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Transoesophageal Echocardiographic - Defined Valvular Strands in Acute Ischaemic Stroke: A Prospective Study

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Declaration

I declare that this thesis, which I submit to RCSI 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 from 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 

Student Number: **09110101**

Date 9/3/2012

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Summary

Background: Transoesophageal echocardiographic (TOE)-defined mobile, thread-like valvular strands (VS) have been associated with acute ischaemic stroke (AIS). The relationship between VS as a possible embolic substrate and the risk of recurrent stroke remains unclear. Our primary aims were to measure the prevalence of VS and explore their association with AIS in a case-control study and then, compare the risk of subsequent poor vascular outcome (vascular events and vascular death) in the stroke cohort patients with or without VS in a follow-up study. Our secondary aims were to determine the relationship of VS to other potential cardiac sources of emboli in TOE, relationship of VS to diastolic dysfunction in stroke cohort on comparison with controls. In addition, we sought to evaluate the relationship of VS to ischaemic stroke subtype and infarct topography on neuroimaging, and also to determine the relationship of hypercoagulable states in young patients with VS in the stroke cohort.

Methods: In the case-control study, the prevalence of VS was estimated from patients consecutively admitted with AIS and from patients underwent TOE for cardiac conditions (those with infective endocarditis and stroke were excluded) in our institution over a two year period. In the follow-up study, patients with AIS were followed to evaluate the risk of poor vascular outcome, including risk of recurrent stroke.

Results: We recruited 170 patients with AIS and of those, 78 underwent TOE. In our case-control study, we found TOE-defined VS in approximately half of the patients with AIS (38/78, 48.7%) compared to one-third of controls (29/89, 32.6%). VS were more commonly seen in stroke patients over the age of 60 years (21/34, 61.8%). Univariate analysis found an association between the presence of VS and risk of AIS (OR = 3.85, p = 0.05), but multivariate analysis reduced the strength of the association (OR = 2.15, p

= 0.06). In stroke subtypes, high prevalence of VS was seen in cardioembolic stroke but it did not reach statistical significance ($p = 0.52$) and there was no increased frequency of VS in cryptogenic stroke subtype. Diastolic dysfunction was seen in 78.9 % of cases with VS and there was a strong association between diastolic dysfunction and VS in the case-control study (OR 7.75, $p = 0.005$). There was no statistically significant association between infarct location (cortical, subcortical, brainstem or cerebellar) in neuroimaging and the presence of VS. There were only few young cases with abnormalities in laboratory testing for hypercoagulable conditions. The risk of recurrent stroke and survival without poor vascular outcome was not statistically different between cases with or without VS in our study (OR = 1.45, 95 % CI 0.30 - 6.96, $p =$ 0.64).

Conclusion: We were able to demonstrate an association between valvular strands and acute ischaemic stroke in our case-control study, however, the strength of the association was reduced after multivariate analysis. We did not find any increased risk of poor vascular outcome or increased recurrent stroke risk in cases with or without VS. Our findings do not support the embolic potential of valvular strands and it may not be a risk factor for stroke.

Chapter 1: Introduction

1.1 Acute ischaemic stroke and pathophysiology

Acute ischaemic stroke (AIS) is characterized by abrupt neurologic dysfunction due to focal brain ischaemia resulting in persistent neurologic deficit or accompanied by characteristic abnormalities on brain imaging (1). History and findings of physical examination facilitate stroke diagnosis. The NIH Stroke Scale (NIHSS) is a validated 15-item scale that is used to assess key components of the standard neurologic examination and measure stroke severity (2). Noncontrast head CT is most readily available in most stroke centres and may be rapidly performed as part of the acute stroke evaluation. MRI with diffusion-weighted imaging sequences is more sensitive for acute cerebral ischaemia and improves diagnostic accuracy (3).

A minimal diagnostic evaluation of stroke includes the following (4):

(a) Assessment of main risk factors: Hypertension, hypercholesterolemia, diabetes, cardiac disease, family history of vascular disease

(b) Laboratory testing for haematocrit, platelets, red and white cell counts and prothrombin time

(c) Electrocardiogram

(d) Assessment of extra and intracranial arteries

(e) Assessment for specific etiologies

Thromboembolism and haemodynamic failure are the two major mechanisms for AIS. Thromboembolism usually occurs as a result of embolism or in situ

thrombosis and leads to an abrupt fall in regional blood supply. The most common sources of embolism are heart and large arteries. Cardioembolism accounts for 20 – 30 % of all ischaemic strokes (5-8). The extension of the infarct on CT and MRI can provide important information towards a cardiogenic embolic stroke mechanism. It is very likely to be cardioembolic mechanism if the neuroimaging shows a cortical extension, multiplicity in space and time, or bilaterality (9). There is also a specific type of subcortical infact, the large 'lenticulostriate infarct' which typically indicate embolic stroke mechanism (10). Other signs of systemic thromboembolism such as wedge shaped infarctions of kidney or spleen, Osler nodes could also help to identify a cardioembolic mechanism (11).

Identification of a cardiac source of embolism in patients with transient ischaemic stroke (TIA) or AIS is important because it influences future therapeutic management. Conditions considered at high risk for cardioembolism include atrial fibrillation, sick sinus syndrome, intracardiac thrombus, left atrial myxoma, mitral stenosis, prosthetic valve, infective endocarditis, recent myocardial infarction, dilated cardiomyopathy, and aortic arch atheromatous plaques. Conditions considered at low or uncertain risk for brain embolization include patent foramen ovale, atrial septal aneurysm, spontaneous echo contrast, mitral annulus calcification, mitral valve prolapse, calcified aortic stenosis, Lambl excrescences (valvular strands), and dyskinetic ventricular wall segment (11-13).

Cardiac evaluation to identify the risk factors for embolization include telemetry or holter monitoring, transthoracic echocardiography (TTE), transoesopahageal echocardiography (TOE), coronary angiography and cardiac CT or MRI based

on history and clinical examination. TOE has revolutionized the search for cardiac sources of embolism due to its non-invasive nature, relatively good sensitivity and high specificity (14). TOE is particularly valuable in indentifying aortic atheromas, valvular vegetations and masses, left atrial thrombi, spontaneous echo contrast and inter-atrial shunts. In current clinical practice, echocardiography is used in over 80% of patients with acute stroke as a major cornerstone in diagnostic work-up with a 1:3 ratio of TTE alone vs. TOE (11).

With this increasingly routine use of TOE in the evaluation of AIS, VS are increasingly detected on cardiac valves. VS have been implicated in systemic embolization (15) and are considered as a risk factor for stroke in young patients (16). It was postulated that VS may themselves break and embolize, or thrombi formed on the surface due to endothelial damage or local trauma subsequently embolize causing stroke (17, 18). Thrombi on giant Lambl excrescences have been previously reported (19). An independent association was identified between mitral VS and ischaemic stroke in elderly (20) however, there are no prospective studies to explore the relationship of stroke with VS in all age groups. There is also a lack of increased risk of recurrent stroke (20) and thus it raises doubts about the possible etiological role of VS in AIS.

1.2 Definition of valvular strands

Valvular strands are thin, mobile, thread-like filaments seen on the edges of cardiac valves (21, 22). Vilem Dusan Lambl, a Czech physician first described small filiform processes on the ventricular surface of aortic valve leaflets (21) in 1856. He identified such processes in 2% of 1000 autopsies performed. Subsequently, Magarey reported the presence of similar filiform excrescences on the auricular surface of mitral valves in 85% of an autopsy series of 250 patients (22). Generally, these excrescences were found to be less than 1 mm thick and 1 to10 mm long. These strands were subsequently named 'Lambl's excrescences' (LE). With the widespread use of sophisticated cardiac imaging modalities, abnormal structures attached to cardiac valves are frequent findings on cardiac investigations (23). In 1990, Lee et al. (24) described strands on the mitral valves identified in TOE, which are pathologically LEs when examined. These were subsequently termed 'valvular strands' (VS). Increasingly, VS are found on TOE, a new window to increase the diagnostic yield of detecting intracardiac abnormalities (24).

There is no consensus on the correct terminology for these valvular excrescences. Review of literature shows that nomenclature has varied widely and these valve structures have been sometimes referred to as papillomas, papillary fibromas, endocardial tumours and giant Lambl's excrescences depending on pathological features observed by different authors. LE is primarily a histological and VS is an echocardiographic description of these valvular excrescences and therefore we have used the term 'valvular strands'

(VS) to denote the above mentioned structures in TOE studies and 'Lambl excrescences (LE) in pathological studies. Moreover, therapeutic approaches in patients with VS are based on the presence or absence of such structures and other risk factors for stroke, without being influenced by histopathologically derived terminologies (25).

1.3 Epidemiology and prevalence of valvular strands

There are limited data on the true prevalence and incidence of VS in the general population. Early reports by Lambl and Magarey were based on post-mortem examinations and no specific pathological significance was attributed to their presence. In 1986, Hurle (26) found LEs in 90% of aortic valves among 56 human subjects (without cardiac disease) examined pathologically. He also noted that the frequency of these excrescences were significantly lower in the first decade of life.

In 1991, Lee et al. (24) was first to note mitral VS in 22% (11/50) of consecutive patients with AIS or TIA undergoing TOE. Few studies have been conducted on the subject of TOE- defined VS and stroke since. The participants were selected from patients referred for TOE in the majority of the studies (15, 16, 27-30). Cohen et al. (20) and Homma et al. (31) recruited from patients who had a clinical stroke event. Estimated prevalence of VS in the group of patients with AIS, TIA or with embolic events ranges from 6.3% to 47% and the variation in prevalence is perhaps due to difference in the study population. In patients without stroke/TIA, the frequency of VS ranges from 0.3% to 38%.

Figure 1.1 and Figure 1.2 show transoesophageal echocardiographic images of VS at aortic valve. The prevalence of VS from previous studies are described in Table 1.1

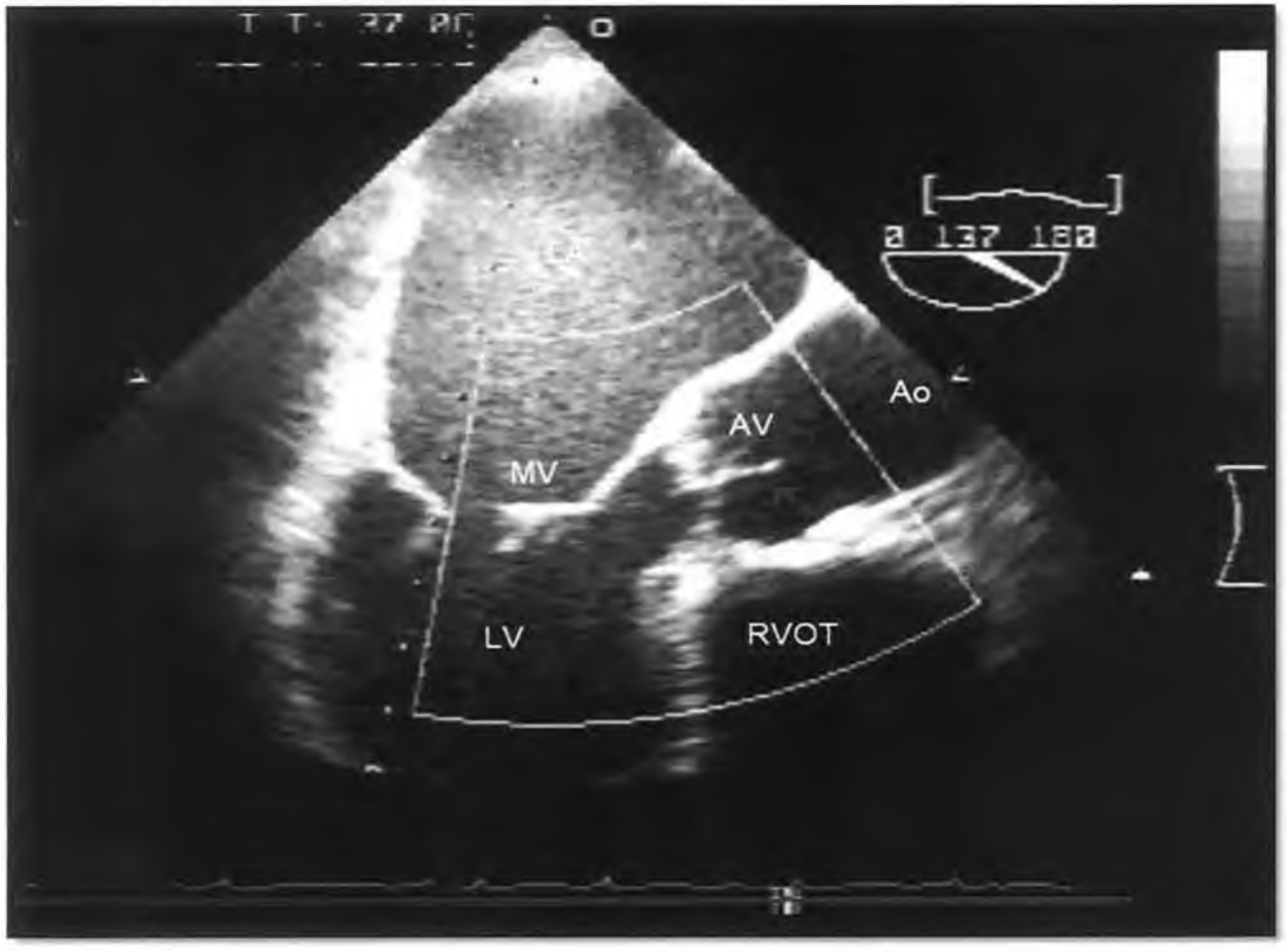

Figure 1.1: *Transoesophageal echocardiographic image of thin threadlike, valvular strand (red arrow) attached to at the aortic surface of aortic valve. LA left atrium, LV left ventricle, AV aortic valve, Ao aorta, RVOT right ventricular outflow tract.*

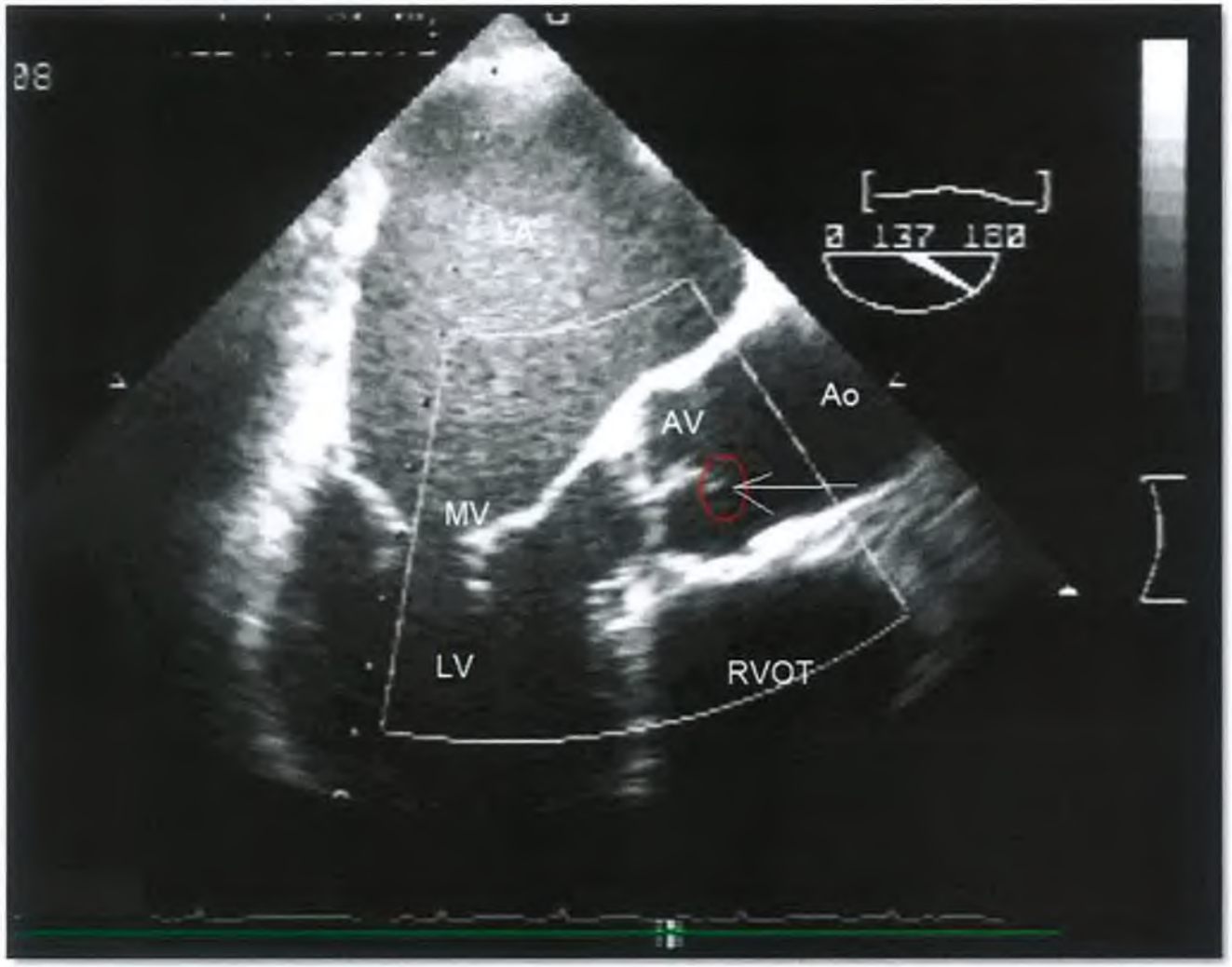

Figure 1.2: *Transoesophageal echocardiographic image aortic valvular strand (red circle) with independent motion to the aortic valve leaflets. LA left atrium, LV left ventricle, AV aortic valve, Ao aorta, RVOT right ventricular outflow tract.*

Table 1.1: Prevalence of valvular strands from previous studies

Author/s	**Cases** (identified from TOE laboratory) underwent TOE for	**Prevalence of VS in cases**	**Controls** (identified from TOE laboratory) underwent TOE for	**Prevalence of VS in controls**	**Statistical Significance**
Freedberg et al. (15)	Embolic events	10.6% (63/597)	All indications excluding cardioembolic events	2.3%(23/962)	OR = 4.8, *P* = 0.0001
Tice et al. (16)	Ischaemic stroke	6.3% (20/318)	All indications excluding stroke	0.3% (2/650)	*P* = <0.00001)
Roberts et al. (27)	Ischaemic stroke or TIA	47% (34/73)	All indications excluding stroke, TIA, IE, valvular prosthesis, peripheral embolism, congenital heart defect	16% (12/73)	OR = 4.4
Cohen et al. (20)	**Patients >60 yrs with ischaemic stroke	22.5% (64/284)	All indications excluding stroke and peripheral embolism	12.1% (31/256)	OR 2.1, *P* = <0.005

Author/s	**Cases** (identified from TOE laboratory) underwent TOE for	**Prevalence of VS in cases**	**Controls** (identified from TOE laboratory) underwent TOE for	**Prevalence of VS in controls**	**Statistical Significance**
Menzel et al. (28)	Embolic events	46%	All indications excluding stroke, IE and severe calcification of aortic cusps or AV ring	34%	$P = 0.09$
Roldan et al. (29)	Patients <60 yrs with ischaemic stroke, TIA and peripheral embolism (group I)	41% (20/49)	Group II- All indications excluding cardioembolic events, IE and prosthetic valves (n = 88). Group III- consisted normal subjects (n= 90).	47% (41/88) (In normal subjects- 38%; 34/90)	P <0.001 overall as well as between III & I; III & II
Nighoghossian et al. (30)	Ischaemic stroke	18.8% (30/160)	Cardiac disease (excluding IE, valvular prosthesis, peripheral embolism, congenital heart defect)	2.2% (4/180)	$P = 0.001$
Homma et al. (31)	**Ischaemic stroke	39.4% (244/619)	Nil	NA	NA

***These cases were identified prospectively from patients admitted with acute stroke and not from patients underwent TOE for different indications in a TOE laboratory*

1.4 Location and distribution of valvular strands

VS have been reported numerous times involving both native (24) and prosthetic valves (32, 33).

1.4.1 Native valves

Initial autopsy series by Lambl (21) described LE on aortic valves and subsequently on mitral valves by Magarey (22). In 1985, Loire (34) analysed 30 consecutive cases to define the anatomy of these LE both macroscopically and histologically. The majority of LE was found on aortic valves with mitral valve location being the next most frequent. He also found LE on both tricuspid and pulmonary valves. Riddle et al. (35) performed scanning electron microscopy on 23 diseased mitral valve leaflets obtained at the time of prosthetic valve insertion. These were from patients over 45 years of age with probable rheumatic heart disease and LEs were seen on 15 of 23 (65%) of these leaflets.

Similarly, TOE studies showed presence of VS predominantly on left-sided cardiac valves and some studies were focused predominantly on the mitral valve as MV is the most common location for VS. The frequency of VS on mitral valves ranges from 6.3% to 76% and on aortic valves from 27% to 50% (Table 1.2). This wide range can be explained by different groups of patients studied over different age groups. VS have been only rarely reported on either tricuspid or pulmonary valves (36).

Table 1.2: Frequency of VS on different cardiac valves derived from previous studies

The number of patients with VS in each location/ total number of patients with VS are described in parentheses.

Author/s	Frequency of VS in cases from previous studies			
	mitral	**aortic**	**left-sided ***	**right-sided**
Freedberg et al.	70% (60/86)	27% (23/86)	3% (3/86)	0
Roberts et al.	61.8% (21/34)	23.5% (8/34)	14.7% (5/34)	0
Roldan et al.	50% (10/20)	25% (5/20)	25% (5/20)	0
Nighoghossian et al.	53.3% (16/30)	20% (6/30)	26.7% (8/30)	0
Lee et al.	22% (11/50)	-	-	-
Tice et al.	6.3% (20/318)	-	-	-
Cohen et al.	22.5% (64/284)	-	-	-
Menzel et al.	-	39% (86/218)	-	-

**combined mitral and aortic VS*

1.4.2 Prosthetic valves

VS on prosthetic valves are frequently detected by TOE and are more commonly detected in patients being evaluated for a suspected cardioembolic event and thus represent a potential cardiac source of embolism (33). Orsinelli et al. (33) identified prosthetic VS in TOE studies performed during a 5- year period for evaluation of valve dysfunction or a suspected cardioembolic event in patients with valve prosthesis. Strands were detected in 56 of 214 (26%) studies. There was a significant difference ($p = 0.0001$) in the prevalence of strands between studies performed for a suspected cardioembolic event (34/64; 53%) versus those performed for suspected valve dysfunction (22/150; 15%). VS were more prevalent on mitral than on aortic valves (32% vs. 13%, $p = 0.0004$) and were more frequently detected on mechanical rather than on bioprosthetic valves (27% vs. 8%, $p = 0.003$).

papillary fibroelastomas. In 1991, Lee et al. (24) reported that gross inspection of a mitral valve removed during a mitral valve replacement and with documented VS by TOE revealed the strands to be consistent with Lambl's excrescences pathologically.

