Stroke patients with atrial fibrillation have a worse prognosis than patients without: data from the Austrian Stroke registry

Christina Steger, Angelika Pratter, Monika Martinek-Bregel, Marion Avanzini, Andreas Valentin, Jörg Slany, Claudia Stöllberger*

II. Med. Department, Krankenanstalt Rudolfstiftung, Vienna, Austria

Received 19 November 2003; revised 20 June 2004; accepted 24 June 2004
Available online 20 August 2004
See page 1670 for the editorial comment on this article (doi:10.1016/j.ehj.2004.08.005)

Aims Stroke patients with atrial fibrillation (AF) have a poorer neurological outcome than stroke patients without AF. Whether stroke patients with AF also have a higher rate of medical complications is unknown. The aim of the study was to compare the in-hospital course of acute stroke patients with and without AF.

Methods and results The Austrian Stroke registry was a prospective multi-centre study involving 57 medical departments documenting the hospital course of consecutive stroke patients from June 1999 to October 2000. AF was diagnosed in 304 (31%) of 992 patients. Patients with AF were older (79 versus 75 years, \( p < 0.0004 \)) than no-AF patients. There were more cases of pneumonia (23% versus 9%, \( p < 0.0004 \)), pulmonary oedema (12% versus 6%, \( p < 0.0004 \)) and symptomatic intracerebral haemorrhage (8% versus 2%, \( p < 0.0004 \)) in AF compared to no-AF. In-hospital mortality was higher in AF (25% versus 14%, \( p < 0.0004 \)), and neurological outcome was poorer (65 versus 90 Barthel index, \( p < 0.0004 \)). On multivariable logistic regression analysis, however, AF was no predictor for mortality, but a Barthel index of zero (odds ratio 5.30, 95% CI 3.10–9.08, \( p < 0.0001 \)), a National Institutes of Health Stroke Scale >21 or comatose (odds ratio 3.13, 95% CI 2.26–4.32, \( p < 0.0001 \)), age >75 years (odds ratio 3.15, 95% CI 1.85–5.37, \( p < 0.0001 \)), heart rate >100 min\(^{-1}\) (odds ratio 2.15, 95% CI 1.26–3.66, \( p = 0.0049 \)), obstructive pulmonary disease (odds ratio 2.58, 95% CI 1.03–6.48, \( p = 0.0442 \)) and creatinine >125 \( \mu \)mol/l (odds ratio 1.84, 95% CI 1.00–3.37, \( p = 0.0479 \)).

Conclusion Stroke in AF is associated with a poor prognosis, an increased rate of medical and neurological complications and a higher in-hospital mortality than in no-AF.

© 2004 The European Society of Cardiology. Published by Elsevier Ltd. All rights reserved.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia and a major problem causing cardiac embolism and acute stroke, especially in the elderly. Stroke patients with AF have been shown to have a poorer neurological outcome than stroke...
Stroke patients with atrial fibrillation have a worse prognosis than patients without.\(^1\) Whether stroke patients with AF also have a higher rate of medical complications is largely unknown.\(^5,6\) Thus, the aim of the present study was to compare the in-hospital course including medical complications in acute stroke patients with and without AF admitted to 57 medical departments in Austria.\(^7\)

Subjects and methods

The Austrian Stroke registry was a prospective multi-centre study. Fifty-seven medical departments all over Austria participated in the trial documenting the in-hospital course of consecutive patients with acute stroke from June 1999 to October 2000. All consecutive patients with acute stroke or prolonged reversible ischaemic neurological deficit were evaluated for documentation. Excluded were patients with transient ischaemic attacks, cerebral tumour, sub- or epidural haemorrhage or other conditions imitating ischaemic stroke. Additionally, patients were excluded if they were transferred to other departments within 3 days after admission or if the onset of stroke was more than 3 days before admission.

Documentation by specific detailed data forms was assessed on admission, during hospitalisation and at discharge by physicians. Among others, the following data were recorded:

1. Baseline characteristics: Age, sex, weight, height, blood pressure, heart rate, blood glucose level, haemoglobin, cholesterol, creatinine, fibrinogen, electrocardiogram, oral anticoagulation (OAC) before stroke. AF was diagnosed by the treating physicians from the admission electrocardiogram.

2. Vascular risk factors and co-morbid conditions: Coronary artery disease, other heart disease (dilated or hypertrophic cardiomyopathy, valvular heart disease, congenital heart disease), previous stroke, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, smoking, alcohol abuse, malignancy, dementia.

3. Neurological findings: Type and localisation of the stroke, Barthel index (BI),\(^8\) Rankin Scale (RS)\(^9\) and National Institutes of Health Stroke Scale (NIHSS)\(^10\) on admission and at discharge.

