THE SIGNIFICANCE OF D-DIMER LEVELS AND AN ELEVATED ESR IN ASSOCIATION WITH A HYPERCOAGULABLE STATE IN PATIENTS WITH CEREBROVASCULAR DISEASE

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of

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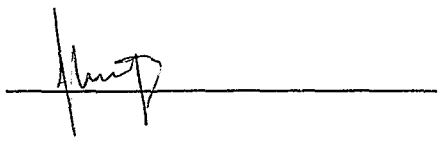
DECLARATION

I, Jina Elise Swartz, declare that this dissertation is my own work. It is being submitted for the degree of Master of Science in Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.



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ABSTRACT

Background and purpose: Predictors of outcome in patients suffering cerebrovascular events (either stroke and/ or transient ischaemic attack) may be important determinants of those at risk for recurrent thrombotic cerebral episodes. Identification of patients with chronic underlying inflammatory processes, as opposed to generalised atheromatous disease, as causative factors in cerebrovascular disease, may have important therapeutic and preventative implications. Levels of D-dimers, markers for the detection of the activation of the coagulation and fibrinolytic systems, were analysed to assess whether patients suffering multiple events had ongoing evidence of a hypercoagulable state. To determine whether those patients with prolonged elevation of D-dimer levels had evidence of concurrent infection and inflammation, the erythrocyte sedimentation ratio (ESR), an inflammatory marker, was evaluated.

Methods: Retrospective analysis was performed on 148 patients referred to the Haemostasis and Thrombosis Unit at the Johannesburg Hospital for evaluation of their thrombotic profiles. All had suffered either single or recurrent cerebrovascular events. A comprehensive history was taken and a complete physical and neurological examination performed, as well as cardiological assessment and neuroimaging studies. In addition to the thrombotic profile, including D-dimer levels, haematological parameters such as ESR, haemoglobin, white cell count, platelet count and others, were evaluated. The variable time interval between the date of most recent event and date of venesection was determined.

Results: D-dimer levels remained elevated in some patients following a cerebrovascular event far in excess of the expected time frame of six weeks, suggesting ongoing thrombosis and fibrinolysis. Elevated D-dimers were not found to be of significant prognostic value in determining those at risk of recurrent episodes. Of the 47 patients assessed within two months of their most recent event, 53.19 % displayed elevated D-dimer levels, but 29.7 % had elevated levels in the group assessed after a two month time interval, $p = 0.010$. D-dimer elevations were not found to be of significant prognostic value in determining those at risk of recurrent episodes, with $p = 0.216$ when comparing patients suffering single, two or multiple events.

However, elevated D-dimers correlate significantly with ESR levels, $p = 0.0094$, in all patients. This was particularly evident when comparing the 70 younger to the 78 older patients with elevated D-dimers ($p = 0.0493$) and the 48 Black to the 82 White patients ($p = 0.0070$) in the anterior cerebral territory of vascular supply ($p = 0.0282$). Both younger and Black patient groups have recognisably less widespread atheromatous disease than older and White patients.

When assessing other markers of inflammation in association with elevated D-dimer levels and ESR, mean fibrinogen levels were significantly elevated at 6.56 g/l ($p = 0.0122$). An elevated white cell count, as a categorical variable was significantly associated with a raised ESR ($p = 0.0092$).

Conclusions: D-dimer elevations for prolonged periods after a thrombotic cerebrovascular episode were not of prognostic value in determining those patients at risk of recurrent events. However, when evaluated together with markers of infective or inflammatory processes such as ESR, fibrinogen and white cell count, a significant association was demonstrated.

Acquired abnormalities of coagulation and fibrinolysis, including chronic infection/ inflammation, may cause or contribute to stroke, especially in those patients at lower risk for generalised atheromatous disease by virtue of age or racial group. These findings have important implications relating to cerebrovascular disease aetiology, investigation, management and, ultimately, prevention.

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CHAPTER 1

1.0 INTRODUCTION

1.1 D-dimers

Epidemiological evidence indicates that several markers of haemostatic and thrombotic function are potent risk factors for both myocardial infarction and stroke (Ridker, 1997). Such markers include those primarily related to fibrinolysis and inflammation, although data for other parameters is also implicated (Ridker, 1997). Potential haemostatic and thrombotic markers for arterial thrombosis include tissue type plasminogen activator, plasminogen activator inhibitor (PAI-I), clot lysis time and D-dimer levels (Ridker, 1997).

1.1.1 D-dimers in cardiovascular disease

The concept that impaired fibrinolysis is a risk factor for future cardiovascular disease is strongly supported by prospective studies in which decreased endogenous fibrinolytic capacity assessed at baseline was found to predict future rates of cardiovascular morbidity and mortality (Ridker, 1997). This has been demonstrated in healthy males at risk for myocardial infarction and stroke and in broad population-based cohorts (Cortellaro,

Cofrancesco & Boschetti et al., 1993; Ridker, Vaughn & Stampfer et al., 1993; Ridker, Hennekens & Stampfer et al., 1994).

There is controversy regarding whether alteration of fibrinolytic function is considered a primary process or the result of pre-clinical atherosclerosis and a resultant dysfunctional endothelium. Significant circadian and age-related variations in fibrinolytic parameters also occur (Ridker, 1997). Depending upon what factors are controlled for, the importance of factors as predictors of thrombotic risk varies (Juhan-Vague, Pyke & Alessis et al., 1996). Correlations have been described between fibrinolytic parameters and several lipid, behavioural, metabolic and inflammatory markers (Folsom, Qamhieh & Wing et al., 1993). Elevation in D-dimers has also been found to correlate with systolic blood pressure levels (Cortellaro et al., 1993). Obesity and subsequent weight loss is associated with alterations in the haemostatic system but does not appear to influence levels of fibrin degradation products (Folsom et al., 1993). Elevations in D-dimers are known to be associated with increasing age (Ono, Koyama & Suehiro et al., 1991).

Studies have been undertaken linking elevated D-dimers to myocardial infarction (Francis, Connaghan & Scott et al., 1987; Ridker, Hennekens & Cerskus et al., 1994), claudication (Fowkes, Lowe & Housley et al., 1993), deep vein thrombosis (Harvey, Roth & Yarnold et al., 1996) and atherosclerosis (Francis et al., 1987; Cortellaro et al., 1993). Cross-sectional studies indicate direct associations between D-dimers and extent of carotid and peripheral arterial stenosis (De Buyzere, Phillippe & Duprez et al., 1993; Herren, Stricker & Haeberli et al., 1994; Salomaa, Stinson & Kark et al., 1995). Positive relationships have been

identified between D-dimers and vascular risk among patients with myocardial infarction or acute ischaemia (Francis et al., 1987). D-dimers rise in disease states associated with v .scular injury and these studies can not distinguish cause from effect.

Patients with D-dimers in the upper level of normal distribution have been found to have a two times increased risk of myocardial infarction compared to normal patients (Ridker et al., 1994). In patients with claudication, D-dimers show proven predictive risks of vascular disease progression as well as incident coronary events (Fowkes et al., 1993).

Few haematological or lipid risk factors have been identified for stroke, as compared to coronary artery disease (Ridker et al., 1993). Increased concentrations of tissue plasminogen activator (tPA) antigen among apparently healthy men are independently associated with high risk of future strokes, especially thrombo-embolic stroke (Ridker et al., 1993). These levels were independent of epidemiological factors found to influence the risk of stroke, namely hypertension, obesity (Folsom et al., 1993), cigarette smoking, diabetes mellitus and age (Ridker et al., 1993). It has been postulated on this basis that activation of the endogenous fibrinolytic pathway occurs many years in advance of arterial vascular occlusion and the detection of this activation may allow prediction of risk of future atherosclerotic disease (Ridker et al., 1994).

Previous studies have shown that the primary mediator of intravascular fibrinolysis, tissue plasminogen activator (tPA), is associated with risks of a first coronary occlusion (Ridker et al., 1993). Plasma fibrinogen was the strongest independent predictor of death from

coronary artery disease (Fowkes et al., 1993). Cross-linked fibrin degradation product (XLFDP) was the only factor, in addition to age and cigarette smoking, independently associated with deterioration in peripheral arterial disease (Fowkes et al., 1993). XLFDP's have been identified as a strong predictor of disease progression and coronary risk, supporting the hypothesis that fibrin formation contributes to progression of coronary and peripheral atherosclerosis (Fowkes et al., 1993).

Aortic thrombi and early gelatinous arterial lesions have been shown to contain high amounts of D-dimers (Smith, Keen & Grant et al., 1990). It has been suggested that patients with peripheral arterial disease have increased levels of XLFDP's which correlates with clinical severity, suggesting that the increased fibrin turnover is related to the extent of arterial disease (Fowkes et al., 1993). Findings that increased concentrations of XLFDP's predict both coronary artery disease and progression of peripheral arterial disease, consistent with ongoing fibrin formation contributing to atherosclerosis, supports the concept that these patients may be at risk for progressive or recurrent cerebrovascular disease (Fowkes et al., 1993).

Different fibrin or fibrin degradation products have a range of pharmacobiological activities, including stimulation of growth of cultured cells, modifications of clotting, vascular tone and permeability and chemotaxis for leukocytes, all of which might influence atherogenesis (Thompson, Evans & Campbell, 1986; Smith et al., 1990). Studies have demonstrated that there is continuous formation of cross-linked fibrin with subsequent

fibrinolysis, both generating fragments with mitogenic and chemotactic properties, which play a significant role in atherogenesis (Smith et al., 1990).

D-dimers are markers for the detection of the activation of the coagulation and subsequent fibrinolytic systems in hypercoagulable states (Hunt, Rylatt & Hart et al., 1985; Wilde, Kitchen & Kinsey et al., 1989) and thrombotic disorders (Heaton, Billings & Hickton et al., 1987; Kruskal, Commerford & Franks et al., 1987; Ono et al., 1991; Ridker et al., 1994).

Marked D-dimer elevations may be compatible with enhanced fibrin degeneration at local injury sites, where plasmin generation escapes PAI-1 inhibitory control, or could reflect a more extensive fibrinolytic response in addition to the index-event (Cortellaro et al., 1993). This may explain the increased number of associated risk factors in patients with elevated D-dimers and recurrent cerebrovascular episodes. If such patients are prothrombotic with increased fibrinolysis occurring recurrently and on a generalized basis, then the association of ischaemic heart disease, peripheral vascular disease and recurrent strokes in such patients might be explained.

Increased D-dimer levels would then be due to numerous but minimal amounts of fibrin degradation products resulting from chronic, extensive intravascular fibrin formation and degeneration, as described in patients with peripheral atherosclerosis (Cortellaro et al., 1993). In view of the correlation with elevated systolic blood pressure, increased D-dimers may be a useful index in the study of the multifactorial phenomena in patients with ischaemic vascular disease (Cortellaro et al., 1993).

1.1.2 D-dimers in cerebrovascular disease

Acute stroke is caused mainly by atherosclerotic or thrombo-embolic disorders in the cerebral circulation (Mohr, Caplan & Melski et al., 1978; Sloan, 1987; Hart & Kanter, 1990). At a pathophysiological level, there is controversy whether the alteration of fibrinolytic function is a primary process or the result of pre-clinical atherosclerosis and a resultant dysfunctional endothelium (Ridker, 1997).

Studies in coronary artery disease, as well as stroke, have shown a divergence between thrombin activity and fibrinolysis. This has been attributed to both deficient levels of plasminogen activators and to the presence of plasminogen activator inhibitors (Hamsten, Wiman & de Faire et al., 1985; Ridker et al., 1993).

Studies identifying markers of fibrin formation and fibrinolysis following thrombotic disease such as stroke have suggested that peak endogenous fibrinolytic activity does not occur acutely following stroke (Feinberg, Bruck & Ring et al., 1989). The rise of fibrinogen after acute stroke begins two to four days after the ischaemic event, reaching a maximum by fourteen days (Elliot & Buckell, 1961). It has been suggested that thrombotic activity and fibrin formation continue for up to four weeks in some patients who have suffered an ischaemic stroke (Feinberg et al., 1989). However, D-dimers should not remain elevated above normal levels for longer than six weeks, unless thrombosis is ongoing.

Feinberg et al. (1989) suggest that prolonged thrombin activity is a property of stroke and not thrombosis in general. Spontaneous lysis of clot has been shown to occur in stroke (Dalal, Shah & Sheth et al., 1965). It is possible that distal migration of clot could generate more thrombin activity. Angiographic changes occur early in the course of stroke and therefore would not seem to explain persistent elevations of fibrin degradation products (Feinberg et al., 1989).

Infarcted brain itself might activate thrombin activity. Brain thromboplastin is a powerful procoagulant. Blood-barrier breakdown as demonstrated by contrast enhancement CT scanning often reaches a maximum two to four weeks after stroke (Tow, Wagner & DeLand et al., 1969; Hornig, Busse & Buettner et al., 1985). Perhaps leakage of brain tissue components into the vascular system may provide ongoing stimulus for thrombin generation.

During the acute period, fibrin formation greatly exceeds degradation. Evidence of fibrinolysis develops slowly post stroke. Prolonged elevation of fibrin degradation products suggest that thrombin activity, fibrin formation and fibrinolysis persist for an extended period after stroke (Feinberg et al., 1989).

1.1.3 D-dimer generation pathway

1.1.3.1 Coagulation pathway

The coagulation pathway involves a series of linked proteolytic reactions culminating in the formation of a fibrin plug.

Arterial thrombosis and thrombus extension involve the processes of endothelial injury, platelet aggregation and release, vasoconstriction and thrombin generation (Schneider, 1947; Davie & Ratnoff, 1964; MacFarlane, 1964, Nemerson, 1966; Kaplan, 1978; Miletich, Jackson & Majerus, 1978; Zur & Nemerson, 1980; Broze, Warren & Novotny et al., 1988; Broze, Girard & Novotny, 1990; Hoffbrand & Pettit, 1995). Thrombin-mediated fibrinogen cleavage results in fibrin formation, which is required for thrombus stabilization (Pisano, Finlayson & Peyton,1968; Hermaus & McDonagh,1982). **(see Figure 1.1)**

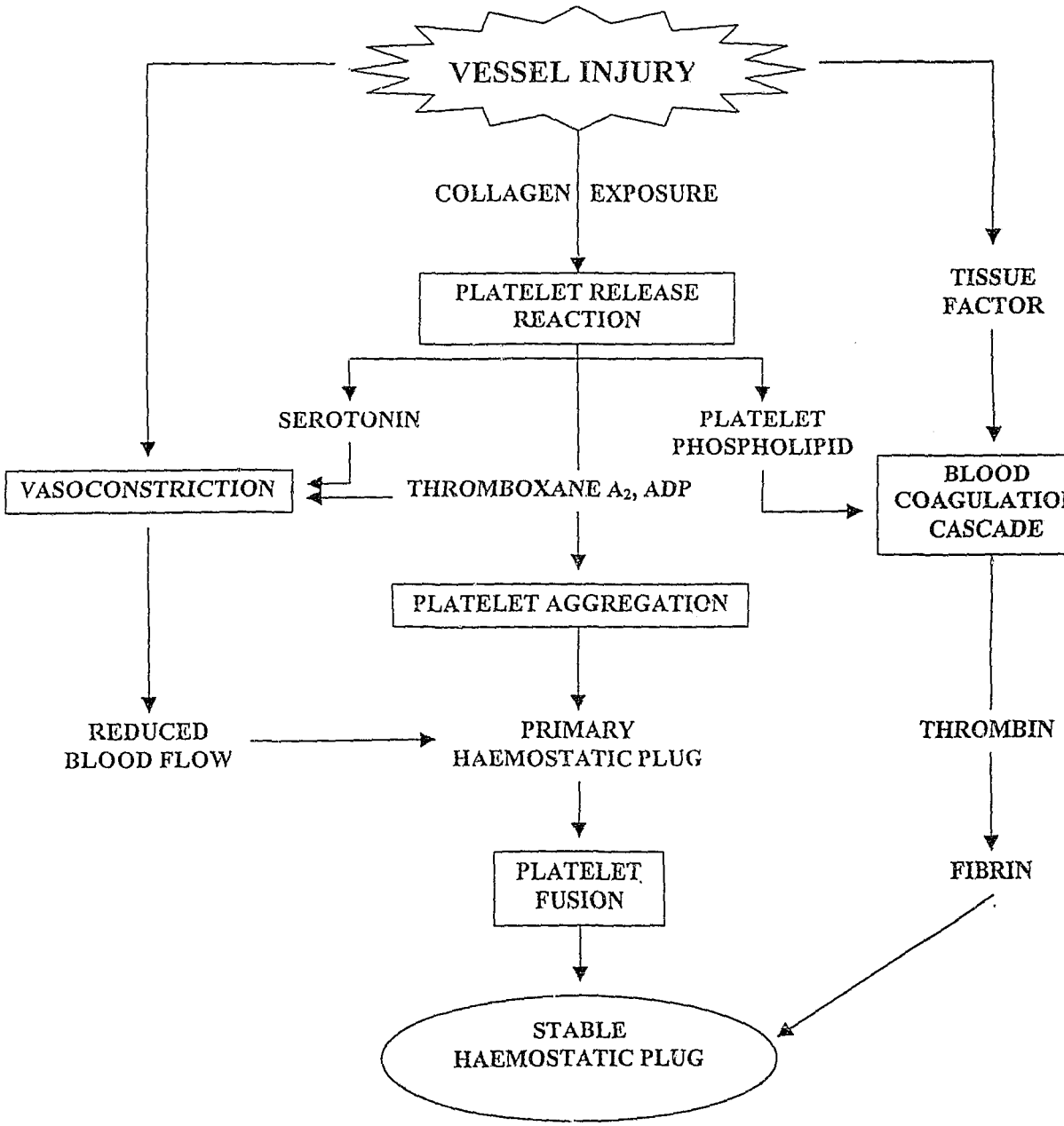


Figure 1.1: Reactions involved in haemostasis (Hoffbrand & Pettit, 1995)

Clotting is initiated by factor VIIa-tissue factor complexes formed on the surfaces of cells in injured tissues (Schneider, 1947). Tissue factor is an integral membrane protein of many cell types not exposed to blood naturally. Its expression is induced by mediators of injury on surfaces of activated endothelial cells, leukocytes, subendothelial components and smooth muscle cells. This allows for activation of factors IX to IXa and X to Xa (Silverberg, Nemerson & Zur, 1977; Zur & Nemerson, 1980; Broze, Warren & Novotny et al, 1988 Broze, Girard & Novotny, 1990), with subsequent formation of thrombin from prothrombin (Del Zoppo, Zeumer & Harker, 1986; Hoffbrand & Pettit, 1995).

Thrombin-mediated fibrin formation also occurs in direct relation to platelet activation by several mechanisms. Platelets promote activation of the early stages of coagulation by a process involving a factor XI receptor (Kaplan, 1978). Factors V and VIII also interact with platelet membrane phospholipids in the presence of calcium, to facilitate the activation of factor X to Xa and conversion of prothrombin to thrombin (Nesheim, Hibbard & Tracy et al., 1980). Platelet-bound thrombin modified factor V (factorVa) serves as a high affinity platelet receptor for factor Xa (Miletich, Jackson & Majerus, 1978). Consequently, the rate of thrombin generation is accelerated 100 000 fold, providing a potent positive feedback mechanism for initiation of thrombin formation on the platelet surface, fibrin network formation in the thrombus and, indirectly, fibrinolysis (Del Zoppo, Zeumer & Harker, 1986). **(see Figure 1.2)**

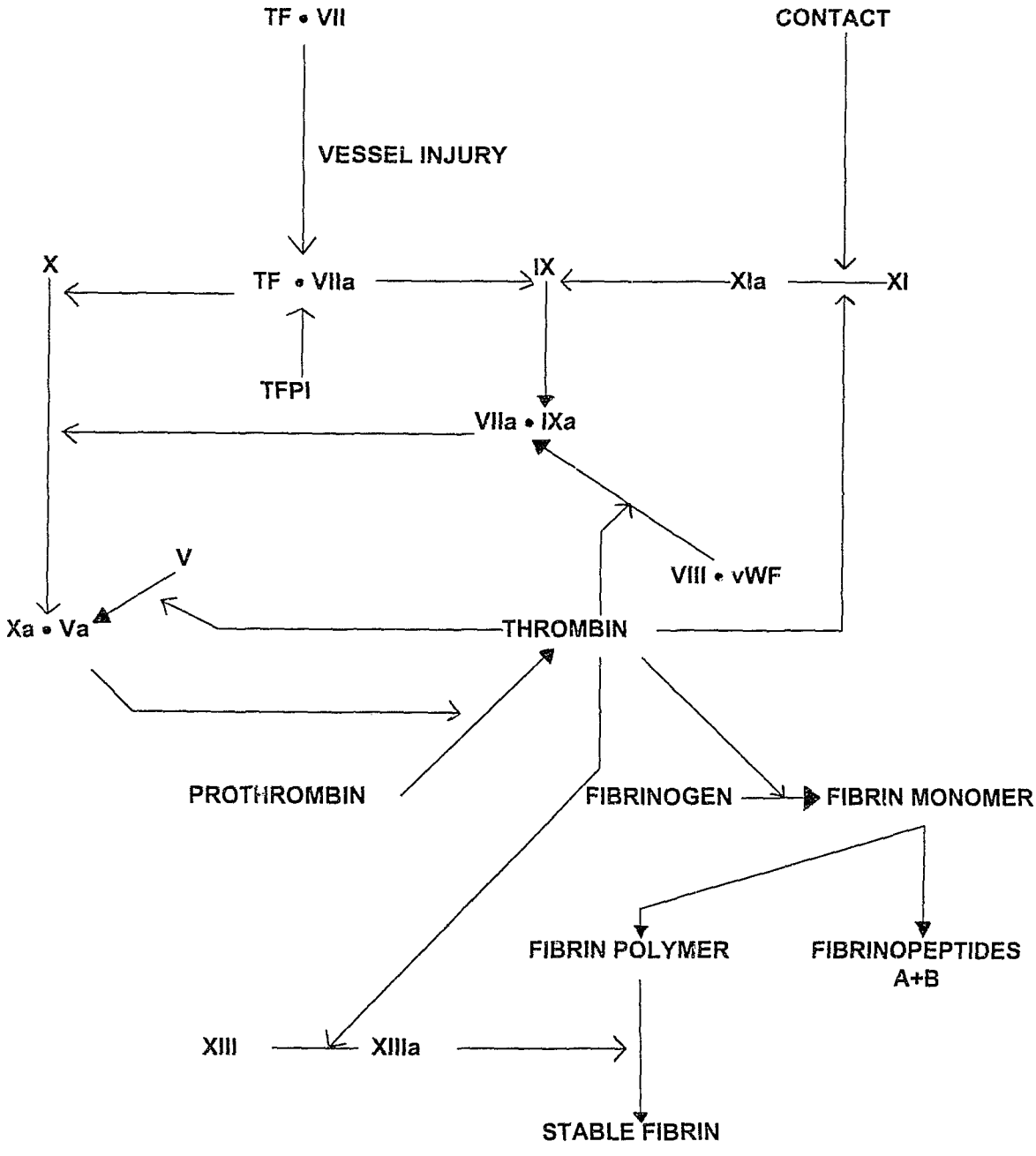


Figure 1.2: **Overview of the coagulation and fibrinolytic systems** (Hoffbrand & Pettit, 1995)

1.1.3.2 Fibrinolysis

D-dimers are terminal breakdown products of cross-linked fibrin degeneration by plasmin. Fibrin is formed during inflammation, tissue repair or haemostasis (Francis & Marder, 1986). It plays a temporary role and must be removed when normal tissue structure and function are restored. The fibrinolytic system is the principal effector of clot removal and controls the enzymatic degradation of fibrin. Its action is coordinated through the interaction of activators, zymogens, enzymes and inhibitors to provide local activation at sites of fibrin deposition without causing systemic effects.

Fibrin orchestrates a number of the components of the fibrinolytic system, notably plasminogen, tissue plasminogen activator (tPA) and α_2-antiplasmin onto its surface. This results in the formation of plasmin which leads to the hydrolytic cleavage of fibrin to fibrin degradation products (FDP's) (Francis & Marder, 1986; Gaffney & Longstaff, 1994). Tissue plasminogen activator (tPA) and urokinase perform the activation of plasminogen, central in fibrinolysis, to yield plasmin (Sloan, 1987). **(see Figure 1.3)**

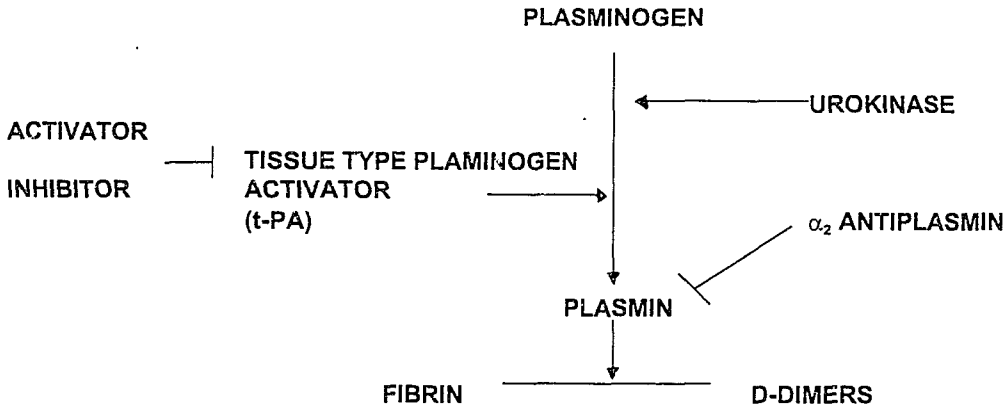


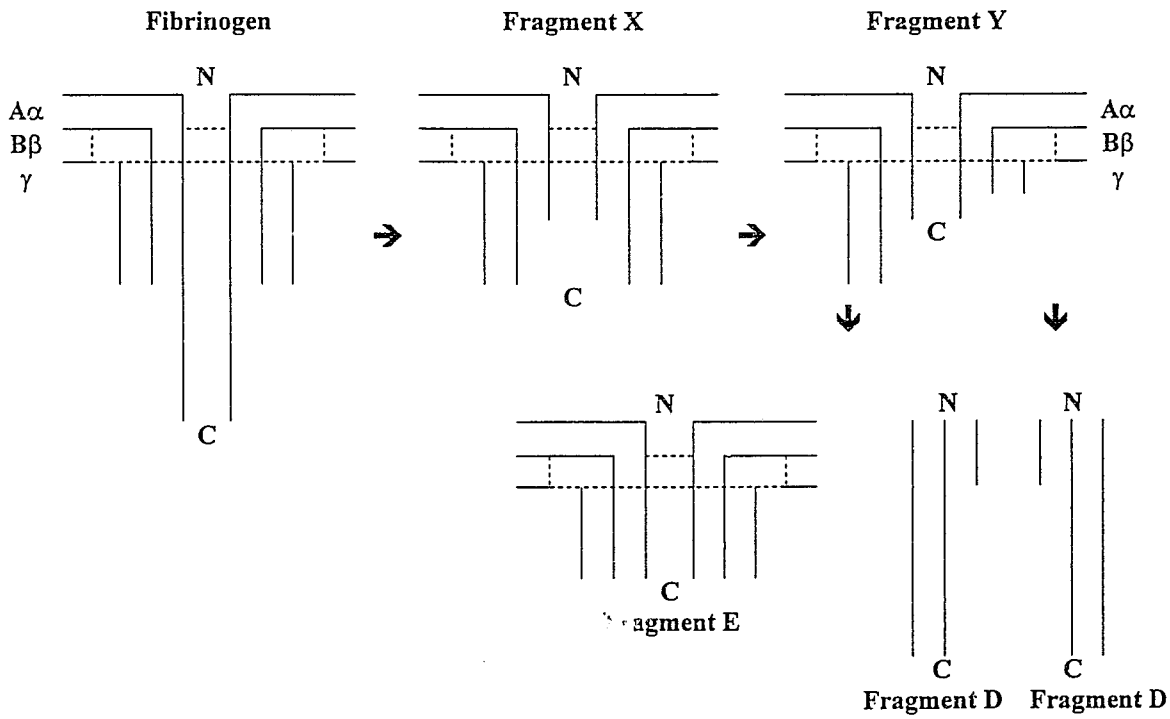
Figure 1.3: Interactions of the principal components of the fibrinolytic system

(Francis & Marder, 1986)

1.1.3.3 Fibrinogen breakdown

Fragments obtained from fibrinogen following plasmin attack, when fractionated on ion-exchange columns, separate into five major fragments called A, B, C, D and E. Fragments D and E are described as plasmin-resistant or terminal core fragments, having molecular weights of 83 000 and 33 000, respectively. (Gaffney & Longstaff, 1994). These core fragments had previously been described as α and β fibrinogens. Fragments D and E are 50% and 20% by weight of the original fibrinogen molecule and represent individually distinct structural and antigenic regions of fibrinogen. Intermediate plasmin-labile

degradation products of fibrinogen, named X and Y fragments are also observed. (see Figure 1.4)



Intermediate fragments X and Y are shown. The polypeptide chain origin of the constituent subunits of each fragment can be related to those of the preceding fragment and to the polypeptide chains of the originating fibrinogen molecule: Aα, Bβ and γ.

Figure 1.4: Schematic diagram of plasmin-mediated conversion of fibrinogen to core fragments D and E (Gaffney, 1977)

The originating fibrinogen is a dimeric molecule consisting of three polypeptide chains Aα, Bβ and γ. The conservation of both the N-terminal amino acids and fibrinopeptides A of the Aα chains suggests early hydrolysis of the carboxyl ends of both these chains. Peptides of about 40 000 mW are rapidly released. The next reaction involves removal of peptides from the N-terminal ends of the Bβ chains. This is followed by the asymmetric splitting of all three polypeptide chains at one side of the partly degraded dimeric X fragments. This last lysis releases fragment D, and thus the cleavage points must be adjacent to the N-terminal ends of all three chains, as fragment D is located near the carboxyl end of each fibrinogen subunit (Gaffney, 1972a).

The remaining major fragment is called fragment Y and the subsequent lysis of its Aα, Bβ and γ chains converts fragment Y to fragment D and E. Thus, total fragmentation of fibrinogen results in two fragments of D and one fragment of E (Gaffney & Longstaff, 1994). It is evident that the "core" fragment D is made up of three polypeptide chain remnants of the Aα , Bβ and γ chains of fibrinogen, while "core" fragment E is a dimer containing two disulfide-bonded subunits, each subunit consisting of three polypeptide chains. **(see Figure 1.4)**

1.1.3.4 Fibrin breakdown

Fibrin formation occurs by thrombin-mediated release of the two small peptides, fibrinopeptides A and B from the N-terminal ends of the fibrinogen Aα and Bβ chains. Fibrin organization results in three major forms of fibrin:

1. Non cross-linked fibrin

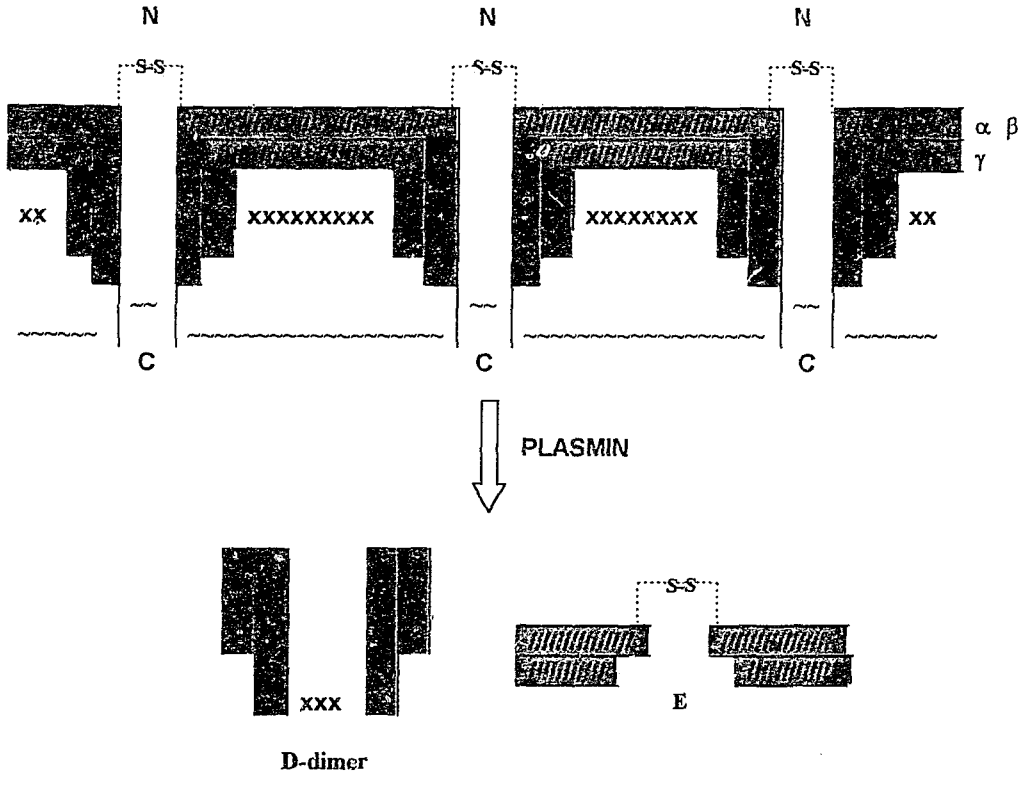
2. γ-γ cross-linked fibrin

3. Fibrin containing cross-linked γ chains and α chains (totally cross-linked fibrin).

These γ-γ cross-links are mediated by Factor XIII (Pisano, Finlayson & Peyton, 1968).

The presence of strategic structures in fibrin enhances the ability of tPA to activate plasminogen and thus, plasmin forms attached to fibrin (Collen, 1980).

