ORIGINAL ARTICLE

Stroke Prevention in Atrial Fibrillation. Findings from the GLORIA-AF Registry

Prevencion del stroke en fibrilacion auricular. Hallazgos del Registro GLORIA-AF

SERGIO DUBNER[1], GREGORY YH. LIP[2], CHRISTINE TEUSCH[3], HANS CHRISTIAN DIENER[4], CECILIA ZEBALLOS[5], JONATHAN L HALPERIN[6], CHANG SHENG MA[7], MINEY PAQUETTE[8], MENNO V. HUISMAN[9]

ABSTRACT

Background: The Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation (GLORIA-AF) is a multinational, prospective, 3-phase study to establish the safety and efficacy of dabigatran in patients with newly diagnosed nonvalvular atrial fibrillation at risk of stroke. Phase II began when dabigatran, the first non-vitamin K antagonist oral anticoagulant (NOAC) became available.
Objectives: The aim of this registry was to describe Phase II baseline clinical data in the general population and the 2-year follow-up of patients treated with dabigatran.
Methods: Among 15,644 patients enrolled in the study, 15,308 were eligible and 4,873 received dabigatran. Atrial fibrillation characteristics, follow-up findings and concomitant diseases were recorded and analyzed using descriptive statistics.
Results: Forty-five percent of eligible patients were women and median age was 71.0 years (interquartile range: 64-78 years). Patients were from Europe (47.9%), North America (22.2%), Asia (20.1%), Latin America (6.0%), and the Middle East/Africa (3.9%). Most of them had high risk for stroke (CHA_2DS_2-VASc score ≥2; 86.1%) and 13.9% had moderate risk (CHA_2DS_2-VASc score=1). In 80.3% of cases, patients received oral anticoagulants: 47.9% NOACs and 32.4% vitamin K antagonists (VKAs); 12.0% received antiplatelet agents and 7.6% did not receive antithrombotic treatment. At the 2-year follow-up, 70.5% remained on dabigatran.
Conclusions: Data from the GLORIA-AF Phase II registry showed that in nonvalvular AF, NOACs have been highly adopted in clinical practice, becoming more frequently prescribed than VKAs. Worldwide, however, a large proportion of patients have remained undertreated.

Key words: Anticoagulants / administration & dosage - Administration, Oral - Atrial Fibrillation Stroke/prevention and control

RESUMEN

Introducción: El GLORIA-AF (Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation) es un registro internacional, prospectivo, en tres fases, para determinar la seguridad y eficacia del dabigatrán en pacientes con fibrilación auricular no valvular recientemente diagnosticada, en riesgo de stroke. La fase II empezó cuando el dabigatrán, el primer anticoagulante oral no antagonista de la vitamina K (NOAC) estuvo disponible.
Objetivos: Describir los datos clínicos basales de la fase II en la población general y el seguimiento a 2 años de aquellos que recibieron dabigatrán.
Material y Métodos: Se reclutaron un total de 15 644 pacientes, de los cuales 15 308 fueron elegibles y 4873 recibieron dabigatrán. Se analizaron las características de la fibrilación auricular, los hallazgos en el seguimiento y las enfermedades concomitantes. Los datos fueron analizados usando estadísticas descriptivas.
Resultados: Del total de pacientes elegibles, el 45,5% eran mujeres, con una edad promedio de 71 (rango intercuartilo: 64-78) años. Los pacientes eran de Europa (47,9%), América del Norte (22,2%), Asia (20,1%), América Latina (6,0%) y Medio Oriente/África (3,9%). La mayoría se encontraba en alto riesgo de stroke (CHA_2DS_2-VASc score >2; 86,1%); un 13,9% tuvieron riesgo moderado (CHA_2DS_2-VASc score >1). El 80,3% recibieron anticoagulantes orales; de ellos, el 47,9% recibieron NOAC y el 32,4%, antagonistas de la vitamina K (VKA); 12,0% recibieron agentes antiagregantes plaquetarios y el 7,6% no recibieron tratamiento antitrombótico. A 2 años de seguimiento, el 70,5% permanecieron en dabigatrán.
Conclusiones: Los datos de la fase II del registro GLORIA-AF demostraron que, en FA no valvular, los NOAC han sido ampliamente adoptados en la práctica clínica y fueron más frecuentemente prescriptos que los VKA. No obstante, una gran proporción de pacientes en todo el mundo permanecieron sin tratamiento.

