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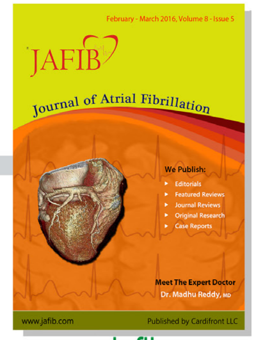

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Clinical and Economic Implications of AF Related Stroke

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Abstract

A major cause of morbidity and mortality among patients with atrial fibrillation (AF) relates to the increased risk of stroke. The burden of illness that AF imparts on stroke is likely to increase with our aging populations and increasingly sophisticated cardiac monitoring techniques. Understanding the clinical and economic differences between AF related ischaemic stroke and non-AF related stroke is important if we are to improve future cost effectiveness analyses of potential preventative treatments, but also to help educate clinical and policy decision makers on use or availability of treatments to prevent AF related stroke. In this article we review the existing evidence that highlights differences in the clinical characteristics and outcomes between AF and non-AF stroke, as well as differences in their economic impact and discuss ways to improve future economic analyses.

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, with a prevalence that increases from 5% in those over 65 years to 10% in those over 80 years.[1,2] These figures are expected to rise exponentially as the population ages such that 7 million Americans will suffer from AF by the year 2020, and 16 million by the year 2050.[1] Indeed, the age-adjusted prevalence of AF has already quadrupled in the US over a period of 50 years from 1958 (20.4 cases per 1000-person years) to 2007 (96.2 cases per 1000-person years),[3] and in the 10 years from 2000 through 2010, AF-related hospitalisations in the US rose by 23%, with increasingly complex and costly admissions.[4] The diagnosis confers significant impairment of quality of life in addition to morbidity and mortality from heart failure, systemic embolisation (SE) and stroke in particular.[5,6] Stroke is the 3rd leading cause of death and the leading cause of serious adult disability in the United States (US) and the United Kingdom (UK).[7,8] Atrial fibrillation is a major risk factor for stroke, generally increasing the risk of ischaemic stroke fivefold,[9] however, age further increases this risk in the setting of AF. The Framingham heart study showed that attributable risk of stroke increases from 1.5% age 50-59 years to 23.5% age 80-89 years,[5] with AF accounting for nearly 25% of strokes in those over the age of 80 years compared to between 10–15% across all age groups.[10] Furthermore, contrary to younger populations, dyslipidaemia and hypertension are less significant risk factors relative to AF in the very old.[11-13] These facts, along with the aging population here in the UK, suggest AF will play an increasingly larger role in contributing to the overall burden of stroke disease.

Anticoagulation with dose adjusted warfarin has been shown to reduce the risk of stroke in AF by around two-thirds.[14-18] Unfortunately numerous studies have shown that utilisation of anticoagulation thromboprophylaxis in AF remains sub-optimal with less than 60% of eligible patients receiving anticoagulation,[19] dropping to around 20% in those over the age of 80 years.[20-22] The introduction of the novel oral anticoagulants (Dabigatran, Rivaroxaban, Apixaban and Edoxaban) may help improve these figures with their relative ease of use and improved intracranial bleeding profiles,[23] however, the costs of their use are increasingly scrutinised among differing health economies. This is understandable in the current economic climate although such economic analyses run the risk of underestimating the cost effectiveness of these agents if they do not utilise AF stroke specific cost data. This is due to the growing body of evidence that suggests patients with AF tend to have larger strokes,[24] that are more severe,[25] and result in higher mortality rates,[26, 27] longer lengths of hospital stay[25] and higher rates of discharge to institutional care,[26] than their sinus rhythm (SR) counterparts. This is likely to result in increased health and societal costs.

In this review we discuss the differences in clinical outcome after stroke among patients with and without AF, what economic implications this imparts and considerations required for future economic evaluations.

Clinical Consequences of AF Stroke

A systematic review of literature investigating differences in stroke

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outcomes among patients with and without AF was undertaken using PUBMED and MEDLINE databases with search criteria consisting of the terms: 'stroke' AND 'outcome' AND 'severity' AND 'atrial fibrillation'. This identified 385 articles, from which 356 were excluded from the title and abstracts alone. Two further reports were excluded due to high patient selectivity.[24,27] This left 27 studies for the final analysis that reported primary data analysis and good (>80%) case inclusion (table 1).

