Antithrombotic treatment is strongly underused despite reducing overall mortality among high-risk elderly patients hospitalized with atrial fibrillation

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Aims To assess the use of antithrombotic treatment (ATT) after hospitalization with atrial fibrillation (AF) and the attributable effectiveness of ATT during follow-up.

Methods and results On the basis of record linkage of administrative registers, 1812 patients discharged with AF were identified and followed-up for major clinical events up to 1 year. Mean age was 79 years. After hospitalization, 56% of the patients received ATT: 29% anticoagulants, 22% antiplatelets (APs), and 5% both agents. Among patients without comorbidities, 63.0% were exposed to ATT. Several factors significantly influence the use of antithrombotic agents, including increasing age [odds ratio (OR) 0.93 (95% confidence interval (CI), 0.92–0.95)], chronic obstructive pulmonary disease [0.77 (0.59–1.00)], malignancy [0.57 (0.39–0.82)], and previous use of ATT [4.56 (3.67–5.67)]. A significantly lower mortality was observed in patients exposed to ATT [hazard ratio (HR) 0.36 (95% CI, 0.28–0.47)], both to anticoagulants [0.23 (0.15–0.35)] and to APs [0.66 (0.50–0.86)]. ATT was associated with the reduction of thrombo-embolic events [0.52 (0.25–1.07)]. Major bleeding did not contribute to increased morbidity. Subgroups analysis, propensity score (PS), and sensitivity analysis confirmed these results.

Conclusion Our data demonstrated that ATT was underused, also in patients without comorbidities. Exposure to ATT is associated with improved survival among elderly high-risk community patients hospitalized with AF.

KEYWORDS
Epidemiology; Medical record linkage; Antithrombotic treatment; Atrial fibrillation

Introduction

The growing clinical and public health relevance of atrial fibrillation (AF) is well documented in several studies which show its close relationship with age (8% prevalence in people above 80 years vs. 1% in those below 60 years) and with age-related clinical conditions, which are known to be associated with AF.1–4

The most feared complication of AF is thrombo-embolism, particularly ischaemic stroke. Several clinical trials5–11 demonstrated that oral anticoagulant (OAC) substantially reduces the risk of thrombo-embolic complications and death, whereas antiplatelet (AP) treatment represents a valid alternative for patients who cannot receive anticoagulant.7,12 Therefore, an antithrombotic preventive treatment is considered mandatory for all patients with AF, excluding only those with ‘lone-AF’.13

However, several observational studies have documented in different settings that compliance with the above recommendations is far from satisfactory, especially with respect to OAC. The reasons for this low compliance are not very clear, but seem to be related with the fear and the difficulties of assuming a safe use in the routine conditions of care.14–17 Curiously, these studies do not extend their attention to the assessment of the impact of poor compliance on clinical outcomes.

The aim of this paper is to explore this specifically important aspect of the problem, with the use of record-linkage analysis of the administrative databases, which has been increasingly recognized as a reliable tool to describe prospectively the history and the outcomes of large cohort representing the real care of populations.18,19

Methods

The databases including the detailed information on hospitalization, pharmacological treatments, and death/life status of a population of 138,069 people aged ≥65 years from three Local Health Authorities (LHAs) have been linked and used in this analysis.

Data sources

Hospital discharge records include information on primary diagnoses and up to five co-existing conditions, performed procedures, date of
admission, discharge, and in-hospital death. All diagnoses are coded according to the International Classification of Disease, Ninth Revision (ICD-9 CM).20

The prescription database provides the community prescriptions reimbursed by the national health system with drugs coded according to the Anatomical Therapeutic Chemical Classification21 and qualified with respect to dosages, date of first prescription, and duration of exposure.

The reliability of this strategy to produce epidemiological information has been validated.22,23

Cohort definition

The study cohort is represented by all patients consecutively discharged over a 12-month period, with a primary or secondary diagnosis of AF and followed-up for 360 calendar days, after the date of index hospital discharge.

For all patients, a 24-month period preceding the index date was analysed to identify several cardiovascular and non-cardiovascular conditions as documented by hospitalizations and/or chronic exposures to pharmacological treatments, which had been used as identifiers of underlying clinical conditions. Cardiovascular comorbidities include risk factors for stroke, previous presence of peripheral vascular disease, embolic episode, and AF. Specifically, risk factors for stroke include previous stroke or transient ischaemic attack (TIA), hypertension, congestive heart failure (CHF), coronary artery disease (CAD), and diabetes, as reported elsewhere.24 Non-cardiovascular conditions include malignancy, previous hospitalization for major bleeding, and chronic obstructive pulmonary disease.

