Clinical, Radiological and Cognitive Features of Arteriovenous Malformations of the Brain: A Prospective Study of Consecutive Patients Presenting to Beaumont Hospital

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Based on research conducted in the Departments of:
- Neurology, Faculty of Medicine, Royal College of Surgeons in Ireland
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- Neuropsychology, Beaumont Hospital, Dublin
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Supervisor: Dr. Joan T. Moroney
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I declare that this thesis, which I submit to RCSI for examination for consideration of the award of the higher degree MD is my own personal effort. Where any of the content presented is the result of input or data from a related collaborative research programme this is duly acknowledged in the text such that it is possible to ascertain how much of the work is my own. I have not already obtained a degree in RCSI or elsewhere on the basis of this work. Furthermore, I took reasonable care to ensure that the work is original and to the best of my knowledge does not breach copyright law and has not been taken from other sources except where such work has been cited and acknowledged within the text.

Signed

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Date 19/5/10
For Lisa
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CHAPTER 1: INTRODUCTION

1. Definition

Arteriovenous malformations are tangled anastomoses of blood vessels of varying calibre. These space-occupying vascular lesions consist of multiple arteries and veins that connect directly without an intervening capillary bed. The feeding arteries converge towards a central portion, known as the nidus (Latin nidus, nest), and blood is transmitted through a high-flow system to enlarged draining veins. Due to the high-pressure within these vascular channels, the nidus and draining veins are at risk of rupture, often with catastrophic results. As arteriovenous malformations are located throughout the entire brain parenchyma the term “cerebral” (implying telencephalon of the forebrain) is inappropriate. These lesions will therefore be defined in this manuscript as arteriovenous malformations of the brain (BAVM).

2. Epidemiology

There are limited data on the true incidence and prevalence of BAVM. Previous reliance on conventional angiography for diagnosis (and biased data towards those with haemorrhage) hampered the emergence of large population-based studies. Detection has increased with non-invasive brain imaging techniques such as computed tomography (CT) and, more recently, magnetic resonance imaging (MRI). As a result, most of the data regarding BAVM have been gleaned from hospital based-studies, which are likely to be unrepresentative of the population in ways that are difficult to assess. Factors such as selection bias and under-ascertainment of particularly mild or severe forms of the disease together serve to distort the true incidence and prevalence figures of BAVM by varying degrees. Although some data exist on haemorrhagic stroke in Ireland, these studies have been predominantly hospital based(1, 2) and have either focused on aneurysmal subarachnoid haemorrhage(3) or intraparenchymal haemorrhage where the underlying cause is not clear.
Up to and during most of the period of recruitment, Beaumont Hospital was the only centre in Ireland offering an endovascular embolisation service to patients with BAVM (Cork University Hospital began to offer this service to the Munster catchment area in 2008). Beaumont’s neurosurgical catchment area includes all provinces except Munster and to date has therefore received the majority of the country’s newly diagnosed BAVM for assessment. There are certainly advantages of using the Beaumont BAVM database to describe patient characteristics and observe treatment effects and outcomes. However, any attempts to make estimates of national incidence and prevalence based on data acquired in one centre are likely to be fraught with difficulty and grossly underestimate the true incidence and prevalence of the disease. Many Irish patients with intraparenchymal haemorrhage die in the community or receive treatment in non-specialist centres where BAVM may remain undiagnosed. Due to the limited availability of catheter-based intracranial angiography and difficulty accessing a highly centralised and under-resourced neurosurgical service, BAVM-related haemorrhage in Ireland is likely to remain considerably under-diagnosed. Therefore, although most of the country’s known BAVM patients are managed in Beaumont, this project is hospital-based and does not aim to describe population-based epidemiological characteristics of the disease. The available international data on incidence and prevalence figures are presented below.

2.1 Unselected Populations

A study from Linköping University in Sweden was carried out over an 11-year period and reported a detection rate of 1.24 per 100,000 person-years. Two further population-based studies on the incidence of BAVM produced a figure of approximately 1 per 100,000 person-years. The first, over a 10-year period, was based in the only hospital serving a population of 155,000 living on the islands of Curaçao and Bonaire in the Dutch Antilles(4). This incidence figure is unlikely to be truly representative: sudden deaths due to undiagnosed BAVM were not accounted for, the authors provided little detail about their detection methods and there was only one source of case
ascertainment. All cases were symptomatic and there was an unusually high number of multiple BAVM (presumably due to the high incidence of hereditary haemorrhagic telangiectasia (HHT) in that ethnic group(5)). The second study, gleaning data from the Mayo Clinic Medical Records Linkage system, identified 26 BAVM between 1965 and 1992 in Olmstead County, Minnesota(6). Unsurprisingly, due to increasing use of more advanced non-invasive brain imaging techniques, the BAVM detection rate increased over the course of the 27-year period. Another population-based study followed 100,000 people in three separate communities in Southern Alabama in a pilot study on stroke. 9 BAVM were detected in 494 stroke sufferers and the authors calculated a detection rate of 4 per 100,000 person-years(7).

Important work in this area is ongoing and yet to be published in full. Large cohorts of patients with newly diagnosed BAVM are being prospectively gathered in both North America and Europe. The New York Islands BAVM Study is based on a population of over 9 million people living in the New York Islands (Manhattan Island, Staten Island and Long Island). This large prospective study is ongoing and once complete will provide robust data, not just regarding incidence and prevalence of the disease, but also its natural history. Preliminary results reveal an average annual BAVM detection rate of 1.34 per 100,000 person-years(8). Similar findings have been noted by Al-Shahi’s Scottish Intracranial Vascular Malformation Study (SIVMS) group in the United Kingdom. Due to their prospective, population-based nature and emphasis on long-term follow-up, both studies will over the coming years provide invaluable insight into the disease (and particularly in cases of unruptured BAVM).

There has been one retrospective, population-based study on the prevalence of BAVM. Based in the Lothian region of Scotland, this found a point prevalence of 15 per 100,000 living adults(9). The true figure is likely to be higher as any study naturally underestimates the prevalence of clinically silent disease. The Irish population is demographically similar to Scotland.
and is also relatively homogenous. It is likely that any population-based study conducted in this country would yield similar results. Conversely, autopsy series have quoted much higher figures of up to 600 per 100,000(10, 11) but these figures are inherently biased as is the case with any epidemiological data based on post mortem studies. Some authors argue that the true prevalence of BAVM will never be known as based on a hypothetical prevalence of 10 BAVM patients per 100 000 population, prior calculations indicate that MRI screening of 1 million people would be necessary to yield estimates with sufficiently narrow confidence intervals(12).

2.2 Selected Populations

Despite the availability of Irish data regarding intracranial haemorrhage(2, 3), epilepsy(13) and headache(14), there has been little reference in this published literature to BAVM as an underlying cause. Although there are inevitably important discrepancies between the populations of Ireland and other countries, it is nonetheless appropriate to examine the international data available in these selected populations.

(a) Primary Intracerebral Haemorrhage (PICH)

Overall, approximately 10% of first-ever-in-a-lifetime strokes in caucasian populations are caused by PICH(15, 16). Studies have varied in the extent of their further investigation of an underlying cause, and their inclusion criteria by aetiology or location of haemorrhage. There is a paucity of satisfactory population-based data on the frequency of BAVM as a cause of first-ever-in-a-lifetime PICH. The only truly population-based study was based in Rochester, Minnesota, USA. It was limited by its retrospective design and the fact that it was performed before CT became widely available, but it did use the comprehensive Mayo Clinic Medical Records Linkage system database. The authors determined that 4%
of first-ever-in-a-lifetime PICH were attributable to BAVM (17). Other studies are hospital-based and either fail to explicitly specify first-ever-in-a-lifetime PICH or combine BAVM with the other intravascular malformations in one aetiological group. Retrospective autopsy studies of fatal spontaneous PICH have found an underlying BAVM in 15–16% of cases, probably an overestimate due to case selection bias (18, 19).

There are no population-based studies, either prospective or retrospective, of the frequency of BAVM as a cause of first-ever-in-a-lifetime PICH in younger populations. The best available estimate comes from a retrospective, hospital-based study of people under 40 years of age with PICH, which confirmed BAVM on MRI or intraarterial digital subtraction angiography (IADSA) in all cases (20). In this study, BAVM were the leading cause of PICH in the young, affecting 33% of people. Other similar, retrospective hospital-based studies did not specifically examine first-ever-in-a-lifetime PICH and variable employment of MRI and IADSA for BAVM detection limits their value.

(b) **Subarachnoid Haemorrhage (SAH)**

In Western populations, the most frequent cause of spontaneous SAH is rupture of a saccular aneurysm on or near the Circle of Willis. BAVM are a significantly less common cause. A prospective, population-based study from Norway studied every patient with CT and 76% of those with IADSA and found BAVM as a cause of SAH in 9% of people (21). All the other studies of SAH that mention BAVM as a cause have been hospital-based, and mostly retrospective. There also appears to be variation between geographical regions and ethnic groups (22). Although the spectrum of BAVM, aneurysms and subarachnoid haemorrhage in Asian
ethnic subgroups may differ to more commonly studied Western populations, claims that BAVM are more common than aneurysms as a cause of SAH in these patients seem unfounded(23).

(e) **Seizures**

Epilepsy comprises a large spectrum of disease and the contribution made by BAVM is seldom clear for different reasons. Firstly, most researchers classify epilepsy syndromes and their aetiologies into broad categories and this classification is usually based on ictal semiology rather than neuroimaging(24, 25). Secondly, the extent and rate of neuroradiological investigation vary widely between studies. Accordingly structural causes, such as BAVM, have not always been reliably identified. Thirdly, despite the frequency of epileptic seizures, there have been few prospective, population-based studies of people with newly diagnosed epilepsy(26). Estimates of the true frequency of epilepsy vary widely due to the difficulty of achieving comprehensive case ascertainment and the heterogeneity of different diseases causing epilepsy. Previously, the use of neuroimaging was only felt to be indicated for patients whose epilepsy could not be controlled with first-line anticonvulsants, and those with localisation-related epilepsies or fixed/progressive neurological deficits(27). Current neurological practice has changed over the last ten years, however, and there is a view that all first unprovoked seizures warrant an MRI as a first-line radiological investigation. It is reasonable to assume that a proportion of those patients with well-controlled epilepsy, who have not undergone MRI or a catheter angiogram as part of their initial work-up, could have an underlying BAVM that may remain undetected. With these caveats in mind, the best data on BAVM as a cause of epilepsy in the general adult population comes from a Swedish prospective, population-based incidence study of first presentations with seizures. Using
either CT or MRI in all cases, Forsgren and colleagues found 0.9% of apparently unprovoked seizures to be attributable to an BAVM(28). On the other hand, within a series of patients where a diagnosis of BAVM has been established, seizures are the first presenting complaint in approximately 30% of cases(29).

(d) **Headache**

BAVM are an infrequent cause of headache in the general population. Many neurologists have in the past been reluctant to expose their patients to unnecessary investigation in the work-up of headache with normal neurological examination, unless history taking reveals so-called “red-flags” such as photophobia (a sign of meningism) or postural symptoms (e.g. early morning headaches may indicate raised intracranial pressure). As a result, studies have not routinely focused on ascertaining the frequency of structural causes of headache syndromes, defined according to the International Headache Society criteria, in unselected populations of people with apparently benign headache. However, in one pooled analysis of a small, retrospective, selected series of patients at tertiary referral centres, imaging studies of the frequency of detection of structural brain abnormalities in people with unspecified headache and no abnormal neurological signs up to 1991, revealed a BAVM in 0.3% of people(30). This figure is likely an underestimate of the true BAVM prevalence in this group as most of the included studies employed early CT technology and did not routinely use intravenous contrast. In similar studies, several of which used MRI, detection rates in a sub-group of migraines were as low as 0.07%(31).

(e) **Relationship to Aneurysms**

Estimates for the prevalence of BAVM have also been based on their frequency relative to that of cerebral aneurysms. The Cooperative
3. **Aetiology**

Unlike fistulae caused by venous occlusion or trauma, BAVM have long been thought to arise earlier in life. It is not clear whether this is at the embryonic or foetal stage or after birth(33-35). Mullan and colleagues showed that it is extremely difficult to detect BAVM in utero(36). Over time BAVM may grow, remain static, or in some cases regress spontaneously(37). Although altered expression of over 900 different genes has been described(38), there is currently no definitive evidence of a single genetic cause outside the setting of a coexistent hereditary disorder such as HHT (also known as the disease of Osler-Weber-Rendu). Research on gene expression patterns and polymorphisms has however suggested a genetic influence not just on the aetiology of sporadic BAVM(39-42), but also on their risk of subsequent haemorrhage(43-45). BAVM typically present as solitary lesions, except in the rare setting of HHT. Clinical presentations of patients with symptomatic BAVM associated with HHT are similar to those of patients with “sporadic BAVM” and include hemorrhage, seizures, headaches, and/or progressive focal neurological deficits. The bleeding rate of BAVM associated with HHT is not known but is likely to be similar to that of sporadic BAVM (approximately 2-4% per year). HHT is inherited as an autosomal dominant
multisystemic vascular dysplasia with an estimated prevalence of 1 in 10,000 to 40,000 persons (46, 47). BAVM are found in 10 to 25% of patients with HHT, and mutations in two genes, *ENG* and *ACVR1*, result in both pulmonary and BAVM. Although there have been case reports of 25 families without HHT where two or more members were affected with BAVM, screening for either *ENG* or *ACVR1* was not performed (48-50). BAVM are frequently discovered in patients with other vascular syndromes such as Von Hippel-Lindau disease (5). A mutation of a positional candidate gene, RASA1, has recently been implicated in 6 families with capillary malformations ("port-wine stain") and associated intracranial vascular anomalies, including BAVM (51).

4. Angioarchitecture

4.1 Grading

The best known grading system (see table 1) was devised by Spezler and Martin in the 1980s and is still used in most neurosurgical centres over 20 years later (52). It comprises three components: 1) size (less than 3 cm, 3-6 cm, or greater than 6 cm); 2) location ("eloquent" such as visual or motor cortex, or "non-eloquent", such as deep white matter); and 3) pattern of venous drainage (superficial or deep). Patients receive a score from 1-5 based on these features. It is important to note that this system was devised to characterise BAVM in terms of the challenge they create for the neurosurgeon (grade 5 considered most difficult to resect) and not necessarily as a predictor of morbidity or mortality. Evidence exists, for example, that smaller BAVM are more likely to rupture (53), even if this is thought by some to be due to the fact that smaller lesions have higher feeding arterial pressure and less draining veins (54).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Points Assigned</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small (&lt;3 cm)</td>
<td>1</td>
</tr>
<tr>
<td>Medium (3-6 cm)</td>
<td>2</td>
</tr>
<tr>
<td>Large (&gt;6 cm)</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 1: Spezler-Martin grading system of BAVM.
<table>
<thead>
<tr>
<th>Location</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-eloquent site</td>
<td>0</td>
</tr>
<tr>
<td>Eloquent site*</td>
<td>1</td>
</tr>
<tr>
<td><strong>Pattern of venous drainage</strong></td>
<td></td>
</tr>
<tr>
<td>Superficial only</td>
<td>0</td>
</tr>
<tr>
<td>Deep component</td>
<td>1</td>
</tr>
</tbody>
</table>

*: sensorimotor, language, visual cortex, thalamus, hypothalamus, brainstem, cerebellar peduncles or nuclei.