4. Treatment during hospitalisation: Parenteral fluid, parenteral nutrition, enteral nutrition, antibiotics, antipyretics, insulin, antihypertensive therapy, heparin (low molecular or unfractionated), acetylsalicylic acid or antiplatelet therapy, thrombolysis, neurological therapy, transfer to an intensive care unit. The heparin dosage was not recorded.

5. Neurological complications: Cerebral oedema (as seen on cerebral computed tomography or magnetic resonance imaging), hydrocephalus, recurrent stroke (new occurrence of a neurologic deficit during hospitalisation), symptomatic intracerebral bleeding (worsening of an already existing neurologic deficit and evidence of intracerebral bleeding by cerebral computed tomography), seizures.

6. Medical complications: Pneumonia (fever, leukocytosis, infiltrate on chest X-ray), urinary tract infection (leukocytosis, positive findings on urine culture), sepsis (fever, leukocytosis, positive findings on blood culture, organ involvement), deep vein thrombosis (demonstrated by venography or ultrasound), pulmonary embolism (demonstrated by helical computed tomography), pulmonary oedema (clinical signs, pulmonary congestion on chest X-ray), extracerebral bleeding.

7. Outcome: Discharge at patients’ homes, nursing homes, rehabilitation centre or transfer to other hospital department; recommended drug therapy; cause of death in patients who had died during hospitalisation.

Statistical analyses were performed using the statistical software package SYSTAT version 10 (SPSS Inc, Chicago IL, USA). Continuous data such as age, seize or weight were expressed as median values and quartiles. Non-continuous data were expressed as percent. In univariate descriptive analysis the Kruskal–Wallis test and the Pearson \(^2\)-test were used. During univariate testing a total of 125 tests have been calculated and so the level of significance was chosen to be \(a = 0.0004\) according to the Bonferroni correction. All tests were two-sided.

Stepwise multivariable logistic regression modelling was used to assess the prognostic significance of predictor variables for mortality. In the course of exploratory analysis, the continuous variables such as age, laboratory variables and scores were plotted against the outcome, using the DWLS smoothing method which depends upon least squares. As expected, there was no linear association with outcome so a transformation was warranted. For virtually all variables a clear threshold could be identified which indicated an increased mortality. For age, this was >75 years, for mean arterial blood pressure <80 mmHg, for heart rate >100 min\(^{-1}\), for blood glucose >7 mmol/l, for haemoglobin <7.1 mmol/l, for serum cholesterol <4 mmol/l, for serum creatinine >125 \(\mu\)mol/l and for fibrinogen >11 \(\mu\)mol/l. The BI showed an increased risk for the value zero at admission versus all higher values. For the RS a value of 5 at admission had a higher risk than all lower values. The distribution of the NIHSS suggested three categories: patients with values above 21 had a moderate risk while those who were comatose had the highest risk. The coding for binary variables followed the “partial method” using “0” for the absence and “1” for the presence of the condition in question. In analogy to that, the binary variables derived from the continuous data were coded with “0” for the absence and “1” for the presence of the criteria shown above. The NIHSS was coded with “0” for values up to 21, with “1” for values above 21 and with “2” for the comatose patients. Sex was coded with “1” for male and “2” for female gender. In order to check for “influential observations” the variable centre was forced into the model and declared as a categorical variable with “dummy” coding. The following independent variables were retained for the analysis: centre, sex, age groups, intracerebral bleeding, localisation: brainstem, BI, RS, NIHSS, previous stroke, coronary artery disease, hypertension, diabetes, AF, obstructive pulmonary disease, malignancy, mean arterial pressure, heart rate, glucose, haemoglobin and creatinine. A forward stepwise selection of the variables was chosen for the multivariable logistic regression. The probability for entry of a variable was set at 0.05 and for the removal of a variable at 0.10.

Results

The Austrian Stroke registry recruited 1100 patients with acute stroke in 57 hospitals. We excluded patients who were transferred to other departments within 3 days after admission (\(n = 55\)) or in whom the onset of stroke was more than 3 days before admission (\(n = 39\)), or where data forms were incomplete (\(n = 14\)). Therefore 992 patients remained for evaluation. The electrocardiogram, recorded at admission, showed AF in 304 patients (31%) and no AF in 688 patients (69%). Among the 992 included patients, 33% were admitted to hospital departments which included >6 patients, 39% were admitted to hospital departments which included 6–20 patients and 28% were admitted to departments which included >20
patients. The median length of hospitalisation was 14 days and did not differ between patients with and without AF.

**Baseline characteristics**, **vascular risk factors and co-morbidities** are listed in Table 1. The frequency of AF in the study population increased with age in female as well as in male patients (Fig. 1). Patients with AF were older and had a slightly lower body mass index than patients without AF. Previous stroke, coronary or other heart disease were more prevalent in patients with than without AF whereas the frequency of arterial hypertension, diabetes, current smoking and further co-morbidities did not differ. The number of vascular risk factors and co-morbidities did not differ between patients with and without AF, although patients with AF had more often 3 or more risk factors (Fig. 2).

