PharmacoEconomics (2015) 33:511–520
DOI 10.1007/s40273-015-0263-1

ORIGINAL RESEARCH ARTICLE

# Cost of Acute Stroke Care for Patients with Atrial Fibrillation Compared with Those in Sinus Rhythm

**Ali N. Ali · Joanne Howe · Ahmed Abdel-Hafiz**

Published online: 19 February 2015


**Abstract**

*Background* Atrial fibrillation (AF) is a major risk factor for stroke. Cost-effectiveness studies of anticoagulants for stroke prevention in AF rarely utilise AF-stroke-specific cost data in their analyses, as data are limited. Data that exist do not account for AF found on prolonged cardiac monitoring after stroke, further underestimating the clinical and economic burden of AF-stroke.

*Objective* Our objective was to investigate differences in direct medical costs of acute stroke care among patients with and without AF.

*Methods* Data were prospectively collected from 213 consecutive patients with confirmed stroke (196 ischaemic [IS], 17 intracranial haemorrhage [ICH]), admitted to a UK district general hospital between November 2011 and October 2012. Sociodemographic, clinical and cardiac monitoring characteristics were recorded, and resource use was calculated using a 'bottom-up' approach. Univariate and multivariate stepwise regressions were performed to identify predictors of direct cost.

*Results* Among patients with IS, 73 had AF (37 %). These patients were older, experienced greater stroke severity, lengths of hospitalisation, inpatient mortality and discharge to institutionalised care than those without AF. Mean acute care costs for the year 2012 were £6,978 (standard deviation [SD] 6,769, range 510–36,952). Mean (SD) costs were significantly higher for patients with AF than for those without (£9,083 [7,381] vs. £5,729 [6,071], $p = <0.001$). AF independently predicted acute care cost along with history of heart failure and stroke severity. The adjusted independent effect of having AF on costs was an additional £2,173 (95 % confidence interval 91–4,254; $p = 0.041$). Costs for patients with an ICH did not differ according to cardiac rhythm.

*Conclusion* Direct medical costs of acute stroke care for patients with AF may be 50 % greater than for patients without. Economic studies should take this into account to ensure the benefits of anticoagulants are not underestimated.

**Key Points for Decision Makers**

The burden of atrial fibrillation (AF)-related stroke is likely to increase with aging populations and increased use of cardiac monitoring methods after stroke.

AF-related stroke is likely to be more costly to health economies than non-AF-related stroke, but prior estimates have not included AF diagnoses found after prolonged cardiac monitoring methods have been undertaken.

This study shows that direct medical acute care costs of stroke among patients with AF can be more than 50 % higher than those for patients in sinus rhythm.

The proportion of patients hospitalised with stroke found to have AF after cardiac monitoring can be as high as one-third.

Economic analyses should take these considerations into account or use AF-specific cost data to avoid underestimating the cost effectiveness of anticoagulants.

**Electronic supplementary material** The online version of this article (doi:10.1007/s40273-015-0263-1) contains supplementary material, which is available to authorized users.

A. N. Ali (✉)
Stroke Unit, Royal Hallamshire Hospital, Sheffield Teaching Hospitals, Glossop Road, Sheffield S10 2JF, UK
e-mail: ali-ali@doctors.org.uk

J. Howe · A. Abdel-Hafiz
Rotherham General Hospital, Moorgate Road, Rotherham S60 2UD, UK

## 1 Introduction

Stroke is the leading cause of adult disability in the UK [1] and costs an estimated £7 billion annually to the healthcare system [2]. Approximately 25 % of strokes are thought to be cardioembolic, with atrial fibrillation (AF) implicated in the large majority of these [3, 4]. Anticoagulation with warfarin or the novel oral anticoagulants (NOACs) has been shown to reduce the risk of stroke in patients with AF by at least two-thirds [5, 6]. A large number of economic analyses have recently been published assessing the cost effectiveness of NOACs, given their greater market cost; however, the vast majority of these studies do not use AF-specific cost data [7–14]. Even the UK National Institute of Health and Care Excellence (NICE) technology appraisals of the NOACs utilise stroke costs based on payment by results tariff, and prior systematic reviews that do not separate the costs of stroke according to AF status [15, 16]. Cardioembolic strokes secondary to AF cause greater neurological disability [17, 18] and longer inpatient stays [19], and may carry greater economic consequences than non-AF stroke. Without taking this into account, current economic analyses risk underestimating the cost benefits of anticoagulants. Previous studies that compared the cost of stroke among patients in AF and sinus rhythm (SR) stratified cardiac rhythm based on a history of AF or on the admission electrocardiogram (ECG) alone [20, 21]. These methods are likely to miss a large number of patients who are found to have AF on subsequent prolonged cardiac monitoring and thus may lead to further underestimation of the overall economic impact of AF stroke.

The primary aim of this study was to investigate predictors of direct acute care costs among patients admitted to hospital with acute stroke, stratifying costs according to the presence of AF present on admission or found after prolonged cardiac monitoring. Secondary aims were to establish the burden of AF amongst this population after such cardiac monitoring, and to investigate clinical differences between patients in AF and SR.