1.5.2 Echocardiographic differential diagnosis (23)

(a) Thrombi: They are very frequently detected on TOEs. They appear as well demarcated, round masses attached to the valves. They are not connected to the valves through a stalk, which is an important diagnostic feature. Their echodensity is usually homogenous and difficult to distinguish from cardiac tumours.

(b) Vegetations: Vegetations are large, highly mobile, irregular structures attached to the valves and might prolapse through the valve and usually associated with significant regurgitation due to disruption of normal valvular structure. However, the diagnosis needs to be made in the context of an infective clinical picture.

(c) Myxomas: They can occur on cardiac valves, but are attached to atrial endocardium through a distinct stalk or pedicle and usually contain small areas of haemorrhage and calcification giving rise to irregularities in echodensity. They can be quite large and usually associated with valvular stenosis or regurgitation.

(d) Fibroelastomas: Larger lesions are often called cardiac papillary fibroelastomas and these are present on valves, away from valvular lines of closure, and also on the endocardial surfaces of the atria and ventricles. Although LEs and fibroelastomas are

histologically very similar (40) and a shared pathogenesis has been suggested (41), they differ in size and shape. LEs are usually long, filiform structures, with a mean size of 8x1 mm and commonly appear as strands on TOE. Fibroelastomas are bulky with a mean size of 12x9 mm and attached to the valve through a stalk or pedicle. Their surface contains multiple small, finger-like projections, which appear as fronds on TOE and TTE. These are absent in VS. Boone et al. (41) examined hearts with grossly classic papillary fibroelastoma and typical Lambl excrescences and noted that they are microscopically indistinguishable while macroscopically LEs are smaller and broader-based.

(e) Myxomatous degeneration of cardiac valves: It affects the structure of the valve itself rather than structures attached to it. Myxomatous degeneration can result in valve thickening with protrusions, which are not mobile when examined by TOE.

(f) Soft calcifications: This refers to mobile, heavily calcified components involving the valvular annulus and the proximal parts of the valves.

(g) Prosthetic sutures: Fibrinised or endothelialised sutures of prosthetic valves can be difficult to differentiate; however, they are usually thick and placed in a uniform manner.

(h) Cardiac mesothelial/monocytic cardiac excrescences: These structures can be found on the cardiac valves, in the atria and in the pericardial space during open heart surgery.

1.5.3 Microscopic description

Histologically LEs are composed of acellular connective tissue core covered by endothelium (22). Loire reported Lambl's excrescences in two forms (34) when examined macroscopically and histologically: mobile, pedunculated either with an acellular fibrous axis containing rings of granular eosinophilic material or with more complex associations of these changes resulting in pseudo-papillomata of the valves. The second form was described as thickening of the valves itself and covered by a layer of flattened endothelium.

Among the two types of LEs, lamellar and filiform identified on aortic valves by Hurle (26), the connective tissue core of the filiform excrescences contained abundant collagen fibrils and elastic material arranged in apposed layers with different collagen fibril orientation on electron microscopy. At the centre of the filiform excrescences, a circular zone devoid of identifiable connective tissue was also described. In 1989, Riddle et al. (35) studied leaflets obtained from 23 diseased mitral valves of patients over 45 years of age removed at the time of prosthetic valve insertion. The clinical diagnosis in all the cases was probable rheumatic heart disease and 6 of them had valvuloplasty previously. LEs were seen on 65% (15/23) of these leaflets. Electron microscopic examination showed that individual LEs varied in size, length and external topography. The ends of some LEs were tapered, whereas others were rounded and blunt. Occasionally a large projection was further divided into several smaller subunits at its base. The exteriors of these

processes were either covered with fibres of varying dimensions or a cellular layer, presumably of endothelial cells.

While VS is an echocardiographic description, Lee et al. (24) reported that inspection of a mitral valve removed during a mitral valve replacement and with documented VS by TOE revealed the VS to be consistent with LE pathologically. In 1998, Hutchinson et al. (42) confirmed VS on a Medtronic-Hall prosthetic valve in a patient with recurrent strokes as LE by histopathological examination.

1.6 Pathogenesis

Magarey (22) who studied these valvular excrescences at autopsy suggested they were more common with advanced age and hypothesized that Lambl's excrescences might be the result of deposition of fibrin over damaged endocardial valvular surfaces that became partially detached from the valve, condensed and hyalinised and ultimately fibrosed. Fresher fibrin deposits were found to be enmeshed with erythrocytes and leucocytes.

Loire (34) suggested several pathogenic mechanisms, all related to local conditions rather than to general circulatory changes:

(a) Folding of the valvular endothelium onto itself followed by organisation into tubular structures filled with oedema and hyaline.

(b) Deposits of fibrin layers on zones of endothelial ulceration caused by trauma on the line of apposition of the cusps with partial detachment of fibrinous material which then endothelialises.

(c) Subendocardial incorporation of oedema, fibrin and red blood cells.

Riddle et al. (35) from the electron microscopic study of diseased mitral valves from probable rheumatic valve disease supported the wear and tear hypothesis of formation of LE. At the denuded areas in the valve leaflets, while one end of broken bundles of collagen or elastic fibers remained anchored within the connective tissue network of the cusp, the free end extended outward from the surface of the valve. Platelets were adhered and aggregated to the protruded broken bundles or collagen or elastic fibers. Fibrin deposition with subsequent organisation followed by endothelialisation of the thrombotic deposit covering

the extended process could explain continuous layering of the LE by endothelial cells in some of them. The wide of range of sizes observed may be explained by variation in the numbers of the fibers initially contained as the core of the projection, and accumulation of different amounts of thrombotic material on the exterior of the process.

1.7 Relation of valvular strands to valve morphology

Autopsy series by Magarey (22) described LE occurring more commonly on thickened valves. The initial description of TOE-defined VS by Lee et al. (24), also suggested that mitral valve thickening was associated with a higher incidence of mitral VS. Subsequently, similar to the findings of Lee et al., a higher incidence of thickening of the valves those with VS was reported by Cohen et al. (20) and Menzel et al. (28) on mitral and aortic valves respectively. Contrary to the previous findings, Freedberg et al. (15) in his study observed that VS were common on normal native valves than on valves that were significantly thickened. He reported than more than 90% of native valves with VS were morphologically normal on TOE. Perhaps, the difference in the prevalence of VS could be due to different inclusion criteria used for VS. The initial studies by Magarey and Lee et al. included valvular excrescences up to 5 mm in width while Freedberg at al. excluded excrescences >1 mm in width. In addition, Freedberg et al. excluded valves with torn chordae or flail leaflets. Tice et al. (16) and Nighoghossian et al. (30), in their TOE studies showed findings similar to Freedberg et al. as there was no echocardiographic evidence of higher incidence of degenerative valvular changes on valves with VS. Despite to the above studies, Roberts et al. (27) described no difference in mitral and aortic valve thickness between those with or without VS and thus there is no consensus in the literature regarding the nature of valves with VS whether they are thickened or normal in nature.

1.8 Role of valvular strands

The role of VS can be described as follows:

1.8.1 As a part of normal aging process

Magarey (22) in his study concluded that the appearance of excrescences on valves is a part of normal aging process as these were present in all individuals older than 60 years. Nighoghossian et al. (30) supported this in a follow-up TOE study performed three months after the initial TOEs in patients with VS. These strands appeared to remain intact without changes in appearance over this period of time.

1.8.2 Obstruction to coronary arteries

In a patient presented with angina pectoris, echocardiographic and angiographic examination suggested that the right ostium was obstructed by a lesion that was attached to the aortic valve (43). Histopathological examination of this lesion after surgical removal confirmed LE. The symptoms of patient resolved after the removal of the same.

1.8.3 Valvular obstruction

Several cases are reported to cause partial occlusion of valves by LE. In a report by Thomas et al., a TOE-diagnosed valvular lesion occluding the mitral valve was consistent with a giant LE when examined histopathologically after its surgical removal (44).

1.8.4 As a peripheral embolus

Fitzgerald et al. (45) reported a giant LE presenting as a peripheral embolus in a 72 year old man. The embolic material recovered by embolectomy was histologically examined and found to be similar to LE.

1.8.5 As a cardiac cause of central embolism (Acute ischaemic stroke/TIA)

In 1991, Lee et al. (24) described TOE-defined VS initially in patients with recent TIA or stroke of embolic origin and speculated on their role in cerebral embolism. They postulated that mitral VS may represent a fissured surface or fibrosis that can serve as a nidus for thrombus formation. As a mechanism for embolic events, it is possible that either the strands themselves break and embolize or that the thrombi formed on the strands which subsequently embolize. Freedberg et al. (15) examined TOE studies performed in patients with an embolic event (TIA or stroke or peripheral emboli) and found that 10.6% (63/597)) had VS compared with only 2.3% (23/962) patients without an embolic event (odds ratio 4.8, 95% confidence interval (CI) 3.0 to 7.9, $p = 0.0001$). In other words, VS were far common in patients with an embolic event. Mitral VS were found to be significantly more common in patients with a recent ischaemic cerebrovascular event compared with patients referred for other indications (6.3% [20/318] versus 0.3% [2/650], respectively; $p < 0.00001$) for TOE (16). Thirty five percent (7/20) of those with mitral VS were believed to have had a probable cardioembolic stroke or TIA on their stroke work-up in this study although it was unable to establish a cause and effect of mitral VS and cerebral embolism. Roberts et al. (27) also confirmed this association between mitral and aortic VS with

cerebral ischaemia but found no association with the number and length of VS with cerebral ischaemia. Similar to previous studies, Cohen et al. (20) also found that VS were significantly associated with the risk of stroke, but the similar prevalence of VS in patients with a '*known cause of brain infarction'* and in those '*without any apparent cause of brain infarction'* raised doubts about the potential causal relation with brain infarction in patients aged 60 years or older. Roldan et al. (29) sought to determine prospectively the evolution and embolic risk of VS in normal subjects and patients with and without suspected cardioembolism. In subjects with a high prevalence of VS, the incidence of cerebrovascular ischaemic events was low (<0.5 per 100 person-years) and similar to that of those without VS. Also, the prevalence of VS was similar in patients with (46%) and without (34%) embolic events. Contrary to the previous studies, this study suggested that VS are neither a primary pathogenic factor nor a marker for embolism.

1.9 Valvular strands and age

Magarey (22) found that no valves from subjects younger than one year had excrescences but that 90% of those between the age 1 to 60 years had excrescences. In the TOE studies, Tice et al. (16) reported a relatively higher prevalence (16%; 7/44) of mitral VS in young patients (age $\leq$ 50 years) with presumed cardioembolic stroke or TIA. VS were the sole cardiac abnormality in 9 % of these young patients. Roberts et al. (27) noted more strands in younger patients, but this observation did not reach statistical significance. In their study, they noted VS were more prevalent in older controls which could be explained by the fact that controls were older than the cases. Roldan et al. (29) found that prevalence of VS was independent of age groups while Menzel et al. (28) reported that VS were increasingly found in older age groups (14% in $\leq$40 years, 32% between >40 but $\leq$60 years, 53% in patients > 60 years, $p = 0.001$). Thus the true prevalence of VS and their association with different age groups of patients remains unclear.

1.10 Valvular strands and stroke subtype

Stroke subtyping of patients with VS and ischaemic stroke has not been uniform in the previous studies reviewing this aspect. The literature is as follows:

(a) Tice et al. (16) subtyped patients with VS into three categories: likely cardioembolic strokes or TIA (35%; 7/20); unlikely cardioembolic stroke which included large vessel atherosclerosis, lacunar, fibromuscular dysplasia, migraine and others (50%; 10/120); and stroke with uncertain aetiology or incomplete work-up (15%; 3/20). If we categorize this whole cohort into two groups such as stroke with uncertain cause (cryptogenic) and with a known cause of stroke (non-cryptogenic), 15% of patients with VS were in the cryptogenic group while 85% were in the group of patients with non-cryptogenic stroke.

(b) Roberts et al. (27) classified patients by criteria adapted from the Stroke Data Bank (46). He identified VS in 50 % (15/30) of cryptogenic, 42% (8/19) of atherothrombotic, 62% (5/8) of lacunar, 27% (3/11) cardioembolic strokes and in 60% (3/5) TIA cases. Overall, strands were not significantly more frequent in cryptogenic stroke patients than in non- cryptogenic stroke patients (50% versus 42%), but the sample size of the study was small.

(c) Based on cause of stroke, Cohen et al. (20) found that VS were present in 24.4% (22/90) patients 'with a likely cause of stroke', 23.1% (12/52) patients 'with a possible cause of stroke', 21.6%

(11/51) patients with a 'lacunar infarct' and in 20.9% (19/91) patients 'with no other apparent cause of stroke'. A similar prevalence of VS was found in patients 'with a likely cause of brain infarction and in those 'without any detectable cause'.

(d) Roldan et al. (29) reported similar prevalence among patients with cardioembolic stroke (25%; 5/20), in cardiac and vasculoembolic (presence of carotid or aortic atheromatous vessel disease) (35%; 7/20), vasculoembolic (15%; 3/20) and in nonembolic stroke (25%; 5/20). There were no patients with VS in the group of stroke of undetermined aetiology.

(e) Homma et al. (31) reported VS in 38.6% (101/262) of patients with cryptogenic stroke compared to 40.1% (143/357) of patients with known cause of stroke and the difference was not statistically significant.

Overall, the prevalence of VS in patients with cryptogenic stroke and in non-cryptogenic stroke was not found to be significantly different.

1.11 Valvular strands and infarct topography

Although no previous studies reviewed infarct topography in stroke patients with VS, it is known that cardioembolic infarcts are generally multiple and bilateral. These infarcts are often large and wedge shaped although smaller infarcts are also identified. Jung et al. (47) described heterogeneous radiologic characteristics of infarcts depending on the risk of cardioembolism. Large single territorial infarcts are common in high risk cardioembolic group. There are uncertainties about incidence of lacunar infarction or small cortico-medullary junction infarction due to cardioembolism (48). A recent study by Cho et al. (49) showed that patients with cardioembolic sources more frequently had unrecognized cerebral infarcts particularly lacunar infarcts than those without; (21/36; 58.3% versus 57/167; 34.1%, $p = 0.008$).

1.12 Valvular strands and hypercoagulable state

Hypercoagulable states such as inherited thrombophilias (eg, protein C, protein S, or antithrombin III deficiency; factor V leiden; or the prothrombin G20210A mutation) and methylenetetrahydrofolate reductase (MTHFR) C677T mutation rarely contribute to adult stroke (50). Activated protein C (APC) resistance, the most prevalent inherited coagulation disorder has been linked to ischaemic stroke in case reports (51). Antiphospholipid (APL) antibodies are associated with increased thrombogenesis (52, 53) and can cause stroke. The association of APL antibodies and stroke is strongest for young adults (< 50 years of age). Saidi et al. (54) in their study demonstrated that the presence of lupus anticoagulant, and elevated anticardiolipin IgG antibody and antiphosphatidylserine antibodies are risk factors for ischaemic stroke. Topcuoglu et al. (55) have suggested that in the acute period of ischaemic stroke secondary to lone atrial fibrillation, enhancement of the coagulatory activity occurs as a result of increased thrombin generation, similar to other possible sources of cardioembolism.

A thrombotic origin of valvular strands has been hypothesized in few of the prior studies (15, 24, 56). VS may represent a fissured surface or fibrosis that can serve as a nidus for thrombus formation. It is possible that either the strands themselves break and embolize or thrombi from the strands subsequently embolize causing stroke. The observation of VS developing in serial TOEs during the resolution of prosthetic MV thrombus suggested that VS are composed of platelet-fibrin material (56).

Roldan et al. (29) tested this thrombotic hypothesis of VS in a population with a high prevalence of antibodies (i.e., patients with connective tissue diseases. The presence or concentration of antiphospholipid antibodies was not associated with the presence of VS (29).

1.13 Valvular strands and risk of recurrent stroke

There are case reports of recurrent strokes in two patients treated on anticoagulation for giant LE after their first stroke (19). Two previous studies have addressed the risk of recurrent strokes in patients with VS.

Cohen et al. (20) in their study of 284 consecutive patients admitted with brain infarction followed the case subjects over a two to four year period and the risk of recurrence of brain infarction was estimated in patients with and without mitral valvular strands. During 646 per 100 person-years of follow-up, the incidence of recurrent brain infarction was 6.0 person-years in patients with strands and 4.2 in those without. In the Cox analysis, including potential confounders and post-stroke treatment, mitral valve strands did not appear as an independent predictor of recurrent brain infarction.

PICSS study showed that in medically treated stroke patients (aspirin or warfarin) the presence of valvular strands did not increase the chance of adverse events (31).

In a study performed by Nighoghossian et al., strands were not found in 15.4% of patients on repeat TOE at three months, but there was no clinical follow-up to detect any recurrent strokes or TIA (30).

1.14 Prosthetic valve strands

Orsinelli et al. in 1995 reviewed all TOEs performed during a 5-year period for evaluation of valve dysfunction or a suspected cardioembolic event in patients with a valve prosthesis (33). VS were detected in 26% (56/214) of studies. There was a significant difference (p =0.0001) in the prevalence of VS between TOE studies performed for a suspected cardioembolic event (53%; 34/64) versus those performed for suspected valve dysfunction (15%; 22/150). Strands were found more prevalent on mitral valves and more frequently detected on mechanical than bioprosthetic valves (27% vs. 8%, p = 0.003). They concluded that prosthetic valve strands were frequently detected on TOE and were more common in patients being evaluated for a suspected cardioembolic event and thus represent a potential cardiac source of embolism.

Robert et al. in 1996 performed a late follow-up study in patients with mitral mechanical prosthesis and noted the prevalence of previous embolic events was significantly higher in the group with VS than the control group (57). The group of patients with VS also contained more patients with a prior history of prosthesis thrombosis; however, long-term follow-up was uneventful.

1.15 Diagnosis

Although valvular strands are detected by TOE, the identification and diagnosis of VS are not standardized. The incremental value of three-dimensional echocardiography over multiplane transoesophageal two-dimensional imaging in the assessment of VS involving the aortic valve has been demonstrated by Samal et al. (58). The following diagnostic criteria can be used as suggested by Wolf et al. (25) (Table 1.3).

Table 1.3: Diagnostic criteria for the detection of VS by TOE: macroscopic and histopathological characteristics (25).

	Criteria	Characteristics
1	Based on TOE	1. Hypermobile, filiform, threadlike echodensities, attached to native or prosthetic valves (15, 16, 30, 59) 2. Mostly left-sided (15, 31, 33, 59) 3. Lesions not sessile or pedunculate (15) 4. Valve morphology usually normal or minimally thickened (15) 5. Variable length (0.5-4.6 cm), but mostly < 1 cm (15, 59)
2	Macroscopic examination	1. Slender, filamentous masses (17, 60) 2. Polypoid aspect (17)
3	Histopathology- Three tissue layers (17, 59-61)	1. Central avascular core, densely hyalinised 2. Peripheral layer of loose connective tissue 3. Outer rim of endothelial cells, which may appear hyperplastic

1.16 Treatment

Definitive therapy for patients with VS and particularly for those who have already had an embolic event without another source of embolism is undetermined. Freedberg et al. (15) in their study did not find any difference in the presence of VS (who also had no other identifiable source of emboli) with respect to use of anticoagulant or antiplatelet therapy. Cohen et al. (20) followed up older ischaemic stroke patients with strands and found the incidence rate of stroke was 7.1 per 100- person years in patients receiving antiplatelet drugs, 6.9 in those receiving oral anticoagulants, and nil in those with no antithrombotic treatment. Roldan et al. (29) found that aspirin or warfarin therapy did not appear to have an effect on the prevalence and evolution of VS. PICSS, the only randomized treatment study of stroke patients with VS showed that neither aspirin nor warfarin had an advantage with respect to treatment efficacy (31). Given that all patients were treated in the PICSS study, it remains undefined whether medical therapy altered the event rates when compared with untreated patients. There are some case reports describing the use of warfarin in patients with thrombus detected on VS (19). Orsinelli and Pearson (33) reported on a patient whom despite a prothrombin time in the therapeutic range had a TIA and TOE showed VS on his mitral prosthesis. These strands were no longer seen after the addition of dipyridamole to his regimen. Loire (62) has suggested surgical resection for papillary fibroelastomas (giant LE) as recurrent cerebral embolism has been reported despite anticoagulation.

The optimal treatment remains unclear, but the following guidelines can be used.

(a) In patients who undergo TOE for reasons other than suspected cardioembolism, the incidental finding of a valve excrescence probably does not warrant the prophylactic use of antiplatelet therapy (29).

(b) If patients have had an embolic event (stroke) and VS is the only identifiable cause of stroke, treatment with antiplatelet agents is appropriate along with treatment of any other cardiovascular risk factors if present.

(c) In patients after recurrent stroke with VS as the only identifiable cause of stroke, oral anticoagulation or antiplatelet therapy can be considered. Surgical resection can also be considered in individual cases. Treatment of other cardiovascular risk factors remains important.

2.3 Secondary Aims

(a) To compare the frequency of TOE-defined valvular strands in young and old age groups in the stroke cohort patients versus controls.

(b) To determine the relationship of valvular strands to other potential cardiac sources of embolism and diastolic dysfunction on TOE in the stroke cohort patients versus controls.

(c) To determine the relationship of TOE-defined valvular strands to ischaemic stroke subtype and infarct topography by imaging in the stroke cohort patients.

(d) To determine the relationship of hypercoagulable states in young patients with or without TOE-defined valvular strands in the stroke cohort patients.

Chapter 3: Methods

This is a single centre study and all subjects were identified from patients admitted to Beaumont Hospital between July 2008 and April 2010 for investigation and treatment of stroke. This research project was reviewed by the Ethics (Medical Research) Committee in Beaumont Hospital and was approved on 10th of July 2008.

3.1 Case-Control study

This is a single-centre observational research study in which the participants were identified from patients admitted to Beaumont Hospital between July 2008 and April 2010 for investigation and treatment. The main case-control study consists of consecutive patients admitted with an acute ischaemic stroke and a control group of patients without stroke, with a second prospective part in which only the cohort of stroke patients is followed up to identify occurrence of further vascular-related outcomes/complications or death (Figure 3.1 and 3.2).

