

The quality of anticoagulation on functional outcome and mortality for TIA/stroke in atrial fibrillation patients

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Received 23 May 2007; received in revised form 30 August 2007; accepted 29 October 2007

Available online 3 January 2008

Abstract

Background: In atrial fibrillation (AF) patients stroke is nearly twice as likely to be fatal as non-AF patients and functional deficits are more likely to be severe among survivors. The incidence of stroke among AF patients is greatly reduced by oral anticoagulant treatment (OAT). However, fluctuation of anticoagulation levels is intrinsically related to OAT and often international normalized ratio (INR) is out of the therapeutic range.

Methods: Since the “anticoagulation history” is an ongoing process, we performed this prospective study in 578 AF patients to investigate the role of the whole quality of OAT and of INR levels at the occurrence of transient ischemic attack (TIA) or stroke on the severity of cerebral ischemia.

Results: During follow-up 13 patients had TIA and 18 had stroke (rate 1.67×100 pt/years). In relation to the quality of anticoagulant treatment, no significant differences were found in the time spent below and within the intended therapeutic range, between patients with and without TIA/stroke. Patients with TIA/stroke spent a longer time above the intended therapeutic range with respect to other patients, even if this difference was not confirmed at multivariate analysis. Forty-six percent of patients with TIA and 66% of patients with stroke had $\text{INR} \geq 2$ at the occurrence of ischemic event.

Conclusion: The severity of stroke was not related to the whole quality of anticoagulation or to INR at the event.

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Keywords: Atrial fibrillation; TIA; Stroke; Oral anticoagulant; Severity; Mortality

1. Introduction

In patients with non valvular atrial fibrillation (AF) oral anticoagulant therapy (OAT) is effective in reducing stroke and peripheral embolism by 68% [1]. Stroke occurrence in AF patients is mainly due to cardiogenic embolism, and the efficacy of OAT in the primary and secondary prevention of stroke has been established by several randomised clinical trials [2]. Prevention is particularly important because

strokes associated with AF are severely large and disabling. An epidemiological survey revealed that stroke mortality is higher and functional outcome is worst when stroke is of cardioembolic origin. [3]. In particular, among AF patients stroke was nearly twice as likely to be fatal as among non-AF patients and functional deficits were more likely to be severe among survivors [4]. The incidence of ischemic stroke among AF patients is greatly reduced by OAT and several studies outlined that the optimal intensity of anticoagulation is obtained with an INR from 2 to 3 [5–7]. Another issue investigated was the effect of warfarin treatment on the severity of stroke and on stroke-related mortality. Previously a reduction of mortality and severity of stroke in patients treated with warfarin was reported when INR, determined at

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the occurrence of the event, was 2.0 or greater [8]. However, it is known that coumarins have a narrow therapeutic window, exhibit considerable variability in dose response among subjects, the laboratory control is difficult to standardize and there are problems in dosing as a result of patients nonadherence [9]. Fluctuation of anticoagulation levels is therefore intrinsically related to OAT and, in the clinical practice, periods in which INR is out of the intended therapeutic range are not avoidable. Therefore, specific methods to determine fluctuation of INR during the entire time of exposure to OA [10] have been developed to evaluate the overall quality of this therapy. Since the “anticoagulation history” of patients is an ongoing process, we performed this prospective study to investigate the role of the whole quality of OAT and of INR related to the event on the occurrence and the severity of cerebral ischemia in AF patients.

2. Materials and methods

2.1. Patients

We prospectively investigated 578 AF patients referred for the control of OAT to the Anticoagulation Clinic of the Azienda Ospedaliero Universitaria Careggi, University of Florence. All patients were treated with warfarin. Patients' demographic and clinical data were collected. A computerized program (P.A.R.M.A System; Instrumentation Laboratory, Milan, Italy) [11] was used for the routine management of OAT. At each follow-up visit OAT was monitored by PT expressed as INR, determined by capillary blood test (Thrombotest®, Nycomed Pharma AS, Oslo Norway, commercialised in Italy by Sentinel Diagnostic, Milan). During each follow-up visit INR, dose prescription, hospital admissions, intercurrent illnesses, bleeding and thrombotic events were recorded. Patients who missed check-ups for more than 2 months were contacted (personally or through their family or general practitioner) and the reason for interrupting treatment monitoring was recorded. In the case of death, further information about its cause was requested. When this information was lacking, national register of causes of death and autopsy results (if available) were consulted.

Data were censored after the occurrence of TIA or stroke, after the cessation of OAT or when the patient stopped being monitored by our Anticoagulation Clinic.

The INRs were maintained at the intended therapeutic range of 2–3.

A software programme was used for the assessment of the quality of anticoagulation by determining the percentage time spent at different INR levels [10].

Stroke was defined as a syndrome characterized by rapidly developing clinical symptoms and/or signs of focal and at times global loss of brain function, lasting >24 h, not explained by other causes and in the absence of primary hemorrhage. Ischemic stroke was defined as a stroke with either a normal brain CT or evidence of a recent infarction in

the clinically relevant area of the brain on a CT or MR scan within three weeks of the event, while previous TIA was diagnosed when neurological defects lasted <24 h. INR was defined as temporally related to the ischemic event when it was obtained at the time of the event or during the preceding 2 days. The presence of traditional cardiovascular risk factors and characteristics associated with ischemic complications in AF was assessed on the basis of patients' interview, echocardiography and hospital records. Hypertension was defined in the presence of blood pressure above 160/90 mmHg and/or an antihypertensive treatment [12] and diabetes was defined according to American Diabetes Association criteria [13]. Coronary artery disease was defined on the basis of a history of myocardial infarction or stable and unstable angina. Impaired left ventricular function was defined as a recent diagnosis of congestive heart failure or a fractional shortening <25% by transthoracic echocardiography [12].

All patients underwent an electrocardiogram and transthoracic echocardiography at the beginning of OAT.

The Modified Rankin Disability Scale was used to measure functional outcome 90 days after stroke [14].

2.2. Statistical analysis

The SPSS statistical software package (Statistical Package for Social Sciences, Chicago USA, software for Windows; version 10.0) was used for data processing. Data are expressed as median and range due to their skewed distribution. Preliminary statistical analysis was performed using Wilcoxon's signed rank test, Kruskal Wallis test or Fisher's exact test (categorical data). The non parametric Mann–Whitney test was used for comparison between individual groups. Multiple logistic regression analysis was used to ascertain which factors (sex, hypertension, diabetes mellitus, history of TIA or stroke, smoking habitus, coronary artery disease and time spent at INR above 3) were significantly associated with risk of ischemic events during follow-up. All odds ratios (OR) are given with their 95% confidence intervals (CI) and a value of $p < 0.05$ was chosen for statistical significance.

3. Results

From June 1995 to May 2006, 578 AF patients (366 males, 212 females) referred to our Anticoagulation Clinic for the management of OAT were prospectively followed up. Characteristics of patients are listed in Table 1. The total period of observation was 1854 patients/years (pt/years) and median time of follow-up was 2.57 years (3 months–11.2 years). The median age of patients at the beginning of follow-up was 75 years (38–92). One hundred ninety-four patients (34%) started OAT after the occurrence of a cerebral ischemic event (TIA or stroke). TIA and stroke occurring during follow-up were recorded. Thirty-one patients developed cerebral ischemic events (rate 1.67×100 pt/years)

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