European Journal of Internal Medicine 26 (2015) 243–249

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original Article

Brain and kidney, victims of atrial microembolism in elderly hospitalized patients? Data from the REPOSI study

S. Corrao [a,b,*], C. Argano [a], A. Nobili [c], M. Marcucci [c,d], C.D. Djade [c,e], M. Tettamanti [c], L. Pasina [c], C. Franchi [c], A. Marengoni [f], F. Salerno [g], F. Violi [h], P.M. Mannucci [e], F. Perticone [i], on behalf of REPOSI Investigators [1]

[a] Biomedical Department of Internal Medicine and Subspecialities (DiBiMIS), University of Palermo, Piazza delle Cliniche 2, 90127 Palermo, Italy
[b] Department of Internal Medicine 2, National Relevance and High Specialization Hospital Trust, ARNAS Civico, Di Cristina Benfratelli, Palermo, Italy
[c] Department of Neuroscience, IRCCS Istituto di Ricerche Farmacologiche Mario Negri, Via Giuseppe La Masa, 19, 20156 Milan, Italy
[d] Department of Internal Medicine, IRCCS Ca' Granda Maggiore Policlinico Hospital Foundation, Milano, Italy
[e] Scientific Direction, IRCCS Ca Granda Maggiore Policlinico Hospital Foundation, Via Pace 9, 20122 Milan, Italy
[f] Department of Clinical and Experimental Science, University of Brescia, Piazzale Spedali Civili 1, 25123 Brescia, Italy
[g] Internal Medicine, IRCCS Policlinico San Donato, Department of Medical and Surgery, Sciences, University of Milano, Via Morandi 30, 20097 San Donato, Milan, Italy
[h] Department of Internal Medicine and Medical Specialties, Sapienza University of Rome, Viale del Policlinico 155, 00161 Roma, Italy
[i] Department of Medical and Surgical Sciences, University "Magna Graecia" of Catanzaro, Campus Universitario di Germaneto, Viale Europa, 88100 Catanzaro, Italy

ARTICLE INFO

Article history:
Received 26 November 2014
Received in revised form 8 February 2015
Accepted 16 February 2015
Available online 5 March 2015

Keywords:
Atrial fibrillation
Dementia
Renal insufficiency, chronic
Aged
Stroke
Anticoagulants

ABSTRACT

Background: It is well known that atrial fibrillation (AF) and chronic kidney disease (CKD) are associated with a higher risk of stroke, and new evidence links AF to cognitive impairment, independently from an overt stroke (CI). Our aim was to investigate, assuming an underlying role of atrial microembolism, the impact of CI and CKD in elderly hospitalized patients with AF.
Methods: We retrospectively analyzed the data collected on elderly patients in 66 Italian hospitals, in the frame of the REPOSI project. We analyzed the clinical characteristics of patients with AF and different degrees of CI. Multivariate logistic analysis was used to explore the relationship between variables and mortality.
Results: Among the 1384 patients enrolled, 321 had AF. Patients with AF were older, had worse CI and disability and higher rates of stroke, hypertension, heart failure, and CKD, and less than 50% were on anticoagulant therapy. Among patients with AF, those with worse CI and those with lower estimated glomerular filtration rate (eGFR) had a higher mortality risk (odds ratio 1.13, $p = 0.006$). Higher disability levels, older age, higher systolic blood pressure, and higher eGFR were related to lower probability of oral anticoagulant prescription. Lower mortality rates were found in patients on oral anticoagulant therapy.
Conclusions: Elderly hospitalized patients with AF are more likely affected by CI and CKD, two conditions that expose them to a higher mortality risk. Oral anticoagulant therapy, still underused and not optimally enforced, may afford protection from thromboembolic episodes that probably concur to the high mortality.

1. Introduction

Atrial fibrillation (AF) is the most common cardiac rhythm disorder [1]. It is expected to affect at least 5.6 million people in the US by the year 2050. The burden of cognitive impairment (CI) and dementia is also rising, as population ages and risk factors for CI increase [2].