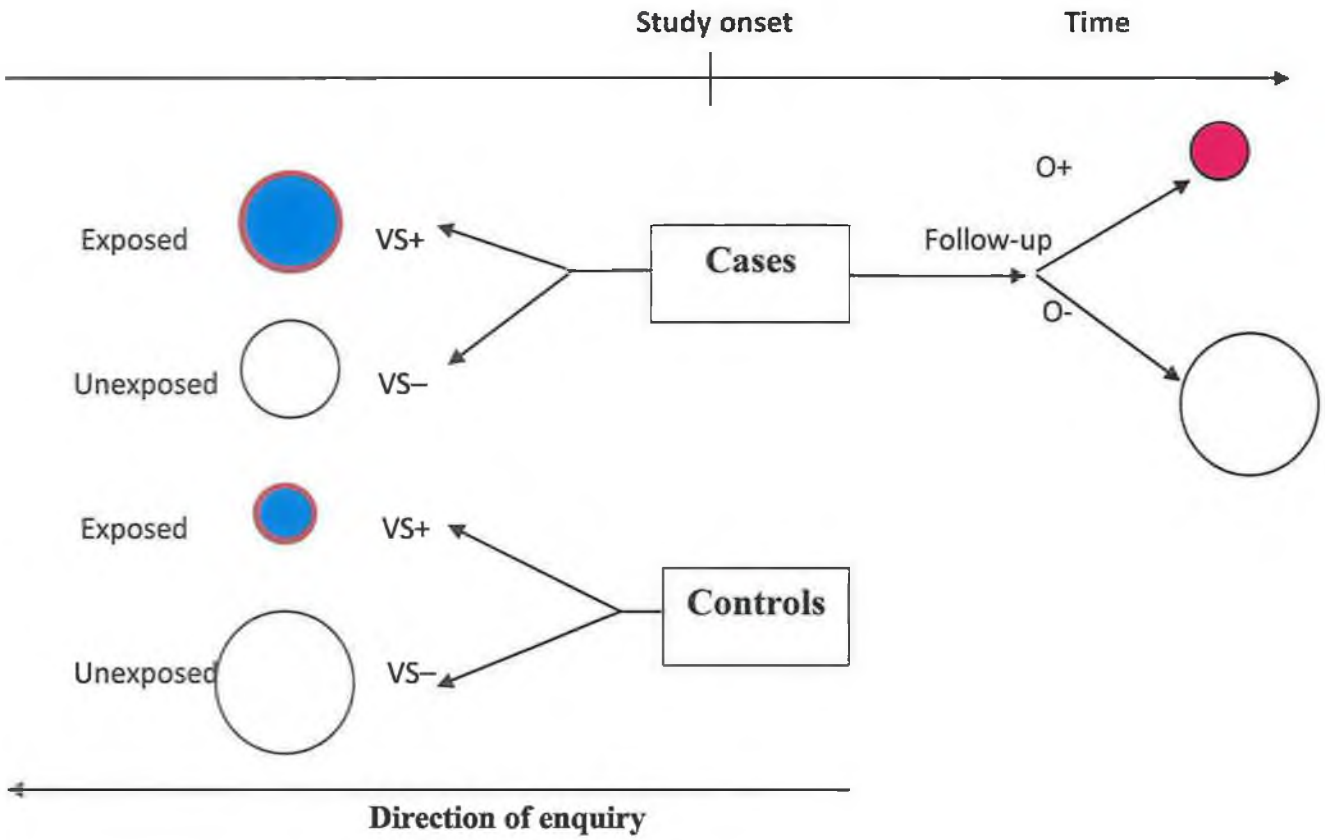

Figure 3.1: Design of the research study

VS+ Valvular strands present; VS – Valvular strands absent; O+ with poor outcome (recurrent infarct/myocardial infarction/vascular death); O– without poor outcome

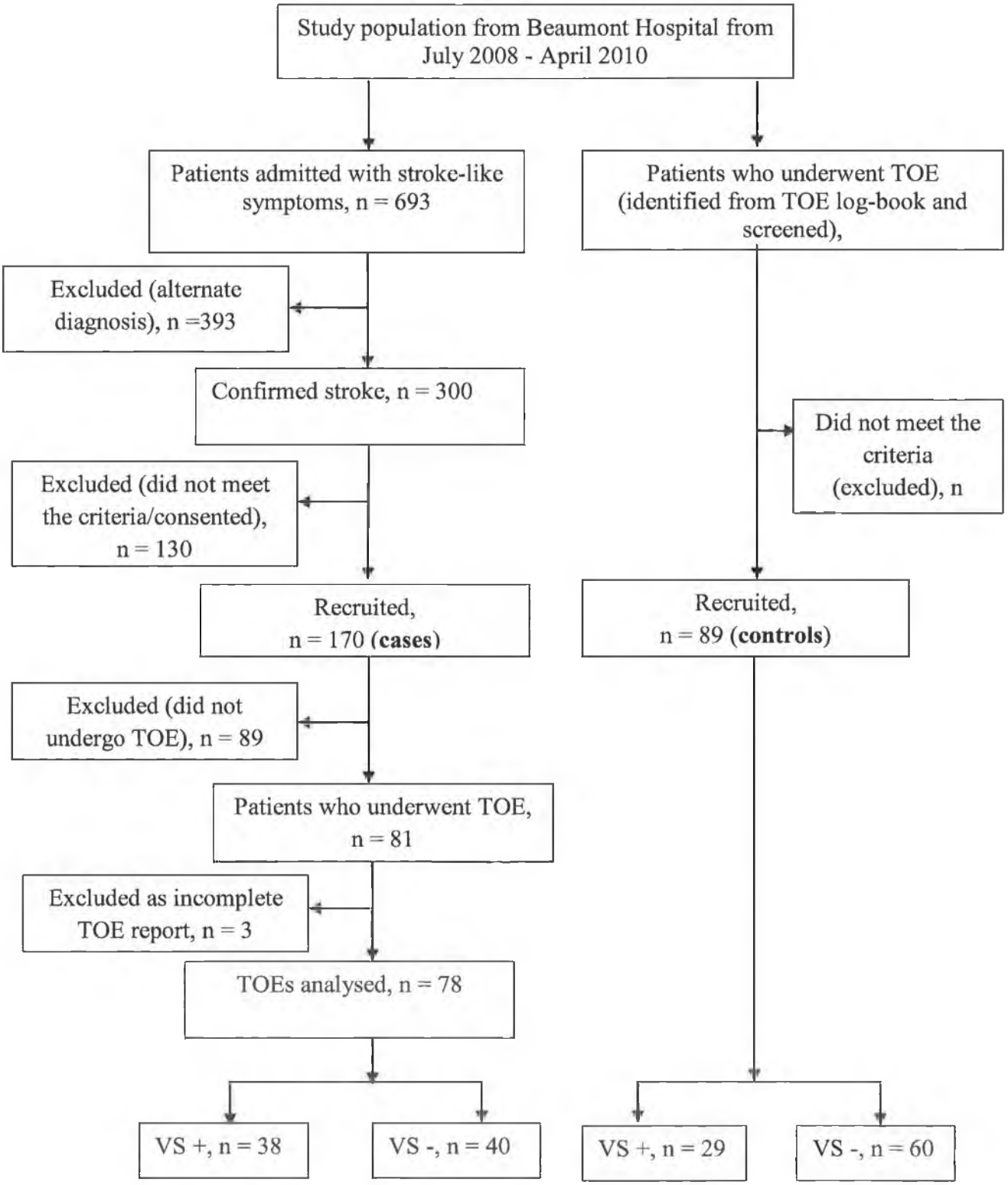

Figure 3.2: Flow chart of case-control study

TOE = Trans-oesophageal echocardiogram; VS = valvular strands

3.1.1 Cases

The surveillance for potential study subjects were carried out using the Accident and Emergency Department computer system, CT brain logbook, the stroke consult service led by the Stroke neurology team and the Acute Stroke Unit, which opened in the hospital in the last quarter of 2009. In addition, daily liaison with the neuroradiology department and neurology bed managers and on-call medical team also helped to recruit patients. Patients with clinically suspected acute ischaemic stroke if they fulfilled the inclusion and exclusion criteria were approached and given verbal and written information concerning the study.

(a) Inclusion criteria

- All male and female adults aged 16 years or more newly diagnosed with acute ischaemic stroke (within 30 days of onset of symptoms) based on clinical presentation and brain imaging.

- Written informed consent- prior to the enrolment, 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. In the case of grossly cognitively impaired patients or with massive stroke or with stroke affecting the dominant hemisphere, information leaflets were given to the next-of-kin/relative and consent was sought. They were asked to sign assent forms as legal representatives.

(b) Exclusion criteria

- Patients with primary intracerebral haemorrhage
- Patients with subarachanoid haemorrhage
- Children and minors (< 16 years)

(c) Assessment of cases

After the consent was obtained, patients were assessed as outlined below:

- A detailed clinical stroke history
- General, cardiovascular and neurological examination. Neurological examination included assigning the National Institute of Health Stroke rating Scale (NIHSS) and functional score (Barthel index). See appendices 5 and 6.
- Screening blood tests for hypercoagulable states if the patients were less than 60 years of age. This included prothrombin time, activated partial thromboplastin time, international normalised ratio, lupus anticoagulant, anticardiolipin antibodies (IgG and IgM), antithrombin III test, protein C and protein S, activated protein C resistance, d-dimer, fibrinogen and factor V Leiden. Other blood tests performed for this age group included complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), vasculitis screen, serum protein electrophoresis and blood homocysteine levels. Patients in all age groups underwent fasting glucose and lipids.

- All patients will undergo noncontrast head CT on admission and subsequently MRI brain as repeat imaging unless there is a contraindication or any other difficulties. Stroke work-up in order to ascertain the mechanism of stroke included a minimum of vascular imaging of neck ± brain and cardiac investigations (ECG, 24 hour Holter monitoring/telemetry and transthoracic echocardiogram (TTE) / TOE). The investigation and management of patients as a result of their participation in the study was not altered. All index stroke will be subtyped by a Consultant neurologist with expertise in stroke and will be based on a predefined criteria modelled after the National Institute of Neurological Diseases and Stroke (NINDS) Stroke Data Bank and Trial of Organon in Acute Stroke Therapy (TOAST) (63).

(d) Trans-oesophageal echocardiography

Transoesophageal echocardiograms were performed using the iE33 Philips echocardiography system and mostly by a single Consultant Cardiologist with specific expertise in performing and evaluating TOEs. A small number of TOEs were performed by Cardiology trainees under his supervision. The procedures were focussed on delineation of cardiac source of emboli including characterization of VS. VS was defined as a thin filamentous material ≤ 1 mm in thickness and extending from the edges of mitral and aortic valve, into the left atrium at systole for mitral valve, and into the left ventricle at diastole for the aortic valve (20, 27). All the echocardiograms were analysed by the same Consultant Cardiologist. TOE performed was based on the following criteria:

- As a part of routine clinical care, those patients were there was a high index of suspicion for cardioembolic source based on their stroke syndrome and infarct topography on brain imaging and where TTE has been negative or not done.

- As a part of routine clinical care, where stroke syndrome and infarct topography were compatible with a cardioembolic mechanism and TTE had been an inadequate study because of poor windows or other technical factors.

- As a part of routine clinical care, where stroke syndrome and infarct topography were compatible with cardioembolic mechanism and TTE shows a possible source, but further definition was required e.g. possible thrombus in the left atrial appendage, possible valvular lesion, and positive bubble study.

- As a part of stroke work-up if no other possible mechanisms were identified by routine investigations i.e. in cryptogenic stroke.

3.1.2 Controls

Patients without stroke, i.e., controls, were identified serially from the TOE log-book which provided the details of all the patients who underwent TOE from July 2008 to April 2010 in the Cardiology Department of Beaumont Hospital as part of their assessment for all clinical indications. Patients who underwent TOE for suspected infective endocarditis were not a valid control group for assessment of valvular lesions due to the nature of their condition and were excluded. We also excluded patients who underwent TOE as a part of their stroke work-up or to rule out any cardiac source of emboli. The controls were not approached for any clinical assessment and only the following information was collected:

- Medical record number
- Date of examination
- Indication for TOE
- Age of the controls
- A full TOE report.

There was no matching possible between cases and controls due to lack of clinical details (vascular risk factors) for control population.

3.2 Follow-up study

All cases were followed-up for 6 to 12 months by clinic visits to assess the risk of recurrent ischaemic stroke, myocardial infarction and or vascular death (defined as poor vascular outcome) (Figure 3.3). In the follow-up clinic visits, information about any new neurological symptoms, investigations, hospital admissions and treatment in the interim were collected. A neurological examination including NIHSS score and functional score (BI) were documented. For patients unable to attend the follow-up clinic, patients or their carers were interviewed over the telephone and information about any new neurological symptoms, investigations, hospital admissions, treatment and BI score were gathered. Their medical notes were also reviewed to confirm and to complete the data collected.

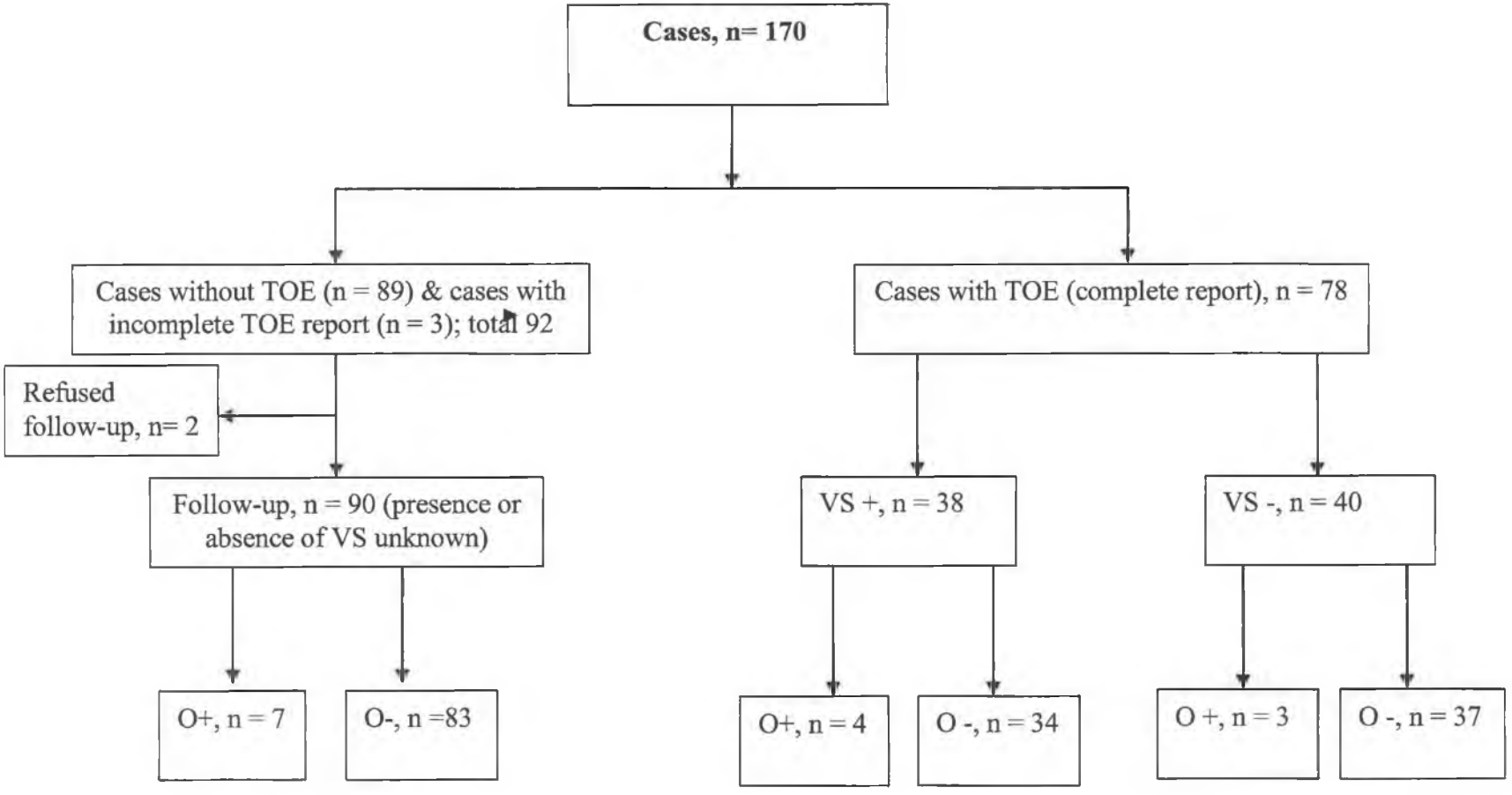

Figure 3.3: Flow chart of follow-up study

TOE = Trans-oesophageal echocardiogram; VS + with valvular strands; VS - without valvular strands; O + with poor outcome; O - without poor outcome

3.3 Statistical methods

3.3.1 Sample size/power calculation

We calculated the sample size required to show a statistically significant difference in frequency of valvular strands between cases and controls. We set α at 0.05 and the power (1-β) at 0.90. We used Lehr's formula: Power = 21 / (Standardized difference)^2. The standard difference was calculated using the formula $P' = (P_1 + P_2)/2$. We derived P_1 (frequency of strands in patients with acute ischaemic stroke) at 0.40 from the PICCS study (31) and P_2 (frequency of strands in control group) at 0.16 from a study done by Robert et al. We determined a minimum sample size of 75 in each group (stroke and control) and given that approximately 220 patients with stroke were admitted over the previous year, reaching the minimum sample size was considered achievable.

We conducted a separate sample size calculation whenever possible to address the power issues related to the planned analysis for the secondary outcomes. For the association of valvular strands in ischaemic stroke with patient age as a sub-study (sub-group analysis) we again used Lehr's formula and P_1 and P_2 were taken from the literature (P_1 at 0.52 and P_2 at 0.23). We found that a minimum of 90 patients would be needed in the two age groups (less than 60 years and more than 60 years groups).

However, to address the power needed to assess the association between VS and ischaemic stroke subtypes, we did not have sufficient data from the literature due to different subtyping classifications used and small numbers in each stroke

subtype reported in the prior studies that investigated this topic (27). No prior studies had investigated the association of infarct topography with VS to allow us to use them for sample size and power calculations. One prior study reviewed the association between antiphospholipids and valvular strands and did not find any significant relationship (29). Therefore, no *a priori* sample size calculation and power estimates were available for these two sub-group analyses (in this sense, these sub-studies can be also considered as pilot investigations. Approximately 220 patients were reviewed by the previous stroke consult service over one year. These numbers included haemorrhagic strokes as well. At the same time some patients transferred directly from the peripheral hospitals to the neurology teams were not included. Overall, given the above calculations, we expected to recruit a minimum of 180 patients with stroke and 180 age-matched controls over a period of two years.

3.3.2 Statistical analysis

In the case-control study, we used standard descriptive statistics as the first step in the analysis of the data to summarise categorical (qualitative) and continuous (quantitative) data and explore if the latter were normally distributed. Unpaired t tests for quantitative data and Chi-square tests of association for categorical data were used to investigate relationships of interest at a univariate level. Univariate analyses as well as multivariate analyses using parametric or logistic regression analysis were used to measure the impact of each independent variable on the outcome, and where appropriate, to adjust for potential confounders. The *p*-value of 0.05 is considered as a level of statistical significance, unless stated otherwise.

In the follow-up study, apart from standard descriptive statistics, we have used Kaplan-Meier survival curves for the whole stroke cohort as well as survival curves based on presence or absence of valvular strands. Cox proportional hazard models were also created including valvular strands, gender and aortic valve abnormalities as potential predictors. The SPSS statistical software package (version 18) was used for data elaboration and analysis.

Chapter 4: Results

4.1Demographics of cases

A total of 693 patients admitted with stroke-like symptoms were assessed between July 2008 and April 2010 in Beaumont Hospital. There were 300 patients with confirmed acute stroke clinically and/or radiologically (Figure 3.2). Among those, 170 patients fulfilled the inclusion criteria, consented and were recruited. Out of these 170 cases, 81 underwent TOE. Information on VS was unavailable on three patients and these three patients were excluded from the subsequent analysis of VS, leaving 78 patients with TOE for the case-control study.

Total number in stroke cohort (follow-up study,) n = 170

Number of cases in case-control study, n = 78

4.1.1 Age

The whole stroke cohort had a mean age of 58.1 years (SD = 15.7, range 17.2 - 87.2) and showed a bimodal distribution (Figure 4.1) while the cases in the case-control study had a mean age of 53 years (SD = 15.1, range 20.5 - 78.5). The cases were grouped into aged <60 years (young) and ≥60 years (old) for some of the analysis (Table 4.1).

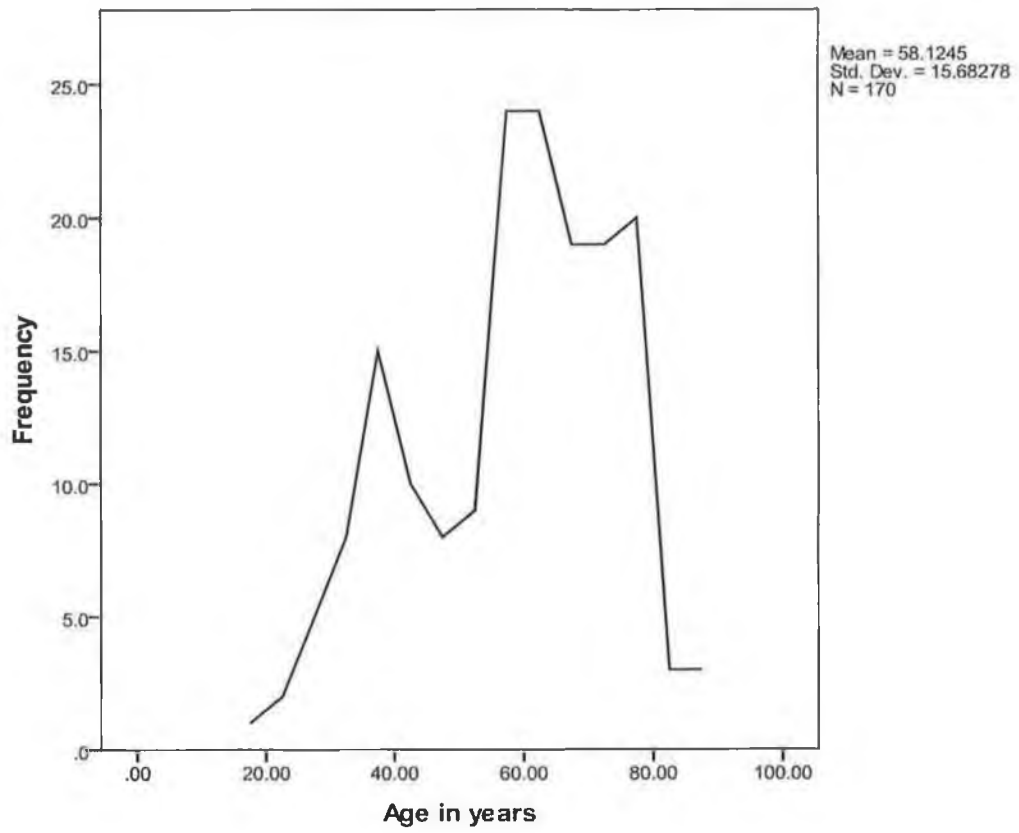

Figure 4.1: Age distribution of cases (the whole stroke cohort of patients)

Table 4.1: Age distribution of cases

Demographics	**Whole stroke cohort, n = 170**	**Case-control study, n = 78**
Age (mean) in years	58.1±15.7	53.0±15.1
Young (<60 years)	47.6 % (81/170)	56.4 % (44/78)
Old (≥60 years)	52.4 % (89/170)	43.6 % (34/78)

4.1.2 Gender

Gender distribution showed more males than females (Table 4.2).

