following EVAR, open aneurysm repair and colon resection at 3, 6 and 12 months post operatively.

The current study is the first to show a significant increase in the level of Cyst C following EVAR, suggesting renal glomerular injury. Of the 29 patients, 25 showed a significant increase in Cyst C levels at 12-months. This increase started 24 hours post-operatively and continued for 12 months following the operation and was significantly higher than pre-operative values. The difference between our findings and those of other studies may be partly explained by the fact that the median baseline Cyst C in our patients was higher than the normal range which was not the case in the previous two studies that used Cyst C.

Previous studies have demonstrated that serum levels of Cyst C correlated more closely with measured and estimated GFR than sCr.(211) Other studies have shown that changes in GFR over time have a stronger correlation with Cyst C than sCr especially in patients with early kidney disease, for example diabetics.(184, 185, 211) In the present study, median Cyst C correlated positively with sCr and negatively with eGFR at the five time points. When we looked at the magnitude of change between time points for both Cyst C and sCr, these correlated significantly for 6 months post-operatively, but not thereafter (Table 12). This, together with the significant increase in Cyst C starting from 24 hours post-operatively, suggests that Cyst C might be more sensitive in detecting minor renal damage.

Patients with high sCr pre-operatively did not have significant changes in sCr levels post-operatively. This may be due to the fact that patients with pre-operative renal impairment had peri-operative hydration and renal protection. This is similar to the finding of Parmer et al who found no significant deterioration in sCr following EVAR for patients with baseline chronic renal insufficiency.(161)

Patients with high Cyst C pre-operatively (20 patients) and seven of the nine patients who started with normal Cyst C, showed a significant increase in Cyst C at the end of the study period. This indicates that Cyst C increases post EVAR regardless of the pre-operative status and regardless of peri-operative renal protection measures.

Recent reports suggested the incidence of renal dysfunction following fenestrated EVAR is 10-30%.(91, 98, 165) These results were based on measuring sCr and CrC. To the best of our knowledge, this paper is the first to assess renal function following fenestrated EVAR using Cyst C. The increase in Cyst C at 24 hours, experienced in the current study, could be explained by the increased contrast dose and catheter and wire manipulations within the renal arteries during fenestrated EVAR. At one month, the fall in Cyst C may be due to the renal arteries stent-grafts improving renal perfusion, but this effect is not apparently maintained at 6 and 12 months. Unfortunately, none of the patients was followed up with CT scan at 12 months (as is our practice) so we cannot comment on the state of the renal vasculature.

8.5 Conclusion:

The present study demonstrates that Cyst C increases significantly following standard and fenestrated EVAR and this is matched by similar results in sCr and eGFR. Cyst C continues to increase at 1, 6 and 12 months following the operation, which was not the case with sCr and eGFR, suggesting that it is capable of detecting progressive deterioration in renal function up to one year following EVAR. This may encourage the use of Cyst C in patients following EVAR to monitor the renal function. Longer follow up is required to determine the relationship between increased Cyst C and clinical renal outcome in this group of patients.

Chapter 9

Summary and Conclusion

9.1 Summary:

All EVAR procedures were undertaken uneventfully with complete exclusion of the aneurysm sac as confirmed by the completion angiography and post procedure CT. Three patients required re-intervention for unilateral claudication due to graft limb stenosis. Two other patients developed asymptomatic type II endoleak, which were treated conservatively. All OARs were undertaken uneventfully without major complications and none of the patients required re-intervention.

The median pre-operative PF1+2 and TAT were significantly higher than normal. At 24 hours and one month, there was no significant change in PF1+2 from the baseline level and stayed above normal levels. There was significant drop in PF1+2 at six months and 12 months ($p<0.001$). TAT increased significantly at 24 hours post-operatively. This was followed by return to the pre-operative level at one, six and 12 months post-operatively. (Figures 3 & 4) TAT and PF1+2 did not correlate at any time point.

The median PAI, t-PA antigen and activity were within normal values. PAI increased significantly at 24 hours. This was followed by significant drop at one and six months. At 12 months, there was a significant increase in PAI to return to the per-operative level. t-PA antigen increased significantly at 24 hours and then returned to the baseline level at one month. This was followed by significant reduction at six months and return back to pre-operative values at 12 months. There was no change in t-PA activity at 24 hours. This was followed by significant increase at one and six months

and return to pre-operative level at 12 months. (Figures 5, 6 & 7) PAI activity correlated significantly with t-PA antigen at all time points.

sP-selec was subnormal pre-operatively with no significant change at 24 hours post-operatively. At one month, there was significant elevation which remained high at six months. There was a significant drop at 12 months from the level of six months, however, the median value was higher than pre-operative level. (Figure 8)

Aneurysm size did not correlate with coagulation, fibrinolytic or inflammatory markers pre or post-operatively.