Stroke Severity

The association between AF and increased stroke severity has been suggested in the literature for the last 45 years. Analysis of some of the earliest published reports, such as that of Marquardsen,[29] however, were limited because of their retrospective nature, poor case ascertainment and the limited diagnostic capabilities of the era. It was not until the early 1980's that systematic analyses of patients were reported and highlighted real differences in stroke severity between those with and without AF (Table 1). The Scandinavian Stroke Scale (SSS)

Table 1: Studies comparing stroke outcomes amongst patients with and without AF

Study	Country	Methods/Population	Sample size (AF vs non-AF)	Outcome Measures	Results (AF vs non-AF)	Sig (P, CI)
Wolf et al (1983) Framingham study[46]	US	Prospective observational evaluation of population based cohort who developed stroke	59 vs 442	30 day mortality 6 month stroke recurrence	17% vs 19% 47% vs 20%	NS <0.05
Britton & Gustafsson (1985)[36]	Sweden	Prospective, consecutive inpatient analysis	92 vs 196	Neurological score (0 – 100 where 100 is normal) Reduced conscious level (%) Inpatient mortality (%)	53 vs 67 33% vs 10% 26% vs 5%	<0.001 <0.001 <0.05
Candelise et al (1991)[47]	Italy	Prospective consecutive stroke admissions	211 vs 837	Severe motor deficit (broad class) 1 month mortality 6 month mortality	54% vs 46% 27% vs 14% 40% vs 20%	NS <0.05 <0.05
Gustafsson & Britton (1991)[48]	Sweden	Retrospective observational analysis of consecutive stroke admission	88 vs 188	1 month - recurrent stroke / SE - mortality 5 year – recurrence stroke / SE - mortality	13% vs 2% 35% vs 7% 26% vs 25% 78% vs 52 %	<0.01 <0.01 NS <0.01
Broderick et al (1992)[49]	US	Retrospective analysis of consecutive hospital and community stroke patients	318 vs 1064	Mortality – 30 days - 1 year - 3 years	23% vs 8% 44% vs 18% 77% vs 43%	<0.001 <0.001 <0.001
Sandercock et al (1992)[50]	UK	Prospective community based registry data of consecutive strokes	115 vs 560	30 day mortality	23% vs 8%	<0.05
Anderson et al (1994)[51]	Australia	Prospective population based registry analysis of consecutive stroke patients	Total 321	1 year mortality	Adjusted RR 2.0	CI (1.1-3.5)
Lin et al (1996) Framingham study[37]	US	Prospective community based observational study	103 vs 398	Proportion stroke severe or fatal (%) – broad classification. Mortality – 30 day - 1 year 1 year stroke recurrence Functional dependence (severe BI): - acute period - 3 months - 6 months - 12 months	39% vs 28% 25% vs 14% 63% vs 34% 23% vs 8% 73.3% vs 32.5% 58.3% vs 16.3% 36.4% vs 15.8% 30% vs 10.9%	<0.05 <0.05 <0.05 - <0.01 <0.01 0.05 NS
Jørgensen et al (1996) Copenhagen stroke study[25]	Denmark	Prospective community based analysis of consecutive stroke admissions	217 vs 968	Admission – stroke severity (SSS) - functional dependence (BI) Inpatient mortality (%) Length of hospital stay (days) Discharged to own home (%)	29.7 vs 37.5 34.5 vs 51.7 33% vs 17% 50.9 vs 39.8 48% vs 69%	<0.0001 <0.0001 <0.0001 <0.001 <0.0001
Vemmos et al (2000)[52]	Greece	Prospective population based registry	189 vs 366	1 year disability (MRS > 2)	Adjusted RR 1.8	CI (1.1-3.2)
Lamassa et al (2001) European biomed study[26]	7 countries in Europe	Prospective multi-centre registry of consecutive first time stroke patients	803 vs 3659	Stroke severity (%) – TACI - LACI Mortality – 28 day - 3 month Length of hospital stay (days) Discharge to own home (%) Functional dependence – 3 month (BI)	33.8% vs 25.1% 16% vs 29.2% 19.1% vs 12% 32.8% vs 19.9% 23.9 vs 22.7 61.4% vs 71.4% 12.8 vs 15.3	<0.001 <0.001 <0.001 <0.001 NS <0.001 <0.001
Saxena et al (2001)[35]	Worldwide multi-centre	Retrospective analysis of stroke patients randomised to IST1	3169 vs 15282	Stroke severity (%) – TACI - LACI - reduced GCS Stroke recurrence at 2 weeks Mortality at 2 weeks	36% vs 21% (OR 2.1) 13% vs 26% (OR 0.4) 37% vs 20% (OR 2.4) 1.2% vs 0.7% 17% vs 7.5% (OR 2.5)	CI (2 – 2.3) CI (0.4- 0.5) CI (2.2- 2.6) NS CI (2.2-2.8)
Appelros et al (2002) & (2003)[53,54]	Sweden	Population based analysis of consecutive stroke patients – second analysis with 12 months follow up	90 vs 287	Stroke severity – NIHSS > 6 Mortality – 28 days - 1 year Dependency at 1 year (MRS >2)	Adjusted OR 1.9 Adjusted OR 2.4 Adjusted HR 2.4 Unadjusted OR 1.6	CI (1.2-3.1) CI (1.3-4.5) CI (1.6-3.6) NS
Dulli et al (2003)[55]	US	Retrospective analysis of consecutive stroke patients admitted to hospital	216 vs 845	Bedridden state (MRS = 5) at discharge	41.2% vs 23.7%	<0.0005
Steger et al (2005)[30]	Austria	Prospective multi-centre hospital based registry of consecutive stroke patients	304 vs 688	Stroke severity – NIHSS > 21- admission MRS >4	13% vs 6% 52% vs 31%	<0.004 <0.004
Kimura et al (2005)[31]	Japan	Prospective multi-centre hospital based registry of consecutive stroke patients	3335 vs 12496	Stroke severity – NIHSS > 23 -NIHSS < 6 Length of hospital stay (days) Mortality at 28 days	19.7% vs 4.5% 31.3% vs 64.4% 40.5 vs 34 11.3% vs 3.4%	<0.0001 <0.0001 <0.0001 <0.0001