**Neurological status**: Patients with AF had more ischaemic strokes than patients without AF (Table 2). Intracerebral haemorrhage was slightly more frequent in patients without AF than with AF. Subarachnoid haemorrhage was found in only 1% of each group. There were no differences between patients with and without AF regarding the localisation – hemispheric, cerebellum or brain stem – of the stroke. Stroke severity, determined by BI, RS and NIHSS, was higher in patients with than without AF.

**Treatment during hospitalisation**: An overview of the treatment is given in Table 3. Only slight differences in the therapy between stroke patients with and without AF were found.

**Neurological and medical complications**: Although only slight differences were found in the incidence of neurological complications (Table 4), the odds ratio for any neurological complication (brain oedema, hydrocephalus, recurrent stroke, symptomatic intracerebral haemorrhage, seizures) was 1.41 for patients with AF (95% CI 1.05–1.76, \( p = 0.013 \)). Among the medical complications, pneumonia and pulmonary oedema occurred
more often in AF patients than in patients without AF. Forty-two per cent of AF patients had at least one medical complication and the odds ratio for any medical complication (infection, thrombosis, pulmonary oedema and extracerebral bleeding) was 1.61 for patients with AF (95% CI 1.35–1.86, p < 0.0004).

**Oral anticoagulation at admission:** Patients with AF who were admitted with OAC did not differ from AF patients without OAC regarding complications. The incidence of symptomatic intracranial haemorrhage did not differ between patients with or without prior OAC.

**Outcome:** At discharge, median BI in the AF group was 60 versus 85 in the group without AF (p < 0.0004). The median RS at discharge was 4 in patients with AF and 2 in patients without AF (p < 0.0004). Less patients with than without AF were discharged to their own homes (44% versus 60%, p < 0.0004).

Mortality did not differ among the hospital departments regarding the number of included patients. Mortality rates were higher in patients with AF than in patients without AF (25% versus 14%, odds ratio 2.14, 95% CI 1.53–3.01, p < 0.0004), whereas the causes of death did not differ. As shown in Table 5, the presence of AF increased mortality in addition to other clinical characteristics.

For multivariable analysis, a total of 88 patients with missing values of any of the variables chosen had to be excluded, leaving 904 patients. Mortality was 17% in this population, showing no change from the original group of 992 patients. Multivariable logistic regression analysis identified the following characteristics as significant predictors for mortality: BI of zero on admission (odds ratio 5.30, 95% CI 3.10–9.08, p < 0.0001), NIHSS >21 or comatose on admission (odds ratio 3.13, 95% CI 2.26–4.32, p < 0.0001), age >75 years (odds ratio 3.15, 95% CI...
1.85–5.37, \( p < 0.0001 \)), heart rate >100 min\(^{-1}\) (odds ratio 2.15, 95% CI 1.26–3.66, \( p = 0.0049 \)), obstructive pulmonary disease (odds ratio 2.58, 95% CI 1.03–6.48, \( p = 0.0442 \)) and creatinine >125 \( \mu \)mol/l (odds ratio 1.84, 95% CI 1.00–3.37, \( p = 0.0479 \)).

**Discussion**

This study in stroke patients admitted to medical departments in Austria shows that the frequency of AF was 31%. Stroke patients with AF were older than patients without AF. Stroke patients with AF had more cerebrovascular risk factors and more severe strokes, and their neurological outcome was worse than in patients without AF. During hospital stay AF patients developed more medical complications like pneumonia and heart failure. In-hospital mortality of stroke patients with AF was higher than of patients without AF. The presence of AF increased mortality in addition to other clinical characteristics. Multivariable analysis, however, failed to disclose AF as an independent predictor for mortality.

Many findings of the present study are in accordance with the results of the International Stroke Trial (IST) a
large, randomised, controlled trial of heparin, aspirin, both or neither in patients with acute stroke. In the IST trial a total of 3169 patients (17%) had AF. IST-AF patients were more likely to be female (56% versus 45%) to be old (78 versus 71 years) and to have a higher rate of death within 14 days (17% versus 8%) than IST patients without AF.

Contrary to the IST study, the present study also assessed the incidence of medical complications. The high incidence of medical complications in patients with AF can be explained in part by the stroke severity. An association between greater neurological deficit and occurrence of medical complications in stroke patients has been previously reported. Greater neurological deficit may account for medical complications due to impaired consciousness, immobilisation and incontinence, contributing to the development of pneumonia by aspiration, and urinary tract infections by the necessity of indwelling urinary catheters. Additionally, AF patients have a higher rate of cardiovascular co-morbidities like coronary artery disease or other heart diseases, which may render patients prone to pulmonary oedema. The occurrence of heart failure has been shown to have a particularly adverse outcome on stroke mortality. Although in the present study the frequency of heart failure was not assessed, we could show that the incidence of pulmonary oedema was more frequent in AF than in no-AF patients, and was an indicator for a poor outcome. Although medical complications are not always life-threatening, they can be serious and often lead to longer hospital stays, transfer to intensive care units, increase the necessity for medical treatment or at least impede neurological rehabilitation.