PF1+2 was significantly higher in patients with AAA pre-operatively in comparison to the AMC group. Post-EVAR and post-OAR were significantly lower than pre-operative level. PF1+2 post-EVAR was not significantly different from post-OAR and both were not significantly different from AMC. The median levels of TAT in the four groups were higher than the normal range. However, there was no statistical significance between the four groups. (Figure 11 & 12)

PAI activity did not differ in patients with AAA pre-operatively from AMC and one year post-EVAR. However, it was significantly higher post-OAR when compared to pre-operative level. t-PA antigen was within the normal range with no significant difference between the four groups. (Figure 13 & 14)

The inflammatory response in patients with AAA pre-operatively was higher than AMC. No significant difference was found between post-EVAR and post-OAR groups. (Figure 15)

Cyst C increased significantly at all time points when compared to the pre-EVAR value. sCr increased significantly at 24 hours with no significant change at any other time points. eGFR showed a significant drop at 24 hours and remained unchanged

for the rest of the study period. Changes in Cyst C, sCr and eGFR at 24 hours, 1, 6 and 12 months are shown in Figures 16, 17 & 18.

Patients with pre-existing renal impairment had significantly higher Cyst C and sCr and lower eGFR at all time points. In patients with normal pre-operative sCr, there was a significant increase at 24 hours and a trend toward an increase at 6 months. (Figure 19).

Cyst C increased significantly in patients who had standard EVAR at the four time points post-operatively. In patients who had F-EVAR, there was a significant increase in Cyst C at 24 hours, no significant change at one month and a significant increase at 6 and 12 months. (Figure 21)

The present study confirms that patients with AAA exhibit a hyper-coagulable state compared to AMC. The high levels of PF1+2 and TAT encountered in this study may indicate excess thrombin production and neutralization respectively. The increase in PF1+2 pre-operatively was related to AAA, while thrombin neutralization is not related to AAA and may be related to other factors like age, atherosclerosis and smoking. There was normalization of thrombin generation at one year post EVAR.

Normal fibrinolysis was found in patients with AAA. This represents relative hypo-fibrinolysis as you would expect increased fibrinolysis secondary to increased thrombin generation.

The significant increase in platelet activity may justify giving dual anti-platelet therapy to patients following EVAR especially during the first year after the operation.

The results of this study showed that inflammatory response may be related to the extent of the aneurysm rather than the size.

Removal (as in OAR) or exclusion (as in EVAR) of the intra-aneurysm thrombus from the circulation resulted in correction of the inflammatory and pro-coagulant drive found in patients with AAA.

We found that one year following EVAR and OAR the coagulation mechanism and the inflammatory response are similar and not different from the AMC.

EVAR was associated with significant increase in the level of Cyst C suggesting renal glomerular injury. This increase started 24 hours post-operatively and continued for 12 months.

Patients with high sCr pre-operatively did not have significant changes in sCr levels post-operatively. Cyst C increased post EVAR regardless of the pre-operative status.

9.2 Conclusion:

AAA is associated with a significant hyper-coagulable and hypo-fibrinolytic state. This is corrected one year following EVAR and OAR. The unchanged thrombin production and increased thrombin neutralization experienced on the first post-operative day may be protective at the early stages following EVAR. The increase in thrombin generation reported previously in the immediate peri-operative period after EVAR and OAR does not continue on the medium term. The normalization of thrombin generation and fibrinolytic response one year after the operation may represent a decrease in the incidence of thrombo-embolic events that is high in patients with AAA.

Following EVAR, dual anti-platelet therapy may be advisable to counteract the increase in platelet activity experienced during the first post-operative year.

Cyst C increases significantly following standard and fenestrated EVAR and this is matched by similar results in sCr and eGFR. Cyst C continues to increase at 1, 6 and 12 months following the operation, which was not the case with sCr and eGFR, suggesting that it is capable of detecting progressive deterioration in renal function up to one year following EVAR. This may encourage the use of Cyst C in patients following EVAR to monitor the renal function.

Chapter 10

Future work

10.1 Long term changes in coagulation and fibrinolysis:

The current study is the first report to describe normalization of thrombin generation detected one year following EVAR. The combination of no increase in thrombin generation and increased thrombin neutralization following EVAR may be protective against cardiovascular complications and thrombo-embolic disorders in this group of patients. However, very little, if any, is known about the changes in coagulation and fibrinolysis beyond one year following EVAR. Longer follow up and investigation is recommended to find out whether the correction of coagulopathy is maintained at the long term. If the correction of the coagulopathy is lost, it is important to find out the relation of these changes with cardiovascular morbidity and mortality.

10.2 Effect of endoleak on haemostatic markers:

Only two patients developed type II endoleak (6.89%). This would lead to leak of the blood flow, albeit low and slow, back to the aneurysm sac and in contact with the mural thrombus. In theory, this could lead to recurrence of the hyper-coagulable state found pre-operatively. Larger cohort of patients is needed to look into the effect of endoleak onto the coagulation and fibrinolysis drive following EVAR. It was previously calculated to have 20 patients to detect changes in the coagulation mechanism. This means that we need a cohort of >300 patients to get the required number of patients with endoleak to detect the change in haemostasis.

However, the majority of endoleak is type II which is considered benign condition that does not require intervention unless there is sac expansion. Moreover, this type of endoleak could easily be identified by the non-invasive duplex ultrasound. The use of haemostatic markers, as non-invasive investigation, will be of great benefit in the cases of sac expansion in absence of radiological evidence of endoleak (e.g. type V endoleak or endotension).