4.2 Feeding Arteries

Angioarchitecture is the term used to describe the size, shape, location and various other anatomical features of BAVM. This vascular conglomerate consists of feeding arteries (and sometimes aneurysms), a central nidus and draining veins. There are usually several tortuous, branching, high flow arterial vessels of varying calibre and wall thickness that supply the central nidus where arteriovenous shunting occurs through one or more fistulae. The arterial feeders may terminate in the nidus, continue to supply brain beyond the nidus (giving 'en passage' supply) or arise indirectly from an artery in close proximity to the nidus. The afferent vessels are typically recruited from more than one intracranial branch of the internal carotid and/or vertebrobasilar system and sometimes through branches of the external and vertebral arteries through transdural anastomoses(55). Most BAVM are located supratentorially (greater than 90%) and about 15% of these are found in deep locations such as basal ganglia, corpus callosum or brainstem(56). Lesions found in deep locations usually recruit
lenticulostrial, choroidal or thalamostriate arteries. The most common variant is wedge-shaped, where the base is situated on the cerebral cortex in a borderzone area between terminal branches of adjacent arteries and the apex of the lesion lies in the white matter. Another variant is restricted to the white matter of the cerebrum or cerebellum and is more cylindrical or globoid in shape. These do not involve the surface of the brain and are commonly supplied by branches of a cerebral artery of one vascular territory. Less commonly, BAVM involve mostly individual arteries (often the anterior cerebral or anterior choroidal arteries) rather than whole brain territories. Many lesions are too small to be detected by non-invasive angiographic techniques and so conventional 4-vessel cerebral angiography remains the diagnostic gold standard.

4.3 Aneurysms

The co-existence of aneurysms and BAVM is a topic of considerable interest. Marks and colleagues were the first to demonstrate increased risk of haemorrhage from aneurysms associated with BAVM (57). Aneurysms are found in association with BAVM in approximately 10% of cases (58, 59) although where super-selective angiographic methods are employed this figure may rise to as much as 50% (60). Aneurysms may occur as infundibula at arterial bifurcations (61), as either saccular or fusiform aneurysms on vessels remote from the BAVM, on feeding arteries and within the BAVM nidus itself (62, 63). Multiple aneurysms are frequently discovered (63). Such aneurysms have subsequently been classified into four types by Perata and colleagues (64). Type-I aneurysms are not flow-related and as they are generally independent of the haemodynamics of the BAVM they are managed separately. Type-II aneurysms are flow-related lesions found on the Circle of Willis at the origin of major vessels feeding the BAVM. These aneurysms present a significant risk of haemorrhage and due to their proximal location are unlikely to resolve with treatment of the BAVM. Type-III aneurysms are flow-related lesions arising distally along
the feeding arteries. Theoretical models have predicted that the greatest increase in pressure is likely to be in the feeding vessels when the nidus is close to obliteration following treatment(65). Finally, type-IV aneurysms are intranidal. Opinions on whether they increase the risk of haemorrhage are divided(66, 67).

The size and location of associated aneurysms have important implications for management of both the aneurysm(s) and the BAVM itself. Type-I aneurysms are managed similarly to intracranial aneurysms in patients without BAVM. Cases involving type-II and type-III aneurysms are more complex. Small to moderate sized feeding-artery aneurysms (less than 5mm in diameter) have been reported to regress after treatment of the BAVM in some cases(62). In other reports they are more likely to rupture after treatment, probably owing to the resultant increase in transmural pressure(68). Where there is concern about possible rupture of larger aneurysms, particularly if greater than 7mm in diameter(69), microsurgical clipping or endovascular coiling of the aneurysm is often performed before treatment of the BAVM. Given their location within the lesion, intranidal aneurysms are treated in conjunction with the BAVM.

4.4 Nidus

The nidus itself is usually compact but occasionally takes a more diffuse configuration occupying a large proportion of a cerebral hemisphere(70). Blood may be shunted through a single, simple fistula or a complex plexus(71) and the diversity of arteriovenous shunts within the nidus has been highlighted with the ongoing refinement of super-selective IADSA techniques. It is clear that nidus size is highly relevant in terms of BAVM prognosis and treatment, but its accurate and consistent measurement is problematic. The definition of a nidus as the area towards which multiple feeding arteries converge and from which enlarged veins drain is somewhat arbitrary. Firstly, the nidus is often not entirely visualised with injection of a
single vascular territory during IADSA. Secondly, the absence of standardised calibration markers and magnification tools makes size interpretation difficult for grading purposes(72). Thirdly, methods of calculating size vary widely, ranging from simply measuring the maximum linear diameter in any dimension(73), to various volume calculations dependent on assumptions about the shape of the nidus(72). Fourthly, attention should be given to the possible presence of a dilated perinidal capillary network. Referred to as the “reserve nidus”, these vessels connect to feeding arteries and draining veins via arterioles and venules. They also connect to normal capillaries, arterioles, and venules and may subsequently become part of the nidus(74). Therefore for grading purposes and subsequent decision making a multi-modality investigative approach is necessary, including IADSA and either contrast-enhanced CT or preferably MRI. In addition, development of functional imaging methods such as functional and diffusion tensor-weighted MRI is likely to be of significant importance in the management of such lesions(75).

4.5 Draining Veins

One or more dilated veins originate deep within the BAVM nidus and drain, directly or via collateral pathways, deeply, towards the ventricular system, or superficially, towards the brain surface. Venous drainage may be superficial, deep or both, regardless of the size or location of the nidus. Through the loss of the normal resistance to flow in the capillary bed, the arteriovenous shunt transmits arterial pressure to the compliant venous system, causing venous hypertension. These haemodynamic stresses can give rise to a variety of venous anomalies(76).

5. Pathophysiology

Blood is shunted through the nidus of the BAVM in a high flow, low resistance manner. This haemodynamic pattern lends itself to the recruitment of collateral supply from surrounding vascular territories in addition to the main feeding vessels
and is sometimes referred to as “angiomatous change”. This abnormal vascular 
recruitment leads to arterialisation of venous structures and gliosis of intervening 
and adjacent brain tissue(77). Arteriovenous shunting transmits high pressure to the 
draining veins resulting in stenosis, ectasia and varix formation(76). The chronic 
high blood flow in the feeding arteries is thought by some to cause stenotic and/or 
dilated arterial “angiopathy” due to endothelial thickening and intimal 
hyperplasia(78), which may resemble the angiographic appearance of moyamoya 
disease(79). The rapid flow through the BAVM can also induce arterial hypotension 
in the feeding vessels, lowering blood flow in the surrounding brain parenchyma 
and possibly resulting in local or distant cortical ischaemia due to the “steal” 
phenomenon(80, 81). Recent research using continuous arterial spin-labeled 
perfusion MRI imaging has revealed that the degree of arteriovenous shunting is 
related to contralateral white matter and thalamic blood flow, with the latter 
possibly exhibiting vascular steal(82). Furthermore, complications resulting from 
post-treatment hyperemia (i.e. cerebral oedema and raised intracranial pressure) are 
most likely to occur in BAVM that are high flow and demonstrate steal(83). 
Conversely, Mast’s transcranial doppler and angiographic catheter-derived data on 
over 100 prospective challenge the steal theory(84, 85). Disagreements between 
authors could be due to a number of reasons including heterogeneity of patient 
demographics and clinical presentation and varying methods of case ascertainment. 
It is difficult to make any robust conclusions regarding vascular steal and its role in 
BAVM. Nonetheless, given the extensive published research on flow dynamics in 
BAVM and their clinical implications, and the lack of consistent, uniform and 
concrete evidence against the steal phenomenon, most clinicians still at least 
consider this theory to be not just a plausible explanation for many of the clinical 
aspects of these lesions but also an area worthy of further investigation.

6. Pathology

On histopathological examination, BAVM lesions demonstrate mature vessel wall 
phenotype and normal structural integrity. The haemodynamic stress of turbulent 
blood flow, however, compromises the contractile properties of vascular smooth
muscle cells within the lesion(77). This is supported by the finding that the expression of smoothelin, a muscle protein found in the endothelium, is significantly less than that observed in normal brain vessels(86). Consistent with BAVM vascular remodeling and instability, matrix metalloproteinase-9 and tissue inhibitors of metalloproteinases, both of which regulate angiogenesis, are increased in the endothelial cell layer of BAVM compared with control vessels(87). Vascular endothelial-derived growth factor (VEGF) has also been shown to demonstrate increased activity in BAVM patients, both in brain parenchyma and plasma(88, 89).

7. **Clinical Presentation and Natural History**

7.1 **Haemorrhage**

As the majority of cases are symptomatic (only a small proportion of BAVM are incidentally discovered) and the tendency up to now has been to treat rather than manage conservatively, the natural history of untreated BAVM is not clearly defined. Estimates of the risk of haemorrhage vary: some studies have predicted that most will rupture at least once during the lifetime of the patient(90, 91). It has been surmised that the risk of haemorrhage is equal to 105 minus age in years (thus, the estimated lifetime risk of haemorrhage for a 25 year-old with a newly diagnosed BAVM is about 80%)(92), while earlier studies suggested that after forty years of age the risk rapidly declines(93). In view of the scarcity of large, population-based studies and bias towards hospital-based data, overestimates of the risk of haemorrhage are likely. The overall risk of haemorrhage of BAVM (with estimates based on the best available population-based natural history studies) is more likely to be 2-4% per year(54, 59, 94). Approximately 53% of known BAVM patients will present with haemorrhage(29) with which there is a 5-10% associated chance of death and 30-50% risk of disabling neurological deficits(91). Those patients who present initially with haemorrhage have a higher risk of rebleeding, suggesting that once bleeding starts, the lesion is destabilised and prone to further bleeding. Patients are
considered to be at the greatest risk in the first year after initial haemorrhage, with rebleeding rates as high as 32.9% (95).

PICH is the principal type of haemorrhagic presentation, although SAH and intraventricular haemorrhage are also well described. In the Olmsted County study, PICH accounted for 41%, SAH for 24%, intraventricular haemorrhage for 12% and a combination of these types for 23% of all haemorrhages (96). Several angiographic and clinical factors that increase the risk of haemorrhage have been identified in hospital-based retrospective studies, including intranidal (57) and flow-related aneurysms (97), deep venous drainage (57), small nidus size (98), high feeding mean arterial pressure (FMAP) (98), deep location (57, 99) venous stenosis (100), a single draining vein (101) and slow filling of feeding arteries (102). Systemic hypertension has also been implicated as a risk for haemorrhagic presentation (99). Some data suggest that risk increases with decreasing diameter of the malformation (53, 54, 69, 103) while the relationship between risk of rupture and both increasing age at presentation (104) and smoking (105) is more tenuous. Other factors have been hypothesized to offer a protective effect, namely arterial stenosis and ectasia (66), dural arterial supply (104), venous recruitment (106) and angiogenesis (66). It is also possible that these individual factors may confound each other: for example, smaller BAVM may present with haemorrhage because have fewer draining veins and a higher FMAP (107) or simply because smaller lesions rarely present with epilepsy or other neurological symptoms before diagnosis (108).

This constellation of features is associated with either an increased or decreased risk of haemorrhage. It is reasonable to hypothesise that such aspects of angioarchitecture and the complex haemodynamic features of these BAVM are not independent of one another: irrespective of the numerous inter-related anatomical components of any single BAVM complex, raised intranidal pressure may be the most significant determinant.
of rupture(109). However, although these factors may be associated with a haemorrhagic presentation, they are not necessarily predictors of either a “first in a lifetime” or recurrent haemorrhage. This has to be tested in large, prospective studies.

7.2 Seizures

BAVM can present themselves by both generalized seizures and simple or complex partial seizures with or without secondary generalization(29). The pathophysiological mechanisms underlying BAVM-related seizures are not entirely understood. The most plausible assumptions relate to either the so-called “steal” phenomenon (where arteriovenous shunting may result in ischaemia of the adjacent cortex) or gliosis of surrounding brain parenchyma due to previous sub-clinical haemorrhage(110). Experience with cavernous angiomas seems to lend support to the latter mechanism: these vascular malformations are usually surrounded by haemosiderin and are usually clinically revealed by epilepsy(111). Retrospective studies on patients with both BAVM and epilepsy have found BAVM to have statistically significant associations with a larger (>6 cm) nidus diameter(112). In addition, it has been postulated that several other features of BAVM angioarchitecture are associated with epilepsy including supratentorial cortical location, feeders from the middle cerebral artery, cortical feeders, venous varix, the absence of intranidal aneurysms(110) and borderzone arterial territories(113). Caution should obviously be exercised when considering any associations as these factors may confound each other. For example, if intranidal aneurysms increase the risk of haemorrhage, then their absence might be expected in a subgroup of BAVM patients presenting with epilepsy (and not haemorrhage). As always, association does not confirm causation. Only long-term, prospective studies can tackle these issues in order that the prognostic value of such anatomical features can be reliably determined.
7.3 Headaches

The frequency of headaches unrelated to haemorrhage has not been thoroughly investigated. The reporting of atypical migraine and cluster headache in BAVM patients is probably influenced by publication bias, as unusual cases are more likely to be reported in the literature. The migraines reported to accompany BAVM are usually characterized by atypical features, although these are not specific for identifying an underlying BAVM in a person with migraine(114). The reported headaches tend to be on the side ipsilateral to the BAVM, with disruption of the classical migraine tempo and sequence(30, 115). A relative frequency of headaches (i.e. headache associated with haemorrhage) has been reported by the Columbia group in 11% of patients on presentation(95). A large study analysing the headache characteristics of over 700 patients treated with radiosurgery found that headache in isolation (i.e. not related to haemorrhage, seizure or neurological deficit) only occurred in 6%(116).

Interestingly, although cited as a frequent presenting feature, there is no convincing causative relationship between headaches and BAVM. The absence of prospective, population-based studies with a validation of headache diagnosis has given rise to differing opinions about whether there is a genuine relationship(117) or if their co-existence is purely by chance(118). Large, prospective studies using standardized interviews and validated questionnaires based on the International Headache Society criteria are required to determine the true prevalence of different types of headache amongst people with BAVM.

7.4 Focal Neurological Deficit

BAVM may also cause focal symptoms or signs unrelated to haemorrhage. The exact frequency of focal neurological deficits in the population is unknown, but they account for less than 10% of presentations in hospital-based series(95, 119). These symptoms may be transient, persistent or
wholly or partly reversible. Onset is usually insidious and clinical course is often fluctuating. The syndrome is often such that, before sophisticated non-invasive imaging techniques were available, symptoms associated with BAVM were sometimes mistakenly interpreted as constituting a brainstem syndrome secondary to multiple sclerosis(120). The anatomical and haemodynamic processes underlying these deficits have been investigated and two mechanisms are commonly proposed. Firstly, the intranidal pressure may increase, such as with occlusion of a draining vein, leading to local mass effect on adjacent brain tissue(121, 122). Secondly, the “steal” theory proposes that blood shunted through the nidus in a high flow manner lowers the feeding artery pressure inducing ischaemia of surrounding brain parenchyma(122, 123). A recent study of 53 BAVM patients found a predominance of focal neurological deficits among women, older patients (perhaps a time dependent effect?) and those with brainstem and deeply located BAVM(124). Interestingly, first presentation with a focal deficit was independent of BAVM size and this may indicate selective white matter pathway-specific vulnerability. The authors even hypothesise that higher frequency among women may suggest gender-specificity of brain tissue vulnerability. These claims may be misleading however as the patients were selected from a much larger database of patients with a variety of BAVM-related presentations and other clinical features. The sample is therefore prone to selection bias and, as always, associations implied by multivariate analysis do not prove causation.