Study	Country	Methods/Population	Sample size (AF vs non-AF)	Outcome Measures	Results (AF vs non-AF)	Sig (P, CI)
Ghatnekar & Glader (2008)[56]	Sweden	Prospective multi-centre hospital based registry of consecutive stroke patients	1619 vs 4992	Length of hospital stay (days) Mortality – 28 days - 3 years	22.4 vs 20.9 13% vs 7% 43% vs 25%	<0.01 <0.01 <0.01
Thygesen et al (2009)[32]	Denmark	Prospective multi-centre hospital based registry of consecutive stroke patients	741 vs 3108	Stroke severity – SSS < 30 Length of hospital stay (days) Mortality – 30 days - 1 year	28.3% vs 13% 15 vs 9 14.7% vs 5.8% 31.7% vs 13.7%	- - <0.05 <0.05
Hannon et al (2010) & (2014)[38,39]	Northern Ireland	Population based prospective cohort study of all stroke patients	177 vs 391	Stroke severity – NIHSS at 72 hrs - MRS at 72 hrs Mortality – 28 days - 3 months	7 vs 5 3.8 vs 3.0 15% vs 12.2% 23.1% vs 16.4%	0.005 <0.001 NS NS
Tu et al (2011)[57]	World-wide multi-centre	Analysis of all placebo controlled arms of 6 RCT's from the VISTA collaborators database	819 vs 2046	Stroke severity – NIHSS Mortality at 3 months Dependency at 3 months (MRS)	15 vs 12 25.2% vs 13.6% 4 vs 3	<0.001 <0.001 <0.001
Saposnik et al (2013)[58]	Canada	Prospective multi-centre hospital based registry of consecutive stroke patients	2185 vs 10501	Mortality – 30 day - 1 year Death or disability (MRS >2) at discharge	22.3% vs 10.2% 37.1% vs 19.5% 69.7% vs 54.7%	<0.0001 <0.0001 <0.0001
Mcgrath et al (2013)[59]	Canada	Prospective multi-centre hospital based registry of consecutive stroke patients	Total 10528	Mortality – 30 day - 1 year Dependency at discharge (MRS 4-5)	Adjusted OR 1.36 Adjusted OR 1.25 Adjusted OR 1.19	CI (1.2-1.6) CI (1.1-1.4) CI (1 – 1.4)
Andrew et al (2013)[60]	Australia	Prospective multi-centre hospital based registry of consecutive stroke patients	2049 vs 3424	Mortality at 1 year	Adjusted OR 1.46	CI (1.1-2.0)
Ali et al (2015)[33]	UK	Prospective observational hospital cohort study consecutive stroke patients	78 vs 135	Stroke severity – NIHSS: - Mild-Mod (0-15) - Severe (>16) - Oxford: LACS TACS Inpatient mortality Length of hospital stay (days) Discharged to own home	11 vs 7 68.1% vs 88.1% 31.9% vs 12.2% 12.6% vs 40.4% 31% vs 18.8% 19.2% vs 4.9% 16 vs 7 38.4% vs 71.5%	<0.001 <0.001 <0.001 <0.001 <0.001 0.001 <0.001 <0.001