## 2 Methods

### 2.1 Study Population

The study enrolled all patients admitted with an acute stroke to Rotherham General Hospital, over a period of 1 year (November 2011–2012). The hospital is a UK district general hospital serving a population of approximately 200,000, whose stroke service includes a 28-bed acute stroke unit and incorporates offsite rehabilitation and an early supported discharge (ESD) team. Case ascertainment was active and included all patients admitted to the stroke unit or peripheral wards with a diagnosis of acute stroke, or those seen and managed via outpatient clinics. All cases were reviewed by a stroke physician and were included in the final analysis if there was evidence of new stroke, determined clinically or radiologically. Patients with transient ischaemic attacks, subdural haematomas, subarachnoid haemorrhage, or stroke mimics were excluded ($n = 24$). The final analysis included 213 patients: 196 with ischaemic stroke (IS) and 17 with intracranial haemorrhage (ICH).

A study clinician reviewed patients within 72 h of diagnosis, recording demographic data including age, sex, marital status, ethnicity, smoking and alcohol history, pre-admission Modified Rankin Score (MRS), medication use and medical history. Record was made of baseline stroke severity using the National Institute of Health Stroke Scale (NIHSS), stroke syndrome according to the Oxford classification and degree of carotid disease. Patients were identified as having AF or flutter if there was documentation of AF in the case notes or general practitioner (GP) summaries within the last 1 year, if AF was present on the admission ECG, or if AF was picked up on prolonged cardiac monitoring during the subsequent 3 months after stroke.

### 2.2 Resource Use and Cost

Data on resource use were collected prospectively using a 'bottom-up' approach. This was achieved by accurate documentation of all aspects of patient activity by healthcare staff (e.g. dressings used, catheters sited, treatments or therapy given) and review of electronic logs of all investigations and procedures undertaken. Each activity was assigned a unit and each unit was given a cost and counted from the point of contact with health services (e.g. GP or ambulance call) to the point of discharge from the stroke services. This included costs of therapists up until discharge from the community ESD team. The summation of the total unit costs provides a detailed 'bottom-up' account of the total acute care costs for each patient.

Unit costs for all patient activity are shown in Table 1. The majority of unit costs were derived from National Health Service (NHS) reference costs for the year 2011–2012 [22]. Unit costs for GP consultations were derived from Curtis and Netten [23]. Bed day costs for the intensive care unit, stroke unit, general medical wards, and offsite rehabilitation were derived from NHS reference costs and included the costs of medical and nursing staff, hotel services, management and administration services and corporate overheads. They excluded costs of therapists, ward consumables, drugs, blood products, diagnostics and interventional treatments. Drug treatments were referenced

**Table 1** Health service unit costs

| Resource unit | Cost (£ sterling 2011/2012) | References |
|---|---|---|
| Hospital admission | | |
| Emergency ambulance | 230 | NHS ref costs [22] |
| GP visit | 36 | Curtis and Netten [23] |
| Emergency department attendance | 114 | NHS ref costs [22] |
| Investigations | | NHS ref costs [22] |
| Pathology | | |
| Haematology | 3 | |
| Biochemistry | 1 | |
| Immunology | 8 | |
| Microbiology/virology | 8 | |
| Histopathology | 31 | |
| Radiology | | |
| CT head | 84 | |
| MRI head | 150 | |
| MR angiogram | 163 | |
| CT 2 areas | 102 | |
| CT 3 areas | 141 | |
| X-ray one area | 26 | |
| Carotid ultrasound | 64 | |
| Abdominal ultrasound | 64 | |
| Cardiology | | |
| ECG | 36 | |
| ECHO | 62 | |
| 24- and 48-h holter monitor | 112 | |
| Transoesophageal ECHO | 281 | |
| Endoscopy | | |
| Upper GI endoscopy | 436 | |
| Lower GI endoscopy | 572 | |
| Insertion gastrostomy tube | 810 | |
| ERCP | 998 | |
| Carotid procedures | | NHS ref costs [22] |
| Carotid stent insertion | 2,350 | |
| Carotid endarterectomy | 3,923 | |
| Drug treatments, dressings and NG or PEG feed | [a] | BNF [24] |
| Blood products | | |
| Unit of blood | 125 | NHS Blood and Transplant [27] |
| Unit of platelets | 280 | Qureshi et al. [26] |
| Intravenous fluids (bundled with lines) | | Rotherham General Hospital Trust private patient list tariff [25] |
| 1 L crystalloids | 6 | |
| 0.5 L crystalloids | 4 | |
| 1 L colloids | 11 | |
| 0.5 L colloids | 7 | |
| Other procedures | | Rotherham General Hospital Trust private patient list tariff [25] |
| Peripheral cannula | 2 | |
| Urinary catheter | 5 | |
| Nasogastric tube | 7 | |

**Table 1** continued

| Resource unit | Cost (£ sterling 2011/2012) | References |
|---|---|---|
| Bed days | | NHS reference costs [22] |
| Stroke unit | 363 | |
| Rehabilitation facility | 228 | |
| General medical ward | 235 | |
| Critical care ward | [b] | |
| Inpatient rehabilitation | | Curtis and Netten [23] |
| Physiotherapy | 23.25 | |
| Occupational therapy | 23.25 | |
| Speech and language therapy | 23.25 | |
| Dietician | 23 | |
| Psychology | 45 | |
| Healthcare assistant | 16.5 | |
| Inpatient specialist referrals | | NHS ref costs [22] |
| First visit | [c] | |
| Follow-up visit | [d] | |

*CT* computed tomography, *ECG* electrocardiogram, *ECHO* echocardiogram, *ERCP* endoscopic retrograde cholangiopancreatography, *GI* gastrointestinal, *GP* general practitioner, *MRI* magnetic resonance imaging, *NG* nasogastric, *NHS* National Health Service, *PEG* percutaneous endoscopic gastrotomy

