Original Paper

Epidemiology of Intracranial Hemorrhage Associated with Oral Anticoagulants in Spain: Trends in Anticoagulation Complications Registry – The TAC 2 Study

Gustavo Zapata-Wainberg^a Sonia Quintas^b
Álvaro Ximénez-Carrillo Rico^a Jaime Masjuán Vallejo^c Pere Cardona^d
Mar Castellanos Rodrigo^e Lorena Benavente Fernández^f
Andrés García Pastor^g José Egido^h José Maciñeirasⁱ
Joaquín Serena^j María del Mar Freijo Guerrero^k Francisco Moniche^l
José Vivancos^a TAC 2 Study Investigators

^aHospital Universitario de La Princesa, Instituto de Investigación Sanitaria La Princesa, Madrid, Spain; ^bHospital Universitario de La Princesa, Madrid, Spain; ^cHospital Universitario Ramón y Cajal, Madrid, Spain; ^dHospital Universitari de Bellvitge, L'Hospitalet de Llobregat, Spain; ^eComplejo Hospitalario Universitario A Coruña, Instituto de Investigación Biomédica A Coruña, Coruña, Spain; ^fHospital Universitario Central de Asturias, Oviedo, Spain; ^gHospital General Universitario Gregorio Marañón, Madrid, Spain; ^hHospital Clínico Universitario San Carlos, Madrid, Spain; ⁱComplejo Hospitalario Universitario de Vigo, Vigo, Spain; ^jHospital Universitario Dr. Josep Trueta, Girona, Spain; ^kHospital de Basurto, Montevideo Etorb, Bilbao, Spain; ^lHospital Universitario Virgen del Rocío, Seville, Spain

Keywords

Direct oral anticoagulants · Incidence · Intracranial hemorrhage · Neuroepidemiology · Oral anticoagulants · Vitamin K antagonists

Abstract

Objective: Patients receiving treatment with oral anticoagulants (OACs) are at risk of intracranial hemorrhage (ICH). In this study, we describe the epidemiological and clinical characteristics of patients receiving OACs who experience ICH and compare those receiving vitamin K antagonists (ICH-VKAs) with those receiving direct OACs (ICH-DOACs). **Methods:** We performed a national, multicenter, descriptive, observational, retrospective study of all adult patients receiving OACs who were admitted to the neurology department with ICH over a 1-year period. The study population was divided into 2 groups (ICH-VKAs and ICH-DOACs). Epide-

A complete list of the study investigators can be found in the Appendix.

Gustavo Zapata-Wainberg, MD
Hospital Universitario de La Princesa
Diego de León St. #62, 7th Fl.
ES-28006 Madrid (Spain)
E-Mail gzapatawainberg@gmail.com

miological, clinical, radiological, and therapy-related variables, as well as functional outcome, were compared at 3 months. A total of 366 cases were included (331 ICH-VKAs, 35 ICH-DOACs). **Results:** The crude annual incidence of OAC-induced ICH was 3.8 (95% CI, 2.78–3.41) per 100,000 inhabitants/year. The mean ($\pm$ SD) age was greater for ICH-DOACs (81.5 ± 8.3 vs. 77.7 ± 8.3 years; $p = 0.012$). The median (IQR) volume of the hemorrhage was lower for ICH-DOACs (11 [30.8] vs. 25 [50.7] mL; $p = 0.03$). The functional independence rate at 3 months (modified Rankin Scale, mRS <3) was similar in both groups, although stroke-related mortality was greater in ICH-VKAs (40 vs. 72.7%; $p = 0.02$). The most frequently indicated poststroke antithrombotic therapy was DOACs (38.7%). **Conclusion:** We found that the incidence of OAC-induced ICH was greater than in previous studies. Hemorrhage volume and mortality were lower in ICH-DOACs than in ICH-VKAs. After stroke, DOACs were the most frequently indicated antithrombotic treatment.