SE – systemic embolism; RR – relative risk; OR – odds ratio; HR – hazard ratio; CI – confidence interval, NS – non-significant; BI – Barthel Index; SSS – Scandanavian Stroke Scale; MRS – Modified Rankin Score, TACI – total anterior circulation infarct; LACI – lacunar infarct; GCS – Glasgow coma scale; NIHSS – national institute of health stroke scale

and National Institute of Health Stroke Scale (NIHSS) are widely used and validated measures of stroke severity. Four studies reported patients with AF to be 3-4 times more likely to suffer strokes categorised as severe according to these scales as compared to patients in SR.[30-34] The Oxford classification divides strokes into 4 groups depending on the combination of neurological impairments. This classification has a strong correlation with prognosis, with total anterior circulation syndrome (TACI) exhibiting the worst prognosis (1year mortality ~ 60% and dependency ~ 35%), and lacunar syndromes (LACI) exhibiting the best (1 year mortality ~ 10% and dependency ~5%).[34] Analysis of patients from the European biomed study,[26] and patients randomised in the first international stroke trial (IST1)[35] both showed that 30-40% of patients with AF suffered TACI strokes compared to between 20% and 25% of patients in SR, while the proportion of LACI strokes was significantly smaller for patients with AF (13-16% AF vs 26-29% SR). AF stroke is associated with lower levels of consciousness[35,36] and greater initial functional impairments as assessed by Modified Rankin scores (MRS) and Barthel indices (BI).[25, 27, 37-39]

A number of mechanisms have been postulated to explain these differences in stroke severity. Firstly, cardioembolic strokes secondary to AF typically result from embolisation of fibrin rich (red) clots from the left atrium, 90% of which come from the left atrial appendage.[40] These are typically larger than the platelet rich (white) clots associated with atheromatous disease and are more likely to occlude a larger vessel calibre resulting in more severe stroke.[35] A post-hoc analysis of patients undergoing magnetic resonance (MR) diffusion and perfusion imaging prior the thrombolysis in a phase 2 RCT, the EPITHET trial, showed that patients with AF typically had greater volumes of infarction (52mL vs 16mL, $p < 0.05$), higher rates of haemorrhagic transformation (63% vs 38%, $p < 0.01$) and greater volumes of brain undergoing severe post infarct hypoperfusion, than in patients in sinus rhythm.[42] This later finding of post infarct hypoperfusion suggests that a second mechanism for greater stroke severity may come from the fact that while atheromatous disease develops gradually, allowing greater brain collaterals to develop, this is unlikely to occur in AF strokes due to the abrupt nature of vessel occlusion. Indeed, the quality of collateral circulation at the time of stroke has itself been shown to predict patient outcome particularly when the extent of penumbral schema is high.[43] A further factor potentially contributing to the state of severe hypoperfusion in AF related stroke is a reduced cardiac output. We typically attribute 15-20% of cardiac output to atrial contraction,[44] which is lost in chronic AF, and results in reduced regional cerebral blood flow even before a stroke occurs.[45]