[a] Generic drugs assumed where available. Average daily prices of drugs and nutrition calculated and multiplied by number of days used. Individual dressing prices calculated

[b] Critical care bed day costs dependent on number of organ support required

[c] Initial inpatient consult billed as consultant led if seen by consultant, and non-consultant led otherwise. Cost dependent on specialty involved as per NHS ref costs [22]

[d] Follow-up visit cost dependent on specialty involved as per NHS ref costs [22]

from the British National Formulary (BNF) 61 [24], while intravenous fluid therapy and other ward consumables (e.g. dressings, intravenous lines, urinary catheters, nasogastric tubes, slings, splints, etc.) were billed at local procurement rates [25]. Blood product use was estimated from UK national audit sources [26, 27]. Interactions with therapists were recorded, with unit costs calculated assuming band 5 levels, while therapy assistants were billed at rates for allied health professional support workers from Curtis and Netten [23]. Sessions involving two therapists were counted as two units.

Cost references dating before the year 2011 were standardised to 2011–2012 values using the NHS hospital and community health services inflation index [23]. Only treatments, investigations or interventions that result from the index stroke were counted in the analysis. For patients experiencing a recurrence of stroke during the study period, another cost episode was initiated as long as the recurrence occurred after discharge from the index event. Patients with stroke either repatriated to or from the unit to a centre where costs could not be retrospectively collected were excluded from the study. The perspective of the UK NHS was adopted throughout the study. Permission to undertake the study was obtained from the local research and development committee.

## 2.3 Statistical Analysis

We calculated sample size requirements based on data from a previous UK study that estimated a 50 % difference between the cost of stroke among patients with AF and those with SR [28]. With an anticipated enrolment ratio of 0.25 for SR and AF [29], one would require approximately 200 patients with IS to detect a significant difference in cost at the level of $p < 0.05$, with a power of 80 % [30]. Sociodemographic and clinical characteristics were stratified according to the presence of AF and compared using non-parametric tests due to non-normal distribution. The Mann–Whitney $U$ test was used for continuous data, and chi-squared for categorical data. Statistical significance was set at $p < 0.05$. Because financial data are often severely skewed, cost data were logarithmically transformed before undergoing stepwise multiple regressions to determine independent predictors of acute care costs [31]. To begin with, the following variables underwent univariate analysis: age, sex, marital status, history of ischaemic heart disease (IHD), congestive cardiac failure (CCF), hypertension (HTN), diabetes mellitus (DM), stroke, dementia, cardiac rhythm, smoking history, alcohol history, degree of carotid stenosis, premorbid MRS, and NIHSS. For a variable to be included in the multiple regressions, the $F$ statistic on univariate testing should be significant at the level of $p < 0.5$. The criteria for retention in the model was set at $p < 0.1$. In the final multivariate model, significance was taken at $p < 0.05$. Continuous data such as age and NIHSS were stratified into groups to detect non-linear relationships (e.g. resource use and cost probably increase with NIHSS score but may decline at very high scores as patients may be more likely to die early, incurring lower costs). In such cases, linear and quadratic regressions were calculated to identify significant relationships that may have otherwise been missed. We estimated the marginal effect of AF on cost after adjustment, using regression model coefficients and 95 % confidence intervals (CIs) calculated from 1,000 bootstrapped estimates to help adjust for the skewed nature of the cost data [32]. Results for patients with IS and ICH are reported separately, as anticoagulation for AF aims to prevent IS while it predisposes to ICH. All statistics were performed using SPSS version 22.

## 3 Results

A total of 213 patients (196 IS and 17 ICH) experienced acute stroke within the study period and were included in the final analysis. The total cumulative direct medical costs for all patients with IS and ICH admitted during this 1-year period was £1,500,530. This represents a summation of all unit costs for each patient. All patients had at least one 12-lead ECG during admission, and NIHSS scores were recorded for 95 % of study participants. All patients with a diagnosis of stroke were followed up until discharge from the stroke services (100 %).

### 3.1 Ischaemic Stroke

Of 196 patients with IS, 73 (37.3 %) had AF. Of the 73 patients with AF, 56 (77 %) were known to have AF prior to admission, while subsequent cardiac monitoring methods picked up another 17 patients (23 %). Cardiac monitoring among this cohort included repeated in-patient ECGs, 65 patients who underwent 24-h holter monitoring and 42 patients who underwent 48-h monitoring. Of the patients known to have AF prior to admission, only 8 (14 %) were anticoagulated prior to admission, while 33 (59 %) took antiplatelets, and 15 (27 %) were receiving no anti-thrombotics at all.

Baseline socio-demographic and clinical characteristics for patients with AF and SR are shown in Table 2. Co-morbid disease was generally prevalent within this cohort of IS patients: 64.8 % had HTN, 25 % IHD, 22.5 % prior stroke, and 18.9 % DM. However, no differences were observed in co-morbid disease or pre-morbid functional state between patients with AF and those with SR. Patients with AF were older, less likely to smoke, and more likely to be resident in nursing homes than patients in SR. They were more likely to experience severe stroke as assessed by the NIHSS and Oxford classification. Pre-morbid MRS and presence of AF were independent predictors of stroke severity after adjustment for age, sex, smoking and alcohol history, comorbid disease (IHD, HTN, DM, CCF, prior stroke, dementia) and degree of carotid stenosis (premorbid MRS: $R^2$ 0.123, standardised beta 0.318, $p < 0.001$; AF: $R^2$ 0.189, standardised beta 0.257, $p < 0.001$). Patients with AF experienced greater inpatient complications, had longer lengths of stay in hospital (16 vs. 7 days, $p < 0.001$), were more likely to die in hospital (19.2 vs. 4.9 %; $p = 0.001$), and were less likely to return home (38.4 vs. 71.5 %, $p < 0.001$).

