Abstract. – OBJECTIVE: Dabigatran is a novel target specific oral anticoagulant for stroke prevention in non valvular atrial fibrillation. Little is still known about its real-world effectiveness and safety in the Italian population. Aim of our study was to evaluate the efficacy and safety of dabigatran in a large single-center cohort of “real-life” Italian population with non-valvular AF and to compare the results with those obtained from the RE-LY trial and the Medicare study.

PATIENTS AND METHODS: We studied a prospective cohort of 2108 patients (1119 male; mean age 69.4 ± 9.4 years) who started the oral anticoagulant treatment with dabigatran 110 mg twice-daily (DAB 110; N = 1075; 51%) or 150 mg twice-daily (DAB 150; N = 1033; 49%). Follow-up data were obtained through patients visits each 3-6 months for assessing the clinical status, adherence to treatment, occurrence of side effects and major cardiovascular complications.

RESULTS: In DAB 150 group the mean age was 64.9 ± 8.8 years, 56.8% of patients was male. CHA2DS2Vasc Score was ≥ 3 in 94.3% and HAS-BLED was ≥ 3 in 59.7%. In DAB 110 group (N = 1075) the mean age was 73.9 ± 7.5 years; 49.5% of patients was male. CHA2DS2Vasc Score was ≥ 3 in 73.4% and HAS-BLED was ≥ 3 in 87.4% of DAB 110 patients. One patient taking Dabigatran 110 mg bid had ischemic stroke without significantly neurological sequelae. In both groups, no patient experienced hemorrhagic stroke during the follow-up period. 147 patients (6.9%) of MonaldiCare population reported adverse effects from treatment with dabigatran, of whom 121 patients (5.7%) discontinued therapy. We reported one case of subarachnoid hemorrhage (0.05%) in a patient with high thrombo-embolic and high hemorrhagic risk score who was taking dabigatran 150 mg bid and one case (0.05%) of bladder bleeding in a patient who was taking dabigatran 110 mg bid. No major gastrointestinal bleeding was observed in the MonaldiCare population.

CONCLUSIONS: MonaldiCare registry showed a safety profile of both dosages of dabigatran regarding major of fatal bleeding in a “real life” single center Italian population at high thromboembolic and hemorrhagic risk. The majority of MonaldiCare patients tolerated dabigatran treatment without significant side effects. The efficacy of dabigatran was demonstrated by very low prevalence of ictus/TIA, also when patients underwent electrical AF cardioversion independently of the transesophageal examination.

Key Words: Dabigatran, Safety, Efficacy, Real life, Bleeding, Stroke, Novel oral Anticoagulants.

Introduction

Atrial fibrillation (AF) is one of the most common supraventricular arrhythmias, characterized by chaotic and uncoordinated atrial activity which predispose to hypercoagulable state and increased risk of thrombo-embolism1,2. Oral anticoagulation with warfarin is an effective treatment for prevention of ischemic stroke and systemic thromboembolism in AF patients3. CHA2DS2VASc score (calculated by assigning 1 point for each of congestive heart failure, hypertension, diabetes, history of vascular disease, age 65 to 74 years, and female sex; and 2 points for age > 75 years and history of stroke) is a validated score of stroke risk estimation for decide which patients with non-valvular AF are likely to benefit from anticoagulant therapy4; according to the European Society of Cardiology guidelines, a CHA2DS2VASc Score ≥ 1 suggests anticoagulation therapy5. Until 2013 the vitamin K antagonists (VKAs) had been the only oral anticoagu-
lants available for the prevention and treatment of thrombosis, however they were associated with a serious risk of major and fatal bleeding. Moreover the need of regular INR checks and significant interaction with diet and drugs are detrimental. The new target-specific oral anticoagulants (TSOACs) are medications that, inhibiting a specific enzyme in the coagulation cascade, offer several advantages over VKAs, including predictable pharmacokinetics, rapid onset of action and comparable efficacy and safety. Dabigatran etexilate (DAB), the first TSOAC available in Italy, is a reversible direct thrombin inhibitor that has rapid and predictable anticoagulant effects. Its pharmacokinetic profile provides fixed twice-daily oral administration and doesn’t require routine blood coagulation monitoring. Elimination is predominantly via renal clearance, with no significant hepatic contribution, and differences in pharmacokinetics are attributed primarily to variations in renal function. RE-LY clinical trial showed that in patients with atrial fibrillation dabigatran, given at a dose of 110 mg bid, was associated with rates of stroke and systemic embolism that were similar to those associated with warfarin, as well as lower rates of major hemorrhage. Dabigatran administered at a dose of 150 mg, as compared with warfarin, was associated with lower rates of stroke and systemic embolism but similar rates of major hemorrhage. These “trial life” data were confirmed by the results of Medicare study, an observational cohort study conducted by United States Food and Drug Administration. Aim of our study was to evaluate the efficacy and safety of dabigatran in a large single-center cohort of “real-life” Italian population with non-valvular AF and to compare the results with those obtained from RE-LY trial and Medicare study.

