



The Prevalence of Extra-cranial Carotid Artery Disease in Chronic Heart Failure

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Authors' contributions

This work was carried out in collaboration between all authors. Author NS designed the study, wrote the protocol, and wrote the first and final draft of the manuscript. Author KW revised the manuscript and managed the literature searches, author JZ performed the statistical analysis, author PP collected the data and revised the manuscript, authors OC, CB and AT collected the data, author AC revised the manuscript, author JGC designed the study and revised the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Background: The prevalence of carotid disease in patients with heart failure (HF) has not been described. This may be of importance for the implementation of novel interventions for heart failure that require surgery close to the carotid artery.

Objective: The aim of this study was to determine the prevalence of extra-cranial carotid artery stenosis (ECAS) in patients with HF.

Methods: The study population comprised consecutive, patients with chronic stable HF due to left ventricular systolic dysfunction (LVSD). Patients were invited to have an ultrasound duplex scan of the internal and common extra-cranial carotid arteries (ECA) and stenoses were classified as minor

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if <50%, moderate if 50-69% and severe if >70%.

Results: Of 102 patients, the median age was 73 (IQR: 66-78) years and 95 were men. Ten patients had moderate ECAS of whom one also had severe ECAS in the contra-lateral artery. Thirteen patients gave a prior history of stroke or transient ischaemic attack. Of patients with ECAS, only three (30%) had had a neurological event and only three (23%) of those with a neurological event had moderate or severe ECAS (95% CI; 6-55%). Most neurological events had occurred in patients without ECAS.

Conclusion: There is a moderately high prevalence of ECAS in patients with HF. However, most patients with chronic heart failure (CHF) who have had a neurological event do not have ECAS and most patients with ECAS do not have neurological symptoms. The value of screening for and management of ECAS in patients with HF remains to be established.

Keywords: Chronic heart failure; carotid artery stenosis; duplex ultrasound.

1. INTRODUCTION

Atherosclerosis is a systemic disease affecting medium and large sized arteries which may affect the coronary, renal, peripheral and cerebral circulation [1]. In a recent meta-analysis, the prevalence of moderate asymptomatic ECAS in the general population ranged from <1.0% in the population aged <50 years to 7.5% in men aged ≥80 years and the prevalence of severe ECAS from <1.0% to 3.0% in similar age groups. ECAS was more common in men than in women and increased with age and with the number and severity of risk factors [2] (Table-1). Studies suggest that the annual risk of an ipsilateral stroke is about 2% for patients with a moderate asymptomatic ECAS and 3-5% for patients with a severe ECAS [3-5]. Rates are higher in patients with neurological symptoms. However, only about half of strokes in patients with asymptomatic ECAS can be attributed either to carotid artery thrombosis or embolism from a carotid stenosis into territories supplied by either the middle cerebral artery (MCA) or the anterior cerebral artery (ACA). Lacunar stroke account for 30-40% of patients with asymptomatic internal carotid artery stenosis and cardio-embolic events for about 10% but haemorrhagic stroke appears rare [6].

HF is an important public health condition with a high mortality and morbidity despite advances in medical care [7]. Myocardial ischaemia and infarction secondary to coronary atherosclerosis, aided and abetted by hypertension and atrial fibrillation (AF), are the main cause of cardiac dysfunction and HF. LVSD, in part related to the risk of AF, may be an important risk factor for stroke [8]. However, a large meta-analysis showed an incidence of stroke in patients with HF of about 1% per year which is little higher than that of an age-matched general population

[9-25] (Table-2). However, a community based study showed the risk of stroke among those with HF was about three times the control population risk over five years [26] and the REasons for Geographic And Racial Differences in Stroke (REGARDS) reported that 26.3% of patients with compared to 8.5% in participants without HF [27]. The extent to which these differences reflect the presence and severity of cardiac dysfunction, the presence and severity of underlying vascular disease or AF or simply age differences is uncertain. The EuroHeart Failure survey suggested that up to 19% of patients with a HF related admission had had a neurological event at some time in the past and that 3% had been admitted primarily due a neurological event [28]. In a large epidemiological study (Rotterdam study), the risk of stroke was highest during the first month following the diagnosis of HF, but the rate decreased over time [29]. The early risk might reflect the importance of AF as a precipitant of HF [30] or of embolisation from mural thrombus after myocardial infarction. Rates may decline due to the benefits of introducing anti-thrombotic therapies and the effects of treatments that reduce blood pressure, improve cardiac function and appear to offer vascular protection. None of these hypotheses is proven.