### 3.2 Resource Use

The direct costs of acute stroke care stratified according to cardiac rhythm are shown in Table 3. The mean cost for an IS was £6,978 (standard deviation [SD] £6,769, range 510–36,952); however, mean (SD) cost for stroke patients with AF were higher than for patients in SR: £9,083 (7,381) vs. 5,729 (6,071); $p < 0.001$. Adding up the total costs for each patient reveals the hospital trust's annual spend on IS to be £1,357,731. Cumulative costs for patients with AF are almost equal those for patients in SR, despite representing only one-third of the cohort (£663,030 vs. 694,701). Length of hospital stay was the main cost driver, accounting for over 80 % of costs for patients, irrespective of cardiac rhythm. Univariate analysis revealed a correlation between higher acute care costs (log rhythmically transformed) and increasing age, pre-morbid MRS, history of CCF, presence of AF, degree of carotid stenosis and NIHSS (Table 4). Adjusting the analysis for stroke severity left age, history of CCF, AF and NIHSS as significant factors, while regressing cost over all predictor variables showed that only NIHSS, AF and history of CCF remained independent predictors. The relationship between stroke severity and acute care costs was not linear, as costs declined sharply with NIHSS scores above 25. This was due to higher early attrition rates for these patients with severe stroke (inpatient mortality for mild, moderate, moderately severe and severe stroke: 1.1, 3.3, 30, 83 %, respectively) resulting in shorter lengths of stay (median of 5, 15, 30 and 11.5 days, respectively). However, quadratic regression did not alter the independent predictors of cost. Table 4 also shows the estimated differences in total cost (£) associated with the independent predictors of log-cost. Presence of AF independently increased acute care costs of stroke by approximately £2,173 (95 % CI 91–4,255; $p = 0.041$). Although this is lower than the unadjusted cost differences between patients with AF and SR, it still represents 38 % of the total cost for patients with SR. The independent effect of having a history of CCF appears high, but this is based on nine patients included in

**Table 2** Socio-demographic and clinical characteristics of patients with ischaemic stroke ($n = 196$) stratified according to cardiac rhythm

| | Total ($n = 196$) | SR ($n = 123$) | AF ($n = 73$) | $p$ value[a] |
|---|---|---|---|---|
| Mean age, years (SD) | 75.3 (13.3) | 72.5 (14.3) | 80.1 (10.1) | 0.001 |
| Female (%) | 55.6 | 54.5 | 57.5 | 0.677 |
| Married (%) | 73.5 | 77.2 | 67.1 | 0.122 |
| Prior residence (%) | | | | |
| Own home | 88.3 | 92.7 | 80.9 | 0.014 |
| Sheltered accommodation | 1.0 | 0 | 2.7 | |
| IMC | 2.0 | 1.6 | 2.7 | |
| RH | 2.0 | 1.6 | 2.7 | |
| NH | 6.7 | 4.1 | 11.0 | |
| Smokers (%) | 21.0 | 28.8 | 8.3 | 0.001 |
| Alcohol excess (%)[b] | 6.3 | 8.5 | 2.8 | 0.117 |
| Comorbidity (%) | | | | |
| IHD | 25.0 | 23.6 | 27.4 | 0.551 |
| CCF | 5.6 | 4.9 | 6.8 | 0.563 |
| HTN | 64.8 | 65.9 | 63.0 | 0.688 |
| DM | 18.9 | 15.5 | 24.7 | 0.112 |
| Prior stroke | 22.5 | 20.3 | 26.0 | 0.356 |
| Dementia | 8.2 | 6.0 | 12.3 | 0.102 |
| Pre-morbid MRS | | | | |
| Mean (SD) | 1.36 (1.5) | 1.26 (1.5) | 1.52 (1.5) | 0.182 |
| Median (IQR) | 1 (2) | 1 (2) | 2 (3) | 0.399 |
| NIHSS | | | | |
| Mean (SD) | 8.1 (7.6) | 6.6 (6.9) | 10.8 (8.2) | <0.001 |
| Median (IQR) | 5 (11) | 3 (7) | 9 (15) | |
| Number not recorded ($n$) (%) | 12 | 8 | 4 | |
| Mild (0–4) | 47.3 | 57.4 | 30.4 | 0.001 |
| Moderate (5–15) | 33.2 | 30.4 | 37.7 | |
| Mod-severe (16–25) | 16.3 | 11.3 | 24.6 | |
| Severe (>25) | 3.2 | 0.9 | 7.3 | |
| Oxford classification (%) | | | | |
| LACI | 30.2 | 40.4 | 12.6 | <0.001 |
| PACI | 38.0 | 36.4 | 40.9 | |
| TACI | 18.8 | 11.6 | 31.0 | |
| POCI | 13.0 | 11.6 | 15.5 | |
| Total number of inpatient complications | | | | |
| Mean (SD) | 1.59 (2.05) | 1.04 (1.55) | 2.51 (2.5) | <0.001 |
| Median (IQR) | 1 (3) | 0 (2) | 2 (3) | |
| Median length of stay, days (IQR) | 9 (19) | 7 (15) | 16 (28) | <0.001 |
| Discharge destination (%) | | | | |
| Own home | 59.2 | 71.5 | 38.4 | <0.001 |
| Sheltered accommodation | 0.5 | 0.8 | 0 | |
| IMC | 15.3 | 12.2 | 20.6 | |
| RH | 2.6 | 1.6 | 4.1 | |
| NH | 12.3 | 8.9 | 19.2 | |
| Inpatient mortality (%) | 10.2 | 4.9 | 19.2 | 0.001 |