Patients and Methods

MonaldiCare Registry

MonaldiCare is an observational, open label registry born to evaluate the real-life effectiveness, safety and discontinuation rates of dabigatran in a large cohort of single-center patients with non-valvular AF. We prospectively enrolled, between June 2013 and December 2014 from Department of Cardiology-Monaldi Hospital, 2108 patients (1119 male; age 69.4±9.4 years) who started the oral anticoagulant treatment with dabigatran 110 mg twice-daily (DAB 110; n=1075; 51%) or 150 mg twice-daily (DAB 150; n=1033; 49%). Follow-up data were obtained trough outpatients visits each 3-6 months for assessing the clinical status, adherence to treatment, occurrence of side effects and major cardiovascular complications. Laboratory exams included kidney and hepatic function, 12 lead electrocardiogram (ECG) and 24h ECG Holter monitoring were performed.

Statistical Analysis

Categorical data were described by percentages and compared using the chi-square test, and Student’s t-test was used for continuous data. p-value < 0.05 was considered significant. All analyses were performed using SPSS Statistics (Version 21; SPSS Inc., IBM Corporation, NY, USA).

Results

Study Population

In the DAB 150 group (n: 1033 patients) the mean age was 64.9±8.8 years, 56.8% of patients was male; 92.9% had arterial hypertension; 1.2% had diabetes mellitus; 15.5% had prior myocardial infarction; 30.9% had prior stroke/transient ischemic attack. CHA2DS2Vasc Score was ≥ 3 in 94.3% and HAS-BLED was ≥ 3 in 59.7% of DAB 150 patients. 40.2% of patients were taking antiplatelets therapy (aspirin or clopidogrel). 84.5% were previously taking warfarin with a time in therapeutic range lower than 60%.

In the DAB 110 group (n: 1075 patients) the mean age was 73.9 ± 7.5 years; 49.5% of patients was male; 97.4% had arterial hypertension; 16% had diabetes mellitus; 24.7% had heart failure; 26.8% had prior myocardial infarction; 19.6% had prior stroke/transient ischemic attack. CHA2DS2Vasc score was ≥ 3 in 73.4% and HAS-BLED was ≥ 3 in 87.4% of DAB 110 patients. 48.9% of patients were taking antiplatelets therapy (aspirin or clopidogrel). 81.8% were previously taking warfarin with a time in therapeutic range lower than 60%.

Ischemic/Hemorrhagic Stroke

One patient who was taking Dabigatran 110 mg bid had ischemic stroke without significantly neurological sequelae. The same patient previously experienced ischemic stroke in therapy with warfarin and refused percutaneous left atrial appendage closure, so the therapy has

not been interrupted. In both groups, no patient experienced hemorrhagic stroke during the follow-up period.

**Adverse Effects and Discontinuation**

147 patients (6.9%) of MonaldiCare population reported adverse effects from treatment with dabigatran, of whom 121 patients (5.7%) discontinued therapy for dyspepsia (n: 114, 5.4%), diarrhea (n: 3, 0.14%), bleeding (n: 2, 0.09%), headache (n: 2, 0.09%). 26 patients (18.5% of dyspeptic patients) reported resolution of dyspepsia with concomitant food intake, copious water, proton pump inhibitors or H2-blocking agents. We reported one case of subarachnoid hemorrhage (0.05%) in a patient with high thromboembolic (CHA2DS2VASc score: 5) and high hemorrhagic risk score (HAS-BLED: 4) who was taking dabigatran 150 mg bid and one case (0.05%) of bladder bleeding, due to unknown bladder cancer, in one patient who was taking dabigatran 110 mg bid. No major gastrointestinal bleeding was observed in the MonaldiCare population.

**Adherence and Satisfaction**

1982 patients (94%) referred no difficulty with adherence to twice daily dosing of dabigatran with no missed doses. Only 216 patients (6%) reported missing occasional doses. The majority of patients (84.5% in DAB 150 group and 81.8% DAB 110 group) had previously been treated with warfarin and everybody preferred taking dabigatran primarily due to the reduced requirement for blood testing and to the absence of food restrictions.