4.1.3 Stroke thrombolysis

A total of 16 (16/170; 9.4%) patients were thrombolysed in the whole stroke cohort and three of them were included in the case-control study.

4.1.4 Medications prior to stroke

Information was available for 169 cases. There were 38.5% (65/169) and 24.4% (19/78) on antiplatelet agents prior to stroke onset in whole cohort and in cases of case-control study respectively (Table 4.3).

4.1.5 Vascular risk Factors

Vascular risk factors for stroke were identified from the whole stroke cohort (Table 4.4). One fourth of cases had a history of some type of heart disease (45/170; 26.5%). The most common cardiac diseases reported were myocardial infarction and atrial fibrillation (Table 4.5).

4.1.6 Clinical stroke syndrome

Based on the Oxfordshire Community Stroke Project Subtype Classification (64), over half of the cases (53.8 % -55.3%) presented with partial anterior circulation infarcts with posterior circulation infarcts (26.9% - 27.1%) the next most frequent clinical stroke syndrome (Table 4.6).

Table 4.2: Gender distribution of cases

Demographics	**Whole stroke cohort, n = 170**	**Case-control study, n = 78**
Males (%)	61.2 % (104/170)	57.7 % (45/78)
Females (%)	38.8 % (66/170)	42.3 % (33/78)

Table 4.3: Medications prior to stroke

Medication	**Whole stroke cohort, n = 169**	**Case-control study, n = 78**
Aspirin	62 (36.7%)	19 (24.4%)
Clopidogrel	13 (7.7%)	3 (3.8%)
Dipyridamole	0 (0%)	0 (0%)
Warfarin	6 (3.6%)	65 (4%)
Dabigatran	0 (0%)	0 (0%)
Antihypertensives	75 (44.4%)	26 (33.3%)
Cholesterol lowering agents	54 (32%)	18 (23.1%)
Diabetic medications	9 (5.3%)	2 (3.8%)

Table 4.4: Vascular risk factors of cases

Risk factors	**Whole stroke cohort, n = 170**	**Case-control study, n = 78**
Hypertension	85 (50%)	31 (39.7%)
Diabetes mellitus Type 1	2 (1.2%)	0 (0%)
Diabetes mellitus Type 2	13 (7.6%)	5 (6.4%)
Any heart disease	45 (26.5%)	16 (20.5%)
Current smokers	58 (34.1%)	39.7%(31/78)
Ex-smokers	31.8% (54/170)	24.4% (19/78)
Alcohol intake > maximum recommended limits	36 (21.2%)	13 (16.7%)
Hypercholesterolemia	75 (44.1%)	31 (39.7%)
Peripheral vascular disease	11 (6.5%)	6 (7.7%)
Prior stroke or transient ischaemic attack	26 (15.3%)	12 (15.4%)
History of malignancy	17 (10%)	5 (6.4%)
Migraine	25 (14.7%)	13 (16.7%)
Family history of stroke	56 (32.9%)	25 32.1%)

Table 4.5: Cardiac diseases in cases

Types of cardiac disease	Frequency	
	whole stroke cohort, n = 170	**case-control study, n = 78**
Atrial fibrillation	17 (10%)	4 (5.1%)
Other arrhythmias	4 (2.4%)	3 (3.8%)
Congestive cardiac failure	4 (2.4%)	2 (2.6%)
Angina	13 (7.6%)	4 (5.1%)
Myocardial infarction	18 (10.6%)	9 (11.5%)
Cardiomyopathy	3 (1.8%)	2 (2.6%)
Left ventricular aneurysm	3 (1.8%)	3 (3.8%)
Valvular heart disease	6 (3.5%)	2 (2.6%)
Others (included patent foramen ovale, previous cardiac arrest and infective endocarditis)	3 (1.8%)	2 (2.6%)

Table 4.6: Clinical stroke syndrome of cases: TACI total anterior circulation infarcts, PACI partial anterior circulation infarcts, POCI posterior circulation infarcts, LACI lacunar infarcts

Stroke subtype	**Whole stroke cohort, n = 170**	**Case-control study, n = 78**
TACI	3 (1.8%)	1(1.3%)
PACI	94 (55.3%)	42 (53.8%)
POCI	46 (27.1%)	21 (26.9%)
LACI	16 (9.4%)	10 (12.8%)
TACI and POCI	01 (6%)	1 (1.3%)
PACI and POCI	10 (5.9%)	2 (3.8%)

4.1.7 Stroke severity

At the time of recruitment, stroke severity was measured using National Institute of Health Stroke Scale (NIHSS) and Barthel index (65) for activities of daily living. The median time of assessment for recruitment after the stroke onset was 7 days (mean is 7.71 days) and ranged between 1- 29 days. The median NIHSS(66) at the time of recruitment was 3 (range 0-21) and the median Barthel Index was 100 at the time of recruitment (range 0-100). (Table 4.7 and 4.8)

4.1.8 Aetiological classification of ischaemic stroke

Aetiological classification of acute ischaemic stroke was based on The Trial of ORG 10172 in Acute Stroke Treatment (TOAST) (63). Cardioembolism was the most common mechanism of stroke. Stroke of undetermined aetiology constituted 24.1% (41/170) in the whole stroke cohort while 30.8% (24/78) were undetermined in cases of case-control study (Table 4.9).

Table 4.9: Stroke subtype based on TOAST criteria (in the order of frequency in the whole stroke cohort)

Stroke subtype	**Whole stroke cohort, n = 170**	**Cases in case-control study, n = 78**
Cardioembolism	58 (34.1%)	29 (37.2%)
Stroke of other determined aetiology	31 (18.2%)	9 (11.5%)
Large-artery atherosclerosis-embolus/Thrombosis	24 (14.1%)	6 (7.7%)
Small-vessel occlusion (lacune)	16 (9.4%)	10 (12.8%)
Stroke of undetermined aetiology- incomplete evaluation	16 (9.4%)	7 (9.0%)
Stroke of undetermined aetiology- negative evaluation	15 (8.8%)	15 (19.2%)
Stroke of undetermined aetiology- two or more causes identified	10 (5.9%)	2 (2.6%)

4.2Demographics of controls

A total of 89 controls were identified from the logbook of all patients who underwent TOE in Beaumont Hospital during the study period. Those who underwent TOE for identifying a cardiac source of emboli (including stroke) or to rule out infective endocarditis were excluded. The control group was not followed up in the study.

4.2.1 Age

Mean age 63 years (SD = 15.4, range 17.7 - 87.9). Controls were grouped into young (33.7%; 30/89) and old (66.3%; 59/89) for some analyses.

4.2.2 Gender

Males represented 56.2% (50/89) and females were 43.8% (39/89) of all patients.

4.2.3 Indications for TOE in controls

The most common indication was atrial fibrillation prior to cardioversion followed by assessment for valvular disease (Table 4.10).

Table 4.10: Indications for TOE in controls

Indications of TOE in controls	**Frequency, n = 89**
Atrial fibrillation/atrial flutter	39 (43.8%)
Assessment of valvular disease	25 (28.1%)
Others (murmurs, cardiomyopathy, amyloidosis etc.)	16 (18%)
Assessment of intra-atrial septum (before/ after closure of PFO/ASD)	5 (5.6%)
Assessment of ventricles	4 (4.5%)

4.3 Results: Case-control study

Independent-samples t-test was conducted to compare the mean age of cases and controls. There was a statistically significant difference in the mean age for cases (mean = 53, SD = 15.1) and controls (mean = 63, SD = 15.4) by both the Mann-Whitney *U* test (as a significant difference in the median age) as well as the mean age by the t-test (t= -4.26, $p<0.01$, two tailed). The magnitude of the difference in the means was -10.08 (95 % CI: 14.76 to -5.41). The finding that the cases were obviously younger than the controls was also seen in the statistically significant difference between the proportions of the age groups (young and old) among the cases and controls ($\chi^2 = 7.79$, $p=0.005$) (Table 4.11).

On comparing the gender in cases (males = 45 and females = 33) and controls (males = 50 and females = 39) by the Chi- Square test, there was no statistically significant difference, $\chi 2$ (1, n = 167) = 0.002, $p = 0.1$, phi = -0.02, (Table 4.12).

Table 4.11: Age in cases and controls

Age	Cases, n = 78	Controls, n = 89	P value
Age (mean) in years	53.0	63.0	**<0.01**
Young (<60 years) %	44 (56.4%)	30 (33.7%)	**0.005**
Old (≥60 years) %	34 (43.6%)	59 (66.3%)	

Table 4.12: Gender in cases and controls

Gender	Cases, n = 78	Controls, n = 89	P value
Males (%)	45 (57.7%)	50 (56.2%)	0.1
Females (%)	33 (42.3%)	39 43.8%)	

4.3.1 Valvular strands in cases

VS were identified in 48.7% (38/78) of cases. The frequency of VS was 38.6% (17/44) in young and 61.8% (21/34) in old. Although the proportion of VS in the old groups was almost twice as high as that in the young group, the Chi-square test did not reveal a statistically significant association between age and VS (χ^2= 3.23, p = 0.07, phi =0.23) (Table 4.13).

If the cut-off for creation of the two age groups in the cases was taken at 50 years, there was a statistically significant association between age and VS (χ^2 = 6.54, p = 0.01, phi =0.32).

There was a statistically significant difference in the presence of aortic VS, χ^2 (1, n = 78) = 5.27, p = 0.02, phi = 0.29 on Chi-Square test (with Yates continuity correction) in the two age groups. For mitral VS, the Chi- Square test revealed no association between the two age groups, χ^2 (1, n = 78) =0.77, p = 0.38, phi = 0.13 (Table 4.14).

Socio-demographic variables, risk factors and stroke characteristics of cases with or without valvular strands are described in Table 4.15.

Table 4.13: Frequency of VS in the different age groups in the cases

Frequency of VS	Young, n = 44	Old, n = 34	*P* value
Cases	17 (38.6%)	21 (61.8%)	0.07

Table 4.14: Frequency of VS in cases based on location in two age groups

Location of VS	Young, n = 44	Old, n = 34	*P* value
Mitral VS	14 (31.8%)	15 (44.1%)	0.38
Aortic VS	4 (9.1%)	11 (32.4%)	**0.02**

Table 4.15: Socio-demographic variables, risk factors and stroke characteristics of cases with or without valvular strands

Variable	With VS, n = 38	Without VS, n = 40	*P* value
Age	58.0±13.9	48.2±14.9	**0.004**
Male	20 (52.6%)	25 (62.5%)	0.514
Hypertension	18 (47.4%)	13 (32.5%)	0.267
Diabetes	4 (10.5%)	1 (2.5%)	*0.195
Any heart disease	11 (28.9%)	5 (12.5%)	0.129
Valvular heart disease	1 (2.6%)	1 (2.6 %)	*1.000
Current Smoking	17 (44.7%)	14 (35%)	0.158
Alcohol intake**	5 (13.2%)	8 (20%)	0.612
Hypercholesterolemia	18 (47.4%)	13(32.5%)	0.269
Prior antiplatelet agents	11 (28.9%)	8 (20%)	0.512
NIHSS (mean ±SD)	3.53 ±3.25	3.13± 3.6	0.612
BI (mean ±SD)	85.92 ±27.82	91.03± 22.7	0.380

**Fisher's exact probability test is used when the rule for the minimum necessary cell count for the Chi-Square test is violated and the latter is not applicable. ** Alcohol intake > maximum recommended limits*

4.3.2 Valvular strands in controls

VS were identified in 32.6% (29/89) of controls. The frequency of VS in young was 30% (9/30) and in the old was 33.9% (20/59) (Table 4.16). There was no significant association between young and old in the presence of VS overall [χ^2 (1, n = 89) = 0.02, p = 0.90, phi =0.04] or on individual valves (mitral or aortic) in the Chi-Square test (Table 4.17).

There was no statistically significant association between the young and old age groups of controls in the presence of VS, χ^2 (1, n=89) = 0.001, p = 0.98, phi =0.03 even if the cut off for age groups was lowered to 50 years.

Table 4.16: Frequency of VS in controls based on age groups

Frequency of VS	Young, n = 30	Old, n = 59	*P* value
Controls	30.0% (9/30)	33.9% (20/59)	0.89

Table 4.17: Frequency of VS in controls based on location in two age groups

Location of VS	Young, n = 30	Old, n = 59	*P* value
Mitral VS	7 (23.3%)	6 (10.2%)	0.18
Aortic VS	3 (10.0%)	14 (23.7%)	0.20

Table 4.18: Frequency of VS in controls based on referral diagnosis

Indications of TOE in controls	Frequency, n = 89	Frequency of VS, n = 29
Atrial fibrillation/atrial flutter	39 (43.8%)	13 (44.8%)
Assessment of valvular disease	25 (28.1%)	5 (17.2%)
Others (murmurs, cardiomyopathy, amyloidosis etc.)	16 (18%)	7 (24.1%)
Assessment of intra-atrial septum (before/ after closure of PFO/ASD)	5 (5.6%)	3 (10.3%)
Assessment of ventricles	4 (4.5%)	1 (3.4%)

4.3.3 Valvular strands between cases and controls

VS as defined by TOE were identified in 48.7% (38/78) of cases and 32.6% (29/89) of controls. There was an association although marginal, between TOE-defined VS and the occurrence of acute ischaemic stroke we found that the risk for stroke in the patients with VS was more than three times the risk of patients without VS (OR = 3.85, χ^2 (1, n = 167) = 3.85, $p = 0.05$, phi = -0.16, Table 4.19).

Chi-square testing revealed a statistically significant association in older cases and controls in the presence of VS [χ^2 (1, n = 93) = 5.71, $p = 0.017$, phi =0.27] (Table 4.20).

Table 4.19: Frequency of VS between cases and controls

Case-control study	Cases, n = 78	Controls, n = 89	P value
Frequency of VS	38 (48.7%)	29 (32.6%)	**0.05**

Table 4.20: Frequency of VS in two age groups of case-control study

Frequency of VS in	Cases	Controls	*P* value
Young	38.6% (17/44)	30% (9/30)	0.60
Old	61.8% (21/34)	33.9% (20/59)	**0.01**
Total	48.7% (38/78)	32.6% (29/89)	**0.05**

4.3.4 Frequency of VS based on location

Among 38 cases with VS, the VS were located on the mitral valve in 23 (60.5%), the aortic valve in 9 (23.7%) and both mitral and aortic valves in 6 (15.8%). Among 29 controls with VS, 11(39.3%) had VS only on mitral valve, 15 (53.6%) had VS on aortic valve, two (7.1%) had VS on both mitral and aortic location and one had VS on tricuspid valve (Table 4.21). There were no VS noted on the tricuspid valve in cases. Neither cases nor controls had VS on the pulmonary valve.

In other words, among the cases, of the total 44 valves with strands, 29 were on mitral and 15 on aortic valves. In controls, of the total 31 valves with strands, 13 were on mitral and 17 were on aortic valves (Table 4.22). Chi-square testing revealed a statistically significant association between cases and controls in the presence of mitral VS [χ^2 (1, n = 167) = 10.08, p = 0.001, phi =0.26].

Among the total 78 mitral valves in the cases, 48 (61.5%) were thickened. Of the 48 thickened mitral valves, 43.8% (21/48) had VS. Among the 30 mitral valves without any thickening, 26.7% (8/30) had VS (Table 4.23). In other words, 72.4% (21/29) of mitral valves with VS had valve thickening compared to 55.1% (27/49) of mitral valves without VS, χ^2 (1, n = 78) = 1.63, p = 0.20, phi =0.17.

Table 4.21: Frequency of left-sided VS in cases and controls

Location	Cases with VS, n = 38	Controls with VS, n = 28*
Mitral VS	60.5% (23/38)	39.3% (11/28)
Aortic VS	23.7% (9/38)	53.6% (15/28)
Both mitral and aortic VS	15.8% (6/38)	7.1% (2/28)

**n = 28 as one patient with VS on tricuspid valve excluded from analysis.*

Table 4.22: Frequency of VS in cases and controls

Location of VS	Cases, n = 78	Controls, n = 89	*P* value
Mitral VS	37.2% (29/78)	14.6% (13/89)	**0.001**
Aortic VS	19.2% (15/78)	19.1% (17/89)	1.000

Table 4.23: Mitral valve thickening and VS

Mitral valve	Thickened, n = 48	Not thickened, n = 30
VS+ (n = 29)	21	8
VS- (n = 49)	27	22

VS+ valvular strands present, VS- valvular strands absent

When all mitral valvular abnormalities were combined, there was no statistically significant association between presence of mitral VS and mitral valve abnormalities, χ^2 (1, n = 78) = 1.49, p = 0.22, phi =0.17. Mitral valvular abnormalities included were valve thickening, calcification, myxomatous changes and stenotic or regurgitant valvular abnormalities with greater than mild in severity.

Similarly, there was no statistically significant association between aortic valve abnormalities and presence of aortic VS, χ^2 (1, n = 78) = 0.00, p = 1.00, phi = 0.00. Aortic valvular abnormalities included were aortic sclerosis and stenotic or regurgitant valvular abnormalities greater than mild in severity.

4.3.5 Valvular strands and other cardiac sources of emboli in TOE

Possible cardiac sources of emboli were categorised into medium and high-risk factors according to TOAST criteria.

(a) Cases : Among the medium-risk cardiac sources of emboli, hypokinesis of left ventricle (LV) was found in 13 % (5/38) of cases with VS and was associated with VS ($p = 0.02$). No other medium-risk or high-risk cardiac sources of emboli had a statistically significant association with VS on further analysis, (Table 4.24 and Table 4.25). When all possible cardiac sources of emboli (including other recognised cardiac sources of emboli such as aortic plaques) were combined, Chi-square testing did not reveal any statistically significant association between presence or absence of VS and other possible cardiac sources of emboli in cases [χ^2 (2, n = 78) = 3.78, $p = 0.15$, phi =0.22], (Table 4.26).

Table 4.24: Valvular strands and other medium-risk (63) **cardiac sources of emboli in cases**

Medium-risk source of emboli	**With VS, n = 38**	**Without VS, n = 40**	***P* value**
PFO with R- L shunt	9 (23.7%)	8 (20%)	0.91
ASD with R – L shunt	1 (2.6%)	1 (2.5%)	*1.00
Atrial septal aneurysm	12 (31.6%)	11 (27.5%)	0.88
SEC in LA/LAA	3 (7.9%)	2 (5%)	*0.67
Mitral annular calcification	1 (2.6%)	1 (2.5%)	*1.00
Hypokinesis of LV	5 (13.2%)	0 (0%)	***0.02**
Mitral valve prolapse	3 (7.9%)	0 (0%)	*0.11
Atrial flutter	0 (0%)	0 (0%)	-
MS without atrial fibrillation	1 (2.6%)	0 (0%)	*0.49
All medium risk factors based on TOAST criteria	21 (58.3%)	15 (41.7%)	0.18

**Fisher's exact probability test is used when the rule for the minimum necessary cell count for the Chi-Square test is violated and the latter is not applicable.*

Table 4.25: Valvular strands and other high-risk (63) cardiac sources of emboli in cases

High-risk source of emboli	With VS, n = 38	Without VS, n = 40	*P* value
Atrial fibrillation	1 (2.6%)	2 (5%)	*1.00
Thrombus in LA, LAA or LV	0 (0%)	0 (0%)	-
Akinesis or global hypokinesis of LV	0 (0%)	0 (0%)	-
Cardiomyopathy	0 (0%)	0 (0%)	-
Infective endocarditis	0 (0%)	1 (2.5%)	*1.00
Mass lesion	2 (5.3%)	0 (0%)	*0.23
All high risk factors based on TOAST criteria	1 (2.6%)	3 (7.5%)	*0.62
Aortic plaques grade 2, 3 and 4	18 (47.4%)	11 (27.5%)	0.11
Aortic plaques 3 and 4	5 (13.1%)	1 (2.5%)	*0.10

**Fisher's exact probability test is used when the rule for the minimum necessary cell count for the Chi-Square test is violated and the latter is not applicable.*

Table 4.26: Possible cardiac source of emboli in cases with valvular strands

Possible cardiac source of in cases with VS	Frequency, n = 38
No risk factors	14 (36.8%)
Medium risk factor/s	16 (42.1%)
High risk factor / both medium and high risk factors	8 (21.1%)

(b) Controls:

In controls, there was a statistically significant association between atrial flutter ($p = 0.03$) in medium-risk and thrombus in left atrium/ left atrial appendage ($p = 0.04$) in high-risk cardiac sources of emboli and VS, (Table 4.27 and Table 4.28).

When all possible cardiac sources of embolism (including other recognised cardiac sources of emboli such as aortic plaques) were combined, Chi-square testing did not reveal any statistically significant association between presence or absence of VS and cardiac sources of emboli in controls, χ^2 (2, n = 89) = 0.70, p = 0.70, phi =0.09.