*AF* atrial fibrillation, *CCF* congestive cardiac failure, *DM* diabetes mellitus, *HTN* hypertension, *IHD* ischaemic heart disease, *IMC* intermediate care, *IQR* interquartile range, *LACI* lacunar infarct, *MRS* Modified Rankin Score, *NH* nursing home, *NIHSS* National Institute of Health Stroke Scale, *PACI* partial anterior circulation infarct, *POCI* posterior circulation infarct, *RH* residential home, *SD* standard deviation, *SR* sinus rhythm, *TACI* total anterior circulation infarct

[a] All variables displayed non-Normal distributions, so unadjusted comparisons between those in SR and AF used non-parametric tests (Mann–Whitney *U* for continuous data and chi squared for categorical data)

[b] Males >21 units per week; females >14 units per week

**Table 3** Mean (standard deviation) unadjusted costs, per patient, of acute stroke care for ischaemic stroke (£)

| | Total ($n$ = 196) | SR ($n$ = 123) | AF ($n$ = 73) | $p$ value* |
|---|---|---|---|---|
| Hospital admission | 308 (156) | 283 (187) | 348 (204) | 0.001 |
| Investigations and procedures | | | | |
| Radiology and cardiology | 344 (171) | 342 (157) | 347 (288) | 0.801 |
| Pathology | 66 (67) | 57 (67) | 83 (66) | <0.001 |
| Treatments | | | | |
| Feed | 6 (24) | 2 (20) | 11 (31) | 0.005 |
| Fluids | 26 (50) | 16 (38) | 42 (64) | <0.001 |
| Blood products | 2 (24) | 2 (22) | 3 (28) | 0.708 |
| Medications | 168 (287) | 144 (285) | 207 (287) | 0.001 |
| Ward consumables | 19 (121) | 6 (49) | 40 (188) | 0.025 |
| Bed days | 5,936 (6,345) | 4,806 (5,716) | 7,839 (6,915) | <0.001 |
| Therapist rehabilitation | 94 (144) | 70 (116) | 134 (175) | 0.003 |
| Specialist referrals and procedures | 22 (98) | 11 (23) | 37 (80) | 0.01 |
| Total direct inpatient costs | 6,978 (6,769) | 5,729 (6,071) | 9,083 (7,381) | <0.001 |
| Total cumulative costs to the trust | 1,357,731 | 694,701 | 663,030 | |

* Costs for all variable displayed non-normal distributions, so comparisons between those in SR and AF used non-parametric tests (Mann–Whitney *U*)

the model with CCF, and thus must be viewed with caution. The incremental independent cost effect of stroke severity can also be seen, up until patients are classified as having severe stroke, where total costs are less than for those with moderately severe stroke.

### 3.3 Intracranial Haemorrhage

Of the 17 patients with ICH, only one underwent neurosurgical intervention. Although numbers were small, in comparison with patients with IS, those with ICH tended to be functionally less dependent on admission (pre-morbid MRS 1.2 for IS vs. 0.6 for ICH, $p = 0.023$), experienced more severe strokes (median NIHSS 8.1 vs. 13.8, $p = 0.01$), and were more likely to die in hospital (10.2 vs. 35.3 %, $p = 0.002$). Mean (SD) acute care costs appeared greater than for IS but were not statistically so: £8,459 (7,021) vs. 6,967 (6,909), $p = 0.74$. Total cumulative annual costs for patients with ICH were £142,799. Of the 17 patients, five had AF (29 %). Mean (SD) costs for patients with AF did not differ significantly to those in SR: £7,058 (6,494) vs. 8,790 (7,054), $p = 0.764$. No comment could be made on the effect of anticoagulation on ICH costs as only two patients were taking anticoagulants on admission; ten patients (59 %) were receiving antiplatelets.

## 4 Discussion

In line with previous studies, our study showed that patients with AF experienced IS that were more severe, resulted in higher complication rates, longer inpatient stays, and incurred greater acute care costs as a consequence, than did patients in SR. Costs for patients with AF were £3,354 greater than those for non-AF patients, representing a 58.5 % increase in comparative cost. Multivariate analysis revealed AF to be an independent predictor of acute care costs for IS, along with NIHSS and history of CCF. The adjusted independent effect of AF on total acute care costs was £2,173; 38 % of the cost of stroke for those in SR. In another hospital-based study, Diringer et al. [33] also showed AF to be a predictor of inpatient costs along with NIHSS, female sex, presence of heart disease and heparinisation, but did not report actual cost differences stratified by cardiac rhythm. Luengo-Fernandez et al. [28] found higher 1-year NHS costs among stroke patients with AF than among those without (£9,667 vs. 5,824, $p < 0.001$) in a population-based UK study. However, AF lost significance as an independent predictor of costs after adjustment for NIHSS. Bruggenjurgen et al. [20] reported on 1-year direct and indirect costs among a hospitalised cohort of stroke patients in Germany. Patients with AF had significantly higher total direct costs (€11,799 vs. 8,817, $p < 0.001$) than did patients in SR; however, no significant differences in indirect costs were observed. The latter finding reflected a greater number of patients without AF who were gainfully employed prior to their stroke; however, costs of unpaid or informal care were not included. In both the above studies, index hospitalisation and rehabilitation costs represented between 65 % [20] and 90 % [28] of 1-year costs. Further, the proportion of patients in these studies with AF was approximately 20 %, much lower than in our cohort. Given that the ages and functional status of patients in these and our cohorts appeared similar, it is likely that our inclusion of