The same criteria have been adopted for the monitoring of the outcome events over the 12 months following the index hospital discharge.

Exposure to antithrombotic treatment (ATT) agents (OAC and/or AP) was also considered with the same criteria in the period preceding and following the index hospitalization: the mean daily dose accepted in international pharmaco-epidemiological surveillance programme was used to categorize the patients chronically exposed to ATT in terms of degree of compliance (<30%; 31–70%; and ≥70%) with recommended strategies.

Statistical analysis

The characteristics of patients hospitalized with AF were reported as percentages and mean ± standard deviation (SD) and were compared with Pearson’s χ² and Mann-Whitney U test for categorical and continuous variables, respectively.

To identify independent characteristics associated with ATT during follow-up, a logistic regression model was used. Variables with a univariate P-value less than 0.10 were entered into the final model, specifically age, sex, previous hospitalization for AF, CHF, diabetes, coronary disease, peripheral vascular disease, hypertension, malignancy, chronic obstructive pulmonary disease, stroke, TIA, hospitalization for major bleeding, embolic episode, and previous exposition to antithrombotic agents. These variables were used as covariates in all adjusted analyses.

Cochran Mantel–Haenszel statistics were used to test for non-zero correlation between exposition to ATT (OAC and AP) and age. The association of ATT at the time of discharge with the 1-year all-cause mortality, major events, was developed using a Cox proportional hazards model. The results are expressed as hazard ratios (HRs) or relative risk reduction per cent [100 × (1 – HRs)] and 95% confidence intervals (CIs). Proportional hazards assumption was checked by graphical inspection of log [–log (survival)] vs. log (time) plot by ATT.

In order to avoid confounding by indication, all analyses were fully adjusted. Additionally, a detailed subgroup analysis of relevant populations (age categories, sex, diabetes, chronic obstructive pulmonary disease, malignancy, number of risk factors for stroke, previous use of ATT, and those who survived 30, 90, and 180 days after hospitalization) has been carried out. HRs in each subgroup analysis were adjusted for all the remaining covariates used in the multivariable analysis.

Further, to adjust for potential residual confounding, we also performed a PS analysis. PS is a common device to reduce bias in treatment comparisons in observational studies.25,26 Therefore, a logistic regression model was first used to predict the probability (PS) to be assigned to ATT. This model included as covariates at treatment assignment the same used for the Cox and logistic analyses with the exception of previous exposure to ATT. PS logistic model was selected in a stepwise fashion, and model-building stopped when adequate covariates balance within PS quintiles was reached26

Covariates residual imbalances within PS quintiles were assessed at each step with a two-way analysis of variance, in which each confounder was considered as outcome and PS quintiles and treatment as factors. Overlapping of the PS distribution between treatment and control groups was also checked.

Next, PS quintiles were introduced in the Cox model to allow an adjusted comparison between patients treated with antithrombotic agents and controls for mortality.

Finally, because PS methodology addresses only imbalances due to measured confounders, we also performed a sensitivity analysis to account for potential residual confounding deriving from the effect of an unmeasured binary covariate.27 This analysis assumes that (i) the unmeasured confounder is binary, (ii) the unmeasured confounder is independent of measured confounders, and (iii) there is no interaction between the unmeasured confounder and exposure.

P-values less than 0.05 were considered significant. All analyses were performed using SPSS 10.0 (SPSS Inc., Chicago, IL, USA) and SAS Statistical Package Release 9.1 (SAS Institute, Cary, NC, USA).

Results

Out of 25 012 patients hospitalized throughout the year 2002, 1920 had a diagnosis of AF.

Baseline clinical characteristics of patients

The risk profile of the cohort is documented in Table 1. Besides the advanced age (up to two-thirds of the whole population were ≥75 years), the majority of the patients had at least one risk factor for stroke: 58% have three or more of the risks listed in Table 1. It is important to underline also the high frequency of previous hospitalizations with chronic obstructive pulmonary disease (20.1%) and AF (19.4%). In Table 1, the baseline characteristics of patients receiving and not receiving ATT are also reported. There were significant differences between these groups: patients previously treated with ATT were younger, more often male, had a higher rate of hypertension, CAD, and TIA, and a lower rate of non-cardiovascular comorbidities. Additionally, they were more likely to be previously treated with antithrombotic agents, both OAC and AP.

Factors associated with the use of antithrombotic agents after the index hospitalization

One hundred and eight (5.6%) patients died during hospitalization and 1812 were discharged and available for follow-up.