Table 4.27: Valvular strands and other medium-risk cardiac sources of emboli in controls

Medium-risk source of emboli	**With VS, n = 29**	**Without VS, n = 60**	***P* value**
PFO with R- L shunt	1 (3.4%)	4 (6.7%)	*1.00
ASD with R – L shunt	0 (0%)	1 (1.7%)	*1.00
Atrial septal aneurysm	1 (3.4%)	5 (8.3%)	*0.66
SEC in LA/LAA	12 (41.4%)	20 (33.3%)	0.61
Mitral annular calcification	1 (3.4%)	4 (6.7%)	*1.00
Hypokinesis of LV	4 (13.8%)	8 (13.3%)	*1.00
Mitral valve prolapsed	4 (13.8%)	4 (6.7%)	*0.43
Atrial flutter	3 (10.3%)	0 (0%)	***0.03**
MS without atrial fibrillation	0 (0%)	0 (0%)	-
All medium risk factors based on TOAST criteria	22 (75.9%)	35 (58.3%)	0.17

**Fisher's exact probability test is used when the rule for the minimum necessary cell count for the Chi-Square test is violated and the latter is not applicable.*

Table 4.28: Valvular strands and other high-risk cardiac sources of emboli in controls

High risk source of emboli	With VS, n = 29	Without VS, n = 60	*P* value
Atrial fibrillation	12 (41.4%)	27 (45%)	0.93
Thrombus	4 (13.8%)	1 (1.7%)	***0.04**
Akinesis or global hypokinesis of LV	5 (17.2%)	5 (8.3%)	*0.28
Cardiomyopathy	1 (3.4%)	2 (3.3%)	*1.00
Infective endocarditis (Not included in the study)	-	-	
Mass lesion	1 (3.4%)	1 (1.7%)	*0.55
Aortic plaques grade 2, 3 and 4	16 (55.2%)	28 (46.7%)	0.60
Aortic plaques 3 and 4	5 (17.2%)	13 (21.7%)	0.84
High risk factors based on TOAST	18 (62.1%)	30 (50%)	0.40

**Fisher's exact probability test is used when the rule for the minimum necessary cell count for the Chi-Square test is violated and the latter is not applicable.*

4.3.6 Valvular strands and diastolic dysfunction

Diastolic dysfunction refers to abnormal mechanical properties of the myocardium. This includes abnormal left ventricular diastolic distensibility, impaired filling, and slow or delayed relaxation- regardless of whether the ejection fraction is normal or depressed and whether the patient is asymptomatic or symptomatic (67).

In cases with VS, 30/38 (78.9%) had diastolic dysfunction while in cases without VS only 21/40 (52.5%) had diastolic dysfunction. There was a statistically significant association [χ^2 (1, n = 78) =4.91, p = 0.03, phi = 0.28] between the presence of VS and diastolic dysfunction in cases.

In controls with VS, 11/29 (37.9%) had diastolic dysfunction while 17/60 (28.3%) without VS had diastolic dysfunction and Chi-square test did not reveal any statistically significant association, χ^2 (1, n = 89) = 0.45, p = 0.50, phi = 0.09.

Case-control study: The Chi-square test revealed a statistically significant association between diastolic dysfunction in cases and controls with VS, χ^2 (1, n = 167) = 7.75, p = 0.005, phi = 0.23.

4.3.7 Valvular strands and hypercoagulable states

In the whole stroke cohort of cases, there were 81 (81/170; 47.6%) young (<60 years) patients. Laboratory blood tests were performed in 74 (74/81; 91.4%) of these patients to rule out hypercoagulable states. Among these 74 patients, 27 were found to have completely normal tests and 47 patients (47/74; 63.5%) with some abnormalities. There were only 16 patients found to have abnormalities such as low protein C, low protein S, low antithrombin III, APC resistance with Factor V Leiden, lupus anticoagulant and elevated anticardiolipin antibodies, (Figure 4.2).

In the case-control study, out of 43 (43/78; 55.1%) cases had been tested for hypercoagulable conditions by laboratory testing, only 9 (9/43; 20.9%) patients were found to have abnormalities as explained above and two of them had VS in TOE, (Table 4.29).

In 81 young cases, 56 patients were tested for homocysteine levels in blood and three of them had mildly elevated levels.

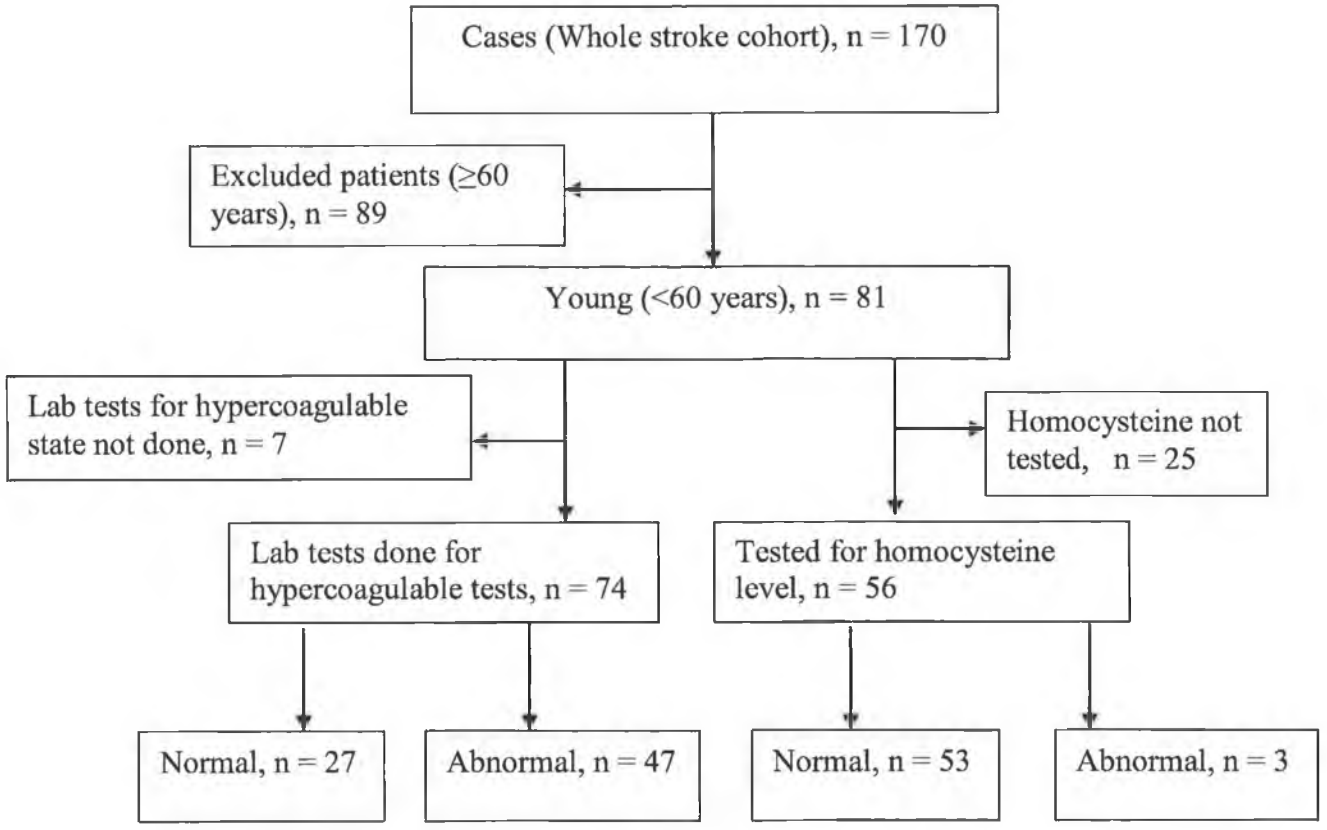

Figure 4.2: Valvular strands and hypercoagulable states in laboratory testing

Table 4.29: Valvular strands and hypercoagulable states on laboratory testing in young cases.

Hypercoagulable state	**With VS, n = 17**	**Without VS, n = 26**	***P* value**
Present	2 (11.8%)	7 (26.9%)	*0.281
Absent	15 (88.2%)	19 (73.1%)	

**Fisher's exact probability test is used when the rule for the minimum necessary cell count for the Chi-Square test is violated and the latter is not applicable.*

4.3.8 Valvular strands and Stroke subtypes

The most common stroke subtype was cardioembolic irrespective of the presence or absence of VS. The distribution of VS in the 38 cases was as follows: 16 (42.1%) with cardioembolic stroke, 7 (18.4%) with cryptogenic stroke with negative evaluation, 5 (13.2%) in small vessel disease, 4 (10.5%) in cryptogenic stroke with incomplete evaluation, 3 (7.9%) in stroke of other determined aetiology, 2 (5.3%) in large-artery atherosclerosis and 1 (2.6%) in stroke with two or more causes identified, (Table 4.30).

Cardioembolism and valvular strands: Sixteen of 38 patients with VS and 13 out of 40 patients without VS were found to have a cardiac source of embolism as stroke aetiology, (Table 4.31). The Chi- Square test did not reveal any significant association between cases with or without VS and presence of a cardiac source of embolism, χ^2 (1, n = 78) =0.41, p = 0.52, phi = 0.1.

Cryptogenic stroke and valvular strands: Twelve of 38 patients with VS and 12 out of 40 patients without VS were found to have cryptogenic strokes, (Table 4.32). The Chi-square test did not reveal any significant association between cases with or without VS and cryptogenic stroke, χ^2 (1, n = 78) =0.00, p = 1, phi = -0.02.

Table 4.30: Valvular strands and Stroke subtypes

Stroke subtype	With VS, n = 38	Without VS, n = 40
Large-artery atherosclerosis	2 (5.3%)	4 (10%)
Cardioembolism	16 (42.1%)	13 (32.5%)
Small-vessel occlusion	5 (13.2%)	5 (12.5%)
Stroke of other determined aetiology	3 (7.9%)	15% (6/40)
Undetermined aetiology-two or more causes	1 (2.6%)	1 (2.5%)
Undetermined aetiology-negative evaluation	7 (18.4%)	8 (20%)
Undetermined aetiology-incomplete evaluation	4 (10.5%)	3 (7.5%)

Table 4.31: Cardioembolic stroke and valvular strands

Stroke subtype	With VS, n = 38	Without VS, n = 40	*P* value
Cardioembolism	16 (42.1%)	13 (32.5%)	0.52

Table 4.32: Cryptogenic stroke and valvular strands

Stroke subtype	With VS, n = 38	Without VS, n = 40	*P* value
Cryptogenic (all three undetermined groups combined)	12 (31.6%)	12 (30%)	1.00

4.3.9 Valvular strands and infarct topography

On admission, among the total 170 cases, 85.3% (145/170) underwent noncontrast head CT and 14.7% (25/170) MRI brain as their initial brain imaging. Repeat brain imaging was performed in 84% (143/170) and the majority underwent MRI brain imaging (98.6%). MRI brain imaging was available for 160 (94.1%) cases to study the infarct topography. The infarcts were most common in subcortical location in cases either with or without VS in TOE. In 54 (54/78; 69.2%) cases with subcortical infarcts approximately half of them had VS. Similarly the proportion of cases with VS was almost equal in cases with cortical and cerebellar infarcts. The Chi-square test showed no significant association between presence of VS and location of infarct (infarct topography), Table 4.33. Similarly, in cryptogenic stroke, infarcts were more frequently found in subcortical location and there is no difference in the presence of VS in infarcts on four locations studied.

The infarcts were commonly found on the left side on neuroimaging irrespective of the presence or absence of VS (Table 4.34). There was no statistically significant association between the side of infarct location and presence of VS, χ^2 (2, n = 78) =4.97, p = 0.08, phi = -0.25. Among cases with VS, there were 8 with mild, 22 with moderate and 7 with severe white matter changes on comparison to 14, 19 and 6 patients respectively in patients without VS. There was no statistically significant association found on Chi-square test, χ^2 (2, n = 76) =1.88, p = 0.39, phi = 0.16.

Table 4.33: Valvular strands and infarct topography

Infarct location	With VS, n = 38	Without VS, n = 40	*P* value
Cortical	18 (47.4%)	20 (50%)	1.00
Subcortical	26 (68.4%)	28 (70%)	1.00
Brainstem	4 (10.5%)	6 (15%)	*0.74
Cerebellar	6 (15.8%)	6 (15%)	1.00

**Fisher's exact probability test is used when the rule for the minimum necessary cell count for the Chi-Square test is violated and the latter is not applicable.*

Table 4.34: Valvular strands and location (side) of infarcts

Infarct location	With VS, n = 38	Without VS, n = 40	*P* value
Left side	16 (42.1%)	26 (65%)	0.08
Right side	14 (36.8%)	11 (27.5%)	
Both sides	8 (21.1%)	2 (7.5%)	

4.3.10 Case-control study: Univariate regression analysis

In the case-control study, univariate regression analyses of different variables including valvular strands, age, gender, atrial fibrillation, diastolic dysfunction, aortic and mitral valvular abnormalities were performed. The *p* value for all the variables except gender was statistically significant ($p < 0.05$), (Table 4.35).

Valvular strands on mitral valve location were associated with stroke at univariate analysis with an Odds ratio of 0.29, (95 % CI 0.14-0.61), $p = 0.001$, (Table 4.36).

Univariate logistic regression analysis showed no statistically significant association between aortic valve abnormalities and presence of aortic VS ($p = 0.982$). Aortic valve abnormalities included aortic sclerosis and valvular disease (trivial or mild aortic stenosis or regurgitation were not included). Similarly there was no statistically significant association between mitral valve abnormalities and presence of mitral VS ($p = 0.144$). Mitral valve abnormalities included valve thickening, calcification, myxomatous changes and valvular disease (trivial or mild mitral regurgitation or mitral stenosis were not included).

Table 4.35: Univariate regression analysis of different variables in case-control study

Variable	B	S.E	Wald	df	Sig	Odds ratio	95 % C.I for Odds ratio	
							Lower	Upper
Valvular strands	0.68	0.32	4.46	1	**0.035**	1.97	1.05	3.68
Age	-0.04.	0.01	15.16	1	**0.000**	0.96	0.94	0.98
Young and old	0.93	0.32	8.52	1	**0.004**	2.55	1.36	4.77
Gender	0.06	0.31	0.04	1	0.844	1.06	0.58	1.97
Atrial fibrillation	2.97	0.63	22.49	1	**0.000**	19.50	5.713	66.56
Diastolic dysfunction	1.42	0.33	18.40	1	**0.000**	4.12	2.16	7.85
Aortic valve abnormalities	1.59	0.34	21.85	1	**0.000**	4.90	2.519	9.57
Mitral valve abnormalities	1.07	0.42	6.42	1	**0.011**	2.91	1.27	6.65

B Intercept (the coefficient for the constant in the null model), S.E. Standard error around the coefficient for the constant, Wald Wald Chi-square test, df degrees of freedom for the Wald Chi-square test, Sig. P-value, Exp(B) Exponentiation of the B coefficient, which is an Odds ratio

Table 4.36: Univariate regression analysis of types of VS and stroke

Variable	B	S.E	Wald	df	Sig	Odds ratio	95% C.I for Odds ratio	
							Lower	Upper
Mitral VS	-1.241	0.38	10.63	1	**0.001**	0.29	0.14	0.61
Aortic VS	-0.01	0.39	0.00	1	0.983	0.99	0.46	2.15

B Intercept (the coefficient for the constant in the null model), S.E. Standard error around the coefficient for the constant, Wald Wald Chi-square test, df degrees of freedom for the Wald Chi-square test, Sig. P-value, Exp(B) Exponentiation of the B coefficient, which is an Odds ratio

4.3.11 Case-control study: Multivariate logistic regression

A two-level logistic regression approach was used to fit a multivariate regression model and test for relationship between the presence of VS and acute ischaemic stroke. There were no corrections made for multiple comparisons in our study. As a first step, 6 variables that are significant at $P < 0.05$ from the univariate analysis were included as potentially independent predictors- valvular strands, age, mitral valve abnormalities, aortic valve abnormalities, atrial fibrillation and diastolic dysfunction in TOE- in the initial regression model. As shown in Table 4.37, only one variable (mitral valve abnormality which had a significance level $p > 0.05$) was removed at step 1. In the second step, the Odds ratio of predicting stroke by the presence of valvular strands is 2.15 (95% CI 0.95- 4.85) and had a p value of 0.065, (Table 4.38). Even though the significance is marginal, there was over two times chance of having an acute ischaemic stroke with presence of VS. All other variables remaining in step 2 of the model were found to have a p value < 0.05. The strongest predictor of stroke was atrial fibrillation with an Odds ratio of 10.95 (95% CI 2.81-42.67).

Notably the final model was constructed of five factors with 84.6% sensitivity and 83.1% specificity and correctly identified 83.8% of cases overall.

Table 4.37: Two-level logistic backward stepwise (conditional) regression analysis of valvular strands in acute ischaemic stroke (Step 1)

Variables		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I. for Exp(B)	
								Lower	Upper
Step 1	Valvular strands	.828	.419	3.912	1	.048	2.290	1.008	5.204
	Age	-.025	.013	3.452	1	.063	.975	.950	1.001
	Aortic valve abnormality	1.479	.457	10.466	1	.001	4.387	1.791	10.743
	Mitral valve abnormality	.942	.586	2.587	1	.108	2.565	.814	8.084
	Atrial fibrillation	2.341	.706	10.995	1	.001	10.388	2.604	41.440
	Diastolic dysfunction	1.170	.458	6.534	1	.011	3.223	1.314	7.906
	Constant	-2.336	1.128	4.290	1	.038	.097		

B Intercept (the coefficient for the constant in the null model), S.E. Standard error around the coefficient for the constant, Wald Wald Chi-square test, df degrees of freedom for the Wald Chi-square test, Sig. P-value, Exp(B) Exponentiation of the B coefficient, which is an Odds ratio

Table 4.38: Two-level logistic backward stepwise (conditional) regression analysis of valvular strands in acute ischaemic stroke (Step 2)

Variables		B	S.E.	Wald	Df	Sig.	Exp(B)	95% C.I. for Exp(B)	
								Lower	Upper
Step 2	Valvular strands	.765	.415	3.400	1	.065	2.149	.953	4.845
	Age	-.028	.013	4.261	1	**.039**	.973	.948	.999
	Aortic valve abnormality	1.662	.444	13.983	1	**.000**	5.270	2.205	12.592
	Atrial fibrillation	2.394	.694	11.903	1	**.001**	10.954	2.812	42.671
	Diastolic dysfunction	.980	.434	5.100	1	**.024**	2.665	1.138	6.242
	Constant	-1.980	1.093	3.279	1	.070	.138		

B Intercept (the coefficient for the constant in the null model), S.E. Standard error around the coefficient for the constant, Wald Wald Chi-square test, df degrees of freedom for the Wald Chi-square test, Sig. P-value, Exp(B) Exponentiation of the B coefficient, which is an Odds ratio

4.4Results: Follow-up study

Among the total 170 patients, 161 (94.7%) patients completed follow-up on time. The majority were seen in outpatient clinics (150/161) and the minority who were unable to attend the clinics for various reasons were interviewed by telephone (11/161). The median time to follow- up was 251.5 days (SD 171.78, range 28-883 days). Two patients refused to attend follow-up clinics and 7 patients (4.1%) died.

4.4.1 Vascular risk factor control

Hypertension: Prior to recruitment, there were 50% (85/170) of cases had a history of hypertension. At the time of follow-up, 53.3% (81/152) of the cases had their blood pressure well controlled (criteria used was <135/85 mm of Hg for non-diabetics and <130/80 mm of Hg for diabetics), (Table 4.39).

Smoking: There was a 50% reduction in smoking at follow-up, (Table 4.40).

Alcohol intake: The alcohol intake over the maximum recommended limit was reduced from 21.2% at recruitment to 6.4% at follow-up, (Table 4.40).

Cholesterol levels: Cholesterol levels were high in similar proportion of cases at follow-up compared to the levels at recruitment, but, only 69.2% of cases underwent testing for the same at follow-up, (Table 4.41).

Glucose levels: Two thirds of cases underwent testing at follow-up, 8.8 % and 4.4% had serum glucose levels ≥7mmol/l and impaired fasting glucose (6.1 - 6.9 mmol/l) respectively, (Table 4.42).

4.4.2 Medications at follow-up

At follow-up, 86.3% were on antiplatelet agents compared to 38.5% prior to the index stroke. There were 68.8% cases on antihypertensive medications and 87.5% on cholesterol lowering agents at follow-up. The use of oral anticoagulants was increased from 3.6% at the time of recruitment to 36% of cases at follow-up, (Table 4.43).

4.4.3 Recovery from stroke

NIH stroke score (NIHSS) was estimated from all 150 patients who attended the outpatient clinics for follow-up and the median NIHSS was 0 (range 0-7). The median Barthel score was 100 (range 25-100) at follow-up and was available for all 161 patients had follow-up, (Table 4.44 and Table 4.45).

4.4.4 Repeat TOEs at follow-up

Eight patients underwent repeat TOE before their follow-up. Of those 8 patients, one patient had VS on mitral valve in the first TOE and was found to have VS not only on the same location but also at a new location (aortic valve) in the repeat TOE. The details of all those eight patients underwent repeat TOE are described in Table 4.46.