**Cardioversion**

In MonaldiCare registry, 120 patients (0.6%; n: 19 in DAB 110 group; n: 101 in DAB 150 group) underwent electrical cardioversion performed administering dabigatran for at least 3 weeks prior the procedure. Transoesophageal echocardiography (TEE) was performed in 54 patients (n: 19, 100% of DAB 110 group; n: 31, 30.7% of DAB 150 group) without evidence of atrial cavity or atrial appendage thrombus. The therapy was continued within 30 days after cardioversion or long-term according to the patient’s clinical indication. No prevalence of stroke, systemic embolism or major bleeding after cardioversion was observed in our study.

**Discussion**

**Population Characteristics**

At present, MonaldiCare is the larger Italian observational registry, which has evaluated the efficacy and safety of both doses of dabigatran in a single center “real-life” population. We observed some differences between MonaldiCare patients cohort and those described in the RE-LY trial and in the Medicare study in terms of thromboembolic and hemorrhagic risk, age,

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Table I. Clinical characteristics of MonaldiCare population compared to Medicare and RE-LY patients.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Medicare</th>
<th>MonaldiCare</th>
<th>RE-LY</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dabigatran</td>
<td>DAB 150 (n = 67207)</td>
<td>DAB 110 (n = 1075)</td>
</tr>
<tr>
<td>Age (± SD)</td>
<td>64.9 ± 8.8</td>
<td>73.9 ± 7.5</td>
<td>71.5 ± 8.8</td>
</tr>
<tr>
<td>Female sex (%)</td>
<td>51</td>
<td>46.9</td>
<td>36.3</td>
</tr>
<tr>
<td>CHADS2 score (± SD)</td>
<td>31</td>
<td>94.3</td>
<td>73.4</td>
</tr>
<tr>
<td>CHADS2 score ≥ 3 (%)</td>
<td>41</td>
<td>59.7</td>
<td>87.4</td>
</tr>
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<td>CHA2DS2-VASc ≥ 3 (%)</td>
<td>87</td>
<td>95.1</td>
<td>78.8</td>
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<tr>
<td>HAS-BLED ≥ 3 (%)</td>
<td>33</td>
<td>15.1</td>
<td>32.2</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>18</td>
<td>20.8</td>
<td>20.3</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>17</td>
<td>44.6</td>
<td>17</td>
</tr>
<tr>
<td>Heart failure (%)</td>
<td>10</td>
<td>30.9</td>
<td>19.6</td>
</tr>
<tr>
<td>Antiplatelets (%)</td>
<td>2</td>
<td>15.5</td>
<td>26.8</td>
</tr>
<tr>
<td>Prior stroke/TIA (%)</td>
<td>84.5</td>
<td>81.8</td>
<td>50.2</td>
</tr>
</tbody>
</table>
sex, comorbidities, background history. Our findings support the hypothesis that real-life patients are often different from those of trial-life and that population characteristics usually change from different countries.

**Thromboembolic Risk:** MonaldiCare population showed a high risk of thromboembolism, as reflected by CHA2DS2-VASc score ≥ 3 in 94.3% in DAB 150 group and 73.4% in DAB 110 group. It was not possible to directly compare between MonaldiCare and RE-LY/Medicare, because the thromboembolic risk in their population were stratified according to CHAD DS2 score. RE-LY population showed a mean CHADS2 score of 2.1 ± 1.1 in dabigatran 110 mg population, and of 2.2 ± 1.2 in dabigatran 150 mg population. 32.7% of RE-LY 110 mg and 35.2% of RE-LY 150 mg population showed CHADS2 score ≥ 3. According to Oldgren et al RE-LY sub-analysis 13, 77.7% of 18.113 AF patients randomized to dabigatran 110 mg, dabigatran 150 mg or warfarin showed CHADS2 score ≥ 3. Medicare population showed CHADS2 score ≥ 3 in 31% of patients.

**Hemorrhagic Risk:** MonaldiCare population showed an high hemorrhagic risk (HAS-BLED score ≥ 3 in 59.7% of DAB 150 patients and in 87.4% of DAB 110 patients). No data about hemorrhagic risk were given in RE-LY trial. Although according to Eikelboom et al analysis 14, 10.4% of RE-LY population study taking dabigatran 150 and 110 mg bid had HAS-BLED score ≥ 3. Medicare population showed a HAS-BLED score ≥ 3 in 41% of patients.