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Introduction

The mean annual risk of ischemic stroke in patients with atrial fibrillation (AF) not treated with anticoagulants is 6–18% [1, 2]. Vitamin K antagonists (VKAs) have traditionally been the first choice for prophylaxis and have reduced the risk of stroke in patients with AF by approximately 67% [1].

The beneficial effect of VKAs can be diminished by the increased risk of hemorrhage. The risk of intracranial hemorrhage (ICH) in patients receiving VKAs is 0.3–3%, i.e., an 8- to 10-fold greater risk than in patients who do not take VKAs [3, 4]. Furthermore, not only is the risk of ICH increased, but once the hemorrhage occurs, the initial volume [5], risk of expansion, severity, and probability of death are also higher [6, 7]. The mortality rate of ICH is 40–67% [3, 4, 6], and the probability of functional recovery is 17–24.3% [3].

Compared with VKAs, the new direct oral anticoagulants (DOACs) [8–14] have been proven to improve or at least equal the reduction in the risk of ischemic stroke/systemic embolism, reduce the risk of ICH by up to 30–70%, and present lower mortality rates, owing mainly to the reduction in fatal bleeds [2, 4]. Other advantages of DOACs are the few associated drug and food interactions, the rapid onset of action, and the fact that anticoagulation does not have to be monitored [15].

The objective of this study was to perform an exhaustive analysis of the epidemiological, clinical, and radiological characteristics and functional outcome of patients receiving treatment with OACs who experience ICH and to make a comparison between ICH-VKAs and ICH-DOACs.

Patients and Methods

Design

We performed a multicenter, observational, retrospective study based on prospective registers of consecutive patients diagnosed with stroke in most Spanish stroke units. The units were representative of most of the autonomous communities of Spain. The objective of the study was to perform an exhaustive analysis of the epidemiological, clinical, and radiological characteristics and functional outcome of patients receiving treatment with OACs who experience ICH and to make a comparison between ICH-VKAs and ICH-DOACs. The inclusion criteria were diagnosis of spontaneous ICH (intraparenchymal and/or intraventricular), age ≥ 18 years, current treatment with an OAC, and admission to the neurology department (stroke unit or general neurology) during the study period. We excluded cases of subarachnoid hemorrhage, epidural hematoma, and subdural hematoma (irrespective of whether they were traumatic or spontaneous). The

participating centers had to fulfill the following requirements: general hospital status, well-established catchment area, 24/7 availability of an emergency department with neuroimaging (cerebral computed tomography), neurology department with a stroke unit, and a prospective database of patients who had experienced a stroke.

Data were collected via an online form where each center uploaded their findings for demographic variables, vascular risk factors, anticoagulant treatment, characteristics of the stroke, bleeding complications during admission, radiology findings, length of stay, and short- and long-term treatment. Functional outcome at 3 months was measured using the modified Rankin Scale (mRS); this evaluation was performed in person by a neurologist and functional independence was considered when mRS <3. Patients with a previous mRS score ≥ 3 (patients who were previously dependent) were excluded from the analysis of functional status at 3 months in order to avoid assigning subsequent dependence to a preexisting condition. International normalized ratio (INR) was measured at admission and the therapeutic range was considered 2–3 in all patients (except for those bearing metallic cardiac valves in which the therapeutic range was considered to be between 2.5 and 3.5). ICH volume was measured by the investigators of each site and extensive hemorrhage was defined as >100 mL, involvement of deep and lobar areas, and undetermined anatomical origin. In order to perform the epidemiological analysis, we collected data on the activity at each of the participating centers during the study period: catchment population, total number of patients admitted to the neurology department, and total number of patients admitted with a diagnosis of acute stroke (ischemic and hemorrhagic).

We included patients admitted from January 1 to December 31, 2015. The study was performed over a natural year in order to avoid seasonal variations.