In 1973, a unique fragment was found in cross-linked fibrin digests which was described as a D-dimer (Gaffney 1972b). This was shown to contain two D domains from adjacent fibrin molecules, held together by the cross-linked γ chain remnants of the originating fibrin. **(see Figure 1.5)**



The cross-linked γ chain dimers (γ-γ cross-links shown by crosses), the cross-linked ∝ chain polymers and the non-cross-linked β chains are related to each other schematically. Disulphide (S-S) bonds link individual polypeptide chains (α, β, γ) of each fibrin molecule. Digestion by plasmin yields a fragment, D, which is cross-linked to another D fragment from an adjacent fibrin molecule, this is called "D-dimer". Fragment E and a variety of other peptides (not shown) are also released during the lysis of cross-linked fibrin.

Figure 1.5: Schematic representation of cross-linked fibrin and its degradation products, D-dimer and fragment E (Gaffney, Brasher & Lord, 1976)

1.1.4 Assessment of fibrinolysis

The most tangible evidence of fibrinolysis is the generation of fibrin degradation products. Fibrin formation is relevant to thrombosis and fibrinolytic activity is promoted by the presence of fibrin. Measuring FDPs therefore allows prediction of onset or monitoring progress of a fibrin-based thrombotic event (Gaffney & Longstaff, 1994). Post thrombotic episode, D-dimers should normalize within six weeks, undergoing catabolism primarily in the liver (Herren et al., 1994).

1.1.5 Measurement of D-dimers

Antibodies have been developed which have specificity for each component within the heterogeneous group of cross-linked fibrin degradation products. Monoclonal antibodies which do not react with fibrinogen or non cross-linked fibrin fragments, but have a positive reaction with specific antigenic determinants on fragment D-dimers, are employed (Gaffney, 1972b; Whitaker, Elms & Masci et al., 1984). By this method, normal D-dimer levels lie below 250 ng/ml (Heaton et al., 1987). Actual D-dimer levels can also be assessed by ELISA, a more sensitive quantitative method, but this test is considerably more costly (Freyburger, Trillaud & Labrouche et al., 1998).

The D-dimer latex agglutination assay is a sensitive test, thus explaining the apparent discrepancy between increased levels of these fibrin degradation products and the findings of reduced basal fibrinolytic activity (Cortellaro et al., 1993; Meade, Ruddock & Stirling et

al., 1993). In this study, the rapid D-dimer latex agglutination test has been used due to cost constrain. . However, the more sensitive ELISA test may be a better, more accurate, investigative tool.

1.2 Erythrocyte Sedimentation Ratio (ESR)

1.2.1 Infection/ inflammation in cardiovascular disease

A trend toward higher D-dimer levels in patients with recent infection or inflammation, compared to other stroke patients, has been shown (Macko, Ameriso & Gruber et al., 1996). The procoagulant abnormalities of elevated D-dimers and anticardiolipin antibodies (ACLA) in patients with brain infarction preceded by febrile infection, has been demonstrated (Ameriso, Wong & Quismorio et al., 1991).

Systemic infection and inflammation have been implicated as risk factors in the aetiology of thrombotic episodes, especially in ischaemic stroke afflicting younger patients (Janaki, Baruah & Jayayaram et al., 1975; Ode & Cronberg, 1976; Hindfelt & Nilsson, 1977; Syrjanen, Valtonen & Iivanainen et al., 1986; Syrjanen et al., 1988; Ameriso et al., 1991; Grau, Buggle & Heindl et al., 1995; Macko, Ameriso & Brandt et al., 1996; Macko et al., 1996).

This view is compatible with data suggesting a causal association between chronic infective agents such as Chlamydia pneumonia (Thom, Grayston & Siscovik et al., 1992;

Patel, Mendall & Carrington et al., 1995; Danesh, Collins & Peto, 1997), Helicobacter pylori (Patel et al., 1995), Cytomegalovirus (Melnick, Adam & DeBakey, 1990), Herpes simplex virus (Ridker, 1997) and atherosclerotic disease. Chronic inflammation would appear to play an important role in initiation and progression of atherosclerosis and possibly in the conversion of stable plaques to unstable, partially occlusive, lesions (Ridker, 1997).

Atherosclerotic lesions are heavily infiltrated with cellular components associated with inflammation (Smith et al., 1990; Entman & Ballantyne, 1993; Ross, 1993). Both macrophage growth factors and monocyte chemo attractants are preferentially expressed in atherosclerotic vessels among patients with unstable coronary artery disease and acute ischaemic stroke (Frenette & Wagner, 1996). Alternatively, infection may alter endothelial function (Vallence, Collier & Bhagat, 1997).

Chlamydia pneumonia, strain TWAR, has been observed ultrasructurally in the lipid-rich core of arterial fibrolipid plaques and in intimal smooth muscle cells of autopsy specimens from patients with coronary artery disease (Shor, Kuo & Patton, 1992). The organisms were detected in localised areas, only in sites of tissue damage, in foam cells and in the central necrotic areas of the plaques. They were not found in adjacent normal arterial tissues (Kuo, Shor & Campbell et al., 1993). Saikku, Loinonen and Tenkanen et al. (1992) described Chlamydia antibody and lipopolysaccharide-containing immune complexes as risk factors for the development of coronary artery disease. Thom and colleagues (1992)

confirmed these findings by associating Chlamydia pneumonia Ig G antibody titres and angiographically diagnosed coronary artery disease.

Chlamydia pneumonia has further been identified in aortic aneurysm plaques. Blasi, Cosentini & Raccanelli et al. (1997) have recently confirmed the possible role of C pneumonia infection in coronary artery disease and suggest that reinfection, superimposed upon existing chronic infection, may trigger the onset of acute myocardial infarction. This implies that this agent is an "inducer" or "enhancer" of plaque destabilization or disruption (Sumpter & Dunn, 1997).

Various potential causative mechanisms that may act either acutely (by precipitating plaque rupture) or chronically (by precipitating plaque growth) have been proposed for the reported associations between infection and cardiovascular disease (Vallence et al., 1997). Some involve possible direct effects of infectious agents on the arterial wall, including endothelial injury or dysfunction (Vallence et al., 1997), smooth muscle proliferation (Ross, 1993) and local inflammation (Danesh et al., 1997). Most of the above involve possible indirect effects mediated in the circulation through chronic inflammation (Mendall, Patel & Ballam et al., 1996; Ridker, Cushman & Stampfer et al., 1997), cross-reactive antibodies or changes in known or suspected cardiovascular risk factors such as lipids, coagulation proteins or oxidative metabolites (Ross, 1993; Danesh et al., 1997).

Many authors have postulated that altered coagulation may represent a link between infection and stroke, possibly mediated by cytokines (interleukin-1 and tumour necrosis factor), known to exert a procoagulant effect (Hallenback, Dutka & Kochanek et al., 1988).

As endotoxins and cytokines have been shown to increase concentrations of PAI-1, the major plasma inhibitor of tissue plasminogen activator (Hindfelt & Nilsson, 1977; Hallenback et al., 1988; Ameriso et al., 1991), this could explain the decreased fibrinolytic response in patients with ongoing chronic infective or inflammatory processes. Thus, even though the presence of subclinical infection promotes a prothrombotic state, with resultant fibrinolysis, the balance of the two processes favours ongoing thrombogenesis and atherogenesis, predisposing to ischaemic vascular events.

Therapeutic intervention both in the prophylaxis and the treatment of thrombovascular disease processes points towards an inflammatory component in its pathogenesis. Aspirin is well known to be beneficial in the acute treatment and prevention of cardio- and cerebrovascular disease (Ridker et al., 1997). The benefit of aspirin is known to arise from its ability to decrease platelet aggregation, but reduction of the vascular inflammatory response may be equally important (Ridker et al., 1997; Sumpter & Dunn, 1997).

The use of an anti-chlamydial agent such as roxithromycin, to reduce the rate of recurrent angina, myocardial infarction and ischaemic death in patients with coronary artery disease, as demonstrated by Gurfinkel and associates, further supports the hypothesis of

atheromatous disease being associated with infective agents (Curfinkel, Bozovich & Daroca et al., 1997).

1.2.2 Acute-phase reactants

Elevated levels of C-reactive protein, an acute-phase reactant that acts as a marker of systemic inflammation, have been described among patients with acute ischaemia (Berk, Weintraub & Alexander, 1990; Ridker, 1997) and cerebrovascular disease (Mendall et al., 1996; Ridker et al., 1997). Other markers of inflammation, such as fibrinogen and erythrocyte sedimentation ratio (ESR), are also associated with ongoing thrombotic processes (Meade et al., 1993).

1.2.2.1 Fibrinogen

Fibrinogen is an acute-phase protein and rises in response to a number of stimuli (Meade, Brozovic & Chakrabarti et al., 1986). Clinical situations in which fibrinogen levels are high, as in the postoperative state, are also characterized by an increase in the incidence of venous thrombosis. Thus, the fact that fibrinogen levels are high due inflammatory stimuli does not mean that these high levels do not influence or contribute to thrombogenesis (Meade et al., 1986).

Increasing levels of fibrinogen within the physiological range have very consistent effects on in-vitro measures of platelet aggregation (Meade, Vickers & Thompson et al., 1985).

Fibrinogen is also a major determinant of blood viscosity that, if increased, probably has a causal role in ischaemic heart disease (Lowe, Drummond & Lorimer et al., 1980). Thus, raised levels of fibrinogen may promote atherogenesis by two general pathways apart from many effects they may also have on local fibrin production.

Normal international fibrinogen reference levels lie between 2 and 4 g/l. Fibrinogen levels in male South Africans have been shown to segregate according to socio-economic status. The higher socio-economic group Whites, Coloureds and Indians have significantly higher values than the lower socio-economic group Coloureds, Indians and rural Blacks. In the urban Black group, although of lower socio-economic status, fibrinogen levels are not significantly different from those of the higher socio-economic groups (Seftel, Asvat & Joffe et al., 1993).

1.2.2.2 ESR

An elevated erythrocyte ratio (ESR) is known to be a non-specific, but reliable, marker of infection and inflammation (Fahraeus, 1921; Westergren, 1921; Hardwicke & Squire, 1952; Dacie & Lewis, 1995). Its elevation may also be associated with ongoing thrombotic processes. Raised levels have been described as an early feature of myocardial infarction (Froom, Margoliot & Caine et al., 1984).

The ESR measures the rate at which red blood cells aggregate. The rate of erythrocyte sedimentation depends on the interaction between opposing physical forces. Settling occurs because the density of the red corpuscles is greater than the density of the medium. The fall of the red blood cells causes an upward displacement of the medium, producing an upward current and retarding force. In blood drawn from normal subjects, the downward and upward forces are nearly equal; consequently, minimal settling occurs when the concentration of the red cells is lower than normal and the red cells themselves cause less retardation of sedimentation (Fahraeus, 1921).

A factor of importance in affecting the sedimentation rate in the diseased state is the size of the sedimenting particle. The larger the volume of the particle, the smaller is the relative surface area. In the presence of rouleaux formation, aggregates of large volume but relatively small surface area are produced, accelerating the sedimentation rate. Rouleaux formation may result from changes in the negative charge of red cells, which in turn is a function of sialic acid groups on the cell membrane. This charge may be attenuated by the dielectric effect of proteins in the surrounding plasma, especially asymmetric macromolecules such as fibrinogen and γ globulin (Bull & Brailsford, 1972; Wintrobe, 1993).

Fibrinogen is the most important plasma protein that bridges cells in red cell aggregation (Hitzman et al., 1981). Red cell aggregation is also promoted by increases in other plasma globulins such as α_2- macroglobulin, immunoglobulins and lipoproteins and also by a

decrease in albumin. Such alterations in plasma proteins occur in acute and chronic disease states, of which the ESR is a time-hallowed measure (Fahraeus, 1921; Lowe, 1987).

The ESR is influenced by proteins of the acute-phase response and by anaemia (Poole & Summers, 1952; Heisto et al., 1969). Although a normal ESR cannot be taken to exclude the presence of organic disease, the vast majority of acute or chronic infections and most degenerative or malignant diseases are associated with changes in the plasma proteins that lead to acceleration of sedimentation (Ansell & Bywaters, 1958; Harkness, 1971). The ESR is influenced by age, stage of menstrual cycle, sex and certain drugs (Dacie & Lewis, 1995).

1.2.3 Measurement of ESR

Normal red blood cells are highly deformable by shear forces in flow, due to cell geometry, a flexible membrane and a low internal viscosity. This ready deformability is responsible for not only low bulk blood viscosity in wide-bore vessels at high shear rates, but also for rapid passage of individual red cells through nutritive capillaries to supply oxygen to the tissues (Lowe, 1994).

With reduction in shear forces, red cells are no longer deformed and are aggregated by plasma macromolecules into linear aggregates (rouleaux), which undergo secondary aggregation to form elastic networks within the blood. Such aggregates disturb flow

streamlines and increase blood viscosity at low shear rates. Red cell aggregation can be measured by low-shear viscometry, by photometry or by sedimentation methods such as the erythrocyte sedimentation rate (Fahraeus, 1921; Westergren, 1921; Lowe, 1994).

The method for measurement of the ESR is based on that of Westergren (Westergren, 1921; International Council for Standardization in Haematology, 1993). Diluted blood is allowed to sediment in a vertically mounted glass tube for an hour. The height of the plasma after this time interval is then read to the nearest 1 mm above the upper limit of the column of sedimented cells. The result is expressed as ESR = x mm/hr.

The upper limit of ESR for 90% of normal males between 17 and 70 is 14. In normal females of the same age range, the upper ESR limit is 20 (Dacie & Lewis, 1996). These values are international reference levels. Although local empirical observations of ESR levels in the South African Black population indicate that the upper limit is higher than in White subjects, no standard reference range has been drawn up for this population group.

1.3 Overall Aims of Study

1.3.1 D-dimer levels

No previous studies have looked at the significance of ongoing elevated levels of D-dimers in patients whom had suffered either single or multiple cerebrovascular episodes (strokes or transient ischaemic attacks). This research project was initiated in an attempt to elucidate whether patients suffering multiple cerebrovascular episodes have elevated D-dimers for a prolonged length of time post event compared to patients experiencing single events, indicative of ongoing thrombosis and fibrinolysis. The postulate was that prolonged D-dimer elevation post event might act as a prognostic marker for those at risk of recurrent cerebrovascular episodes. This appeared to be the case from a clinical viewpoint, when patients' results were inspected in clinic and it was hoped to prove this with scientific analysis.

D-dimer levels were analysed according to the following parameters:

- Age
- Sex
- Race
- Territory of vascular supply
- Degree of internal carotid artery stenosis
- Time interval post event
- Nature of events (CVA or TIA)

- Number of events

1.3.2 ESR levels

Additional factors that might influence prolonged elevation of D-dimers were sought, and the question of the role that chronic infection and inflammation might play was explored. The hypothesis that patients who continued to exhibit elevated levels of D-dimers for a prolonged period after a cerebrovascular event might have concurrent infective or inflammatory processes, as manifested by an elevated ESR, hence maintaining a hypercoagulable state, was investigated.

ESR levels were investigated in association with the following:

- D-dimer levels
- Age
- Sex
- Race
- Territory of vascular supply
- Degree of internal carotid artery stenosis
- Time interval post event
- Nature of events (CVA or TIA)
- Number of events
- Fibrinogen levels
- White cell count (WCC)

CHAPTER 2

2.0 MATERIALS AND METHODS

2.1 Study Sample

Patients referred to the Haemostasis and Thrombosis Unit at the Johannesburg Hospital for analysis of their thrombotic profiles post ischaemic cerebrovascular event were assessed over the time period 1 January 1995 to 31 August 1997. All of the 148 patients studied had suffered either single or multiple cerebrovascular episodes, either cerebrovascular accident (CVA) or transient ischaemic attack (TIA).

2.1.1. History and examination

A comprehensive history was taken from each patient or relative. A complete neurological and physical examination was performed to determine the nature of event, vascular territory of involvement and number of episodes.

Most patients were assessed at the Cerebrovascular Disease Prevention Clinic at the Johannesburg Hospital. They had been treated previously for the acute episode. The time interval between the date of the most recent event and date of venesection was calculated and therefore variable for each patient. A small proportion of the study sample were in-

patients, admitted acutely to the medical wards of the Johannesburg Hospital or referred from surrounding hospitals, namely Hillbrow and Helen Joseph, for haematological assessment post cerebrovascular event.

Risk factors for vascular disease were recorded for each patient on history, namely ischaemic heart disease, peripheral vascular disease, diabetes mellitus, hypertension, migraine, gout, smoking, alcohol consumption, hormonal alteration, hyperlipidaemia, valvular heart disease, arrhythmias, previous cardiac or vascular surgery, previous venous thrombo-embolic disease, family nistory of atheromatous vascular disease, hyperthyroidism and illicit drug abuse. A current drug history was taken from all patients and the usage of all anticoagulant agents was noted.

Further, the presence and frequency of known risk factors associated with elevation of plasma D-dimers was assessed including increasing age, ischaemic heart disease, peripheral vascular disease, concurrent infection and a greater than 50% stenosis of the internal carotid arteries.

Patients were also evaluated for concurrent infective and/ or inflammatory states, such as auto-immune vasculitides. This included any evidence of infection or chronic inflammatory process on history, features suggestive on clinical examination and measurement of white cell count (WCC) and Westergren erythrocyte sedimentation ratio (ESR). Syphilis serology was also performed on all patients. The 43 patients who

consented to testing for the human immunodeficiency virus were all found to be negative for this agent.

2.1.2 Laboratory investigations

The thrombotic profile performed on each patient included analysis of the following haematological parameters: INR; PTT; D-dimer levels; Protein C assay; Protein S assay; Antithrombin assay; Activated Protein C Resistance (APCR); APCR Polymerase Chain Reaction for Factor V Leiden mutation; Lupus Anticoagulant (LAC); Fibrinogen levels and Thrombin time.

Other laboratory parameters assessed were: haemoglobin; white cell count; platelet count; ESR; random glucose; total cholesterol; HIV; anti-cardiolipin antibodies (ACLA); anti-nuclear factor (ANF); syphilis serology (RPR and TPHA) and free T_4.

Patients were venesected when they presented, whether acutely or in follow-up, resulting in a random time interval between most recent event and date of venesection. The level of plasma D-dimers in different patient groups was assessed and it was determined whether venesection had been performed within, or after, a two and then a six month time interval following the most recent cerebrovascular event.

2.1.3 Other investigations

All patients underwent thorough cardiological assessment, including electrocardiogram and echocardiography, to elucidate whether a cardio-embolic aetiology might play a role in their presentation. Radiological scanning procedures such as CT scan or MRI scan of the brain were performed on the patients to exclude a haemorrhagic aetiology and discern the territory of vascular supply involved. Patients also underwent carotid artery doppler studies and/ or angiography to determine the status of their carotid and vertebro-basilar vasculature.

2.2 Methods of Measurement

2.2.1 D-dimers

Blood was collected in test tubes containing 0.015 M trisodium citrate, as citrated sodium was used routinely for this D-dimer analysis. The BIOPOOL Minutex D-dimer Latex Kit was employed for testing. This used monoclonal antibody shown to be specific for fibrin fragment D-dimer and fragment D, but was non-reactive to fibrinogen or fibrin degradation products. The monoclonal antibody was coated on latex beads that agglutinate in the presence of D-dimer levels in excess of 250 ng/ml.

If the neat sample was positive, serial dilutions were made of the patient's plasma to obtain quantitative results. This was done by serially diluting 100 ul of sample 1: 2, 1: 4 and 1: 8 with saline solution. Agglutination was read and the results interpreted as follows:

- < 250 ng/ml
- 250 < 500 ng/ml
- 500 < 1000 ng/ml
- 1000 < 2000 ng/ml

The dilutions were continued until negative agglutinations were obtained.

2.2.2 ESR

The Westergren method, as recommended by the International Council for Standardization in Haematology was used to determine the ESR (1993). Blood was collected in a test tube containing 0.129 M trisodium citrate. The test was performed on venous blood diluted accurately in the proportion of one volume of citrate to four volumes of blood. Diluted blood was sedimented in a glass tube of 30 cm in length mounted vertically on a stand. The blood sample was thoroughly mixed and drawn into the Westergren tube to the 200 mm mark by a mechanical device. The tube was placed vertically and left undisturbed for sixty minutes. The height of the plasma was then read to the nearest 1 mm above the upper limit of the column of sedimented cells.

2.3 Statistical Analysis

The statistical analysis was performed making use of the SAS computer software package. Data was summarised using frequency, percentage, mean and standard deviation. Depending on the distributional properties of the parameters observed either parametric or nonparametric analyses were done. For continuous variables (age, time interval post event, D-dimer levels, ESR and fibrinogen levels) the one-way analysis of variance or Student's t-test was employed depending on whether two, or more than two, categories needed to be compared. Where necessary, when sample sizes were small or when the assumptions of the latter two tests were violated, use was made of Mann-Whitney's U-test and the Kruskal-Wallis one-way analysis of variance.

In the case of testing for association between categorical variables, use was made of the chi-square test. When sample sizes were small Fisher's exact tests were performed. The categorical variables and their categories were: normal or elevated D-dimer levels within age groups, sex, racial groups, two and six month time intervals post event, number and nature of events, territory of vascular supply and degree of carotid artery stenosis; normal or elevated ESR within white cell count (WCC), then versus D-dimer levels.

Correlation analysis was also done between continuous variables using Pearson's correlation coefficient. One-way analysis of variance was considered for associations between a continuous variable and a categorical variable with more than two categories.

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Correlation analysis was also done between continuous variables using Pearson's correlation coefficient. One-way analysis of variance was considered for associations between a continuous variable and a categorical variable with more than two categories.

The D-dimer levels were categorized either as an ordinal variable, normal (≤ 250 ng/ml) versus elevated (> 250 ng/ml), as well as continuously within each subgroup of elevation. Comparisons were made between patients 45 years and younger and patients older than 45 years.

Results are given in text as mean (standard deviation). All testing was conducted at a 0.05 level of significance.

2.4 Ethical Clearance

The University of the Witwatersrand Ethics Committee granted ethical clearance. The clearance number is M980130.

2.5 Patient Consent

No patient consent for the investigations was required, as all tests performed comprise part of the routine work-up for patients suffering cerebrovascular events at the Johannesburg Hospital. All analyses were performed on a retrospective basis, i.e. post event.

CHAPTER 3

3.0 RESULTS – D-DIMERS

Analysis of the D-dimer levels in the patients studied was performed within demographic groups. Of the 148 patients assessed, 93 demonstrated normal levels of D-dimers below 250ng/ml at the time of testing, whereas 55 had elevated D-dimers above this level. Assessment was performed within categories of sex, racial group, age territory and nature of event. Patients were then stratified into three groups, according to whether they had suffered single, two or multiple (≥3) cerebrovascular events. Further analysis of the association between D-dimer levels and elevated ESR was also performed within these demographic categories.

3.1 Age

3.1.1 Age range

The age range studied was 15.2 to 79 years (mean 46.8 years). The mean age of the 93 patients with normal D-dimers was 44.5 years and the mean age of the 55 patients with elevated D-dimers was 50.2 years ($p = 0.0403$). **(see Figure 3.1)**

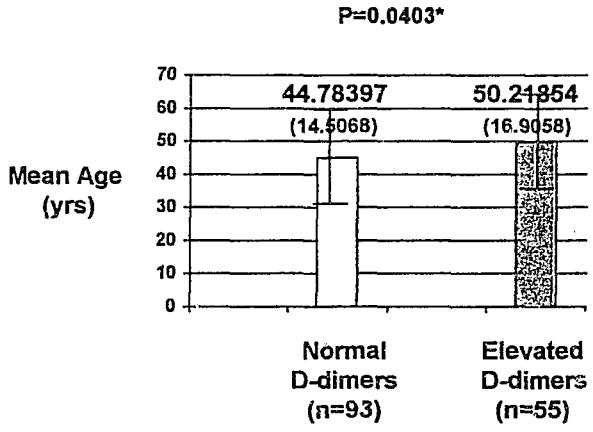


Figure 3.1: Mean age versus normal and elevated D-dimer levels in all patients

A statistically significant difference was observed between the mean age of patients with normal D-dimers, compared to the higher mean age of those with elevated D-dimers.

3.1.2 Age groups

As aetiological factors and pathogenesis of stroke differs in younger patients, patients were stratified into those 45 years and younger, and those older than 45. Atherosclerotic risk factors are more prevalent in older stroke patients, whilst young stroke patients have a higher incidence of other aetiological factors. These include haematological hyperthrombotic abnormalities, alteration in hormonal status, cardio-embolic disease, non-atheromatous vasculopathy and infection. It was postulated that younger patients might exhibit an overall higher incidence of hyperthrombotic abnormalities, as evidenced by elevated D-dimer levels. **(see Figure 3.2)**

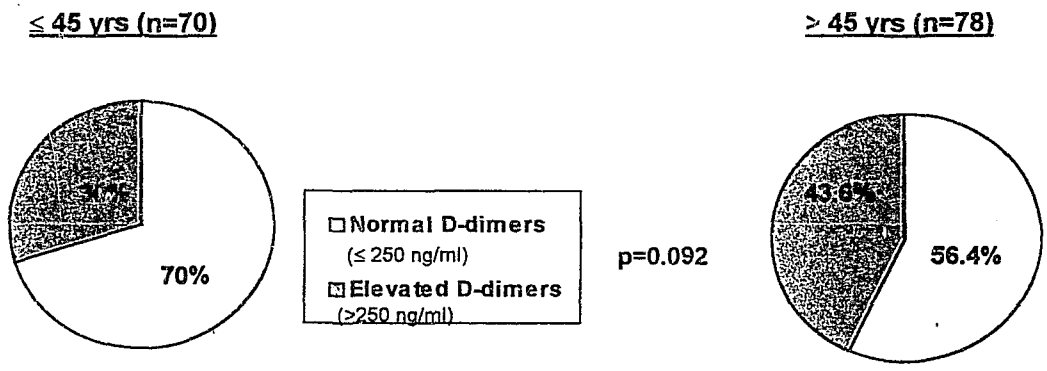


Figure 3.2: Levels of D-dimers (categorical variable) within age groups in all patients

In the 70 patients 45 years and younger at the time of their initial event, 49 (70%) had normal D-dimer levels and 21 (30%) had elevated levels. When compared to the 78 patients older than 45 years, where 44 (56.4%) had normal D-dimers and 34 (43.6%) elevated levels, no significant statistical difference was found ($p = 0.092$).

3.2 Sex

Of the 90 females studies, 62 (68.9%) had normal D-dimer levels and 28 (31.1%) elevated levels above 250ng/ml. Thirty-one (53.4%) of the 58 males had normal D-dimer levels and 27 (46.6%) had elevated levels ($p = 0.081$). **(see Figure 3.3)**

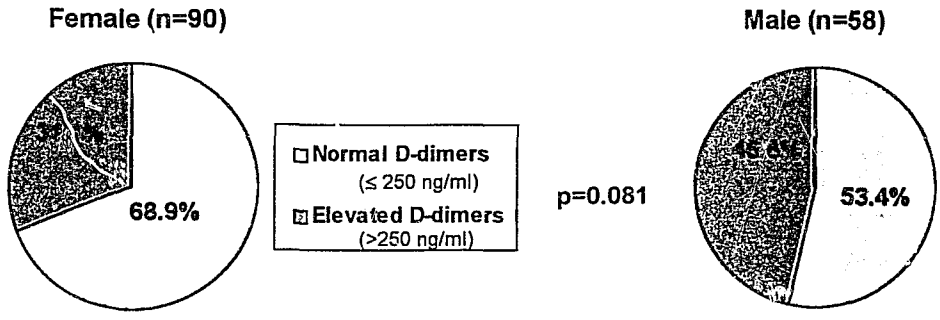


Figure 3.3: Levels of D-dimers (categorical variable) within sex

There was no significant difference between the distribution of normal and elevated D-dimers in females and males in this study.

3.3 Race

When comparing normal versus elevated levels of D-dimers amongst racial groups, no significant differences were observed. **(see Table 3.1)**

Table 3.1: Normal and elevated D-dimer levels within racial groups

		Normal D-dimers		Elevated D-dimers		p-value
	N	n	%	n	%	
Racial Groups	148	93		55		
Asian	9	9	100	0	0	
Black	48	29	60.4	19	39.6	
Coloured	9	5	55.6	4	44.4	0.097
White	82	50	61	32	39	

No Asian patients showed an elevation in D-dimer levels, but in view of the small number of Asian and Coloured patients studied, this result cannot be seen as representative. However, the distribution of normal and elevated D-dimers in the Black, Coloured and White patients was very similar ($p = 0.097$).

3.4 Territory of Vascular Supply

Attempts were made to determine whether more patients suffering events in the anterior circulatory territory of vascular supply had elevated D-dimer levels than those patients suffering events in posterior, or both, territories. **(see Table 3.2)**

Table 3.2: Normal and elevated D-dimer levels within territory of vascular supply

		Normal D-dimers		Elevated D-dimers		p-value
	N	n	%	n	%	
Territory of Supply	148	93		55		
Anterior	127	79	62	48	38	
Posterior	18	12	66.7	6	33.3	0.911
Both	3	2	66.7	1	33.3	

The majority of patients, 127, suffered cerebrovascular events in the anterior circulatory territory of blood supply (either anterior or middle cerebral artery), with 79 (62%) having normal D-dimers and 48 (38%) having elevated D-dimers. Eighteen patients had suffered events in the posterior circulatory territory of vascular supply (posterior cerebral artery or vertebro-basilar system), with a similar distribution of normal D-dimer levels, 12 (66.7%) and elevated D-dimers, 6 (33.3%). Although only three patients were identified as having events in both territories of supply and, therefore, had suffered more than one event, the distribution of normal to elevated D-dimers was again similar (p = 0.911).

3.5 Degree of Internal Carotid Artery Stenosis

The degree of internal carotid artery stenosis was assessed using carotid artery doppler studies and/or angiography. Stenosis was characterized as being absent (0%) in 106 patients, greater than 50% in 26 patients and less than 50% in 16 patients. **(see Table 3.3)**

Table 3.3: Normal and elevated D-dimer levels within degree of internal carotid artery stenosis

		Normal D-dimers		Elevated D-dimers		p-value
	N	n	%	n	%	
Degree of Stenosis	148	93		55		
No stenosis	106	72	68	34	32	
≥50% stenosis	26	14	53.8	12	46.2	0.102
<50% stenosis	16	7	43.8	9	56.2	

Of those patients with no identifiable stenosis of the internal carotid arteries, 72 (68%) had normal D-dimer levels and 34 (32%) had elevated levels. No further statistical difference was found between those patients with 50% or greater stenosis and those with less than 50% stenosis (p = 0.102).

3.6 Time Interval Post Event

The time interval between the most recent cerebrovascular event and date of measurements of D-dimer levels ranged between 0.01 and 22.8 years. **(see Figure 3.4)**

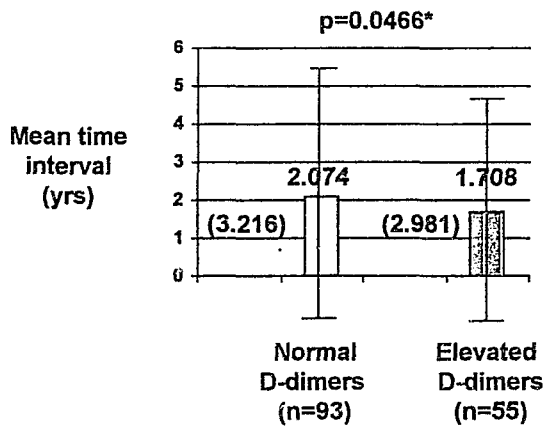


Figure 3.4: Mean time interval versus normal and elevated D-dimers levels in all patients

In those patients with normal D-dimer levels, the time interval between event and assessment ranged from 0.01 to 22.8 years, mean time interval = 2.074 (3.216) years. When compared to those patients with elevated D-dimers, the time interval ranged between

0.03 to 14.36 years, mean time interval = 1.708 (2.981) years, achieving a statistically significant difference (p = 0.0466).

3.6.1 Specified time interval post event

As D-dimers should fall to normal levels within six weeks post thrombotic episode, it was expected that after such a time interval had elapsed, D-dimer levels would not remain elevated. Any persistent elevation could then be assumed to indicate ongoing thrombosis and fibrinolysis. Patients were thus divided and analysed according to the time frame within which blood levels of D-dimers had been ascertained, post most recent cerebrovascular event. Those patients with elevated levels for a prolonged time period post event could be assumed to be hypercoagulable. Patients were assessed within a two and a six month time interval.

3.6.1.1 Two month time interval

Of the 47 patients assessed within two months of their most recent cerebrovascular event, 25 (53.19%) displayed elevated D-dimer levels, while 101 patients were assessed after a two month time interval had intervened and only 30 (29.7%) had elevated D-dimer levels. **(see Figure 3.5)**

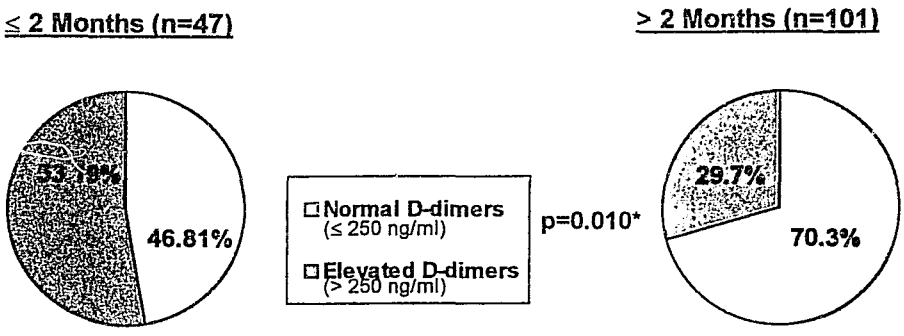


Figure 3.5: Levels of D-Dimers (categorical variable) within two month time interval post event

This statistically significant result ($p = 0.010$) is in keeping with expectations that D-dimer levels would remain elevated for six weeks post thrombotic event.