**Age:** MonaldiCare DAB 150 group showed a medium age significantly lower (64.9 ± 8.9 vs. 71.5 ± 8.8, p < 0.001) than RE-LY 150 population, while in MonaldiCare DAB 110 group the medium age did not significantly differ (73.9 ± 7.5 vs. 71.4 ± 8.6; p < 0.1) from RE-LY 110 population. Medicare patients taking dabigatran 150 mg bid were more likely to be older than in RE-LY. The 59% of Medicare patients presented an age ≥ 75 years.

**Sex:** MonaldiCare population was more likely to be female compared to RE-LY population (46.9% vs. 36.3%; p = 0.004), while the gender distribution is similar to the Medicare population (46.9% vs. 51%; p = 0.3).

**Arterial Hypertension:** MonaldiCare population showed an higher percentage of patients with arterial hypertension in both DAB groups compared to RE-LY (95.1% vs. 78.8%; p = 0.004) and Medicare (95.1% vs. 87%, p < 0.04) population.

**Diabetes Mellitus:** MonaldiCare population showed lower percentage of patients affected by diabetes mellitus, compared to RE-LY (15.1% vs. 23.2%; p < 0.04) and Medicare (15.1% vs. 33%, p = 0.006) population.

**Prior Myocardial Infarction:** In MonaldiCare population the percentage of myocardial infarction history was higher in DAB 110 group compared to RE-LY 110 (26.8% vs. 16.8%; p = 0.01) and Medicare (26.8% vs. 2%; p = 0.002) population, while the percentage of previous MI was similar in DAB 150 group compared to RE-LY 150 population (15.5% vs. 17%; p = 0.07)

**Heart Failure:** MonaldiCare population showed a lower percentage of heart failure patients, compared to RE-LY (20.8% vs. 32%; p = 0.03), but it was similar to Medicare (20.8% vs. 18%, p = 0.08) population.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>MonaldiCare vs Medicare</th>
<th>MonaldiCare vs RE-LY</th>
<th>MonaldiCare 150 vs RE-LY 150</th>
<th>MonaldiCare 110 vs RE-LY 110</th>
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<tbody>
<tr>
<td>Age (± SD)</td>
<td>&lt; 0.001</td>
<td>&lt; 0.1</td>
<td></td>
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<tr>
<td>Female sex (%)</td>
<td>= 0.3</td>
<td>= 0.004</td>
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<tr>
<td>CHA2DS2-VASc ≥ 3 (%)</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAS-BLED ≥ 3 (%)</td>
<td>= 0.002</td>
<td>= 0.003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>= 0.04</td>
<td>= 0.004</td>
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<td></td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>= 0.006</td>
<td>&lt; 0.04</td>
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</tr>
<tr>
<td>Heart failure (%)</td>
<td>= 0.08</td>
<td>= 0.03</td>
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<tr>
<td>Antiplatelets (%)</td>
<td>= 0.003</td>
<td>= 0.005</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior stroke/TIA (%)</td>
<td>= 0.005</td>
<td>= 0.002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior MI (%)</td>
<td>= 0.07</td>
<td>= 0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior VKA (%)</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
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</table>

Table II. Level of significance of clinical characteristics between MonaldiCare population and RE-LY/Medicare patients.
Prior Stroke/TIA: In MonaldiCare population the percentage of stroke history was higher in DAB 150 group compared to RE-LY 150 (30.9% vs. 20.3%, p = 0.002) and Medicare population (30.9% vs. 10%, p = 0.005), while in DAB 110 group it was similar to RE-LY 110 population (19.6% vs. 19.9%; p = 0.8).

Antiplatelets Therapy: In MonaldiCare population the percentage of patients taking continuously antiplatelets therapy during the treatment period was higher than RE-LY (44.6% vs. 20.4%; p = 0.005) and Medicare (44.6% vs. 17%; p = 0.003) population.

The study cohort included also small groups of special populations at high risk of developing atrial fibrillation according to our previous evaluations, such as patients with obesity\textsuperscript{15}, neuromuscular disorders\textsuperscript{16-23}, beta thalassemia major\textsuperscript{24-25}, congenital diseases\textsuperscript{26-27}.