10.3 Cyst C as marker of renal function:

The current study is the first to show a significant increase in the level of Cyst C following EVAR, suggesting renal glomerular injury. Of the 29 patients, 25 showed a significant increase in Cyst C levels at 12-months. This increase started 24 hours post-operatively and continued for 12 months following the operation and was significantly higher than pre-operative values. This is matched by similar results in sCr and eGFR in the immediate post-operative period but not at one month post-operatively. None of the patients required renal replacement therapy. Longer follow up is required to determine the relationship between increased Cyst C and clinical renal outcome in this group of patients. It is also needed to determine whether the Cyst C will continue to increase after 12 months.

Chapter 11

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REVIEW ARTICLE

Richard P. Cambria, MD, Section Editor

Coagulation, fibrinolysis, and platelet activation in patients undergoing open and endovascular repair of abdominal aortic aneurysm

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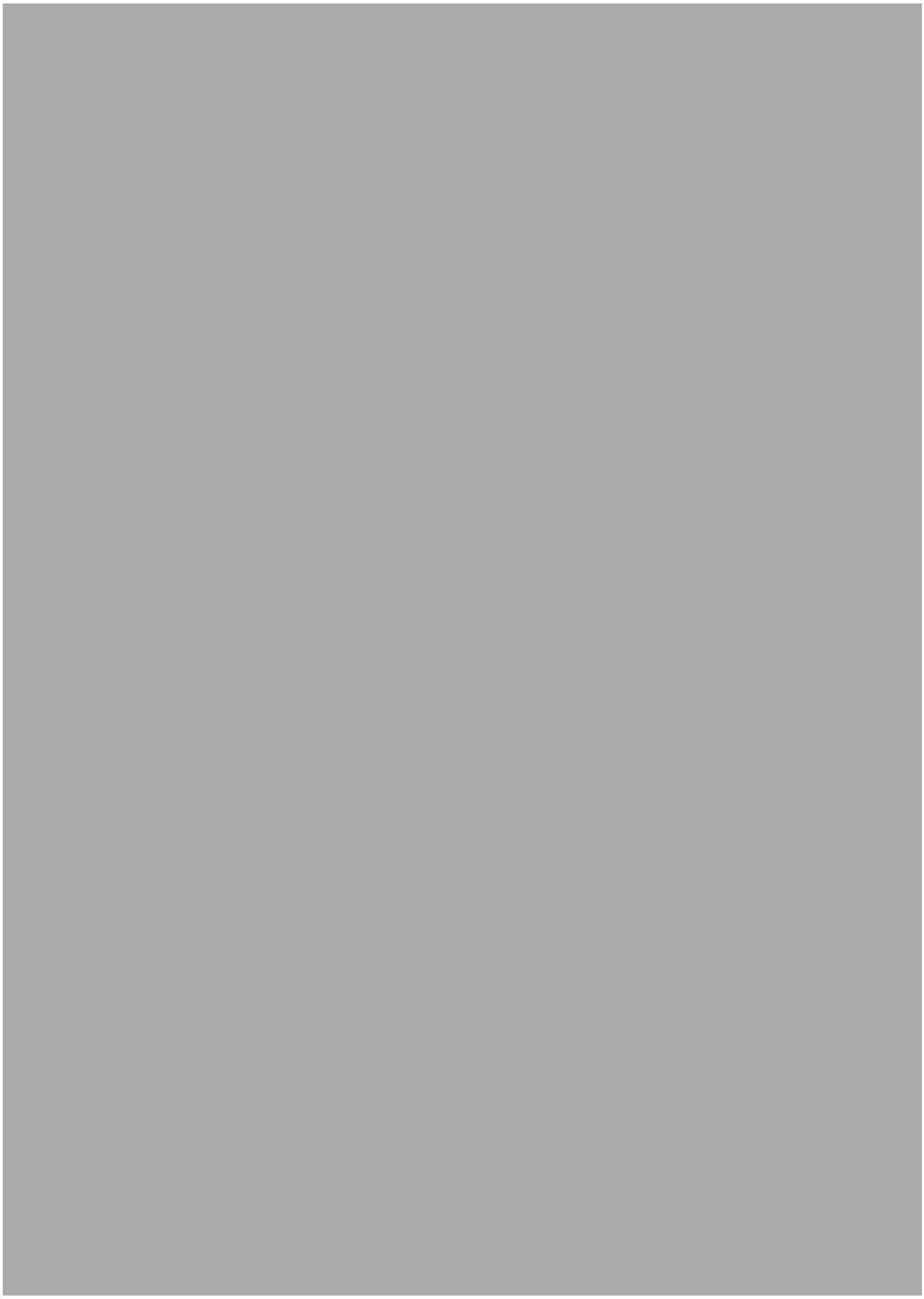
Background: **Endovascular aneurysm repair (EVAR) is associated with an improved perioperative mortality compared to open surgical repair. This benefit may reflect reduced incidence of microvascular and macrovascular thrombotic complications after EVAR.**