3.6.1.2 Six month time interval

Thirty (41.67%) of the 72 patients assessed within six months of their cerebrovascular episode displayed elevated D-dimers, compared to 25 (32.89%) of the 76 patients assessed after this time frame. **(see Figure 3.6)**

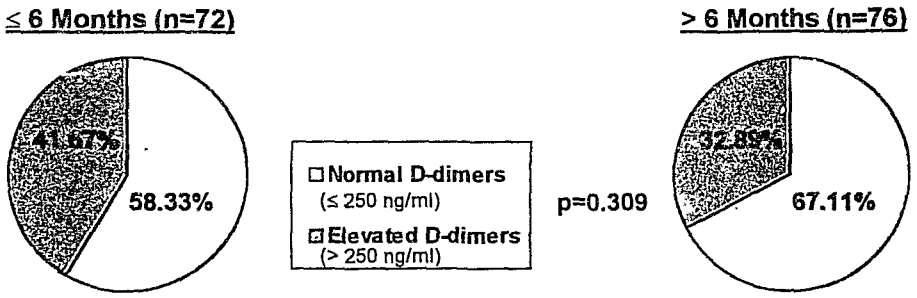
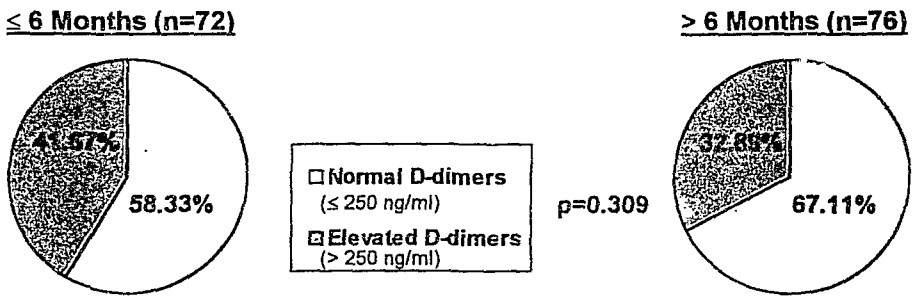


Figure 3.6: Levels of D-dimers (categorical variable) within six month time interval post event

This difference was not found to be of statistical significance ($p = 0.309$). However, it is of interest that up to a third of patients assessed after a six month time interval post event had elevated D-dimers, implying a persistent hypercoagulable state.

3.7 Nature of Events

A cerebrovascular accident (CVA) or stroke is characterised by the persistence of neurological deficit for longer than 24 hours. The pathogenesis of the deficit is that of ischaemia of sufficient severity, extent and duration, resulting in anoxic cerebral tissue damage or death, without subsequent recovery. A transient ischaemic attack (TIA) is, by definition, an ischaemic event in which neurological deficit recovers within a 24 hour period, because the area of hypoxic tissue is reperfused and regains function. Nevertheless, TIAs remain a powerful predictor of stroke.



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Because the degree and extent of thrombosis differs between a CVA and a TIA, D-dimer levels were assessed in patients experiencing either one or the other, or both type of events. This was to discern if an underlying hypercoagulable state could be linked to the severity of the cerebrovascular event. **(see Table 3.4)**

Table 3.4 Normal and elevated D-dimer levels within nature of cerebrovascular events

		Normal D-dimers		Elevated D-dimers		p-value
	N	n	%	n	%	
Nature of events	148	93		55		
CVA	97	61	62.9	36	37.1	
TIA	43	26	60.5	17	39.5	0.840
Both	8	6	75	2	25	

Of the 97 patients suffering CVAs, 61 (62.9%) had normal D-dimers and 36 (37.1%) had elevated levels. In those 43 suffering TIAs, 26 (60.5%) had normal D-dimers and 17 (39.5%) elevated levels. Only eight had experienced both type of events, with 6 (75%) having normal levels and 2 (25%) elevated levels of D-dimers. No statistical significance was shown ($p = 0.840$).

3.8 Number of Events

To determine whether D-dimers might act as prognostic markers in those patients suffering recurrent cerebrovascular events, patients were stratified into three groups and D-dimer levels compared. Seventy-nine patients had suffered a single event, 29 had suffered two and 40 patients had experienced three or more episodes. (see **Figure 3.7**)

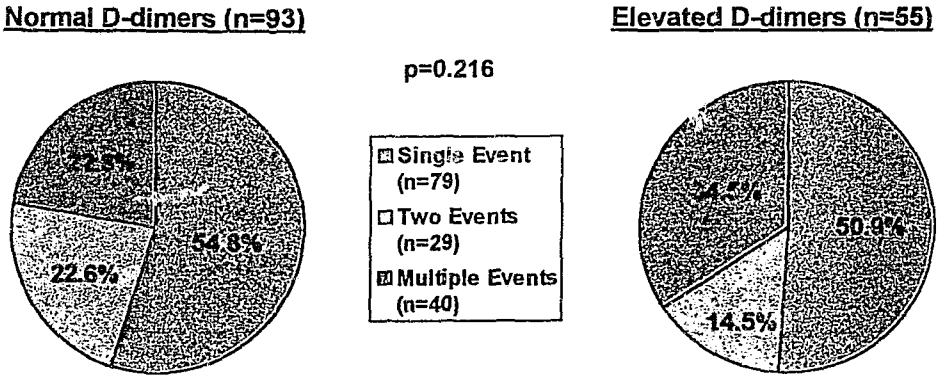

Figure 3.7: Number of cerebrovascular events within levels of D-dimers (categorical variable)

Of the 93 patients with normal D-dimers, 51 (54.8%) had suffered a single event, 21 (22.6%) had suffered two events and 21 (22.6%) had experienced three or more. When compared to the 55 patients with elevated D-dimer levels, where 28 (50.9%) had suffered a single event, 8 (14.5%) two events and 19 (34.5%) more than two episodes, no statistical difference was observed ($p = 0.216$).

3.8.1 Specified time interval post event

Because D-dimer levels are expected to decrease to normal levels within six weeks of a thrombotic event, the patients were then further stratified according to those who had been measured within a two month and six month time frame post event. This was to determine whether those patients suffering multiple cerebrovascular episodes might have elevated D-dimer levels for a prolonged period post episode, suggesting a persistent underlying hypercoagulable state and possibly acting as prognostic markers in those at risk of recurrent events.

3.8.1.1 Two month time interval

The spectrum of distribution of D-dimers in patients having suffered single, two or multiple events measured within or after a two month interval post event was not found to be of statistical significance. **(see Table 3.5)**

Table 3.5: Normal and elevated D-dimer levels in two month time interval within number of cerebrovascular events

		≤ 2 months		> 2 months		p-value
	N	n	%	n	%	
Normal D-dimers	93					
Single event	51	11	21.57	40	78.43	
Two events	21	6	28.57	15	71.43	0.817
Multiple events	21	5	23.81	16	76.19	
Elevated D-dimers	55					
Single event	28	13	46.43	15	53.57	
Two events	8	5	62.5	3	37.5	0.468
Multiple events	19	7	36.84	12	63.16	

In all three patient groups, a considerable percentage of patients were found to have elevated D-dimers after a two month time interval post ischaemic event. However, even though a larger percentage of those patients who had suffered multiple events had elevated D-dimers after a two month time interval (63.16%), this was not significantly higher than those who had suffered a single event (53.57%) or two events (37.5%), $p = 0.468$.

3.8.1.2 Six month time interval

It has already been demonstrated (Chapter 3.6.1.1) that within a two month time interval of a thrombotic cerebrovascular event, D-dimers were elevated in a statistically significant percentage of patients. By six months, this significant elevation was lost, confirming that D-dimer levels should eventually return to within normal levels post thrombotic event.

Hence, it was decided to assess whether patients suffering multiple cerebrovascular episodes might have sustained elevations in D-dimer levels after a six month time interval. This would support the hypothesis that such patients had an underlying hypercoagulable state, with ongoing thrombosis and fibrinolysis occurring, possibly resulting in recurrent events.

Again, as the results for the two month time interval demonstrated, no statistically significant differences were found in patients who had suffered single, two or multiple events either before or after a six month time interval post episode had elapsed. **(see Table 3.6)**

Table 3.6: Normal and elevated D-dimer levels in six month time interval within number of cerebrovascular events

		≤ 6 months		> 6 months		p-value
	N	n	%	n	%	
Normal D-dimers	93					
Single event	51	22	43.14	29	56.86	0.911
Two events	21	10	47.62	11	52.38	
Multiple events	21	10	47.62	11	52.38	
Elevated D-dimers	93					
Single event	28	18	64.28	10	35.72	0.124
Two events	8	6	75	2	25	
Multiple events	19	7	36.84	12	63.16	

However, of possible clinical significance is the fact that 35.72% of patients suffering single events, analysed after a six month time interval, had elevated D-dimers. This is to

be compared to 63.16% of patients with elevated D-dimers six months post event, who had suffered multiple episodes. Although this was not of statistical significance ($p = 0.124$), this difference appears more marked than when comparisons were made over a two month time period.

CHAPTER 4

4.0 RESULTS - ESR

All results in the text, tables and figures are expressed as the mean value, with the standard deviation enclosed by brackets i.e. mean (standard deviation).

4.1 ESR and D-dimer Levels

Levels of D-dimers were first assessed as a continuous variable within each level of D-dimer titre elevation, then as a categorical variable (i.e. normal versus elevated).

When D-dimer levels were assessed as a continuous variable and mean ESRs within each sublevel of elevation were compared, no statistically significant difference was found, p = 0.117. **(see Table 4.1)**

Table 4.1: Levels of D-dimers (continuous variable) versus mean ESR in all patients

Level of D-dimers (ng/ml)	N	Mean ESR (mm/hr)	p-value
< 250	93	8.125 (8.096)	p = 0.117
250 < 500	29	11.365 (11.532)	
500 < 1 000	13	18.538 (18.301)	
1 000 < 2 000	6	23.166 (37.79)	
2 000 < 4 000	2	9.5 (3.53)	
4 000 < 8 000	3	43.33 (34.53)	
8 000 < 16 000	1	11	
16 000 < 32 000	-	-	
32 000 < 64 000	1	3	

There was however a trend which indicated that the mean ESR became progressively elevated as levels of D-dimers increased.

D-dimer levels assessed as a categorical variable versus mean ESR levels, showed a statistically significant difference. In the 93 patients with normal D-dimer levels, mean ESR was 8.125 with a range from 0 to 45. In the 55 patients with elevated D-dimers, mean ESR was 15.87, ranging from 0 to 100 ($p = 0.0094$). **(see Figure 4.1)**

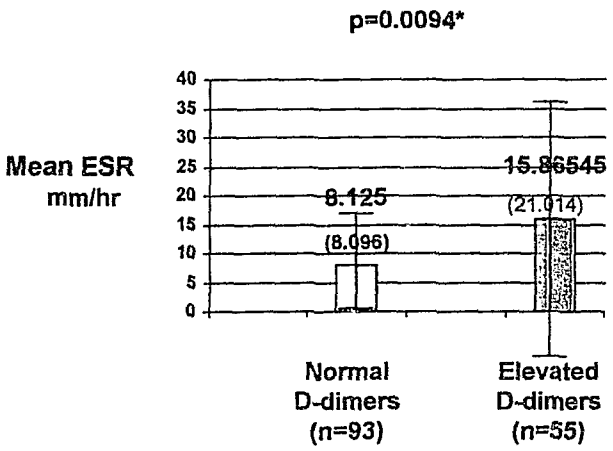

Figure 4.1: Mean ESR (continuous variable) versus normal and elevated D-dimer levels in all patients

Having noted a statistically significant association between raised D-dimer levels and an elevated ESR, analysis of other demographic parameters was also performed, as previously assessed for D-dimer levels. Additional factors associated with inflammation and hyperthrombosis, including fibrinogen levels and white cell count, were also analysed.

4.2 Age

4.2.1 Age groups

Patients were again stratified into those 45 years and younger, and those older than 45 years at the time of their first cerebrovascular event. ESR levels were compared in these two groups. **(see Figure 4.2)**

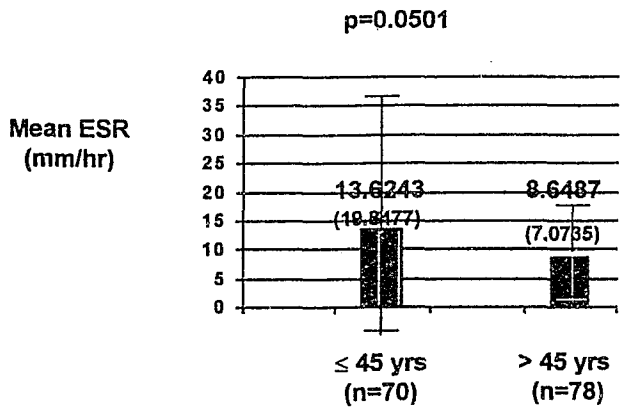

Figure 4.2: Mean ESR (continuous variable) versus age groups in all patients

In the 70 younger patients, mean ESR was 13.642 (19.848) whilst in the 78 older patients mean ESR was 8.649 (7.074) with student's t-test showing p = 0.0501, implying marginal statistical significance.

4.2.1.1 Within D-dimer levels

To assess whether ESR levels might be associated with a state of heightened thrombosis and fibrinolysis, patients were further assessed according to their D-dimer levels. **(see Figure 4.3)**

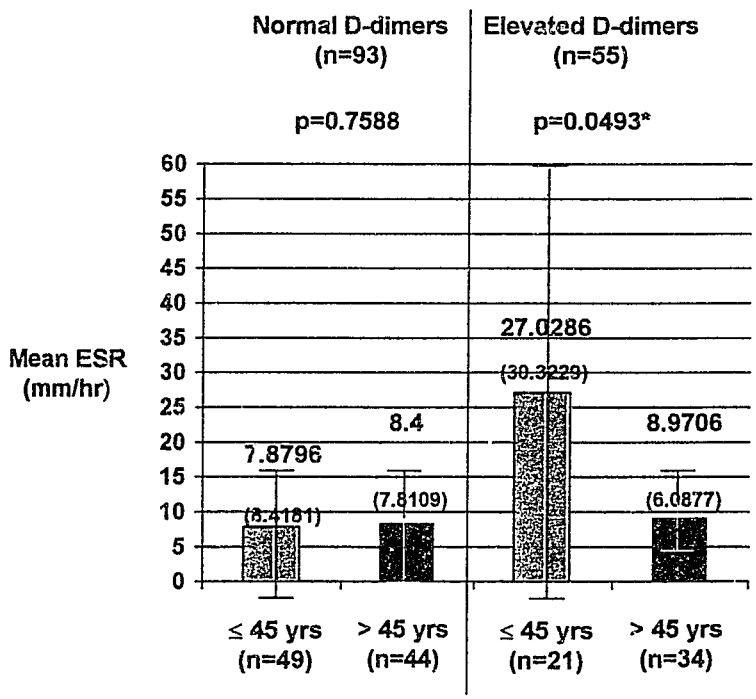

Figure 4.3: Mean ESR (continuous variable) within D-dimer levels versus age groups

Comparison of the mean ESR between the 49 younger and 44 older patients with normal D-dimers revealed no significant statistical difference, p = 0.7588. The mean ESR in the 21

younger patients compared to the 34 older patients with elevated D-dimers was significantly higher, p = 0.0493.

4.3 Sex

A statistically significant difference amongst both females and males was observed when comparing ESRs between those patients with normal and elevated levels of D-dimers. **(see Figure 4.4)**

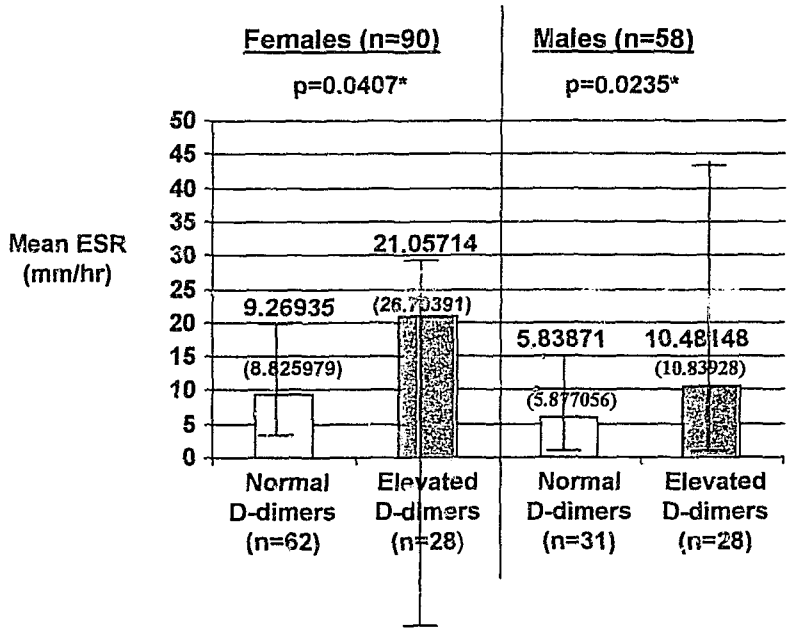

Figure 4.4: ***Mean ESR (continuous variable) versus D-dimer levels for each sex***

Amongst the 90 females assessed, 62 had normal D-dimers, mean ESR = 9.269 (8.826) and 28 had elevated levels, mean ESR = 21.057 (26.704) which was a statistically significant difference (p = 0.0407). The 31 males with normal D-dimers had a mean ESR of 5.84 (5.877) compared to the 28 males with elevated D-dimers and mean ESR of 10.481 (10.839). This again, was of statistical significance with a p-value of 0.0235.

4.4 Race

Mean ESR values, as a continuous variable, were assessed in each racial group for patients with normal and elevated levels of D-dimes. **(see Figure 4.5)**

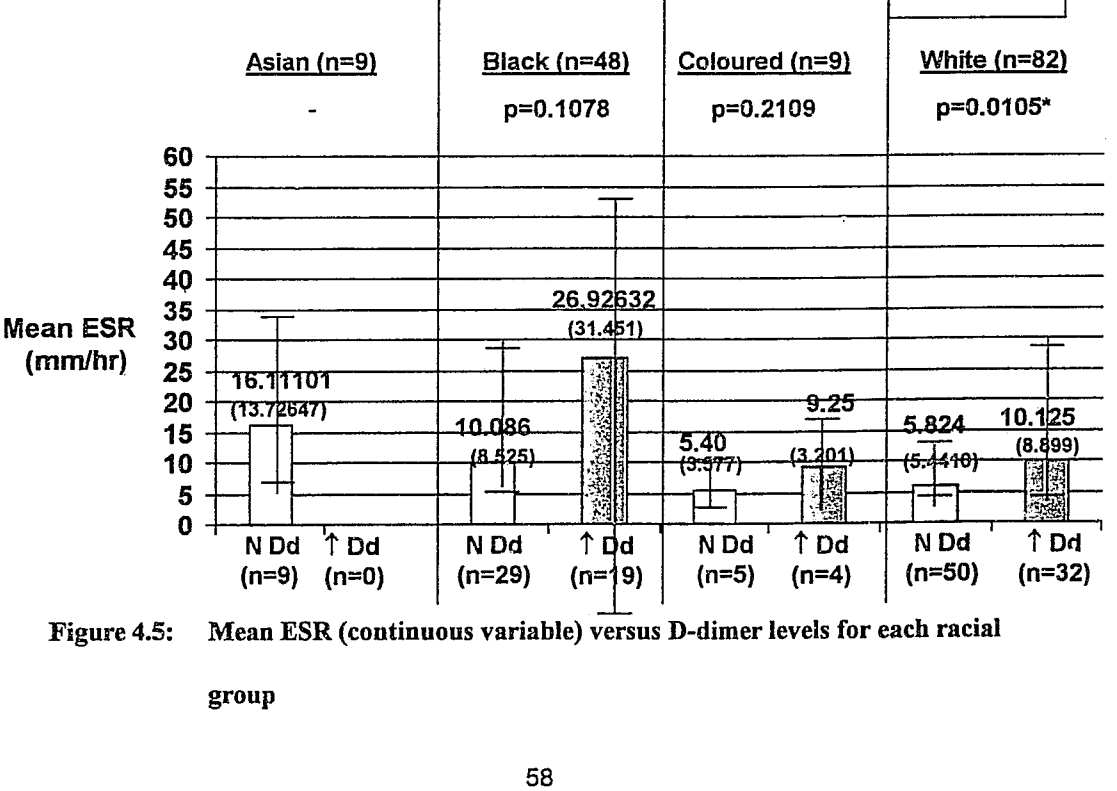

Figure 4.5: Mean ESR (continuous variable) versus D-dimer levels for each racial group

Of the nine Asian patients, all had normal levels of D-dimers with mean ESR = 16.111 (13.73). Five of the 9 Coloured patients had normal D-dimer levels and a mean ESR of 5.4 (3.578) whilst four had elevated D-dimers and a mean ESR of 9.25 (3.201), of no significant statistical difference ($p = 0.2109$). Amongst the 48 Black patients, 29 had normal D-dimer levels, mean ESR = 10.086 (8.525), compared to the 19 patients with elevated D-dimers, mean ESR = 26.926 (31.451), $p = 0.1078$. Of the 82 White patients, 50 had normal D-dimers, mean ESR = 5.834 (5.44) and 32 had elevated D-dimers, mean ESR = 10.125 (8.899). This difference was of definite statistical significance, with the U-test of Mann-Whitney showing a p-value of 0.0105.

Mean ESR values were then compared between White and Black patients, and within levels of D-dimers. **(see Figure 4.6)**

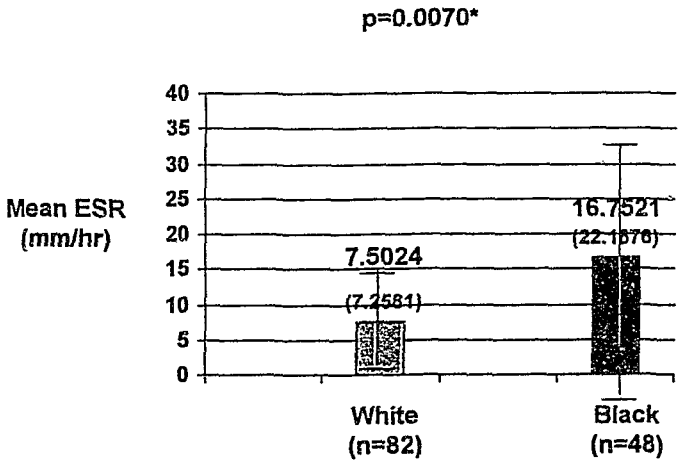

Figure 4.6: Mean ESR (continuous variable) versus White and Black racial groups

The mean ESR in the 82 White patients was 7.502 (7.258) and in the 48 Black patients 16.752 (22.168), which was significantly different according to the Student's t-test (p = 0.0070).

Mean ESR levels, as a continuous variable, were then compared within levels of D-dimers between White and Black patients. **(see Figure 4.7)**

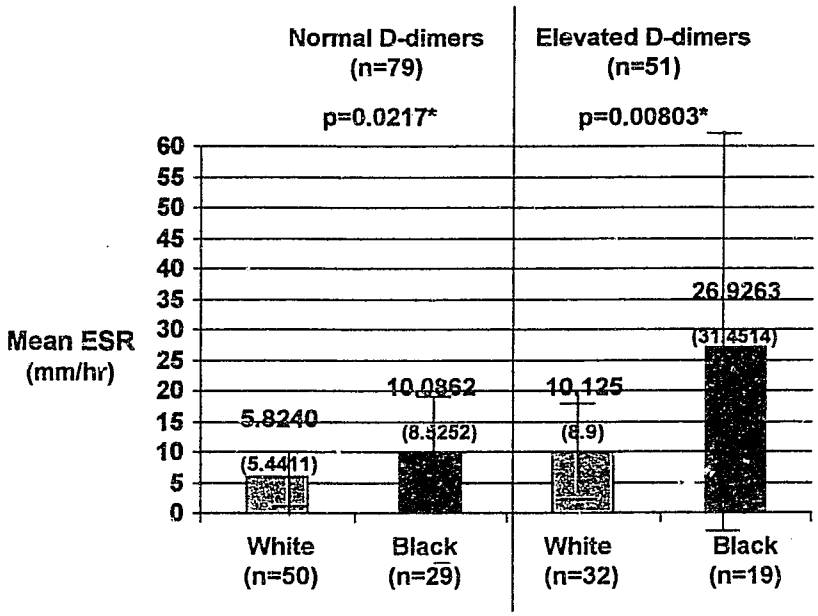

Figure 4.7: Mean ESR (continuous variable) within D-dimer levels versus White and Black racial groups

Within the 79 patients with normal D-dimer levels, 50 were White with a mean ESR of 5.824 (5.441) compared to the 29 Black patients with a mean ESR of 10.086 (8.525). This difference was of statistical significance with a p-value of 0.0217. Of the 51 patients with elevated D-dimers, the 32 White patients had a mean ESR of 10.125 (8.9) and the 19 Black

patients had a mean ESR of 26.926 (31.451). These results were highly significant, with p-value = 0.00803.

4.5 Territory of Vascular Supply

Mean ESRs for anterior, posterior and both vascular territories of blood supply were compared within D-dimer levels. **(see Figure 4.8)**

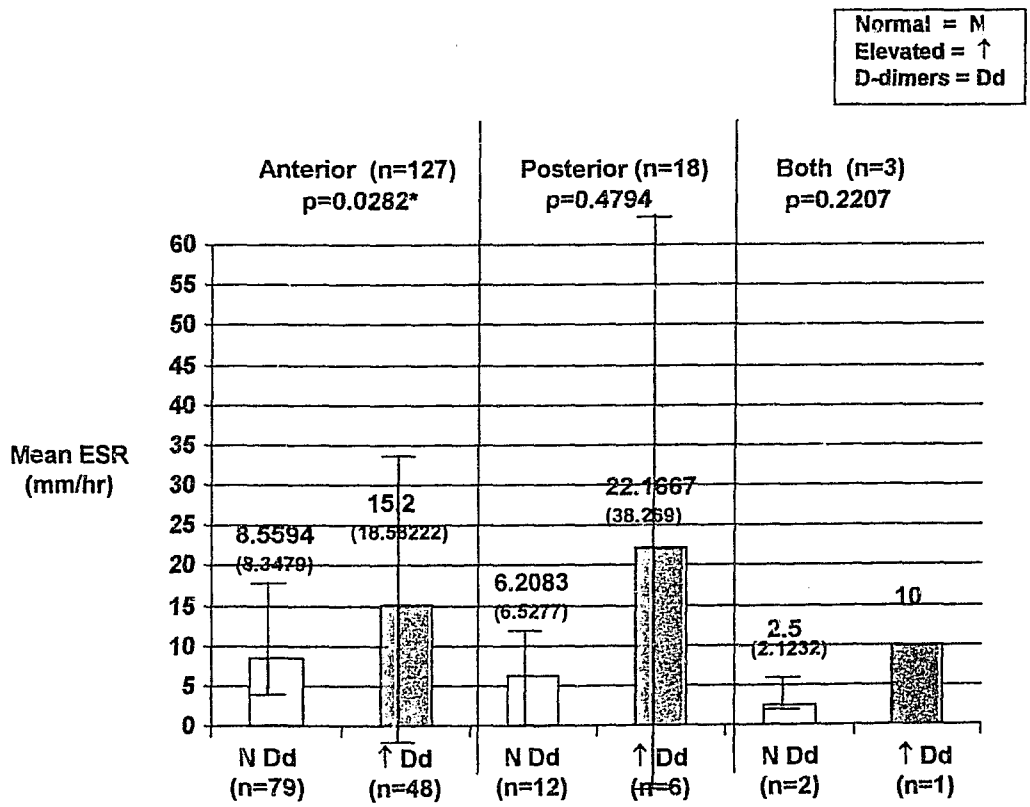

Figure 4.8: Mean ESR (continuous variable) versus D-dimer levels for vascular territory of event

Of the 127 patients who had suffered anterior circulatory cerebrovascular events, 79 had normal D-dimer levels with mean ESR of 8.56 (8.348) compared to the 68 patients with elevated D-dimers and mean ESR of 15.2 (18.582). This was of statistical significance and Student's t-test showed a p-value of 0.0282. This significance was not demonstrated in patients with posterior circulatory events, p = 0.4794. However, the number of patients assessed, n = 18, was considerably smaller with 12 having normal D-dimers, mean ESR = 6.208 (6.528) and six having elevated D-dimers, mean ESR = 22.167 (38.269). Only three patients had experienced events in both territories, two having normal D-dimers with mean ESR of 2.5 (2.121) and one with elevated D-dimers and an ESR of 10 (p = 0.2207).

4.6 Degree of Internal Carotid Artery Stenosis

In the light of the above results, ESR levels were related to degree of stenosis in the internal carotid artery in an attempt to discern whether chronic infection/inflammation might be associated with progressive severity of artheromatous occlusion of the carotid tree. **(see Figure 4.9)**

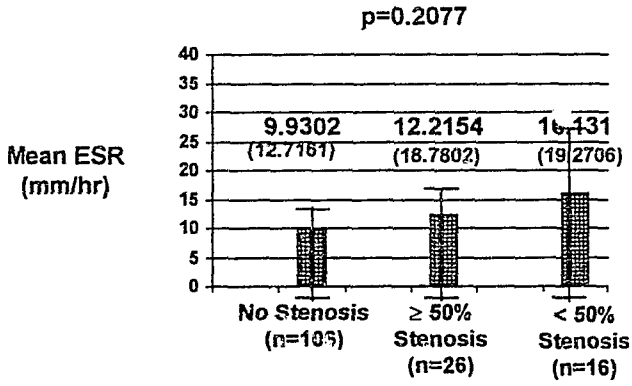

Figure 4.9: Mean ESR (continuous variable) versus degree of carotid stenosis

In the 106 patients with no evidence of stenosis, mean ESR was 9.93 (12.72), compared to the 26 patients with ≥50% stenosis, mean ESR of 12.215 (18.78) and the 16 patients with <50% stenosis, mean ESR of 16.131 (19.27). There was no statistically significant difference between these results, p = 0.2077.

Mean ESR levels were then compared within levels of D-dimer elevation.

(see Figure 4.10)

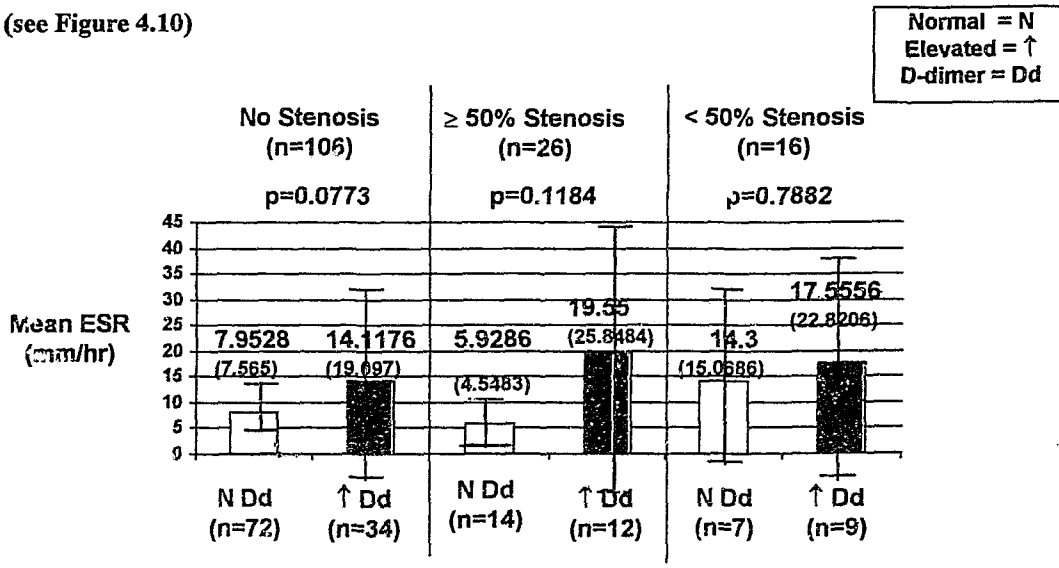

Figure 4.10: Mean ESR (continuous variable) versus D-dimer levels within degree of carotid stenosis

In those patients with no identifiable stenosis, no significant difference was noted between mean ESRs in patients with normal or elevated D-dimers (p = 0.0773). Similarly, no statistical significance was seen in those with 50% and greater stenosis (p = 0.1184), or in

those with less than 50% stenosis (p = 0.7882), when comparing normal and elevated levels of D-dimers.

4.7 Time Interval Post Event

ESR levels were analysed against time interval post event at which they were measured by correlation analysis to determine if any association existed between these two variables. Further correlation was sought within age groups, sex, racial groups, territory of vascular supply and number of cerebrovascular events. ESR levels, as a categorical variable, were then compared to time interval for the total study population and within these subgroups, to elucidate whether an elevated ESR (above 20mm/hr) might be significantly associated with a shorter time interval post event.