Table 1. Prevalence (%) of asymptomatic carotid artery stenosis in the general population (n= 23,706), modified from [2]

Age	<50	50-59	60-69	70-79	>80
Moderate					
Men	0.2	0.7	2.3	6.0	7.5
Women	0.0	0.5	2.0	3.6	5.0
Severe					
Men	0.1	0.2	0.8	2.1	3.1
Women	0.0	0.1	0.2	1.0	0.9

Table 2. Studies Reporting Stroke among Persons with Heart Failure, modified from [9]

Study	Study Period	Patients			Stroke Incidence	
		Number	Age (years)	Female Sex (%)	Strokes/1000/year	F/U* (Days)
Studies where N>100						
Natterson [10]	1985–92	224	50	21	16	301
Griffith [11]	1952	603	73	59	23	365
Cioffi [12]	1992–95	406	54	1	13.1	480
Katz [13]	1988–89	264	62	32	12	720
Andersson [14]	1980–87	842	58	32	14	1110
Ciaccheri [15]	1980–87	126	54	25	21	1236
Cleland [16]	1995–97	279	62	26	4	810
Dunkman 1 [17]	1980–85	642	58	0	41	832
Dunkman 2 [17]	1986–91	804	61	0	47	934
Summary Data		4190	59	22	21	6788
Clinical trials where N>1,000						
ELITE-II [18]	1997–98	3152	72	31	6	548
RALES [19]	1995–96	1663	65	27	10	720
CHARM-Alt-T [20]	1999–01	2028	67	32	14	1011
Mathew [21]	1991–93	7788	64	25	14	1110
CHARM-Overall-P[22]	1999–01	7599	66	32	5	1131
Dries [23]	1986–89	6378	60	4	11	1197
CHARM-added [24]	1999–99	2548	64	21	10	1230
COMET [25]	1996–99	3029	62	0.2	10	1740
Summary data		34.185	65	21.4	10	8687

*Duration of observation for stroke

The pathology underlying stroke in patients with HF will be heterogeneous. Patients with HF will not be immune to lacunar strokes due to occlusion of an intra-cerebral artery. They will be at increased risk of cerebral haemorrhage due to anti-thrombotic medication, although this may be reduced by low arterial pressure due to HF itself or its treatment. They will be at increased risk of thromboembolic disease due to mural thrombus in the left atrium or left ventricle due to dilatation and stasis or to endocardial damage due to acute myocardial infarction or endocardial disease. Thromboembolism from disease in the aortic arch is also possible [31].

Although the risk factors and arterial pathology underlying stroke and HF share many common features, little is known about the prevalence of carotid pathology in HF. Indeed, we were unable to find any previous study on this subject. The purpose of this study was to determine the prevalence and severity of ECAS in patients with chronic stable HF using duplex ultrasonography of the extra-cranial carotid arteries, a simple and safe method to detect and quantify obstructive atherosclerotic lesions.

2. METHODS

The study population comprised consecutive, clinically stable patients with HF due to LVSD

attending a specialist clinic serving the local community (population circa 550,000) at Castle Hill Hospital-UK over a period of approximately 3 months. All patients were clinically stable, on optimised medical treatment for HF and provided written informed consent for this epidemiological study. The diagnosis of HF was based on the clinical symptoms and signs and an echocardiographic LV ejection fraction (LVEF) <50% measured using the modified Simpson's rule. Clinical information obtained included medical history, current symptom severity, using the New York Heart Association (NYHA) classification system, current medications and a physical examination, including assessment of height and weight, heart rate, rhythm, and blood pressure. In addition to an echocardiogram, all patients also had an electrocardiogram and routine blood tests including tests for renal function, lipid profile and amino-terminal pro-brain natriuretic peptide (NT-proBNP).

Diabetes was categorized as patients with a clinical diagnosis of diabetes treated with insulin, an oral hypoglycaemic, or by diet. Hypertension was defined as a systolic blood pressure >140mmHg or diastolic >90mmHg or receiving medications for hypertension. Prior history of ischaemic events, coronary artery bypass grafting (CABG), hypercholesterolemia, AF, transient ischemic attack (TIA), stroke, renal dysfunction and other co-morbidities were all

obtained from medical records. Stroke was defined as a clinical diagnosis based on a history of the sudden onset of focal neurological signs that persisted for at least 24 hours. TIA was defined as a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction. All patients with stroke or TIA underwent neuroimaging either by Computerised tomography scan (CT-Scan) and or Magnetic resonance imaging (MRI).