7.5 Other Presenting Features

BAVM have been known to present with a number of other symptoms and signs. Some of these appear to be influenced to a large degree by the complex haemodynamic nature of BAVM, such as tinnitus(125) and raised intracranial pressure(126) (thought to arise secondary to CSF outflow obstruction or poor CSF resorption by enlarged draining veins and/or venous hypertension). Other presentations such as movement disorders(127)
(including hemifacial spasm(128) and torticollis(129)), visual disturbances(130), trigeminal neuralgia(131) and cranial nerve palsies(132) are more influenced by the strategic location of the lesion.

8. **Neuropsychology**

Despite early reports of neuropsychological disturbances in up to 50% of cases(133, 134), there have been few systematic studies of the cognition of patients with BAVM (and none on Irish populations). Little is known about the impact these vascular abnormalities have on the neurobehavioural or cognitive ability of patients. This becomes problematic both in terms of managing patients' functioning or quality of life and in judging the outcome of therapeutic interventions(135). Recent studies have been undertaken to evaluate neuropsychological outcomes in patients with intra-cranial aneurysms(136) but the scant data available for those with BAVM date back almost twenty years and only represents patients undergoing surgery. Two main theories exist for possible cognitive deficits in these patients, namely vascular steal(137) and less likely “cortical reorganization”(138). It is hypothesized that high flow through a BAVM in one hemisphere may compromise blood supply in the contralateral hemisphere thus impacting on cortical function. This may manifest by deficits across one or more cognitive domains. It is also possible that BAVM may result in specific cognitive deficits, depending on their strategic location within the brain. This has not yet been clearly demonstrated for two main reasons. Firstly, neuropsychological studies of these patients have so far used small numbers and have been insufficiently powered to detect meaningful correlations between specific cognitive deficits and location of the BAVM. Secondly, whereas many higher cortical functions were at one time attributed to a specific lobe of the brain, it is now widely appreciated that neuronal circuitry is far more complex than this.

Despite these limitations, there is a small body of published literature regarding how BAVM may impact on the neuropsychological ability of these patients. In the early nineties, Mahalick performed cognitive assessments on 24 patients: he found baseline deficits in both verbal and visuospatial processing compared with
controls(137). These deficits appeared more pronounced in the hemisphere contralateral to that of the BAVM, supporting the steal theory. In a subgroup (14 patients) of the same cohort undergoing microsurgery, he observed postoperative neuropsychological gains in areas of learning, memory and higher integrative thought(139). Mahalick's findings are at conflict with an earlier study also involving surgical patients(140). Although adults diagnosed with BAVM seem to have met their developmental milestones during childhood, a single, retrospective case–control study found that 44 patients affected by BAVM were more likely to have had a disorder of learning or behaviour during their school years(141). Unlike those observed with other focal lesions of a similar size, such as tumours and infarctions, BAVM-related neuropsychological deficits seem to be related to the hemisphere both ipsilateral and contralateral to the lesion(142). Again, this seems to support the theory of vascular steal. There are scant data on the cognitive aspects of BAVM (and none on Irish populations). This study tests the hypothesis that BAVM patients are susceptible to neuropsychological deficits at the time of diagnosis, and where they do exist, that these deficits may improve following treatment of the underlying lesion.

9. Coagulation

There are no available data on the relationship of endovascular embolisation of BAVM with blood coagulation. Previous studies involving embolisation of hepatic(143), renal(144) and uterine(145) arteries have all shown an increase in surrogate markers of hypercoagulability post-treatment. These findings suggest that a prothrombotic state may arise during or shortly after the procedure. The authors of these studies analysed pre- and post-procedural serial assays of numerous factors and found there were significantly elevated levels of thrombin-antithrombin complex, prothrombin fragment, platelet factor 4, D-dimer and plasmin-α2-antiplasmin complex following embolisation.

Von Willebrand factor (VWF) is a large plasma glycoprotein that plays a crucial role in haemostasis. Although this protein has mostly been of interest to scientists
in terms of its role in various bleeding diatheses such as the eponymous von Willebrand disease, it is well documented that elevated levels are observed in acute ischaemic stroke(146-148). The location of VWF synthesis and storage also offers a clue to its physiological function, which is closely linked to that of blood platelets. Platelets pass through the circulation uninterrupted until they detect any vascular defects, at which point they will adhere to and aggregate at the site of vascular injury. This process, known as primary haemostasis, represents the first line of defence against bleeding from an injured vessel. Although VWF is not an enzyme and has no catalytic activity, one of its major functions is to act as “mediator” between platelets and the collagen receptors of the endothelium(149). Secondary haemostasis comprises later events of stimulated clotting, which generate thrombin and finally lead to fibrin formation that stabilizes the platelet aggregate at the site of vessel wall injury.

VWF is synthesised by and stored in both endothelial cells and megakaryocytes, the platelet precursor haematopoietic cells residing in the bone marrow(150). In effect, arterial embolisation is deliberately induced ischaemia and damage of endothelium. Endothelial cell activation subsequently results in elevated levels of VWF which in turn promotes haemostasis by way of platelet adhesion and aggregation(151). Disruption of normal haemostatic mechanisms may therefore have implications for the neurological outcomes of BAVM patients undergoing endovascular embolisation. Haemostasis in humans is regulated by a series of complex anti and prothrombotic factors. Many of these factors are intimately related to platelets, their subunits and associated regulatory enzymes such as ADAMTS-13(152, 153). VWF also serves as a stabilizing carrier of factor VIII: deficiency of VWF can prolong the activated partial-thromboplastin time and increased levels may reduce it. The focus of our study however was limited to two assays: levels of VWF antigen (VWF:Ag) and the VWF collagen binding assay (CBA, or referred to also as VWF:CB). The CBA gives an indication of the ‘state’ of the VWF multimers that are present in that plasma sample. The VWF:Ag assay is a direct assay to determine the concentration of VWF in the plasma, while the CBA gives the level of binding of these VWF multimers to collagen. Smaller multimers (broken down by ADAMTS-13) would
give a lower reading in the CBA compared to the VWF assay. Derangement in VWF and CBA assays may serve as a guide to whether more complex experiments or studies (such as ADAMTS-13 activity) should be done on those samples. It would also be reasonable to postulate that such derangement might predispose to a prothrombotic state by activation of platelets.

10. Diagnosis

10.1 Computed Tomography (CT)

BAVM have been recognized increasingly since the development of catheter angiography in 1927 by the Portuguese neurologist Dr. Egas Moniz(154). Image resolution of CT and MRI has steadily improved over the last thirty years and increased their detection further, especially when used in conjunction with intravenous contrast agents(6). The widespread availability of CT make it the first test an individual with an BAVM might have had at their initial presentation. Unenhanced scans may only show an asymmetry in the density of brain parenchyma to suggest an underlying vascular malformation and smaller BAVM can be missed altogether. Contrast-enhanced CT is a more sensitive tool because it may reveal the dilated vasculature of an BAVM with a serpiginous pattern of contrast enhancement(155). Even following the administration of an intravenous contrast agent however, BAVM can occasionally be confused with low-grade gliomas, especially when the BAVM is thrombosed(156).

10.2 Magnetic Resonance Imaging (MRI)

A particular strength of MRI lies in its evaluation of BAVM nidus size and its anatomical relationships(157). It is also helpful in the detection of BAVM underlying intraparenchymal haemorrhage, especially in the context of recurrent haemorrhage(158, 159). With the development of increasingly sophisticated technologies such as 3 Tesla MRI, the accuracy of such non-invasive techniques may even match that of conventional angiography.
What is clear is that even with the limitations of spatial resolution found with CT or 1.5T MRI, this technology plays an important role in the investigation of BAVM: they are non-invasive, cheaper and more widely available than conventional angiography, and occasionally underlying vascular malformations suspected on CT or MR are not even confirmed on formal angiography (so-called “cryptic” or “occult” vascular malformations)(160, 161). Although it is true that BAVM may not be evident on an initial angiogram because of compression of the nidus by haematoma, careful retrospective review of imaging often confirms subtle abnormalities to suggest the diagnosis(162).

10.3 Functional Imaging

Advances in functional imaging may facilitate future management of patients with BAVM. The current clinical role of these modalities is predominantly reserved for pre-operative characterisation of lesions which are felt to lie close to or within eloquent areas of the brain. For example, functional magnetic resonance imaging (fMRI) can identify subtle increases in metabolic activity in specific areas of the brain during certain speech or motor tasks. Diffusion tensor magnetic resonance imaging (“tractography”) may be used to identify important white matter tracts which run within or close to the lesion. These tools are now widely available and there are recent published data regarding localization of functionally important areas of the brain in the presence of BAVM(163-165). The importance of these imaging techniques is becoming more evident as correlations are made between radiologically acquired functional data and the neuropsychological aspects of BAVM. A number of recent studies support the idea of “cortical reorganization”: Lazar and Vikingstad have both used fMRI to show that BAVM patients have evidence of transfer of language from one cerebral cortex to another(138, 166) while research from Switzerland described nine patients with BAVM located in the main motor cortex that showed there was either reorganisation within the main motor strip or displacement of
functions to unaffected regions both of the primary and non-primary motor cortex (167).

10.4 Intra-Arterial Digital Subtraction Angiography (IADSA)

There is, therefore, no single definitive investigation for BAVM. Although many clinicians have a preference for lower-risk, non-invasive imaging at least as an initial step towards diagnosis, and non-invasive techniques such as CT are cheaper and more widely available, the complex anatomical and haemodynamic nature of these vascular lesions still requires invasive catheter angiography for thorough evaluation and planning of a subsequent management strategy. In patients with primary intracerebral haemorrhage where a cause has not been established, IADSA should generally be performed in everyone apart from those over 45 years of age with pre-existing hypertension and haemorrhage in deep locations (168). As mentioned already, IADSA is not 100% sensitive for BAVM diagnosis, and a negative cerebral angiogram in the hyperacute stage may justify a delayed angiogram. Regarding subarachnoid haemorrhage of possibly occult aneurysmal aetiology, there is almost unanimous agreement that repeat IADSA should be pursued if the patient suffers a recurrent haemorrhage, or if the initial examination was technically inadequate, affected by vasospasm or did not cover both carotid and vertebral arteries (169-171). With intracerebral haemorrhage where an underlying BAVM is more likely, however, authors have differed in their opinions on whether MRI is sufficient in these situations (172) and a prospective comparison of MRI with IADSA in the follow-up of occult BAVM is needed.

Research on the utility of other techniques such as transcranial Doppler ultrasonography (173) and multiplanar reconstructed CT angiography (174) also have potential in the evaluation of a condition for which a multimodal investigative approach remains so crucial.
11. **Treatment**

The last decade has ushered in significant advances in the management of cerebral BAVM. Multimodal treatment strategies are now often employed, offering hope to those patients previously deemed untreatable. Information on the natural history of BAVM is scarce and to date there has been no published randomized controlled trial comparing different treatment modalities with each other, or indeed with no treatment at all. One large, ongoing, multicentre trial examining this issue is A Randomised trial of Unruptured Brain BAVM (ARUBA), which aims to capture 800 consecutive patients in approximately 100 institutions from around the globe (www.arubastudy.org). This work will hopefully serve to address some of the difficult questions regarding which interventional therapy is best in a given situation, as compared with the natural history risk.

11.1 **Microsurgery**

Microsurgical resection still remains the gold standard of treatment and has the advantage of offering complete removal of the lesion in one session. The efficacy of surgery in obtaining angiographic cure is in the region of 94-100% with low morbidity (1.3-10.6%) in small BAVM (<3.0cm in diameter)(175, 176) although even for small lesions with Spetzler-Martin grade 1-3, BAVM in eloquent locations often entail significant and perhaps disproportionate morbidity(177, 178). Risk factors for surgical complications include nidus size and location, and presence of deep venous drainage(52). General consensus is that for small (<10ml volume nidus), cortically-based, non-eloquent BAVM, surgery in an experienced BAVM centre offers a high cure rate with a low risk of complications.

11.2 **Embolisation**

The aim of endovascular therapy is to obliterate feeding arteries at the site of the nidus with embolic agents. N-butyrylcyanoacrylate (NBCA), detachable metal coils, polyvinyl alcohol particles and Onyx liquid polymer have all
been used (179, 180), but only NBCA has been shown to offer a chance of permanent vascular occlusion (181, 182). Usually one or more embolisation procedures is required and the treatments are staged according to the overall management plan. As it is the least successful technique for outright cure when used in isolation (some studies have reported efficacy of as little as 10% (183, 184)), embolisation is often employed for the purpose of BAVM size reduction prior to surgery, radiosurgery or both as part of a multidisciplinary approach. Despite the low rates of outright cure for large lesions, partial embolisation targeted towards “weak spots” such as intranidal aneurysms and fistulae has been shown to reduce the long term risk of haemorrhage by between 24-78% when compared with the natural history of BAVM as described by Crawford et al (119). On the other hand, complete occlusion of BAVM with a nidus less than 1cm have been documented in 85% in one recent series (185). In reality, partial embolisation is often the only treatment option, as many large BAVM are unsuitable for radiosurgery and lie in unresectable locations such as the brainstem.

11.3 Stereotactic Radiosurgery

This treatment modality uses a gamma knife, particle beam or linear accelerator to deliver high-energy beams to the site of the nidus. It offers many advantages over surgery. When used alone or in conjunction with endovascular embolisation, it avoids the need for a surgical incision and general anaesthetic. It is suitable for many deep-seated lesions which the neurosurgeon deems inoperable. It is also fundamentally different from embolisation and surgery in that the outcome is largely predictable and thus suitable for accurate outcome models: the frequency of obliteration is independent of patient and BAVM parameters and only depends on the radiation dose to the periphery of the lesion (186). Observations that obliteration may come later and success rates are lower in large BAVM are misleading. Large BAVM do not have a lower sensitivity to radiation, but
these BAVM do receive lower doses to reduce the risk of radiation-related complications.

Radiosurgery is not without its disadvantages. Careful consideration should be given to the expected delay in complete obliteration following treatment. This is generally accepted to be at least two years but recent data suggest this “latent” period is considerably longer, extending to almost five years post-treatment in some cases(187). Because of this delay to complete cure, many clinicians (and patients) are reluctant to pursue radiosurgery where haemorrhage has been presenting feature. Due the lower doses employed, it is less effective for treating large BAVM (volume >10ml). Total doses of ionizing radiation are often very high. These high doses frequently result in complications such as haemorrhage in the early phases post-treatment, and cranial palsies, radionecrosis and pseudocyst formation later on(188, 189). The risk of haemorrhage post treatment is related to the age of the patient and volume of the BAVM nidus, and approximately half of all haemorrhages occur in the first six months following treatment(190). A study of 756 patients treated with linear accelerator radiosurgery over a 15-year period revealed that 7% of patients experienced haemorrhage post-treatment and 10% of these cases proved fatal(191). The effectiveness of radiosurgery has been established in the treatment of arteriovenous malformations with a diameter of 3cm or less, and angiographic cure can be expected in 81-90% of these patients, with lower rates for larger lesions(192, 193).