**Table 4** Acute care costs (£) for acute ischaemic stroke in relation to and adjusted for stroke severity and clinical characteristics

| Variable | Mean cost (SD) | Univariate analysis for log cost (*p*) | Adjusted for stroke severity (*p*) | Multivariate analysis for log cost (*p*) | Multivariate analysis of log LOS (*p*) |
|---|---|---|---|---|---|
| Age (years) | | | | | |
| <65 | 4,285 (4,600) | <0.001 | 0.01 | 0.061 | 0.065 |
| 65–75 | 7,426 (6,443) | | | | |
| >75 | 7,716 (7,265) | | | | |
| Gender | | | | | |
| Male | 6,400 (6,221) | 0.451 | 0.623 | 0.578 | 0.415 |
| Female | 7,430 (7,164) | | | | |
| Marital status | | | | | |
| Yes | 6,656 (6,549) | 0.175 | 0.814 | 0.997 | 0.932 |
| No | 7,870 (7,338) | | | | |
| Pre-morbid MRS | | | | | |
| 0 | 5,981 (6,087) | 0.004 | 0.168 | 0.269 | 0.186 |
| 1 | 6,946 (6,281) | | | | |
| 2 | 6,854 (5,354) | | | | |
| 3 | 11,061 (9,061) | | | | |
| 4 | 6,100 (4,733) | | | | |
| 5 | 6,733 (5,437) | | | | |
| History of stroke | | | | | |
| Yes | 8,201 (8,313) | 0.168 | 0.359 | 0.499 | 0.363 |
| No | 6,624 (6,240) | | | | |
| History of DM | | | | | |
| Yes | 6,563 (6,881) | 0.702 | 0.507 | 0.262 | 0.324 |
| No | 7,075 (6,761) | | | | |
| History of HTN | | | | | |
| Yes | 7,016 (6,536) | 0.650 | 0.289 | 0.336 | 0.333 |
| No | 6,908 (7,237) | | | | |
| History of CCF | | | | | |
| Yes | 12,619 (12,410) | 0.024 | 0.031 | 0.029 | 0.031 |
| No | 6,642 (6,179) | | | | |
| History of IHD | | | | | |
| Yes | 7,120 (7,320) | 0.908 | 0.472 | 0.330 | 0.297 |
| No | 6,931 (6,601) | | | | |
| History of dementia | | | | | |
| Yes | 8,384 (5,655) | 0.091 | 0.606 | 0.731 | 0.626 |
| No | 6,861 (6,854) | | | | |
| Atrial fibrillation | | | | | |
| Yes | 9,084 (7,381) | <0.001 | 0.005 | 0.005 | 0.005 |
| No | 5,729 (6,071) | | | | |
| Carotid stenosis | | | | | |
| <49 % | 4,936 (4,264) | 0.012 | 0.061 | 0.084 | 0.076 |
| 50–99 % | 5,589 (3,647) | | | | |
| Total occlusion | 13,486 (11,509) | | | | |
| Stroke severity (NIHSS) | | | | | |
| Mild (0–4) | 4,484 (5,403) | <0.001 | | <0.001 | <0.001 |
| Moderate (5–15) | 8,353 (7,020) | | | | |
| Mod-severe (16–25) | 11,621 (8,130) | | | | |
| Severe (>25) | 5,627 (2,695) | | | | |

**Table 4** continued

Independent predictors in bootstrapped (1,000) multiple regression analysis

| | Log cost per pt | | | Regression-adjusted cost (£) difference per pt | | |
|---|---|---|---|---|---|---|
| | β-coefficient | 95 % CI for β | $p$ | Difference (£) | 95 % CI for difference | $p$ |
| Atrial fibrillation | 0.371 | 0.10–0.65 | 0.009 | 2,173 | 91–4,255 | 0.041 |
| CCF | 0.633 | 0.05–1.21 | 0.029 | 6,827 | 2,410–11,243 | 0.003 |
| NIHSS-class | 0.354 | 0.20–0.51 | <0.001 | | | |
| Mild vs. moderate | | | | 3,549 | 1,230–5,867 | 0.003 |
| Moderate vs. mod-severe | | | | 4,021 | 1,398–6,644 | 0.003 |
| Mod-severe vs. severe | | | | −3,348 | −8,997–2,301 | 0.244 |

Multiple regression equations and goodness-of-fit are provided in online supplementary materials

*CCF* congestive cardiac failure, *CI* confidence interval, *DM* diabetes mellitus, *HTN* hypertension, *IHD* ischaemic heart disease, *log Tx* logarithmic transformation, *LOHS* length of hospital stay, *NIHSS* National Institute of Health Stroke Scale, *pt* patient, *SD* standard deviation, *β* beta coefficient

more detailed screening for AF accounts for the majority of this difference. However, this should reflect a more accurate picture of the economic impact of AF stroke. It is possible that previous cost comparisons may have included AF-related cardioembolic strokes in the non-AF groups without allowing for more detailed cardiac monitoring. There is increasing awareness that silent AF may account for up to 20 % of patients thought to have cryptogenic stroke [34].