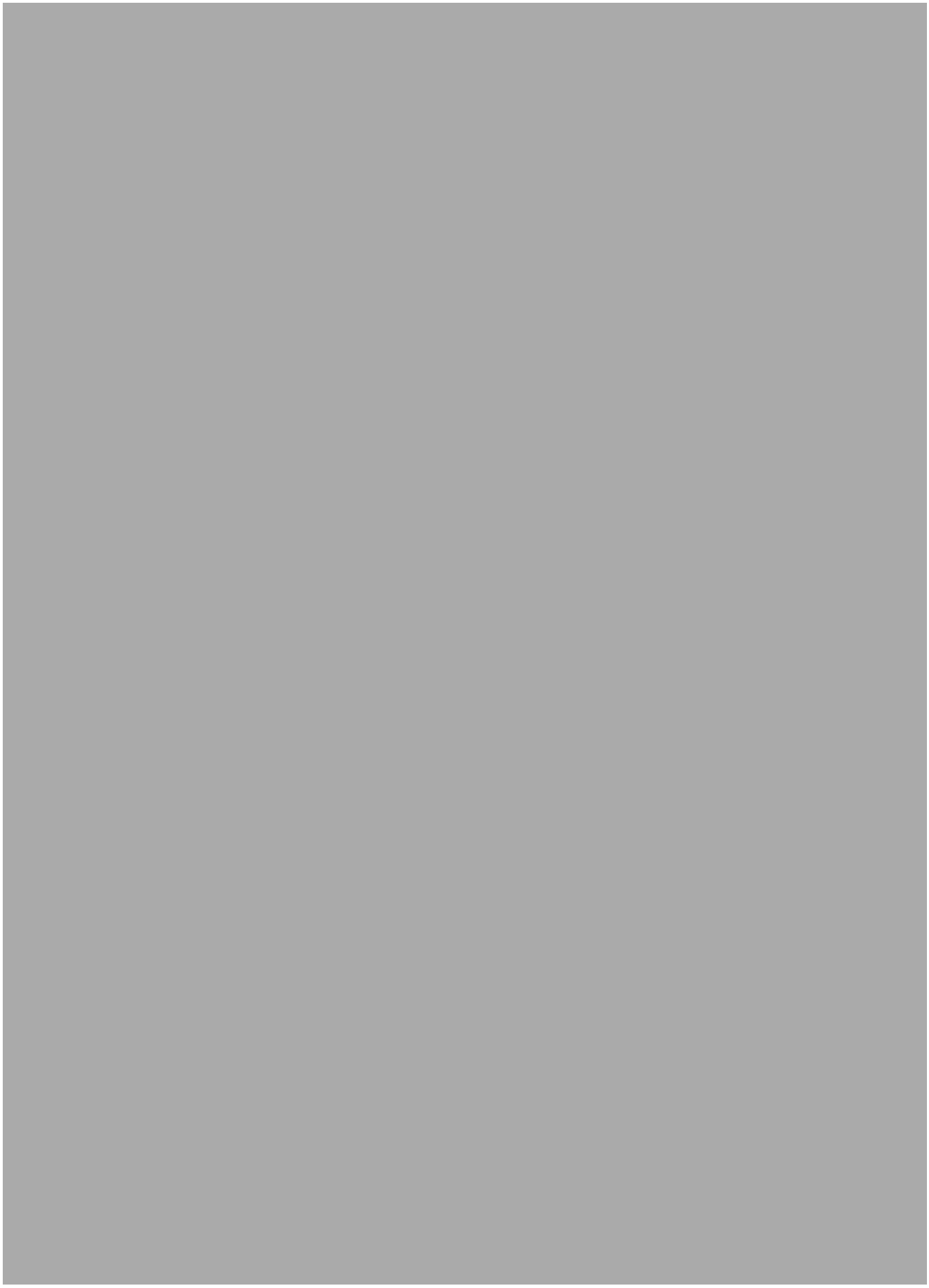
Purpose: **The purpose of this study was to review and compare the effects of abdominal aortic aneurysm (AAA), open surgical repair, and EVAR on coagulation, fibrinolysis, and platelet activation.**