After hospitalization, 1002 patients (55.3%) received ATT: 521 (28.7%) only anticoagulants, 392 (21.6%) only APs, and 89 (4.9%) both drugs. Among the 610 patients prescribed with anticoagulants, 67 (11%), 122 (20%), and 421 (69%)
received this treatment <30, from 31 to 70, and >70% of their follow-up time, respectively. Similarly, among the 481 patients prescribed with APs, 101 (21%), 122 (25.4%), and 258 (53.6%) received this treatment <30, from 31 to 70, and >70% of their follow-up time, respectively. Multivariable analysis identified factors associated with ATT during follow-up (Table 2). Age was the most important factor: the probability of being exposed to ATT declined by 7% per each incremental year. In absolute terms, this overall probability corresponds to a decrease of exposure from 67.2% in the group 65–74 years to 58.6% for those 75–84 and to 29.0% in those >85 years, with a partially inverse trend for OAC vs. AP (Table 3).

Previous use of ATT was independently associated with an approximately four-fold increase in the odds of receiving antithrombotic agents. The presence of cardiovascular conditions does not appear to influence ATT exposure; in contrast, non-cardiovascular comorbidities (i.e. malignancy, chronic obstructive pulmonary disease, and previous major bleeding) were significantly associated with a decreased likelihood of receiving antithrombotic drugs (Table 2). However, if we exclude patients who had any non-cardiovascular comorbidity and those dead during the first 30 days after hospital discharge, the proportion of patients on ATT was still low. Among these 1018 patients, 420 (41.3%) received anticoagulant agents and 289 (28.4%) were prescribed with APs.

### Exposure to ATT and mortality

During follow-up, 336 patients died. Survival at 3, 6, and 12 months was 92.0 ± 0.6, 87.5 ± 0.8, and 81.0 ± 0.9%, respectively.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Main characteristics vs. antithrombotic drug use of patients hospitalized with AF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All(^a) (n = 1920)</td>
</tr>
<tr>
<td>Mean age (SD)</td>
<td>78.8 (7.5)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>866 (45.1)</td>
</tr>
<tr>
<td>Definite risk factors for stroke (%)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1502 (78.2)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>969 (50.5)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>393 (20.5)</td>
</tr>
<tr>
<td>CAD</td>
<td>389 (20.3)</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>121 (6.3)</td>
</tr>
<tr>
<td>Previous TIA</td>
<td>37 (1.9)</td>
</tr>
<tr>
<td>Other cardiovascular comorbidities (%)</td>
<td></td>
</tr>
<tr>
<td>Previous hospitalization with AF</td>
<td>372 (19.4)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>132 (6.9)</td>
</tr>
<tr>
<td>Previous embolic episode</td>
<td>23 (1.2)</td>
</tr>
<tr>
<td>Non-cardiovascular comorbidities (%)</td>
<td></td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>385 (20.1)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>172 (9.0)</td>
</tr>
<tr>
<td>Previous major bleeding</td>
<td>43 (2.2)</td>
</tr>
<tr>
<td>Previous treatment (%)</td>
<td></td>
</tr>
<tr>
<td>Antithrombotic agents</td>
<td>946 (49.3)</td>
</tr>
<tr>
<td>Anticoagulants only</td>
<td>459 (23.9)</td>
</tr>
<tr>
<td>Antiplatelets only</td>
<td>390 (20.3)</td>
</tr>
<tr>
<td>Both</td>
<td>97 (5.0)</td>
</tr>
</tbody>
</table>

\(^a\)All patients hospitalized with AF (n = 1920).

\(^b\)Patients discharged alive (n = 1812) and stratified by the prescription of ATT at discharge.

Patients exposed to ATT had a significantly lower mortality. The reduction in all-cause mortality with anticoagulant agents was 77% (65–85%) (P < 0.0001) and with AP agents 34% (14–50%) (P = 0.003). Overall, ATT was associated with a 64% (53–72%) (P < 0.0001) reduction in total mortality (Figure 1). These results were confirmed using the PS methodology [reduction of 62% (51–70%)]. The sensitivity analysis showed that to affect these findings, an unmeasured binary confounder should have an HR for mortality of at least 4 and a difference in prevalence between ATT-treated and control groups of at least 20%.

These results were consistent and homogeneous throughout different subgroups of patients, including age categories (≥75 or <75 years), sex, number of risk factors for stroke, diabetes, and previous use of antithrombotic agents. Moreover, in patients with non-cardiovascular comorbid...
conditions as malignancy and chronic obstructive pulmonary disease, the attributable effectiveness of ATT was similar to that observed in the main cohort (Figure 2).