Each subject underwent duplex ultrasound scanning (General Electric VIVID-7) of both right and left ECA. B-mode duplex imaging was used to detect atheromatous plaques in the internal and common ECA and also in the carotid bifurcation which were defined as and quantified by focal thickening. The maximum peak systolic velocity (PSV) and end diastolic velocity (EDV) of the ICA, and the PSV and EDV of CCA were measured using spectral pulse wave Doppler sampling. The degree of carotid stenosis was assessed and defined according to validated criteria based on recommendations from The Society of Radiologists in Ultrasound Consensus Conference [32]. ECAS was considered minor if <50% and significant if \geq 50%, which was further categorised as moderate if 50-69%, high-grade if 70-99% or totally occluded.

3. STATISTICS

Descriptive statistics were used. Continuous variables were represented as a median and inter quartile range (IQR) or a mean and standard deviation (SD) and categorical variables were expressed as numbers and proportions. Comparisons were made using t-test or Mann-Whitney test, depending on normality of distribution. For discrete variables, Fisher's exact test was used. P value less than 0.05 was considered as significant.

4. RESULTS

Of 102 patients, the median age was 73 (IQR: 66-78) years and 95 (93%) were men (Table 3). Ten patients had moderate ECAS of 50-69% of whom one also had severe ECAS of >70% in the contra-lateral artery. Thus, the prevalence of ECAS in this population was 11% [95% confidence interval (CI) was 4.9-17.1%].

Patients with moderate to severe ECAS have more history of hypertension (80% versus 39%) than patients without, had a lower HDL/LDL ratio

and had a trend to higher systolic blood pressure is higher (145mmHg vs 129mmHg, $p=0.069$) and left ventricular ejection fraction (41% vs 37%, $p=0.076$). Patient characteristics were otherwise similar for patients with and without ECAS. Among patients with ECAS, 3 patients (33.3%) had a history of stroke or TIA as compared to 10 patients (11%) with no stenosis ($p = 0.115$). The apparently substantial numerical differences did not achieve statistical significance. This may reflect the relatively small number of patients with ECAS.

In the 13 patients with a previous history of stroke or TIA, three (23% with 95% CI: 6% - 55%) patients had ECAS compared with ten in those with no history of stroke or TIA ($p = 0.115$). Patients who had a stroke or TIA were slightly older and 77% had a myocardial infarction, compared with 47% in patients who did not have a stroke/TIA ($p=0.073$) (Table 4).

5. DISCUSSION

This survey is the first to investigate the prevalence of ECAS systematically in patients with HF. The study suggests there may be a modest increase in prevalence compared to the general population but perhaps no higher than in other groups of patients with a high prevalence of established cardiovascular disease. For instance, high rates of moderate (5.3% to 27%) and severe (3.7% to 13.4%) ECAS have been reported in large series of patients being considered for coronary bypass surgery. The confidence intervals around the estimates in our series are wide and overlap prevalence estimates for older people in epidemiological studies of the general population [2]. The prevalence of important ECAS appears much lower than the prevalence of important coronary disease that affected >50% of this population. The reason why atherosclerosis preferentially affects specific parts of the circulation is unclear. The prevalence of clinically overt coronary artery disease (CAD) amongst patients with stroke is much higher than is clinically overt neurological events in patients with CAD and the prevalence of severe CAD in patients with stroke would be higher still if coronary angiography were done routinely [33,34]. In contrast, the prevalence of severe asymptomatic ECAS in patients with CAD is relatively low.

Amongst patients with ECAS, 30% gave a history of a neurological event compared to only 10% of those without ECAS. The study was not large

enough to exclude the possibility that this occurred by chance. Amongst thirteen patients who had experienced a neurological event only three had ECAS, only five had chronic AF, only one had severe LVSD and only seven patients had one or other of these problems. Ventricular function assessed either by echocardiography or natriuretic peptides did not appear substantially different between groups. We did not exclude aortic arch disease as a source of thromboembolic disease nor tested for patent foramen ovale as possible alternative reasons for stroke nor did we exclude lacunar infarcts. It is also possible that factors precipitating stroke were transient, such as paroxysmal AF or mural thrombus, which had resolved. These data support the concept that neurological events are multi-factorial in this population [35].