A growing body of research links AF with a higher risk for CI and dementia [3,4]. Patients with AF are known to have a four to five-fold higher risk of stroke [5]; however, whether this is associated with CI and dementia, and if so, how, is not fully understood. A recent review found a significant association between AF and dementia after a stroke [6]. Other evidence, and in particular a systematic review of the literature, suggests that AF may favor cognitive decline before and independently from an overt stroke [7,8]. Patients with persistent AF have been found to have smaller total brain and gray matter volume, more areas of silent cerebral ischemia and worse visual–spatial abilities than patients with paroxysmal AF [9–11]. These findings suggest a possible cumulative effect of AF on brain functions that worsens with time from first diagnosis.

On the other hand, it is well known that chronic kidney disease (CKD) patients are at higher risk for ischemic stroke/cardiogenic cerebral embolism, with the risk increasing parallel to the fall in estimated

Abbreviations: AF, atrial fibrillation; CKD, chronic kidney disease; CI, cognitive impairment; OAC, oral anticoagulant; NOAC, new oral anticoagulant; SBT, Short Blessed Test; BI, Barthel index.

* Corresponding author at: Dipartimento Biomedico di Medicina Interna e Specialistica, University of Palermo, Piazza delle Cliniche, 2-90127 Palermo, Italy. Tel.: +39 0916552065; fax: +39 0916662830.
E-mail addresses: s.corrao@tiscali.it, salvatore.corrao@unipa.it (S. Corrao).

[1] REPOSI denotes the REgistro POliterapie SIMI, Società Italiana di Medicina Interna. The participating units and co-authors are listed in the Online-only Appendix.

http://dx.doi.org/10.1016/j.ejim.2015.02.018
0953-6205/

glomerular filtration rate (eGFR) [12–14]. CKD is, in fact, an important predictor of stroke among patients with non-valvular AF [15,16]. Furthermore, CKD alone is associated with CI [17] and with brain lesions, including silent cerebral ischemia and brain atrophy, predictive of stroke, CI, and dementia, similar to findings reported in patients with AF [10,18].

Taken together this evidence suggests that microemboli may contribute to dementia in AF, and that the rate of atrial microthrombus formation may be higher in CKD.

Recently, for stroke prevention in patients with AF, new oral anticoagulants (NOACs) have been approved, and new guidelines have been published [19,20]. While the European Society of Cardiology (ESC) 2012 guidelines did not recommend the use of NOACs in patients with creatinine clearance (CrCl) <30 mL/min, [20] the new American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) 2014 guidelines approved the use of rivaroxaban at a reduced dose in individuals with severe renal impairment (CrCl between 15 and 50 mL/min). Prescribing information indicates the use of apixaban and rivaroxaban at a reduced dose in patients with CrCl ≥ 15 mL/min, while dabigatran is not recommended when CrCl is less than 30 mL/min [21–23]. These facts imply some limitations for stroke prevention in patients with AF and CKD [19].

Given this background, the aim of our study was to examine the association between AF and CI, and the relationship with CKD, in a cohort of elderly patients hospitalized in internal medicine and geriatric wards, participating to the prospective REPOSI registry study.

2. Methods

2.1. Data collection and study population

We retrospectively analyzed the data collected in the frame of the REPOSI project from January 2010 to December 2010 in 66 Italian hospitals. REPOSI is an independent and collaborative registry, organized by the Italian Society of Internal Medicine (SIMI) and the Mario Negri Institute for Pharmacological Research. It involved the creation of a network of internal medicine and geriatric wards that collected information on elderly hospitalized patients, affected by multiple diseases and on polytherapy, in a registry. The design of the project has been previously described in detail [24]. All patients with and without AF who were recruited for the REPOSI study during the year 2010 were included in the present study analysis.

All patients provided informed consent. Data were collected in full compliance with the Italian law on personal data protection, and the REPOSI study was approved by the Ethics Committee of each participating center.

2.2. Socio-demographic and clinical characteristics

We compared laboratory-clinical characteristics and socio-demographic variables of patients with AF with those without AF.