In general, increased age has been shown to be an independent risk factor that influences mortality after acute stroke. A higher age of stroke patients with AF has been postulated as a major contributing factor for the poor prognosis. Another study, however, found that stroke associated with AF was more severe than in non-AF patients and that this increased severity was independent of advanced age and other stroke risk factors.

In our study AF patients had a higher mortality than non-AF patients, but the multivariable logistic regression analysis did not confirm our initial assumption that AF was a relevant factor in the prognosis of stroke. Instead, neurological parameters such as the NIHSS and the BI and age >75 years turned out to be a risk factor. The other three predictors in the model — tachycardia, obstructive pulmonary disease and elevated creatinine — show that apart from neurological conditions, cardiovascular, pulmonary and renal co-morbidity plays an important prognostic role.

We found an AF frequency of 31% in our patients compared to 15–21% described by other authors. The Framingham study reported a frequency of 14.5% in AF patients with acute stroke or transient ischaemic attack aged 50–89 years, whereas in stroke patients 75 years the frequency of AF was 25%. Thus, discrepancies in the frequency of AF in stroke patients are most probably explained by age differences in the studied populations. In agreement with other studies, stroke patients with AF were older than stroke patients without AF. The frequency of AF according to age groups, however, was very similar in our study to the Copenhagen Stroke Study. The higher proportion of female gender among the AF patients has also been found by other studies and might be a consequence of increased age of the patients.

More cases of symptomatic intracerebral haemorrhages in AF patients than in patients without AF were observed. This may be due to the localisation and severity of stroke in AF patients or to inadequately high dosages of heparin. Previous OAC seemed not to have influenced the rate of intracerebral haemorrhage since it did not differ between AF patients with and without OAC on admission (4% with, 8% without). These findings, however, have to be considered with caution since our sample is too small to provide evidence.

The attributable risk of stroke from AF increases significantly with age. In the age group 50–59 years, the risk is 1.5%, between 60 and 69 years 2.8%, between 70 and 79 years 9.9% and between 80 and 89 years 23.5%. Because of the high risk of stroke, OAC is generally
recommended as primary prophylaxis in AF patients >75 years. Concerning the age group between 65 and 75 years, the stroke risk classification schemes and recommendations about OAC differ; it is therefore the decision of the treating physician whether to recommend OAC to patients with AF at the one or the other age limit.\textsuperscript{16–19}

The bad prognosis of AF patients with stroke which was found in our study, should alert clinicians to also consider OAC in AF patients <75 years. This is further stressed by the better outcome of patients with AF suffering a stroke despite adequate OAC as was shown recently.\textsuperscript{120}

For secondary stroke prevention in AF patients with a recent transient ischaemic attack or minor ischaemic stroke, OAC has been shown to reduce the risk of recurrent stroke from 12% to 4% per year.\textsuperscript{21} However, such a figure can only be achieved if the patients are carefully selected and if the conditions for OAC are optimised in order to minimise the risk of bleeding complications. Unfortunately, no study addresses this issue, after which time OAC should be started in AF patients after an embolic stroke. Additionally, studies about secondary stroke prevention in AF only included patients after transient ischaemic attacks or minor strokes, thus for patients with major and disabling strokes in AF no data concerning the benefit of OAC are available at present. In the present study 33% of patients with AF received OAC at discharge, 85% with AF received at least antiplatelet or OAC therapy. This is in accordance with data showing that OAC is prescribed to 15% to 44% of the patients with AF with stroke or transient ischaemic attacks.\textsuperscript{2,22–24} In the present study, unfortunately, reasons for not prescribing OAC in AF patients were not evaluated, thus it can only be speculated that the high co-morbidity and the poor neurological status might have precluded OAC.

Limitations of the study are the lack of a differentiation whether the patients suffered from paroxysmal or permanent AF. Inter-observer reliability studies regarding measurement of BI, RS and NIHSS have not been performed. The heparin dosage was not recorded. No follow-up investigations were performed. Furthermore, the exact location and side of the strokes was not documented.

From our findings we conclude that stroke in AF patients is associated with a poor prognosis, an increased rate of medical and neurological complications and a higher in-hospital mortality than in patients without AF. These findings stress the importance of primary and secondary prophylaxis of stroke or embolism as soon as AF is diagnosed.

Acknowledgement

The study was supported by the working group for cerebrovascular diseases of the Austrian Cardiologic Society.

References