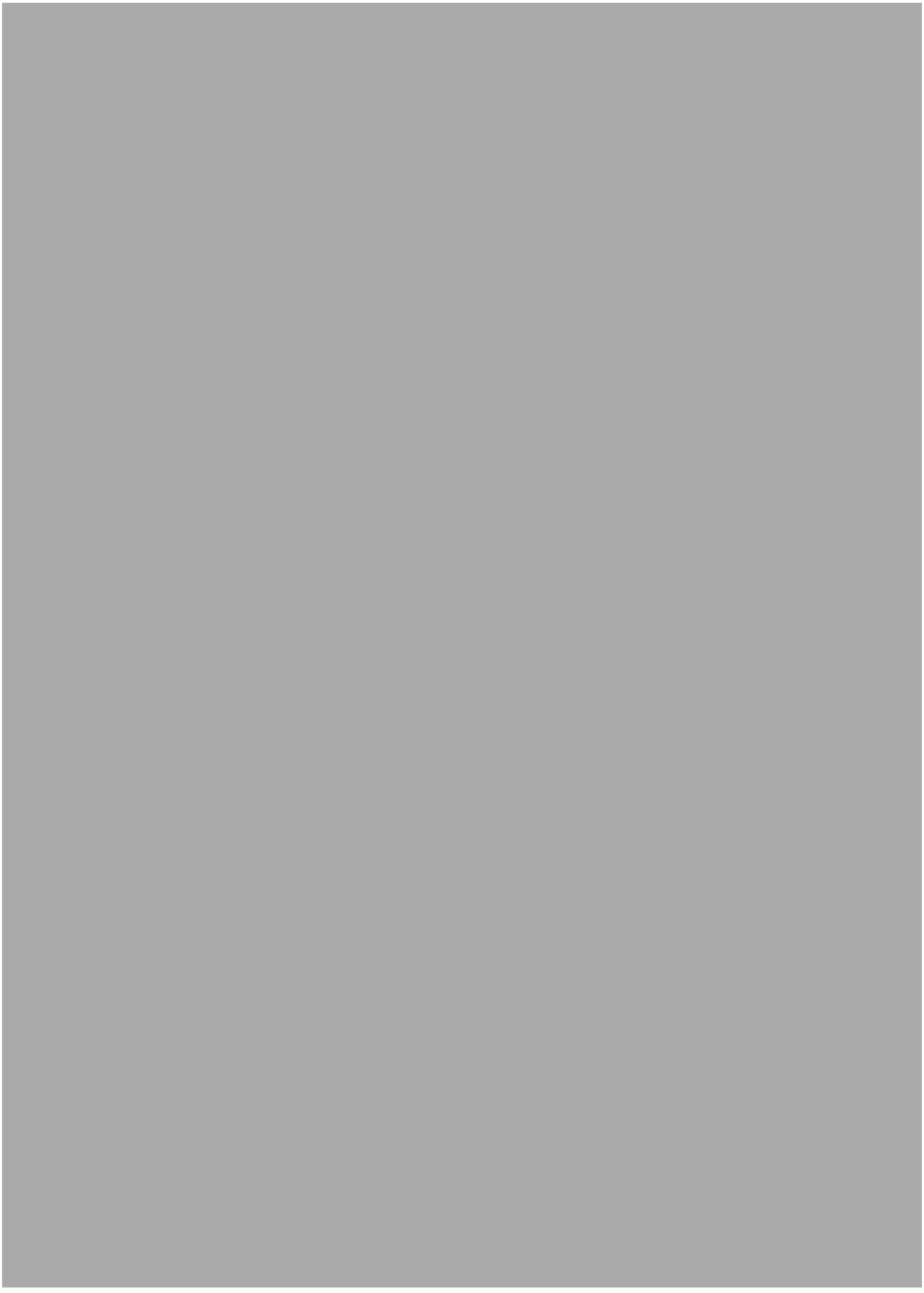
Methods: **A MEDLINE (1966-2010) and Cochrane library search for articles relating to the effects of AAA, open surgical repair, and EVAR on hemostasis was performed utilizing and cross-linking terms such as clotting, fibrinolysis, AAA, EVAR, and open surgical repair. Studies with a small cohort of patients (less than 7) or in which values of assessed biomarkers were not included were rejected.**

Results: **AAA is associated with increased thrombin generation, activity, and fibrin turnover as evidenced by increased plasma levels of thrombin-antithrombin III-complex (TAT), activated protein C-protein C inhibitor (APC-PCI), fibrin-monomer-fibrinogen (FM-F), F1+2, fibrinogen, and D-dimer. The extent of hemostatic derangement correlates with the volume of intraluminal thrombus. This procoagulant state is exaggerated in the immediate perioperative period after both open surgical repair and EVAR, but is attenuated at medium-term follow-up although not normalized.**

Conclusion: **The resultant prothrombotic diathesis after open surgical repair and EVAR may account for the high level of perioperative thrombotic complications. (J Vasc Surg 2011;54:865-78.)**







Effect of endovascular and open abdominal aortic aneurysm repair on thrombin generation and fibrinolysis

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Background: **Abdominal aortic aneurysm (AAA) is associated with a prothrombotic diathesis that may increase the risk of cardiovascular events. This diathesis is exacerbated in the short term by open aneurysm repair (OAR) and endovascular aneurysm repair (EVAR). However, the effect of EVAR and OAR on coagulation and fibrinolysis in the medium and long term is poorly understood. The purpose of this study was to investigate the medium-term effects of EVAR and OAR on thrombin generation, neutralization, and fibrinolysis.**

Methods: **Prothrombin fragment (PF)1 + 2, thrombin antithrombin (TAT) complex, plasminogen activator inhibitor (PAI) activity, and tissue-plasminogen activator (t-PA) antigen were measured in eight age-matched controls (AMCs), 29 patients with AAA immediately before (preoperatively) and 12 months after EVAR (post-EVAR), and in 11 patients at a mean of 16 months after OAR (post-OAR).**

Results: **Preoperatively, PF1 + 2 levels were significantly higher in patients with AAAs than in AMC. PF1 + 2 levels post-EVAR and post-OAR were significantly lower than preoperative values and similar to AMC. There was no significant difference in TAT, PAI, or t-PA between AMC, AAA preoperatively, and post-EVAR. Post-OAR, PAI activity was significantly higher than in preoperative patients.**

Conclusions: **AAA is associated with increased thrombin generation without upregulation of fibrinolysis. The prothrombotic, hypofibrinolytic diathesis observed in patients with AAA returns toward normal in the medium term after EVAR and OAR, although there is a trend toward decreased fibrinolysis post-OAR. (J Vasc Surg 2013;57:103-7.)**