4.7.1 For total patients

Correlation analysis between mean ESR and time interval post event for all patients showed a poor correlation (correlation coefficient = -0.07777). **(see Table 4.2)**

Table 4.2: Mean ESR versus mean time interval for total patients-correlation analysis

	N	Mean ESR (mm/hr)	Mean Time Interval (yrs)	Pearson Correlation Coefficient
Total Patients	148	11.002 (14.742)	1.938108 (3.125546)	-0.07777

Of the total patients, 132 had a normal ESR level, with a mean time interval of measurement made 2.039 (3.257) years post event. The 16 patients with an elevated ESR had measurements made at a mean of 1.11 (1.506) years post event, but this difference was not of statistical significance, p = 0.3672. **(see Figure 4.11)**

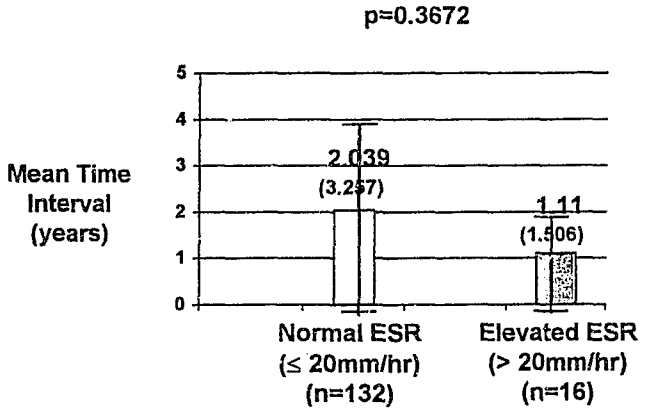

Figure 4.11: Normal and elevated ESR (categorical variable) versus mean time interval for total patients

4.7.2 Within age groups

No correlation between ESR level and time interval after event at which ESR is measured was shown in either younger or older patients. **(see Table 4.3)**

Table 4.3: Mean ESR versus mean time interval within age groups-correlation analysis

Age Groups	N	Mean ESR (mm/hr)	Mean Time Interval (yrs)	Pearson Correlation Coefficient
≤ 45 years	70	13.624 (19.848)	1.401 (2.243)	-0.08074
>45 years	78	8.649 (7.073)	2.42 (3.694)	-0.04556

No statistically significant differences in normal and elevated ESR levels versus time interval of measurements were noted for patients 45 years and younger ($p = 0.3058$) and patients older than 45 years ($p = 0.7287$). **(see Table 4.4)**

Table 4.4: Normal and elevated ESR levels versus mean time intervals within age groups

Age Groups	N	Normal ESR (≤20mm/hr)		Elevated ESR (≤20mm/hr)		p-value (t-test)
		n	Time Interval (yrs)	n	Time Interval (yrs	
≤ 45 years	70	60	1.529 (2.372)	10	0.635 (0.962)	0.3058
>45 years	78	72	2.463 (3.807)	6	1.902 (1.99)	0.7287

4.7.3 Within sex

No correlation between ESR level and time interval post event was seen in females or males. *(see Table 4.5)*

Table 4.5: Mean ESR versus mean time interval within sex-correlation analysis

Sex	N	Mean ESR (mm/hr)	Mean Time Interval (yrs)	Pearson Correlation Coefficient
Female	90	12.937 (17.316)	1.906 (3.206)	-0.09476
Male	58	8.000 (8.788)	1.988 (3.023)	-0.02924

The 78 females with normal ESRs were measured over a mean time interval of 2.054 (3.391) years compared to the 12 females with elevated ESRs, measured over a mean time interval of 0.943 (1.242) years, p = 0.3363. No significant difference was observed between the 54 males with normal ESRs, mean time interval 2.016 (3.085) years when compared to the four with an elevated ESR, mean time interval 1.61 (2.297) years, p = 0.9266. **(see Table 4.6)**

Table 4.6: Normal and elevated ESR levels versus mean time intervals within sex

Sex	N	Normal ESR (≤20mm/hr)		Elevated ESR (≤20mm/hr)		p-value (t-test)
		n	Time Interval (yrs)	n	Time Interval (yrs	
Female	90	78	2.054 (3.391)	12	0.943 (1.242)	0.3363
Male	58	54	2.016 (3.085)	4	1.61 (2.297)	0.9266

4.7.4 Within race

No correlation between ESR level and time interval was demonstrated in Asian, Black, Coloured or White patients. **(see Table 4.7)**

Table 4.7: Mean ESR versus mean time interval within race-correlation analysis

Race	N	Mean ESR (mm/hr)	Mean Time Interval (yrs)	Pearson Correlation Coefficient
Asian	9	16.11 (13.724)	1.597 (1.792)	0.06716
Black	48	16.752 (22.168)	0.984 (1.698)	-0.04064
Coloured	9	7.111 (3.79)	1.486 (1.824)	-0.24385
White	82	7.502 (7.258)	2.584 (3.796)	-0.00280

No significant differences were noted in any racial group when comparing normal and elevated ESRs to time interval of measurement. **(see Table 4.8)**

Table 4.8: Normal and elevated ESR levels versus mean time interval within race

Race	N	Normal ESR (≤20mm/hr)		Elevated ESR (≤20mm/hr)		p-value (t-test)
		n	Time Interval (yrs)	n	Time Interval (yrs	
Asian	9	7	1.499 (1.754)	2	1.94 (2.63)	0.7697
Black	48	38	1.055 (1.851)	10	0.718 (0.938)	0.7221
Coloured	Insufficient Data					
White	82	78	2.630 (3.863)	4	1.675 (2.244)	0.9228

However, a much higher percentage of Black patients were seen to have elevated ESRs than White patients.

4.7.5 Within territory

No correlation between ESR level and time interval was shown in patients suffering events in either anterior or posterior vascular territories of blood supply. However, a strong correlation of 81% (correlation coefficient = 0.89823) was demonstrated in the three

patients with events in both territories. This is likely to be a spurious result, relating to the small sample size. **(see Table 4.9)**

Table 4.9: Mean ESR versus mean time interval within territory-correlation analysis

Territory	N	Mean ESR (mm/hr)	Mean Time Interval (yrs)	Pearson Correlation Coefficient
Anterior	127	11.069 (13.505)	1.972 (3.245)	-0.08425
Posterior	18	11.528 (22.765)	1.751 (2.476)	-0.08116
Both	3	5.0 (4.583)	1.627 (1.467)	0.89823

Within patients with events in the anterior circulatory territory of supply, as well as in those with posterior territorial events, no statistically significant differences were observed between categorical levels of ESR and time interval of measurement. Too few patients for analysis had suffered events in both territories. **(see Table 4.10)**

Table 4.10: Normal and elevated ESR levels versus mean time interval within territory

Age Groups	N	Normal ESR (≤20mm/hr)		Elevated ESR (≤20mm/hr)		p-value (t-test)
		n	Time Interval (yrs)	n	Time Interval (yrs)	
Anterior	128	113	2.077 (3.384)	14	1.122 (1.593)	0.4035
Posterior	18	16	1.842 (2.601)	2	1.025 (1.252)	0.5270
Both	3	Insufficient Data				

4.7.6 Within number of events

No correlation between ESR level and time interval was observed in patients suffering either single, two or multiple events. **(see Table 4.11)**

Table 4.11: Mean ESR versus mean time interval within number of events-correlation analysis

No. of Events	N	Mean ESR (mm/hr)	Mean Time Interval (yrs)	Pearson Correlation Coefficient
Single	79	11.786 (17.372)	1.924 (3.441)	-0.07832
Double	29	9.038 (11.140)	2.162 (3.487)	-0.17883
Multiple	40	10.878 (11.062)	1.804 (2.087)	-0.05098

No significant differences in ESR levels were demonstrated within patients suffering variable numbers of events when compared to time interval of measurement. **(see Table 4.12)**

Table 4.12: Normal and elevated ESR levels versus mean time interval within number of events

No. of Events	N	Normal ESR (≤20mm/hr)		Elevated ESR (≤20mm/hr)		p-value (t-test)
		n	Time Interval (yrs)	n	Time Interval (yrs	
Single	79	72	2.019 (3.58)	7	0.951 (1.044)	0.7561
Double	29	26	2.394 (3.616)	3	0.157 (0.203)	0.2668
Multiple	40	34	1.809 (2.117)	6	1.772 (2.097)	0.9849

4.8 Nature of Events

To ascertain whether chronic infection/inflammation might influence the extent and severity of the thrombotic episode, hence influencing the nature of event experienced, ESR levels were compared in patients with CVAs and TIAs. **(see Figure 4.12)**

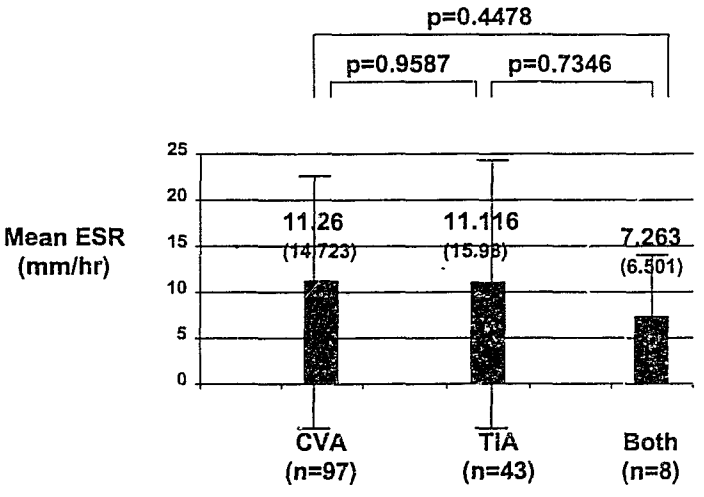

Figure 4.12: Mean ESR (continuous variable) versus nature of cerebrovascular events

In the 97 patients who had suffered CVAs, mean ESR was 11.26 (14.723) compared to mean ESR of 11.116 (15.98) in the 43 patients who had suffered TIAs, p = 0.9587. The eight patients who had suffered both type of events had a mean ESR of 7.263 (6.501), not of any statistical significance.

When comparing mean ESR levels within categories of normal and elevated D-dimers, no significant differences were observed between patients suffering CVAs, TIAs or both type of events. **(see Figure 4.13)**

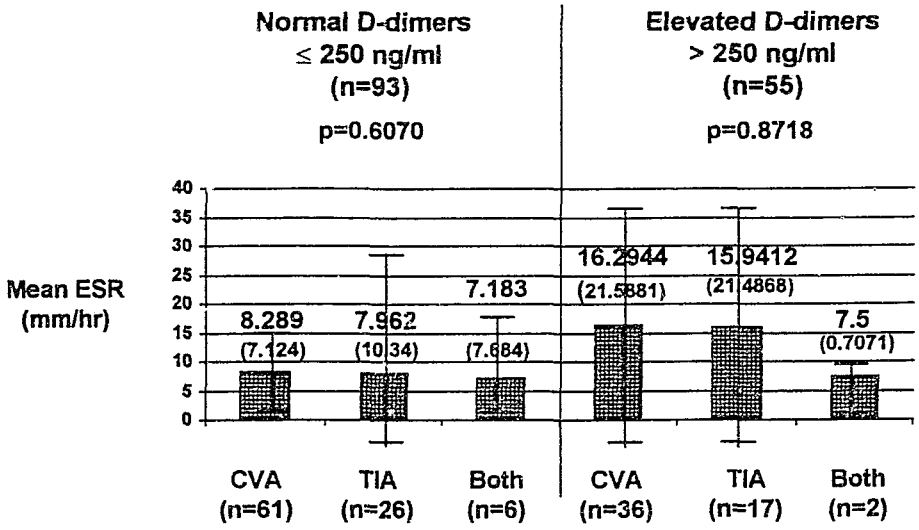

Figure 4.13: Mean ESR (continuous variable) within D-dimer levels versus nature of cerebrovascular events

4.9 Number of Events

To determine whether chronic infection/inflammation might play a role in the aetiology of recurrent cerebrovascular events, mean ESR levels were compared amongst patients who had experienced single, two or multiple events. **(see Figure 4.14)**

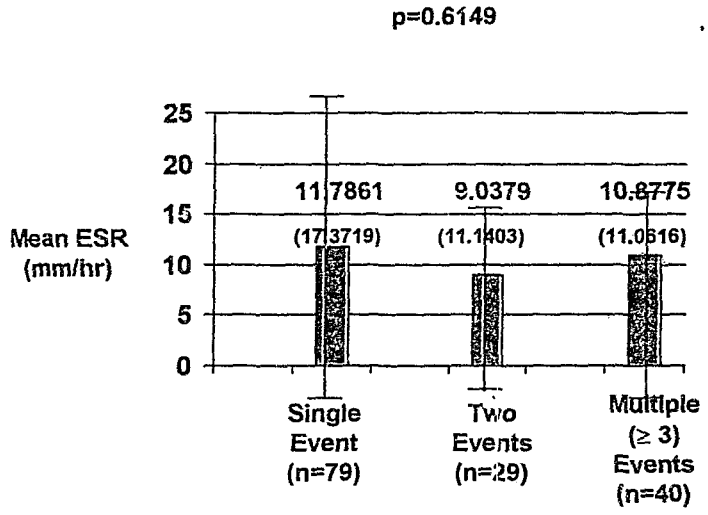

Figure 4.14: Mean ESR (continuous variable) versus number of cerebrovascular events

No statistically significant differences in the mean ESRs were observed when comparing patients suffering single, two or multiple events ($p = 0.6149$).

Mean ESR levels within normal and elevated D-dimer levels were also compared amongst patients suffering single or recurrent events. This was performed to elucidate whether an elevated ESR might be significantly associated with a hypercoagulable state. **(see Figure 4.15)**

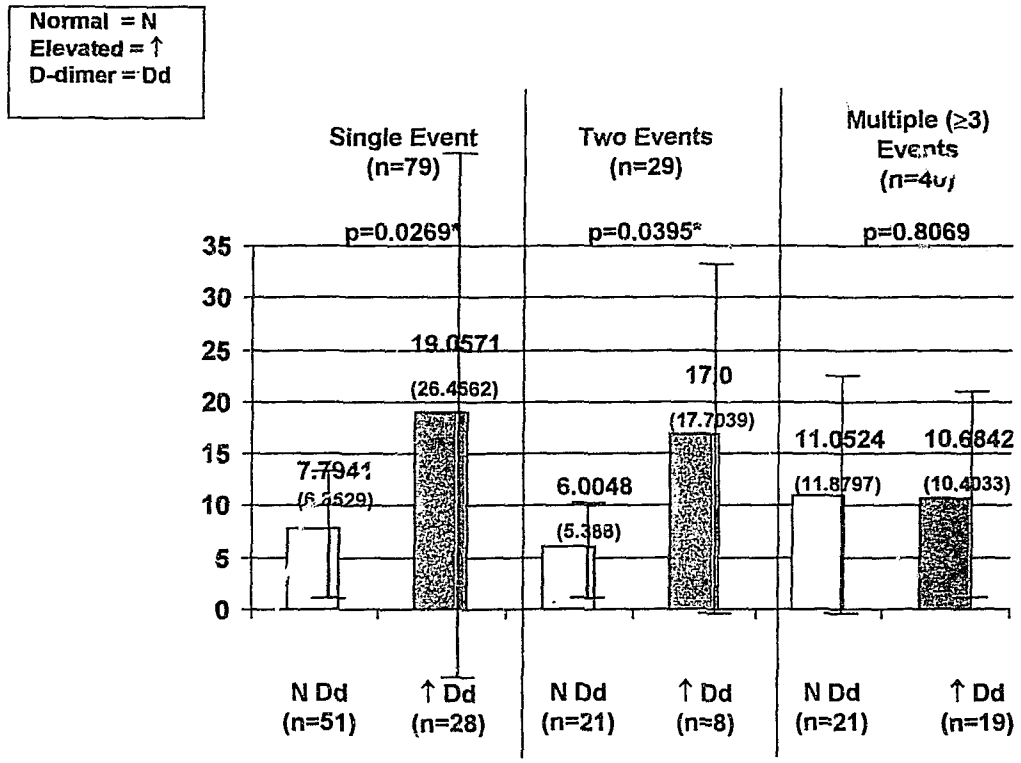

Figure 4.15: Mean ESR (continuous variable) versus D-dimer levels within number of cerebrovascular events

In patients who had suffered a single event, those patients with elevated D-dimer levels had a significantly higher mean ESR of 19.057 (26.456) when compared to those patients with normal D-dimer levels with a mean ESR of 7.794 (6.853), p = 0.0269. Similarly, a significant difference was shown in patients suffering two events, with a mean ESR of 17 (17.704) in those with elevated D-dimers compared to a mean ESR of 6.005 (5.388) in

those with normal D-dimers, p = 0.0395. Interestingly, this significance was lost in patients suffering multiple events, with the mean ESRs being similar and p = 0.8069.

4.10 Fibrinogen Levels

Fibrinogen is an acute phase reactant that increases with a hypercoagulable state and in certain inflammatory conditions. Mean fibrinogen levels were compared within ESR and D-dimer levels to determine whether any associations existed with these other markers of inflammation and fibrinolysis.

ESR levels were analysed in relation to fibrinogen levels (both as continuous variables) and within level of D-dimers. Correlation analysis showed no correlation between the mean ESR of 11.002 (14.742) and mean fibrinogen levels of 4.334 (1.927)g/ℓ, the Pearson correlation coefficient being 0.29498. **(see Table 4.13)**

Table 4.13: Mean ESR versus mean fibrinogen level for total patient-correlation analysis

N	Mean ESR (mm/hr)	Mean Fibrinogen (g/ℓ)	Pearson Correlation Coefficient
148	11.002 (14.742)	4.334 (1.927)	0.29498

When patients were analysed within D-dimer levels, no correlation was shown between mean ESR and fibrinogen levels in those patients with normal D-dimers, Pearson correlation coefficient = 0.05394. However, amongst those with elevated D-dimers a weak correlation of 23% was shown between the mean ESR of 15.865 (21.014) and mean fibrinogen level of 4.518 (1.956) g/ℓ, Pearson correlation coefficient = 0.4831. **(see Table 4.14)**

Table 4.14: Mean ESR versus mean fibrinogen level within D-dimer levels-correlation analysis

D-dimer Levels	N	Mean ESR (mm/hr)	Mean Fibrinogen (g/ℓ)	Pearson Correlation Coefficient
Normal D-dimers	93	8.126 (8.097)	4.224 (1.912)	0.05394
Elevated D-dimers	55	15.865 (21.014)	4.518 (1.956)	0.4831

When comparing the 131 patients with a normal ESR and a mean fibrinogen level of 4.189 (1.762) g/ℓ to the 16 patients with an elevated ESR and a mean fibrinogen level of 5.527 (2.748) g/ℓ, a statistically significant difference was observed (p = 0.0102). **(see Figure 4.16)**

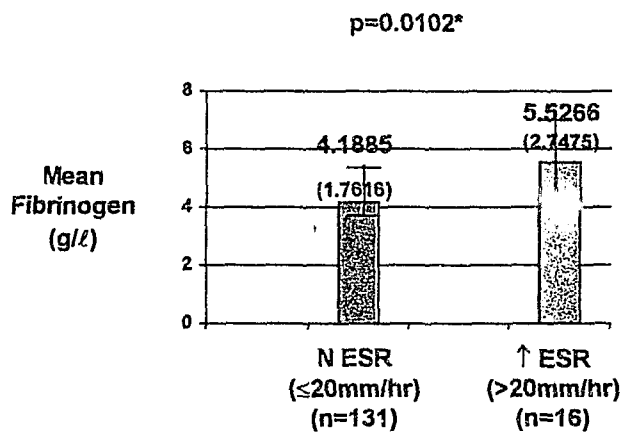

Figure 4.16: Mean fibrinogen (continuous variable) versus ESR levels (categorical variable)

Mean fibrinogen levels were then compared in those patients with normal and elevated ESRs within levels of D-dimer elevations.

In those patients with normal D-dimers, 86 had normal ESRs with a mean fibrinogen level of 4.198 (1.972) g/ℓ compared to eight with elevated ESRs and a mean fibrinogen level of 4.493 (1.135) g/ℓ. In the patients with elevated D-dimer levels, the 47 with a normal ESR had a significantly lower mean fibrinogen level of 4.171 (1.323) when compared to the eight patients with an elevated ESR and mean fibrinogen level of 6.559 (3.528), p = 0.0122. **(see Figure 4.17)**

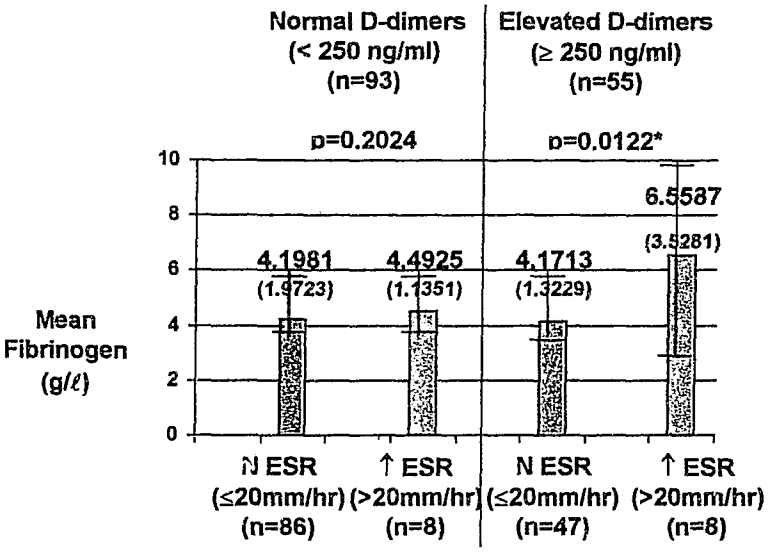

Figure 4.17: Mean fibrinogen (continuous variable) within D-dimer levels versus ESR levels (categorical variable)

4.11 White Cell Count

White cell counts elevate moderately in association with many acute infective processes. Hence, white cell counts were compared to ESRs to determine whether such a marker might indicate an underlying infectious aetiology in patients with elevated ESRs. Normal white cell counts range between 4 and 11 x $10^9/\ell$.

No correlation was demonstrated between mean ESR and WCC for the total patients, Pearson correlation coefficient = 0.07964. **(see Table 4.15)**

Table 4.15: Mean ESR versus mean WCC for total patients-correlation analysis.

N	Mean ESR (mm/hr)	Mean WCC ($x10^9/\ell$)	Pearson Correlation Coefficient
148	11.002 (14.742)	7.216 (2.209)	0.07964

Similarly, no correlation was seen between mean ESRs and WCC in patients with normal or elevated D-dimer levels. **(see Table 4.16)**

Table 4.16: Mean ESR versus mean WCC within D-dimer levels-correlation analysis.

D-dimer levels	N	Mean ESR (mm/hr)	Mean WCC ($x10^9/\ell$)	Pearson Correlation Coefficient
Normal D-dimers	93	8.126 (8.097)	7.08 (2.009)	0.10794
Elevated D-dimers	55	15.865 (21.014)	7.446 (2.515)	0.04271

There were only five patients who demonstrated an elevated WCC at the time of measurement. When comparing mean ESR to white cell count as a categorical variable, those five patients with an elevated WCC had a significantly elevated mean ESR of 38 (31.097), whilst the 143 patients with a normal WCC had a mean ESR of 10.058 (13.084), $p = 0.0299$. **(see Figure 4.18)**

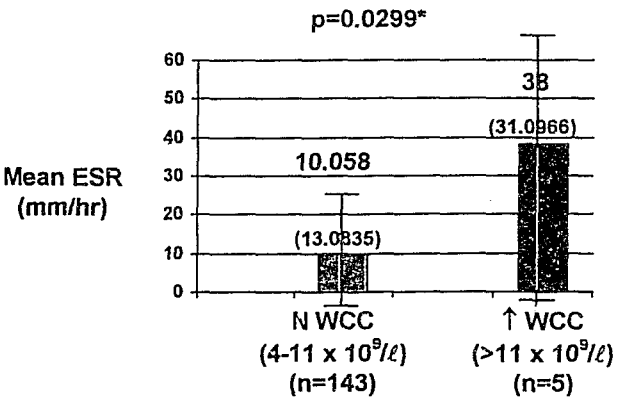

Figure 4.18: Mean ESR (continuous variable) within white cell count (categorical variable)

When ESR and WCC were both compared as categorical variables, a strongly significant difference was demonstrated (p = 0.0092). Thirteen (9.09%) of the 143 patients with normal WCC had an elevated ESR, whilst three (60%) of the five with an elevated WCC also exhibited a raised ESR. **(see Figure 4.19)**

Figure 4.19: ESR levels (categorical variable) within white cell count (categorical variable)

When ESR and WCC were assessed within groups of D-dimers, no statistical significance was shown in patients with normal D-dimers ($p = 0.165$). In those patients with elevated D-dimers, six (11.54%) of the 52 patients with a normal WCC exhibited an elevated ESR, whereas two (66.67%) of three patients with a raised WCC had a raised ESR ($p = 0.052$), of marginal statistical significance. **(see Figure 4.20)**

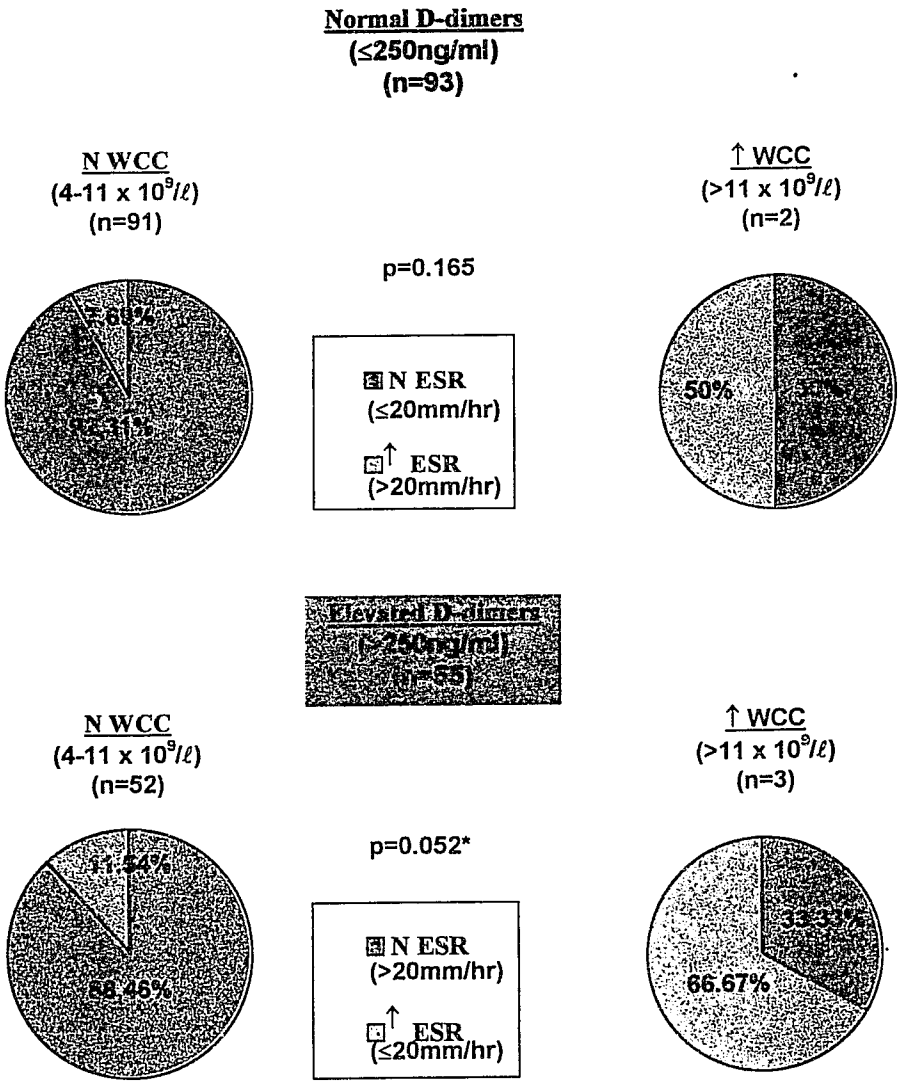

Figure 4.20: ESR levels (categorical variable) within white cell count (categorical variable) for normal and elevated D-dimer levels

4.12 Concurrent Infection/Inflammation

Although this study was performed retrospectively and patients may not have been aware of an infective process at the time of their stroke, attempts were made on history and examination to determine whether patients had evidence of acute infection at the time of their cerebrovascular events. It was easier and more reliable to obtain evidence of a chronic auto-immune disease, by analysis of history and previous hospital admissions and investigations.

Only three patients had identifiable infection at the time of their cerebrovascular events, such as bronchopneumonia, meningoencephalitis and concurrent pelvic inflammatory disease (PID) with tonsillitis. The patient with PID and tonsillitis was the only one of those three to demonstrate an elevated ESR in association with an elevated level of D-dimers. The patient with bronchopneumonia had an ESR of 11, but had markedly elevated D-dimers of >8000 <16000. The patient with meningoencephalitis had an ESR of eight and a normal D-dimer level of ≤250ng/ml. **(see Table 4.17)**

Table 4.17: Patients with identifiable infection at time of cerebrovascular event

IDENTIFIABLE INFECTION	ESR (mm/hr)	D-DIMER DILUTION (ng/ml)	AGE GROUP (yrs)	SEX	RACE	TERRITORY	NO. OF EVENTS
Broncho-pneumonia	11	>8000<16000	>45	Female	Black	Anterior	1
Meningo-encephalitis	8	≤250	≤45	Female	Black	Anterior	1
Tonsillitis; PID	77	>4000<8000	≤45	Female	Black	Anterior	1

Interestingly, all three patients were Black females who had suffered a single event in the anterior circulatory territory of vascular supply.

Of the 12 patients who exhibited clinical features of an auto-immune disease or vasculitis, as manifested by Takayasu's arteritis, rheumatoid arthritis, Reynaud's phenomenon and systemic lupus erythematosis (SLE), only three demonstrated an elevated ESR at the time of testing. Two of these three had an associated elevation in D-dimer levels. **(see Table 4.18)**

Table 4.18: Patients with clinical features of auto-immune disease/vasculitis

CLINICAL FEATURES	ESR (mm/hr)	D-DIMER DILUTION (ng/ml)	AGE GROUP (yrs)	SEX	RACE	TERRITORY	NO. OF EVENTS
Behcet's; Reiter's	3	≤250	>45	Male	White	Anterior	3
SLE; Sarcoid	1	≤250	>45	Female	White	Anterior	3
SLE; Sjogren's	4	≤250	>45	Female	White	Both	3
Vasculitis; Optic atrophy	32	≤250	>45	Female	Black	Anterior	1
Antiphospholipid syndrome; Reynaud's phenomenon	44	>500 <1000	≤45	Female	White	Anterior	3
Reynaud's phenomenon	7	≤250	≤45	Female	Black	Anterior	1
Vasculitis	87	>250 <500	≤45	Female	Black	Anterior	1
Reynaud's phenomenon	5	>250 <500	<45	Female	Black	Anterior	3
Behcet's	4	≤250	≤45	Female	Black	Anterior	2
Reynaud's phenomenon; Livedo reticularis; Malar rash	1	≤250	≤45	Female	White	Both	2
Rheumatoid arthritis	8	≤250	≤45	Female	White	Anterior	2
Takayasu's arteritis	10	≤250	≤45	Female	Black	Anterior	3

Eleven of these 12 patients were females and half were White. Nine (75%) of the 12 patients had experienced more than a single cerebrovascular episode and all had events in the anterior circulatory territory of supply (although two had suffered additional events in the posterior territory).

CHAPTER 5

5.0 DISCUSSION AND CONCLUSIONS

5.1 D-dimers

Younger patients suffering cerebrovascular events are known to have a different aetiological spectrum. These include a higher incidence of hyperthrombotic abnormalities when compared to older patients, who tend to have a greater number of risk factors for atheromatous vasculopathy (Janaki et al., 1975; Giovannoni & Fritz, 1993). In 1% of all patients with ischaemic stroke and in up to 4% of young adults with stroke, the major precipitant is thought to be a haematological disorder or coagulopathy that predisposes to thrombosis (Hart & Kanter, 1990). However, no statistically significant difference in D-dimer levels was observed when stratifying patients into younger and older age groups, to support this hypothesis. It is possible that the known association of elevation in D-dimers with increasing age, confirmed in this study, offsets evidence of a hypercoagulable state in younger patients. Also, if ongoing atheromatous vascular disease is present with higher incidence in older patients, the subsequent thrombosis and fibrinolysis in this population would further serve to increase D-dimer levels in the elderly.

Although the results seen in the small number of Asian and Coloured patients studied can not be viewed as representative, no significant variation in D-dimer levels was observed amongst racial groups.

No statistically significant difference between normal and elevated levels of D-dimers was shown amongst patients suffering events in the anterior, posterior or both territories of vascular supply. This parameter was assessed with particular interest, because previous studies have shown an association between elevated D-dimers and progressive carotid artery stenosis.

Patients with early, asymptomatic and minor degrees of carotid artery atherosclerosis have been shown to demonstrate higher concentrations of D-dimers than control patients (Salomaa et al., 1995). Haemodynamic theories argue for a direct proportion between the degree of carotid stenosis and frequency of TIA or stroke. Thrombo-embolic theories lead to the expectation that the extent of platelet accumulation on carotid plaques correlates with ipsilateral ischaemic events. Neither prediction has been conclusively fulfilled in past studies (Busuttil, Baker & Davidson et al., 1982; Harrison & Marshall, 1982; Grotta, Bigelow & Hu et al., 1984).

The hypothesis was that patients with anterior circulatory territorial events, with possible atherosclerotic disease in the carotid tree, might have elevated levels of D-dimers when compared to those patients suffering posterior vascular territorial events. However, this

was not confirmed in this study, when degree of internal carotid artery stenosis and levels of D-dimers were compared. Patients with varying degrees of vascular stenosis did not always exhibit elevated D-dimer levels.

The mean time interval between event and measurements of D-dimer levels was significantly shorter in the patient group with elevated D-dimers, implying that levels tend to normalize with progressive time passage from episode. This is as expected, considering that an elevated D-dimer level reflects ongoing thrombosis and subsequent fibrinolysis, which is certainly the case after a thrombo-embolic cerebrovascular episode.

These results also imply that the mean time interval in which D-dimers are elevated post vasculo-occlusive event is far in excess of the expected time frame of six weeks, within which time they should normalize. Fisher and Francis (1990) found D-dimer levels to be significantly elevated acutely in stroke patients, but not at two month follow-up, indicating increased fibrin formation and dissolution in the acute phase and not after recovery. This supports the concept that cerebral arterial patency increases with time from stroke onset, as demonstrated by angiographic-based studies. Many patients have been shown to undergo spontaneous early recanalisation within six to eight hours (del Zoppo, 1997). Other investigators have reported that fibrinolysis is diminished in stroke (Feinberg et al., 1989).

This study suggests that D-dimers are elevated in some patients for a prolonged period post ischaemic event, implying that there is ongoing thrombosis and fibrinolysis, possibly

precipitated by other factors inducing a hypercoagulable state. Such patients may have generalised widespread atheromatous disease, contributing to the maintenance of elevations in D-dimer levels.