As expected, because of the lower statistical power due to the low number of events in the subgroups surviving beyond 30, 90, and 180 days, the attributable effectiveness of treatment was 0.48 (0.35–0.66), 0.69 (0.48–1.00), and 0.71 (0.43–1.17), respectively.

Because of the possibly expected influence of the care setting in the determination of the degree of OAC use, it is worth noting also the very close consistency of the data found in the three health districts, from which the overall cohort has been drawn (Figure 2).

### Thrombo-embolic events during follow-up

For 65 patients, either a first stroke, TIA, or an embolic episode was reported.

Thirty-four out of 810 patients (4.2%) not receiving ATT and 31 out of 1002 (3.1%) receiving ATT experienced a first stroke, TIA, or an embolic episode.

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**Table 3** Exposure to ATT during follow-up, stratifying by categories of age

<table>
<thead>
<tr>
<th>Age</th>
<th>All subjects with AF</th>
<th>ATT (%)</th>
<th>AOC (%)</th>
<th>AP (%)</th>
<th>Both (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>65–74</td>
<td>625</td>
<td>420 (67.2)</td>
<td>277 (44.3)</td>
<td>102 (16.3)</td>
<td>41 (6.6)</td>
</tr>
<tr>
<td>75–84</td>
<td>804</td>
<td>471 (58.6)</td>
<td>233 (29.0)</td>
<td>194 (24.1)</td>
<td>44 (5.5)</td>
</tr>
<tr>
<td>≥85</td>
<td>383</td>
<td>111 (29.0)</td>
<td>11 (2.9)</td>
<td>96 (25.1)</td>
<td>4 (1.1)</td>
</tr>
<tr>
<td>Total</td>
<td>1812</td>
<td>1002 (55.3)</td>
<td>521 (28.8)</td>
<td>392 (21.6)</td>
<td>89 (4.9)</td>
</tr>
</tbody>
</table>

*Exposition to antithrombotic agents during follow-up.

-Anticoagulation only.

-Antiplatelets only.

-Anticoagulation and antiplatelets.
thrombo-embolic episode. Considering that the median follow-up was 225 and 291 days, respectively, the annualized rate of thrombo-embolic episode was 68 per 1000 patients-years and 39 per 1000 patients-years. The overall adjusted probability of having a major event in patients on ATT therapy was 0.86 (0.50–1.50), \( P = 0.60 \).

Specifically, for the 610 patients prescribed with anticoagulants, the rate of thrombo-embolic events was 21 per 1000 patients-year. The overall adjusted probability of having a major event in patients on anticoagulants was 0.52 (0.25–1.07), \( P = 0.07 \).

**Bleeding episodes**

For 17 patients, a first episode of major bleeding or CNS bleeding was reported (annualized rate 13 per 1000 patients-years).

**Discussion**

**Major findings**

The main results of these analyses could be summarized under five points. (i) High-risk elderly patients hospitalized with AF were inadequately exposed to ATT prior to the index hospitalization (despite their high cardiovascular risk) as well as after hospital discharge (despite the additional diagnosis of AF). (ii) Under-treatment involves both anticoagulant and AP agents: only one-third of the patients were prescribed with anticoagulants and among those who were not, only one-third received APs. (iii) ATT was associated with a significant reduction in total mortality and anticoagulation was associated with a reduction of thrombo-embolic events to a greater extent than that reported in the clinical trial.\(^5\)\(^-\)\(^13\) (iv) The benefit of treatment is consistent and equally distributed among different categories of population. (v) Epidemiological data collected by record linkage should become a major tool for clinical research aimed at surveying and improving routine clinical care.