Changes in thrombin generation, fibrinolysis, platelet and endothelial cell activity, and inflammation following endovascular abdominal aortic aneurysm repair

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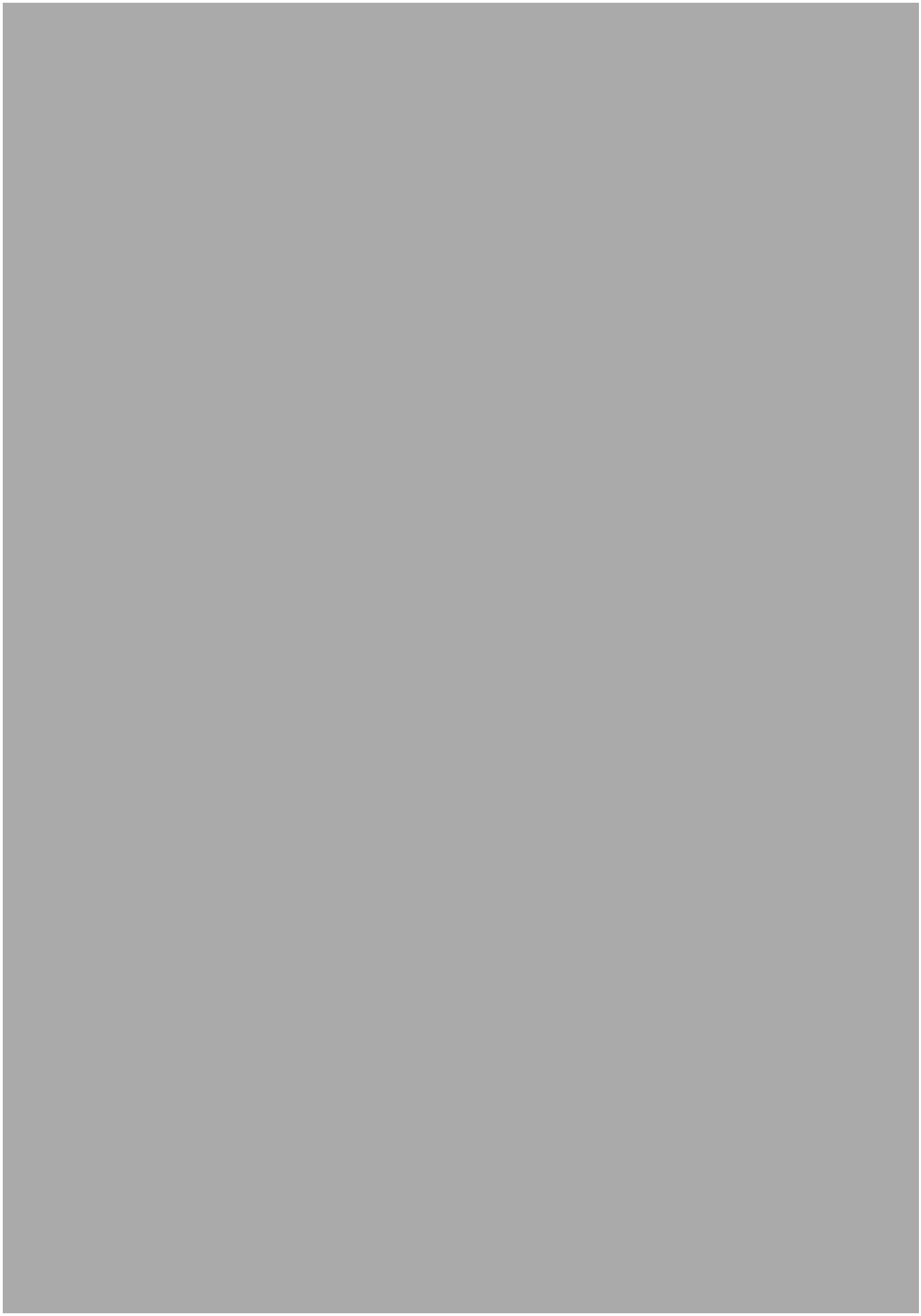
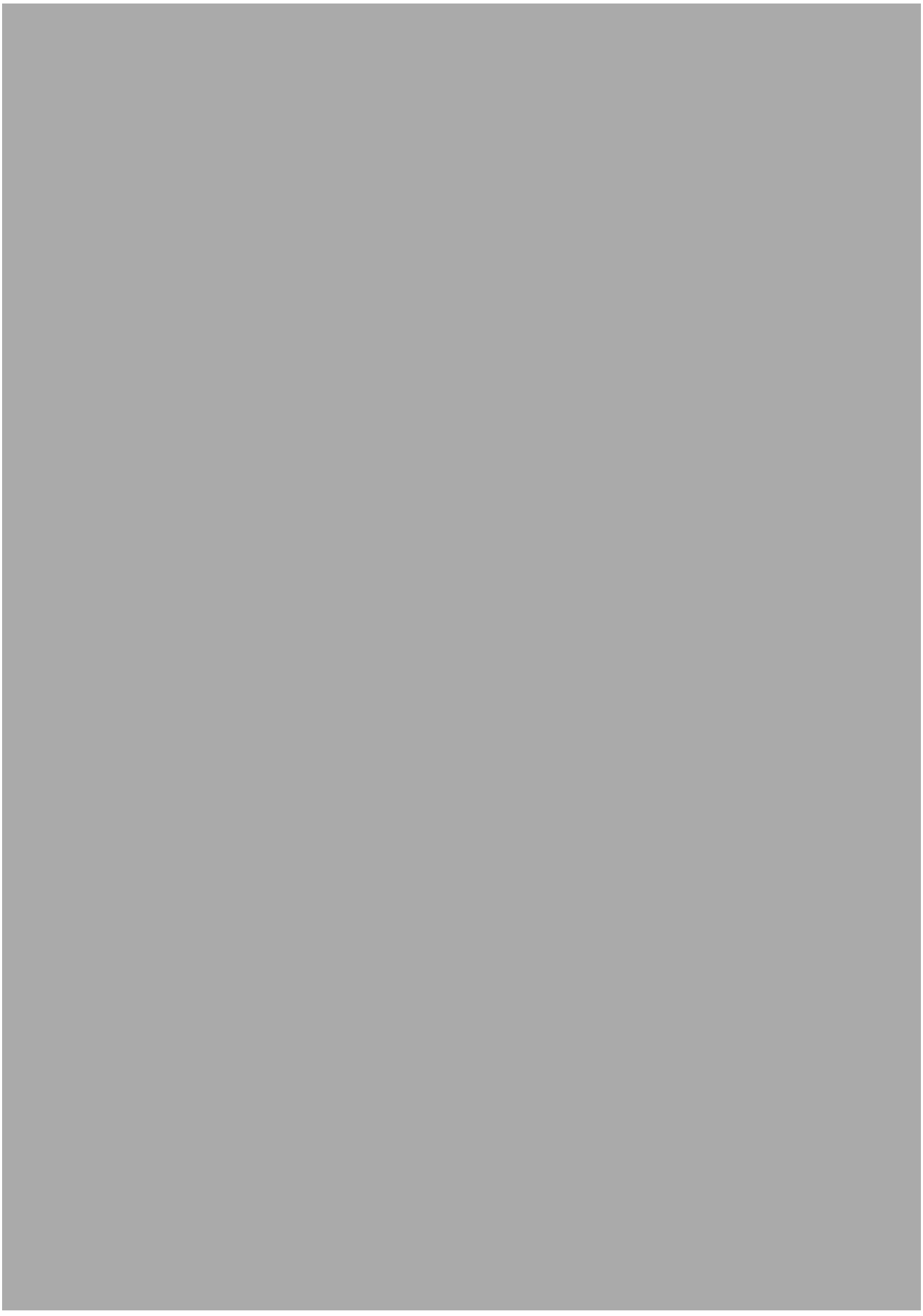
Background: **Abdominal aortic aneurysm (AAA) is a chronic inflammatory condition associated with a prothrombotic, hypofibrinolytic diathesis that may increase the risk of cardiovascular events. The effect of endovascular aneurysm repair (EVAR) on this prothrombotic diathesis is not fully understood, especially over the medium and long term. A better understanding of these postintervention changes may improve the risk of cardiovascular complications in the long term. The purpose of this study was to examine thrombin generation, fibrinolysis, platelet and endothelial activation, and the inflammatory response during the 12 months following EVAR.**