12. **Outcome**

12.1 **Risk of Death**

There have been no prospective, long-term, population-based, purely epidemiological studies on the risk of death due to BAVM. It is important to distinguish between the BAVM “mortality rate” (number of deaths per 1000 of the general population in a given time period) and the “case fatality” rate,
which is the number of deaths within a group of patients who are known to harbour an BAVM. For this reason, detailed information about the early and long-term risk of death for people with an BAVM is sparse. A methodical review of 2 large population-based studies by Al-Shahi’s group(194) has recently determined that the case fatality of BAVM-related haemorrhage is 12% over a two year follow-up period, compared with 61% in so-called “spontaneous” intracranial haemorrhage (where an underlying cause is not revealed and the clinical event is attributed to one or more of a number of vascular risk factors such as arterial hypertension). The authors used multivariate analysis to demonstrate that these findings were independent of age and other known predictors of intracranial haemorrhage outcome. In the longer term, crude annual case fatality rates appear to lie between 1 and 1.5% per annum(90, 119). Data from the Co-operative study also suggest that people with a haemorrhagic presentation of an BAVM have a lower case fatality compared with aneurysm rupture(32). Case fatality rates as low as 0% over a 1 year follow-up in hospital-based series published by the Columbia group(95, 195) are probably influenced significantly by selection-bias as severe cases of BAVM-related haemorrhage are more likely to avoid ascertainment (i.e. die in the community). Selection-bias in hospital-based studies is not uncommon and the only way these obstacles can be overcome is by conducting more prospective, population-based studies with a sound epidemiological basis.

12.2 Risk of Haemorrhage

Our poor understanding of the natural history of unruptured BAVM lends itself to a culture of intervention even though we have no concrete evidence that this tactic results in better outcomes than a conservative “watch and wait” approach. The best population-based studies suggest an annual risk of haemorrhage of between 2-4%(90, 108, 119). These figures are supported by more recent estimates by a Finnish group of 2.4% per year in a study conducted over a 13-year period(196). Brown also found that the co-
existence of aneurysms at baseline conferred a higher annual rate of haemorrhage for people with unruptured BAVM(59). As haemorrhage is the most common presentation of BAVM, there has been more extensive research into the causes of recurrent events rather than first-ever-occurrence. Those patients who have already bled carry a risk greater than 2-4% per year quoted above. Evidence exists that a ruptured BAVM has become destabilized, pushing the risk of re-haemorrhage to as high as 18% in the first year(95).

12.3 Morbidity Associated with Haemorrhage

Morbidity related to BAVM rupture is difficult to measure as different studies have used different outcome measures: a scale with four grades ("good", "fair", "poor", and "dead")(197), five grades ("no deficits", "moderate disability", "severe disability", "persistent vegetative state", and "death")(119) and the modified Rankin scale (0=no symptoms at all to 5=severe disability, bedridden, incontinent and requiring constant nursing care and attention)(195). Even some well-known studies have used no specific scale of functional outcome at all(90, 108). When comparing population-based data of patients with BAVM-related ICH and those with spontaneous ICH, the SIVMS investigators(194) found that the median modified Rankin score (mRS) 1 year post-haemorrhage was 2 in the BAVM group compared with 6 in all other patients. Higher numbers of patients experiencing spontaneous ICH were dead or dependent (mRS ≥3) at 1 and 2 years follow-up than those with BAVM-related haemorrhage. The risk of death or dependence for patients with spontaneous ICH was more than seven times higher than BAVM-related ICH at 1 year, and 15 times higher at 2 years. The risk of death and dependence remained significantly higher even when adjusting for age. Brown et al. did not find any severe or disabling outcomes in a study of 166 patients with ruptured BAVM during 8 years of follow-up(108) and similar results were found by the Columbia group in a study of 119 patients(195). These observations could be for a number of
reasons. BAVM patients tend to be younger, BAVM-related haemorrhage generally arises from vessels at a lower pressure than aneurysmal subarachnoid haemorrhage (SAH) or spontaneous ICH, vasospasm due to BAVM-related haemorrhage (unlike SAH) is uncommon and when it does occur it is usually very mild(198), and haemorrhage is usually parenchymal and limited to the nidus of the BAVM.

12.4 Risk of Developing Seizures

Approximately 30% of BAVM patients present with seizures(119). Although a number of aspects of angioarchitecture has been linked to a first presentation of seizures, such as cortical location and increasing size(110), these associations are difficult to validate as the complex anatomical features underlying BAVM and their numerous modes of presentation may confound each other. Epilepsy syndromes related to BAVM seem to respond well to treatment: one study reported that 66% of patients were seizure free following treatment with surgery, radiosurgery, embolisation or a combination of two or more of these (although 6% of patients who had not had seizures prior to treatment developed epilepsy de-novo)(199). BAVM-related seizures also appear to respond well to anticonvulsant therapy, with one study reporting a success rate of 78%(200). From the available data, it appears that patients with BAVM carry an annual risk of developing de novo seizures of 1%, and they may be at a greater risk following presentation with haemorrhage, or if they are older(112).
CHAPTER 2: STUDY AIMS AND HYPOTHESES

1. Study Aims

1.1 Primary Aims

(a) To determine prospectively the epidemiological characteristics and range of clinical presentations in consecutive patients referred to the specialist interventional neurovascular service of a single centre over an 18 month period. Our study provides data on the relative frequencies of different modes of presentation such as PICH, seizures and headaches in a consecutive hospital sample. Although the cohort is small and not entirely representative of the frequencies of these syndromes in the Irish population for the reasons outlined above, this will be the only detailed insight into the epidemiology of BAVM in Ireland and the range of associated clinical presentations. In addition, the study examines the range of modes of presentation in an Irish patient sample and how they compare with published international data. Although the cohort is hospital-based and relatively small, this single-centre experience in a busy specialised centre of neuroscience will provide valuable and novel data on clinical characteristics of BAVM of patients in this country;

(b) To define the angioarchitecture in the patient cohort and correlate with haemorrhagic vs. non-haemorrhagic clinical presentation. To date, no published Irish data exist on the range of anatomical features in these patients. This study documents the various aspects of angioarchitecture in a consecutive hospital cohort of Irish patients presenting with BAVM and comparisons with the available international literature are made. We examine the use of differing imaging modalities in an Irish setting and their application in management and treatment of BAVM in an Irish patient cohort. Although imaging technologies are constantly developing, our
institution has benefited from the recent installation of a new, 1.5 Tesla MRI machine (Siemens) and a €1.5 million upgrade to the neuro-interventional suite where embolisation procedures take place. These state-of-the-art facilities permit sensitive detection of BAVM and comprehensive evaluation of associated angioarchitectural features;

(c) To determine the treating clinician's choice of management (i.e. endovascular vs. surgical vs. radiosurgery) in the cohort either alone or in combination and investigate the associations of treatment choice with clinical presentation and angioarchitecture. In the chapters below, the various treatment strategies are presented in a consecutive hospital cohort of Irish patients. The multimodality approach to the management of BAVM is described in detail. We outline the relative frequencies of patients receiving different treatments and what features of angioarchitecture may influence these treatment decisions;

(d) To determine BAVM cure rate and reduction in BAVM size overall in the cohort and according to treatment modality based on follow-up imaging (either with MRI or catheter angiography) at one-year. The methodology of BAVM size measurement is discussed below;

(e) To use a standardized neuropsychological battery formally to assess cognitive function before and after treatment and explore 1) baseline deficits when compared with matched controls and 2) potential factors associated with cognitive improvement or decline in the cohort post-treatment. This study uses sensitive and psychometrically sound instruments to evaluate serially the cognitive functioning in BAVM patients. This is challenging for a number of reasons, not least of which is the need to use measures which are 1) psychometrically stable when repeated over time and 2) sufficiently
sensitive to identify subtle areas of cognitive impairment in otherwise normal functioning patients. Furthermore, it is possible that the location of the BAVM will impact significantly on the cognitive processes associated with that region or circuitry and as such, a detailed neuropsychological protocol that examines a range of cognitive domains is also essential. The study systematically employs a range of standardised and validated neuropsychological instruments to evaluate the cognitive performance of patients before and after treatment for BAVM. Unlike the few studies available in the literature, most of our patients underwent endovascular embolisation either as a lone therapy or combined with another treatment. This study therefore aims to provide novel data on 1) baseline neuropsychological characteristics of patients with BAVM and on 2) subtle cognitive deficits that may result from small reductions in the volume of the underlying BAVM. The tests employed are listed in Appendix I;

(f) To assess independently the effects of the different treatment modalities selected by the clinician on new neurological and cognitive impairment and mortality at a structured follow-up assessment. Comparisons between the different treatment groups are made in terms of level of disability at follow-up. Particular focus is placed on treatment-related complications which in some cases have major implications for the independence and level of functioning of individuals within the cohort.

1.2 Secondary Aims

(a) To measure plasma levels of specific surrogate markers of endothelial cell activation (and subsequent predisposition to haemostasis) in the patient cohort in the peri- and post-embolisation period. Elevations of these markers were sought to determine
whether thrombosis within a BAVM (as induced by endovascular embolisation) is associated with new neurological impairment or cognitive decline in the cohort. In this preliminary investigation of haemostasis in a subset of our cohort, we seek to provide novel data on the impact of endovascular embolisation on endothelial cell function in patients with BAVM. Iatrogenic disruption of coagulation cascades could have serious implications for both the clinical and cognitive outcome of these individuals.

2. Hypotheses

2.1 That BAVM are associated with impaired cognitive function at the time of diagnosis, as determined by assessment using a validated neuropsychological test battery.

2.2 That these specific deficits may be attributable either to the location of the lesion or the contralateral hemisphere.

2.3 Where such cognitive deficits exist, that there is an improvement in baseline cognitive function following treatment as determined by implementation of the same test battery at 12 month follow-up.

2.4 That embolisation of BAVM results in alteration of both the concentration and molecular state of VWF, indicating in turn that these patients are predisposed to a prothrombotic state by means of platelet activation and subsequent.

2.5 That such a prothrombotic state is associated with an alteration in cognitive status within the cohort as a result of increased thrombosis within or around the BAVM.
CHAPTER 3: METHODS

1. General

This was an observational, prospective, hospital-based cohort study which recruited patients admitted to Beaumont Hospital between January 2007 and June 2008 for investigation and management of BAVM. Ethics approval was sought from and granted by the Beaumont Hospital Medical Research Ethics Committee. Patients were newly diagnosed on the basis of either IADSA or MRI. All patients considered suitable for treatment underwent IADSA as part of their workup. All MR imaging included an axial T2-weighted sequence to demonstrate flow void within the nidus of the BAVM. All catheter angiography was performed via either common femoral artery and the Seldinger puncture technique. A 5-French sheath and 5-French Weinberg angled-tip catheter was used as standard. Selective contrast injections of both internal and external carotid arteries and both vertebral arteries was performed. Imaging was acquired by means of a biplanar, flat-panel, digital detector. Most, but not all, patients had a CT scan of the brain, either with or without intravenous contrast.

The study was carried out on hospital inpatients only and all participating patients received standard clinical care, investigations and monitoring during the study period. Enrollment did not alter normal patient management or affect clinical decisions made by the primary caring neurologist or neurosurgeon.

The study consisted of the following:

1.1 Inpatient interview with data collected on patient demographics (age, gender and educational level), medical and neurological history, medications, vascular risk factors, including hypertension, diabetes, dyslipidaemia, heart disease, smoking and excess alcohol consumption, migraine, prior stroke/TIA;

1.2 Structured medical and neurological examinations;

1.3 Administration of standardised stroke rating and functional scales (National Institutes of Health Stroke Scale [NIHSS] and Barthel Index: see appendices II and III);
Structured analysis of the BAVM angioarchitecture based on formal cerebral angiography and determination of Spetzler-Martin grade. BAVM size was determined collaboratively by two consultant neuroradiologists by measurement of the maximum diameter of the lesion on either MRI or IADSA;

Comprehensive neuropsychological assessment before treatment and at 18-month follow-up using standardised and validated scoring systems. This battery is sufficiently detailed to permit a comprehensive evaluation of cognitive functioning in these patients but reasonably brief such that it can be completed in approximately 1 hour on at least two occasions;

Measurement of plasma levels of specific surrogate markers of endothelial cell function before and after treatment in a sub-group of the sample.

2. **Inclusion Criteria for patients**

2.1 All male and female adults (aged sixteen years or more) admitted to Beaumont Hospital with newly diagnosed BAVM. Prior to enrollment, all patients were given a detailed information leaflet to read and then asked to sign a consent form explaining the reasons for and aims of the study;

2.2 In the case of grossly cognitively impaired patients, assent from the next-of-kin/relative was sought: information leaflets were also given to them explaining the study and they were asked to sign assent forms as legal representatives.

3. **Exclusion Criteria for patients**

3.1 Prior stroke;

3.2 Recent history of significant head trauma;

3.3 Extracranial and spinal AVM;

3.4 Dural arteriovenous fistulas and cavernous or venous angiomas (all vascular malformations, but with characteristics different to AVM);
3.5 Children and Minors (<16 years);

3.6 Known history of systemic bleeding or clotting diathesis;

3.7 Patients taking oral or intravenous anticoagulant therapy prior to first presentation (warfarin or heparin).

4. **Inclusion criteria for controls**

4.1 Healthy age- and education-matched adult volunteers were selected from the patients’ immediate families (spouse, partner or sibling). Where this was not possible, healthy age- and education-matched volunteers from the Beaumont Hospital staff list were selected (where a supervisory or dependent relationship did not exist). Controls were given information leaflets and asked to sign a consent form before enrollment;

5. **Exclusion criteria for controls**

5.1 Prior stroke;

5.2 Recent history of significant head trauma;

5.3 Extracranial and spinal AVM;

5.4 Dural arteriovenous fistulas and cavernous or venous angiomas (all vascular malformations, but with characteristics different to AVM);

5.5 Children and Minors (<16 years);

6. **Participants**

Surveillance for potential participants was carried out using the A+E computer system and the stroke consult service. In addition, daily liaison with the neurosurgery and neuroradiology departments in Beaumont Hospital ensured that electively admitted patients were also approached. Patients with radiologically confirmed BAVM who fulfilled the inclusion and exclusion criteria were approached and given verbal and written information concerning the study.
7. **Neuropsychology**

All patients presenting to Beaumont Hospital between January 2007 and June 2008 with a new diagnosis of BAVM were approached. Those considered well enough were asked to participate in the neuropsychological limb of the study. Following written consent, individuals were assessed as soon as possible following diagnosis and before commencement of endovascular embolisation, microsurgery, stereotactic radiosurgery or a combination of these treatments. The author was trained in the use of a battery of standardized cognitive instruments and questionnaires. Neuropsychological evaluation was performed in a quiet environment and implementation of the entire battery took approximately one hour. 20 of the 31 patient cohort participated in the neuropsychological limb of the study. 6 patients presented with haemorrhage and were too unwell to co-operate with the assessment. 5 other patients were embolised or brought to theatre for surgical intervention before there was time to perform a full cognitive assessment. Patients were reassessed at a later date following treatment with one or more of the above modalities. Mean follow-up was 18 months and the earliest was 10 months after initial assessment. Premature follow-up (i.e. less than 6 months) was avoided to prevent the “practice effect”, where patients may have spuriously high test scores because of the familiarity of the questions in the test battery. Control subjects were also assessed following detailed explanation and written consent. These controls were age- and education-matched and were either close family members or recruited from the Beaumont Hospital staff list provided that a supervisory or dependent relationship did not exist. Results of patients’ assessments pre-treatment were firstly compared with controls to detect baseline cognitive deficits. Pre- and post-treatment comparisons were then performed to detect any changes in cognitive function that had arisen from the intervention.