We did not measure intima-media thickness (IMT) [36] in this study as it is a measure of subclinical atherosclerosis [37] and appears related to the burden of CAD [38,39]. Recently,

an increased carotid wall thickness was identified as a marker of an increased risk of vascular events in asymptomatic subjects with internal carotid artery stenosis >60% [40].

Several pharmacological interventions may reduce the risk of stroke in patients with HF. In patients in sinus rhythm, Warfarin appears more effective than aspirin in reducing the risk of stroke but does not improve overall survival [41-43]. Statins may also reduce the risk of non-fatal stroke in patients with HF but, again, do not reduce mortality [44]. Angiotensin Converting Enzymes Inhibitors (ACE inhibitors), Angiotensin Receptor Blockers (ARBs) and Mineralocorticoid Receptor Antagonists (MRAs) [19,20,22,24] may reduce the rate of stroke, possibly by reducing blood pressure. Slightly more patients had a stroke if assigned to Bisoprolol rather than placebo in the CIBIS-II study [45] but the risk of stroke was lower in patients assigned to Carvedilol rather than Metoprolol tartrate in the COMET study [25].

Table 3. Baseline characteristics by stenosis

Variables	No Stenosis	Stenosis	p-value
Age (years)	72 (8.4)	70 (7.8)	0.523
Sex (men) (%)	86(93%)	9 (90%)	0.526
Smoking (%)	16 (17%)	3 (30%)	0.390
BMI (kg/m ²)	28.7(25.4-32.7)	26.6(25.0-30.5)	0.713
HTN (%)	36 (39%)	8(80%)	0.018
Diabetes (%)	21 (23%)	3 (30%)	0.696
IHD (%)	65 (71%)	7 (70%)	1.000
MI (%)	45(49%)	7(70%)	0.319
TIA/CVA (%)	10(11%)	3 (33.3%)	0.115
AF (%)	24 (26%)	1 (10%)	0.569
Heart rate(bpm)	68(60-76)	63(60-78)	0.444
Systolic BP(mmHg)	129 (114-141)	145(140-158)	0.069
Diastolic BP(mmHg)	75.8(11.67)	75.8(18.3)	0.993
NYHA class (III)(%)	21 (23%)	2 (20%)	1.000
EF (%)	37(7.33)	41(8.49)	0.076
LV Aneurysm/thrombus	None	None	
NT-proBNP (ng/L)	1336(507-2334)	846(710-2157)	0.398
Urea(mol/L)	7.3 (5.4-10.3)	7.0(6.5-13.4)	0.702
Creatinine (mol/L)	107(89-143)	107(98-119)	0.915
Total Cholesterol	3.95(3.20-4.55)	4.15(3.60-5.80)	0.272
HDL/LDL	0.47(0.39-0.61)	0.36(0.28-0.43)	0.015
Statins (%)	67(74%)	7 (70%)	0.725
Aspirin (%)	48 (53%)	5(50%)	1.000
Warfarin(%)	31 (34%)	3 (30%)	1.000
Clopidogrel(%)	12 (13%)	0	0.603

*Median with IQR/mean (SD) or counts (%).

AF=atrial fibrillation; BMI=body mass index; BP =blood pressure; EF=ejection fraction; HTN=hypertension; IHD= Ischaemic heart disease; LV=left ventricle; MI=Myocardial infarction; HDL= high density lipoprotein; LDL= low density lipoprotein