Statistical Analysis

Quantitative variables were assessed using measures of central tendency and dispersion depending on the distribution and normality of the variables. Normally distributed variables were expressed as mean $\pm$ SD; nonnormally distributed variables were expressed as median (IQR). Variables were compared using the *t* test or Mann-Whitney test depending on whether the variables fulfilled the criteria for each test. The qualitative variables were expressed as percentages between groups, and associations were analyzed using the χ^2 test (significance was adjusted in multiple comparisons using the Bonferroni correction). Statistical significance was set at $p < 0.05$. Data were analyzed using IBM SPSS® Statistics for Windows, Microsoft Excel® 2016, R v3.3.3 [16], and OpenEpi [17].

Results

Description of the Sample: Clinical and Epidemiological Characteristics

The study population comprised 366 patients from 29 hospital stroke units throughout Spain (Fig. 1). The hospitals attended a population of 11,864,971 inhabitants (25% of the population of Spain during the year of the study); therefore, the crude incidence of OAC-induced ICH was 3.8 (95% CI, 2.78–3.41) cases per 100,000 inhabitants. OAC-induced ICH accounted for 18.2% of the total admissions for ICH, and ICH-DOACs accounted for 1.7% of these admissions (Table 1). Of the 366 cases of OAC-induced ICH, 35 (9.5%) involved ICH-DOACs. Table 2 summarizes the clinical characteristics of both groups and highlights that ICH-DOACs had a higher mean age (81.5 ± 8.3 vs. 77.7 ± 8.3 years; $p = 0.012$) and more often had a history of ischemic stroke (34.3 vs. 19.95; $p = 0.049$). Stroke seemed to be more severe in ICH-VKAs than in ICH-DOACs (median National Institutes of Health Stroke Scale [NIHSS], 9 [14] vs. 7 [12]), although the difference was not statistically significant ($p = 0.37$).

Data on Previous Treatment

The median (IQR) duration of treatment was greater for ICH-VKAs (36 [57.5] vs. 12 [7.75] months; $p < 0.001$). The mean INR in the ICH-VKA group was 2.7 ± 1.1 ; the INR was supratherapeutic in only 28.7% of patients in this group. There were no differences in aPTT

Fig. 1. Geographical distribution of cases: the dots show the location of the main city in the autonomous region.

Table 1. Epidemiological characteristics of ICHs by group

	VKA (n = 331)	DOAC (n = 35)	Total (n = 366)
Crude incidence × 100,000 inhabitants/ year (95% CI)	2.79 (2.5–3.1)	0.3 (0.20–0.40)	3.085 (2.78–3.41)
% with respect to total admissions to the neurology department	1.2	0.1	1.3
% with respect to the total number of cases of stroke	2.0	0.2	2.3
% with respect to the total number of cases of hemorrhage	16.4	1.7	18.2
ICH, intracranial hemorrhage; DOAC, direct oral anticoagulant; VKA, vitamin K antagonist.			

between the groups (ICH-VKA: 48.7 ± 52 s vs. ICH-DOACs: 49.7 ± 66.4 s; $p = 0.9$). We found no significant differences between the groups with respect to concomitant treatment (contraceptives, antiepileptic drugs, digoxin, aspirin, clopidogrel, and nonsteroidal anti-inflammatory drugs).

Radiological Characteristics

Median (IQR) hemorrhage volume was significantly lower in ICH-DOACs than in ICH-VKAs (25 [50.7] vs. 11 [30.8] mL; $p = 0.03$). The topographical distribution of the hemorrhages was comparable in both groups, although the absence of extensive hemorrhaging was noteworthy in the ICH-DOAC group (Table 3). Similarly, in the ICH-DOAC group, we found a lower frequency of ventricular involvement because of the absence of primary intraventricular hemorrhage in ICH-DOACs compared with ICH-VKAs (3.3%).