Disability and Mortality

A greater index stroke severity is likely to result in greater disability, and indeed 8 of the 9 studies reporting on functional outcomes revealed a significantly greater dependency, as measured by MRS or BI, at 3, 6 and 12 months following AF stroke.[26, 37, 52-55, 57-59] Lin and colleagues[37] performed a very comprehensive comparative analysis of function following stroke showing AF stroke to be associated with at least double the proportion of patients classed as severely dependent compared to non-AF stroke at 3, 6 and 12 months following stroke, but that this difference declined with time and was not statistically significant at 12 months. This may be related to a higher early mortality of severely impaired AF stroke patients that excluded these patients from longer term follow up.

Twenty-one studies reported on differences in mortality, from 1 month up to 5 years, and all but 2[38, 46] suggested significantly higher mortality rates in patients with AF compared to those without. The analysis by Wolf and colleagues[46] included patients suffering transient ischaemic attacks (TIA's) representing 10% of the cohort, which may have contributed to why no difference was seen. Pooling

Table 2: Pooled analysis of mortality rates following stroke in patients with and without AF

	AF	Non-AF
30 day mortality rate (%)*	16.3	7.5
1 year mortality rate (%)**	37.4	19.5

* Candelise et al,[47] Gustaffson & Britton,[48] Broderick et al,[49] Sandercock et al,[50] Lin et al,[37] Lamassa et al,[26] Kimura et al,[31] Ghatnekar et al,[56] Thygesen et al,[32] Hannon et al,[38] Saposnik et al.[58]

** Broderick et al,[49] Lin et al,[37] Thygesen et al,[32] Saposnik et al.[58]

the data from 11 of the studies that prospectively or retrospectively reported absolute figures for 1 month mortality, and 4 studies reporting the same for 1 year mortality, reveals that overall, stroke associated with AF is twice as likely to be fatal compared to non-AF stroke (table 2). Although the majority of difference seen in disability and mortality between AF and non-AF stroke can be attributed to stroke severity and age, it is interesting to note that some of the more recent published analyses,[32, 58, 59] report an increased death and disability in patients with AF stroke even when age and stroke severity were adjusted for in multivariate models. This may be related to an increase in cardiac complications following stroke. In fact, Tu et al[57] investigated the rate of serious cardiac adverse events (SCAE's) following stroke in nearly 3000 patients from 6 RCT registries and found an independent association with AF stroke patients, which included acute coronary syndromes, pulmonary oedema, ventricular tachycardia/fibrillation and cardiac arrest.

Length of Stay and Discharge Destination

An increased stroke severity and inpatient dependency associated with AF stroke is reflected in longer lengths of hospital stay, and was reflected in all 6 studies that reported this outcome comparison.[25, 26, 31, 32, 33, 56] The overall average lengths of hospital stay (LOHS) vary dramatically between studies (9 days to 51 days), and are likely to reflect differences in the models of care provided for stroke in different cities and countries. The studies by Jørgensen et al,[25] Lamassa et al,[26] and Ali et al[33] also highlight that patients suffering AF related stroke are significantly more likely to require institutional care on discharge. Both hospital stay and institutional care are likely to incur significant direct healthcare and societal costs.

Longer-Term Prognosis

The effect of atrial fibrillation as an independent predictor of longer-term mortality has been studied. Long term follow up of patients evaluated in the Copenhagen stroke study revealed atrial fibrillation to be an independent predictor of survival at 5 years but not 10 years.[61] A similar study from Norway failed to show that atrial fibrillation was associated with overall mortality at 12 years following stroke,[62] suggesting this lack of association may be explained by the high early attrition rate in patients with AF.