8. **Coagulation**

We conducted a pilot study to determine plasma levels of VWF:Ag perform the collagen binding assay (VWF:CB) at set time intervals: The endpoint of this preliminary investigation was to determine firstly whether the embolic material used in a standard brain BAVM embolisation procedure induced endothelial cell activation (as indicated by elevated levels of VWF:Ag) and secondly the level of
binding of these multimers to collagen (VWF:CB). Where abnormalities in the above assays existed, our intention was to pursue whether such abnormalities signified a prothrombotic state that could be associated with new neurological impairment or cognitive decline post-embolisation.

In our institution, all brain BAVM are embolised with a liquid tissue adhesive compound of N-butyl-2-cyanoacrylate and methacryloxyxsulfolane (Glubran 2®), diluted with lipciodol, an iodinated, radio-opaque, oil-based contrast agent. Volumes used for embolising are small (approximately 0.5-1ml in total for each embolisation procedure).

BAVM patients undergoing embolisation were asked to donate 2 ml of venous blood on five different occasions: 1) at baseline (immediately prior to the procedure); 2) immediately after the procedure; 3) one hour after the procedure; 4) two hours after the procedure; and 5) 24 hours after the procedure. Following written consent, the samples were collected into 3.2% citrate and immediately placed on ice. After centrifugation at 3000g for 20 minutes at 4°C, plasma aliquots were obtained and stored at -80°C until assessment. Plasma VWF:Ag levels were determined by using a standard sandwich ELISA technique. Ninety-six-well plates were coated with rabbit polyclonal anti-human VWF antibodies (Dako) diluted 1:500 in 0.05 mol/L (pH 9.6) carbonate buffer overnight at room temperature. After a washing with Tris-buffered saline (TBS) containing 0.05% Tween, the plates were blocked for nonspecific binding with TBS containing 1% bovine serum albumin (Sigma Chemical Co.) for 1 hour. After 3 further washings, the plasma samples were added to the wells and incubated for 2 hours at room temperature. All samples were tested in duplicate at 6 different dilutions. The plates were washed with TBS/Tween and then incubated with a rabbit polyclonal anti-human VWF peroxidase conjugate (Dako) diluted 1:500 in TBS/Tween for 1 hour. After 3 further washings, the plates were incubated with a substrate solution. The reaction was stopped with 1 mol/L H₂SO₄, and the optical density was measured at a wavelength of 492 nm. Dilutions of 100% reference plasma (VWF:Ag 1.05 IU/mL, Immuno) were used to construct standard curves for calibration. The intra-assay and interassay coefficients of variation were <5%. VWF:CB levels were also measured using the commercial ELISA technique (Technoclone, UK) but ambient
temperature was maintained at 37°C for the 2 hour plasma incubation period as per the manufacturer’s guidelines. The concentrations of VWF:Ag were derived from a standard curve that had been processed using industrial reference plasma.

9. Statistical Methods

Chi-squared analysis was performed to compare proportions between patient groups in terms of their clinical, demographic and radiological characteristics. Formal power calculations were not applicable to the overall descriptive aims of the study (i.e. reporting the epidemiological characteristics, range of presentations and defining the angioarchitecture in the patient cohort). Prior to undertaking primary comparisons of cognitive function, we calculated that to detect a primary difference of 10% in neuropsychological test variables between patients and controls (setting α at 0.05 1-β at 0.80) we would need 25 patients. Our entire cohort included 31 patients but only 20 were suitable for participation in the neuropsychological limb of the study. Our study was therefore underpowered to detect subtle differences between both the independent (patients vs. controls) and paired groups (time 1 vs. time 2). Numerous cognitive outcomes of the patient group at baseline were compared with those of the control group. As those patients presenting with haemorrhage would perhaps be expected to under-perform across different cognitive domains, separate comparisons were also made between unruptured cases and controls. Despite a very well matched control group, exploration of the dataset revealed that the results of a number of the cognitive sub-tests were not normally distributed. Non-parametric methods were therefore used for both independent and and paired samples analysis. The Mann Whitney test was used to compare medians of the patient and control groups, and the Wilcoxon signed-rank order test was used to perform before and after treatment comparisons of the inter-patient median cognitive scores. Because of the relatively large number of median comparisons in the cognitive dataset, the alpha level was lowered with a Bonferroni adjustment to reduce the risk of committing a type-1 error. Using non-parametric analysis by means of the Kruskal-Wallis test, correlations were also sought between clinical, demographic and radiological features and cognitive outcome. All statistical analyses were performed using a validated statistical software package (SPSS 17.0, California).
CHAPTER 4: RESULTS

1. Clinical and Radiological

1.1 Clinical and Radiological - Patient Characteristics

In Beaumont Hospital over the 18-month period from January 2007 to June 2008, 31 patients were diagnosed with BAVM. The individual characteristics of these patients are outlined in table 2. The vast majority of BAVM in our cohort were located supratentorially, with two in the brainstem and one in the cerebellum. Interestingly, one patient had two small separate BAVM, one in close relation to the insular grey matter and the other in the contralateral deep white matter of the frontal lobe. This patient was of Irish origin and had no relevant medical or family history. The mean age at presentation was 41 years (SD 14.2, range 21-65) and 16 (51%) patients were male. 13 (42%) presented with haemorrhage, 12 (39%) with seizures, 4 (13%) with headache unrelated to haemorrhage and 2 (6%) with focal deficits. One patient in the haemorrhagic group had subarachnoid haemorrhage with no underlying aneurysm and another had intraventricular haemorrhage without a parenchymal component. Both of these patients presented with an incongruous homonymous hemianopia. No cases were diagnosed incidentally. 12 (39%) patients were smokers and 4 (13%) had underlying hypertension or cardiovascular disease. Mean NIHSS and Barthel scores at presentation were 2.4 (SD 4.2) and 94.2 (SD 16.1) indicating minimal overall stroke severity and dependence respectively.

When these cases were sub-divided into haemorrhagic and non-haemorrhagic presentations, the patients in the haemorrhagic group still had relatively low morbidity (mean NIHSS score 5.38 and Barthel index score of 86.15 indicating mild disability). Those in the non-haemorrhagic group unsurprisingly had very low mean NIHSS score (0.17) and no disability (mean Barthel index score 100). The majority of lesions were located supratentorially. In two patients they were located in the brainstem and in one case in the cerebellum. The other features of angioarchitecture are outlined in table 3.
A major complication of treatment was defined as a stroke event. One hour following embolisation, patient 3 developed a partial third cranial nerve palsy which was incompletely resolved at 30-month follow-up. Patient 7 experienced rupture of an intranidal vessel during embolisation and had resultant subarachnoid haemorrhage. She had no neurological deficits immediately after the procedure and had good recovery. Patient 18 underwent primary resection of deep seated temporal lobe lesion. He developed a dense hemiparesis secondary to vasospasm following surgery and was still wheelchair-bound at 19-month follow-up. Patient nineteen also had vessel rupture during embolisation and developed a dense hemiparesis. Despite emergent evacuation of the intraparenchymal haematoma and underlying BAVM, she remained wheelchair-bound at 17-month follow-up. Patient 28 had intranidal vessel rupture during embolisation and developed a mild hemiparesis which was almost completely resolved at 14-month follow-up. Major complications occurred in 4 patients during embolisation and 1 during surgery. Although this indicates that 17% of patients experienced a complication of treatment, it is important to note that those undergoing embolisation had multiple procedures over the study period. Of a total 92 embolisation procedures in 24 patients, this equates to a stroke risk of 4.3% per embolisation procedure.

The mean duration of follow-up was 18 months (range 11-30 months) at which time 11 cases (36%) had angiographically confirmed obliteration of the BAVM. 24 of 31 patients had embolisation as part of their treatment strategy. 9 patients (38% of all patients embolised) had ≥50% residual volume of BAVM nidus remaining at follow-up (table 4). This figure does not prove that endovascular treatment is less successful than surgery and radiosurgery in terms of cure: patients in whom embolisation was employed as a treatment strategy did not have identical demographic profiles, similar types and locations of BAVM and they were not all felt suitable for any modality of treatment. All six patients undergoing surgical resection had no evidence of residual BAVM on follow-up angiography. Of the 2 patients who travelled abroad for stereotactic radiosurgery, one had angiographically-proven
obliteration (19 months after the procedure) and the other had less than 50% residual (13 months after the procedure) at follow-up.

In terms of symptom control, none of the subjects presenting with haemorrhage had spontaneous re-bleeding of their BAVM. Among the four patients presenting with non-haemorrhagic headache, all those undergoing treatment reported either significant improvement or complete resolution of their symptoms at follow-up. The number is too small to draw correlations between symptom control and BAVM residual volume post-treatment. Eleven patients presented with seizures: only three of these had total seizure control at follow-up. It is interesting to note that none of these three patients had angiographic obliteration of their BAVM at follow-up. It is widely recognised that partial embolisation of BAVM offers little seizure control: this is usually achieved only by complete obliteration or concomitant medical therapy. Both patients with focal deficits (hemianopias) had mild improvement but still significant residual visual field deficits at follow-up. Of the five patients who experienced treatment-related complications, none had ruptured BAVM: three presented with headache, the fourth had a focal deficit (hemianopia) and the fifth presented with seizures. Only one of these patients was neurologically intact at follow-up (she had experienced subarachnoid haemorrhage during embolisation). On the other hand, as mentioned above, two were left wheelchair-bound.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex (MF)</th>
<th>Mode of presentation</th>
<th>Location (&amp; vascular supply)*</th>
<th>Presumed dominant hemisphere affected? (Y/N)</th>
<th>Spetzler-Martin grade</th>
<th>Treatment</th>
<th>Number of embolisation procedures</th>
<th>Major treatment complication (Y/N)</th>
<th>Follow-up duration (months)</th>
<th>NIHSS on presentation</th>
<th>NIHSS on follow-up</th>
<th>Barthel score on presentation</th>
<th>Barthel score on follow-up</th>
<th>Follow-up imaging (% residual)</th>
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<td>Seizure</td>
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<td>3</td>
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<td>33</td>
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<td>100</td>
<td>100</td>
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</tr>
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<td>Right occipital (PC/EC)*</td>
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<td>Embolisation</td>
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<td>100</td>
<td>100</td>
<td>≥50%</td>
</tr>
<tr>
<td>26</td>
<td>M</td>
<td>Haemorrhage</td>
<td>Left parietal (AC/MC/PC)</td>
<td>Y</td>
<td>4</td>
<td>Embolisation</td>
<td>6</td>
<td>N</td>
<td>12</td>
<td>2</td>
<td>1</td>
<td>100</td>
<td>100</td>
<td>≥50%</td>
</tr>
<tr>
<td>27</td>
<td>M</td>
<td>Seizure</td>
<td>Left parietal (MC)</td>
<td>Y</td>
<td>1</td>
<td>Embolisation</td>
<td>3</td>
<td>Y (†)</td>
<td>14</td>
<td>0</td>
<td>0</td>
<td>100</td>
<td>100</td>
<td>≥50%</td>
</tr>
<tr>
<td>28</td>
<td>M</td>
<td>Headache</td>
<td>Left midbrain (PC/MC)</td>
<td>N</td>
<td>3</td>
<td>Embolisation</td>
<td>3</td>
<td>N</td>
<td>13</td>
<td>0</td>
<td>0</td>
<td>100</td>
<td>100</td>
<td>≥50%</td>
</tr>
<tr>
<td>29</td>
<td>F</td>
<td>Seizure</td>
<td>Right temporal (MC/PC)</td>
<td>N</td>
<td>2</td>
<td>Embolisation</td>
<td>4</td>
<td>N</td>
<td>12</td>
<td>0</td>
<td>0</td>
<td>100</td>
<td>100</td>
<td>≥50%</td>
</tr>
<tr>
<td>30</td>
<td>M</td>
<td>Seizure</td>
<td>Left frontal (AC/MC/EC)</td>
<td>N</td>
<td>5</td>
<td>Embolisation</td>
<td>4</td>
<td>N</td>
<td>12</td>
<td>0</td>
<td>0</td>
<td>100</td>
<td>100</td>
<td>≥50%</td>
</tr>
<tr>
<td>31</td>
<td>M</td>
<td>Headache</td>
<td>Right frontal (AC/MC)</td>
<td>N</td>
<td>2</td>
<td>Embolisation</td>
<td>2</td>
<td>N</td>
<td>11</td>
<td>0</td>
<td>0</td>
<td>100</td>
<td>100</td>
<td>≥50%</td>
</tr>
</tbody>
</table>

*: lobe affected. Vascular supply is via anterior, middle, posterior cerebral (AC, MC, PC) and/or external carotid (EC) arteries. Lesions also supplied with crossflow from contralateral hemisphere are marked with Y.

Δ: not involved in neuropsychological analysis.

†: developed third cranial nerve palsy following third embolisation procedure.

‡: vessel rupture during third embolisation with subsequent haemorrhage (no significant residual deficits).

§: vessel rupture during second embolisation with subsequent vasospasm and large right middle cerebral artery territory infarct. Had successful delayed surgical resection.

Ψ: vessel rupture on third embolisation with subsequent seventh cranial nerve palsy and mild right hemiparesis.

ζ: vasospasm following surgical resection with subsequent large right middle cerebral artery territory infarct.