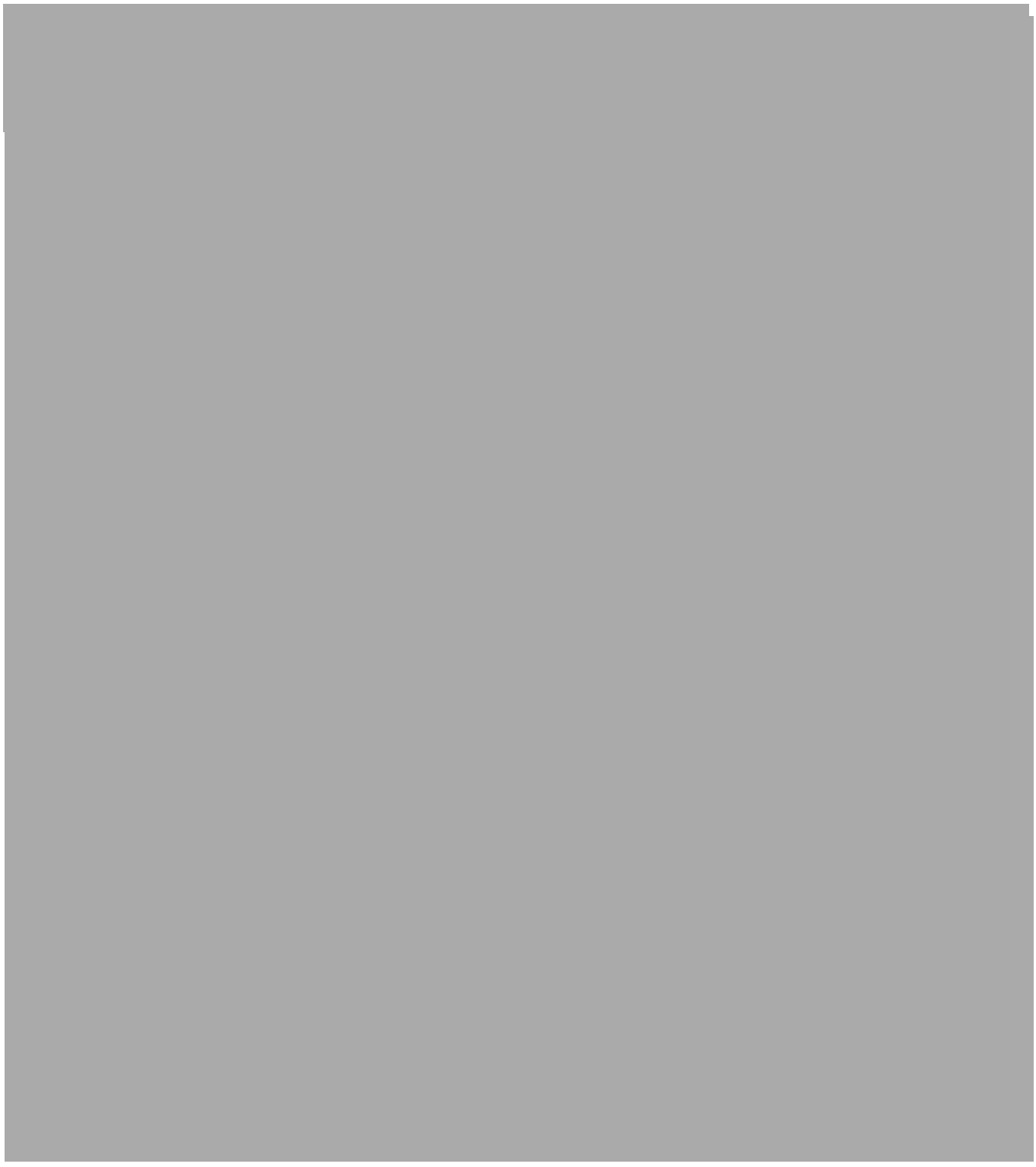
Methods: **Twenty-nine patients (mean age, 76.9 years) undergoing EVAR for AAA (mean diameter 6.9 cm) had prothrombin fragment (PF) 1 + 2, thrombin-antithrombin complex (TAT), plasminogen activator inhibitor (PAI) activity, tissue plasminogen activator (t-PA) activity and antigen, soluble P- and E-selectin, and highly sensitive C-reactive protein (hsCRP) measured before and at 24 hours, and 1, 6, and 12 months after surgery.**