The highly significant elevation in D-dimer levels seen within the first two months post ischaemic cerebrovascular event, confirms the hypothesis that there is evidence of ongoing fibrinolysis following such a thrombotic event. This significant elevation is lost when patients are assessed within a six month time frame post event. These results suggest that during this extended time period, D-dimer levels fall to normal, thus negating the significant elevations seen in the immediate two month time interval post ischaemic episode.

It is interesting to note that up to a third of patients assessed after a six month time interval post thrombotic event exhibited elevated D-dimer levels. This suggests that many patients have an ongoing thrombotic and fibrinolytic background state. In an attempt to discern possible causes for such a hypercoagulable state, the ESR was assessed in order to elucidate whether a concurrent chronic infective or inflammatory aetiology might play a role in patients with cerebrovascular disease.

No significant differences were noted in patients with normal and elevated D-dimer levels having suffered either a CVA, TIA or both events. Thus, D-dimer levels do not appear to be elevated in those suffering more extensive thrombo-occlusive events.

Previous studies have shown that activation of the endogenous fibrinolytic system occurs many years in advance of arterial vascular occlusion and that detection of this activation may predict the risk of future athero-embolic and atherosclerotic disorders (Ridker et al., 1994). On this basis, it was postulated that elevated D-dimer levels might act as prognostic markers for those at risk of recurrent events after an initial cerebrovascular episode. However, in this study, the levels of D-dimers in patients having suffered single, two or multiple cerebrovascular events were not found to be of prognostic value in determining those at risk of recurrent events.

Although not of statistical significance, it appears that the higher percentage of patients suffering multiple events with elevated D-dimers six months post cerebrovascular event may be of clinical significance. Thus, this study was unable to prove the hypothesis that D-dimers remain elevated in those patients with an underlying hypercoagulable state, resulting in increased risk for recurrent thrombovascular events. Ongoing studies should be performed with a greater number of patients included to improve the statistical power, to either prove or refute this result.

In a previous study, D-dimer levels were found to be highest in subjects with cardiogenic stroke, less high in those with large vessel disease and not elevated in subjects with TIA (Fisher & Francis, 1990). These results suggest that plasma D-dimer levels correlate with the size of the fibrin thrombus and that patients with TIAs either have thrombi too small to

produce detectable elevations of plasma D-dimer, or that fibrin formation does not occur to a significant extent in these subjects.

The lack of any significant differences in D-dimer levels amongst the patients suffering CVAs, TIAs or both type of events in this study, discounts the hypothesis that patients experiencing more severe and extensive episodes have a state of ongoing thrombosis and fibrinolysis. Those patients suffering both types of events did not demonstrate significant elevations in D-dimers so that, although TIAs are shown to be strongly predictive of stroke (Whisnant, Motsumoto & Elveback, 1973), D-dimer levels were not identified as prognostic markers in those at risk of more severe, recurrent episodes.

ELISA methods for D-dimer measurement are known to be extremely reliable in the exclusion of thrombosis. They exhibit 100% sensitivity when compared to the latex agglutination tests, which demonstrate a sensitivity of 65% to 75% (Freyburger et al., 1998). However, when comparing the cost effectiveness of the two tests, the considerably greater expense of the ELISA method proved to be prohibitive in terms of usage for this study. The more sensitive, quantitative-discriminant Dimer test Gold EIA Agen ELISA method costs approximately R77.00 per test, the Stago D-DI Asserachrom ELISA in the region of R35.00 per test as opposed to the BIOPOOL Minutex latex agglutination test which costs R8.46 per dilution performed. In order to reduce the total costs of this study, and to keep patient investigative costs within the hospital budget, the BIOPOOL Minutex latex agglutination test was the method used to assess D-dimer levels.

5.2 ESR

Having demonstrated that up to a third of patients showed elevated D-dimer levels when assessed after a six month interval post thrombotic cerebrovascular event, possible causes for such a persistent hypercoagulable state were sought. ESR levels were examined to determine if concurrent chronic infection and inflammation might play a role in maintaining ongoing thrombosis and fibrinolysis.

Syrjanen et al. (1988) reported that younger patients presenting with acute cerebral infarction had a significantly higher incidence of febrile infections in the preceding month than community-matched controls. Grau et al. (1995) implicated infection as an aetiological factor in older, as well as younger, patients. Macko et al. (1996) suggest that both febrile and non-febrile infectious and inflammatory syndromes may be a common predisposing risk factor for brain infarction. It has been proposed that bacterial infections predominate acutely in stroke patients (Syrjanen et al., 1986). Case-control studies have suggested that up to 10% of all strokes may be associated with preceding bacteraemic infections (Valtonen, Kuikka & Syrjanen et al., 1993).

Although previous studies have indicated that an elevated ESR is a poor marker for those at risk of cerebrovascular disease, no previous investigations have examined the association between a raised ESR and the promotion of a hypercoagulable state (Bottiger & Carlson, 1980; Pollock, Harrison & Thomas et al., 1982; Rafnsson & Bengtsson, 1982). In this study, however, a statistically significant association between raised D-dimer levels

and an elevated mean ESR was established, suggesting that chronic infection/ inflammation might be incriminatory in the aetiology of cerebrovascular disease.

Younger patients, below 46 years at the time of their initial cerebrovascular event, were shown to have a considerably higher mean ESR than older patients. The ESR is known to increase with advancing age and this would allow for an expectation of a higher mean ESR in the older age group (Dacie & Lewis, 1995). Thus, although this difference was only of marginal statistical significance, it suggests that infective or inflammatory mediators, as evidenced by an elevated ESR, are more prevalent in younger patients with cerebrovascular disease.

The mean ESR was significantly higher in younger patients with elevated D-dimer levels when compared to the older patients. This result suggests that younger patients exhibiting a hypercoagulable state post cerebrovascular event as evidenced by elevated D-dimers, may have a concurrent inflammatory condition acting as an aetiological agent in the promotion of thrombosis and subsequent fibrinolysis.

In both females and males, those patients with elevated D-dimers had significantly higher ESR levels when compared to those patients with normal D-dimer levels. This, again, points towards elevated ESR levels indicative of infection/ inflammation, being associated with a hypercoagulable state.

The differences in values of mean ESRs in patients with normal and elevated levels of D-dimers were shown to be significant only in the White racial group, most likely because the numbers of Black and Coloured patients assessed were too small. However, the significant difference between mean ESR results in the White patients seem to indicate that those patients with a hypercoagulable state, as evidenced by elevated D-dimer levels, have a significantly higher mean ESR, incriminating a chronic inflammatory state in the aetiology of their cerebrovascular disease.

The statistically significant difference found when comparing Black and White patients seems to suggest that Black patients, having suffered a cerebrovascular event, demonstrate much higher ESR levels, particularly in association with elevated D-dimers.
The probable increased exposure to, and increased prevalence of, infective disease in the Black population may help to explain these results. This may further support the hypothesis of subclinical infection/ inflammation being incriminatory in the causation of cerebrovascular disease. This factor may contribute to the high overall incidence of stroke seen in our Black population, where atheromatous vascular disease has a markedly lower incidence than other populations. This should prompt further research to look specifically for agents such as Chlamydia and Helicobacter in young stroke, and especially, Black patients.

The possibility of Chlamydia pneumoniae infection playing a role in the pathogenesis of atherosclerosis has received important support by Shor and colleagues (1992). They demonstrated the presence of this organism in atheromatous plaques of coronary arteries

and aorta by morphological and molecular biological techniques. Melnick, Shahar & Folsom et al. (1992) presented data pertaining to asymptomatic persons determined to have carotid wall thickening by ultrasound imaging. Those subjects with carotid abnormalities more frequently had TWAR Ig G antibody.

These findings raise the question that patients with atheromatous disease of their carotid vessels might have associated infection with C pneumoniae, thus generating intravascular plaques leading to cerebral thrombo-embolism and resultant ischaemia in the anterior circulatory vascular territory.

A significant association was identified amongst patients with anterior circulatory cerebrovascular events in terms of elevated D-dimers and ESR levels, as opposed to patients with events confined to the posterior, or both, circulatory territories. This would support the idea that ongoing inflammation, raising the ESR, might be responsible for progressive thrombosis and fibrinolysis in the carotid arterial tree, predisposing such individuals to ischaemic events in the distribution of supply of these vessels. The lack of significant results in other vascular territories is likely attributable to the small sample size of patients with posterior or dual territory events. Further studies of larger patient groups are needed to confirm or discount these findings.

Although mean ESR levels were not significantly different when comparing patients with no carotid stenosis, greater or less than 50% stenosis, it is interesting to note that the highest ESR levels were among those with less than 50% stenosis.

When comparing mean ESRs within levels of D-dimer elevation, only patients with greater than 50% stenosis exhibited a significantly higher mean ESR in association with raised D-dimer levels. This would suggest that patients with more extensive atheromatous occlusion of the carotid vascular tree might have an underlying chronic inflammatory condition, possibly C pneumoniae infection, promoting their hypercoagulable state. Unfortunately, no Chlamydia pneumoniae serological tests were performed on this study population to determine whether such subclinical infection might play a role. Further studies should be performed to analyse this parameter and discern any associations between C pneumoniae infection, hypercoagulability and elevated ESR in stroke patients.

The absence of any positive or negative correlations demonstrated between mean ESR levels and time interval of measurement after event in the total population, or within age groups, sex, racial groups, anterior and posterior vascular territories and patients experiencing single or multiple events, shows that ESR does not appear to be elevated immediately after the event, nor does it rise or fall over time. Thus, an elevated ESR does not appear to be a direct consequence of a thrombotic cerebrovascular event. Although a strong correlation was demonstrated in the three patients with events in both territories, it is likely that this result is a spurious one, relating to the small sample size, particularly as the mean ESR amongst these patients was only 5.0 (4.583).

In a recent prospective population-based study, haematocrit, ESR and white cell count were demonstrated to be the only rheological parameters able to be considered as independent predictors of 30-day case fatality in stroke patients (Czlonkowska, Ryglewicz

& Lechowicz, 1997). In this study, chronic infection/ inflammation seemed not to play a role in the severity, extent and duration of the ischaemic event, as evidenced by the lack of significant differences seen in ESR levels in patients suffering either CVAs or TIAs. This is also in contrast to reports by Chamorro, Vila & Ascaso et al. (1995), who showed that the ESR might be of help in the early prediction of stroke outcome.

Patients who had suffered single or two cerebrovascular events demonstrated a significantly higher mean ESR in association with a hypercoagulable state, as manifested by elevated D-dimer levels. However, this significance was lost in those patients who had suffered multiple events, possibly down playing the role of chronic infection/inflammation in the aetiology of recurrent episodes.

Prospective studies have shown that fibrinogen levels predict the development of cardiovascular disease (Meade et al., 1993). The predictive value of fibrinogen in stroke was found to be independent of other risk factors. The weak correlation identified between mean ESR and mean fibrinogen levels in patients with elevated D-dimers implies that in patients with a heightened fibrinolytic state, fibrinogen levels may act as concurrent markers of associated inflammation and a hypercoagulable state. This would support previous studies that have suggested that a systemic inflammatory response increases the risk of atheromatous disease by raising the concentration of circulating clotting factors such as fibrinogen (Woodhouse, Khan & Plummer et al., 1994).

The highly significant difference seen in mean fibrinogen levels when comparing patients with normal and elevated ESRs who also have elevated D-dimer levels, further implies that patients with ongoing fibrinolysis have associated elevations of both acute-phase reactants, namely ESR and fibrinogen. This may again suggest that patients with a hypercoagulable state have an associated infective/inflammatory process. The elevations seen in fibrinogen levels may be due to an acute-phase response or a prothrombotic state.

The seasonal variation demonstrated in fibrinogen levels, with highest levels seen in the winter months (Stout & Crawford, 1991), may relate to the higher mortality rates noted in winter for myocardial infarction and stroke (Hindfelt & Nilsson, 1977; Alderson, 1985). The higher incidence of infective diseases in the winter months, often of a subclinical nature, may act as a link between cerebrovascular disease and elevated acute–phase reactants such as fibrinogen and ESR. Although the seasonal distribution of events was not analysed in this study, this may be worth looking at in future studies.

Patients with normal D-dimer levels did not exhibit any significant association between ESR and WCC. However, in those with elevated D-dimers, significance was shown in associating raised ESR with an elevated WCC. This suggests that patients with ongoing fibrinolysis may have a raised WCC in association with an elevated ESR, once again supporting the possibility of a concomitant inflammatory process playing a role in the aetiology of the vascular event.

Clinical studies have shown a significant association between leukocyte count and vascular events (Ernst, Dale & Hammerschmidt et al., 1987). The PLAT study results suggested that an elevated leukocyte count is an associated finding in patients suffering transient ischaemic attacks (Cortellaro, Boschetti & Cofrancesco et al., 1992). Elevation in WCC was found to be an independent predictor of 30-day case fatality in acute stroke (Czlonkowska et al., 1997) and influence prognosis after stroke (Silvestrini, Pietroiusti & Magrini, 1994).

It has been suggested that leukocyte activation may occur as a consequence of infection preceding onset of stroke (Syrjanen et al., 1988; Grau et al., 1995) or as a result of ischaemia and brain damage (Czlonkowska et al., 1997). Regardless of the reason for their activation, leukocytes probably contribute to ischaemia by limitation of cerebral blood flow by vessel plugging or vasoconstrictive mediator release, exacerbation of blood-brain-barrier or parenchymal injury via hydrolytic enzyme release or initiation of thrombosis (Ernst et al., 1987; Grau, Sigmund & Hacke, 1994; Czlonkowska et al., 1997).

Elevated WCC was not found to be indicative of infection in the study population. No direct correlation was observed between WCC and ESR levels either. In those few patients with an elevated WCC, a statistically significant percentage had an elevated ESR. Ameriso et al. (1991), similarly, did not find recent infection to be associated with a concomitant elevated leukocyte count in patients suffering stroke.

It is of interest that those few patients identified with obvious clinical infection or known vasculitis did not demonstrate marked thrombotic and subsequent fibrinolytic activity, as evidenced by the majority having normal D-dimer levels. Most of those patients did not demonstrate markedly elevated ESRs either. These results would seem to indicate that obviously florid infection is not solely responsible for a thrombotic state in stroke patients.

This study was conducted retrospectively and therefore the absence of infection in those not assessed acutely can only be assumed, based on the patients' histories and medical records. A prospective study should be initiated to determine infective status on admission by history and examination. Baseline parameters, including ESR, D-dimers, WCC, fibrinogen levels, CRP and bacteriological/ viral serology could be correlated with clinical condition and reassessed on follow-up to determine association and trends.

Eleven of the 12 patients with auto-immune disease were females, half were White and a third 45 years or younger. This may mirror the epidemiological spectrum of auto-immune disease in the general population. The high percentage of these patients having suffered more than a single event, mainly affecting the anterior circulatory territory of vascular supply, is probably in keeping with vasculitic small vessel disease, affecting multiple smaller areas of cerebral tissue.

5.3 Recommendations for Future Research

The potential limitations of this study merit consideration, so that future research may be initiated. The analyses were all based on a single base-line determination of haematological parameters that may not accurately reflect infective or inflammatory status over long time periods.

The majority of patients were analysed retrospectively, having suffered their cerebrovascular episodes in advance of inclusion in the study. Further studies, on a prospective basis, should be employed so that immediate base-line parameters could be recorded. Recurrent evaluations should then be performed at specific time intervals post event, so that comparisons could be made and patterns observed. In addition, markers of ongoing thrombosis and fibrinolysis that remain elevated for prolonged periods after an ischaemic event, especially in association with an elevated ESR, should be looked at. The ESR should also be correlated with D-dimer levels at recurrent defined time intervals post event, to assess whether a decrease in ESR corresponds with a fall in D-dimer levels.

Although some of the results appeared, in clinical practice, to be relevant, scientific statistical significance could not be attached to them. This was particularly so in those patients suffering multiple events, with elevated D-dimer levels. A future study, analysing a larger study population, would enhance the power and either confirm or refute these findings. Further investigation of greater numbers of Asian and Coloured patients should be performed to determine if trends in these populations follow those of either Black or

White patients. A control study, too, should be implemented so that the parameters assessed in this study can be compared with age-matched healthy individuals.

The interplay of ESR and D-dimer levels with other rheological factors that promote a hypercoagulable state, including protein C, protein S and antithrombin levels, anti-cardiolipin antibodies (ACLA), antinuclear factor (ANF) and low activated protein C ratio (APCR), needs to be assessed.

The effects of known risk factors for atheromatous vascular disease such as smoking, alcohol, hypertension, family history, hypercholesterolaemia, hormonal alteration and others on the parameters evaluated in this study needs to be explored.

The influence of known anti-inflammatory agents such as aspirin, used in acute stroke for its anti-platelet effect (Sandercock, 1997; Royal College of Physicians of Edinburgh, 1998) on parameters such as D-dimers, ESR and fibrinogen levels should be evaluated.

5.4 Recommendations for Future Patient Management

Acquired abnormalities of coagulation inhibition and fibrinolysis, including chronic infection/ inflammation, may cause or contribute to stroke, but these remain difficult to define. Increasing evidence points to such abnormalities occurring, perhaps only transiently, precipitating thrombosis in synergy with atherosclerotic disease (Hart & Kanter, 1990).

Presently, the special laboratory screening tests for a prothrombotic state in patients, as employed in this study have relatively limited implications for prevention and management of cerebrovascular disease. As knowledge of the interactions between inflammatory mediators, infection, endothelial injury, auto-immune mediated cross-reactivity with bacterial antigens and classic risk factors for atheromatous disease improves (Ross, 1993; Danesh, Collins & Peto, 1997), so too will our diagnostic, investigative and therapeutic skills be enhanced. Hopefully, too, clearly definable prognostic markers for those at risk of disease will be defined to allow for prophylactic intervention.

The results of this study have important implications for the investigations performed in patients suffering acute cerebrovascular events. Immunological markers of acute or ongoing infection should be tested for, including WCC, fibrinogen, D-dimers, ESR and CRP. Serological evidence of infective agents such as Chlamydia pneumoniae, particularly in young Black patients at higher risk for exposure to these, and other, infectious agents should be carried out. The background incidence of exposure to these patients in patients with, and without, atheromatous cerebrovascular disease should be determined, to ascertain whether exposure to infective organisms is causal or merely coincidental.

The results of future investigations and studies may have significant therapeutic implications in terms of identifying those patients who should be treated with antiplatelet agents, anti-inflammatories, anticoagulants and/ or appropriate antibiotic agents to prevent recurrent focal or generalised thrombotic events.

APPENDIX A CLINICAL AND LABORATORY DATA

NUMBER	SURNAME	FIRST NAME	INITIAL	HOSPITAL NUMBER	BIRTH DATE	SEX
1	Koetle	Tsepo		2302652	30-Nov-49	M
2	Mogale	Harriet		1048672	02-Jul-23	F
3	Mailer	Susan		2202576	31-Jan-30	F
4	Marcal	Jose	A	963723	14-Oct-25	M
5	Douvaras	Panagiotis		1023274	15-Jul-30	M
6	Netto	Mary		1301104	17-Dec-25	F
7	Lang	Ethel	L	2246825	20-Nov-24	F
8	Morajane	Anna		1317740	10-Oct-48	F
9	Lahoud	Mansour		2169857	20-Oct-36	M
10	Louw	Henry	R	2300965	18-Apr-50	M
11	Moffett	Gladys	F	307668	25-Apr-40	F
12	Dennis	Terry		309470	21-Apr-45	M
13	Hiscock	George		1046439	14-Jan-21	M
14	Roux	Johannes		2233098	27-Apr-32	M
15	Andrew	Kennith	C	2026750	02-Mar-16	M
16	Weinstein	Basil	B	2302418	21-Mar-33	M
17	Gill	Harold		1101008	04-Sep-17	M
18	Moyo	Shadrack		2326869	19-Feb-49	M
19	Nunes	Jose		2186626	04-Mar-32	M
20	Andraos	Valentino	M	206897	21-Jun-02	M
21	Bekker	Elizabeth		607929	26-May-39	F
22	Bennett	Vincent		878368	03-Dec-31	M
23	Neveling	Clarence		106512	10-Jan-30	F
24	O'Neill	Margaret		904721	19-May-18	F
25	Maud	Doreen		256549	14-Aug-33	F
26	Richter	Martha	J	991644	14-Dec-33	F
27	Jenkinson	Christian		1224256	02-May-32	M
28	Salamone	Franca		116107	23-Sep-40	F
29	Adam	Khatija		2190243	24-Jan-29	F
30	Peters	Yvonne		1306007	20-Sep-32	F
31	Booysen	Douglas	A	930070	07-Apr-17	M
32	Geyle	Millicent		202711	01-Jan-22	F
33	Valab	Jivi		2324256	15-Aug-34	F
34	Dadabhay	Bibi		2108552	07-Oct-37	F
35	Venketamma	Subiah		2303304	06-Aug-28	F
36	Van der Merwe	Elsie		2287205	06-Jul-36	F
37	Steyn	Stephanus		1096469	29-Dec-32	M
38	Ramsay	Marie		2012361	28-Jul-29	F
38	Diljan	Bhagwathi		1300164	29-Oct-46	F
40	Wells	Michael	J	1163435	03-Aug-34	M
41	Ross	Catherine		2040711	01-Mar-26	F
42	Taylor	Anne		717923	04-Aug-18	F
43	Keyser	Andries		2198568	23-Jun-22	M
44	Gwilt	David		2071832	30-Mar-28	M
45	Maud	Frederick		660954	07-Sep-20	M
46	Nsele	Samuel		2277716	28-Dec-32	M
47	Jaffit	Olla		325661	15-Jul-22	F
48	Desousa	Raquel		883563	27-May-19	F
49	Taljaard	Tina		289388	31-Aug-27	F
50	Lacquet	Mignonne		915772	23-Nov-32	F
51	Balnave	Matthew		703609	06-Jun-18	M
52	Mathansi	Leonard		239948	11-Nov-46	M
53	Bhembe	Lena		2310954	10-Feb-40	F
54	Mannie	Loraine		2175419	10-Jun-29	F
55	Matchikiri	Johannes		2098723	15-Apr-31	M

APPENDIX A CLINICAL AND LABORATORY DATA

NUMBER	SURNAME	FIRST NAME	INITIAL	HOSPITAL NUMBER	BIRTH DATE	SEX
56	Schouw	Peter	J	2336504	08-Jun-32	M
57	Dikgole	Christina		2331974	15-Jun-42	F
58	Hartog	Phoebie		1093401	18-Jul-46	F
59	Jossie	Dawn		2331364	21-May-42	F
60	Mokwa	Salamina		2334315	08-May-50	F
61	De Waal	Aletta		955692	14-Nov-27	F
62	Duke	Robert		105074	07-Jun-25	M
63	Mabaso	Ephraim		2200689	16-Dec-46	M
64	Moremi	Herman		2301372	07-Dec-49	M
65	Turner	Sydney		904293	05-Apr-30	M
66	Skopelitis	Stavros		238654	06-Aug-33	M
67	Bacharach	Eric		964887	15-Sep-46	M
68	Delima	Raul	G	549810	30-Oct-30	M
69	Buskin	Allan		2212938	07-Jan-50	M
70	Baloyi	Thomas		2236234	01-Mar-48	M
71	Kromberg	Johannes		920471	29-Aug-29	M
72	Scrooby	Marie		2215374	04-Dec-42	F
73	Thanjekwayo	Susan		2122452	05-Jan-41	F
74	Phalatse	Motsatsi	O	2336897	01-Sep-27	F
75	Crowngold	John		2175672	27-May-40	M
76	Ndlovu	Noki		2326475	24-Oct-40	F
77	King	Esther		2342111	06-Feb-42	F
78	Dube	Solly		2228326	30-Nov-60	M
79	Meyer	Gert		1087260	28-Sep-53	M
81	Brits	Darrel		1016672	01-Jan-66	F
81	Molokeng	David		2134871	01-Jan-59	M
82	Bianchina	Martin		1018917	16-Oct-81	M
83	Phillips	Bernadette		2280015	28-Apr-54	F
84	Morabe	Emily		2271937	01-Jan-73	F
85	Madela	Maria		2253079	05-May-65	F
86	Bhamjee	Isha		2054636	19-Jan-51	F
87	Ngwenya	Amelia		2100931	06-Apr-69	F
88	Philip	Joanne		2287164	14-Apr-78	F
89	Swanepoel	Hester		2305308	03-Aug-53	F
90	Heilig	Lisa		2044995	08-Jun-66	F
91	Gobey	Barry		2290331	25-Oct-59	M
92	Chiloane	Gillian		2081706	13-Dec-72	F
93	Mofokeng	Rose		1168496	25-Jun-67	F
94	Prinsloo	Brenda		1211812	05-Jun-50	F
95	Zanazo	Esther		2318940	14-Aug-63	F
96	Olifant	Anastasia		1261570	23-Oct-53	F
97	Klaasen	Ruth		HJ 12016627	12-Jan-66	F
98	Erasmus	Willem		2324253	09-Jan-58	M
99	Siswane	Oliver		2245351	23-Jan-51	M
100	Smuts	Lynette		1179508	10-Jun-48	F
101	Ngake	Matumelo		2097881	19-Nov-59	F
102	Lucas	Alvin	J	2301530	22-May-52	M
103	Zulu	Lolly		2327119	01-Jan-71	F
104	Nkosi	Enoch		2327146	04-Aug-65	M
105	Phakathi	Endorah		2026308	04-Jan-67	F
106	Baloyi	Beauty		H 645688	10-Oct-58	F
107	Ratladi	Enoch		H 656185	23-Nov-65	M
108	Lebota	Emily		2253097	12-May-57	F
109	Mehlape	Mpinana		2109358	12-Oct-69	F
110	Khaba	Joyce		H 656851	04-Apr-60	F

APPENDIX A CLINICAL AND LABORATORY DATA

NUMBER	SURNAME	FIRST NAME	INITIAL	HOSPITAL NUMBER	BIRTH DATE	SEX
111	Setlhare	Abe		2108114	30-May-52	M
112	Visagie	Willem	D	2343889	16-Aug-62	M
113	Abrie	Charlotte	I	2346526	16-Oct-53	F
114	Nkwe	Angela	T	2330291	02-Mar-67	F
115	Rosdien	Roschin		2307591	04-Jan-57	F
116	Mahlangu	Ellen		2085752	13-Feb-55	F
117	Fabiyo	Emily		219952	09-Sep-50	F
118	Von Zeeberg	Eustacia	R	2094299	14-Dec-47	F
119	Tilly	Amod		1262802	07-Feb-48	M
120	Klopper	Anna		1059511	24-Feb-34	F
121	Campanerut	Celio		2108162	02-Feb-48	M
122	Lewis	Marie	S	1024709	18-Aug-40	F
123	Spiller	Lesley	A	1048386	12-Sep-70	F
124	Cassels	Edward		2133637	02-Feb-54	M
125	Antonites	Adrienne		2215237	14-Nov-66	F
126	Du Preez	Annamarie		2221456	06-Oct-41	F
127	Gumbi	Kenetsi		2252245	27-Mar-57	F
128	Mavuso	Caroline		1107447	04-Sep-49	F
129	Mohammed	Christopher		2274464	14-Dec-69	M
130	Niewenhuizen	Paul		2150610	14-Jun-57	M
131	Harris	Elizabeth		841355	30-Jan-52	F
132	Khala	Siyakholwa		2234735	17-Jan-78	F
133	Mdlungu	Margaret		2115651	19-Apr-53	F
134	McMurray	Gwithian		743904	04-Oct-55	F
135	Olson	John		2133458	27-Feb-63	M
136	Payne	Roeland	H	2091655	22-Nov-73	M
137	Radebe	William		2245905	01-Jan-81	M
138	Soudien	Anna	B	1215747	03-Jun-60	F
139	Subrayan	Minnie		1315601	10-Dec-49	F
140	Thusi	Angelinah		2114021	23-Jun-71	F
141	Petia	Nenova		2350911	21-Dec-72	F
142	Zwane	Thandi		2339468	08-Jan-54	F
143	Makwale	Melida		2027772	10-Jun-58	F
144	Laher	Shereen		2312604	20-Aug-68	F
145	Basson	Linnet		315125	21-Jun-57	F
146	Olifant	Mirriam		2351688	13-Feb-72	F
147	Hetem	Nuala		2250431	14-Aug-73	F
148	Pienaar	Madeline		HJ 31015651	31-Jan-56	F
REFERENCE RANGE						
UNITS						
KEY				HJ=Helen Joseph		F=Female
				H=Hillbrow		M=Male
				All others=Johannesburg		

APPENDIX A CLINICAL AND LABORATORY DATA

NUMBER	RACE	FIRST EVENT	AGE AT FIRST EVENT	RECENT EVENT	DATE OF BLOC
1	B	21-Jan-97	47.14	21-Jan-97	13-Mar
2	B	15-Dec-88	65.46	15-Dec-88	13-Mar
3	W	13-Dec-95	65.86	13-Dec-95	13-M
4	W	10-Oct-88	62.99	10-Oct-88	28-Feb-97
5	W	01-Mar-96	65.63	03-Mar-96	13-Mar-97
6	W	01-Sep-92	66.71	01-Sep-95	13-Mar-97
7	W	23-May-96	71.50	23-May-96	13-Mar-97
8	B	03-Sep-96	47.90	03-Sep-96	27-Feb-97
9	W	15-Apr-95	58.48	09-Jul-95	27-Feb-97
10	W	29-Nov-96	46.62	29-Nov-96	27-Feb-97
11	W	06-Jul-88	48.20	29-Dec-96	06-Mar-97
12	W	01-Sep-96	51.36	01-Feb-97	27-Feb-97
13	W	15-Jan-89	68.00	23-Dec-95	13-Mar-97
14	W	15-Jun-89	57.13	15-Feb-97	27-Feb-97
15	W	13-Apr-92	76.11	13-Apr-92	28-Feb-97
16	W	15-Apr-96	63.07	15-Jan-97	06-Mar-97
17	W	15-Feb-90	72.45	15-Feb-90	28-Feb-97
18	B	26-Apr-97	48.18	26-Apr-97	26-Apr-97
19	W	15-Feb-90	57.95	15-Sep-95	23-Apr-97
20	W	15-Jun-80	77.98	15-Jun-94	24-Apr-97
21	W	03-Feb-97	57.69	03-Feb-97	28-Feb-97
22	W	15-Jun-80	48.53	07-Dec-88	17-Apr-97
23	W	15-Jun-92	62.43	31-Oct-94	03-Apr-97
24	W	09-Sep-84	66.31	20-Nov-96	10-Apr-97
25	W	15-Dec-88	55.34	15-Oct-96	03-Apr-97
26	W	15-Sep-94	60.75	15-Jun-95	03-Apr-97
27	W	15-Feb-92	59.79	15-Apr-93	03-Apr-97
28	W	15-Jan-93	52.31	15-Jan-93	03-Apr-97
29	A	01-Jan-90	60.94	15-Jun-93	03-Apr-97
30	W	29-Dec-93	61.27	04-Jan-94	10-Apr-97
31	W	15-Apr-96	79.02	15-Mar-97	17-Apr-97
32	W	01-Dec-96	74.92	30-Dec-96	17-Apr-97
33	A	15-Jan-95	60.42	23-Jan-97	18-Apr-97
34	A	15-Jun-93	55.69	15-Mar-95	03-Apr-97
35	A	20-Jan-97	68.46	20-Jan-97	27-Apr-97
36	W	18-Aug-96	60.12	18-Aug-96	10-Apr-97
37	W	22-Jan-90	57.07	22-Jan-90	10-Apr-97
38	W	14-Dec-93	64.38	14-Dec-93	10-Apr-97
38	C	21-Mar-93	46.39	21-Mar-93	10-Apr-97
40	W	15-Jun-87	52.87	15-Jun-95	10-Apr-97
41	W	15-Jun-93	67.29	15-Jun-93	10-Apr-97
42	W	15-Jun-82	63.86	16-Jun-93	17-Apr-97
43	W	15-Jun-90	67.98	06-Nov-95	06-Mar-97
44	W	11-May-94	66.11	11-May-94	06-Mar-97
45	W	20-Oct-94	74.12	20-Oct-94	06-Mar-97
46	B	09-Oct-96	63.79	09-Oct-96	08-May-97
47	W	15-Jun-97	74.92	08-Oct-93	08-May-97
48	W	14-Feb-97	77.73	25-Apr-97	08-May-97
49	W	15-Mar-86	58.54	19-Jan-89	28-Feb-97
50	W	01-Jul-90	57.60	15-Feb-95	13-Mar-97
51	W	29-Dec-82	64.56	29-Dec-82	08-May-97
52	B	15-Apr-97	50.43	15-Apr-97	14-May-97
53	B	15-Sep-96	56.60	15-Sep-96	14-May-97
54	W	07-Jul-74	45.07	07-Jul-74	24-Apr-97
55	B	17-Sep-74	43.43	17-Oct-96	24-Apr-97