50
### Table 3: Collective Demographic, Clinical and Radiological Characteristics of BAVM Cohort.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number of patients (n=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>16 (51.6%)</td>
</tr>
<tr>
<td>Mean age (SD, range)</td>
<td>41 (14.2, 21-65)</td>
</tr>
<tr>
<td>Mean follow-up in months (SD, range)</td>
<td>17.8 (6.7, 10-33)</td>
</tr>
<tr>
<td>Type of presentation</td>
<td></td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>13 (42%)</td>
</tr>
<tr>
<td>Seizure</td>
<td>12 (39%)</td>
</tr>
<tr>
<td>Headache</td>
<td>4 (13%)</td>
</tr>
<tr>
<td>Focal deficit</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Mean NIHSS at presentation (SD)</td>
<td>2.4 (4.2)</td>
</tr>
<tr>
<td>Mean Barthel score at presentation (SD)</td>
<td>94.2 (16.1)</td>
</tr>
<tr>
<td>Smoking</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>12 (39%)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>Spetzler-Martin grade</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>5 (16%)</td>
</tr>
<tr>
<td>II</td>
<td>9 (29%)</td>
</tr>
<tr>
<td>III</td>
<td>10 (32%)</td>
</tr>
<tr>
<td>IV</td>
<td>4 (13%)</td>
</tr>
<tr>
<td>V</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>Size</td>
<td></td>
</tr>
<tr>
<td>&lt;3cm</td>
<td>19 (61%)</td>
</tr>
<tr>
<td>3-6cm</td>
<td>8 (26%)</td>
</tr>
<tr>
<td>&gt;6cm</td>
<td>4 (13%)</td>
</tr>
<tr>
<td>Eloquent of brain area</td>
<td></td>
</tr>
<tr>
<td>Non-eloquent</td>
<td>12 (39%)</td>
</tr>
<tr>
<td>Eloquent</td>
<td>19 (61%)</td>
</tr>
<tr>
<td>Venous drainage pattern</td>
<td></td>
</tr>
<tr>
<td>Superficial</td>
<td>12 (39%)</td>
</tr>
<tr>
<td>Deep</td>
<td>19 (61%)</td>
</tr>
<tr>
<td>Associated aneurysms</td>
<td>6 (19%)</td>
</tr>
</tbody>
</table>

### Table 4: Intervention Used and Extent of Angiographic Obliteration.

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Obliterated</th>
<th>&lt;50% residual</th>
<th>≥50% residual</th>
</tr>
</thead>
<tbody>
<tr>
<td>Embolisation</td>
<td>24</td>
<td>7</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Microsurgery</td>
<td>6</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Radiosurgery</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

1: 2 of 6 patients had surgery in conjunction with embolisation.
2: both patients had radiosurgery in conjunction with embolisation.
1.2 **Clinical and Radiological - Analysis**

Chi-squared analysis was used to compare proportions of patients in the dataset in terms of their clinical and radiological characteristics. The findings are outlined in table 5. All six patients undergoing surgical resection demonstrated angiographic obliteration of BAVM on follow-up (p=0.001) but no other significant relationships were found between mode of presentation, angioarchitectural features, type of treatment received and angiographic outcome at follow-up. Spearman’s rank order test was used to confirm that there was no significant correlation between age at presentation and both NIH stroke score (p=0.837) and Barthel Index score (p=0.935). NIH stroke scores and dependence were low at presentation, even in patients with ruptured BAVM. Although unruptured BAVM were associated with virtually complete independence at baseline, post treatment follow-up described a different picture. Mann-Whitney analysis confirmed that although NIHSS (p=0.000) and Barthel (p=0.005) scores pre-treatment were significantly different in the haemorrhagic vs non-haemorrhagic group, in the post-treatment follow-up phase this discrepancy between the two groups had resolved (p=0.260 for NIHSS, p=0.696 for Barthel). Follow-up duration was similar in the two groups: mean follow-up was at 15.8 months in those presenting with haemorrhage compared with 19.2 months in those presenting with symptoms other than haemorrhage. However, it cannot be concluded that patients with ruptured AVM fared no worse at follow-up than unruptured cases as 1) only two patients with haemorrhage didn’t undergo treatment and 2) some patients who did not have a haemorrhagic presentation and were well at baseline had subsequent complications of treatment and as a consequence had developed new disability by follow-up. If the study group had an equal distribution of haemorrhagic and non-haemorrhagic cases, and these patient groups were followed-up for a similar duration, then more robust conclusions could be made regarding the benefits of treatment according to different modes of presentation. Five patients had treatment-related complications. One of these was from surgery and four resulted from embolisation. Four of these five patients were left with residual deficits (see table 2). Within this group of five patients, the mean NIHSS and Barthel scores were in the pre-treatment phase.
were 0.2 and 100 respectively, and 6.6 and 82 respectively in the post-treatment phase.
Table 5: Chi-squared Analysis to Compare Proportions in terms of Clinical and Radiological Variables.

<table>
<thead>
<tr>
<th>Comparison of variables</th>
<th>p value&lt;sup&gt;*&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mode of presentation&lt;sup&gt;+&lt;/sup&gt; vs. SM grade&lt;sup&gt;†&lt;/sup&gt;</td>
<td>0.405</td>
</tr>
<tr>
<td>Mode of presentation vs. surgery</td>
<td>0.172</td>
</tr>
<tr>
<td>Mode of presentation vs embolisation</td>
<td>0.072</td>
</tr>
<tr>
<td>Mode of presentation vs. angiographic outcome&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>0.454</td>
</tr>
<tr>
<td>SM grade vs. surgery</td>
<td>0.180</td>
</tr>
<tr>
<td>SM grade vs. embolisation</td>
<td>0.521</td>
</tr>
<tr>
<td>SM grade vs. angiographic outcome</td>
<td>0.037</td>
</tr>
<tr>
<td>Surgery vs. angiographic outcome</td>
<td>0.001</td>
</tr>
<tr>
<td>Embolisation vs. angiographic outcome</td>
<td>0.168</td>
</tr>
</tbody>
</table>

<sup>*</sup>: set for significance at 0.01  
<sup>†</sup>: haemorrhagic vs. non-haemorrhagic presentation  
<sup>‡</sup>: Spetzler-Martin grade of lesion (1-5)  
<sup>‡</sup>: obliteration; <50% residual or ≥50% residual volume on follow-up catheter angiogram
2. **Neuropsychological**

2.1 **Neuropsychological – Patient Characteristics**

Controls were matched to patients in terms of their age and educational background. The mean age of patients was 39.5 years and that of controls was 38.4 years. The mean value for total years of formal education was 12.4 years. Both groups were also administered the Weschler Test of Adult Reading (WTAR), which is a standardised and validated tool for estimating pre-morbid intellectual functioning. The mean score for the patient group was 88 and that of controls was 90. These characteristics (depicted in table 6) indicate that both patient and control cohorts were very accurately matched in terms of age and educational background. This is important to eliminate the possibility of selection bias when assessing cognitive performance in the 2 groups.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients (n=20)</th>
<th>Controls (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>7 (35%)</td>
<td>9 (45%)</td>
</tr>
<tr>
<td>Mean age (SD, range)</td>
<td>39.5 (2.9, 21-62)</td>
<td>38.4 (3.1, 21-60)</td>
</tr>
<tr>
<td>Mean years of education (SD, range)</td>
<td>12.4 (0.4, 9-16)</td>
<td>12.4 (0.5, 9-16)</td>
</tr>
<tr>
<td>Mean scaled WTAR (SD, range)</td>
<td>88 (3.7, 62-115)</td>
<td>90 (3.4, 64-110)</td>
</tr>
</tbody>
</table>

SD: standard deviation
Range: minimum-maximum

Table 6: Baseline Characteristics of Patients and Controls undergoing Neuropsychological Evaluation
2.2 Neuropsychological - Analysis

The Mann Whitney test was used to compare the patients with controls at baseline: Significant differences in performance were noted across multiple cognitive domains. Control subjects outperformed patients in almost every subsection of the neuropsychological test battery. Even when those patients who had presented with haemorrhage were excluded from the analysis, significant differences still existed between patients with unruptured BAVM and controls. The baseline differences between the groups are outlined in table 7. Only one patient failed the cortical vision screening test and there was no significant difference between the 2 groups with Chi-squared analysis (p=0.311). Although there was also a significant baseline difference between the Hospital Anxiety and Depression scores of patients and controls, median scores in the patient group for depression (4.6 vs. 1.8 for controls) were still in the normal range. Median anxiety scores of patients (9.0 vs. 4.5 for controls) were slightly above normal. Mild symptoms of anxiety are commonly experienced by hospital in-patients: on a daily basis they ponder bad news and have worries about imminent procedures. The scores in the patient group signified “mild anxiety” and were not considered to impact on the patients’ performance in other parts of the neuropsychological evaluation.

An attempt was also made to investigate any potential relationship between BAVM location and cognitive dysfunction attributable to that location. In the case of supratentorial lesions, BAVM in the cohort were categorised according to the presumed dominance of the hemisphere in which they reside. Left hemispheric lesions were therefore classified as dominant, even in left-handed subjects (considering 95-99% of right-handed individuals are left hemisphere-dominant, compared with approximately 80% in those who are left-handed). The patient group was not subdivided according to specific lobes of the brain as with just 20 subjects the cohort was deemed to small for such analysis. There were equal numbers of patients with dominant and non-dominant hemispheral lesions (nine each). Two patients with midbrain lesions were excluded from the analysis, since brainstem pathology is not classically thought to be associated with cognitive dysfunction. The median cognitive
test scores of the dominant and non-dominant group were compared. Independent samples analysis was performed using the Mann-Whitney U test and no statistically significant differences were noted between the two groups. However, when the median cognitive scores of these subgroups were compared with controls, those with a lesion residing in the non-dominant lobe demonstrated statistically significant cognitive deficits. These deficits were evident in tasks of both memory (logical memory (p=0.001), word lists delayed recall (p=0.001), Rey complex figure test (p=0.004)) and executive function (Stroop test (p=0.000) and D-KEFS (p=0.003)). These findings are consistent with previous studies, some of which are cited in the introductory chapter, which noted differential BAVM-associated deficits relating to both ipsilateral and contralateral hemispheric cognitive domains.
Table 7: Mann Whitney U Test to Show Associations Between Scaled Cognitive Test Scores in Patients vs. Controls at Baseline (analyses were subdivided with ruptured BAVM patients excluded from the total BAVM group)

<table>
<thead>
<tr>
<th>Neuropsychological test employed</th>
<th>Unruptured patients vs. controls</th>
<th>All patients versus controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Z score</td>
<td>Sig. (2-tailed)*</td>
</tr>
<tr>
<td>Logical memory immediate recall</td>
<td>-2.179</td>
<td>0.029</td>
</tr>
<tr>
<td>Logical memory delayed recall</td>
<td>-3.693</td>
<td><strong>0.000</strong></td>
</tr>
<tr>
<td>Word lists immediate recall</td>
<td>-1.851</td>
<td>0.064</td>
</tr>
<tr>
<td>Word lists delayed recall</td>
<td>-3.015</td>
<td><strong>0.003</strong></td>
</tr>
<tr>
<td>Total digit span</td>
<td>-1.223</td>
<td>0.221</td>
</tr>
<tr>
<td>Backward digit span</td>
<td>-2.434</td>
<td>0.015</td>
</tr>
<tr>
<td>Stroop</td>
<td>-2.898</td>
<td><strong>0.004</strong></td>
</tr>
<tr>
<td>Brixton</td>
<td>-2.904</td>
<td><strong>0.004</strong></td>
</tr>
<tr>
<td>Complex figure immediate</td>
<td>-2.352</td>
<td>0.019</td>
</tr>
<tr>
<td>Complex figure delayed</td>
<td>-2.596</td>
<td>0.009</td>
</tr>
<tr>
<td>Anxiety</td>
<td>-3.235</td>
<td><strong>0.001</strong></td>
</tr>
<tr>
<td>Depression</td>
<td>-3.085</td>
<td><strong>0.002</strong></td>
</tr>
<tr>
<td>D-KEFS†</td>
<td>-2.893</td>
<td><strong>0.004</strong></td>
</tr>
</tbody>
</table>

(bold values imply significance)

*: using Bonferroni adjustment, p value <0.004 implies significance
†: Number-letter trail making task of the Deltis and Kaplan Executive functioning System
The Wilcoxon signed ranks test was used to compare cognitive scores of patients at baseline (in the few days following diagnosis) with those at follow-up to determine if treatment in the interim had any effect on outcome. The sample size was considered too small to permit subdivision of the patient group into different treatment categories (i.e. surgery vs. radiosurgery vs. embolisation). When paired-sample analysis was performed on the entire patient group, no significant differences were observed in cognitive performance between the pre- and post-treatment phases. Five patients undergoing psychological assessment experienced a major complication (defined as a stroke event) during the course of their treatment. Although no meaningful analysis could be performed separately on these five patients, it was felt possible that their cognitive scores could skew the overall results of the patient group. The pre- and post-treatment analysis of the cognitive dataset was therefore repeated with those five patients excluded from the analysis. The results are noted in Table 8. There was a statistically significant difference noted between the baseline and follow-up scores of the patient group. Post-treatment improvements in scores were noted across a number of cognitive domains, namely logical memory recall, word list recall and the Brixton Spatial Anticipation test. The likely explanation for these findings is that treatment-related complications had a negative impact on the cognitive status of these five patients and that their scores skewed the overall results.
Table 8: Wilcoxon Signed Ranks Test to Show Associations Between Scaled Cognitive Test Scores in Patients Before and After Treatment (patients with treatment-related complications were removed from analysis)

<table>
<thead>
<tr>
<th>Neuropsychological test employed</th>
<th>Patients pre- vs. post-treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Z score</td>
</tr>
<tr>
<td>Logical memory immediate recall</td>
<td>-1.475</td>
</tr>
<tr>
<td>Logical memory delayed recall</td>
<td>-2.752</td>
</tr>
<tr>
<td>Word lists immediate recall</td>
<td>-2.360</td>
</tr>
<tr>
<td>Word lists delayed recall</td>
<td>-2.290</td>
</tr>
<tr>
<td>Total digit span</td>
<td>-0.157</td>
</tr>
<tr>
<td>Backward digit span</td>
<td>-0.792</td>
</tr>
<tr>
<td>Stroop</td>
<td>-1.177</td>
</tr>
<tr>
<td>Brixton</td>
<td>-2.187</td>
</tr>
<tr>
<td>Complex figure immediate</td>
<td>-1.396</td>
</tr>
<tr>
<td>Complex figure delayed</td>
<td>-1.381</td>
</tr>
<tr>
<td>Anxiety</td>
<td>-0.690</td>
</tr>
<tr>
<td>Depression</td>
<td>-0.208</td>
</tr>
<tr>
<td>D-KES§</td>
<td>-1.809</td>
</tr>
</tbody>
</table>

(bold values imply significance)
*: using Bonferroni adjustment, p value < 0.004 implies significance
§: Number-letter trail making task of the Delis and Kaplan Executive functioning System

The Kruskal-Wallis test was used to explore the relationship between mode of presentation and Spetzler-Martin grade and scores relating to the same cognitive test variables outlined in table 7. No significant correlations were found. It is possible that with a larger sample size, correlations could be demonstrated between poor baseline cognitive performance and individual clinical or radiological features such as the size or angioarchitecture of BAVM.

3. Coagulation

This was a pilot study on the impact of endovasular embolisation on blood coagulation so approximately half of all recruited patients were asked to donate a blood sample. Patients were not selected according to any specific demographic
features or clinical presentation but were approached in an alternate fashion. A total of 14 patients were approached and 3 declined. We therefore analysed the plasma of 11 patients treated with embolisation. Two individuals (patient 8 and patient 10) presented with haemorrhage and the remaining nine had a non-haemorrhagic presentation. Both patients who presented with haemorrhage had elevated levels of both VWF:Ag and VWF:CB at baseline. This was presumably secondary to endothelial cell activation following vessel rupture. One-way analysis of variance (ANOVA) methods were used to detect significant alterations in the mean levels of these assays at intervals following embolisation. No significant change in either VWF:Ag or VWF:CB was noted following treatment (see tables 9 - 12, graphs 1 and 2).
Table 9: VWF:Ag Levels* in Patients Over Time$^8$.

<table>
<thead>
<tr>
<th>Timepoints</th>
<th>0</th>
<th>0.1</th>
<th>1</th>
<th>2</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>17.57</td>
<td>17.76</td>
<td>31.56</td>
<td>18.10</td>
<td>16.60</td>
</tr>
<tr>
<td>Patient 2</td>
<td>9.90</td>
<td>13.61</td>
<td>7.74</td>
<td>7.18</td>
<td>11.00</td>
</tr>
<tr>
<td>Patient 3</td>
<td>13.42</td>
<td>11.97</td>
<td>10.71</td>
<td>9.82</td>
<td>9.66</td>
</tr>
<tr>
<td>Patient 4</td>
<td>5.35</td>
<td>4.59</td>
<td>6.70</td>
<td>7.63</td>
<td>11.28</td>
</tr>
<tr>
<td>Patient 5</td>
<td>6.33</td>
<td>5.37</td>
<td>5.44</td>
<td>5.86</td>
<td>6.25</td>
</tr>
<tr>
<td>Patient 6</td>
<td>8.025</td>
<td>8.33</td>
<td>8.38</td>
<td>8.48</td>
<td>6.70</td>
</tr>
<tr>
<td>Patient 7</td>
<td>3.08</td>
<td>3.07</td>
<td>2.87</td>
<td>2.83</td>
<td>4.98</td>
</tr>
<tr>
<td>Patient 8</td>
<td>33.41</td>
<td>28.54</td>
<td>34.19</td>
<td>32.56</td>
<td>30.60</td>
</tr>
<tr>
<td>Patient 9</td>
<td>14.79</td>
<td>13.74</td>
<td>14.38</td>
<td>13.58</td>
<td>15.51</td>
</tr>
<tr>
<td>Patient 10</td>
<td>21.23</td>
<td>18.62</td>
<td>17.67</td>
<td>22.79</td>
<td>24.31</td>
</tr>
<tr>
<td>Patient 11</td>
<td>9.59</td>
<td>9.01</td>
<td>9.98</td>
<td>10.51</td>
<td>11.63</td>
</tr>
</tbody>
</table>

*: measured in micrograms per millilitre (µg/ml)
$^8$: measured in hours after treatment

Table 10: One way analysis of variance (ANOVA) of levels of VWF:Ag at five different time intervals.