Table 4.39 Vascular risk factor control- Hypertension

At recruitment: known hypertensives, n = 170	Blood pressure at follow-up, n = 152	
	Controlled	Uncontrolled
85 (50%)	81 (53%)	71 (46.7%)

Table 4.40: Vascular risk factor control- Smoking and alcohol intake

Variables	At recruitment	At follow-up
Current smokers	34.1% (58/170)	17% (27/159)
Alcohol >max recommended limit	21.2% (36/170)	6.4% (10/156)

Table 4.41: Vascular risk factor control- Cholesterol levels

Cholesterol level	At recruitment, n = 170	At follow-up, n = 159
Normal	70 (41.2 %)	48 (30.2%)
Low HDL, others normal	20 (11.8%)	7 (4.4%)
High	59 (34.7%)	55 (34.6%)
Tests not done	21 (12.4%)	49 (30.8%)

As per the National Cholesterol Education program (NCEP) expert panel on detection, evaluation, and treatment of high cholesterol in adults guidelines(68), for patients with atherosclerotic ischemic stroke or TIA and without known CHD, it is reasonable to target a reduction of at least 50% in LDL-C or a target LDL-C level of <70 mg/dL (to obtain maximum benefit) (Class II a; Level of Evidence B).
1 mmol = 39 mg/dL; 70 mg/dL is approx 1.8 mmol/L

Table 4.42: Vascular risk factor control- Glucose levels

Serum glucose level	At recruitment, n = 170	At follow-up, n = 160
Normal *	104 (61.2%)	94 (58.8%)
Impaired**	18 (16.6%)	7 (4.4%)
High***	21 (12.4%)	14 (8.8%)
Tests not done****	27 (15.9%)	45 (28.1%)

3.6-6.0 mmol/L, **6.1-6.9 mmol/L, * >7 mmol/L, **** Included some of the known diabetic patients on treatment.*

Table 4.43: Medications at follow-up

Medications	Prior to stroke, n = 169	At follow-up, n = 161
Aspirin	62 (36.7%)	128 (79.5%)
Clopidogrel	13 (7.7%)	51 (31.7%)
Dipyridamole	0 (0%)	12 (7.5%)
any antiplatelet agents	65 (38.5%)	139 (86.3%)
Oral anticoagulants *	6 (3.6%)	58 (36%)
Antihypertensives	75 (44.4%)	110 (68.8%)**
Diabetic medications	9 (5.3%)	15 (9.3%)
Cholesterol lowering medications	54 (32%)	140 (87.5%)*

** Warfarin, dabigatran, **n = 160*

Table 4.44: Recovery from stroke- NIHSS at follow-up

NIHSS	At recruitment, n = 169	At follow-up, n = 150
Mild (score < 6)	76.3% (129/169)	95.3% (143/150)
Moderate (score 6- 13)	20.1% (34/169)	4% (6/150)
Severe (score ≥ 14)	3.6% (6/169)	0% (0/150)

Table 4.45: Functional score (Barthel Index) at follow-up

Barthel index	At recruitment, n = 169	At follow-up, n = 161
Favourable (≥ 95)	103 (60.9%)	130 (80.7%)
Unfavourable (< 95)	66 (39.1%)	66 (39.1%)

Table 4.46: Repeat TOE at follow-up

Patients	First TOE		Second TOE	
	VS	**Other findings**	**VS**	**Other findings**
Patient 7	No	ASD, quadricusp AV	No	ASD, quadricusp AV
Patient 142	No	PFO with R-L shunt, ASA	No	PFO closure device well seated
Patient 146	No	-	No	No CSOE
Patient 150	No	Large vegetations at AV (IE)	No	Prosthetic AV and no vegetations
Patient 151	Mitral VS	Thickening of right coronary cusp of AV	Mitral and aortic VS	-
Patient 160	No	PFO with R-L shunt, ASA	Aortic VS	Well seated PFO closure device
Patient 163	No	PFO with R-L shunt, ASA	No	Well seated PFO closure device
Patient 168	No	Tiny PFO with L-R shunt, poor valsalva manoeuvre	No	PFO with R-L shunt, ASA, MVP

First TOE- TOE performed as a part of stroke work-up, Second TOE- TOE performed after the first TOE before the follow-up had completed, ASD atrial septal defect, AV aortic valve, AS aortic stenosis, PFO patent foramen ovale, R-L right to left, ASA atrial septal aneurysm, CSOE cardiac source of emboli, IE infective endocarditis, MVP mitral valve prolapse.

4.4.5 Stroke-like symptoms at follow-up

Since the discharge from the index stroke there were 44 patients [26.3% (44/167)] admitted to hospital due to various reasons and are described in Table 4.47. There were 28 patients [16.8 % (28/167)] reported to have had new stroke-like symptoms since their index stroke but only 7 patients (7/28; 25%) had confirmed acute infarct on neuroimaging, (Table 4.48). In 10 patients although no acute infarct was found, the aetiology of their symptoms were unclear.

4.4.6 Outcome of whole stroke cohort

'Poor vascular outcome' has been defined as fatal and non fatal vascular events. Vascular events included TIA, ischaemic stroke and myocardial infarction. 'Poor combined outcome' included all deaths and all vascular events.

Two patients had recurrent TIA and 7 had recurrent ischaemic stroke. Four patients had confirmed myocardial infarction. There were 7 deaths in the whole stroke cohort and five of them were vascular deaths. Poor vascular outcome and poor combined outcome were recorded in 16 and 17 patients respectively at the time of follow-up. Table 4.49 shows the different aspects of the outcome in the whole stroke cohort.

Table 4.47: Recurrent hospital admission- Causes

Causes of hospital admission	Frequency, n = 44
Stroke related	20 (45.5%)
Cardiac cause	7 (15.9%)
Both stroke and cardiac related	1 (2.3%)
Bleeding related to antiplatelet agents/anticoagulants	4 (9.1%)
Others	12 (27.3%)

Table 4.48: Stroke-like symptoms at follow-up: Diagnosis

Stroke-like symptoms- Diagnosis	Frequency, n = 28
Post stroke epilepsy	8 (28.6%)
TIA	2 (7.1%)
Confirmed acute infarct	7 (25%)
CADASIL encephalopathy	1 (3.6%)
Unclear diagnosis but no evidence of acute stroke on neuroimaging	10 (35.7%)

Table 4.49: Outcome of whole stroke cohort

Outcome	Frequency
Recurrent ischaemic stroke	4.2% (7/167)
Recurrent TIA/ ischaemic stroke	5.4% (9/167)
Myocardial infarction	2.4% (4/167)
Vascular death	2.9% (5/170)
Death from all causes*	4.1% (7/170)
Poor vascular outcome (vascular events** and vascular death)	9.5% (16/168)
Poor combined outcome (all deaths and all vascular events)	10.1% (17/168)

Two patients refused to attend follow-up clinic or telephonic interview.

**The causes of death included recurrent ischaemic stroke (2/7), complications from existing malignancy (2/7), and from respiratory and cardiac complications post stroke (2/7). One patient had sudden unexpected death and consensus was of a vascular death, the exact cause of death was unavailable.*

***Vascular events include TIA, stroke and myocardial infarction.*

4.4.7 Analysis of outcome: Poor vascular outcome

There were 16 events which can be classified as "poor vascular outcome" in the whole stroke cohort. Poor vascular outcome included fatal and non fatal vascular events. Vascular events included TIA, Ischaemic stroke and myocardial infarction.

The survival curve of the whole stroke cohort from poor vascular outcome is shown in Figure: 4.3. The mean survival time was 777.30 days (Std. Error 26.79, 95% CI: 724.80- 829.80).

Kaplan-Meier survival curves in stroke cohort with or without valvular strands from poor vascular outcome were not statistically significant different from one another, (Figure 4.4).

Univariate logistic regression analysis of the variables including valvular strands, age, gender, some TOE findings, antiplatelet agents and anticoagulant treatment at follow-up showed no statistically significant association (p = >0.05) between the variables and poor vascular outcome at follow-up, (Table 4.50).

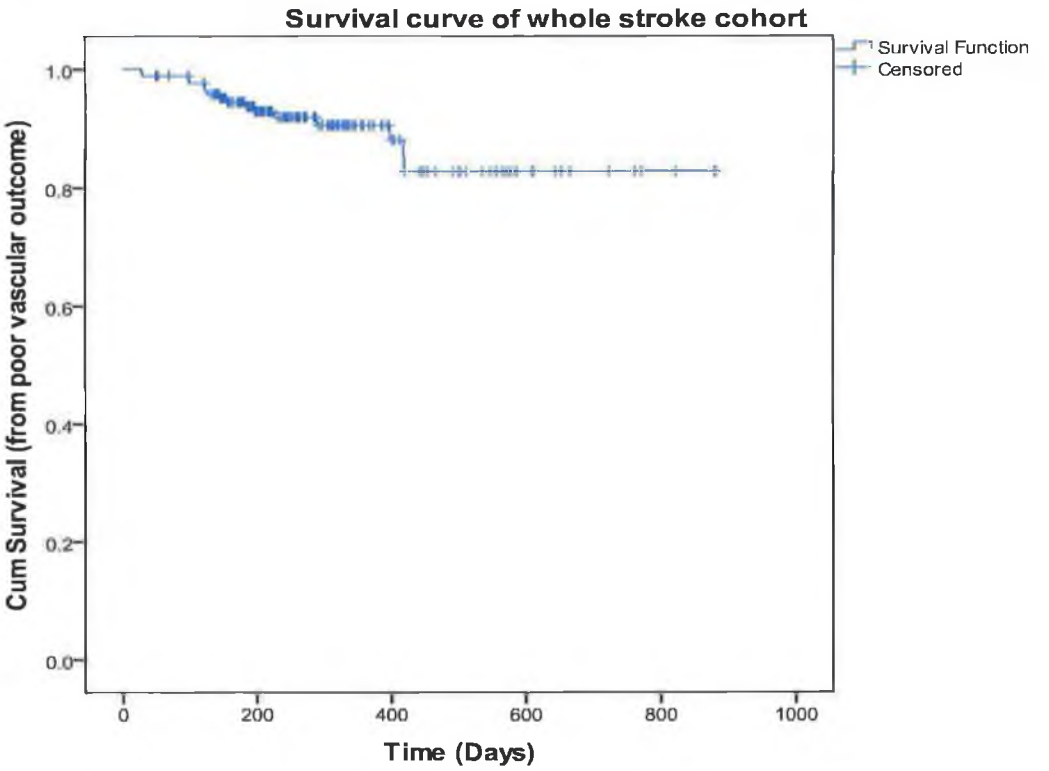

Figure 4.3: Survival curve of whole stroke cohort from poor vascular outcome.

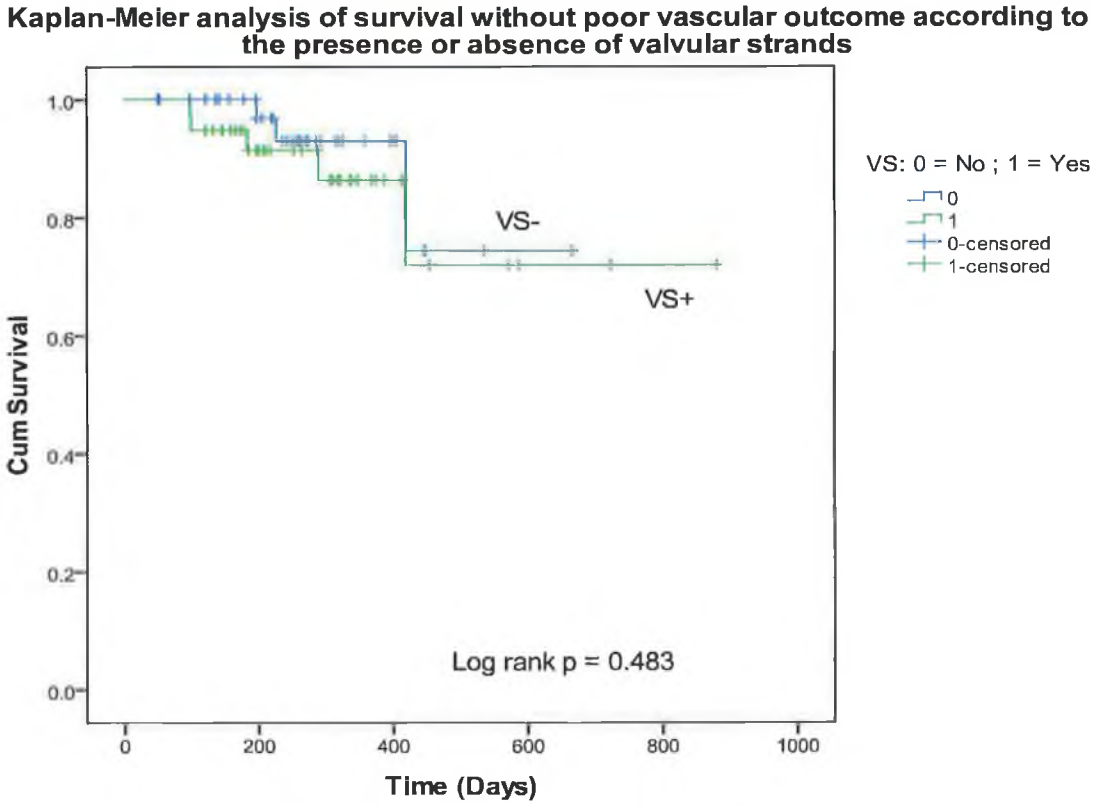

Figure 4.4: Kaplan-Meier survival curves from poor vascular outcome according to the presence or absence of valvular strands

Table 4.50: Univariate logistic regression analysis of poor vascular outcome of the whole stroke cohort

Variable	B	S.E	Wald	df	Sig	Odds ratio	95 % C.I for Odds ratio	
							Lower	Upper
Valvular strands	0.37	0.80	0.22	1	0.642	1.45	0.30	6.96
Age	-0.00	0.02	0.00	1	0.969	1.00	0.97	1.04
Yong and old	0.10	0.56	0.04	1	0.852	1.11	0.37	3.32
Gender	1.42	0.78	3.32	1	0.068	4.15	0.90	19.20
Diastolic dysfunction	-0.38	0.80	0.23	1	0.633	0.68	0.14	3.29
Aortic valve abnormality	1.48	1.11	1.79	1	0.181	4.39	0.50	38.40
Mitral valve abnormality	0.09	0.88	0.01	1	0.918	1.10	0.20	6.13
Atrial fibrillation	-1.75	1.30	1.82	1	0.177	0.17	0.01	2.21
Antiplatelet agents	-0.37	1.08	0.12	1	0.729	0.69	0.08	5.71
Anticoagulants	0.18	0.67	0.07	1	0.787	1.20	0.32	4.43

B Intercept (the coefficient for the constant in the null model), S.E. Standard error around the coefficient for the constant, Wald Wald Chi-square test, df degrees of freedom for the Wald Chi-square test, Sig. P-value, Exp(B) Exponentiation of the B coefficient, which is an Odds ratio

4.4.8 Analysis of outcome: Poor combined outcome

There were a total of 17 events which met the end point poor combined outcome in the whole stroke cohort. The survival curve of the whole stroke cohort from poor combined outcome is shown in Figure: 4.5. The mean survival time was 772.34 days (Std. Error 27.02, 95% CI: 719.36 - 825.31). Kaplan-Meier survival curves in stroke cohort with or without VS from poor combined outcome were the same as the survival curves obtained for poor vascular outcome as the number of events were same in both. The log rank (Mantel-cox) test showed, χ^2 (1) = 0.49, p = 0.483, (Figure 4.6).

Univariate logistic regression analysis of VS, age, gender, some TOE findings and antiplatelet and anticoagulant treatments showed no statistically significant association (p = >0.05) between the variables and poor combined outcome, (Table 4.51). Further application of a Cox proportional hazard model showed that there was no significant difference in the survival between those patients with or without VS. Total of cases = 78, total number of events (either poor vascular outcome or poor combined outcome) = 8, (Table 4.52). The relative risk is 1.66 for developing a poor vascular outcome or poor combined outcome for cases with VS on TOE but p = 0.488 and the 95% CI for odds ratio includes 1. A multivariate Cox proportional hazard model including gender and aortic valve abnormalities, the relative risk of poor vascular outcome or poor combined outcome was 0.31 (95% CI 0.07- 1.44, p = 0.135) and both curves seem to meet after 400 days similar to the above model, (Table 4.53).

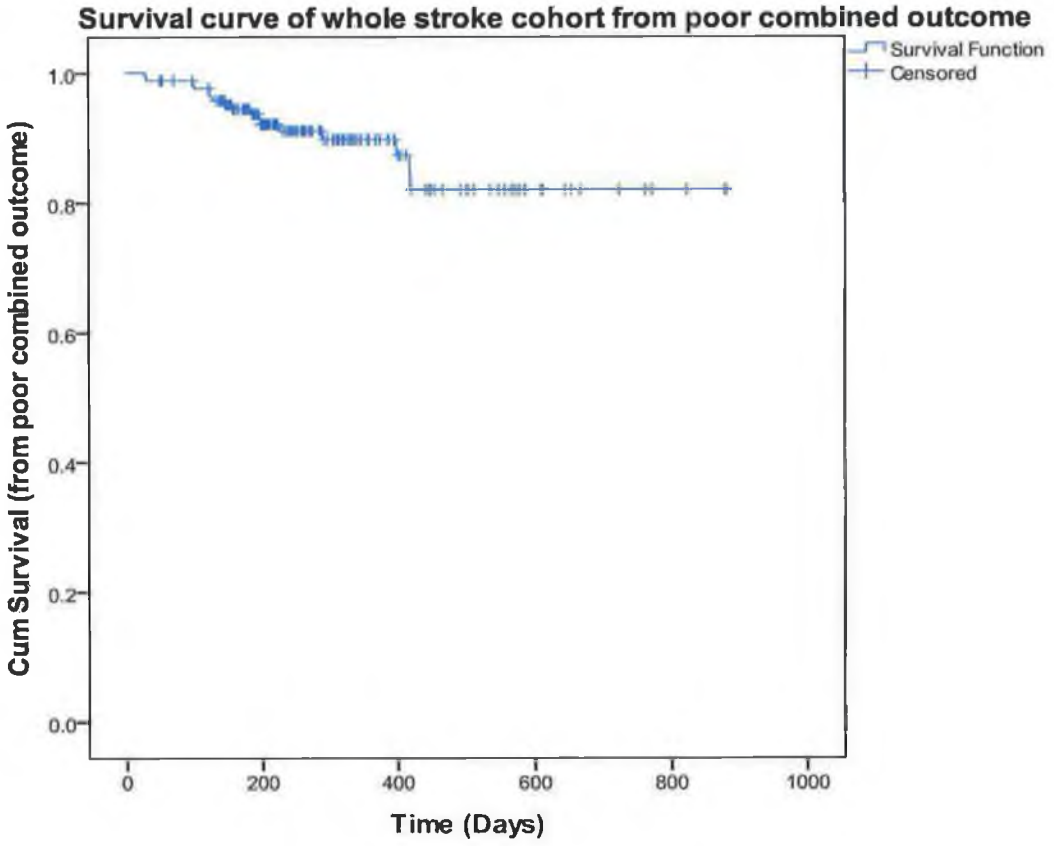

Figure 4.5: Survival curve of whole stroke cohort from poor combined outcome

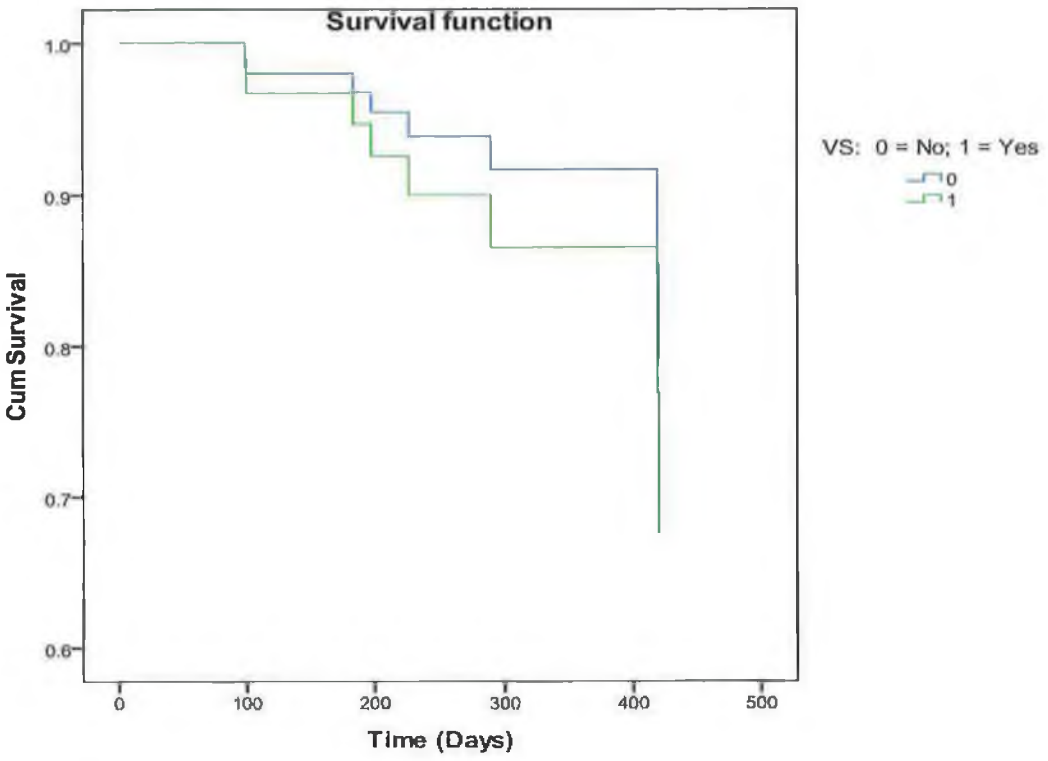

Figure 4.6: Survival curves from poor vascular outcome based on valvular strand

Table 4.51: Univariate logistic regression analysis of poor combined outcome of the whole stroke cohort

Variable	B	S.E	Wald	df	Sig	Odds ratio	95 % C.I for Odds ratio	
							Lower	Upper
Valvular strands	0.63	0.77	0.66	1	0.416	1.87	0.41	8.43
Age	0.00	0.02	0.04	1	0.836	1.00	0.97	1.04
Yong and old	0.24	0.51	0.21	1	0.646	1.26	0.46	3.45
Gender	0.80	0.60	1.79	1	0.182	0.69	7.11	19.20
Diastolic dysfunction	-0.72	0.75	0.90	1	0.342	0.49	0.11	2.14
Aortic valve abnormality	1.66	1.10	2.29	1	0.130	5.25	0.61	44.99
Mitral valve abnormality	-0.11	0.86	0.02	1	0.897	0.90	0.17	4.82
Atrial fibrillation	-1.58	1.29	1.51	1	0.220	0.21	0.02	2.57
Antiplatelet agents	-0.37	1.08	0.12	1	0.729	0.69	0.08	5.71
Anticoagulants	0.18	0.67	0.07	1	0.787	1.20	0.32	4.43

B Intercept (the coefficient for the constant in the null model), S.E. Standard error around the coefficient for the constant, Wald Wald Chi-square test, df degrees of freedom for the Wald Chi-square test, Sig. P-value, Exp(B) Exponentiation of the B coefficient, which is an Odds ratio

Table 4.52: Cox proportional hazard model based on presence or absence of VS

Variable	B	S.E	Wald	df	Sig	Odds ratio	95 % C.I for Odds ratio	
							Lower	Upper
Valvular strands	0.51	0.73	0.48	1	0.488	1.66	0.40	6.99

B Intercept (the coefficient for the constant in the null model), S.E. Standard error around the coefficient for the constant, Wald Wald Chi-square test, df degrees of freedom for the Wald Chi-square test, Sig. P-value, Exp(B) Exponentiation of the B coefficient, which is an Odds ratio

Table 4.53: Cox proportional hazard model including valvular strands, gender and aortic valve abnormalities

Variable	B	S.E	Wald	df	Sig	Odds ratio	95 % C.I for Odds ratio	
							Lower	Upper
Valvular strands	-1.18	0.79	2.24	1	0.135	0.31	0.07	1.44
Gender	1.17	0.88	1.79	1	0.181	3.22	0.58	17.90
Aortic valve abnormality	2.38	1.14	4.40	1	**0.036**	10.83	1.17	100.35

B Intercept (the coefficient for the constant in the null model), S.E. Standard error around the coefficient for the constant, Wald Wald Chi-square test, df degrees of freedom for the Wald Chi-square test, Sig. P-value, Exp(B) Exponentiation of the B coefficient, which is an Odds ratio

Chapter 5: Discussion

5.1Case-control study

In our single-centre case-control study, TOE-defined VS were found in approximately half of the patients with acute ischaemic stroke (AIS) and one third of controls. The analysis of our data showed an association between VS and risk of AIS (OR = 3.85, $p = 0.05$). When adjusted for possible confounders, we found that those with VS were twice likely to have had an acute ischaemic stroke (OR = 2.15, $p = 0.06$), but this finding did not reach statistical significance.