Adverse Effects and Discontinuation
In MonaldiCare registry, we identified an overall discontinuation rate of 5.7% after a median 38 days of treatment with dabigatran. This percentage is lower than 16% one year discontinuation rate demonstrated in the RE-LY trial. No data about the one year discontinuation rate were given in Medicare study; but only one time drug prescription was reported that 52% of dabigatran patients from October 2010 to December 2012 had made. Reported adverse events rate in MonaldiCare population was 6.9%, much lower compared to the RE-LY trial data (78% total adverse effects). Dyspepsia, which was the most common adverse event, occurred in 6.8% of the MonaldiCare population compared to over 11% in the RELY trial. No data about dyspepsia rate was given in Medicare study. However, only 5.7% of MonaldiCare patients discontinued dabigatran therapy for dyspeptic symptoms, unresolved by taking dabigatran therapy with concomitant food intake, copious water, proton pump inhibitors or H\textsubscript{2}-blocking agents. The majority of MonaldiCare patients (84.5% of DAB 150 group and 81.8% of DAB 110 group) were previously treated with warfarin and everybody preferred taking dabigatran primarily due to the reduced requirement for blood testing and no foods intake restriction.

Safety
A total bleeding complication rate of 0.1% was identified in MonaldiCare population, much lower than 2.87% and 3.32% major bleeding rate described in the RE-LY group taking respectively dabigatran 110 and 150 mg and than 4.3% annual rate described in the Medicare population. After a critical revision of our results, we hypothesized that the low rate of reported adverse events might be related to the small sample size, compared to the RE-LY and the Medicare population; the accurate clinical anamnesis and physical examination; and the use of dabigatran 110 mg according to a “patient centered tailoring approach”.

Cardioversion
In our clinical experience we didn’t report stroke and systemic embolism and major bleeding after cardioversion. The use of TEE was higher in patients assigned to DAB 110 group compared with those assigned to DAB 150 group. This difference was attributable to investigator preference for cardioverting with prior TEE on novel oral anticoagulant therapy\textsuperscript{28}. Nagarakanti et al\textsuperscript{29} reported a posthoc analysis based on the RE-LY trial. A total of 1.983 cardioversions were performed in 1.270 patients during the course of the trial. Stroke and systemic embolism rates at 30 days were 0.8%, 0.3%, and 0.6% (D110 versus warfarin, p = 0.71; D150 versus warfarin, p = 0.40) and similar in patients with and without transesophageal echocardiography. Major bleeding rates were 1.7%, 0.6%, and 0.6% (D110 versus warfarin, p = 0.06; D150 versus warfarin, p = 0.99).

Limitations
This is a single-hospital registry but, to our knowledge, it is the largest Italian cohort taking dabigatran. The observation and reporting of adverse effects are usually more accurate and careful in randomized controlled trials than in clinical practice. The median CHA\textsubscript{2}-DS\textsubscript{2}VASc score of 3 seen in our study population is comparable to the RE-LY CHADS\textsubscript{2} score finding and clearly identifies the individuals in this cohort as high thromboembolic risk population. We opted for the use of the CHA\textsubscript{2}-DS\textsubscript{2}VASc score in preference to CHADS\textsubscript{2} given the improved performance in terms of stroke risk stratification. The comparison of our data with those from RE-LY and Medicare was affected by the limitations due to different types of study design and the different used dabigatran dosages. RE-LY is a randomized controlled trial, Medicare refers to dabigatran new user cohorts of propensity score-matched elderly patients, while MonaldiCare is an observa-
tional trial. RE-LY and Medicare included warfarin as comparator for dabigatran, while in the MonaldiCare registry dabigatran in the real life setting is the only observed anticoagulant treatment. In RE-LY and MonaldiCare dabigatran 110 mg or 150 mg twice daily were used, while in Medicare dabigatran 75 mg or 150 mg twice daily were used. Data collection may have been subject to inter-observer variability. In order to minimize the potential for error, standardized database definitions and interview questions were utilized.

Conclusions

MonaldiCare registry showed a safety profile of both dosages of dabigatran regarding major or fatal bleeding in a "real life" single center Italian population at high thromboembolic and hemorrhagic risk. The majority of MonaldiCare patients tolerated dabigatran treatment without significant side effects. Successful adherence to twice daily dosing with dabigatran was high. A percentage higher than 80% in both MonaldiCare groups, who previously experienced treatment with both warfarin and dabigatran, preferred novel oral anticoagulation treatment. The efficacy of dabigatran was demonstrated by very low prevalence of ictus/TIA, also when patients underwent electrical AF cardioversion independently of the transesophageal examination.

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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