<table>
<thead>
<tr>
<th>ANOVA</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>P value</td>
<td>0.9956</td>
</tr>
<tr>
<td>P value summary</td>
<td>ns</td>
</tr>
<tr>
<td>Are means signif. different? (P &lt; 0.05)</td>
<td>No</td>
</tr>
<tr>
<td>Number of groups</td>
<td>5</td>
</tr>
<tr>
<td>F</td>
<td>0.0475</td>
</tr>
<tr>
<td>R square</td>
<td>0.0038</td>
</tr>
</tbody>
</table>
Graph 1: Mean levels of VWF:Ag Over Time.
Table 11: VWF:CB Activity* in Patients Over Time§.

<table>
<thead>
<tr>
<th>Timepoints:</th>
<th>0</th>
<th>0.1</th>
<th>1</th>
<th>2</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>17.85</td>
<td>17.40</td>
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<td>10.82</td>
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</table>

*: measured in micrograms per millilitre (µg/ml)
§: measured in hours after treatment

Table 12: One way analysis of variance (ANOVA) of activity of VWF:CB at five different time intervals.

<table>
<thead>
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<td>P value summary</td>
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<tr>
<td>Are means signif. different? (P &lt; 0.05)</td>
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</tr>
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<td>Number of groups</td>
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<td>0.04391</td>
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</table>
Graph 2: Mean activity of VWF:CB Over Time.
CHAPTER 5: DISCUSSION

1. Clinical and Radiological

In this prospective, hospital-based study, we have outlined the range of anatomical features of BAVM in the patient cohort. Spetzler-Martin grade was distributed among the patients in a similar fashion to what has been described in larger studies(11). The majority (61%) had a lesion of either grade 2 or 3, with the remaining patients distributed equally between the other grades. Most (61%) had a nidus diameter again of less than 3cm, again in keeping with available published data. Location in an eloquent region (61%) corresponds with other published figures which quote approximately 50% distribution between eloquent and non-eloquent areas(32). Almost two thirds of our cohort (61%) had some component of deep venous drainage, which is higher than recent figures quoted by Wedderburn et al(201). They found that 20% of lesions had superficial drainage. We attribute the discrepancy with our own data to abnormal distribution of a small sample size. This is also possibly due to selection bias: patients with deeper seated lesions are more likely to present with haemorrhage(57) (and are subsequently more likely to be transferred to a tertiary referral centre for specialist treatment). Our cohort had an unexpectedly high incidence of associated aneurysms (19%). This is almost twice the incidence quoted by Marks from the early 1990’s(58). This can probably be explained by two factors. Firstly, with ongoing development of more sophisticated imaging techniques detection of such is lesions is probably increasing. Secondly, our department is a large referral centre for the surgical and endovascular treatment of intracranial aneurysms, so in-patients with intracranial haemorrhage will be demographically skewed towards haemorrhage of aneurysmal origin.

Similar numbers of males and females were found in the patient group. Haemorrhage was slightly more common than seizures as a presentation (42% vs 39%), with the remaining cases attributable to either headache or focal deficits. These figures for haemorrhagic presentation are lower than Brown’s population-based study from Olmsted County, which reported a haemorrhagic presentation in 69% of cases(96). The Olmsted study was conducted from the 60’s to the 90’s however, when detection rates of unruptured lesions were significantly lower. 13% of our patients presented with headache unrelated to haemorrhage which is similar
to the international literature. Our two patients with focal deficits presented with homonymous hemianopia (one of these was discovered by a community-based optician who was assessing the patient for a spectacle prescription). There were no incidental diagnoses.

In terms of treatments received, our data are distributed similarly to those already described in similar hospital-based studies. Most of our cohort (24 of 31) underwent embolisation either as monotherapy or in conjunction with microsurgical resection or stereotactic radiosurgery. Only 2 patients were treated with radiosurgery (6.5%), an uptake figure significantly lower than is usual in standard practice in the United Kingdom, where radiosurgical management is undertaken as frequently as conventional surgery, in up to 40% of cases at times (201). Also consistent with international data are our success rates in terms of angiographic obliteration. Microsurgical resection has long been recognised as the most successful intervention for achieving “outright cure”. This is somewhat misleading. Firstly, lesions deemed suitable for surgery tend to be small and peripherally located and associated drainage is usually superficial. Secondly, although radiosurgery is also reserved for small lesions, BAVM amenable to radiation therapy are frequently found in surgically inaccessible places such as deep white matter, basal ganglia and brainstem. Thirdly, endovascular embolisation is frequently offered where the goal from the outset is not to obliterate the nidus, but to reduce it in size making the lesion more amenable to adjunctive treatment with surgery or radiation. Just over one quarter of our cohort (7 of 24) undergoing embolisation had completely obliterated AVM at follow-up which is close to previously published success rates.

It is worth noting, however, that the mode of Spetzler-Martin grade in this group was 3, compared with 1 in the surgical group. None of the surgical patients had a Spetzler-Martin grade of greater than 3, whereas exactly one third of the embolisation group had either a grade 4 or 5 lesion. The baseline BAVM characteritics of the embolisation group therefore provided a much greater treatment challenge. Only 2 patients had radiosurgery. One was grade 2 and the other was grade 5 (the latter achieving obliteration following concomitant embolisation). All 6 patients undergoing surgical resection achieved complete obliteration at follow-up. Obviously, treatment-related complications are an important consideration in the management of these patients. In our cohort of 31 patients, there were five major
complications (defined as a stroke event). These complications are described in the footnotes of table 1. Four of these occurred during embolisation, and 3 of these patients had measurable deficits at follow-up (one was wheelchair-bound). The fifth patient developed vasospasm and a dense hemiparesis after surgery. He also was wheel-chair bound at follow-up. The embolisation-related complication rate may initially seem very high (24 patients treated with 4 associated stroke events: approximately 17%) but this is somewhat misleading. Among a total of 24 patients, a total of 92 embolisation procedures were performed in the 18-month period. This equates to a major complication risk of 4.3% for each embolisation procedure. The Columbia group have quoted a risk 14%(202) but again this is per patient and not procedure. The complication rate in our institution is similar to other big centres with similar patient demographics.

In terms of standardised stroke and disability scores, BAVM burden was very low, even for those patients who presented with haemorrhage. No patients died during the study period. Interestingly, although there were significant differences between the haemorrhagic and non-haemorrhagic group in terms of functional outcome at initial presentation, these differences were no longer significant post-treatment. Stroke severity and dependence were still low at follow-up, with respective mean NIHSS scores of 1.6 in both groups and mean Barthel scores of 98 in the haemorrhagic and 95 in the non-haemorrhagic group. These figures are consistent with previous reports by the Columbia group that BAVM-related haemorrhage is associated with a significantly lower morbidity than many other forms of intracranial haemorrhage, including aneurysm rupture(195). Results above suggest that BAVM were associated with almost complete independence at baseline. In terms of stroke severity and dependence, there were no significant differences post-treatment between patients who had presented with haemorrhage and those with symptoms other than haemorrhage at baseline. However, it cannot be concluded that patients with ruptured AVM fared no worse at follow-up than unruptured cases as 1) only two patients with haemorrhage didn’t undergo treatment and 2) some patients who did not have a haemorrhagic presentation and were well at baseline had subsequent complications of treatment and as a consequence had developed new disability by follow-up. If the study group had an equal distribution of haemorrhagic and non-haemorrhagic cases, and these patient groups were followed
up for a similar duration, then more robust conclusions could be made regarding treatment outcomes according to different modes of presentation. Despite the lack of robust evidence supporting treatment of unruptured BAVM (an issue which it is widely hoped the ARUBA study will address), all of our patients were offered some form of intervention: only three declined and remain well. As mentioned above, there were five major treatment-related complications in our cohort and none of these patients had initially presented with haemorrhage. Although good evidence exists to support the treatment of ruptured BAVM, questions again are raised regarding the benefit of intervention in patients with a non-haemorrhagic presentation. All four patients who had presented with headaches (which were controlled to varying degrees) underwent treatment and three were left with significant residual deficits from complications relating to treatment. One of these patients was wheelchair-bound at follow-up. Only one patient with a treatment-related complication had presented with seizures. This patient also was wheelchair-bound at follow-up. The study group is small and symptoms relating to headache and seizures were not assessed with validated tools such as those of the International Headache Society. Neither were quality-of-life issues addressed in a formal manner. In retrospect, it appears doubtful that treatment was justified in these patients, mostly because they all had unruptured BAVM at the time of diagnosis and the headaches and seizures were not intractable. However this was an observational study. The findings are based on a small, highly selected population and the patients were not randomised according to different treatment options. On the basis of current peer-reviewed evidence, it is still unclear whether or not treatment of unruptured BAVM is justified (a question which the ARUBA trial aims to address). Without definitive and reproducible evidence to the contrary, the author is of the opinion that there still may be some benefit in treating these patients. It is crucial to highlight, however, that this requires careful multidisciplinary discussion and assessment of potential risks and benefits for individual patients. There is even uncertainty regarding those patients presenting with haemorrhage: as outlined in the introductory chapter there is a significant risk of rebleeding once a BAVM has already ruptured. The larger international studies have reported varying results, and this is likely a reflection of the extreme heterogeneity of these patients in terms of their clinical, radiological and demographic characteristics.
The final aspect of clinical and radiological data analysis was directed at exploring clinical and radiological correlations within the dataset. The purpose of this was to identify any potential aspects of angioarchitecture which may independently influence mode of presentation or clinical outcomes. Using the Kruskal-Wallis statistical method, no significant correlations were found between clinical features such as age or mode of presentation and radiological aspects of BAVM. Perhaps with a greater sample size significant associations may be detected and subsequent predictions could be made regarding likely treatment response and functional outcome.

2. Neuropsychology

There are few published data regarding the cognitive sequelae of BAVM. Previous studies date back almost 20 years. Mahalick demonstrated baseline cognitive deficits which seemed more pronounced in the hemisphere contralateral to the lesion(137). He later demonstrated improvements in these domains following surgery(139). No data exist on the effects of brain embolisation on cognition however. Our cohort demonstrated quite significant deficits at baseline when compared with age- and education-matched controls. These findings were statically significant even when patients with ruptured BAVM were excluded from the analysis. Patients significantly underperformed in tasks relating to memory and executive function. With a small sample size, however, it is probably more appropriate to describe these observations as a global effect, rather than specific to any one lobe or either hemisphere of the brain. The small sample size did not permit detection of significant correlations between these deficits and clinical features or aspects of angioarchitecture. Similarly, recruits were too few to permit sub-analysis of the distribution of lesions throughout different locations of the brain. Correlation of cognitive test scores with specific cognitive circuitry that was anticipated to be affected was therefore not feasible.

On analysis of the entire cohort, no significant alterations in cognitive status were observed following treatment, despite 11 (36%) of these patients having successful angiographic obliteration of their BAVM and 8 (26%) having <50% residual volume. It is interesting to note, however, that with exclusion of the data relating to five patients with treatment-related complications, statistically significant
improvements were noted in a number of the the cognitive subscores. This suggests that these patients with treatment-related stroke syndromes performed more poorly in the follow-up cognitive assessment and masked improvements elsewhere in the cohort by skewing the test scores averaged across the entire group.

The author hypothesises three reasons why the improvements post-treatment were not more dramatic. Firstly, sequential reductions in nidus volume by intermittent embolisation are slight and spread over a period of many years in some cases. Secondly, with only 20 participants, the neuropsychological arm of the study was underpowered to detect a 10% difference in cognitive test variables. Despite this limitation, significant baseline deficits in the patient group were still detected when compared with controls. It is therefore possible that, with a larger sample size, subtle differences between pre- and post-treatment groups would be evident. Thirdly, the observation that there were baseline deficits which were not altered by treatment raises the issue of possible neurodevelopmental deficiencies in these patients. In a retrospective review of 44 random adults from the Columbia BAVM database, Lazar reported developmental deficits in two thirds of cases(141). It is possible that these deficits become “hard-wired” with the normal ageing process and are irreversible by the time these patients come to medical attention.

Attempts were also made to investigate any potential relationship between BAVM location and cognitive dysfunction attributable to that location. BAVM in the cohort were categorised according to the presumed dominance of the hemisphere in which they reside. Left hemispherical lesions were therefore classified as dominant, even in left-handed subjects (considering 95-99% of right-handed individuals are left hemisphere-dominant, compared with approximately 80% in those who are left-handed). The patient group was not subdivided according to specific lobes of the brain as with just 20 subjects the cohort was deemed to small for such analysis. The median cognitive test scores of the dominant and non-dominant group were compared. Independent samples analysis was performed using the Mann-Whitney U test. No statistically significant differences were noted between the two groups. However, when the median cognitive scores of these subgroups were compared with controls, subjects with a lesion residing in the non-dominant lobe demonstrated statistically significant cognitive deficits. A possible explanation for this is by way
of increased flow towards the lesion and reduced flow away from the dominant lobe (which is predominantly responsible for tasks of speech and executive function). These findings are strongly supportive of the steal theory and suggest there is a possible correlation between anatomical location and cognitive function. Much larger sample sizes would be required to have sufficient power to detect statistically significant correlations between BAVM (and perhaps even complex vascular supply) and cognitive dysfunction attributable to that location.

There is surely potential in functional methods of imaging such as fMRI and diffusion tensor MRI(163, 164), particularly in terms of planning treatment strategies. These technologies may compliment traditional imaging methods in the evaluation of cognitively impaired patients, especially in demonstrating “cortical reorganisation” following a specific treatment. It has already been shown, for example, that patients with left frontal BAVM show evidence of transfer of expressive language and fMRI-defined activity in Broca’s area to the equivalent part of the contralateral hemisphere(138). Other modalities which are potentially valuable investigative tools are positron-emission tomography (PET) and single-photon emission computed tomography (SPECT). Both of these nuclear isotope techniques have already been shown to be a value in demonstrating blood flow within or around BAVM and could be of use in identifying patients most likely to demonstrate the “vascular steal” phenomenon(123, 203). It should be emphasised that this study found very significant differences in cognitive performance between patients and controls, despite the small sample size. A larger study with longer duration of follow-up would be likely to support our findings and help identify independent aspects of clinical history or angioarchitecture that may correlate with cognitive decline.