The following clinical characteristics were evaluated: disease distribution at hospital admission (the classification was based on the International Classification of Diseases-Ninth Revision); cognitive status and mood disorders (tested with the Short Blessed Test [SBT] [25] and the Geriatric Depression Scale [26]); functional status at hospital admission (measured by means of the Barthel index [BI] [27]) classified as mild (BI 75–90), moderate (BI 50–74), severe (BI 25–49), and total dependence (BI 0–24); severity and comorbidity indexes (evaluated by the Cumulative Illness Rating Scale [28]); kidney function by means of eGFR (calculated using the Chronic Kidney Disease Epidemiology Collaboration formula [29]); oral anticoagulant therapy; length of hospital stay; destination at hospital discharge; and in-hospital and 3-month mortality rate. The associations between variables and mortality (in-hospital and at 3-month follow-up) were analyzed.

2.3. Cognitive status and anticoagulant therapy

We subdivided patients with AF according to cognitive status: without CI (SBT score 0–4), moderate CI (SBT score 5–9), and severe CI (SBT score 10–28). In these subsets of the population, we analyzed the available information on socio-demographic and clinical characteristics; length of hospital stay; in-hospital and 3-month mortality rates; and antithrombotic therapy at admission, discharge, and at 3-month follow-up. Vitamin K antagonists (VKAs) were considered as oral anticoagulants (OACs), and aspirin, clopidogrel, ticlopidine, and other anti-aggregating agents were considered as antiplatelet drugs. According to the Anatomical Therapeutic Chemical classification, these drug types were coded in the treatment database section as B01AA and B01AC, respectively. Variables that could be related to lower prescription rates were analyzed: age, male sex, eGFR, cirrhosis, systolic blood pressure, BI, and stroke. 11 patients with AF were not included in these analyses, since data on their SBT score was not available.

2.4. Statistical analysis

Data are reported as percentages for categorical variables and as means (95% confidence intervals) for quantitative variables. Analyses were referred to the whole group, and gender categorization was applied. A BI score of ≤40 was used to select patients with significant disability according to our population characteristics. The comparison between groups was made using Fisher's exact test for contingency tables and the z test for comparison of proportions. The non-parametric Mann–Whitney *U* test was used for comparison of quantitative variables. Multivariate logistic analysis was used to explore the relationship between variables and outcomes (in-hospital and 3-month follow-up mortality). Odds ratios and 95% confidence intervals were computed. The variables were chosen according to the Hosmer–Lemeshow methodology [30]: after univariate analysis, only variables with a $p < 0.20$ were included in the final model; then, through a backward process, variables were excluded until a significance level of $p < 0.20$ was reached for each variable. A two-tailed $p < 0.05$ was considered statistically significant.

Stata Statistical Software 2011, Release 12 (StataCorp, College Station, TX, USA) was used for database management and analysis.

3. Results

During the 4 index weeks, out of 1384 patients enrolled, 321 had AF (47% male and 53% female). Among those with AF 45.2% had one or more previous hospital admission and 58.2% had a caregiver. Patients with AF were older (80.8 vs 78.5 years, $p < 0.0001$), had higher rates of previous hospital admissions (one previous admission 30.2% vs 24.3%; more than one previous admission 15% vs. 12.2%; $p = 0.011$), and were admitted to the hospital from the Emergency Departments more frequently (85.3% vs 78.2%, $p \leq 0.005$) than patients without AF. No statistically significant differences were found in sex, marital status, and living arrangement at hospital admission between patients with and without AF.

3.1. Clinical characteristics of patients with AF

At hospital admission, patients with AF had higher heart rates, lower eGFR values, higher hemoglobin levels, higher body mass index (BMI), worse CI (higher SBT scores) and disability, and higher Illness Severity and Comorbidity indexes than those without AF (Table 1). 280 patients had permanent AF, while 41 had an episode of paroxysmal AF. Patients with AF were taking more medications, and a higher percentage of them was on OAC therapy. Nevertheless, the percentage of patients with AF taking OACs was less than 50%.

At hospital admission, the most frequent diagnoses in patients with AF were hypertension (84.4%), heart failure (37.1%), chronic obstructive