Palabras claves: Anticoagulantes /administración & dosificación - Administración Oral - Fibrilación Auricular - Accidente Cerebrovascular/prevención y control

Rev Argent Cardiol 2020;88:282-288. http://dx.doi.org/10.7775/rac.v88.i4.18386

SEE RELATED ARTICLE: Rev Argent Cardiol 2020;88:279-81. http://dx.doi.org/10.7775/rac.v88.i4.18624.

Received: 05-06-2020 – *Accepted:* 05-29-2020

Address for reprints: Dr. Sergio Jose Dubner, Arenales 2463 CABA 1124 - Argentina. email:dubnermd@gmail.com Fax 11 48273654

[1] Clínica y Maternidad Suizo Argentina and Sanatorio De Los Arcos, Buenos Aires, Argentina
[2] Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart and Chest Hospital, Liverpool, UK
[3] Boehringer Ingelheim International GmbH, Ingelheim, Germany
[4] University of Duisburg-Essen, Essen, Germany
[5] Instituto de Cardiología de Buenos Aires, Argentina
[6] Icahn School of Medicine at Mount Sinai, New York, NY, USA
[7] Atrial Fibrillation Center, Beijing AnZhen Hospital, Capital Medical University, Beijing, People's Republic of China
[8] Department of Medicine, Boehringer Ingelheim, Burlington, Canadá.
[9] Department of Thrombosis and Hemostasis, Leiden University Medical Center, Leiden, the Netherlands

Abbreviations

AF	Atrial Fibrillation	**VKAs**	Vitamin K antagonists
NOACs	Non-vitamin K antagonist oral anticoagulants		

INTRODUCTION

Atrial fibrillation (AF) patients have five times greater risk for stroke than those without AF. Patients with stroke and AF also have a worse prognosis than those with stroke without AF, in terms of stroke severity, recurrence, motor deficit, cardiac complications, and mortality (1).

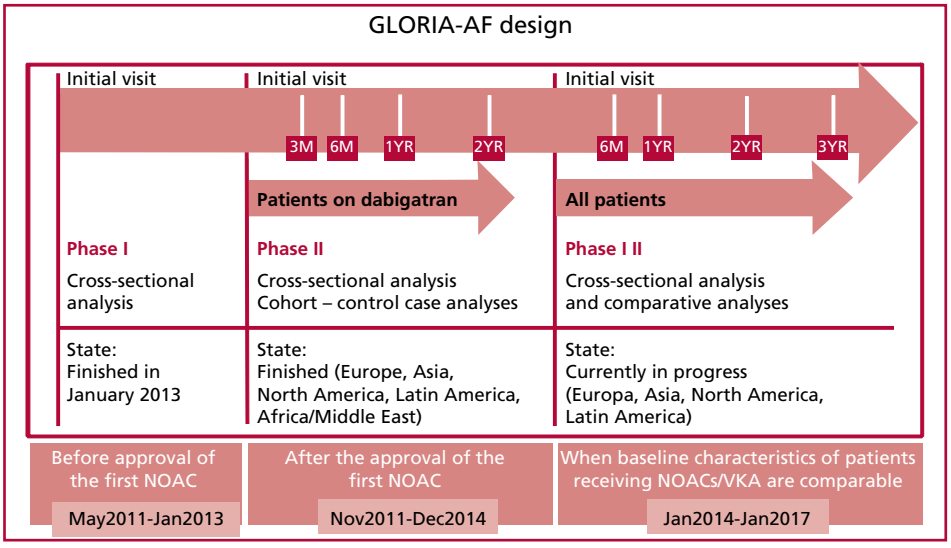
Over the past 50 years, patients with AF have generally received anticoagulants (as warfarin) to reduce their risk of stroke, decreasing ischemic stroke by 64% and all-cause mortality by 26%, compared with control drugs or placebo. (2, 3) The introduction of new non-vitamin K antagonist oral anticoagulants (NOACs) in 2010 has changed the paradigm of anticoagulation and the management of patients with nonvalvular atrial fibrillation (AF).

Currently, there are four large, multicenter, randomized studies that have shown that NOACs are at least similar to or more effective than warfarin [RELY (4), ROCKET (5), ARISTOTLE (6) and ENGAGE AF-TIMI (7)]. However, the use and effectiveness of NOACs in the real world is not well documented. (8) The Global Registry on Long-Term Oral Antithrombotic Treatment in patients with Atrial Fibrillation (GLORIA-AF™) is a multicenter, multinational, prospective registry that describes the patterns of antithrombotic treatment in patients with newly diagnosed AF (<3 months; Latin America <4.5 months) who are at risk of stroke (>1 risk criterion) to assess the long-term safety and effectiveness of dabigatran exilate. (9) The aim of this registry is to help characterize anticoagulant treatment patterns and conducts and their evolution, including stroke percentages and bleeding complications in real life using data from more than 900 randomly selected research centers from 44 countries, representing different types of healthcare settings.