The risk of stroke recurrence also appears to be higher in patients with AF. The Framingham analyses by Wolf et al[46] and Lin et al[37] both show higher rates of stroke recurrence at 6 and 12 months, while a retrospective evaluation of a Spanish stroke cohort of 915 patients (22% AF) suggested this association persists for up to 5 years.[63] Reassuringly however, they also showed that stroke recurrence rates in patients with AF could be reduced to non-AF rates by the use of anticoagulation.

Effect of AF on The Cost of Stroke

We found 9 studies that directly compared the costs of stroke among patients with AF or cardioembolism (CE) and those without. These are highlighted in table 3. Studies distinguishing cardioembolic stroke have been included as AF tends to account for 75-80% of these.[38, 64] Studies vary in their methodology, perspective, duration, and cost inclusions. Cost studies can be generated in two ways. 'Top down' analyses utilise epidemiological data and diagnoses related cost to produce data that are usually generalisable across a broad group of individuals e.g. national, but may compromise on accuracy. 'Bottom up' studies, often undertaken prospectively, apply a unit cost to all aspects of care associated with a diagnosis, that cumulatively produce a more accurate account of true costs, but are less generalisable across differing health and social economies. Both can provide useful insights into cost differences for patients with AF.

Acute Costs

Acute care costs were reported by 6 studies, all of which reported significantly higher costs among patients with AF/CE than without.[33, 38, 64-67] Although overall costs vary significantly between differing countries and according to study methodology, strokes related to AF/CE are associated with a 25-37% increase in inpatient costs compared to stroke patients without AF/CE. Although the study by Diringer et al[65] did not report actual cost differences, they did show that AF was an independent predictor of inpatient cost along with length of stay, NIHSS, heparin use, male sex and history of ischaemic heart disease (IHD). Studies that included post-acute rehabilitation phases[33, 64] also revealed cost increases of 50-60% compared to non-AF patients. In a UK analyses, Ali et al[33] estimated that the adjusted independent effect of having AF on costs was an additional £2,173 (95% confidence interval 91-4,254), which represented nearly 40% of the costs for non-AF stroke. Wang et al[67] also reported the presence of AF to independently add 26% to the acute costs of stroke in a US 'top down' study, however they excluded patients over the age of 65 years, and thus are likely to underestimate the cost differences between these groups as AF related stroke is likely to be more prevalent among this older excluded cohort.

Longer Term Costs

Four of the studies analysed cost data for periods of up to 3 years, and also report higher costs among patients with AF/CE. Luengo-Fernandez et al[68] performed a population-based prospective study to analyse predictors of 1-year direct stroke costs in the UK. They followed 346 patients suffering ischaemic or haemorrhagic stroke, as well as subarachnoid haemorrhage, through the Oxford Vascular Study between 2002 and 2004, and showed 1 year costs to be significantly higher among patients with AF (£9,667 vs £5,824, p=<0.001). While univariate analysis did indicate AF to be a predictor of 1-year costs, the significance of this association disappeared when adjustments were made for stroke severity (NIHSS), which accounted for approximately 50% of cost variance. The Berlin Acute Stroke Study[69] was one of the first cost comparative studies to include both direct and indirect costs. They reported higher total 1 year costs among patients with AF compared to those without (€ 14,924 vs € 13,330, p=<0.01), driven by differences in direct costs. Indirect costs were greater among non-AF patients as they were younger and more likely to be in paid employment at the time of stroke. They did not however include the indirect costs of loss of productivity from informal care arrangements which may have influenced this finding. The only study comparing costs up to 3 years post stroke utilises national registry data from Sweden.[56] Atrial fibrillation was present in 24.5% of the 6,611 patients studied and was associated with higher 1 year (€ 9,012 vs € 8,447, p= <0.001) and total discounted 3-year costs (€ 10,192 vs € 9,374, p= <0.001), but cost differences in years 2 and 3 were not

Table 3: Summary of studies comparing costs of stroke in patients with and without AF and cardioembolic (CE) stroke. Both 'bottom up' and 'top down' studies included.