APPENDIX A CLINICAL AND LABORATORY DATA

NUMBER	RACE	FIRST EVENT	AGE AT FIRST EVENT	RECENT EVENT	DATE OF BLOODS
56	W	09-Apr-97	64.84	09-Apr-97	10-Jun-97
57	B	20-May-97	54.93	20-May-97	22-May-97
58	W	15-Jan-97	50.50	15-Jan-97	09-Jul-97
59	C	15-Mar-97	54.82	15-Mar-97	20-May-97
60	B	23-Mar-97	46.87	23-Mar-97	02-Jul-97
61	W	15-Jun-87	59.58	15-Sep-94	29-May-97
62	W	15-Sep-91	66.27	15-Sep-92	29-May-97
63	B	15-Nov-95	48.91	15-Nov-95	29-May-97
64	B	11-Jan-97	47.10	11-Jan-97	22-May-97
65	W	15-Oct-96	66.53	15-Oct-96	22-May-97
66	W	15-Jun-84	50.86	06-Feb-96	22-May-97
67	W	28-Mar-96	49.53	30-Apr-96	18-Apr-96
68	W	01-Jul-83	52.67	01-Jul-83	31-Jan-95
69	W	14-Jan-96	46.02	14-Jan-96	16-Jan-96
70	B	17-Feb-96	47.96	17-Feb-96	11-Apr-96
71	W	01-Jul-91	61.84	01-Jul-91	11-Jun-96
72	W	15-Jan-96	53.11	15-Jan-96	29-Feb-96
73	B	25-Sep-94	53.72	25-Sep-94	27-Jul-95
74	B	01-Nov-95	68.17	07-Jun-97	24-Jul-97
75	W	15-Sep-96	56.30	01-Jul-97	24-Jul-97
76	B	15-Apr-97	56.47	15-Apr-97	28-Jul-97
77	W	15-Jan-97	54.94	15-Jun-97	07-Jul-97
78	B	09-Mar-96	35.27	09-Mar-96	22-Mar-96
79	W	10-Jul-96	42.78	10-Jul-96	13-Mar-97
81	W	15-Jun-96	30.45	15-Feb-97	12-Mar-97
81	B	05-Jan-95	36.01	05-Jan-95	13-Mar-97
82	W	20-Dec-96	15.18	20-Dec-96	30-Dec-96
83	C	09-Oct-96	42.45	09-Oct-96	25-Feb-97
84	B	10-Sep-96	23.69	10-Sep-96	17-Apr-97
85	B	01-Jun-96	31.07	01-Jun-96	10-Apr-97
86	A	24-Jan-94	43.01	24-Jan-94	03-Apr-97
87	B	16-Mar-96	26.94	16-Mar-96	07-Mar-97
88	W	28-Dec-95	17.71	28-Dec-96	03-Apr-97
89	W	15-Nov-96	43.29	15-Nov-96	16-Apr-97
90	W	13-Nov-93	27.43	13-Nov-93	17-Apr-97
91	W	20-Nov-96	37.07	20-Nov-96	17-Apr-97
92	B	15-Jul-94	21.59	15-Jul-94	17-Apr-97
93	B	25-Apr-91	23.83	14-Aug-95	17-Apr-97
94	W	06-Jan-92	41.59	15-Mar-97	17-Apr-97
95	B	15-Jun-92	28.84	23-Jan-97	17-Apr-97
96	B	15-Oct-92	38.98	09-Sep-94	17-Apr-97
97	W	06-Apr-97	31.23	06-Apr-97	16-Apr-97
98	W	15-Feb-94	36.10	15-May-94	17-Apr-97
99	B	18-May-96	45.32	18-May-96	06-Mar-97
100	W	15-Oct-90	42.35	15-Oct-90	06-Mar-97
101	B	17-Jul-94	34.66	10-Oct-94	08-May-97
102	W	15-Jun-94	42.06	05-May-97	08-May-97
103	B	28-Apr-97	26.32	28-Apr-97	02-May-97
104	B	28-Apr-97	31.73	28-Apr-97	02-May-97
105	B	28-Jan-97	30.07	28-Jan-97	22-May-97
106	B	15-Dec-83	25.18	13-May-97	22-May-97
107	B	22-May-97	31.49	22-May-97	29-May-97
108	B	22-May-96	39.03	22-May-96	30-Apr-97
109	B	03-Apr-97	27.47	29-Apr-97	22-May-97
110	B	30-May-97	37.15	30-May-97	10-Jul-97

APPENDIX A CLINICAL AND LABORATORY DATA

NUMBER	RACE	FIRST EVENT	AGE AT FIRST EVENT	RECENT EVENT	DATE OF BLOODS
111	B	25-Aug-96	44.24	25-Aug-96	10-Jul-97
112	W	15-Mar-97	34.58	15-Apr-97	10-Jun-97
113	W	27-Jun-97	43.70	23-Jul-97	21-Jul-97
114	B	15-May-97	30.20	15-May-97	05-Jun-97
115	A	01-Jan-97	39.99	04-Feb-97	07-Mar-97
116	B	26-Mar-97	42.11	26-Mar-97	22-May-97
117	B	15-Dec-94	44.27	15-Dec-96	23-May-97
118	C	15-Jun-86	38.50	20-Apr-95	13-Mar-97
119	A	04-Nov-92	44.74	04-Nov-92	10-Apr-97
120	W	15-Jun-77	43.30	15-Dec-88	06-Mar-97
121	W	15-Jun-84	36.37	15-Dec-94	12-Mar-97
122	W	15-Jun-62	21.82	05-Aug-88	13-Mar-97
123	W	01-Jul-91	20.80	01-Jul-91	23-Jun-96
124	C	01-May-94	40.24	01-May-94	22-Feb-95
125	W	15-Nov-94	28.00	25-Apr-96	13-May-96
126	W	15-Jun-70	28.69	04-May-96	30-May-96
127	B	17-Jun-96	39.23	17-Jun-96	20-Jun-96
128	B	03-Apr-90	40.58	03-Apr-90	26-Jan-09
129	C	26-Dec-95	26.03	26-Dec-95	23-Oct-96
130	W	15-Dec-94	37.50	15-May-95	14-Jun-95
131	W	12-Mar-96	44.11	12-Mar-96	23-May-96
132	B	21-Feb-96	18.09	21-Feb-96	21-Aug-96
133	B	22-Nov-94	41.59	22-Nov-94	17-Jan-95
134	W	26-Dec-95	40.23	03-Jan-96	03-Jan-96
135	W	22-Feb-95	31.99	22-Feb-95	15-Jun-95
136	C	15-Apr-94	20.39	15-Oct-94	03-Jan-95
137	B	13-May-96	15.36	13-May-96	04-Jun-96
138	C	15-Jul-91	31.11	15-Jul-92	12-Jul-96
139	A	15-Sep-94	44.76	16-Nov-95	04-Jan-96
140	B	15-Feb-93	21.65	15-Feb-93	13-Jan-95
141	W	22-Jul-97	24.58	22-Jul-97	07-Aug-97
142	B	15-Jun-97	43.43	15-Jun-97	07-Aug-97
143	B	01-May-97	38.89	01-May-97	19-May-97
144	A	15-Aug-94	25.98	15-Jan-97	24-Mar-97
145	W	15-Jun-88	30.98	15-Jun-88	09-Jul-97
146	B	15-Aug-90	18.50	15-Aug-90	14-Aug-97
147	W	07-Jul-97	23.90	07-Aug-97	14-Aug-97
148	C	15-Jun-88	32.37	06-Jun-97	10-Jun-97

Years

A=Asian
B=Black
C=Coloured
W=White

APPENDIX A CLINICAL AND LABORATORY DATA

NUMBER	TIME INTERVAL	[illegible]ORY	EPISODE	EPISODE NUMBERS	ISCHAEMIC HEART DISEASE
1	0.14	2	1	1	0
2	8.23	1	1	1	0
3	1.25	1	2	1	0
4	8.38	2	2	2	0
5	1.03	1	2	3	0
6	1.53	1	2	3	0
7	0.80	1	1	1	0
8	0.48	2	1	1	0
9	1.64	1	1	2	0
10	0.25	2	1	1	0
11	0.18	1	3	3	0
12	0.07	1	2	3	0
13	1.22	2	2	3	0
14	0.03	1	2	3	0
15	4.88	1	1	1	0
16	0.14	2	2	3	0
17	7.03	1	1	1	0
18	0.00	1	1	1	0
19	1.60	1	1	2	1
20	2.86	2	3	3	0
21	0.07	1	1	1	0
22	8.35	1	2	3	0
23	2.42	2	2	3	0
24	0.39	1	3	2	0
25	0.47	1	1	3	0
26	1.80	1	3	3	1
27	3.96	1	2	2	0
28	4.21	1	1	1	0
29	3.80	1	2	3	0
30	3.26	1	1	2	0
31	0.09	1	2	3	1
32	0.30	1	2	3	1
33	0.23	1	2	2	1
34	2.05	1	1	2	0
35	0.27	1	1	1	0
36	0.64	1	1	1	0
37	7.21	2	1	1	0
38	3.32	1	2	1	1
38	4.05	2	1	1	1
40	1.82	1	2	3	0
41	3.82	1	1	3	0
42	3.83	1	3	3	1
43	1.33	1	2	3	0
44	2.82	3	1	2	0
45	2.37	1	1	1	1
46	0.58	2	1	1	0
47	3.58	1	2	3	1
48	0.04	1	1	2	1
49	8.10	1	2	2	1
50	2.07	3	3	3	1
51	14.35	1	2	2	0
52	0.08	1	1	1	0
53	0.66	1	1	1	0
54	22.78	1	1	1	0
55	0.52	1	2	2	0

APPENDIX A CLINICAL AND LABORATORY DATA

NUMBER	TIME INTERVAL	TERRITORY	EPISODE	EPISODE NUMBERS	ISCHAEMIC HEART DISEASE
56	0.17	2	1	1	0
57	0.01	1	1	1	0
58	0.48	1	1	1	0
59	0.18	2	1	1	0
60	0.28	1	1	1	0
61	2.70	1	1	3	1
62	4.70	1	2	3	1
63	1.53	1	1	1	0
64	0.36	1	1	1	0
65	0.60	1	2	1	1
66	1.29	1	2	3	1
67	-0.03	1	2	3	0
68	11.58	1	1	1	0
69	0.01	1	1	1	0
70	0.15	1	1	1	0
71	4.94	1	1	3	0
72	0.12	1	2	1	0
73	0.83	1	1	1	0
74	0.13	1	1	2	0
75	0.06	1	2	3	1
76	0.28	1	1	1	0
77	0.06	1	2	1	0
78	0.04	1	1	1	0
79	0.67	2	1	1	0
81	0.07	1	1	3	0
81	2.18	1	1	1	0
82	0.03	1	1	1	0
83	0.38	2	1	1	0
84	0.60	1	1	1	0
85	0.86	1	1	1	0
86	3.19	1	1	1	1
87	0.97	1	1	1	0
88	0.26	1	3	2	0
89	0.42	1	1	1	1
90	3.42	1	1	1	0
91	0.40	1	1	1	0
92	2.75	1	2	1	0
93	1.67	1	2	3	0
94	0.09	1	2	3	0
95	0.23	1	2	2	0
96	2.60	1	1	3	0
97	0.03	1	1	1	0
98	2.92	1	1	2	1
99	0.80	1	1	1	0
100	6.39	1	1	1	0
101	2.57	1	1	2	0
102	0.01	1	2	2	1
103	0.01	1	1	1	0
104	0.01	1	1	1	0
105	0.31	1	1	1	0
106	0.02	1	1	2	0
107	0.02	1	1	1	1
108	0.94	1	1	1	0
109	0.06	1	2	2	0
110	0.11	1	1	1	0

APPENDIX A CLINICAL AND LABORATORY DATA

NUMBER	TIME INTERVAL	TERRITORY	EPISODE	EPISODE NUMBERS	ISCHAEMIC HEART DISEASE
111	0.87	1	1	1	1
112	0.15	1	2	2	0
113	-0.01	3	1	2	0
114	0.06	1	1	1	0
115	0.08	1	2	3	0
116	0.16	2	2	1	0
117	0.43	1	1	3	0
118	1.90	1	1	3	0
119	4.43	1	1	1	0
120	8.22	1	1	3	1
121	2.24	1	2	3	0
122	8.60	1	1	2	0
123	4.98	1	1	1	0
124	0.81	1	1	1	0
125	0.05	1	2	3	0
126	0.07	1	1	3	1
127	0.01	1	1	1	0
128	18.80	1	2	1	0
129	0.83	1	1	1	1
130	0.08	1	1	3	0
131	0.20	1	1	1	1
132	0.50	1	1	1	0
133	0.15	1	1	1	0
134	0.00	1	2	2	0
135	0.31	2	1	1	0
136	0.22	1	1	2	0
137	0.06	1	1	1	0
138	3.99	1	1	1	0
139	0.13	1	1	2	0
140	1.91	2	1	1	0
141	0.04	1	1	1	0
142	0.14	1	1	1	0
143	0.05	1	1	1	0
144	0.19	1	1	3	0
145	9.06	1	1	1	0
146	6.99	1	1	1	0
147	0.02	1	2	2	0
148	0.01	1	3	2	1
					Negative
	Years				
		1=Anterior	1=CVA	1=Single event	0=Negative
		2=Posterior	2=TIA	2=Two event	1=Positive
		3=Both	3=Both	3=Three/more events	

APPENDIX A CLINICAL AND LABORATORY DATA

NUMBER	PERIPHERAL VASCULAR DISEASE	DIABETES MELLITUS	HYPERTENSION	MIGRAINE
1	0	0	1	0
2	0	0	1	0
3	0	0	0	0
4	0	0	1	0
5	0	0	1	0
6	0	0	1	0
7	0	0	1	0
8	0	0	1	0
9	0	0	1	0
10	0	0	0	0
11	0	0	1	0
12	0	0	1	0
13	0	0	0	0
14	0	0	1	0
15	0	0	1	0
16	0	0	0	0
17	1	0	0	0
18	0	0	1	0
19	0	0	0	0
20	1	0	0	0
21	0	0	1	0
22	0	0	1	0
23	0	0	1	0
24	0	0	1	0
25	0	0	1	0
26	0	0	1	0
27	0	0	0	0
28	0	0	0	0
29	0	0	1	0
30	0	0	1	0
31	0	0	0	0
32	0	0	1	0
33	0	0	1	0
34	0	1	0	0
35	0	1	1	0
36	1	0	1	0
37	0	0	1	0
38	0	0	1	1
38	0	1	1	0
40	0	0	0	0
41	0	0	1	0
42	0	0	1	1
43	0	0	1	0
44	0	0	1	0
45	0	0	1	0
46	0	1	1	0
47	0	0	0	0
48	0	0	1	1
49	0	0	1	1
50	1	0	1	1
51	0	0	1	0
52	0	0	0	0
53	0	0	1	0
54	0	0	1	0
55	0	0	1	0

NUMBER	PERIPHERAL VASCULAR DISEASE	DIABETES MELLITUS	HYPERTENSION	MIGRAINE
56	0	0	0	0
57	1	0	1	0
58	0	0	1	0
59	0	0	0	0
60	0	0	0	0
61	0	0	1	0
62	0	0	1	0
63	0	0	0	0
64	0	0	1	0
65	0	0	1	0
66	1	0	1	0
67	0	0	0	0
68	1	0	1	0
69	0	0	0	0
70	0	1	1	0
71	0	0	0	0
72	0	0	0	0
73	0	0	1	1
74	0	0	1	0
75	0	0	1	0
76	0	0	0	0
77	0	0	1	0
78	0	0	1	0
79	0	1	0	0
81	0	0	0	0
81	0	0	0	0
82	0	0	0	1
83	0	0	0	0
84	0	0	0	0
85	0	0	0	0
86	0	0	1	0
87	0	0	0	0
88	0	0	0	0
89	0	0	1	0
90	0	0	0	0
91	1	0	1	0
92	0	0	0	0
93	0	0	0	0
94	0	0	0	1
95	0	0	0	1
96	0	0	1	0
97	0	0	0	0
98	0	0	1	0
99	0	0	1	0
100	1	0	1	0
101	0	0	0	0
102	0	0	0	0
103	1	1	0	0
104	0	0	0	0
105	1	0	1	0
106	0	0	1	0
107	0	0	0	0
108	0	0	1	0
109	0	0	0	0
110	0	0	1	0

APPENDIX A CLINICAL AND LABORATORY DATA

NUMBER	PERIPHERAL VASCULAR DISEASE	DIABETES MELLITUS	HYPERTENSION	MIGRAINE
111	0	0	1	0
112	0	0	0	0
113	0	0	1	0
114	0	0	0	0
115	0	0	0	1
116	0	0	0	0
117	0	0	1	0
118	0	0	0	0
119	0	0	0	0
120	1	0	1	0
121	0	0	1	0
122	0	0	0	1
123	0	0	0	0
124	0	0	0	0
125	0	0	0	0
126	1	0	1	0
127	0	0	0	0
128	0	0	0	1
129	0	0	1	0
130	0	0	1	0
131	0	0	0	1
132	0	0	0	0
133	0	0	1	0
134	0	0	0	1
135	0	0	0	0
136	0	0	0	0
137	0	0	0	0
138	0	0	1	0
139	0	0	1	0
140	1	0	0	0
141	0	0	0	0
142	0	0	0	0
143	0	0	0	0
144	0	0	0	1
145	0	0	0	0
146	0	0	0	0
147	0	0	0	1
148	0	0	1	0
	Negative	Negative	Negative	Negative
	0=Negative 1=Positive	0=Negative 1=Positive	0=Negative 1=Positive	0=Negative 1=Positive

APPENDIX A CLINICAL AND LABORATORY DATA

NUMBER	SYSTOLIC BP	DIASTOLIC BP	GOUT	SMOKING	HORMONAL CHANGE
1	180	100	0	15	0
2	170	86	0	0	0
3	140	80	0	1	0
4	160	100	1	1	0
5	160	90	1	1	0
6	140	80	0	0	0
7	170	110	0	60	0
8	150	105	0	0	0
9	160	100	1	1	0
10	140	60	0	40	0
11	140	90	0	1	0
12	150	110	1	0	0
13	120	70	0	0	0
14	140	100	0	20	0
15	120	80	1	0	0
16	170	70	0	40	0
17	110	80	0	10	0
18	186	118	0	0	0
19	140	80	0	0	0
20	180	30	0	30	0
21	140	100	0	15	0
22	200	100	0	1	0
23	190	70	1	1	0
24	200	90	0	0	0
25	150	100	0	0	0
26	160	80	0	15	0
27	150	80	1	1	0
28	110	70	0	10	1
29	140	80	0	1	1
30	110	70	1	60	0
31	110	80	0	1	0
32	160	80	0	0	0
33	200	110	0	0	0
34	150	90	0	0	1
35	170	100	0	0	0
36	140	90	0	30	0
37	150	95	1	20	0
38	190	85	0	0	0
38	140	86	0	0	0
40	140	80	1	0	0
41	215	110	0	10	0
42	140	96	0	1	0
43	180	100	0	40	0
44	140	80	0	1	0
45	130	55	0	1	0
46	240	130	0	0	0
47	120	60	1	6	0
48	140	70	1	0	1
49	120	80	0	1	0
50	150	90	0	0	1
51	150	84	1	1	0
52	130	80	0	10	0
53	180	130	0	0	0
54	140	80	0	1	1
55	155	100	1	0	0

APPENDIX A CLINICAL AND LABORATORY DATA

NUMBER	SYSTOLIC BP	DIASTOLIC BP	GOUT	SMOKING	HORMONAL CHANGE
56	120	80	0	0	0
57	160	100	0	0	0
58	140	90	0	1	1
59	120	80	0	0	0
60	120	70	0	4	1
61	160	100	0	1	0
62	160	100	0	1	0
63	150	100	0	0	0
64	140	100	0	2	0
65	165	90	0	0	0
66	160	90	0	20	0
67	130	70	0	70	0
68	150	100	0	1	0
69	130	70	0	80	0
70	160	100	0	5	0
71	160	90	0	1	0
72	125	80	0	1	1
73	140	80	0	0	0
74	160	100	0	0	0
75	110	70	0	1	0
76	150	90	0	0	0
77	130	60	0	0	1
78	170	108	0	1	0
79	124	74	0	20	0
81	115	70	0	15	0
81	110	60	0	1	0
82	120	80	0	0	0
83	130	85	0	0	0
84	120	90	0	0	0
85	125	70	0	0	0
86	140	90	0	1	0
87	120	70	0	0	1
88	110	80	0	0	1
89	130	80	0	0	0
90	146	92	0	30	1
91	150	120	0	20	0
92	120	70	0	0	1
93	130	60	0	0	0
94	110	60	0	15	1
95	120	80	0	0	1
96	140	100	0	0	0
97	125	70	0	10	0
98	140	80	0	40	0
99	200	140	0	40	0
100	110	60	0	15	1
101	135	80	0	1	1
102	120	86	0	0	0
103	140	86	0	0	1
104	120	80	0	1	0
105	150	100	0	0	0
106	130	96	0	0	1
107	115	80	0	12	0
108	140	90	0	0	0
109	110	70	0	0	1
110	130	90	0	0	0

APPENDIX A CLINICAL AND LABORATORY DATA

NUMBER	SYSTOLIC BP	DIASTOLIC BP	GOUT	SMOKING	HORMONAL CHANGE
111	200	140	0	10	0
112	110	60	0	1	0
113	130	95	0	6	1
114	130	80	0	2	0
115	100	70	0	20	0
116	130	95	0	6	0
117	240	140	0	1	0
118	100	70	0	10	0
119	120	75	0	20	0
120	150	90	0	0	1
121	140	100	1	30	0
122	100	80	0	20	0
123	130	80	0	15	1
124	120	80	0	20	0
125	108	70	0	0	1
126	160	95	0	0	0
127	120	80	0	0	1
128	130	90	0	0	0
129	110	80	0	10	0
130	140	90	0	1	0
131	140	70	0	15	1
132	120	70	0	0	0
133	130	70	0	0	0
134	140	80	0	1	1
135	110	70	0	0	0
136	120	80	0	2	0
137	110	70	0	0	0
138	120	80	0	20	1
139	160	100	0	20	1
140	120	70	0	0	0
141	110	70	0	20	0
142	120	80	0	0	1
143	100	80	0	0	0
144	130	80	0	0	1
145	100	60	0	10	0
146	130	80	0	0	0
147	100	80	0	7	0
148	130	84	0	20	0

	90-140	50-90	Neg	Non-smoker	Negative
	mm Hg	mm Hg			
	BP=Blood pressure	BP=Blood pressure	0=Neg	0=Non-smoker	0=Negative
			1=Pos	1=Ex-smoker	1=Positive
				2+=Cigs/day	

APPENDIX A CLINICAL AND LABORATORY DATA

NUMBER	ALCOHOL	HYPERCHOLESTEROLAEMIA	VALVULAR HEART DISEASE	ARRHYTHMIA
1	0	0	0	0
2	0	0	0	0
3	0	0	0	1
4	0	0	0	1
5	0	1	1	0
6	0	0	0	0
7	0	0	0	1
8	0	1	0	0
9	1	1	0	0
10	1	0	0	0
11	0	1	0	0
12	1	1	0	0
13	0	0	0	0
14	0	1	0	1
15	0	0	0	0
16	1	0	1	1
17	0	0	0	1
18	0	0	0	0
19	0	1	1	0
20	1	0	0	0
21	0	0	0	0
22	0	1	0	0
23	0	1	1	1
24	0	1	0	0
25	0	0	0	0
26	0	1	0	0
27	0	1	0	0
28	0	1	0	0
29	0	0	0	0
30	1	1	0	0
31	0	1	0	0
32	0	1	1	0
33	0	0	0	0
34	0	1	1	0
35	0	1	0	0
36	0	1	0	0
37	1	1	0	1
38	0	0	0	0
38	0	0	0	0
40	0	1	1	0
41	0	1	0	0
42	0	1	0	0
43	1	1	0	0
44	0	0	0	0
45	0	0	0	0
46	0	0	0	0
47	0	1	0	0
48	0	1	0	1
49	0	0	0	0
50	0	0	0	0
51	0	1	0	0
52	1	0	0	0
53	0	0	0	0
54	0	1	0	0
55	0	1	0	1

NUMBER	ALCOHOL	HYPERCHOLESTEROLAEMIA	VALVULAR HEART DISEASE	ARRHYTHMIA
56	0	0	0	0
57	0	0	0	0
58	0	0	1	0
59	1	1	0	0
60	0	0	0	0
61	0	0	0	0
62	0	1	0	0
63	0	0	1	0
64	0	0	0	0
65	0	1	0	0
66	1	1	1	0
67	0	0	0	0
68	1	0	0	0
69	0	0	0	0
70	1	1	0	0
71	0	1	0	0
72	0	0	0	0
73	0	0	0	0
74	0	0	0	0
75	0	1	0	1
76	0	0	0	0
77	0	1	0	0
78	0	0	0	0
79	0	1	0	0
81	0	0	0	0
81	0	0	0	0
82	0	0	0	0
83	0	0	1	0
84	0	0	0	0
85	0	0	0	0
86	0	1	0	0
87	0	0	0	0
88	0	0	0	0
89	0	1	0	0
90	0	1	0	0
91	1	0	0	0
92	0	0	0	0
93	0	0	1	0
94	0	0	0	0
95	0	0	0	0
96	0	0	0	0
97	1	0	0	0
98	0	0	1	0
99	1	0	0	0
100	0	0	0	0
101	0	0	0	0
102	0	0	1	1
103	0	0	0	0
104	0	1	0	1
105	0	0	0	0
106	0	0	0	0
107	0	0	0	0
108	0	0	0	0
109	0	0	0	0
110	0	0	1	0

NUMBER	ALCOHOL	HYPERCHOLESTEROLAEMIA	VALVULAR HEART DISEASE	ARRHYTHMIA
111	1	0	0	0
112	0	0	0	0
113	0	0	0	0
114	0	0	0	0
115	0	0	0	0
116	0	0	0	0
117	1	0	0	0
118	0	0	1	0
119	0	1	0	0
120	0	1	0	0
121	0	1	0	0
122	0	1	0	0
123	0	0	1	0
124	0	0	0	0
125	0	0	0	0
126	0	0	0	0
127	0	0	0	0
128	0	0	0	0
129	1	1	0	0
130	0	1	0	0
131	0	0	0	0
132	0	0	0	0
133	0	0	0	0
134	0	0	0	0
135	0	0	0	0
136	0	0	0	0
137	0	0	0	0
138	0	0	0	0
139	0	1	0	0
140	0	0	0	1
141	0	0	0	0
142	0	0	0	0
143	0	0	0	0
144	0	0	0	0
145	1	1	1	0
146	0	0	0	0
147	0	0	0	0
148	0	0	1	0
	Negative	Negative	Negative	Negative
	0=Negative	0=Negative	0=Negative	0=Negative
	1=Positive	1=Positive	1=Positive	1=Positive

APPENDIX A CLINICAL AND LABORATORY DATA

NUMBER	VASCULAR SURGERY	FAMILY HISTORY	HYPERTHYROIDISM	ANTICOAGULANTS
1	0	0	0	1
2	0	0	0	1
3	0	0	0	1
4	0	0	0	2
5	0	0	0	1
6	0	0	0	5
7	0	0	0	2
8	0	1	0	1
9	0	1	0	1
10	0	0	0	1
11	1	0	0	1,5
12	0	0	0	6
13	0	1	0	1
14	0	0	0	1
15	0	1	0	1
16	0	0	0	2
17	0	1	0	1
18	0	1	0	0
19	1	0	0	3
20	1	0	0	5
21	0	0	0	1
22	1	1	0	1,5
23	0	1	0	2
24	0	0	0	1
25	0	0	0	1
26	1	0	0	1
27	1	0	0	1
28	0	0	0	1
29	0	0	0	1,5
30	0	1	0	1
31	1	1	0	1
32	0	0	0	1
33	0	1	0	0
34	0	1	0	2
35	0	0	0	1
36	0	0	0	1
37	0	0	0	1
38	0	0	0	1
38	0	0	0	0
40	0	0	0	1
41	0	0	0	1
42	1	0	0	1
43	0	0	0	1
44	0	0	0	1
45	0	0	0	1
46	0	0	0	1
47	0	0	0	1
48	0	0	0	2
49	0	1	0	2
50	0	0	0	1
51	1	0	0	1
52	0	1	0	1
53	0	0	0	1
54	1	0	0	3
55	0	1	0	3

APPENDIX A CLINICAL AND LABORATORY DATA

NUMBER	VASCULAR SURGERY	FAMILY HISTORY	HYPERTHYROIDISM	ANTICOAGULANTS
56	0	0	0	1
57	0	0	0	1
58	0	0	0	1
59	0	0	0	1
60	0	0	0	1
61	0	0	0	1
62	0	0	0	1
63	0	0	0	2
64	0	0	0	0
65	1	0	0	0
66	1	0	0	1
67	0	1	0	1
68	1	0	1	1
69	0	0	0	0
70	0	0	0	1
71	0	0	0	3
72	0	1	1	1
73	0	0	0	1
74	0	0	0	1
75	1	1	0	3
76	0	0	0	1
77	0	0	0	1
78	0	0	0	0
79	0	1	0	2
81	0	0	0	1
81	0	0	0	2
82	0	1	0	1
83	0	0	0	2
84	0	0	0	1
85	0	0	0	1
86	1	1	0	1
87	0	0	1	0
88	0	0	0	1
89	0	1	0	0
90	0	1	0	1
91	0	1	0	2
92	0	0	0	1
93	0	0	0	0
94	0	0	0	1
95	0	0	0	0
96	0	0	0	1
97	0	0	0	1,6
98	0	0	0	1
99	0	1	0	1
100	0	0	0	2
101	0	0	0	1
102	0	0	0	2
103	0	0	0	1
104	0	0	0	2
105	0	1	0	1
106	0	0	0	1
107	0	0	0	3
108	0	0	0	1
109	0	1	0	1
110	0	0	0	1

APPENDIX A CLINICAL AND LABORATORY DATA

NUMBER	VASCULAR SURGERY	FAMILY HISTORY	HYPERTHYROIDISM	ANTICOAGULANTS
111	0	0	0	1
112	0	0	0	0
113	0	0	0	1,5
114	0	0	0	1
115	0	0	0	1
116	0	0	0	1
117	0	0	0	0
118	0	0	0	3
119	1	0	0	1
120	0	0	0	1
121	1	1	0	1
122	0	1	0	5
123	0	1	0	1
124	1	0	0	0
125	0	0	0	2
126	0	0	0	0
127	0	0	0	1
128	0	0	0	1
129	0	0	0	1
130	0	1	0	1
131	0	1	0	1
132	0	0	0	0
133	0	0	0	1
134	0	0	0	1
135	0	0	0	1
136	0	0	0	1
137	0	0	0	1
138	0	0	0	1
139	0	1	0	1
140	0	0	0	2
141	0	0	0	0
142	0	0	0	1
143	0	0	0	1
144	0	0	0	1
145	0	1	0	1
146	0	0	0	0
147	0	0	0	0
148	0	0	0	1
	Negative	Negative	Negative	None
	0=Negative	0=Negative	0=Negative	0=None
	1=Positive	1=Positive	1=Positive	1=Aspirin
				2=Warfarin
				3=Aspirin + Warfarin
				4=Non-steroidals
				5=Persantin
				6=Heparin

APPENDIX A CLINICAL AND LABORATORY DATA

NUMBER	OTHER DRUGS	Hb	WCC	PLT	ESR	RECREAT DRUGS	URIC ACID
1	1	16.6	9.2	227	23	0	0.58
2	1,5	12.7	4.9	200	2	0	0.24
3	1,4	13.9	7.7	321	9	0	0.42
4	1	16.8	5.6	138	0	0	0.37
5	1,2,3	13.4	5.18	163	12	0	0.5
6	1	14.7	6.28	293	8	0	0.34
7	1	11.4	5.1	164	8	0	0.26
8	1,4	14.1	8.65	344	7.5	0	0.31
9	1,3	16.6	8.5	265	10	0	0.63
10	0	12.4	10.1	202	8	0	0.48
11	1,2	13.7	10	411	9.1	0	0.43
12	1,5 (steroids)	14.1	5.39	192	3	0	0.48
13	4,5	14.9	4.8	231	0	0	0.3
14	1	14.8	5.4	193	1	0	0.54
15	1,3	14.1	6.6	284	19	0	0.66
16	1,5	16.8	9.86	157	5	0	0.61
17	0	14.9	5.2	190	8	0	0.3
18	1	14.6	6.5	202	8	0	0.31
19	2	14	6	200	8	0	0.35
20	0	12.3	8.2	171	7	0	0.31
21	1,5	14.2	7.31	390	7	0	0.3
22	1,2	14.4	8.8	290	10	0	0.38
23	1,5	16	8.7	231	1	0	0.41
24	1,5	13.3	7.6	234	21	0	0.41
25	1,5	14.1	10.6	330	1	0	0.24
26	1,2,4	14.8	10.1	141	1	0	0.49
27	2	14.6	7.5	207	8	0	0.45
28	2	13.3	7.6	251	15	0	0.3
29	1	11.8	5.95	435	33	0	0.32
30	1	16.5	9.8	265	7	0	0.41
31	5	12.8	7.3	393	3	0	0.35
32	1,2	12.4	10	295	15	0	0.3
33	5	13.7	5.4	276	8	0	0.3
34	1,2,5	15.1	9.3	282	8	0	0.25
35	1,2	14.4	10.8	224	8	0	0.55
36	1,2	11.8	6.3	418	8	0	0.3
37	2,3,5	16.9	7.9	212	2	0	0.51
38	1,5	14.1	9	258	18	0	0.13
38	1	13.4	7.6	308	8	0	0.32
40	[illegible]	14.6	8.4	187	8	0	0.51
41	1,5	16.6	9.9	229	6	0	0.3
42	1,5	14.6	6.82	218	8	0	0.29
43	1,2	15.8	9.6	210	7	0	0.43
44	1,4,5	13.4	4.3	271	10	0	0.26
45	1,5	14.9	4.8	200	20	0	0.68
46	1,5	15.7	4.92	262	12	0	0.41
47	1,2	15	9.7	220	12	0	0.52
48	1,3,5	14.5	10.5	208	8	0	0.43
49	1,5	14.7	7	329	2	0	0.37
50	1,5	14.6	6.93	277	4	0	0.57
51	1,2,3	16.1	9.7	366	8	0	0.34
52	0	16.4	5.7	702	0	0	0.33
53	1,5	10.9	5.1	359	10	0	0.34
54	2	13.5	6.8	273	7	0	0.27
55	1,2,3	13.9	5.3	208	0	0	0.59