There is limited data available from an international perspective on the characteristics, clinical management and evolution of patients with AF at risk for stroke. The objective of this study was to describe the baseline characteristics of the study population and the 2-year clinical follow-up of patients who received dabigatran.

METHODS

The GLORIA-AF design has been previously published (9) (Figure 1). Basically, it included consecutive patients with recent diagnosis of nonvalvular AF at risk of nonvalvular stroke [CHA_2DS_2-VASc scores ≥1, based on the presence of heart failure, hypertension, age ≥75 years (double), diabetes, stroke (double), vascular disease, age 65–74 years and sex (female)]. Patients were included within 3 months before the initial visit and within 4.5 months in Latin America by local researchers' decision. The registry consisted of three phases: Phase I was a cross-sectional analysis prior to the authorization of dabigatran, the first NOACs available, in the participating countries; Phase II was a cross-sectional study after the approval of dabigatran, with a 2-year follow-up of only those patients who received dabigatran, and Phase III was a cross-sectional evaluation comparing dabigatran and the different anticoagulants used, mainly warfarin, with a 3-year follow-up regardless of the anticoagulant received. The plan was to include up to 56,000 patients in 44 countries in the three phases. Phase II, to which this work refers, incorporated 15,644 consecutive patients between November 2011 and December 2014. Among these patients 15,308 were eligible to enter the independent registry of prescribed therapy



Huisman MV, et al. Am Heart J. 2014;167:329–334.

Fig. 1. Design of the GLORIA AF registry.

and the follow-up of those who received dabigatran ended in 2016. An electronic form completed through a webpage was used to enter the data and ensure safety. Baseline medical history, concomitant medications, and prescribed antithrombotic therapy were recorded and events during follow-up were collected at visits planned at 3, 6, and 12 months and 2 years after the initial visit.

GLORIA-AF™ is a multinational, prospective registry that included consecutive patients with recent diagnosis of nonvalvular AF and risk factor ≥1 (CHA_2DS_2-VASc score ≥1), and which was carried out in different healthcare settings in 44 countries from 5 regions of the world.

Patients were excluded for any of the following reasons: carriers of a mechanical heart valve or valve disease requiring replacement during the course of the registry, more than 60 days of VKA treatment at any time of life for any indication, AF secondary to a reversible cause, life expectancy <1 year, or any other indication for VKA other than AF.

Statistical analysis

Descriptive statistics was used for baseline data. Patients taking at least one dose of dabigatran were clinically followed up for 2 years (including stroke, major bleeding, and vascular death data), and the rate of events and 95% confidence intervals (CI) were evaluated based on the exposed treatment time (treatment-based analysis). Patients who were prescribed dabigatran but failed to take any dose were excluded from the study.

Clinical research record:
https://clinicaltrials.gov/ct2/home;
Study registration numbers NCT01468701, NCT01671007, NCT01937377.

Ethical considerations

The GLORIA-AF registry was conducted in accordance with the Declaration of Helsinki and the protocols and procedures approved by the European Medicine Agency, as well as the ethical committees and review groups of the participating institutions. All patients provided informed consent before entering the registry.

RESULTS

Among 15,308 eligible patients included from 982 centers, 45.5% were women, and mean age was 70.5±11.0 years. Patients were from Europe (47.9%), North America (22.2%), Asia (20.1%), South America (6.0%), and the Middle East/Africa (3.9%) (Figure 2).

Most patients had high risk for stroke (CHA_2DS_2-VASc score ≥2; 86.1%) and 13.9% moderate risk (CHA_2DS_2-VASc score=1). In 80.3% of cases, patients received oral anticoagulants: 47.9% NOACs and 32.4% warfarin or acenocoumarol (VKAs); 12.0% received antiplatelet treatment and 7.6% had no antithrombotic treatment.

Paroxysmal AF occurred in 53.3% of patients, persistent AF in 35.6%, and permanent AF in 11.1%. Atrial fibrillation was symptomatic in 28.2% of cases and minimally symptomatic or asymptomatic in the remaining 71.8%.