Acute care costs for patients with ICH were no different if stratified according to cardiac rhythm, although numbers were small. From this cohort it seems that, to the NHS, the economic burden of disease from the complications of AF (i.e. IS) appears to be greater than that of the complications of anticoagulation (i.e. ICH).

It is important to note that our study had several limitations. First, our costs were limited to the acute care episode, and we did not include direct social care costs or indirect costs from loss of productivity to patients or caregivers. Thus, we are likely to have underestimated the financial impact of AF stroke to society as a whole. Second, our study was of a single UK district general hospital stroke service incorporating inpatient and outpatient rehabilitation and an ESD team. Thus, the results will be applicable to health systems of a similar structure, mainly in the UK. However, the predictors of acute cost may be generalisable to other healthcare organisations. Third, we did not include stroke patients who were not hospitalised. However, studies have shown annual health costs for patients treated in the community to be less than 5 % that of hospitalised patients, mostly due to low stroke severity [28]. Fourth, although efforts were made to accurately record all cost aspects of patient care, we cannot exclude the possibility that some interventions (e.g. use of ward consumables, therapy sessions) were not recorded. However, this is unlikely to have altered our results significantly, as these interventions accounted for only 12 % of total costs.

## 5 Conclusion

The annual acute care cost of stroke was over £1.5 million in this single-centre study (£1,357,731 for IS and £142,799 for ICH). Half of the cost for IS occurred in patients with AF. Because anticoagulation can reduce stroke risk in patients with AF by approximately two-thirds, it has the potential to impart great clinical and financial savings. We have shown that acute care costs for AF stroke are at least 50 % greater than those for stroke in patients with SR, with an estimated independent effect of AF increasing stroke costs by nearly 40 %. Further evidence suggests this effect persists in the post-acute period [19]. Economic analyses regarding anticoagulation should take these differences into account or use AF-specific cost data to ensure cost benefits are accurate. AF was found in one-third of our IS cohort. Its burden is likely to increase with the ageing UK population and increasing use of cardiac monitoring. We are in need of further work to help establish longer-term health and societal costs in this population, particularly the indirect costs of unpaid and informal care. This will further aid accurate policy decision making. Parallel to this is the continued need to educate clinical decision makers on the risks and benefits of different antithrombotics for AF, particularly given the low anticoagulation rates seen in our cohort. This should highlight the extra burden AF stroke incurs to the individual patient as well as to society as a whole.

**Acknowledgments** Neither the data nor the models or methodology within the study are proprietary. No financial support for this study was sought. Publication of the study is not contingent on any sponsor approval.

The authors acknowledge Jeanette Harris for help with data collection and Caroline Leggot from the finance department at Rotherham General Hospital. This study was completed without any funding support. No conflicts of interest existed for any of the named authors of this study.

**Author contributions** Ms Joanne Howe undertook data collection and manuscript editing. Dr Ali Ali undertook study design, assisted in data collection, performed data analysis and manuscript writing and submission. Dr Abdel-Hafiz assisted in study design, data analysis and manuscript editing and acts as guarantor for the study.