Table 2. Clinical characteristics of the sample

	Type of oral anticoagulant		p value
	VKA (n = 331)	DOAC (n = 35)	
Female sex	129 (39.00)	18 (51.40)	0.153
Age (mean ± SD), years	77.7±8.3	81.5±8.3	0.012
Baseline NIHSS, median (IQR)	9 (14)	7 (12)	0.336
Prestroke functional independence (mRS <3)	270 (81.60)	24 (68.60)	0.066
Arterial hypertension	265 (80.10)	30 (85.70)	0.421
Diabetes mellitus	113 (34.10)	9 (25.70)	0.315
Hyperlipidemia	160 (48.30)	13 (37.10)	0.207
Ischemic heart disease	59 (17.80)	2 (5.70)	0.068
Atrial fibrillation	263 (79.50)	27 (77.10)	0.748
Previous ischemic stroke	66 (19.90)	12 (34.30)	0.049
Previous hemorrhagic stroke	9 (2.70)	3 (8.60)	0.064
Leukoaraiosis on CT or MRI	48 (14.50)	8 (22.90)	0.192
Smoking	39 (11.80)	1 (2.90)	0.108
Alcohol consumption	20 (6.00)	0 (0.00)	0.135
Anticoagulant drug			
Acenocoumarol	303 (91.50)	–	–
Warfarin	28 (8.50)	–	–
Dabigatran	–	–	–
Rivaroxaban	–	8 (22.90)	–
Apixaban	–	17 (48.60)	–
OAC indication (other than atrial fibrillation)	–	10 (28.60)	–
Pulmonary embolism	13 (3.90)	1 (2.90)	0.7
Deep venous thrombosis	11 (3.30)	0 (0)	0.6
Thrombophilia	3 (0.90)	0 (00)	1
Metallic prosthetic cardiac valves	16 (4.8)	0 (0)	0.4

Values are n (%) unless otherwise indicated. DOAC, direct oral anticoagulant; IQR, interquartile range; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; VKA, vitamin K antagonist.

Table 3. Topographical distribution of hemorrhages by treatment group

	Type of anticoagulant		p
	VKA	DOAC	
Lobar	113 (34.10)	9 (25.70)	0.31
Deep	153 (46.20)	22 (62.90)	0.061
Brainstem	9 (2.70)	1 (2.90)	0.96
Cerebellum	34 (10.30)	3 (8.60)	0.75
Extensive hemispheric	18 (5.40)	0 (0.00)	0.23
Intraventricular (primary or associated)	81 (24.50)	3 (8.60)	0.03

Values are n (%). DOAC, direct oral anticoagulant; VKA, vitamin K antagonist.

Table 4. Hemorrhagic complications, acute-phase treatments, length of stay, and functional outcomes at 3 months

	Type of anticoagulant		p
	VKA	DOAC	
Bleeding complications			
Upper digestive tract bleeding	2 (0.60)	0 (0.00)	0.64
Lower digestive tract bleeding	3 (0.90)	0 (0.00)	0.57
Hematuria	1 (0.30)	0 (0.00)	0.74
Hemoptysis	1 (0.30)	0 (0.00)	0.74
Epistaxis	2 (0.60)	0 (0.00)	0.64
Treatment administered			
Decompressive craniectomy	5 (1.50)	0 (0.00)	0.46
Drainage of hematoma	7 (2.10)	0 (0.00)	0.38
External ventricular drain	19 (5.70)	1 (2.90)	0.47
Minimally invasive surgery	0 (0.00)	0 (0.00)	–
Vitamin K	200 (60.40)	3 (8.60)	<0.001
Hemodialysis	4 (1.20)	0 (0.00)	0.51
Fresh frozen plasma	9 (2.70)	1 (2.90)	0.96
Prothrombin complexes	162 (48.90)	8 (22.90)	0.03
Monoclonal antibodies (reversal agents)	0 (0.00)	0 (0.00)	–
Withdrawing/withholding therapy	60 (18.10)	3 (8.60)	0.15
Stay in ICU during admission	44 (13.30)	1 (2.90)	0.07
Length of stay (mean ± SD), days			
In the stroke unit	2.19±2.6	1.7±2.5	0.35
Total length of stay	12.49±13.7	10.9±11	0.49
Outcome at 3 months ^a			
Functional independence (mRS <3)	85 (31.50)	10 (42.90)	0.28
Death	113 (42.00)	7 (28.60)	0.06
Cause of death (all patients)	101 (72.70)	4 (40.00)	
Stroke-related			0.02
Other cardiovascular causes	7 (5.00)	0 (0.00)	0.5
Other	19 (13.70)	5 (50.00)	0.002
Unknown	12 (8.60)	1 (10.00)	0.88