Patients were mainly treated by cardiologists (87.5%), and were followed up in community hospitals (29.5%), specialist offices (36.4%), university hospitals (21.7%), primary care centers (7.4%), as

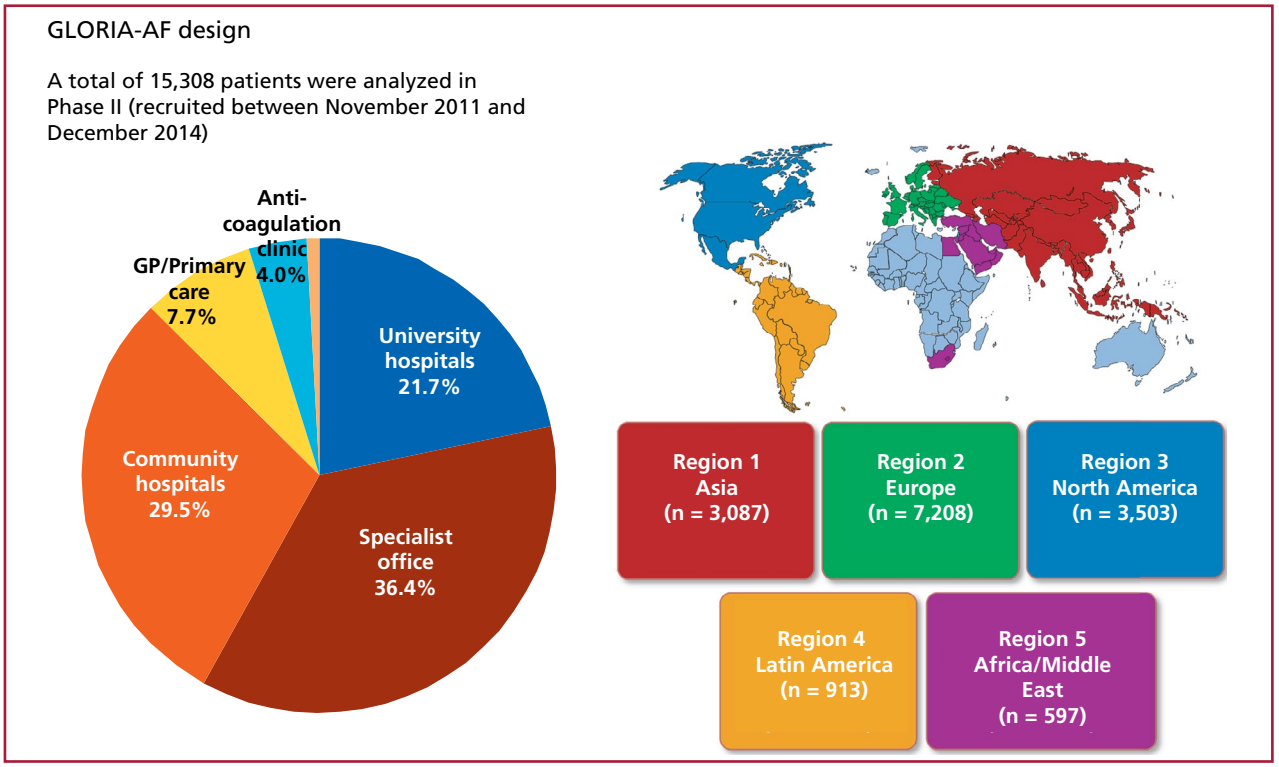


Fig. 2. Distribution of patients by country and treatment location

ambulatory patients (4.0) or in other healthcare centers (0.8.%).

Regional differences in antithrombotic treatment

In Europe, treatment with NOACs was more common than with VKAs (52.7% and 37.7%, respectively); 5.9% of patients received antiplatelet treatment and 3.7% had no antithrombotic treatment. In North America, NOACs were indicated in 52.1% of patients and VKAs in 26.2%; in 14.1% of cases, patients received antiplatelet treatment, while no antithrombotic treatment was administered in 7.3%. In Asia, 27.7% of patients received VKA treatment while 27.6% were treated with NOACs. Antiplatelet therapy was given to 25.1% of patients, and 19.7% did not receive any antithrombotic therapy.