Study	Country (year)	Mean age (yrs)	Design	Diagnosis		N	% AF	Time period	Cost inclusion	Costs of IS (£)		Comments
				AF/ CE	Stroke					AF/CE	SR	
AF vs SR												
Diringer et al (1999)[65]	USA 1996 Tertiary centre	70 yrs	Prospective hospital cohort	ECG	Assessment and imaging	191	7.3%	IP stay	IP direct costs excluding physician fees	-	-	AF independently associated with IP cost. High use of ICU (16%) but low proportion of patients with AF. Average IP cost of stroke £3,871 ($4408)
Luengo-Fernandez et al (2006)[68]	UK 2002	75 yrs	Population based prospective cohort	ECG	Assessment and imaging	346	21 %	1 year	Direct health and social costs	£9667	£5824	Association of AF with 1 year costs lost significance in multivariate analysis.
Bruggenjurgen et al (2007)[69]	Germany 2001 Tertiary centre	74 yrs	Prospective cohort	ECG	Assessment and imaging	367	19.3%	1 year	Direct indirect Total	€11,979 €3125 €14,924	€88117 €4513 €13330	AF independent predictor of acute care costs. Indirect costs for patients with SR> AF. Excluded patients that died (7.5%)
Ghatnekar & Glader (2008)[56]	Sweden 2001	74 yrs	Retrospective evaluation of national registry data - top down	ECG	ICD – 10 codes 161/163/164	6611	24.5%	1 year	DRG related direct health costs	€ 9012	€ 8447	Direct costs for first year significantly higher for AF patients but not for second or third year. At 3 years, still significant difference overall.
								3 year	As above	€10,192	€ 9374	
Hannon et al (2014)[39]	Ireland 2006	71 yrs	Prospective population cohort	ECG, Clinical records	Assessment and imaging	568	31%	IP stay	Direct costs 'bottom up'	$15,025	$11,196	Cost differences were statistically significant (p<0.005). Proportion of patients in work significantly lower among patients with AF prior to index stroke. Indirect costs included.
								2 yrs	Direct and indirect costs 'bottom up'	$36,865	$18,691	
Ali et al (2015)[33]	UK 2012	75 yrs	Prospective hospital cohort	ECG, clinical record, exam	Assessment and imaging	213	37.3%	IP and OP care costs	Direct costs 'bottom up'	£9,083	£5,729	Significant differences in direct costs (p=<0.001). Adjusted independent effect of AF was an additional £2,173.
Wang et al (2015)[67]	US 2010-12	54 yrs	Retrospective evaluation of national commercial claims data	DRG code	DRG code of follow up events	33,500	7.2	IP stay – first stroke	Direct costs 'top down'	$23,770	$18,779	Cost differences statistically significant (p=<0.002). Excluded patients aged > 65 yrs, therefore likely underestimate of costs differences. Adjusted independent effect of AF was an additional $4,905 for first time stroke & $3,315 for repeat stroke.
								IP stay – repeat strokes	Direct costs 'top down'	$24,199	$20,929	
CE vs Non-CE												
Yoneda et al (2003)[66]	Japan 2000 Tertiary centre	70 yrs	Prospective hospital cohort	ECG, records, clinical exam	Assessment and imaging	179	33% (27% AF)	IP stay	IP direct costs excluding meals	$8356	$6163	Significant differences cost of CE stroke vs non-CE stroke. High rates of ICU use (55%), low mortality (3%), younger population.
Winter et al (2008)[64]	Germany 1999 Tertiary centre	68 yrs	Prospective hospital cohort	ECG, records, clinical exam	Assessment and imaging	379	26.7% (20% AF)	IP stay	IP direct costs – only PT & SALT	€ 4890	€ 3550	Duration of post acute care not documented. Cost differences statistically significant.
								Post acute period	IP rehab facility or therapy clinic	€16,480	€10,500	