APPENDIX A CLINICAL AND LABORATORY DATA

NUMBER	OTHER DRUGS	Hb	WCC	PLT	ESR	RECREAT DRUGS	URIC ACID
56	5 (steroids)	15.6	9.8	184	2	0	0.3
57	1	12.4	4.6	312	11	0	0.42
58	1,4	14.5	4.3	267	8	0	0.28
59	3	14.8	7	204	7	0	0.86
60	5	13.1	2.8	213	6	0	0.3
61	1	12.7	7.7	279	16	0	0.41
62	1,3	15.3	6.2	153	2	0	0.37
63	1	15	5.4	197	8	0	0.3
64	1	14.9	6.5	141	8	0	0.46
65	1,3	12.6	7.2	218	8	0	0.41
66	1,4	12.8	5.3	323	29	0	0.41
67	0	14.4	7.2	250	1	0	0.38
68	1	13.7	8.1	250	1	0	0.37
69	5	14.4	7	198	4	1	0.21
70	1,2,5	16.1	7.7	259	7	0	0.4
71	4,5	13.3	6.3	250	24	0	0.3
72	5	12.8	6.74	302	4	0	0.26
73	1,5 (steroids)	13.3	4.61	277	32	0	0.29
74	1	14.4	7.9	245	3	0	0.3
75	1,2,5	15.8	7.7	131	1	0	0.45
76	0	14.1	7	265	9	0	0.32
77	1	13.3	6.2	198	16	0	0.35
78	1	14.5	8.58	295	10	0	0.58
79	2,5	16.2	6.25	198	0	1	0.21
81	4	15.1	6.9	220	44	0	0.32
81	1	14.8	5.4	251	8	0	0.3
82	0	14.7	7.9	169	5	0	0.3
83	0	12.7	8.7	321	10	0	0.33
84	0	12.6	8.4	217	7	0	0.22
85	5	15.6	5.7	200	8	0	0.24
86	1,3	11.5	6.9	349	15	0	0.37
87	0	14.7	5.9	242	12	0	0.28
88	4,5	14.3	6.39	256	0	0	0.28
89	1,3	14.2	6.5	246	1	0	0.27
90	1,3,4	15.3	7.6	241	1	0	0.29
91	1	16.4	7.2	194	0	0	0.45
92	4,5	13.3	5.1	268	87	0	0.27
93	1,5 (steroids)	13.8	3.66	228	10	0	0.22
94	5	14.2	10.3	289	2	0	0.37
95	0	13.1	6.3	116	16	0	0.3
96	1,4,5	12.6	6.39	308	5	0	0.3
97	5	13.5	16.7	280	3	1	0.54
98	1	15.7	8.8	213	1	0	0.43
99	1	15.4	6.7	286	8	0	0.39
100	1,4	14.3	10.72	191	2	0	0.19
101	5	14.3	3.7	219	4	0	0.17
102	5	16.7	6.5	177	1	0	0.3
103	5	12.7	14.7	340	77	0	0.37
104	1,5	13.7	4.4	168	13	0	0.54
105	1,5	9.6	4.4	395	19	0	0.31
106	5	14.3	8.2	257	45	0	0.36
107	1	16.3	4.91	265	8	0	0.3
108	4	13.1	6.2	379	31	0	0.12
109	4	11.4	7.8	169	46	0	0.18
110	1	11.7	3.87	175	15	0	0.3

APPENDIX A CLINICAL AND LABORATORY DATA

NUMBER	OTHER DRUGS	Hb	WCC	PLT	ESR	RECREAT DRUGS	URIC ACID
111	1	10	6.5	273	8	0	0.49
112	0	15.8	7.32	180	5	0	0.3
113	1	13.2	8.4	254	1	0	0.42
114	0	15	8.2	219	0	0	0.36
115	5	9.5	12.2	398	45	0	0.28
116	5	12.3	7.2	231	8	0	0.13
117	1,4	11.6	7.2	277	23	0	0.46
118	4,5	12.8	9.6	270	14	0	0.3
119	2,4	13.3	14.7	387	10	0	0.44
120	1,2	13	7.3	397	16	0	0.38
121	1,2,3	14.9	6.9	238	8	0	0.56
122	1,2	16	8.3	277	9.1	0	0.3
123	0	15	7.2	200	2	0	0.26
124	0	15	8.2	274	5	0	0.32
125	5	13	7.2	230	4	0	0.3
126	1,5	13.3	8.2	233	16	0	0.29
127	5	16	6.1	250	3	0	0.23
128	0	14.1	6.28	313	1	0	0.21
129	0	16.3	5.71	428	2	0	0.45
130	1,3,4	14	7	250	7	0	0.3
131	5	14	7	250	8	0	0.3
132	0	14.4	4.1	225	1	0	0.22
133	1,4	14	3.63	272	8.6	0	0.3
134	5	13.5	6.69	259	8	0	0.34
135	0	15.2	7.3	216	7	1	0.3
136	4,5	14	7	280	8	0	0.3
137	0	10	12.2	1256	55	0	0.3
138	1	13.8	5.9	285	2	0	0.2
139	1,2	15.2	8.1	255	4	0	0.3
140	0	12.3	4.4	356	100	0	0.3
141	0	14.9	6.09	214	6	0	0.26
142	0	10.9	8.2	330	6	0	0.28
143	0	11.3	8	236	9	0	0.38
144	5	12.2	5.6	260	14	0	0.34
145	4	10.7	7.6	297	5	0	0.23
146	4	13.7	8.2	259	6	0	0.3
147	5	13.7	5.4	235	5	0	0.24
148	1	14.6	9.8	236	8	0	0.3
	None	Female=12-16	4.0-11	140-400	0-20	Negative	F=0.1-0.39
		Male=14-18					M=0.2-0.48
		g/dl	x10*9/l	x10*9/l	mm/hr		mmol/l
	0=None					0=Negative	
	1=Antihypertensives					1=Positive	
	2=Anticholesterols						
	3=Antigout						
	4=Anticonvulsants						
	5=Others						

APPENDIX A CLINICAL AND LABORATORY DATA

NUMBER	GLUCOSE	PI	INR	PTT	D-DIMERS	PROTEIN C	PROTEIN S
1	5.1	7.95	0.82	29.2	< 250	121	92
2	4.5	10	1.01	30.9	< 250	91	118
3	5.1	8.4	0.87	28.9	< 250	122	134
4	4.6	19	1.81	43.2	< 250	46	101
5	4.4	8.55	0.88	30.2	> 2000 < 4000	98	127
6	4.8	7.95	0.83	32.9	> 500 < 1000	128	116
7	5.3	28.9	2.47	31.4	> 500 < 1000	42	79
8	4	7.5	0.81	23.2	< 250	106	143
9	4.3	8.1	0.87	26.4	< 250	100	79
10	5.2	7.2	0.78	29.2	< 250	145	158
11	4.2	8.1	0.84	30.9	< 250	128	107
12	4.7	7.8	0.84	25.2	< 250	128	139
13	4.1	9.6	0.98	32.4	< 250	106	144
14	5	8.4	0.89	29.2	> 250 < 500	128	132
15	4.7	8.1	0.87	33.4	> 250 < 500	113	127
16	5.7	24.6	2.21	40.2	> 250 < 500	51	85
17	5.8	8.55	0.91	30.4	> 250 < 500	65	124
18	11.7	8.25	0.87	27.4	< 250	85	117
19	4.8	22.5	2.11	47	< 250	45	65
20	4.2	10.9	1.07	39.9	> 500 < 1000	70	101
21	5	7.95	0.85	27.9	> 2000 < 4000	114	136
22	5.2	8.25	0.88	28.9	> 250 < 500	95	141
23	6.2	26.4	2.35	39.2	< 250	42	119
24	5.2	7.8	0.84	27.4	< 250	123	132
25	5	7.05	0.75	23.4	< 250	148	119
26	4.7	9.15	0.94	28.4	< 250	95	128
27	4.9	7.95	0.83	26.9	< 250	118	184
28	5.3	7.35	0.77	28.4	< 250	143	129
29	4.9	7.5	0.79	33.4	< 250	142	154
30	6	7.95	0.85	30.4	< 250	96	133
31	5.4	8.4	0.89	34.2	> 250 < 500	72	135
32	5.3	7.65	0.82	30.2	< 250	106	126
33	5	7.05	0.77	30.4	< 250	108	147
34	4.2	27.6	2.44	40.7	< 250	43	89
35	13.8	7.35	0.77	25.7	< 250	139	172
36	4.3	8.7	0.92	24.2	< 250	145	160
37	5.1	8.7	0.92	24.2	< 250	110	125
38	4.8	7.65	0.82	28.4	> 250 < 500	120	152
38	9.3	7.65	0.82	24.2	< 250	104	139
40	5.4	7.95	0.85	27.9	> 250 < 500	71	111
41	5	7.65	0.82	28.4	> 250 < 500	97	167
42	5	7.8	0.84	29.7	< 250	96	164
43	4.1	8.55	0.88	24.2	> 1000 < 2000	111	144
44	4.6	8.46	0.87	33.4	> 250 < 500	103	73
45	4.4	7.95	0.83	31.4	> 250 < 500	144	132
46	15.7	8.1	0.83	24.9	> 500 < 1000	81	124
47	5	8.25	0.84	28.2	< 250	96	130
48	7.5	8.22	6.06	65.2	> 4000 < 8000	19	47
49	5.3	25.2	2.3	37.4	< 250	58	60
50	5.5	7.35	0.77	26.9	< 250	152	125
51	5.4	7.2	0.75	32.7	> 1000 < 2000	108	167
52	4.6	8.4	0.85	35.4	< 250	82	159
53	8.4	7.8	0.8	30.7	< 250	88	107
54	3.9	25.9	2.25	36.4	< 250	34	60
55	4.2	14.8	1.78	42.9	< 250	35	88

APPENDIX A CLINICAL AND LABORATORY DATA

NUMBER	GLUCOSE	PI	INR	PTT	D-DIMERS	PROTEIN C	PROTEIN S
56	7	8.4	0.85	27.2	> 250 < 500	122	128
57	4	8.25	0.84	32.9	> 8000 < 16000	83	112
58	4	8.25	0.89	26.9	< 250	120	92
59	5.6	7.95	0.81	27.4	> 500 < 1000	93	131
60	4	7.8	0.8	33.4	> 1000 < 2000	107	79
61	5.2	7.8	0.79	28.9	> 250 < 500	136	156
62	4.6	8.85	0.89	30.9	< 250	81	95
63	5.6	5.4		51.7	< 250	19	54
64	4	7.8	0.8	33.9	< 250	116	110
65	4.1	7.65	0.79	26.4	> 250 < 500	109	166
66	7.1	8.4	0.85	30.7	> 500< 1000	102	154
67	5.1	9	0.88	32.4	> 250 < 500	97	94
68	5.3	14.6	1.06	27.5	> 500 < 1000	53	116
69	5	7.05	0.73	26.2	> 1000 < 2000	140	136
70	6.1	8.1	0.83	29.4	> 500 < 1000	108	120
71	5	8.1	0.86	39.9	< 250	NR	NR
72	4.7	7.95	0.81	28.2	< 250	197	104
73	6.4	7.2	0.79	29.5	< 250	190	97
74	5.1	8.25	0.81	26.7	> 250 < 500	96	102
75	5	20.8	1.88	32.9	< 250	40	92
76	4.2	9	0.72	30.1	> 250 < 500	95	109
77	5.3	8.1	0.8	26.7	> 250 < 500	114	132
78	5.2	10.9	1.06	10.2	> 500 < 1000	163	88
79	14.9	15.8	1.5	34.4	< 250	56	87
81	9	9.45	0.96	32.2	> 500 < 1000	116	108
81	4	28.2	2.49	38.4	< 250	41	76
82	5.5	9.45	0.97	31.9	< 250	126	129
83	5.4	19.6	1.86	42.7	< 250	49	89
84	3.8	8.8	0.88	29.9	< 250	59	101
85	3.8	8.85	0.94	34.4	< 250	64	145
86	5.7	7.95	0.83	34.7	< 250	110	130
87	4.2	8.25	0.85	31.9	< 250	88	92
88	4.3	7.8	0.81	31.4	< 250	103	141
89	4.3	8.25	0.88	28.2	< 250	91	110
90	4.2	8.25	0.88	25.7	< 250	82	126
91	5.3	16.5	1.61	40.4	< 250	27	87
92	4	8.7	0.92	28.2	> 250 < 500	78	77
93	4.7	10.1	0.8	36.3	< 250	48	103
94	4	9.9	0.84	30.5	< 250	122	113
95	4	9.8	0.84	29.4	< 250	83	100
96	4	9.8	0.84	29.7	> 250 < 500	80	97
97	3.5	9	0.95	26.9	> 250 < 500	87	123
98	4	7.5	0.77	30.7	< 250	88	127
99	6.9	9	0.92	36.7	< 250	73	116
100	5.2	7.95	0.83	31.4	< 250	113	110
101	4	7.8	0.8	28.9	< 250	80	94
102	6.9	8.1	0.83	27.4	< 250	91	118
103	7.8	7.5	0.77	26.4	< 4000 < 8000	89	138
104	7.6	10.3	1.02	42.4	> 250 < 500	41	104
105	4.3	7.65	0.79	26.2	< 250	71	85
106	5.6	9.9	0.86	23.6	> 4000 < 8000	114	125
107	5	13.5	1.28	36.2	< 250	32	42
108	6.1	7.35	0.76	19.4	< 250	123	100
109	4.1	7.35	0.76	28.7	> 500 < 1000	73	70
110	4	9.75	0.95	37.2	< 250	48	94

APPENDIX A CLINICAL AND LABORATORY DATA

NUMBER	GLUCOSE	PI	INR	PTT	D-DIMERS	PROTEIN C	PROTEIN S
111	5.4	8.25	0.81	35.4	> 250 < 500	94	118
112	4	8.4	0.83	38.4	< 250	90	145
113	4	7.65	0.76	25.4	< 250	142	84
114	4	7.95	0.81	29.4	< 250	88	134
115	4.4	7.8	0.81	25.2	< 250	81	117
116	4	8.9	0.85	28.9	< 250	64	88
117	4.9	8.7	0.88	27.4	< 250	62	93
118	3.9	28.3	2.5	41.2	> 1000 < 2000	43	44
119	4.8	8.25	0.88	26.2	< 250	122	154
120	4.5	7.65	0.8	30.4	> 250 < 500	175	125
121	5.1	7.95	0.83	33.4	< 250	124	129
122	4.6	7.5	0.79	27.9	< 250	156	151
123	4.6	11.9	1.02	36.7	< 250	93	42
124	5.1	8.1	0.85	32.8	< 250	125	108
125	5	9.9	1.08	39.4	> 250 < 500	71	68
126	5.3	8.55	0.87	29.4	< 250	148	57
127	4.6	9.1	0.9	32.2	> 32000 < 64000	106	90
128	4.4	14.6	1.12	32.4	< 250	67	85
129	4.3	8.55	0.91	25.7	< 250	74	142
130	5	7.8	0.83	23.4	> 500 < 1000	161	81
131	5	7.05	0.76	34.4	< 250	148	103
132	4.5	9	0.96	34.7	< 250	121	84
133	5.3	13.4	1	23.6	> 250 < 500	88	97
134	5.2	7.35	0.75	28.7	< 250	127	121
135	4.9	9.45	0.98	32.5	< 250	113	112
136	3.6	16.7	1.27	42.5	> 250 < 500	58	73
137	5.1	9.3	0.94	35.7	> 500 < 1000	63	66
138	3.8	8.25	0.87	35.7	< 250	89	132
139	5.5	7.35	0.75	25.9	< 250	144	113
140	5	15.2	1.14	27.8	> 1000 < 2000	71	131
141	5.8	7.8	0.77	30.4	< 250	112	130
142	4	8.25	0.81	24.[illegible]	>250 < 500	46	111
143	5.7	9.5	0.85	31.4	< 250	94	73
144	4.4	7.2	0.76	33.9	< 250	164	97
145	3.9	8.25	0.81	25.9	< 250	98	132
146	3.1	8.4	0.83	32.4	< 250	90	86
147	5.3	9.6	0.93	36.5	< 250	60	83
148	5	7.95	0.81	30.7	> 250 < 500	91	119
	3.3-6.2	variable	<1.25	22.6-43.6	< 250	70 - 160 %	60 - 140 %
	mmol/l	secs	ratio	secs	ng/ml	%	%
						NR=No record	NR=No record

APPENDIX A CLINICAL AND LABORATORY DATA

NUMBER	GLUCOSE	PI	INR	PTT	D-DIMERS	PROTEIN C	PROTEIN S
111	5.4	8.25	0.81	35.4	> 250 < 500	94	118
112	4	8.4	0.83	38.4	< 250	90	145
113	4	7.65	0.76	25.4	< 250	142	84
114	4	7.95	0.81	29.4	< 250	88	134
115	4.4	7.8	0.81	25.2	< 250	81	117
116	4	8.9	0.85	28.9	< 250	64	88
117	4.9	8.7	0.88	27.4	< 250	62	93
118	3.9	[illegible]	2.5	41.2	> 1000 < 2000	43	44
119	4.8	8.25	0.88	26.2	< 250	122	154
120	4.5	7.65	0.8	30.4	> 250 < 500	175	125
121	5.1	7.95	0.83	33.4	< 250	124	129
122	4.6	7.5	0.79	27.9	< 250	156	151
123	4.6	11.9	1.02	36.7	< 250	93	42
124	5.1	8.1	0.85	32.8	< 250	125	108
125	5	9.9	1.08	39.4	> 250 < 500	71	68
126	5.3	8.55	0.87	29.4	< 250	148	57
127	4.6	9.1	0.9	32.2	> 32000 < 64000	106	90
128	4.4	14.6	1.12	32.4	< 250	67	85
129	4.3	8.55	0.91	25.7	< 250	74	142
130	5	7.8	0.83	23.4	> 500 < 1000	161	81
131	5	7.05	0.76	34.4	< 250	148	103
132	4.5	9	0.96	34.7	< 250	121	84
133	5.3	13.4	1	23.6	> 250 < 500	88	97
134	5.2	7.35	0.75	28.7	< 250	127	121
135	4.9	9.45	0.98	32.5	< 250	113	112
136	3.6	16.7	1.27	42.5	> 250 < 500	58	73
137	5.1	9.3	0.94	35.7	> 500 < 1000	63	66
138	3.8	8.25	0.87	35.7	< 250	89	132
139	5.5	7.35	0.75	25.9	< 250	144	113
140	5	15.2	1.14	27.8	> 1000 < 2000	71	131
141	5.8	7.8	0.77	30.4	< 250	112	130
142	4	8.25	0.81	24.7	>250 < 500	46	111
143	5.7	9.5	0.85	31.4	< 250	94	73
144	4.4	7.2	0.76	33.9	< 250	164	97
145	3.9	8.25	0.81	25.9	< 250	98	132
146	3.1	8.4	0.83	32.4	< 250	90	86
147	5.3	9.6	0.93	36.5	< 250	60	83
148	5	7.95	0.81	30.7	> 250 < 500	91	119
	3.3-6.2	variable	<1.25	22.6-43.6	< 250	70 - 160 %	60 - 140 %
	mmol/l	secs	ratio	secs	ng/ml	%	%
						NR=No record	NR=No record

APPENDIX A CLINICAL AND LABORATORY DATA

NUMBER	ANTITHROMBIN	APCR	LUPUS ANTICOAGULANT	FIBRINOGEN	THROMBIN TIME
1	122	2.31	0	5.5	1.1
2	92	2.3	0	4.6	1
3	117	2.79	0	4.35	1.09
4	101	NR	0	5.2	0.94
5	72	2.04	0	3.82	0.96
6	119	2.84	0	4.26	0.86
7	126	NR	0	5.3	1.14
8	112	1.93	0	2.62	1.15
9	102	2.19	0	4.34	1
10	121	2.4	0	2.69	1
11	127	2.7	0	3.68	1.03
12	108	1.71	0	2.99	1
13	104	2.43	0	2.14	1.14
14	98	2.82	0	6.4	0.9
15	105	1.6	0	6.7	0.94
16	81	4.1	0	5.3	1.11
17	82	2	0	4.1	0.93
18	125	2.32	0	3	1
19	125	NR	0	9.5	0.91
20	124	1.51	0	3.19	1.02
21	133	2.1	0	5.4	1.04
22	115	2.91	0	4.15	0.98
23	140	NR	0	12.8	0.98
24	119	2	BORDERLINE	2.7	1.07
25	121	NR	0	3.47	0.98
26	137	2.72	0	3.06	1.15
27	127	2.81	0	4.16	0.96
28	116	1.72	0	5.27	0.97
29	126	1.91	0	5.99	1.11
30	113	2.1	0	4.02	1.12
31	94	1.47	0	2.11	1.07
32	109	1.83	0	3.54	1.07
33	109	2.85	0	3.97	1.01
34	97	NR	0	8.26	1.1
35	120	2.03	0	4.2	0.96
36	99	1.8	0	3.02	1.12
37	90	2.25	0	1.47	1.17
38	110	2.34	0	3.7	1.03
38	117	2.83	0	3.57	1.09
40	106	2.03	0	5.57	1
41	121	1.58	0	7.26	0.98
42	121	2.07	0	3.9	1.1
43	112	2.42	0	5.09	0.88
44	120	2.01	0	3.61	0.98
45	100	2.46	0	3.99	0.9
46	111	2.25	0	5.56	1.17
47	113	3.11	0	5.4	1.2
48	112	NR	0	5.4	1.18
49	114	3	0	6.9	1.2
50	130	1.55	0	2.67	0.9
51	118	3.15	0	4.92	1.12
52	120	2.67	0	3.03	1.24
53	138	1.68	0	3.53	1.21
54	112	NR	0	10.42	0.97
55	112	NR	0	6.93	1.11

APPENDIX A CLINICAL AND LABORATORY DATA

NUMBER	ANTITHROMBIN	APCR	LUPUS ANTICOAGULANT	FIBRINOGEN	THROMBIN TIME
56	140	2.3	0	5	1.02
57	90	3	0	3.5	0.97
58	131	2.4	0	2.46	1.01
59	103	1.66	0	3.18	1.08
60	121	2.95	0	3.07	1.05
61	139	3.09	0	4.06	1.06
62	106	3.07	0	4.36	1
63	104	4.9	0	9.58	1
64	124	2.94	0	3.19	1.14
65	131	1.78	0	5.95	0.87
66	127	3.09	0	7.16	0.95
67	122	3.6	0	2.55	1.12
68	101	2.6	0	3.56	1
69	132	3.2	0	3.3	0.98
70	115	3.61	0	3.2	1.2
71	NR	NR	0	3.4	1
72	105	3.49	0	2.05	0.91
73	138	2.43	0	3.99	1
74	130	3.11	0	3.67	1.04
75	121	5.6	0	4.85	1.02
76	91	2.58	0	3.18	0.96
77	126	3.52	0	2.71	1.05
78	136	3.65	0	5.82	1.07
79	105	3.26	0	4.95	1
81	118	2.1	0	3.7	0.9
81	124	3.58	0	8.29	1.02
82	119	2.6	0	3.9	0.9
83	112	2.39	0	3.83	0.98
84	105	3	0	3.44	1.13
85	119	3	0	3	1.07
86	103	2.41	0	5.6	1
87	112	2.2	0	3.5	0.92
88	138	3	0	3.6	1
89	111	2.76	0	3.35	1.1
90	131	2	0	2.35	1.02
91	110	1.53	0	3.47	1.06
92	130	1.71	0	4.5	1.23
93	108	2.64	0	4.62	0.92
94	104	2.34	0	2.84	0.99
95	127	2.49	0	3.49	0.99
96	114	2.41	0	3.03	1
97	104	2.51	0	3.03	1.01
98	102	3.09	0	3.86	1.09
99	100	3.24	0	5.29	0.95
100	119	1.94	0	4.65	0.94
101	118	2.8	0	2.43	1.13
102	108	3.54	0	4.27	1.15
103	76	1.95	0	14.48	0.97
104	94	NR	0	3.69	> 4.78
105	122	1.34	0	2.28	1.08
106	108	1.72	0	5.82	1.01
107	100	4.09	0	6.08	0.94
108	93	1.7	0	5.39	0.98
109	105	1.77	0	6.28	0.9
110	97	2.47	0	2.56	1.06

APPENDIX A CLINICAL AND LABORATORY DATA

NUMBER	ANTITHROMBIN	APCR	LUPUS ANTICOAGULANT	FIBRINOGEN	THROMBIN TIME
111	133	4.1	0	5.6	1
112	133	3.55	0	3.58	0.99
113	123	2.86	0	2.94	1.07
114	118	3.32	0	5.62	0.98
115	94	2	0	4.1	0.95
116	104	1.41	0	2.57	0.99
117	88	2.97	0	4.87	1.21
118	115	3.98	0	6.01	0.94
119	111	2.93	0	2.78	1.04
120	111	2.14	0	5.83	1.06
121	96	2.15	0	4.42	0.86
122	132	2.2	0	4.11	0.89
123	103	2.31	0	3.28	1.02
124	120	2.5	0	2.9	1.13
125	116	1.99	0	3.88	1.09
126	100	2.01	0	5.2	1.16
127	116	2.1	0	3.13	1.03
128	95	3.3	0	2	0.92
129	112	4.12	0	2.57	1.02
130	113	1.67	0	2.94	1.13
131	115	2.06	0	7.05	0.94
132	129	2	0	4.63	1.1
133	94	2.41	0	3.3	1.1
134	108	3.9	0	3.7	0.95
135	100	2.59	0	2.35	0.88
136	96	2.54	0	1.71	1.18
137	128	2.16	0	3.31	1.04
138	111	2.4	0	3.51	1
139	108	4.23	0	4.2	1.05
140	134	2.77	0	7.22	1.14
141	132	3.18	0	4.77	0.93
142	117	2.78	0	2.19	0.86
143	103	1.6	0	2.5	1
144	124	2.6	0	4.33	1.06
145	142	2.2	0	3.7	0.89
146	128	3.3	0	3.2	0.97
147	141	3.1	0	3.09	0.93
148	126	2.42	0	3.13	0.93
	87 - 125 %	2.0-5.0	Negative	2 - 4	0.90-1.3
	%	ratio		g/l	ratio
	NR=No record	NR=No record	0=Negative		
			1=Positive		

APPENDIX A CLINICAL AND LABORATORY DATA

NUMBER	APCR PCR	HIV	CHOLESTEROL	WR	FT4	ANTINUCLEAR FACTOR
1	0	0	5.1	0	16.6	0
2	0	99	5.6	1	13.9	0
3	0	99	6.5	0	15.6	0
4	0	99	4.6	0	12.7	1
5	0	99	7.7	0	16	1
6	0	99	4.8	0	16	0
7	0	99	6.8	0	14.8	0
8	0	99	6.6	0	13.3	0
9	0	99	5.2	0	16.7	0
10	0	99	4.8	0	15.5	0
11	0	99	5.3	0	20.3	0
12	0	99	6.5	0	12.1	0
13	0	99	4	0	16	0
14	0	99	7.5	0	14.1	0
15	Heterozygote	99	5.3	0	20.7	0
16	0	99	5.2	0	15.3	0
17	0	99	4.2	0	16	1
18	0	99	5.7	0	16	0
19	0	99	6.3	0	16	0
20	0	0	10.6	0	16	0
21	0	99	5.8	0	15.1	0
22	0	99	9	0	14.4	0
23	0	99	8.3	0	19	0
24	0	99	9	0	22.7	1
25	0	99	7	0	16	0
26	0	99	9	0	14.2	0
27	0	99	5.7	0	19.7	0
28	0	99	6.8	0	16	0
29	0	99	5.4	0	12	1
30	0	99	7.7	0	20.2	0
31	0	99	5.5	0	12.9	0
32	0	99	5.3	0	11.8	0
33	0	99	4	0	15.4	0
34	0	99	3.6	0	15.5	0
35	0	99	6.6	0	18.3	0
36	0	99	7.5	0	18	0
37	0	99	7.9	0	16	ANCA
38	0	99	6.9	0	20.3	1
38	0	0	6	0	16	0
40	0	99	7.5	0	25.6	0
41	0	99	8.4	0	18	0
42	0	0	6.9	0	16	Anti-parietal antibody
43	0	99	5.1	0	13.8	1
44	0	99	5.3	0	16.3	1
45	0	99	6.3	0	16.6	1
46	0	0	5.2	0	16.2	0
47	0	99	6	0	16	1
48	0	99	5.8	0	7.7	0
49	0	99	5.6	1	12.8	0
50	0	99	7.5	0	9.9	0
51	0	99	7.2	0	16	0
52	0	0	3.91	0	16	0
53	0	0	5.5	0	16	0
54	0	99	6.8	0	18.6	0
55	0	99	7.44	1	17.4	0

APPENDIX A CLINICAL AND LABORATORY DATA

NUMBER	APCR PCR	HIV	CHOLESTEROL	WR	FT4	ANTINUCLEAR FACTOR
56	0	0	4	0	16	1
57	0	0	4	0	16	0
58	0	99	5.7	0	13.9	0
59	0	99	6.1	0	14.1	0
60	0	0	4	0	16	Anti-RNP; Anti-Sm antibodies
61	0	99	6	0	16.6	0
62	0	99	7	0	22.9	0
63	0	99	6.8	0	16	0
64	0	99	6.2	0	12.8	1
65	0	99	5.5	0	16.5	1
66	0	99	6.6	0	16	0
67	0	99	5.4	0	13.9	0
68	0	99	4.6	0	14	0
69	0	99	6.5	0	15	1
70	0	0	6.5	0	21.1	0
71	0	99	7.7	1	13.4	0
72	0	99	5.4	0	18.9	0
73	0	0	4.7	0	13.1	1
74	0	99	5.6	0	14.6	1
75	0	99	4.2	0	15.8	0
76	0	99	5.9	1	17.5	1
77	0	99	9.3	0	15.6	0
78	0	99	3.3	0	15.6	0
79	0	99	5.9	0	13.7	0
81	0	99	4	0	22.08	0
81	0	0	3.88	0	21.8	0
82	0	0	4	0	16	0
83	0	99	5.7	0	14.9	0
84	0	99	3.4	0	16	1
85	0	0	4.5	0	12.7	0
86	0	0	7.1	0	14.6	0
87	0	99	4.2	1	15.2	0
88	0	99	4.4	0	17.2	1
89	0	99	8.8	0	16	1
90	0	99	5.8	0	24.4	0
91	Heterozygote	0	2.9	0	13.6	0
92	0	0	4.8	0	16	1
93	0	99	3.1	0	16	1
94	0	99	2.7	0	14.2	1
95	0	99	5.9	0	19.6	0
96	0	99	4.7	0	16.7	0
97	0	0	4.26	0	16	0
98	0	99	4.4	0	16	1
99	0	0	5.2	1	17	0
100	0	99	6	0	16	1
101	0	0	4.2	0	18.2	0
102	0	0	6.8	0	16	0
103	0	0	4.5	0	16	0
104	0	0	4.7	0	16	0
105	0	99	3.9	1	12.8	0
106	0	0	4	0	16	0
107	0	0	3.66	1	16	0
108	0	0	4	0	16	0
109	0	0	6.8	0	16	0
110	0	99	3.33	0	12.7	0

APPENDIX A CLINICAL AND LABORATORY DATA

NUMBER	APCR PCR	HIV	CHOLESTEROL	WR	FT4	ANTINUCLEAR FACTOR
111	0	99	4.5	0	12.3	0
112	0	99	4.7	0	20.1	0
113	0	99	5.7	0	12.5	AntiDNAse B
114	0	99	5.3	0	16.6	0
115	0	99	4.8	0	[illegible]	0
116	0	0	5.4	0	12.4	0
117	0	0	4.3	1	10.4	0
118	0	99	5.6	0	14.8	1
119	0	99	6.3	0	15	0
120	0	99	7	0	12.6	0
121	0	99	7.3	0	14.9	0
122	0	99	6.3	0	17.8	0
123	0	99	4.7	0	12	0
124	0	99	4.9	0	12.1	0
125	0	99	4.88	0	16	Rheumatoid factor
126	0	99	6.6	0	15	Anti-La antibody
127	0	99	4	0	17.4	0
128	0	0	5.5	0	11.7	c-ANCA
129	0	0	4.3	0	16.8	0
130	0	99	8.2	0	14	1
131	0	99	4	0	15	0
132	0	0	5.5	0	16.4	0
133	0	0	4.2	0	23	0
134	0	99	7	0	10.3	0
135	0	99	4	0	14	0
136	0	0	4	0	13	0
137	0	0	2.9	0	15	0
138	0	99	5.1	0	16.6	0
139	0	0	8.1	0	15.8	0
140	0	99	4	0	14	1
141	0	0	5	0	17.5	0
142	0	0	2.8	0	11.9	1
143	0	0	3.8	0	13.5	0
144	0	0	6	0	13.6	1
145	0	0	6.7	0	12.8	0
146	0	0	5.2	0	16	0
147	0	99	2.9	0	16.9	0
148	0	99	4.9	0	16	0
	Negative	Negative	< 5.2	Neg	11.5-23	Negative
			mmol/l		pmol/l	
	0=Negative	0=Negative		0=Neg		0=Negative
		1=Positive		1=Pos		1=Positive
		99=Not done				RNP=Ribonucleoprotein antibody
						Sm=Sm antibody
						Anti-La=La antibody
						ANCA=Neutrophil cytoplasmic ab
						Anti DNAse B=AntiDNAse B ab

APPENDIX A CLINICAL AND LABORATORY DATA

NUMBER	ACLA	OTHERS	ECHOCARDIOGRAM
1	0		N
2	0		N
3	0		N
4	0		N
5	0		AR
6	G		Mixed aortic valve disease
7	0		Mild AS
8	99		N
9	0		N
10	99		N
11	0		N
12	99	HLA (Human leucocyte antigen) B 27	N
13	G;M		N
14	0		N
15	99		N
16	99		MR
17	99		N
18	0		N
19	0		Atrial septal defect
20	99		N
21	99		N
22	G;M		N
23	0		Prosthetic MV and AV
24	0		N
25	0		N
26	0		N
27	0		N
28	0		N
29	0		N
30	0		N
31	0		N
32	0		N
33	0		N
34	M		Mitral valve prolapse
35	0		N
36	99		N
37	0		N
38	G		N
38	0		N
40	M		Mitral valve prolapse
41	0		N
42	0		N
43	99		N
44	99		N
45	0		N
46	99		N
47	G		N
48	0		Hypertensive heart disease
49	99		N
50	M		N
51	0		N
52	99		N
53	0	Parkinson's disease	N
54	0		Mild MS; AS
55	0		Dilated LV; EF = 35 %