In Latin America, 941 consecutive patients were selected; 44.64% were women and mean age was 69.6±11.7 years; 43.8% of patients had paroxysmal AF, 34.7% persistent AF and 21.5% permanent AF. Mean CHA2DS2VASc score was 3.2±1.5 and the HAS-BLED score was 1.2±0.9. Dabigatran was prescribed in 379 patients: 54.7% received 150 mg and 43.0% 110 mg twice daily. The proportion of patients on aspirin was 10.9% and 4.5% were without therapy. In Argentina, 167 patients were included in the registry: 88.8% (95% CI: 83-93) received anticoagulants (50% NOACs and 38.8% VKAs), 8.7% antiplatelet agents and 2.5% remained without therapy. (10)

Elderly patients: Age was between 65-74 years in 34.0% of patients, between 75-84 years in 30.5% and ≥85 years in 8.6%. In these three age groups, 83.7%, 86.8% and 85.4% of patients received oral anticoagulants, respectively (NOACs in 49.7%, 48.7 and 45.6% of cases, respectively), except those who were at high risk of bleeding (HAS-BLED ≥3). In these subgroups, the proportion of anticoagulated patients was 64.1%, 63.5% and 64.5% and 31.1, 30.3 and 31.3% received antiplatelet drugs, exclusively. In patients ≥85 years old, oral anticoagulants were used in 88.1% of cases in Europe (NOACs 45.1%), 79.5% in North America (NOACs 44.8%) and 54.1% in Asia (NOACs 40.2%).

Two-year follow-up: Among the 15,308 eligible patients admitted in Phase II (2011–2014), 4,873 received dabigatran for a mean duration of 18.0±9.4 months. Mean age was 70.5±11.0 years, and 86.1% had CHA2DS2-VASc score >2. The most common comorbidities were hypertension (74.5%), heart failure (24.0%), and diabetes (23.1%). Nearly forty-eight percent of patients (47.9%) were from Europe, 22.2% from North America, 20.1% from Asia, 6.0% from Latin America and 3.9% from Africa/Middle East.

Table 1 shows clinical findings at follow-up. Ninety-four percent (4,580/4,873) of patients presented no significant findings (stroke, major bleeding, myocardial infarction (MI) and all-cause mortality) during follow-up. The incidence rate for stroke was 0.65 (95% CI: 0.48 to 0.87) per 100 person-years (70% were ischemic, 12.8 were classified as primarily hemorrhagic and 4.3% as secondary to hemorrhagic transformation); the rate of major bleeding was 0.97 per 100 person-years (95% CI: 0.76 to 1.23), the rate of life-threatening bleeding (mainly gastrointestinal and less frequent intracranial) was 0.62 per 100 person-years (95% CI: 0.46 to 0.84) and of fatal bleeding 0.10 per 100 person-years (95% CI: 0.04 to 0.20). The incidence rate for MI, vascular death and all-cause mortality was 0.50 (95% CI: 0.35 to 0.69), 0.85 (95% CI: 0.65 to 1.09) and 2.48 (95% CI: 2.13 to 2.87), respectively.

Persistence: The probability of dabigatran treatment persistence was 83.6% at 6 months, 77% at 12 months and 70.5% at 24 months. The incidence of clinical events during the 2-year follow-up per 100 patient-years (95% CI) was as follows: severe secondary effects 0.33% (0.04-1.17); major bleeding 0.49% (0.1-1.42) and all-cause mortality 4.06% (2.63-6.0). Patients in North America and Asia had a greater discontinuation rate than in Europe, and patients in Latin America and Africa/Middle East had less discontinuation. The risk of discontinuation was higher in the period following the start of treatment and most of the reasons for its discontinuation were not related to adverse events. Figure 3 shows the probabilities and reasons for discontinuation of dabigatran, with or without change to another oral anticoagulant, in 2 years. (11)

DISCUSSION

The introduction of NOACs with dabigatran exilate in 2010, changed the paradigm of antithrombotic treatment in nonvalvular AF. (12, 13)

These data also demonstrate that NOACs have been adopted in clinical practice as a treatment strategy and that the pattern has changed accordingly, particularly in Europe and North America, where NOACs have been prescribed more than VKAs. Additionally, these results show a high number of patients without treatment or treated with antiplatelet agents (ASA), particularly in Asia and North America (14). In North America, 14.0% received antiplatelet therapy, and this may reflect American guideline recommendations, where antiplatelet therapy is suggested as an alternative to oral anticoagulation in patients with a CHA_2DS2-VASc score of 1. (15) Other registries have presented their data describing treatment patterns in patients with AF. However, the comparison between different registries can be challenging for a number of reasons. Thus, for example, differences in the inclusion/exclusion criteria, the specialties of the treating physicians and medical practice location (community, academic hospitals, etc.) can generate disparity in the selection of patients or therapeutic preferences. (16-19) With this large inclusion of patients, the GLORIA-AF registry contributes to increase our understanding of stroke prevention in patients with nonvalvular AF and helps to define future treatment strategies that could eventually influence patient follow-up.