3. **Coagulation**

We also conducted a preliminary investigation into VWF expression and the impact of endovascular treatment on VWF expression in patients with BAVM. The goal of this pilot project was to determine if there was any disruption of either the concentration or molecular state of VWF multimers in the period immediately following embolisation. The VWF:Ag assay is a direct assay to determine the concentration of VWF in the plasma, while the VWF:CB indicates the ‘state’ of the
VWF multimers and reflects the level of binding of these VWF multimers to collagen. Any such abnormalities in these assays could indicate a prothrombotic tendency in this patient group in the immediate post-treatment phase, which could have implications for angiographic, neurological and neuropsychological outcomes. As this was a pilot project, only 11 patients were enrolled and the assays were analysed once. No significant alterations in the levels of VWF:Ag or VWF:CB were noted following treatment, although it was observed that the 2 patients who had presented with haemorrhage in the group had higher baseline levels. That there was no significant overall change in the levels of these markers (and hence no convincing evidence of endothelial cell activation) may reflect the very small volumes of embolic material used in a standard embolisation. Although there was no trend towards in VWF expression in many cases post-treatment, this could be a reflection of the short follow-up duration. Plasma analysis beyond a 24-hour period (even up to weeks or months following embolisation) may reveal evidence of endothelial cell activation. It is also possible that successful embolisation and reduced flow through a BAVM could reduce shear stress on the endothelium, reduce endothelial activation and lead to a fall in VWF levels in some patients, with or without a haemorrhagic presentation. In a laboratory environment, shear stress can be induced by using a flow chamber. Many studies have been carried out on human platelet function where different factors are introduced into these chambers to observe the effect they have on platelet aggregation (204, 205). This area of research may also have potential with regard to BAVM patients undergoing embolisation.

4. Strengths

This study is the first of its kind in Ireland. Its strengths are that it comprehensively describes a single centre experience capturing all patients presenting over an 18-month period. By means of consecutive case ascertainment and detailed descriptive analysis, the epidemiological and clinical characteristics and range of clinical presentation of BAVM in Ireland have been prospectively determined. It confirms that the range of clinical presentations and treatment outcomes are similar to previously published international data. It also shows that patients with both ruptured or unruptured BAVM firstly have significant cognitive deficits at the time of diagnosis, and secondly that these deficits may be irreversible even with resection
of the lesion. The novel insight it provides into the neuropsychological sequelae of BAVM may also have an impact on future treatment strategies.

5. Weaknesses

The main weakness of our study is the small sample size. We did not detect any differences in cognitive function between the pre- and post-treatment assessments. It is possible that over a period of years following treatment, remodelling of tissue within and surrounding the BAVM may be manifested by an alteration of cognitive function that was not evident at initial follow-up. Home visits of the same patient cohort by future Beaumont Hospital research fellows could address this issue. A larger cohort would facilitate detection of important relationships between clinical, radiological and cognitive variables by means of detailed multivariate regression analysis. This would also be of great value in controlling for independent variables which may confound the results (e.g. anticonvulsant medications inducing fatigue in patients with epilepsy). BAVM size was measured collaboratively by two consultant neuroradiologists at the various stages of treatment. Clearly they could not be blinded to treatment although independent BAVM size assessment may have been less prone to bias. Also, as mentioned in the introductory chapter, there is a degree of subjectivity regarding measurement of lesions demonstrated on IADSA. This is due to the absence of standardised calibration systems in even the most modern fluoroscopy units and is unavoidable due to the specific method of image acquisition that these systems employ. Cross-sectional imaging modalities such as CT and MRI do not have this limitation. Most, but not all, of our subjects had MRI performed as part of their pre-treatment workup and post treatment and this may have slightly limited the accuracy of BAVM assessment. Post-treatment results should be interpreted with care in view of the fact that follow-up assessments were carried out at varying intervals (range 10-30 months). This difficulty was anticipated during the design phase of the study. Beaumont Hospital is a tertiary referral centre serving counties as far reaching as Donegal, Galway and Clare. Outpatient attendances vary as a result. Ideally, the follow-up duration should be more consistent but these logistical difficulties are unlikely to be overcome due to the aforementioned geographical issues. Lastly, no significant conclusions are made regarding the data on VWF expression and endothelial cell expression. This was a preliminary investigation into a novel area of BAVM science. Larger patient
numbers and follow-up of patients’ haemostatic markers over a longer period would undoubtedly lead to more robust conclusions regarding this arm of the study.

6. **Future Direction and Plan**

It is clear that a multimodality approach is crucial in the management of BAVM. The logistical and economic difficulties of providing the necessary services to Irish patients with this condition are all too apparent to those who work in this field. There are two neurosurgical centres in the country offering treatment to a population of 4.5 million. Staff shortages and pressures on funding of various subspecialties extend beyond neurology, neurosurgery, neuroradiology and radiation oncology(206) (there are currently no stereotactic radiosurgery facilities in Ireland and patients requiring this treatment are added to a waiting list to travel to Sheffield, UK for assessment). BAVM management encompasses a wide range of nursing and ancillary medical services such as neuroanaesthesia(207) and neurorehabilitation(208). Firstly, like most other areas of the increasingly burdened Health Service Executive, more funding is needed to boost staff numbers and improve facilities. Secondly, more emphasis on the epidemiological research of BAVM is required in Ireland. This should include construction of a national database as there is currently no Irish hospital- or community-based dataset to record prospectively the clinical presentation, treatment and outcome of these patients. The geographical layout of BAVM services in Ireland gives us an advantage over many bigger European countries. All BAVM are primarily managed in one of the two national centres of neurosurgery (CUH and Beaumont Hospital, Dublin). This would facilitate inter-hospital transfer of relevant details for the purposes ongoing clinical care and research-related activities.

On the foot of the research outlined above, an extensive retrospective review of BAVM has already commenced. This comprises a detailed analysis of the case records and imaging of approximately 300 patients with BAVM managed in Beaumont Hospital from 1995 to 2010. Despite the retrospective nature of case ascertainment, this case-control analysis will be sufficiently powered to detect relevant correlations between clinical and radiological data. Where funding and logistics allow, our aim is that in the coming years all patients with newly diagnosed BAVM will undergo a formal baseline cognitive assessment by our
neuropsychology department at the time of diagnosis. Longer duration of
neuropsychological follow-up may be made possible by the appointment of future
research fellows. It is important to pursue this strategy for two reasons. Firstly,
cognitive deficits should be documented and monitored as part of "quality control"
during patients’ ongoing treatment (many patients return for repeated embolisations
over a number of years). Secondly, considering the natural history of this disease is
still so poorly understood, long term cognitive outcomes may constitute one of the
most important markers of treatment response. In addition, although this study did
not detect any meaningful alterations in VWF expression in the periprocedural
period, further investigation of the long-term effect of embolisation on haemostasis
in these patients may be of value. For example, it is likely there is reduced shear
stress on the walls of vessels within BAVM as they demonstrate incrementally
reduced flow over time. This may reflect redistribution of flow elsewhere in the
brain and lessening of the ‘vascular steal’ phenomenon.

Large, well-designed, prospective randomised controlled trials in BAVM are
essential to improve our understanding of this disease. These studies should place a
strong emphasis on not just the epidemiology and neurological aspects of BAVM
but also on exploring any potential clinical-cognitive-anatomical correlations to
understand better the relationship between BAVM and cognitive dysfunction. In
addition, large studies are needed to investigate more thoroughly the benefits of
intervention versus conservative management of these patients. This can only be
achieved by means of large, controlled trials where subjects are randomised to
intervention versus no intervention and followed in a careful manner. Beaumont
Hospital’s participation in such trials would not only contribute to the growing
international body of knowledge of this disease but would also lead to enhancement
of the neurointerventional service at a local level. Future research on long-term
outcomes of non- haemorrhagic BAVM in particular will provide invaluable insight
into the natural history of this condition. Although the data contained in this thesis
do not wholly support treatment of unruptured BAVM: the authors advise careful
multidisciplinary management and treatment on a case-by-case basis. It will be
interesting to note if the conclusions of the ARUBA authors’ investigation into
unruptured BAVM support the findings regarding our own relatively small cohort of
patients in Beaumont Hospital. We must not forget, however, that the real-life
implications of BAVM for these patients may extend far beyond headaches, seizures and haemorrhage. This study promotes a holistic approach to the management of BAVM, and highlights the important cognitive implications of this disease.
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APPENDICES

Appendix I: Neuropsychology Test Battery:

1. Intellectual Ability & General Functioning

   a. Wechsler Test of Adult Reading (WTAR)(209), a measure of premorbid ability. The WTAR is used to estimate an individual’s level of intellectual functioning. It takes 10 minutes to complete and is a useful and reliable tool to estimate IQ. It is composed of a list of 50 words that have atypical grapheme to phoneme translations. The intent in using words with irregular translations is to minimize the current ability of the client to apply standard pronunciation rules and assess previous learning of the word.

2. Memory tests (which provide information about the encoding, storage and retrieval of both auditory and visual stimuli)

   a. Logical Memory and Wcrd Lists (immediate and delayed recall) of the Wechsler Memory Test-III(210)

   b. Rey Complex Figure Test(211)

   c. Digit span test (forward and backward)

3. Executive Tests (examine functions associated with frontal-striatal circuitry and include planning, problem solving, response generation and divided attention)

   a. Verbal Fluency (category and phonological)(212)

   b. Stroop Tests(213). This specifically assesses selective attention, cognitive flexibility and processing speed. Subjects are required to read aloud a list of written colours. The first experiment consists of the participant reading the word independently of the colour of the ink: for a given word such as “green” they would have to read “green” despite the ink being of a different colour. The second experiment required the participants to read the colour of the ink
independently of the word: if the word “green” was written in red they would have to read “red” and not “green”. When a word is printed in a colour differing from the colour expressed by the word’s semantic value (e.g. the word “green” printed in red) naming the colour of the word takes longer and is more prone to errors than when the meaning of the word is congruent with its ink colour. In certain frontal lobe disorders, in particular those of the anterior cingulate cortex and dorsolateral prefrontal cortex, a greater disparity in the time taken to complete these 2 experiments may be observed, when compared with normal subjects.

c. The Brixton Spatial Anticipation Test for problem solving(214). This measures the ability to detect rules in sequences of stimuli. It is perceptually simple and does not require a verbal response. It is thus appropriate for people who are suffering from a wide range of associated deficits such as those involving speech production or reading. Research has shown that the Brixton Test is sensitive to problems not only with rule detection but also to tendencies toward impulsive and bizarre behavior, thus allowing the clinician to gain qualitative as well as quantitative information about a subject’s performance.

d. Trail Making Test of the Delis Kaplan Executive Functioning System(215). This incorporates measures of motor speed, scanning, letter and number sequencing, task switching and divided attention. The task comprises 25 consecutive targets and the subject is required to “connect-the-dots”. The goal is to complete the task in the shortest time possible. The subject must follow 5 patterns in total.

4. Language

a) Boston Naming Test (full 60-item version) to evaluate confrontational naming skills(216). It represents a measure of object naming from line drawings that takes into account the finding that patients with dysnomia often have greater difficulties with the naming of low frequency objects. Thus, instead of there being a simple category of anomia, naming difficulties may be rank ordered along a continuum. Items have been rank ordered in terms of their ability to be named, which is thought to correlate with their frequency. Although often used in the examination of children with learning disabilities, this type of picture-naming vocabulary test
is also helpful in the evaluation of brain-injured adults.

5. Vision/perception

a) Cortical Vision Screening Test (217). This is a useful measure of acuity and early visual perceptual processing and is designed to detect visual impairments in individuals with normal (corrected) or near-normal vision. It comprises 10 separate components, each of which reflects a different aspect of visual processing in higher cortical centres.

6. Mood

a) Hospital Anxiety and Depression Scale (HADS) (218). This is a standardized questionnaire designed to screen for symptoms which may have an adverse effect on an individual’s performance across a variety of cognitive domains. It useful as a brief self-reported measure of mood and is not confounded by physical/medical symptomatology.
Appendix II: Stroke and Brain Attack NIH Stroke Scale

1.a. Level of Consciousness:
   0  Alert
   1  Not alert, but arousable with minimal stimulation
   2  Not alert, requires repeated stimulation to attend
   3  Coma

1.b. Ask patient the month and their age:
   0  Answers both correctly
   1  Answers one correctly
   2  Both incorrect

1.c. Ask patient to open and close eyes:
   0  Obeys both correctly
   1  Obeys one correctly
   2  Both incorrect

2. Best Gaze (only horizontal eye movement):
   0  Normal
   1  Partial gaze palsy
   2  Forced deviation

3. Visual Field Testing:
   0  No visual field loss
   1  Partial hemianopia
   2  Complete hemianopia
   3  Bilateral hemianopia (blind including cortical blindness)

4. Facial Paresis (Ask patient to show symmetrical movement teeth or raise eyebrows and close eyes tightly):
   0  Normal
   1  Minor paralysis (flattened nasolabial fold, asymmetry on smiling)
   2  Partial paralysis (total or near total paralysis of lower face)
   3  Complete paralysis of one or both sides (absence of facial movement in the upper and lower face)

5. Motor Function - Arm (right and left): (extends arms 90 (or 45) degrees for 10 seconds without drift)
   0  Normal
   1  Drift
   2  Some effort against gravity
   3  No effort against gravity
   4  No movement
   9  Untestable (Joint fused or limb amputated)

6. Motor Function - Leg (right and left): (hold leg 30 degrees position for 5 seconds)
   0  Normal
   1  Drift
   2  Some effort against gravity
   3  No effort against gravity
   4  No movement
   9  Untestable (Joint fused or limb amputated)

7. Limb Ataxia:
   0  No ataxia
   1  Present in one limb
   2  Present in two limbs

8. Sensory (Use pinprick to test arms, legs, trunk and face -- compare side to side)
   0  Normal
   1  Mild to moderate decrease in sensation

92
2. Severe to total sensory loss

9. Best Language (describe picture, name items, read sentences):
   0. No aphasia
   1. Mild to moderate aphasia
   2. Severe aphasia
   3. Mute

10. Dysarthria (read several words):
    0. Normal articulation
    1. Mild to moderate slurring of words
    2. Near unintelligible or unable to speak
    9. Intubated or other physical barrier

11. Extinction and Inattention:
    0. Normal
    1. Inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities
    2. Severe hemi-inattention or hemi-inattention to more than one modality
Appendix III: The Barthel Index

Activity Score

FEEDING
0 = unable
5 = needs help cutting, spreading butter, etc., or requires modified diet
10 = independent ______

BATHING
0 = dependent
5 = independent (or in shower) ______

GROOMING
0 = needs help with personal care
5 = independent face/hair/teeth/shaving (implements provided) ______

DRESSING
0 = dependent
5 = needs help but can do about half unaided
10 = independent (including buttons, zips, laces, etc.) ______

BOWELS
0 = incontinent (or needs to be given enemas)
5 = occasional accident
10 = continent ______

BLADDER
0 = incontinent, or catheterized and unable to manage alone
5 = occasional accident
10 = continent ______

TOILET USE
0 = dependent
5 = needs some help, but can do something alone
10 = independent (on and off, dressing, wiping) ______

TRANSFERS (BED TO CHAIR AND BACK)
0 = unable, no sitting balance
5 = major help (one or two people, physical), can sit
10 = minor help (verbal or physical)
15 = independent ______

MOBILITY (ON LEVEL SURFACES)
0 = immobile or < 50 yards
5 = wheelchair independent, including corners, > 50 yards
10 = walks with help of one person (verbal or physical) > 50 yards
15 = independent (but may use any aid; for example, stick) > 50 yards ______

STAIRS
0 = unable
5 = needs help (verbal, physical, carrying aid)
10 = independent ______

TOTAL (0–100): ______