CE – cardioembolic; ECG – electrocardiogram; IS – ischaemic stroke; IP – inpatient; PT – physiotherapy; SALT – speech and language therapy; ICD – international classification of diseases; ICU – intensive care unit; DRG – diagnosis related group; > - more than

significantly different to those without AF. Costs however only included recurrent inpatient admissions and excluded outpatient visits, rehabilitation, social care costs and indirect costs, which may explain the apparent small differences seen. Despite this, AF remained an independent predictor of 3-year costs after adjustment for age, sex, co-morbid disease, stroke recurrence, mortality, institutionalisation and healthcare region. More recently, Hannon et al[39] undertook a well conducted, prospective, population based, 'bottom up' comparison of direct and indirect costs after stroke among patients with and without AF in Ireland. Costs among patients with AF were double those of non-AF patients ($ 36,865 vs $ 18,691, p= <0.001) despite fewer patients in paid employment at the time of stroke in the AF group.

Economic Implications of AF-Stroke

The evidence to date thus suggests that strokes due to AF are significantly more costly than non-AF stroke. This is important for a number of reasons. First, as our population ages, the proportion of stroke due to AF will undoubtedly increase, and without significant improvements in the use of anticoagulation, overall costs of stroke to health and social economies are likely to rise. Studies already inform us that AF-strokes account for 40-50% of an economy's total stroke costs, despite making up only a third of these patients.[33,39] Second, this increase in AF burden may be accelerated by the increasing use of prolonged cardiac monitoring techniques, particularly among patients with cryptogenic stroke. Studies have suggested that the use of 30-day cardiac monitors post cryptogenic stroke can uncover a diagnosis of AF in over 10% of patients;[70] this compares to less than 2% using only 24 hours of monitoring.[71] Third, if we are to undertake cost effectiveness analyses for interventions aimed at preventing AF-stroke, then cost of stroke data should be AF specific. Such economic analyses compare changes in health state as a result of an intervention with the associated change in the total cost to the economy. Taking anticoagulants for example, using general cost of stroke data may underestimate their cost effectiveness, as anticoagulants aim to prevent AF-stroke, a more costly health outcome to the economy, than non-AF-stroke. In a recent systematic review of 18 cost effectiveness studies of the novel oral anticoagulants for stroke prevention in AF, only 2 utilised stroke cost data that were AF specific.[72] Further, the distribution of stroke severities among patients anticoagulated for AF that are used in these economic analyses are generally derived from randomised control trial (RCT) data. A unit cost is then applied to these stroke severities e.g. mild, moderate, severe or fatal. This may not translate into what is seen in clinical practice due to the selection bias among RCT participants (younger and fitter), and due to the fact that anticoagulation control among warfarin users is often better among trial participants. For patients who suffer strokes while on warfarin, early and late outcomes are improved if INR is therapeutic on admission.[73] It is not surprising thus to find that stroke severity distributions among patients with AF from epidemiological data reveal greater proportions of severe and fatal strokes than reported in RCT data (45% vs 7-34%).[74] Thus, unless analysts use real-life data on stroke severity distribution among patients with AF, they further risk underestimating cost effectiveness of preventative strategies. Such analyses are now available, from UK cohorts at least.[39, 75] These are timely developments given the introduction of even newer oral anticoagulants to healthcare markets (e.g. Edoxaban), as well and the emergence of novel convenient patch cardiac monitors (e.g. Zio patch monitor©), and endovascular approaches to stroke prevention (e.g. Watchman©). Cost effectiveness analyses of all of these interventions will enable policy decision makers to make informed decisions regarding their provision and use.

Conclusion

AF is a growing problem across both developed and developing countries. Patients with AF are likely to suffer strokes that are more severe than patients without AF, and are twice as likely to be dead at 30 days and at 1 year. Stroke sufferers are more disabled and more costly to their health and social care economies as a consequence of their AF. Unfortunately, economic studies often underestimate the cost effectiveness of interventions such as anticoagulants to prevent stroke among these patients as they do not take into account the excess costs of AF related stroke. Despite the clinical evidence to support anticoagulation in patients with AF, anticoagulation use in this population remains sub-optimal, and suggests an ongoing need to educated clinical decision makers. Adjustment of future economic analyses of interventions to prevent AF-stroke to improve accuracy of cost effectiveness, may help improve the availability of such interventions, and ultimately help reduce the disease burden.

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