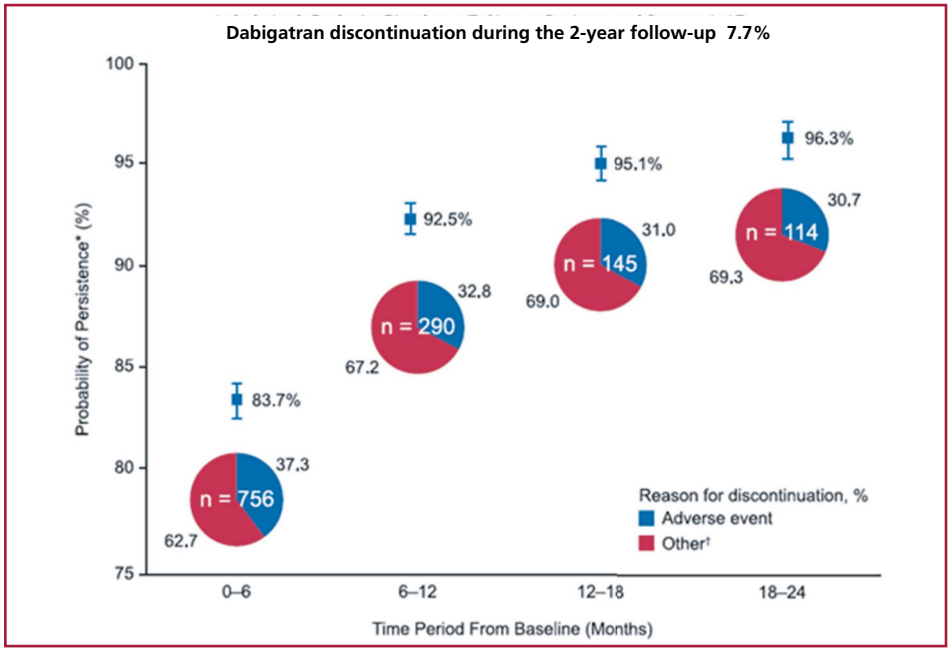
When evaluating the incidence of complications at

Table 1. Crude incidence rates at 2 years of clinical follow-up in patients treated with dabigatran (N = 4,859)

Evolution	Patients with events	PY	Crude IR per 100 PY (95% CI)
Stroke	47	7.192	0.65 (0.48-0.87)
Ischemic	31	7.197	0.43 (0.29-0.61)
Secondary hemorrhagic transformation	2	7.213	0.03 (0.00-0.10)
Hemorrhagic	6	7.213	0.08 (0.03-0.18)
Unknown/uncertain classification	10	7.212	0.14 (0.07-0.26)
Systemic embolism	3	7.212	0.04 (0.01-0.12)
Major bleeding	70	7.199	0.97 (0.46-0.84)
Life-threatening	33	7.209	0.62 (0.32-0.64)
Fatal	5	7.215	0.10 (0.04-0.20)
Bleeding location	12	7.213	0.17 (0.09-0.29)
Intracranial Hemorrhage Gastrointestinal	43	7.206	0.60 (0.43-0.80)
Others	13	7.210	0.18 (0.10-0.31)
Unknown	2	7.215	0.03 (0.00-0.10)
AMI	36	7.204	0.50 (0.35-0.69)
All-cause mortality	179	7.215	2.48 (2.13-2.87)
Vascular	61	7.215	0.85 (0.65-1.09)
Non-vascular	70	7.215	0.97 (0.76-1.23)
Unknown	48	7.215	0.67 (0.49-0.88)

CI = Confidence interval; IR = incidence rate; PY = patient-years.

Fig. 3. Causes of dabigatran discontinuation at the 2-year follow-up



Paquette et al. Amer J Cardiol 2020;125;383-391. (with permission)

2 years in patients who received dabigatran, the percentage of bleeding and stroke was low, confirming the safety and sustained efficacy of dabigatran during the 2-year follow-up, in agreement with previous RE-LY and RE-LY ABLE study results (20). However, there are differences across regions: the incidence of stroke was <1.0/100 patient-years and comparable in all regions; major bleeding was higher in North America (approximately 2.1/100 patient- years) and lower in Europe and Asia (approximately 0.9/100 patient-years). All-cause mortality was higher in North America than in Asia, and in Europe it was between the values of these two regions.