**Antithrombotic therapy in clinical practice**

This study identifies a sizeable underuse of ATT in a population of old, high-risk, unselected community patients hospitalized with AF. Despite the results of randomized trials\(^5\)\(^-\)\(^12\) as well as institutional recommendations,\(^13\) anticoagulation was not prescribed up to two-thirds of patients following hospitalization with AF. Furthermore, among those patients who did not receive anticoagulants, AP treatment was also withheld in two-thirds of patients. Although confirming in a cohort of patients with AF and a very severe risk profile for stroke (because of age and important comorbidities), the data of poor compliance with existing recommendations for ATT,\(^14\)\(^-\)\(^17\) the specifically new contribution of this study must be seen in its focus on the quantification and qualification of the outcomes implications of a prescription practice. The findings are striking: in a national health system in which treatments (as well as all control visits) are fully reimbursable and easily accessible, the data show that the unsatisfactory compliance translates...
directly into an excess of deaths, which could be potentially avoidable. Another interesting contribution of this data could be seen in the interpretation of the causes of low compliance with the recommendations and the guidelines. Patients in general practice differ substantially from those from clinical trials.\(^{28,29}\) It is thus unclear whether treatment benefits also community AF, who, in this analysis, are on average 79 years old. An additional reason for this low use of ATT could be the high rate of non-cardiovascular comorbidities (e.g. chronic obstructive pulmonary disease and malignancy). However, among patients without comorbidities, exposure to ATT was similarly low.

It appears to be abundantly clear that the responsibility of the situation is mostly on the side of the caring doctors. In fact, physicians could perceive this therapy (particularly anticoagulation) difficult to handle in elderly patients in real practice,\(^{17,30}\) mostly because of the complications. Nevertheless, our analysis did not find a rate of major bleeding that precludes the use of these compounds, although the low number of events limited this conclusion. Actually, some studies demonstrated that carefully educating and monitoring geriatric patients are associated with low bleeding rates.\(^{31–33}\)

In addition, patients are usually reluctant to receive anticoagulant. One study\(^{16}\) documented that only 61% of the patients would prefer anticoagulation to no treatment. In our analysis, adherence to treatment was shown to be feasible, given the physicians’ decision and the patients’ willingness. Almost 70% of the patients prescribed with anticoagulants received the treatment for at least 70% of their follow-up time. This finding confirms and extends recent results\(^{34}\) that suggest adherence as a strong factor related to outcome.

Notwithstanding both feasibility and willingness of anticoagulation, some physicians would prefer not to use anticoagulants. Clinical trials and current guidelines strongly support APs as an alternative.\(^{7,12,13}\) For this reason, it is difficult to explain the low use of APs in our study. Low exposure to APs was particularly surprising, considering that the attributable effectiveness in terms of death reduction was 35%.

In our study, the most important factor associated with ATT during follow-up was treatment before hospitalization. This implies that patients who were previously treated continued to be treated after hospitalizations as well as those who were not previously treated remained untreated. This data showed that hospitalization did not contribute to (re)consideration of risk. This fact seems to suggest that ‘clinical risk’ is not handled as a dynamic notion, but as a ‘static’ concept where clinical events appear not to contribute to global management.

### Antithrombotic therapy and prognosis

We found that ATT reduced more significantly mortality than thrombotic events. We speculate that this fact could be related to a more significant reduction of fatal than non-fatal strokes among elderly patients. In our cohort, the reduction in total mortality with both anticoagulant and AP agents appears to be even greater than that observed in randomized trials, suggesting also that the attributable effectiveness is larger with increasing clinical risk.

### Limitations of the study

The inherent limitations of this type of analysis are related to 'confounding by indication'. In order to avoid this, four methodological techniques were applied that confirmed main results: multivariable statistical model, several subgroups analysis, the use of PS, and a sensitivity analysis. In fact, treatment effect was independent of major comorbidities and was equally distributed among various subgroups of high-risk patients. The results were additionally consistent among patients who survived 30, 60, or 90 days after the index hospitalization and they were materially unchanged, using correction with PSs. Moreover, these findings were consistent across three unrelated health-care settings.

We should mention that we studied only patients hospitalized with AF and that the high rate of under-treatment observed applies only to these patients. We can hypothesize that the rates of treatment could be even lower among ambulatory patients; however, our data could not provide definitive conclusions.

We assessed safety on the basis of hospitalization-associated diagnosis for major bleeding. This approach has two main limitations: (i) it does not permit to study minor/frequent episodes of bleeding and (ii) it is based on a codification that could not express the real burden of bleeding. However, available data can certainly rule out an excess of fatal bleeding among patients exposed to ATT.

Finally, these results have been obtained in one country: they are, however, very consistent with those who have described other situations.\(^{5–12,35}\) More substantially, data reflecting practices usually have a limited degree of generalization. Conversely, the correlation between exposures and outcomes provides a high degree of generalization: as is the case of the present condition, any time we face a situation of unsatisfactory compliance, dramatic negative implications must be expected to occur.

In conclusion, our data demonstrated that ATT was under-used, also in patients without comorbidities. Exposure to ATT is associated with improved survival among elderly high-risk community patients hospitalized with AF.

### Conflict of interest

none declared.

### References