Values are n (%) unless otherwise indicated. DOAC, direct oral anticoagulant; ICU, intensive care unit; mRS, modified Rankin scale; VKA, vitamin K antagonist. ^a Only previously independent patients.

In-Hospital Outcome and Medium-Term Outcome

The overall rate of hemorrhagic complications was low, the most frequent type being upper digestive tract bleeding, which affected 0.9% of ICH-VKAs (Table 4). No systemic bleeding events were detected in ICH-DOACs during admission. The distribution of treatment administered during the acute phase was similar in both groups, although it is noteworthy that in ICH-DOACs, no patients underwent surgery and the frequency of admission to the intensive care unit was lower. Administration of vitamin K and prothrombin complexes was more common in ICH-VKAs. The mean total length of stay seemed to be greater – albeit without statistical significance – in ICH-VKAs (12.49 ± 13.7 vs. 10.9 ± 11 days; $p = 0.35$), as was the need to remain in the stroke unit (2.19 ± 2.6 vs. 1.7 ± 2.5 days; $p = 0.49$). There were no statistically significant differences in functional status between ICH-DOACs and ICH-VKAs groups at 3 months (mRS <3 at 3 months: 42.9 vs. 31.5% respectively; Fig. 2)

Fig. 2. Functional outcome (modified Rankin Scale, mRS) of patients at 3 months after stroke. DOAC, direct oral anticoagulant; VKA, vitamin K antagonist.

Fig. 3. Antithrombotic treatment at 3 months according to the type of previous treatment. DOACs, direct oral anticoagulants; VKAs, vitamin K antagonists; LMWH, low molecular-weight heparin.

More patients died in the ICH-VKA group, and the most frequent cause of death was cerebral hemorrhage; stroke-related mortality was greater in ICH-VKAs (40 vs. 72.7%; $p = 0.02$). The most frequently indicated treatment in survivors was DOACs (33.6%), followed by antiplatelet agents (18.9%), and then by withholding of antithrombotic treatment (16.6%) (Fig. 3).

Discussion

In our study, we found the incidence of OAC-induced ICH to be 3.8 cases per 100,000 inhabitants, i.e., 18.2% of all admissions for ICH. DOACs were the anticoagulants administered at admission in 9.5% of cases of OAC-induced ICH. Patients in the ICH-DOAC group were older and more frequently had a previous ischemic stroke, lower ICH volume at admission, and lower stroke-related mortality (all differences statistically significant).

The EPICES study (a prospective study of patients with stroke admitted to the neurology department based on registries of data collected over 4 nonconsecutive months between 2008 and 2009 throughout Spain) showed that anticoagulant-associated ICH accounted for 8.4% of all brain hemorrhages [18]; this percentage was 13.6% in the TAC Registry study [3]. Part of the increased percentage in our study could be due to better control of arterial hypertension, which could have helped to reduce the incidence of the main cause of spontaneous ICH [19]. Nevertheless, global incidence in our study was greater than previously described (2.9 per 100,000 inhabitants/year in the TAC Registry 1 study), possibly due in part to the increase in the incidence of AF coinciding with aging of the population or prescription of anticoagulants.