## References

1. Stroke Association. Available at: http://www.strokecenter.org/patients/about-stroke/stroke-statistics. Accessed July 2014.
2. Saka O, McGuire A, Wolfe C. Cost of stroke in the United Kingdom. Age Ageing. 2009;38(1):27–32.
3. Singer D, Albers G, Dalen J, Go A, Helperin J, Manning W. Antithrombotic therapy in atrial fibrillation: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest. 2004;126(S3):429S–56S.
4. Hannon N, Sheehan O, Kelly L, Marnane M, Merwick A, Moore A, Kyne L, Duggan J, Moroney J, McCormack P, Daly L, Fitz-Simon N, Harris D, Horgan G, Williams E, Furie K, Kelly P. Stroke associated with atrial fibrillation—incidence and early outcomes in the North Dublin population stroke study. Cerebrovasc Dis. 2010;29:43–9.
5. Hart R, Pearce L, Aguilar M. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have non-valvular atrial fibrillation. Ann Intern Med. 2007;146:857–67.
6. Ruff C, Guigliano R, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a metanalysis of randomised trials. Lancet. 2014;383:955–62.
7. Freeman J, Zhu R, Owens D, Garber A, Hutton D, Go A, Wang P, Turakhla M. Cost-effectiveness of dabigatran compared with warfarin for stroke prevention in atrial fibrillation. Ann Intern Med. 2011;154:1–11.
8. Edwards S, Hamilton V, Nherera L, Trevor N, Barton S. Rivaroxaban for the prevention of stroke and systemic embolism in people with atrial fibrillation: a single Technology Appraisal. London: BMJ-TAG; 2011.
9. Gonzalez-Juanatey J, Alvarez-Sabin J, Lobos J, Martinez-rubio A, Reverter J, Oyaguez I, Gonzalez-Rojas N, Becerra V. Cost-effectiveness of dabigatran for stroke prevention in non-valvular atrial fibrillation in Spain. Rev Esp Cardiol. 2012;65:901–10.
10. Kansal A, Sharma M, Bradley-Kennedy C, Clemens A, Monz B, Peng S, Roskell N, Sorensen S. Dabigatran versus rivaroxaban for the prevention of stroke and systematic embolism in atrial fibrillation in Canada. Comparative efficacy and cost-effectiveness. Thromb Haemost. 2012;108:672–82.
11. Kamel H, Johnston S, Easton J, Kim A. Cost-effectiveness of dabigatran compared with warfarin for stroke prevention in patients with atrial fibrillation and prior stroke or transient ischaemic attack. Stroke. 2012;43:881–3.
12. Lee S, Anglade M, Meng J, Hagstrom K, Kluger J. Cost-effectiveness of apixaban compared with aspirin for stroke prevention in atrial fibrillation among patients unsuitable for warfarin. Circ Cardiovasc Qual Outcomes. 2012;5:472–9.
13. Lee S, Anglade M, Piscane R, Kluger J, Coleman C. Cost-effectiveness of rivaroxaban compared to warfarin for stroke prevention in atrial fibrillation. Am J Cardiol. 2012;110:845–51.
14. Lee S, Mullikn R, Blazawski J, Coleman C. Cost-effectiveness of apixaban compared with warfarin for stroke prevention in atrial fibrillation. Plos One. 2012;7:e47473.
15. National Institute of Clinical Excellence. Dabigatran etixilate for the prevention of stroke and systemic embolism in atrial fibrillation. 2012. Available at: http://www.nice.org.uk/guidance/ta249/resources/guidance-dabigatran-etexilate-for-the-prevention-of-stroke-and-systemic-embolism-in-atrial-fibrillation-pdf. Accessed Nov 2014.
16. National Institute of Clinical Excellence. Rivaroxaban for the prevention of stroke and systemic embolism in atrial fibrillation. 2012. Available at: http://www.nice.org.uk/guidance/ta256/resources/guidance-rivaroxaban-for-the-prevention-of-stroke-and-systemic-embolism-in-people-with-atrial-fibrillation-pdf. Accessed Nov 2014.
17. Lin H, Wolf P, Kelly-Hayes M, Beiser A, Kase C, Benjamin E, D'Agostino R. Stroke severity in atrial fibrillation. The Framingham Study. Stroke. 1996;27:1760–4.
18. Saxena R, Lewis S, Berge E, Sandercock P, Coastal P. Risk of early death and recurrent stroke and effect of heparin in 3,169 patients with acute ischaemic stroke and atrial fibrillation in the International Stroke Trial. Stroke. 2001;32(10):2333–7.
19. Jorgensen H, Nakayama H, Reith J, Raaschou H, Olsen T. Acute stroke with atrial fibrillation. The Copenhagen Stroke Study. Stroke. 1996;27:1765–9.
20. Bruggenjurgen B, Rossnagel K, Roll S, Andersson F, Selim D, Muller-Nordhorn J, Nolte C, Jungehulsing G, Villringer A, Willisch S. The impact of atrial fibrillation on the cost of stroke: The Berlin Acute Stroke Study. Value Health. 2007;10:137–43.
21. Ghatnekar O, Glader E. The effect of atrial fibrillation on stroke—related inpatient costs in Sweden: a 3-year analysis of registry data from 2001. Value Health. 2008;11:862–8.
22. Department of Health. NHS reference costs 2011–2012. Available at: https://www.gov.uk/government/publications/nhs-reference-costs-financial-year-2011-to-2012. Accessed July 2012.
23. Curtis L, Netten A. Unit costs of health and social care. Canterbury: Personal Social Services Research Unit; 2012. Available at: http://www.pssru.ac.uk/project-pages/unit-costs/2012/. Accessed July 2012.
24. British National Formulary 61, 2011. Available at: http://www.bnf.org. Accessed Nov 2012 to Oct 2013.
25. Rotherham General Hospital Foundation Trust: private patient list tariff; 2012.
26. Qureshi H, Lowe D, Dobson P, Grant-Casey J, Parris E, Dalton D, Hickling K, Waller F, Howell C, Murphy M. National comparative audit of the use of platelet transfusions in the UK. Transfus Clin Biol. 2007;14:509–13.
27. Pamphilon D, Griffin C, Gerrard R, Neuberger J, Norfolk D, Richardson P, Rooney P, Webster R. Blood and transplant matters. Information for hospitals served by the NHS Blood and Transplant. NHS Blood and Transplant, 2011, Issue 34. Available at: http://www.blood.co.uk/pdf/publications/blood_matters_34.pdf. Accessed Oct 2012.
28. Luengo-Fernandez R, Gray A, Rothwell P. Population-based study of determinants of initial secondary care costs of acute stroke in the United Kingdom. Stroke. 2006;37:2579–87.
29. Arboix A, Alio J. Cardioembolic stroke: clinical features, specific cardiac disorders and prognosis. Curr Cardiol Rev. 2010;6:150–61.
30. Rosner B. Fundamentals of biostatistics. 7th ed. Boston: Brooks/Cole; 2011.
31. Briggs A, Gray A. The distribution of healthcare costs and their statistical analysis for economic evaluation. J Health Res Policy. 1998;3:233–45.
32. Afifi A, Kotlerman J, Ettner S, Cowan M. Methods for improving regression analysis for skewed continuous or counted responses. Annu Rev Public Health. 2007;28:95–111.
33. Diringer M, Edwards D, Mattson D, Akins P, Sheedy C, Hsu C, Dromerick A. Predictors of acute hospital costs for treatment of ischaemic stroke in an academic centre. Stroke. 1998;30:724–8.
34. Christensen L, Krieger D, Hojberg S, Pedersen O, Karlsen F, Jacobsen M, Worck R, Nielsen H, Aegidius K, Jeppesen L, Rosenbaum S, Marstrand J, Christensen H. Paroxysmal atrial fibrillation occurs in cryptogenic ischaemic stroke. Final results from the SURPRISE study. Eur J Neurol. 2014;21:884–9.