Different causes might explain these findings. First, important disparities in the clinical characteristics of patients were observed between the different regions. Coronary heart disease, diabetes, hypertension, and previous bleeding were more prevalent in North America than in Europe. When comparing North America and Asia, diabetes, previous bleeding,

and previous MI were more frequent in Asia. These different comorbidities were also reflected in the established treatment. Aspirin was used twice more frequently in North America compared with Europe or Asia (21.9% vs. 10.9%/12.1%). Additionally, the use of non-steroid anti-inflammatory drugs (NSAIDs) was particularly higher in North America than in Europe or Asia (10.3% vs. 1.6%/1.4%). Concomitant use of these drugs increased the risk of bleeding and may have contributed to the higher incidence of bleeding seen in North America.

An important potential advantage of using NOACs is therapy persistence. After 2 years of follow-up, approximately 70% of patients with AF (77% in the first year) continued taking dabigatran, which compares favorably with the reported 45% of warfarin persistence (21). The risk of discontinuation is greater in the period immediate to treatment initiation.

Limitations

Phase II of the GLORIA-AF registry included follow-up of patients treated with dabigatran only. Therefore, comparisons cannot be made with other anticoagulant drugs. In Phase III of the same registry, data follow-up will be carried out on all patients, so that the safety and effectiveness analysis can be done with all anticoagulants. No comparisons can be made between those who received 150 mg and the 110 mg doses twice daily since the population differs by their small size and the low number of events, so only crude incidence percentages are reported. This cohort presented a low HAS-BLED, which resulted in a low incidence of major bleeding. Furthermore, it included a high proportion of patients from Europe and North America, making it difficult to compare these populations with those of other regions. Nevertheless, this prospective registry is the longest in the literature of patients followed up with dabigatran.

CONCLUSIONS

Low rates of stroke, major bleeding and MI were observed in this prospective cohort of patients with AF treated with dabigatran, confirming the safety and efficacy of dabigatran after 2 years of follow-up in clinical practice.

Data from the GLORIA-AF Phase II registry demonstrate that NOACs have been adopted in clinical practice and treatment patterns have been modified, particularly in Europe and North America, where NOACs have been prescribed more frequently than VKAs. At the same time, it has been observed that a considerable group of patients remains without treatment or only with antiplatelet agents.

Conflicts of interest

Sergio J. Dubner receives fees for his participation as a member of the GLORIA AF Registry Scientific Committee supported by Boehringer Ingelheim as well as research grants from Abbott (St Jude Medical) and Medtronic.

Gregory YH. Lipb has been a consultant for Bayer/Janssen, Bristol-Myers Squibb/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Microlife, and Daiichi-Sankyo, and as speaker for Bayer, Bristol-Myers Squibb/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche, and Daiichi-Sankyo;

Hans Christian Dienerd has received fees for participating in clinical research, scientific committees, and oral presentations from Abbott, Allergan, AstraZeneca, Bayer Vital, Bristol-Myers Squibb, Boehringer Ingelheim, CoAxia, Corimmun, Covidien, Daiichi-Sankyo, D-Pharm , Fresenius, GlaxoSmithKline (GSK), Janssen-Cilag, Johnson & Johnson, Knoll, Lilly, Merck Sharp & Dohme, Medtronic, MindFrame, Neurobiological Technologies, Novartis, Novo Nordisk, Paion, Parke-Davis, Pfizer, Sanofi Aventis, Schering- Plow, Servier, Solvay, St Jude Syngis, Talecris, Thrombogenics, WebMD Global, Wyeth, and Yamanouchi;

Chang Sheng Ma receives fees for his participation as a member of the GLORIA AF Registry Scientific Committee and research grants from Bristol-Myers Squibb, Boehringer Ingelheim, Bayer HealthCare, Pfizer, AstraZeneca, and Johnson & Johnson.

Jonathan L Halperin receives fees for his participation as a member of the GLORIA AF Registry Scientific Committee Member, supported by Boehringer Ingelheim and has received consultation fees from Bayer HealthCare, Janssen-Ortho-McNeil, and Pfizer, MVH and presentation and consultation fees from Boehringer Ingelheim, Bayer HealthCare, Pfizer, GlaxoSmithKline and Actelion Pharmaceuticals.
The remaining authors are Boehringer Ingelheim employees.

(See authors' conflicts of interest forms on the website/ Supplementary material).