NUMBER	ACLA	OTHERS	ECHOCARDIOGRAM
56	0	Thyroglobulin antibody	N
57	0		N
58	0	Lactate;pyruvate	Mitral valve prolapse
59	G		N
60	0	Pyruvate	N
61	0		N
62	0		N
63	0		MS/MR; AS/AR
64	M		N
65	0		Mild MR; EF = 45 %
66	0		N
67	99		N
68	99		N
69	0	Cocaine	N
70	99		Left ventricular hypertrophy
71	99	Low factor 12	N
72	0	Previous thyroid cancer	N
73	0	Migraine; steroids	N
74	0		Hypertensive heart disease
75	0		N
76	99		N
77	0		N
78	0		N
79	0		Atrial septal defect
81	M		N
81	0		N
82	0		Soft MR; mitral valve prolapse
83	0		MS/MR; AS/AR
84	0		N
85	0		N
86	0	B Thallassaemia minor	N
87	0		N
88	0		N
89	0		N
90	0		N
91	99		N
92	M		N
93	0		AR
94	G;M		N
95	0		N
96	M	Eosinophilia	N
97	0		N
98	0		Trivial AR
99	0		N
100	0		N
101	0	High ACE	N
102	0		Infarct
103	0	Tonsillitis; PID	N
104	0		AR/AS; MS
105	0		N
106	0		N
107	0		Mural thrombus
108	0		N
109	0		N
110	0		AR/AS; MR

APPENDIX A CLINICAL AND LABORATORY DATA

NUMBER	ACLA	OTHERS	ECHOCARDIOGRAM
111	G	Renal failure	Left ventricular hypertrophy
112	0		N
113	0		N
114	0		N
115	99		N
116	0		N
117	0		N
118	99		Mixed mitral valve disease
119	0		N
120	99		N
121	0		N
122	0		N
123	99	Pregnancy	Abnormal cardiac valve
124	99		N
125	G;M	Low VWB factor antigen and activity	N
126	0	Abortions X 2	N
127	99		N
128	0	Homocystinuria	N
129	99		N
130	0		N
131	99		N
132	99		N
133	0	Artrial myxoma	N
134	99	Rheumatoid arthritis	N
135	99	Ex-IVDA	Patent foramen ovale
136	0	Venous angioma	N
137	99	Homocystinuria	N
138	0	Post-partum 4 months	N
139	0		N
140	99		N
141	0		N
142	0		N
143	G;M		N
144	0		N
145	0		MR/ MS; Left atrial clot
146	0		N
147	0		N
148	99		Mild MR
	Negative		Normal
	0=Negative	ACE=Angiotensinogen converting enzyme	N=Normal
	99=Not done	PID=Pelvic inflammatory disease	MR=Mitral regurgitation
	G=Ig G pos	IVDA=Intravenous drug abuse	MS=Mitral stenosis
	M=Ig M pos	VWD=Van Willebrand's disease	AR=Aortic regurgitation
			AS=Aortic stenosis
			AVD=Aortic valve disease
			MV=Mitral valve
			AV=Aortic valve
			EF=Ejection fraction
			LV=Left ventricle

APPENDIX A CLINICAL AND LABORATORY DATA

NUMBER	ECG	STENOSIS >50%	NON INVASIVES/ DOPPLER
1	N	0	N
2	LVH	0	N
3	Sick sinus syndrome	0	N
4	N	0	N
5	LVH	2	ICA plaque
6	N	0	N
7	AF	2	L ICA < 50 % occluded
8	N	0	VBA dissection
9	N	0	N
10	N	1	R brachiocephalic trunk stenosis
11	N	2	R ICA < 50 % occluded
12	N	0	N
13	N	0	N
14	Capture beats	0	N
15	N	2	L and R ICA < 50 % occluded
16	AF	0	N
17	AF	1	R ICA occluded
18	LVH	0	N
19	Old infarct	0	N
20	N	1	R ICA 50-79 % occluded
21	LVH	2	R ICA plaque
22	LVH/ Ischaemia	1	Bilateral carotid stenosis
23	AF/ LVH	0	N
24	N	0	N
25	Right BBB	0	N
26	Old infarct	1	R ICA 50-79 %; L ICA 16-49 % occluded
27	N	1	R ICA occluded; L ICA 50-79 % occluded
28	N	0	N
29	N	0	N
30	N	0	N
31	N	0	N
32	N	0	N
33	N	0	N
34	N	0	N
35	Inferior infarct	2	L and R ICA < 50 % occluded
36	N	2	L ICA 16-49 % occluded
37	N	0	N
38	LVH	0	N
38	N	0	N
40	N	0	N
41	N	1	L ICA occluded
42	N	1	L ICA occluded; R ICA 50-74 % occluded
43	LVH	1	L ICA occluded
44	LVH	0	N
45	Atrial ectopics	0	N
46	N	0	N
47	N	0	N
48	Arrhythmia	2	L ICA < 50 % occluded
49	N	0	N
50	N	0	N
51	N	1	L ICA 99% occluded
52	N	1	L ICA 50-80 % occluded (angio 43 %)
53	N	0	N
54	N	1	L ICA occluded; R ICA 16-49 % occluded
55	AF	0	N

APPENDIX A CLINICAL AND LABORATORY DATA

NUMBER	ECG	STENOSIS >50%	NON INVASIVES/DOPPLER
56	N	0	N
57	N	0	N
58	N	0	N
59	N	0	N
60	N	0	N
61	LVH	2	R ICA 1-15 % occluded
62	N	2	L and R ICA 15-49 % occluded
63	N	0	N
64	N	0	N
65	LVH; old infarct	1	L ICA 50-79 % occluded
66	N	1	R ICA occluded; L ICA 50-79 % occluded
67	N	0	N
68	Ischaemia	1	R ICA occluded; L ICA > 50 % occluded
69	N	0	N
70	LVH	0	N
71	N	0	N
72	N	0	N
73	N	0	N
74	LVH	2	L ICA 1-15 % occluded; R ICA plaque
75	Old infarct; WPW	0	N
76	N	0	N
77	N	0	N
78	LVH	0	N
79	N	0	N
81	N	0	N
81	N	0	N
82	N	2	Low flow R ICA; diffuse MCA abnormality
83	N	0	N
84	N	0	N
85	N	0	N
86	LVH	1	L ICA 50-79 % occluded
87	N	0	N
88	N	1	L ICA occluded
89	N	0	N
90	N	1	R ICA occluded
91	N	0	N
92	N	1	R ICA occluded
93	N	1	L CCA occluded
94	N	0	N
95	N	0	N
96	N	0	N
97	N	0	N
98	N	0	N
99	LVH	0	N
100	N	0	N
101	N	0	N
102	Infarct; VE	0	N
103	LVH	2	L ICA 16-49 %; R ICA 1-15 % occluded
104	N	0	N
105	N	0	N
106	N	0	N
107	Old MI	0	N
108	N	0	N
109	N	0	N
110	LVH	0	N

APPENDIX A CLINICAL AND LABORATORY DATA

NUMBER	ECG	STENOSIS >50%	NON INVASIVES/DOPPLER
111	LVH	2	L ICA and R ICA 1-15 % occluded
112	N	0	N
113	N	0	N
114	N	0	N
115	N	2	R ICA < 50 % occluded
116	N	0	N
117	LVH	2	Calcified plaque R bifurcation
118	LVH	0	N
119	N	1	L ICA 50-90 % occluded
120	Ischaemia	0	N
121	N	1	R ICA 50-74 % occluded
122	N	0	N
123	N	0	N
124	N	1	R ICA occluded
125	N	0	N
126	N	0	N
127	N	0	N
128	N	0	N
129	Inferolateral infarct	0	N
130	N	0	N
131	N	0	N
132	N	0	N
133	N	1	R ICA occluded
134	N	0	N
135	N	0	N
136	N	0	N
137	N	1	Stenosis L ICA; Basilar irregularity
138	N	1	R ICA occluded
139	N	0	N
140	N	0	N
141	N	0	N
142	N	0	N
143	N	0	N
144	N	0	N
145	N	0	N
146	N	0	N
147	N	0	N
148	N	0	N

	Normal	No stenosis	Normal
	N=Normal	0=No stenosis	N=Normal
	LVH=Left ventricular hypertrophy	1=50 % + stenosis	ICA=Internal carotid artery
	VE=Ventricular ectopics	2=< 50 % stenosis	L=Left
	MI=Myocardial infarction		R=Right
	AF=Atrial fibrillation		MCA=Middle cerebral artery
	BBB=Bundle branch block		VBA=Vertebrobasilar artery
	WPW=Wolff-Parkinson-White		CCA=Common carotid artery

NUMBER	CT SCAN/MRI	VASCULITIS
1	Hypodensity L internal capsule	0
2	N	0
3	R insular infarct	0
4	N	0
5	Old lacunar infarct	0
6	N	0
7	Atrophy	0
8	R infarct	VBA dissection
9	L and R infarcts	0
10	N	0
11	N	0
12	Multiple small infarcts	Behcet's; Reiter's
13	Lacunar infarct	0
14	N	0
15	N	0
16	N	0
17	N	0
18	N	0
19	L frontal and R posterior infarcts	0
20	N	0
21	L thalamic infarct	0
22	N	0
23	N	0
24	N	0
25	MRI = 3 bright objects	SLE; Sarcoid
26	N	0
27	N	0
28	N	0
29	N	0
30	N	0
31	N	0
32	N	0
33	N	0
34	N	0
35	N	0
36	L internal capsule infarct	0
37	N	0
38	N	0
38	Bilateral occipital and brainstem infarcts	0
40	N	0
41	Multiple infarcts	0
42	L parietal infarct	0
43	N	0
44	L internal capsule; R pontine infarct	0
45	N	0
46	Vessel L pontomedullary junction	0
47	N	0
48	R watershed infarct R MCA and PCA	0
49	N	0
50	Atrophy	SLE; Sjogren's
51	N	0
52	2 infarcts L parietal lobe	0
53	N	0
54	N	0
55	N	0

NUMBER	CT SCAN/MRI	VASCULITIS
56	N	0
57	R parietofrontal temporal infarct	0
58	R parietal infarct	0
59	L caudate and R cerebellar infarcts	0
60	R occipitoparietal infarct	Fibromuscular dysplasia
61	L MCA CVA	0
62	Multiple infarcts	0
63	L parietal infarct	0
64	N	0
65	N	0
66	N	0
67	N	0
68	L MCA infarct	0
69	L thalamocapsular infarct	0
70	R parietal lacunar infarcts	0
71	Multiple infarcts-Biswanger's	0
72	N	0
73	L MCA CVA	Vasculitis; optic atrophy
74	L parietotemporal infarct	0
75	N	0
76	R MCA CVA	0
77	L temperofrontal infarct	0
78	R parietal hypodensity	0
79	Pontine infarct	0
81	Multiple infarcts	APLA syndrome; Reynaud's
81	N	0
82	R infarct	Dissection
83	MRI = small lesions	0
84	L MCA CVA	Reynaud's
85	N	0
86	L MCA CVA	0
87	N	0
88	L internal capsule and lenticular infarct	0
89	N	0
90	R ICA infarct	0
91	L internal capsular infarct	0
92	N	Vasculitis
93	N	Takayasu's arteritis
94	N	0
95	N	0
96	N	Reynaud's
97	L frontoparietal infarct	0
98	Venous angioma	0
99	L internal capsular infarct	0
100	N	0
101	N	Behcet's
102	MRI = cortical hyperintensities	0
103	L frontoparietal infarct	0
104	R frontal infarct	0
105	N	0
106	L and R parietal infarcts	0
107	R MCA CVA	0
108	Venous sinus thrombosis	0
109	N	0
110	N	0

NUMBER	CT SCAN/MRI	VASCULITIS
111	R MCA CVA	0
112	N	0
113	R occipitoparietal and L occipital infarcts	Reynaud's; Livedo; Malar rash
114	N	0
115	N	0
116	N	0
117	L parietal and occipital infarcts; WM degen	0
118	Multiple infarcts	0
119	N	0
120	N	0
121	N	0
122	Multiple hypodensities	0
123	N	0
124	L parieto occipital lesion	0
125	N	0
126	NR	0
127	R MCA CVA	0
128	N	0
129	L apopleptic cyst	0
130	L MCA CVA	0
131	N	0
132	R internal capsular infarct	0
133	R MCA CVA	0
134	N	Rheumatoid arthri[illegible]
135	L midbrain infarct	0
136	Bilat frontoparietal hypodensities; bilat SDH	0
137	L ACA and MCA infarct	0
138	R ACA and MCA infarct	0
139	Multiple lacunar infarcts	0
140	L pontine infarct	0
141	N	0
142	N	0
143	N	0
144	N	0
145	L MCA CVA	0
146	R periventricular hypodensity; atrophy	0
147	N	0
148	L parieto occipital infarct	0

	Normal	Negative
	N=Normal	0=Negative
	MCA=Middle cerebral artery	APLA=Antiphospholipid antibody
	CVA=Cerebrovascular accident	SLE=Systemic lupus erythematosis
	ACA=Anterior cerebral artery	VBA=Vertebrobasilar artery
	SDH=Subdural haemorrhage	
	WM=White matter	
	R=Right	
	L=Left	
	PCA=Posterior cerebral artery	
	NR=Not recorded	

APPENDIX A CLINICAL AND LABORATORY DATA

NUMBER	HORMONAL CHANGE	D-DIMERS	HEREDITARY COAGULATION FACTORS
1	0	0	0
2	0	0	0
3	0	0	0
4	0	0	INR; C; warfarin
5	0 D		AT
6	0 D		0
7	0 D		INR; C; warfarin
8	0	0	APCR
9	0	0	0
10	0	0	0
11	0	0	0
12	0	0	APCR
13	0	0	0
14	0 D		0
15	0 D		APCR-HETERO
16	0 D		INR; C;AT; warfarin
17	0 D		C;AT
18	0	0	0
19	0	0	INR;C; warfarin
20	0 D		APCR; borderline C
21	0 D		0
22	0 D		0
23	0	0	INR; C; warfarin
24	0	0	0
25	0	0	0
26	0	0	0
27	0	0	0
28	1	0	0
29	1	0	0
30	0	0	0
31	0 D		APCR
32	0	0	APCR
33	0	0	0
34	1	0	INR; C; warfarin
35	0	0	0
36	0	0	APCR
37	0	0	0
38	0 D		0
38	0	0	0
40	0 D		Borderline C
41	0 D		APCR
42	0	0	0
43	0 D		0
44	0 D		0
45	0 D		0
46	0 D		0
47	0	0	0
48	1 D		INR; C; warfarin
49	0	0	INR; C; warfarin
50	1	0	APCR
51	0 D		0
52	0	0	0
53	0	0	APCR
54	1	0	INR; C;warfarin
55	0	0	INR; C; warfarin; APCR-HETERO

NUMBER	HORMONAL CHANGE	D-DIMERS	HEREDITARY COAGULATION FACTORS
56	0	D	0
57	0	D	0
58	1	0	0
59	0	D	APCR
60	1	D	0
61	0	D	0
62	0	0	0
63	0	0	INR; C; warfarin
64	0	0	0
65	0	D	APCR
66	0	D	0
67	0	D	Abnormal platelet sensitivity
68	0	D	C
69	0	D	0
70	0	D	0
71	0	0	Low factor 12; warfarin
72	1	0	0
73	0	0	0
74	0	D	0
75	0	0	INR; C; warfarin
76	0	D	0
77	1	D	0
78	0	D	0
79	0	0	INR; C; warfarin
81	0	D	0
81	0	0	INR; C; warfarin
82	0	0	0
83	0	0	INR; C; warfarin
84	0	0	C
85	0	0	C
86	0	0	0
87	1	0	C;S
88	1	0	0
89	0	0	0
90	1	0	0
91	0	0	INR; C; warfarin; APCR-HETERO
92	1	D	APCR
93	0	0	C
94	1	0	0
95	1	0	0
96	0	D	0
97	0	D	0
98	0	0	0
99	0	0	0
100	1	0	APCR; warfarin
101	1	0	0
102	0	0	Warfarin
103	1	D	APCR; AT
104	0	D	C; TT; warfarin
105	0	0	APCR
106	1	D	APCR
107	0	0	INR; C; S; warfarin
108	0	0	APCR
109	1	D	APCR
110	0	0	C

APPENDIX A CLINICAL AND LABORATORY DATA

NUMBER	HORMONAL CHANGE	D-DIMERS	HEREDITARY COAGULATION FACTORS
111	0	D	0
112	0	0	0
113	1	0	0
114	0	0	0
115	0	0	0
116	0	0	C;APCR
117	0	0	C
118	0	D	INR;C;S; warfarin
119	0	0	0
120	1	D	0
121	0	0	0
122	0	0	0
123	1	0	S; abnormal platelet sensitivity
124	0	0	Abnormal platelet sensitivity
125	1	D	APCR; abnormal platelet sensitivity; warfarin
126	0	0	S
127	1	D	0
128	0	0	C
129	0	0	ELT
130	0	D	APCR
131	1	0	0
132	0	0	ELT; abnormal platelet sensitivity
133	0	D	0
134	1	0	0
135	0	0	0
136	0	D	C
137	0	D	C
138	1	0	ELT
139	1	0	0
140	0	D	Warfarin
141	0	0	0
142	1	D	C
143	0	0	0
144	1	0	0
145	0	0	0
146	0	0	0
147	0	0	C
148	0	D	0
	Negative	Negative	Negative
	0=Negative	0=Negative	0=Negative
	1=Positive	D=Elevated D-dimers	APCR=Activated Protein C Resistance
			HETERO=Heterozygote for Factor V Leiden
			AT=Low Antithrombin
			S=Low Protein S
			C=Low Protein C
			INR=Prolonged INR
			TT=Abnormal thrombin time
			ELT=Abnormal euglobulin lysis test

APPENDIX A CLINICAL AND LABORATORY DATA

NUMBER	ACQUIRED COAGULATION FACTORS	SMOKING	ALCOHOL	HYPERTENSION
1	Fib	15	0	1
2	Fib	0	0	1
3	Fib	1	0	0
4	Fib; ANF	1	0	1
5	ANF	1	0	1
6	Fib; ACLA	0	0	1
7	Fib	60	0	1
8	0	0	0	1
9	Fib	1	1	1
10	0	40	1	0
11	0	1	0	1
12	0	0	1	1
13	ACLA	0	0	0
14	Fib	20	0	1
15	Fib	0	0	1
16	Fib	40	1	0
17	Fib; ANF	10	0	0
18	0	0	0	1
19	Fib	0	0	0
20	0	30	1	0
21	Fib	15	0	1
22	Fib; ACLA	1	0	1
23	Fib	1	0	1
24	LAC; ANF	0	0	1
25	0	0	0	1
26	0	15	0	1
27	Fib	1	0	0
28	Fib	10	0	0
29	Fib; ANF	1	0	1
30	Fib	60	1	1
31	0	1	0	0
32	0	0	0	1
33	0	0	0	1
34	Fib; ACLA	0	0	0
35	Fib	0	0	1
36	0	30	0	1
37	ANCA	20	1	1
38	ANF; ACLA	0	0	1
38	0	0	0	1
40	Fib; ACLA	0	0	0
41	Fib	10	0	1
42	Anti-parietal antibody	1	0	1
43	Fib; ANF	40	1	1
44	ANF	1	0	1
45	ANF	1	0	1
46	Fib	0	0	1
47	Fib; ANF; ACLA	6	0	0
48	Fib	0	0	1
49	Fib	1	0	1
50	ACLA	0	0	1
51	Fib	1	0	1
52	0	10	1	0
53	0	0	0	1
54	Fib	1	0	1
55	Fib	0	0	1

APPENDIX A CLINICAL AND LABORATORY DATA

NUMBER	ACQUIRED COAGULATION FACTORS		SMOKING	ALCOHOL	HYPERTENSION
56	Fib; ANF		0	0	0
57		0	0	0	1
58		0	1	0	1
59	ACLA		0	1	0
60	ANF (Anti-RNP; Anti- Sm)		4	0	0
61	Fib		1	0	1
62	Fib		1	0	1
63	Fib		0	0	0
64	ANF; ACLA		2	0	1
65	Fib; ANF		0	0	1
66	Fib		20	1	1
67		0	70	0	0
68		0	1	1	1
69	ANF		80	0	0
70		0	5	1	1
71		0	1	0	0
72		0	1	0	0
73	ANF		0	0	1
74	ANF		0	0	1
75	Fib		1	0	1
76	ANF		0	0	0
77		0	0	0	1
78	Fib		1	0	1
79	Fib		20	0	0
81	ACLA		15	0	0
81	Fib		1	0	0
82		0	0	0	0
83		0	0	0	0
84	ANF		0	0	0
85		0	0	0	0
86	Fib		1	0	1
87		0	0	0	0
88	ANF		0	0	0
89	ANF		0	0	1
90		0	30	0	0
91		0	20	1	1
92	Fib; ANF; ACLA		0	0	0
93	Fib; ANF		0	0	0
94	ANF; ACLA		15	0	0
95		0	0	0	0
96	ACLA		0	0	1
97		0	10	1	0
98	ANF		40	0	1
99	Fib		40	1	1
100	Fib; ANF		15	0	1
101		0	1	0	0
102	Fib		0	0	0
103	Fib		0	0	0
104		0	1	0	0
105		0	0	0	1
106	Fib		0	0	1
107	Fib		12	0	0
108	Fib		0	0	1
109	Fib		0	0	0
110		0	0	0	1

NUMBER	ACQUIRED COAGULATION FACTORS	SMOKING	ALCOHOL	HYPERTENSION
111		10	1	1
112	0	1	0	0
113	AntiDNAse B	6	0	1
114	Fib	2	0	0
115	Fib	20	0	0
116	0	6	0	0
117	Fib	1	1	1
118	ANF	10	0	0
119	0	20	0	0
120	Fib	0	0	1
121	Fib	30	0	1
122	Fib	20	0	0
123	0	15	0	0
124	0	20	0	0
125	Rheumatoid factor	0	0	0
126	Anti-La	0	0	1
127	0	0	0	0
128	c-ANCA	0	0	0
129	0	10	1	1
130	ANF	1	0	1
131	Fib	15	0	0
132	Fib	0	0	0
133	0	0	0	1
134	0	1	0	0
135	0	0	0	0
136	Fib	2	0	0
137	0	0	0	0
138	0	20	0	1
139	Fib	20	0	1
140	ANF	0	0	0
141	Fib	20	0	0
142	ANF	0	0	0
143	ACLA	0	0	0
144	ANF	0	0	0
145	0	10	1	0
146	0	0	0	0
147	0	7	0	0
148	0	20	0	1
	Negative	Negative	Negative	Negative
	0=Negative	0=Non-smoker	0=Negative	0=Negative
	ANF=Antinuclear factor positive	1=Ex-smoker	1=Positive	1=Positive
	ACLA=Anticardiolipin antibody positive	2+=Cigs/day		
	LAC=Lupus anticoagulant positive			
	ANCA=Antineutrophil cyoplasmic antibody			
	RNP=Ribonucleoprotein antibody positive			
	Sm=Sm part of extractable nuclear protein ab			
	Antiparietal=Antiparietal antibody positive			
	Anti DNAse B=AntiDNAse B antibody positive			
	Fib=Elevated fibrinogen			
	Anti-La=Anti-La antibody positive			

NUMBER	VASCULOPATHY (2 or more risk factors)		VASCULOPATHY RISK FACTORS
1		1	FH
2	H		0
3	S		0
4		1	0
5		1	Chol; Gout; Abdominal aortic aneurysm
6	H		0
7		1	0
8		1	Chol
9		1	Chol; Gout; FH
10		1	R brachiocephalic trunk stenosis FH
11		1	Chol
12		1	Chol; Gout
13		0	0
14		1	Chol; FH
15		1	Gout
16		1	FH
17		1	R ICA occluded; PVD
18		1	FH
19	FH		FH
20		1	L ICA 50-79 % occluded; PVD
21		1	0
22		1	Chol; Bilateral carotid stenosis
23		1	Chol; Gout; FH
24		1	Chol; FH
25		0	0
26		1	Chol; MI; 50-79 % occl
27		1	Chol; Gout; R ICA occl; L ICA 50-79 % occl
28		1	Chol
29	S		0
30		1	Chol; Gout; FH
31		1	Chol; IHD; FH; Abdominal aortic aneurysm
32		1	Chol; Angina
33		1	Angina
34		1	Chol; NIDDM; FH
35		1	Chol; NIDDM
36		1	Chol; PVD
37		1	Chol; Gout
38	H		0
38		1	Angina; NIDDM
40		1	Chol; Gout
41		1	Chol; L ICA occl
42		1	Chol; L ICA occl; R ICA 50-79 % occl
43		1	Chol; L ICA occl
44		1	0
45		1	IHD
46		1	NIDDM
47		1	Chol; Myocardial infarction; Gout
48		1	Chol; Angina; Gout
49		1	Angina; FH
50		1	Angina; DVT
51		1	Chol; Gout; Carotid endarterectomy; L ICA 99 % occl
52		1	L ICA 50-80 % occluded; FH
53		0	0
54		1	Chol; Bilateral Carotid endarterectomy; L ICA occl
55		1	Chol; Gout

NUMBER	VASCULOPATHY (2 or more risk factors)	VASCULOPATHY RISK FACTORS
56	0	FH
57	1	DVT
58	1	0
59	1	Chol
60	S	0
61	1	Myocardial infarction
62	1	Chol; Angina
63	0	0
64	1	0
65	1	Chol; MI; Angioplasty; L ICA 50- 79 % occl
66	1	Chol; Ang; PVD; AAA; R ICA occl; L ICA 50-79% occl
67	1	Gout; FH
68	1	IHD; PVD (claud); R ICA occl; L ICA > 50 % occl
69	S	0
70	1	Chol; NIDDM
71	1	Chol
72	1	FH
73	H	0
74	H	0
75	1	); MI; Coronary artery bypass graft; FH
76	0	0
77	1	Chol
78	1	0
79	1	Chol; DM; FH
81	0	0
81	S	0
82	FH	FH
83	0	0
84	0	0
85	0	0
86	1	Chol; Angina; CEA; R ICA 50-79 % occl; FH
87	0	0
88	0	0
89	1	Chol; Angina; FH
90	1	Chol; R ICA occluded; FH
91	1	DVT; FH
92	1	R ICA occluded
93	0	0
94	S	0
95	0	0
96	H	0
97	1	0
98	1	Myocardial infarction
99	1	FH
100	1	PVD; Pulmonary embolism
101	S	0
102	1	Chol; MI
103	1	IDDM; DVT
104	1	0
105	1	PVD; FH
106	H	0
107	1	MI
108	H	0
109	FH	FH
110	H	0

NUMBER	VASCULOPATHY (2 or more risk factors)	VASCULOPATHY RISK FACTORS
111	1	Renal failure
112	S	0
113	1	0
114	0	0
115	S	0
116	0	0
117	1	0
118	S	0
119	1	Chol; Carotid endarterectomy; R ICA 50-90 % occl
120	1	Chol; DVT
121	1	Chol; Gout; CEA; FH; R ICA 50- 74 % occl
122	1	Chol; FH
123	1	FH
124	1	R ICA occluded; CEA
125	0	0
126	1	Ang; PVD (DVT X 2)
127	0	0
128	0	0
129	1	Chol; IHD
130	1	Chol; FH
131	1	Angina; FH
132	0	0
133	1	R ICA occluded
134	1	Chol
135	0	0
136	S	0
137	0	0
138	1	R ICA occl
139	1	Chol; FH
140	0	PVD (DVT)
141	0	0
142	0	0
143	0	0
144	0	0
145	1	Chol; FH
146	0	0
147	S	0
148	1	Angina
	Negative	Negative
	0=Negative	0=Negative
	1=Positive (for 2 or more risk factors)	Chol=Hypercholesterolaemia
	FH=Family history, single factor	PVD=Peripheral vascular disease
	S=Smoking, single factor	IHD=Ischaemic heart disease
	H=Hormonal change, single factor	Ang=Angina
		NIDDM=Non-insulin dependant diabetes mellitus
		DVT=Deep vein thrombosis
		MI=Myocardial infarction
		CEA=Carotid endarterectomy
		ICA=Internal carotid artery
		FH=Family history
		Occl=Occluded

APPENDIX A CLINICAL AND LABORATORY DATA

NUMBER	OTHER FACTORS	EMBOLISM RISK FACTORS	INFECTION
1	0	0	ESR
2	0	0	WR
3	0	Sick sinus syndrome	0
4	0	0	0
5	0	AR; MR	0
6	0	AR/ AS	0
7	0	Atrial fibrillation/ flutter	0
8	VBA dissection	0	0
9	0	0	0
10	0	0	0
11	Cancer breast-mastectomy	0	0
12	Human leucocyte antigen B27; steroids	0	0
13	0	0	0
14	0	Sick sinus syndrome;pacemaker	0
15	0	0	0
16	0	Atrial fibrillation/ MR	0
17	0	Atrial fibrillation	0
18	0	0	0
19	0	0	0
20	0	0	0
21	0	0	0
22	0	0	0
23	0	Atrial fib; prosthetic MV and AV	0
24	0	0	ESR
25	Steroids	0	0
26	0	0	0
27	0	0	0
28	0	0	0
29	0	0	ESR
30	0	0	0
31	Myxoedema - Eltroxin; Microsomal antibody	0	0
32	Hypothyroid - Eltroxin	RHD; mitral valve replacement	0
33	0	0	0
34	0	RHD; mitral valve prolapse	0
35	0	0	0
36	0	0	0
37	0	Arrhythmia	0
38	Migraine	0	0
38	0	0	0
40	0	Mitral valve prolapse	0
41	0	0	0
42	Migraine	0	0
43	0	0	0
44	0	0	0
45	0	Atrial ectopics	ESR
46	Angiotensinogen converting enzyme	0	0
47	0	0	0
48	0	Arrhythmia	WR
49	Migraine	0	0
50	Migraine; Myxoedema;Ca bladder and sinus	0	0
51	0	0	0
52	Elevated platelet count	0	0
53	0	0	0
54	0	0	0
55	0	Dilated CMO;atrial fibrillation	WR

NUMBER	OTHER FACTORS	EMBOLISM RISK FACTORS	INFECTION
56	Thyroglobulin; steroids	0	0
57	0	0	Bronchopneumonia
58	RP; Epilepsy; Lactate; Pyruvate	Mitral valve prolapse	0
59	0	0	0
60	0	0	0
61	0	0	0
62	0	0	0
63	0	MR/ MS	0
64	0	0	0
65	0	MR	0
66	0	Mitral valve prolapse	ESR
67	Abnormal platelet sensitivity	0	0
68	0	0	0
69	Cocaine	0	0
70	0	0	0
71	Low factor 12	0	ESR;WR
72	Previous thyroid cancer - Thyroxine	0	0
73	Migraine; steroids	0	ESR
74	0	0	0
75	0	Atrial fibrillation; WPW	0
76	0	0	WR
77	0	0	0
78	0	0	0
79	Recreational drugs	Atrial septal defect	0
81	0	0	ESR
81	0	0	0
82	Migraine	MR; mitral valve prolapse	0
83	0	MS/ MR; AS/ AR	0
84	0	0	0
85	0	0	Meningoencephalitis
86	B Thallassaemia minor	0	0
87	Abortions x 4	0	WR
88	Dehydration	0	0
89	0	0	0
90	0	0	0
91	0	0	0
92	0	0	ESR
93	Antituberculosis drugs; steroids	AR	0
94	Migraine	0	0
95	Migraine	0	0
96	Eosinophilia	0	0
97	Recreational drugs	0	0
98	Venous angioma	RHD	0
99	0	0	WR
100	0	0	0
101	Angiotensinogen converting enzyme	0	0
102	0	RHD; ventricular ectopics	0
103	0	0	ESR; tonsillitis; PID
104	0	AS/ AR; MR	0
105	0	0	WR
106	0	0	ESR
107	0	0	WR
108	Venous sinus thrombosis	0	ESR
109	0	0	ESR
110	Motor vehicle accident	AS/ AR; MR	0

APPENDIX A CLINICAL AND LABORATORY DATA

NUMBER	OTHER FACTORS	EMBOLISM RISK FACTORS	INFECTION
111	Renal failure	0	0
112	0	0	0
113	AntiDNAse B antibody	0	0
114	0	0	0
115	Migraine	0	ESR
116	0	0	0
117	0	0	ESR;WR
118	0	RHD; MS/MR	0
119	0	0	0
120	0	0	0
121	0	0	0
122	Migraine	0	0
123	Pregnancy	Leaky' heart valve	0
124	0	0	0
125	Low VWB factor antigen and antibody	0	0
126	Abortions X 2	0	0
127	0	0	0
128	Homocystinuria; Migraine as child	0	0
129	ELT	0	0
130	0	0	0
131	Migraine	0	0
132	ELT	0	0
133	Atrial myxoma	Atrial myxoma	0
134	Migraine	0	0
135	Ex-IVDA	Patent foramen ovale; IVDA	0
136	Venous angioma	0	0
137	Homocystinuria; elevated platelet count	0	ESR
138	ELT	0	0
139	0	0	0
140	0	Atrial fibrillation	ESR
141	0	0	0
142	0	0	0
143	0	0	0
144	Abortions X 2	0	0
145	0	MR/ MS	0
146	0	0	0
147	0	0	0
148	0	RHD; MR	0
	Negative	Negative	Negative
	0=Negative	0=Negative	0=Negative
	VWB=Van Willebrand's disease	MR=Mitral regurgitation	WR=Positive WR
	IVDA=Intravenous drug abuse	MS=Mitral stenosis	PID=Pelvic in lam dis
	VBA=Vertebrobasilar artery	AR=Aortic regurgitation	ESR=Raised ESR
	RP=Retinitis pigmentosa	AS=Aortic stenosis	
	ELT=Abnormal euglobulin lysis test	AV=Aortic valve	
	Ca=Cancer	MV=Mitral valve	
		WPW=Wolff-Parkinson-White	
		RHD=Rheumatic heart disease	
		CMO=Cardiomyopathy	
		IVDA=Intravenous drug abuse	

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