The prevalence of TOE-defined VS (48.7%) in patients with AIS in our study is at the high end of the range in the available published data (ranges from 6.3% to 47%) (27). As the indication for TOEs were not blinded, a search for all possible cardiac sources of embolism might have contributed to increased detection of VS compared to previous studies. Valvular strands were found more frequently in older patients (61.8%) compared to the young (38.6%). Although this finding is in contrast to two previous studies (16, 27), a higher percentage (53%) has been previously reported by Menzel et al. (28). The presence of VS in one-third of controls (32.6%) was also higher than in two previous case-control studies (2.3% to 16%) (15, 27), but a similar higher frequency (38%) has been reported in normal subjects by Roldan et al. (29). The normal subjects in the later study were young with a mean age of 35years (SD = 8) but the prevalence of VS matches to our controls (with a mean age of 63 years, SD = 15.4). As the method of selection of cases and controls was different to some of the previous studies, the difference in the prevalence of VS in cases and controls could be attributed to that as well.

The association between TOE-defined VS and ischaemic stroke was previously demonstrated (OR 2.1, 95 % CI 1.3-3.6; $p = 0.05$) in a case-control study with similar study design to ours and the subjects were recruited prospectively after their index stroke and controls from patients underwent TOE for cardiac conditions (20). While the latter study was focussed only on mitral valve strands in the elderly, our study included VS on both mitral and aortic valve location in all the age groups. Although we were able to demonstrate a significant association (OR 3.85 $p = 0.05$) between VS and AIS in our case-control study, the adjusted odds ratio was 2.15 with a significance level of 0.06 in the two-level logistic backward stepwise (conditional) regression analysis. We believe that there is a significant association as described in previous studies (15, 16, 20, 27) even though, the p valve is slightly >0.05. As the majority of our controls either had an established or a suspected cardiac disease, they would be at higher risk of having a cardiac source of emboli. Thus our control group would not be the ideal group of controls to compare the frequency of VS (a possible cardiac source of embolism, at least theoretically) versus stroke patients. Although we have adjusted for all known possible confounding variables, the lack of knowledge of vascular risk factors and the lack of follow-up for poor vascular outcome in controls might have reduced the significance level ($p = <0.05$) slightly in our multivariate logistic regression model compared to previous studies (20).

An association between mitral and aortic VS with VS was demonstrated independently with an Odds ratio of 3.5 and 3.7 respectively (with an overall Odds ratio of 4.4) by Roberts et al. (27) in patients referred for TOE for both stroke and other conditions. Although there was a strong association (OR 10.08, $p = 0.001$) between mitral VS and stroke demonstrated, the lack of association between aortic

VS and stroke (OR 0.00, $p = 1.00$) in our study supports the possible aetiology of a long term change in the cardiac valves for the development of VS (30) at least in the aortic location. This was also supported by the increased frequency of aortic valvular strands in our controls.

Mitral valve was the most common location for VS (60.5%) in cases similar to previous studies. The high prevalence of VS on the aortic valve (53.6%) in our controls was not observed before and perhaps this is due to our controls being older. Majority of mitral valves with VS (21/29; 72.4%) in our study were thickened. Nighoghossian et al. (30) and Freedberg et al. (15) identified valve thickening in 10.5% (4/38) and 8 % (7/89) in all cardiac valves with VS respectively. This difference in the above studies may be explained by the methodological difference in the assessment of the valves in TOEs.

When the strokes were subtyped according to TOAST criteria (63), we have found similar prevalence of VS in both patients with an identified stroke mechanism (26/54; 48.1%) and those without a determined mechanism (12/24; 50%) after extensive stroke work-up. Our finding is at the upper limit of the previously reported prevalence of VS (15- 50%) (16, 20, 27, 31) in cryptogenic stroke. VS were present in half of the patients with other identified cardioembolic sources (16/29; 55.2%) and this is higher compared to previously reported (25-35%) frequency of VS in cardioembolic stroke. We attribute the wide range of prevalence of VS in cardioembolic group due to the difference in the stroke subtyping used and the different ways of reporting in the studies that have investigated this topic. Some studies after subtyping the stroke mechanism reported the prevalence of VS in each while others identified patients with VS and reported the stroke aetiology of those patients. In the category of undetermined mechanism of stroke, the prevalence of VS

in cases with negative evaluation (7/15; 46.7%) was similar to cases with an incomplete evaluation (4/7; 57.1%).

It has been reported that VS are associated with systemic embolization (15) and to represent another risk factor for embolic cerebral ischaemia (16). Although cardioembolic stroke subtype in our study was found to have more VS (42.1%), we did not find any statistically significant association between VS and cardioembolic stroke ($p = 0.52$). Thus the association between VS and ischaemic stroke does not necessarily mean that VS are an actual embolic source as suggested by Roberts et al. (27). The prevalence of VS in cryptogenic (31.6%) versus non-cryptogenic stroke (30%) are same and there is no statistically significant association between VS and cryptogenic stroke ($p = 1.00$).

On neuroimaging of cases, the infarcts were found most commonly in subcortical areas. There was no statistically significant association between any infarct location (subcortical, cortical, cerebellar and brain stem) and the presence of VS. The findings were similar in cases with cryptogenic stroke on subsequent analysis and raises suspicion of embolic potential of VS further. There was no association between the severity of white matter changes and the presence of VS in our study.

The most common medium-risk cardiac sources of emboli in our cases were atrial sepal aneurysm and PFO with R-L shunt but the proportion of cases with or without VS and the above findings were comparable. When all individual medium-risk factors were analysed, hypokinesis of the left ventricle was found to be associated with VS (P value = 0.02) and the reason for this association is unclear. Although there were more cases with aortic plaques (grade 2, 3 and 4) and VS in cases and controls, it did not reach a statistical significance on analysis. The number of cases

with high-risk sources of emboli was small and we were unable to find any association between any of the high-risk factors and VS.

Diastolic dysfunction is a preclinical heart disease most commonly found in people with hypertension or advanced age. While half of our cases without VS had diastolic dysfunction on TOE, only one fifth of cases with VS did not have diastolic dysfunction. The strong association between diastolic dysfunction and valvular strands in case-control study has not been observed previously, to our knowledge.

We were unable to demonstrate any association between the presence of VS and hypercoagulable states by laboratory testing in young strokes. This could be due to small number of patients (9/43) with abnormalities which may be relevant in ischaemic stroke (69-71). This finding does not support the thrombotic origin of VS similar to one previous study (29) which investigated this topic.

5.2 Follow-up study

In our study, approximately one in 10 patients of the whole cohort had a poor vascular outcome (16/168; 9.5%) during the follow-up period. This poor vascular outcome rate is less than the rate of vascular outcome (stroke and death) reported in PICSS (31) study. The difference in the rate this could have been due to inclusion of only cryptogenic stroke, large numbers and longer period of follow- up in PICCS study. The majority of the cases were followed-up in a dedicated 'stroke follow-up clinic' in our centre which was in addition to the study follow-up. The reduced rate of poor vascular outcome could have been due to the implementation of the best secondary preventive treatment with antiplatelet therapy (86.3%), anticoagulant therapy (36%), improved blood pressure control and lifestyle modification (smoking cessation, reduced salt and alcohol intake, weight reduction etc.) after the primary stroke event.

There was no difference noted in the survival without poor vascular outcome of stroke patients with or without VS in our study. Our finding is consistent with the previous report by Cohen et al. (20) but we acknowledge similar limitations to their study such as lack of follow-up of controls for poor vascular outcome and a smaller number of primary outcome events. A relatively shorter follow-up period in our study might also have reduced our ability to detect any increased rate of poor vascular outcome in cases with VS. We were unable to fit a logistic regression model (Cox proportional hazard model) to our data, probably because of the small number of outcomes.

The association of VS with AIS may not be cause and effect relationship due to the absence of increased prevalence of VS in cardioembolic stroke or cryptogenic stroke subtypes compared to controls. In addition, the lack of increased number of poor vascular outcome in cases with VS also queries the previously reported theory of VS being an embolic cause (15, 24, 56). The management of stroke was unaffected by the presence or absence of VS and the secondary prevention after the index stroke is unlikely to reduce the number of poor vascular outcome in our cases with VS

5.3Limitations

Most of the recruited patients had a milder stroke (only 19.5% had NIHSS >6). A number of factors could have contributed, including time of assessment for recruitment (median 7 days) and difficulty obtaining consent from family members allowing patients with more severe, debilitating stroke to undergo TOE. While all cases with 'stroke of undetermined aetiology- negative evaluation' underwent TOE, only one fourth of cases with a stroke mechanism of large artery disease underwent TOE. This should not affect our ability to understand the overall prevalence of VS in the stroke cohort as we believe that the cases in the case-control study were representative of the whole stroke cohort of patients. The indication for TOE in cases was not blinded and the analysis of the TOEs was done by a single experienced Consultant Cardiologist and not by a panel of observers.

Although we were able to follow-up majority of cases in clinics, we had to perform telephonic interview and chart review in a minority those who did not attend the clinic. In those 5%, the information about vascular risk factor control and stroke recovery was limited and less reliable. TOEs were repeated only for 8 patients and we did not have sufficient resources to ensure repeat TOEs in our study participants. Other studies have reviewed the natural course of VS (29, 30) and the clinical outcome of cases with VS on antiplatelet agent versus anticoagulant treatment (31). We do not believe that we could have contributed any other major findings and would not have been cost effective in repeating TOEs for all the participants. The reduced number of poor vascular outcome in cases with VS may be due to a relatively shorter follow-up period in our study.

When multiple statistical tests are performed, some fraction will be false positives (72). There were no corrections made for multiple comparisons in our study and we acknowledge that there is a random chance of misinterpretation of the results (i.e. false positive or type 1 error). There was no matching done between cases and controls and we acknowledge that this is a deficiency of our study. In the future, this difficulty may be overcome by collecting the data on vascular risk factors at the time of TOE using a face-to-face interview or by asking patients to fill in a short questionnaire, which can be subsequently verified by examining medical notes if necessary.

5.4Strengths

All the cases were recruited prospectively in our study after a detailed neurological examination and had extensive investigations to determine their stroke mechanism. Although, the patient population in case-control study may seem relatively limited (due to the difficulty in obtaining TOE for all cases), the sample size of the patients included in the analysis (78 cases and 89 controls) was more than sufficient to achieve the primary aim of the case-control study (2.2.a) and to ensure sufficient power (>80%) of the results according to our *a priori* sample size computations.

In the case-control study, there were only 7 patients in the group of cryptogenic stroke with incomplete investigation. All the patients were recruited prior to the finding of interest identified by investigation. All the neuroimaging was reviewed by an experienced Consultant Neurologist and Consultant Neuroradiologists. The stroke subtyping based on clinical findings and investigations was performed by a Neurologist with special expertise in stroke. The majority of TOEs were performed by an experienced Cardiologist. The association between other possible cardiac sources of emboli and VS was investigated thoroughly. We were able to investigate infarct topography in patients with VS which had not been studied previously. A hypercoagulable state had been tested for the majority of young cases to investigate the possibility VS being thrombotic in origin and their association with other hypercoagulable states in patients with stroke.

5.5 Future direction

Valvular strands identified by TOE performed following stroke could have developed any time prior to the index stroke. Although an association has been identified between VS and stroke we were unable to identify a 'cause- effect' relationship from our study. VS were not significantly more frequent in cardioembolic and cryptogenic stroke subtype in our study, suggesting that VS were less likely to be an embolic risk factor (15, 16). There could be an unrecognised common factor to initiate the development of risk factors for stroke as well as for VS. There is a possibility of overestimating the prevalence of VS in a group of controls identified from those who underwent TOE for evaluating suspected or existing cardiac disease. To address the above, all participants of the study should be identified from healthy subjects of all age groups and all should undergo TOE. Subjects with VS (the possible risk factor) and without VS (without risk factor) should be followed up for longer periods than previously studied in order to capture vascular events (including stroke). Thus the true prevalence of VS can be estimated and the rate of vascular events/ stroke can be calculated in those with or without VS. Such a study would involve extensive resources and could not be undertaken unless it is a part of a large epidemiological study. Without establishing a 'cause-effect', the indication of TOE for identification of a possible risk factor (VS) for stroke cannot be recommended currently without the absence of any other cardiac disease. Unless there is a high risk of causing recurrent embolic stroke (similar to atrial fibrillation), the management of acute ischaemic stroke with antiplatelet therapy is unlikely to change irrespective whether they have VS or not.

5.6 Conclusion

Valvular strands were found in half of the patients with AIS compared to one third of controls. Similar to previous studies, we found an association between TOE-defined VS and acute ischaemic stroke, however, the strength of the association was reduced in multivariate analysis. We showed a statistically significant association between diastolic dysfunction and VS in case-control study. Due to lack of increased frequency of VS in cardioembolic and cryptogenic stroke subtype and absence of increased risk of recurrent stroke in patients with VS versus those without, the causal relationship of VS to stroke as an embolic risk factor is unlikely.

Appendices

Appendix 1 Patient Information Leaflet

Study Title: A prospective study of trans-oesophageal echocardiogram (TOE) defined valvular strands in a hospital cohort with acute ischaemic stroke

Principal Investigator's Name: Joan Moroney

Principal Investigator's Title: Dr

Telephone No. of Principal Investigator: 01 809 2258

You are being invited to take part in a clinical research study carried out at Beaumont Hospital. Before you decide whether or not you wish to take part, you should read the information provided below carefully and if you wish discuss it with your family, friends or GP. Take time to ask questions – do not feel rushed or under any obligation to make a hasty judgement. You should clearly understand the risks and benefits of participating in this study so that you can make a decision that is right for you – this process is known as Informed Consent.

You are not obliged to take part in this study and failure to participate will have no effect on your future care.

You may change your mind at any time (before the start of the study or even after you have commenced the study) for whatever reason without having to justify your decision and without any negative impact on the care you will receive from the medical staff.

Why is this study being done?

You are undergoing investigation and management of what is called an "ischaemic stroke." Ischaemic stroke means stroke caused by a lack of blood supply to certain areas

of brain normally due to a clot. Abnormalities on a heart scan can be seen in some individuals with stroke. The aim of this study is to increase our understanding of one such abnormality called "valvular strands" (strands on heart valves). In general as a part of routine stroke work up, some individuals might undergo a special heart scan called transoesophageal echocardiogram (TOE). It is done by putting a small camera down through the food pipe and then taking pictures of chambers and valves of the heart. In people with certain abnormalities in the scan the current practice by cardiologists is to repeat the scan in 6 months.

Who is organising and funding this study?

No funding is organised for this study.

How will it be carried out?

We plan to include patients presenting to Beaumont Hospital with stroke over a fixed period. These patients will be approached by Dr Albi Chalissery, one of the doctors involved in conducting this study.

What will happen to me if I agree to take part?

If you agree to participate in the study, a doctor from the research team will take a detailed history of your present condition and other medical problems. He or she will examine you on a few occasions during your hospital stay. Our study will not affect the decisions regarding the choice of tests made by your doctors. We will analyse all the results of the blood tests, x rays and scans you undergo as a part of your treatment. You will be required to attend our follow- up clinic 6 months after your hospital discharge. During this visit you will be fully examined by a qualified doctor.

Benefits

There is no immediate benefit. But the information received will be analysed after the completion of study and this will increase the knowledge and understanding of the causes of stroke.

Risks

There are no risks associated with your participation in this study. There are no painful procedures.

Confidentiality issues

Your general practitioner will be notified by a letter stating that you are participating in the research. Your medical notes will be examined by the investigators. The details collected will be coded to protect your identity. This data will be stored in paper form and digitally in Beaumont Hospital. The data in the paper form will be kept in a locked office in Beaumont Hospital; access will be available only to the research team. Digital access will require passwords which are known only to the investigators. At the end of the study the coded data will be analysed by a statistician. All data will be destroyed after two years of completing the study.

The final results will be submitted in the form of a thesis for the degree of Doctorate of Medicine (MD) for one of the co-investigators (Dr. Albi Chalissery)

If you have any further questions about the study or if you wish to withdraw from the study you may do so without justifying your decision and your future treatment will not be effected.

For additional information now or any future time please contact:

Name: Dr Joan Moroney

Address: Consultant Neurologist, Beaumont Hospital, Dublin., Phone No: 01 809 2258

Appendix 2 Information Leaflet for Next of Kin/ Relatives

Study Title: A prospective study of transoesophageal echocardiogram (TOE) defined valvular strands in a hospital cohort with acute ischaemic stroke.

Principal Investigator's Name: Joan Moroney

Principal Investigator's Title: Dr

Telephone No. of Principal Investigator: 01 809 2258

Your relative is invited to take part in a clinical research study carried out at Beaumont Hospital. Before you decide whether or not you wish he/she to take part, you should read the information provided below carefully and if you wish discuss it with your family, friends or GP. Take time to ask questions – do not feel rushed or under any obligation to make a hasty judgement. You should clearly understand the risks and benefits of him/her participating in this study so that you can make a decision that is right for your relative.

Your relative is not obliged to take part in this study and failure to participate will have no effect on his/her future care.

You may change your mind at any time (before the start of the study or even after he/she have commenced the study) for whatever reason without having to justify your decision and without any negative impact on the care your relative will receive from the medical staff.

Why is this study being done?

Your relative is undergoing investigation and management of what is called an "ischaemic stroke." Ischaemic stroke means stroke caused by a lack of blood supply to certain areas of brain normally as a result of a clot. Abnormalities on a heart scan can be

seen in some individuals with stroke. The aim of this study is to increase our understanding of one such abnormality called "valvular strands" (strands on heart valves). Some individuals might undergo a special heart scan called transoesophageal echocardiogram (TOE) as apart of their routine stroke workup to find out the cause of stroke. It is done by putting a small camera down through the food pipe and then taking pictures of chambers and valves of the heart. In people with certain abnormalities in the scan the current practice by cardiologists is to repeat the scan in 6 months.

Who is organising and funding this study?

No funding is organised for this study. The final results will be submitted in the form of a thesis for the degree of Doctorate of Medicine (MD) for one of the co-investigators (Dr. Albi Chalissery)

How will it be carried out?

We plan to include patients presenting to Beaumont Hospital with stroke over a fixed period. These patients will be approached by Dr Albi Chalissery, one of the doctors involved in conducting this study.

What will happen to your relative if you agree to take part?

If your relative agrees to participate in the study, a doctor from the research team will take a detailed history of his/her present condition and other medical problems. He or she will be examined on a few occasions during your hospital stay. Our study will not affect the decisions regarding the choice of tests made by his/her doctors. We will analyse all the results of the blood tests, X rays and scans he/she undergo as a part of the treatment. He/she will be required to attend our follow- up clinic 6 months after the discharge from the hospital. During this visit he/she will be fully examined by a qualified doctor.

Benefits

There is no immediate benefit. But the information received will be analysed after the completion of study and this will increase the knowledge and understanding of the causes of stroke.

Risks

There are no risks associated with the participation in this study. There are no painful procedures.

Confidentiality issues

His/her general practitioner will be notified by a letter stating that he/she is participating in the research. The medical notes will be examined by the investigators. The details collected will be coded to protect his/her identity. This data will be stored in paper form and digitally in Beaumont Hospital. The data in the paper form will be kept in a locked office in Beaumont Hospital; access will be available only to the research team. Digital access will require passwords which are known only to the investigators. At the end of the study the coded data will be analysed by a statistician. All data will be destroyed after two years of completing the study.

The final results will be submitted in the form of a thesis for the degree of Doctorate of Medicine (MD) for one of the co-investigators (Dr. Albi Chalissery)

If you have any further questions about the study or if you wish to withdraw your relative from the study you may do so without justifying your decision and his/her future treatment will not be effected.

For additional information now or any future time please contact:

Name: Dr Joan Moroney

Address: Consultant Neurologist, Beaumont Hospital, Dublin., Phone No: 01 809 2258

Appendix 3 Consent form

Study Title: A prospective study of transoesophageal echocardiogram (TOE) defined valvular strands in a hospital cohort with acute ischemic stroke.

Please tick the appropriate answer:

I confirm that I have read and understood the Patient Information Leaflet dated _____ attached, and that I have had ample opportunity to ask questions all of which have been satisfactorily answered.

□Yes □No

I understand that my participation in this study is entirely voluntary and that I may withdraw at any time, without giving reason, and without this decision affecting my future treatment or medical care.

□Yes □No

I understand that my medical notes may be viewed by investigators in the research study

□Yes □No

I understand that my identity will remain confidential at all times.

□Yes □No

I am aware of the potential risks of this research study.

□Yes □No

I have been given a copy of the Patient Information Leaflet and this Consent form for my records.

□Yes □No

Future use of coded data:

I agree that I will not restrict the use to which the results of this study may be put. I give my approval that unidentifiable data concerning my person may be stored or electronically processed for the purpose of scientific research and may be used in related or other studies in the future. (This would be subject to approval by an independent body, which safeguards the welfare and rights of people in biomedical research studies - the Beaumont Hospital Ethics (Medical Research) Committee.)

☐Yes ☐No

Patient _____ _____

Signature and dated Name in block capitals

To be completed by the Principal Investigator or his nominee.

I the undersigned have taken the time to fully explain to the above patient the nature and purpose of this study in a manner that he/she could understand. I have explained the risks involved, as well as the possible benefits and have invited him/her to ask questions on any aspect of the study that concerned them.

_____ _____ _____ _____

Signature: Name in Block Capitals: Qualification: Date:

Appendix 4 Assent form

Study Title: A prospective study of transoesophageal echocardiogram (TOE) defined valvular strands in a hospital cohort with acute ischemic stroke.