REFERENCES

1. Peters NS, Schilling RJ, Kanagaratnam P, Markides V. Atrial fibrillation: strategies to control, combat, and cure. Lancet 2002;359:593-603. https://doi.org/10.1016/S0140-6736(02)07748-6

2. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med 2007;146:857-67. https://doi.org/10.7326/0003-4819-146-12-200706190-00007

3. Nieuwlaat R, Capucci A, Lip GY et al. Antithrombotic treatment in real-life atrial fibrillation patients: a report from the Euro Heart Survey on Atrial Fibrillation. Eur Heart J 2006;27:3018-26. https://doi.org/10.1093/eurheartj/ehl015

4. Connolly SJ, Ezekowitz MD, Yusuf S et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139-51. https://doi.org/10.1056/NEJMoa0905561

5. Patel MR, Mahaffey KW, Garg J et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365:883-91. https://doi.org/10.1056/NEJMoa1009638

6. Granger CB, Alexander JH, McMurray JJ et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365:981-92. https://doi.org/10.1056/NEJMoa1107039

7. Giugliano RP, Ruff CT, Braunwald E et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2013;369:2093-104. https://doi.org/10.1056/NEJMoa1310907

8. Ruff CT, Giugliano RP, Braunwald E et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet 2014;383:955-62. https://doi.org/10.1016/S0140-6736(13)62343-0

9. Huisman MV, Lip GY, Diener HC et al. Design and rationale of Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation: a global registry program on long-term oral antithrombotic treatment in patients with atrial fibrillation. Am Heart J 2014;167:329-34. https://doi.org/10.1016/j.ahj.2013.12.006

10. Zeballos C, Caccavo A, Huisman M, Giniger AG, Aguinaga L, Maid GF y cols.. Patrones de tratamiento antitrombotico en la era de los nuevos anticoagulantes orales. Datos argentinos del registro GLORIA AF. 44° Congreso Argentino de Cardiologia (octubre 2018) 443(Abstract)

11. Paquette M, Franca LR, Teutsch C, et al. Dabigatran Persistence and Outcomes Following Discontinuation in Atrial Fibrillation Patients from the GLORIA-AF Registry. Am J Cardiol 2020;125:383-91. https://doi.org/10.1016/j.amjcard.2019.10.047

12. Camm AJ, Kirchhof P, Lip GY et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J 2010;31:2369-429. https://doi.org/10.1093/eurheartj/ehq278

13. Camm AJ, Lip GY, De CR, Savelieva I, Atar D, Hohnloser SH, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. Eur Heart J 2012;33:2719-47. https://doi.org/10.1093/europace/eus305.

14. Huisman MV, MD, Rothman KJ, Paquette M, Teutsch C, Diener HD, Dubner SJ et al on behalf of the GLORIA-AF Investigators. The Changing Landscape for Stroke Prevention in AF Findings From the GLORIA-AF Registry Phase 2. J Am Coll Cardiol 2017;69:777-85. https://doi.org/10.1016/j.jacc.2016.11.061

15. NICE. Atrial fibrillation: management NICE guidelines [CG180]. 2014. Ref Type: Online Source

16. Mazurek M, Huisman MV, Rothman K, Paquette M, Teutsch C, Diener HC, Dubner SJ, Halperin JL, Ma CS, Zint K, Elsaesser A, Lu S, Lip GYH, on behalf of the GLORIA-AF Investigators. Regional Differences in Antithrombotic Treatment for Atrial Fibrillation: Insights from the GLORIA-AF Phase II Registry Thromb Haemost 2017;117:2376–88. https://doi.org/10.1160/TH17-08-0555

17. Dubner SJ; Martinenghi N. Edoxaban in Latin America. J Am Coll Cardiol 2018;72:1466-7. https://doi.org/10.1016/j.jacc.2018.07.038

18. Lip GY, Laroche C, Dan GA et al. A prospective survey in European Society of Cardiology member countries of atrial fibrillation management: baseline results of EURObservational Research Programme Atrial Fibrillation (EORP-AF) Pilot General Registry. Europace 2014;16:308-19. https://doi.org/10.1093/europace/eut373

19. Kakkar AK, Mueller I, Bassand J, Fitz Maurice DA, Goldhaber SZ, Goto S, et al. Risk profiles and antithrombotic treatment of patients newly diagnosed with atrial fibrillation at risk of stroke: perspectives from the international, observational, prospective GARFIELD registry. PLoS One 2013;8:e63479. https://doi.org/10.1371/journal.pone.0063479

20. Connoly SJ, Wallentin L, Ezekowitz M, Eikelboom J, Oldgren J, Reilly PA et al. Long term multicenter observational study of Dabigatran treatment in patients with atrial fibrillation (RE-LY ABLE study. Circulation 2013;128:237-43.

21. Spivey CA, Qiao Y, Liu X, Mardekian J, Parker RB, Phatak H, et al. Discontinuation/Interruption of warfarin therapy in patients with nonvalvular atrial fibrillation. J Manag Care Spec Pharm 2015;21:596-606. https://doi.org/10.18553/jmcp.2015.21.7.596