Table 4. Baseline characteristics by stroke and TIA

Variables	No stroke/TIA (N=89)	Stroke/TIA (N = 13)	p-value
Age (years)	71 (8.4)	76(6.5)	0.045
Sex (men) (%)	82(92%)	13(100%)	0.591
Smoking (%)	18(20%)	1(8%)	0.453
BMI (kg/m ²)	28.7(25.4-32.7)	26.6(25.0-32.5)	0.910
HTN (%)	36(40%)	8(62%)	0.230
Diabetes (%)	20(22%)	4(31%)	0.498
IHD (%)	61(69%)	11(85%)	0.335
MI (%)	42(47%)	10(77%)	0.073
AF(AF, paced and SR) (%)	20(22%)	5(38%)	0.317
Carotid Stenosis (%)	7 (8%)	3(23%)	0.115
Heart rate(bpm)	68(60-77)	63(60-72)	0.197
Systolic BP(mmHg)	130 (20.7)	128(26.1)	0.670
Diastolic BP(mmHg)	77 (12.4)	71(11.4)	0.109
NYHA class (III) (%)	20(22%)	3(23%)	0.792
EF (%)	37(7.6)	37(7.1)	0.849
LVEF <25% (n =)	6	1	
NT-proBNP (ng/L)	1057(448-2309)	1362(1159-2628)	0.124
Urea(mol/L)	7.2 (5.3-10.2)	7.3 (6.5-16.3)	0.168
Creatinine(mol/L)	106(90-132)	126(83-154)	0.208
Total Cholesterol	4.0(3.3-4.8)	3.7(3.4-4.2)	0.802
HDL/LDL	0.46(0.38-0.61)	0.44(0.28-0.47)	0.167
Statins (%)	64(73%)	10(77%)	1.000
Aspirin (%)	46(52%)	7(54%)	1.000
Warfarin (%)	28(32%)	6(46%)	0.353
Clopidogrel (%)	11(13%)	1(8%)	1.000

*Median with IQR or counts (%)

Treatment of carotid stenosis depends on the proximity of neurological symptoms, the degree of stenosis, other medical co-morbidities and carotid artery vascular morphology. Treatment options include carotid endarterectomy (CEA), carotid artery stenting or medical management alone. Invasive treatment is associated with a modest risk of procedure-related stroke that may be similar to one or more years risk with medical management alone. In other words, patients have to survive long enough to gain benefit from intervention. Surgical treatment of severe symptomatic carotid stenosis in patients without HF reduces the 5-year risk of death or a disabling stroke from 6.1% to 3.5% with an operative risk of disabling stroke of about 2% [46,47]. A recent large randomised controlled trial, suggested that carotid artery stenting and endarterectomy were associated with similar rates of peri-procedural stroke, myocardial infarction, or death (5.2% and 4.5 respectively; hazard ratio for stenting 1.18; 95% CI, 0.82 to 1.68; P= 0.38) and subsequent ipsilateral stroke (2.0% and 2.4%, respectively; P=0.85), among patients with symptomatic or asymptomatic ECAS [48]. In the first 30 days after a stroke,

90% of deaths are due to the direct effects of the brain lesion or due to complications of immobility resulting from the stroke. However, if the stroke patient survives the initial cerebrovascular event, the most likely cause of death from 6 months onwards is non-stroke cardiovascular or sudden death [49].

The Society for Vascular Surgery guidelines for the management of carotid artery stenosis [50] recommends medical treatment for low-grade carotid stenosis (< 50% in symptomatic, and < 60% in asymptomatic patients) rather than revascularisation. On the other hand, carotid revascularisation plus medical management is recommended in asymptomatic patients with moderate to severe carotid stenosis ≥ 60% as long as the perioperative risk is low. Revascularization should be performed for all symptomatic patients presenting with at least 50% stenosis. However, they did not make any specific recommendations about modifying advice for patients with HF.

New concepts for the treatment of HF are vagal and baro-receptor stimulation devices [51,52].

These both require implants around the carotid bulb. Clearly, caution is required when implanting these devices in patients with significant ECAS. Our study provides an estimate of how commonly ECAS might be encountered.

5.1 Study Limitation

This study population is relatively small, and also the majority of patients were men, we may probably overestimate the results therefore we might not describe accurately the prevalence of ECAS in general population with HF. It should be considered as a preliminary observation. The measurements of peak systolic and end diastolic velocities of internal and common carotid arteries might have been underestimated in some patients with severe HF and a low cardiac output. Use of continuity equations or use of alternative imaging methods, such as computerised tomographic angiography (CTA) or magnetic resonance angiography (MRA) may be required. Not all patients with cerebrovascular event underwent brain MRI therefore it is imprecise to quantify how many patients had had a stroke rather than TIA.

6. CONCLUSION

Not unsurprisingly, the prevalence of ECAS appears to be higher in patients with HF than in the general population and may be associated with a substantial increase in the risk of stroke. However, ECAS appears to account for a rather small proportion of strokes in this population. The value of screening for ECAS in patients with HF and how ECAS should be managed in this population are yet to be determined.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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