Results: **PF1 + 2 were markedly elevated prior to EVAR and remained so at 24 hours and 1 month, but had decreased significantly at 6 and 12 months. TAT was also elevated prior to EVAR and increased still further by 24 hours, but fell to below baseline levels thereafter. PAI activity and t-PA antigen were normal prior to EVAR, increased significantly at 24 hours, and then fell to baseline levels. t-PA activity was only detectable at 1 and 6 months; there was a significant rise in soluble P- and E-selectin after EVAR, which was sustained for 12 months. hsCRP increased transiently in response to EVAR but returned to preoperative levels by 1 month.**

Conclusions: **The prothrombotic, hypofibrinolytic diathesis associated with AAA is normalized 12 months after EVAR. This beneficial systemic effect of EVAR for AAA disease may help protect patients against future thromboembolic cardiovascular events. (J Vasc Surg 2012;55:41-6.)**







ELSEVIER

Assessment of Renal Function by Means of Cystatin C Following Standard and Fenestrated Endovascular Aneurysm Repair

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Background: Cystatin C (Cyst C) is more sensitive marker for early renal injury. However, serum creatinine (sCr) and estimated glomerular filtration rate (eGFR) are still used as the standard renal markers after endovascular aortic aneurysm repair (EVAR). The goal of this study was to compare the efficacy of Cyst C, sCr, and eGFR as markers of renal function after EVAR.
Patients and Methods: This study examined 29 patients (27 men) with a mean age of 76.9 years (range, 55−89 years) undergoing standard ($n = 19$) and fenestrated ($n = 10$) EVAR for abdominal aortic aneurysm (AAA) of mean diameter 6.9 cm (range, 5.5−10 cm). Cyst C and sCr were measured and eGFR calculated before and 1 day and 1, 6, and 12 months after EVAR.
Results: At 24 hours after procedure, a significant increase in Cyst C ($P < 0.005$) and sCr ($P = 0.028$) and significant decrease in eGFR ($P = 0.04$) were seen. Cyst C continued to increase and was significantly higher at 1 ($P < 0.002$), 6 ($P < 0.005$), and 12 ($P < 0.005$) months compared with baseline. By contrast, sCr and eGFR did not show any significant change at 1, 6, and 12 months from the baseline level. Cyst C increased significantly postoperatively regardless of the baseline renal function. None of the patients required renal replacement therapy.
Conclusions: EVAR is associated with a significant increase in Cyst C starting 24 hours after the procedure and is maintained for 12 months. sCr and eGFR only show significant change at 24 hours and therefore may underestimate long-term renal damage after EVAR.