Please tick the appropriate answer:

I confirm that I have read and understood the Information Leaflet for Next of Kin/Relatives dated _____attached, and that I have had ample opportunity to ask questions all of which have been satisfactorily answered.

□Yes □No

I understand that participation of my relative in this study is entirely voluntary and that he/she may withdraw their participation at any time, without giving reason, and without this decision affecting his/her future treatment or medical care.

□Yes □No

I understand that his/her medical notes may be viewed by investigators in the research study

□Yes □No

I understand that his/her identity will remain confidential at all times. □Yes □No

I am aware of the potential risks of this research study.

□Yes □No

I have been given a copy of the Information Leaflet for Next of Kin/Relatives and this Assent form for my records.

□Yes □No

Future use of coded data:

I agree that I will not restrict the use to which the results of this study may be put. I give my approval that unidentifiable data concerning my relative may be stored or

electronically processed for the purpose of scientific research and may be used in related or other studies in the future. (This would be subject to approval by an independent body, which safeguards the welfare and rights of people in biomedical research studies - the Beaumont Hospital Ethics (Medical Research) Committee.)

☐Yes ☐No

Patient's name _____

Next of Kin/Relative's _____ _____

Signature and dated Name in block capitals

To be completed by the Principal Investigator or his nominee.

I the undersigned have taken the time to fully explain to the above patient's next of kin/relative the nature and purpose of this study in a manner that he/she could understand. I have explained the risks involved, as well as the possible benefits and have invited him/her to ask questions on any aspect of the study that concerned them.

_____ _____ _____ ____

Signature: Name in Block Capitals: Qualification: Date:

Appendix 5 Stroke and Brain Attack - NIH Stroke Scale

1.a. Level of Consciousness:

0 Alerts

1 Not alert, but arousable with minimal stimulation

2 Not alert, requires repeated stimulation to attend

3 Comma

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 Answers both correctly

1 Answers 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

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 6 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 to 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): _____

Provided by the Internet Stroke Center — www.strokecenter.org

Appendix 7 Prevalence of valvular strands from previous studies

a) In a fairly large case-control study conducted between 1991 and 1993, Freedberg et al. (15) noted that VS were found in 5.5% (86/1559) of patients undergoing TOE. Of the 597 patients with an embolic event (included stroke, TIA and peripheral emboli), 10.6% (63/597) had VS, compared with only 2.3% (23/962) of patients without an embolic event (odds ratio 4.8, 95% confidence interval [CI] 3.0 to 7.9, $p = 0.0001$).

b) In 1996 Tice et al. (16) evaluated mitral valves in 968 patients referred for TOE over a period of two years and mitral VS were identified in 2.3% (22/968). VS were present in 6.3% (20/318) of patients who had a recent ischaemic cerebrovascular event compared with 0.3% (2/650) patients studied for other indications ($p < 0.00001$).

c) In 1997, Roberts et al. (27) selected 73 cases and controls from a group of 453 consecutive patients referred for TOE over a 9-month period. He reported a VS frequency of 47% (34/73) in the group of patients undergoing TOE for indications of ischaemic stroke or TIA and a frequency of 16 % (12/73) in the control group undergoing TOE for indications other than stroke or TIA.

d) In a case-control study by Cohen et al. (20) published in 1997, mitral VS were reported in 22.5% (64/284) of cases selected from 385 patients older than 60 years consecutively admitted to neurology departments for brain infarction (information on VS was missing in 51 cases). Mitral VS were found in 12.1 % (31/256) of control subjects with no history of brain embolisation or peripheral embolisation. Controls included patients with endocarditis, intracavitary masses, suspicion of aortic dissection, pulmonary embolism and inadequate TTE.

e) In 1997 Menzel et al. (28) in a prospective study, examined prevalence and echocardiographic characteristics of VS on native aortic valves. He found VS in 39% (86/218) of patients who had undergone TOE for several indications excluding endocarditis, severe calcification of aortic cusps or aortic valve ring. The prevalence was 46% in patients with a recent history of embolism who had undergone TOE compared to 34% prevalence without such a history.

f) In 1997, Roldan et al. (29) prospectively studied the prevalence, evolution and embolic risk of VS in normal subjects and patients aged $\leq$ 60 years with and without suspected cardioembolism. This study showed a similar prevalence of VS in normal subjects (38%; 34/90) and in patients with (41%; 20/49) or without (47%; 41/88) suspected cardioembolism regardless of age and gender.

g) In 1998, Nighoghossian et al. (30) estimated changes in the VS in patients who were referred for TOE for stroke or cardiac pathology through a serial TOE study. This study showed that 10% (34/340) patients had VS on any cardiac valves. Among 34 patients with VS, 18.8% (30/340) were referred for stroke whereas 2.2% (4/340) were admitted with cardiac pathology.

h) More recently in 2004, Homma et al. (31) analyzed 619 TOE studies in stroke patients enrolled in the Patent Foramen Ovale in Cryptogenic Stroke Study (PICSS), a randomized study which investigated the rate of recurrent ischaemic stroke or death on aspirin or warfarin. VS were present in 39.4% (244/619) of the study population.

References

1. Albers GW, Caplan LR, Easton JD, Fayad PB, Mohr JP, Saver JL, et al. Transient ischemic attack--proposal for a new definition. N Engl J Med. 2002;347(21):1713-6. Epub 2002/11/22.

2. Lyden P, Lu M, Jackson C, Marler J, Kothari R, Brott T, et al. Underlying structure of the National Institutes of Health Stroke Scale: results of a factor analysis. NINDS tPA Stroke Trial Investigators. Stroke. 1999;30(11):2347-54. Epub 1999/11/05.

3. Fiebach JB, Schellinger PD, Jansen O, Meyer M, Wilde P, Bender J, et al. CT and diffusion-weighted MR imaging in randomized order: diffusion-weighted imaging results in higher accuracy and lower interrater variability in the diagnosis of hyperacute ischemic stroke. Stroke. 2002;33(9):2206-10. Epub 2002/09/07.

4. Amarenco P, Bogousslavsky J, Caplan LR, Donnan GA, Hennerici MG. Classification of stroke subtypes. Cerebrovasc Dis. 2009;27(5):493-501. Epub 2009/04/04.

5. Grau AJ, Weimar C, Buggle F, Heinrich A, Goertler M, Neumaier S, et al. Risk factors, outcome, and treatment in subtypes of ischemic stroke: the German stroke data bank. Stroke. 2001;32(11):2559-66. Epub 2001/11/03.

6. Kolominsky-Rabas PL, Weber M, Gefeller O, Neundoerfer B, Heuschmann PU. Epidemiology of ischemic stroke subtypes according to TOAST criteria: incidence, recurrence, and long-term survival in ischemic stroke subtypes: a population-based study. Stroke. 2001;32(12):2735-40. Epub 2001/12/12.

7. Petty GW, Brown RD, Jr., Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO. Ischemic stroke subtypes : a population-based study of functional outcome, survival, and recurrence. Stroke. 2000;31(5):1062-8. Epub 2000/05/08.

8. Sacco RL, Kargman DE, Gu Q, Zamanillo MC. Race-ethnicity and determinants of intracranial atherosclerotic cerebral infarction. The Northern Manhattan Stroke Study. Stroke. 1995;26(1):14-20. Epub 1995/01/01.

9. Ringelstein EB, Koschorke S, Holling A, Thron A, Lambertz H, Minale C. Computed tomographic patterns of proven embolic brain infarctions. Ann Neurol. 1989;26(6):759-65. Epub 1989/12/01.

10. Weiller C, Ringelstein EB, Reiche W, Thron A, Buell U. The large striatocapsular infarct. A clinical and pathophysiological entity. Arch Neurol. 1990;47(10):1085-91. Epub 1990/10/01.

11. Pepi M, Evangelista A, Nihoyannopoulos P, Flachskampf FA, Athanassopoulos G, Colonna P, et al. Recommendations for echocardiography use in the diagnosis and management of cardiac sources of embolism: European Association of Echocardiography (EAE) (a registered branch of the ESC). Eur J Echocardiogr. 2010;11(6):461-76. Epub 2010/08/13.

12. Ferro JM. Cardioembolic stroke: an update. Lancet Neurol. 2003;2(3):177-88. Epub 2003/07/10.

13. Doufekias E, Segal AZ, Kizer JR. Cardiogenic and aortogenic brain embolism. J Am Coll Cardiol. 2008;51(11):1049-59. Epub 2008/03/18.

14. Flachskampf FA, Decoodt P, Fraser AG, Daniel WG, Roelandt JR. Guidelines from the Working Group. Recommendations for performing transesophageal echocardiography. Eur J Echocardiogr. 2001;2(1):8-21. Epub 2002/03/27.

15. Freedberg RS, Goodkin GM, Perez JL, Tunick PA, Kronzon I. Valve strands are strongly associated with systemic embolization: a transesophageal echocardiographic study. J Am Coll Cardiol. 1995;26(7):1709-12. Epub 1995/12/01.

16. Tice FD, Slivka AP, Walz ET, Orsinelli DA, Pearson AC. Mitral valve strands in patients with focal cerebral ischemia. Stroke. 1996;27(7):1183-6. Epub 1996/07/01.

17. Fox E, Brunson C, Campbell W, Aru G. Cardiac papillary fibroelastoma presents as an acute embolic stroke in a 35-year-old African American male. Am J Med Sci. 2006;331(2):91-4. Epub 2006/02/16.

18. Grandmougin D, Fayad G, Moukassa D, Decoene C, Abolmaali K, Bodart JC, et al. Cardiac valve papillary fibroelastomas: clinical, histological and immunohistochemical studies and a physiopathogenic hypothesis. J Heart Valve Dis. 2000;9(6):832-41. Epub 2000/12/29.

19. Nighoghossian N, Derex L, Loire R, Perinetti M, Honnorat J, Riche G, et al. Giant lambl excrescences. An unusual source of cerebral embolism. Arch Neurol. 1997;54(1):41-4. Epub 1996/01/01.

20. Cohen A, Tzourio C, Chauvel C, Bertrand B, Crassard I, Bernard Y, et al. Mitral valve strands and the risk of ischemic stroke in elderly patients. The French Study of Aortic Plaques in Stroke (FAPS) Investigators. Stroke. 1997;28(8):1574-8. Epub 1997/08/01.

21. Lambl VA. Papillare exkrescenzen an der semilunarklappe des aorta. Wien Med Wochenschr. 1856;6:244-7.

22. Magarey FR. On the mode of formation of Lambl's excrescences and their relation to chronic thickening of the mitral valve. J Pathol Bacteriol. 1949;61(2):203-8, 5 pl. Epub 1949/04/01.

23. Voros S, Nanda NC, Thakur AC, Winokur TS, Samal AK. Lambl's Excrescences (Valvular Strands). Echocardiography. 1999;16(4):399-414. Epub 2001/02/15.

24. Lee RJ, Bartzokis T, Yeoh TK, Grogin HR, Choi D, Schnittger I. Enhanced detection of intracardiac sources of cerebral emboli by transesophageal echocardiography. Stroke. 1991;22(6):734-9. Epub 1991/06/01.

25. Wolf RC, Spiess J, Vasic N, Huber R. Valvular strands and ischemic stroke. Eur Neurol. 2007;57(4):227-31. Epub 2007/02/22.

26. Hurle JM, Garcia-Martinez V, Sanchez-Quintana D. Morphologic characteristics and structure of surface excrescences (Lambl's excrescences) in the normal aortic valve. Am J Cardiol. 1986;58(13):1223-7. Epub 1986/12/01.

27. Roberts JK, Omarali I, Di Tullio MR, Sciacca RR, Sacco RL, Homma S. Valvular strands and cerebral ischemia. Effect of demographics and strand characteristics. Stroke. 1997;28(11):2185-8. Epub 1997/11/22.

28. Menzel T, Mohr-Kahaly S, Arnold KJ, Kolsch B, Kopp H, Spiecker M, et al. Detection of strands in native aortic valves by transesophageal echocardiography. Am J Cardiol. 1997;79(11):1549-52. Epub 1997/06/01.

29. Roldan CA, Shively BK, Crawford MH. Valve excrescences: prevalence, evolution and risk for cardioembolism. J Am Coll Cardiol. 1997;30(5):1308-14. Epub 1997/11/14.

30. Nighoghossian N, Derex L, Perinetti M, Honnorat J, Barthelet M, Loire R, et al. Course of valvular strands in patients with stroke: cooperative study with transesophageal echocardiography. Am Heart J. 1998;136(6):1065-9. Epub 1998/12/08.

31. Homma S, Di Tullio MR, Sciacca RR, Sacco RL, Mohr JP. Effect of aspirin and warfarin therapy in stroke patients with valvular strands. Stroke. 2004;35(6):1436-42. Epub 2004/04/10.

32. Stoddard MF, Dawkins PR, Longaker RA. Mobile strands are frequently attached to the St. Jude Medical mitral valve prosthesis as assessed by two-dimensional transesophageal echocardiography. Am Heart J. 1992;124(3):671-4. Epub 1992/09/01.

33. Orsinelli DA, Pearson AC. Detection of prosthetic valve strands by transesophageal echocardiography: clinical significance in patients with suspected cardiac source of embolism. J Am Coll Cardiol. 1995;26(7):1713-8. Epub 1995/12/01.

34. Loire R, Tabib A, Saint-Pierre G. [Lambl's excrescences]. Arch Mal Coeur Vaiss. 1985;78(2):202-7. Epub 1985/02/01. Les excroissances de Lambl.

35. Riddle JM, Wang CH, Magilligan DJ, Jr., Stein PD. Scanning electron microscopy of surgically excised human mitral valves in patients over 45 years of age. Am J Cardiol. 1989;63(7):471-7. Epub 1989/02/15.

36. Voros S, Nanda NC, Thakur AC, Narayan VK, Samal AK. Lambl's Excrescences Involving the Pulmonary Valve Detected by Transesophageal Echocardiography. Echocardiography. 1999;16(1):35-9. Epub 2001/02/15.

37. Pomerance A. Papillary tumours of heart valves. J Pathol Bacteriol. 1961;81:135-40.

38. Bhagwandien NS, Shah N, Costello JM, Jr., Gilbert CL, Blankenship JC. Echocardiographic detection of pulmonary valve papillary fibroelastoma. J Cardiovasc Surg (Torino). 1998;39(3):351-4. Epub 1998/07/25.

39. Jaffe W, Figueredo VM. An example of Lambl's excrescences by transesophageal echocardiogram: a commonly misinterpreted lesion. Echocardiography. 2007;24(10):1086-9. Epub 2007/11/16.

40. Heath D, Best PV, Davis BT. Papilliferous tumours of the heart valves. Br Heart J. 1961;23:20-4. Epub 1961/01/01.

41. Boone SA, Campagna M, Walley VM. Lambl's excrescences and papillary fibroelastomas: are they different? Can J Cardiol. 1992;8(4):372-6. Epub 1992/05/01.

42. Hutchinson K, Hafeez F, Woods TD, Chopra PS, Warner TF, Levine RL, et al. Recurrent ischemic strokes in a patient with Medtronic-Hall prosthetic aortic valve and valve strands. J Am Soc Echocardiogr. 1998;11(7):755-7. Epub 1998/08/06.

43. Quinson P, de Gevigney G, Boucher F, Delahaye F, Perinetti M, Jegaden O, et al. [Fibrous aortic valve tumor (Lambl's excrescence) trapped in the right coronary artery. Apropos of a case]. Arch Mal Coeur Vaiss. 1996;89(11):1419-23. Epub

1996/11/01. Tumeur fibreuse valvulaire aortique (excroissance de Lambl) enclavee dans la coronaire droite. A propos d'un cas.

44. Thomas MR, Jayakrishnan AG, Desai J, Monaghan MJ, Jewitt DE. Transesophageal echocardiography in the detection and surgical management of a papillary fibroelastoma of the mitral valve causing partial mitral valve obstruction. J Am Soc Echocardiogr. 1993;6(1):83-6. Epub 1993/01/01.

45. Fitzgerald D, Gaffney P, Dervan P, Doyle CT, Horgan J, Nelligan M. Giant Lambl's excrescence presenting as a peripheral embolus. Chest. 1982;81(4):516-7. Epub 1982/04/01.

46. Foulkes MA, Wolf PA, Price TR, Mohr JP, Hier DB. The Stroke Data Bank: design, methods, and baseline characteristics. Stroke. 1988;19(5):547-54. Epub 1988/05/01.

47. Jung JM, Kwon SU, Lee JH, Kang DW. Difference in infarct volume and patterns between cardioembolism and internal carotid artery disease: focus on the degree of cardioembolic risk and carotid stenosis. Cerebrovasc Dis. 2010;29(5):490-6. Epub 2010/03/20.

48. Helgason CM. Cardioembolic stroke: topography and pathogenesis. Cerebrovasc Brain Metab Rev. 1992;4(1):28-58. Epub 1992/01/01.

49. Cho AH, Kwon SU, Kim TW, Lee SJ, Shon YM, Kim BS, et al. High prevalence of unrecognized cerebral infarcts in first-ever stroke patients with cardioembolic sources. Eur J Neurol. 2009;16(7):838-42. Epub 2009/05/29.

50. Hankey GJ, Eikelboom JW, van Bockxmeer FM, Lofthouse E, Staples N, Baker RI. Inherited Thrombophilia in Ischemic Stroke and Its Pathogenic Subtypes. Stroke. 2001;32(8):1793-9.

51. Simioni P, de Ronde H, Prandoni P, Saladini M, Bertina RM, Girolami A. Ischemic Stroke in Young Patients With Activated Protein C Resistance : A Report of Three Cases Belonging to Three Different Kindreds. Stroke. 1995;26(5):885-90.

52. Khamashta MA, Cuadrado MJ, Mujic F, Taub NA, Hunt BJ, Hughes GR. The management of thrombosis in the antiphospholipid-antibody syndrome. N Engl J Med. 1995;332(15):993-7. Epub 1995/04/13.

53. Love PE, Santoro SA. Antiphospholipid antibodies: anticardiolipin and the lupus anticoagulant in systemic lupus erythematosus (SLE) and in non-SLE disorders. Prevalence and clinical significance. Ann Intern Med. 1990;112(9):682-98. Epub 1990/05/01.

54. Saidi S, Mahjoub T, Almawi WY. Lupus anticoagulants and anti-phospholipid antibodies as risk factors for a first episode of ischemic stroke. J Thromb Haemost. 2009;7(7):1075-80. Epub 2009/05/09.

55. Topcuoglu MA, Haydari D, Ozturk S, Ozcebe OI, Saribas O. Plasma levels of coagulation and fibrinolysis markers in acute ischemic stroke patients with lone atrial fibrillation. Neurol Sci. 2000;21(4):235-40. Epub 2001/02/24.

56. Narins CR, Eichelberger JP. The development of valvular strands during thrombolytic therapy detected by transesophageal echocardiography. J Am Soc Echocardiogr. 1996;9(6):888-90. Epub 1996/11/01.

57. Robert F, Roudaut R, Pepin C, Garrigue S, Labbe T, Bonnet J. Significance of "Strands" on Mitral Mechanical Prostheses During Late Follow-Up After Surgery. Echocardiography. 1996;13(3):265-70. Epub 1996/05/01.

58. Samal AK, Nanda N, Thakur AC, Narayan VK, Ocak O, Lee TY, et al. Three-Dimensional Echocardiographic Assessment of Lambl's Excrescences on the Aortic Valve. Echocardiography. 1999;16(5):437-41. Epub 2001/02/15.

59. Sun JP, Asher CR, Yang XS, Cheng GG, Scalia GM, Massed AG, et al. Clinical and echocardiographic characteristics of papillary fibroelastomas: a retrospective and prospective study in 162 patients. Circulation. 2001;103(22):2687-93. Epub 2001/06/08.

60. Aggarwal A, Leavitt BJ. Images in clinical medicine. Giant Lambl's excrescences. N Engl J Med. 2003;349(25):e24. Epub 2003/12/19.

61. al-Mohammad A, Pambakian H, Young C. Fibroelastoma: case report and review of the literature. Heart. 1998;79(3):301-4. Epub 1998/05/29.

62. Loire R, Pinede L, Donsbeck AV, Nighoghossian N, Perinetti M. [Papillary fibroelastoma of the heart (giant Lambl excrescence). Clinical-anatomical study on 10 surgically treated patients]. Presse Med. 1998;27(16):753-7. Epub 1998/10/13. Fibroelastomes papillaires cardiaques (excroissances de Lambl geantes). Etude anatomo-clinique de 10 cas operes.

63. Adams HP, Jr., Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke. 1993;24(1):35-41. Epub 1993/01/01.

64. Bamford J, Sandercock P, Dennis M, Warlow C, Burn J. Classification and natural history of clinically identifiable subtypes of cerebral infarction. The Lancet. 1991;337(8756):1521-6.

65. Mahoney FI, Barthel DW. Functional Evaluation: The Barthel Index. Md State Med J. 1965;14:61-5. Epub 1965/02/01.

66. Dhamoon MS, Moon YP, Paik MC, Boden-Albala B, Rundek T, Sacco RL, et al. Long-Term Functional Recovery After First Ischemic Stroke: The Northern Manhattan Study. Stroke. 2009;40(8):2805-11.

67. Gaasch WH, Zile MR. Left ventricular diastolic dysfunction and diastolic heart failure. Annu Rev Med. 2004;55:373-94. Epub 2004/01/30.

68. Furie KL, Kasner SE, Adams RJ, Albers GW, Bush RL, Fagan SC, et al. Guidelines for the Prevention of Stroke in Patients With Stroke or Transient Ischemic Attack: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2011;42(1):227-76.

69. Hankey GJ, Eikelboom JW, van Bockxmeer FM, Lofthouse E, Staples N, Baker RI. Inherited thrombophilia in ischemic stroke and its pathogenic subtypes. Stroke. 2001;32(8):1793-9. Epub 2001/08/04.

70. De Lau LML, Leebeek FWG, De Maat MPM, Koudstaal PJ, Dippel DWJ. Reviews: A review of hereditary and acquired coagulation disorders in the aetiology of ischaemic stroke. International Journal of Stroke. 2010;5(5):385-94.

71. Morris JG, Singh S, Fisher M. Testing for Inherited Thrombophilias in Arterial Stroke: Can It Cause More Harm Than Good? Stroke. 2010;41(12):2985-90.

72. Gordi T, Khamis H. Simple solution to a common statistical problem: Interpreting multiple tests. Clinical Therapeutics. 2004;26(5):780-6.