Although up to 18% of patients aged >80 years in Spain have AF, the latest population-based studies place the overall prevalence of AF in Spain at 4.4%, a percentage that has remained stable since 1999 [20]. In the TAC Registry 2 study, we included patients receiving DOACs and not only those receiving VKA, as was the case in the TAC Registry 1 study. Therefore, given the results of pivotal clinical trials with DOACs, increasingly more patients with previously known AF may not have been receiving anticoagulant therapy because of the high risk of hemorrhage and are now receiving DOACs.

Observational studies [21, 22] showed that ICH-DOACs had a greater previous risk of hemorrhage than ICH-VKAs. In our study, both age and frequency of previous ischemic stroke were higher in the ICH-DOAC group. Both factors are included in bleeding risk scales, as are arterial hypertension, history of ICH, and leukoaraiosis, which in our study were more frequent – albeit not statistically significantly – in ICH-DOACs [23].

Nevertheless, almost 10% of OAC-induced ICH in our study and up to 20% in published series [4] were in patients taking DOACs; therefore, the risk of hemorrhage associated with these drugs, while significantly lower, cannot be underestimated. When DOACs were first introduced, they were thought to have 2 main disadvantages: the absence of a monitoring parameter and the absence of an antidote to reverse their effect [15]. First, of note, only 1 in 3 ICH-VKAs (28.7% in our study) occur when the INR is supratherapeutic; therefore, a monitoring method is not necessarily valid for predicting the risk of bleeding. Second, although VKAs have a specific antidote, the effect takes hours to appear; in addition, other treatments, such as prothrombin complex and fresh frozen plasma have been proven to rapidly correct INR but were not associated with a lower mortality rate [6, 24, 25]. Furthermore, monoclonal antibodies that can reverse the anticoagulant effect of DOACs have been developed in recent years [26, 27], although none of the patients in the present study received these drugs; therefore, we were unable to evaluate their usefulness.

Other factors that affect the prognosis of ICH include age, infratentorial location, and Glasgow scale score on admission [28]. Hematoma growth is also a key determinant of prognosis and depends in turn on the initial ICH volume, recurrence of ICH, previous anticoagulation therapy with VKAs, and extension to the ventricles [29]. Therefore, in our study, it was noteworthy that in ICH-DOACs, the bleed was smaller, an intraventricular component was less frequent, and stroke-related mortality was lower than in ICH-VKAs (all differences statistically significant). In other studies [4, 21, 30], there was also a greater trend toward functional independence at 3 months, which in our study, as in a recent study in Portugal [22], did not reach statistical significance.

Large observational studies have shown that the risk of thromboembolic events is greater in patients who do not restart anticoagulation therapy and that restarting treatment after the favorable outcome of the previous ICH is confirmed does not increase the risk of death [31–33]. Some authors believe that anticoagulation therapy is commonly recommended after ICH, with DOACs as the treatment of choice owing to their safety profile [34]. Under these circumstances, there is no evidence for greater safety with one DOAC over another; therefore, this decision, which in our series favors apixaban, seems to depend on individual factors [14, 35].

In most cases, given that the combined risk of recurrence of ICH and stroke seems to be lowest at some time between week 1 and week 30 [27, 36], the most recent clinical practice guidelines recommend restarting anticoagulation therapy between weeks 4 and 8, especially when the cause of bleeding has been resolved [34]. In the present study, 18.89% of patients were receiving antiplatelet treatment and 16.59% were not receiving treatment 3 months after their ICH, possibly reflecting the lack of adherence to guidelines.

Our study is subject to a series of limitations. The fact that it is a retrospective study based only on data from patients attended in the neurology departments of the Spanish National Health System could have led to underrecording. Furthermore, for each patient, we only have neuroimaging findings and laboratory findings at admission; therefore, we were unable to evaluate the effect of therapy on these surrogate parameters and the possible association with morbidity and mortality. Additionally, different investigators measured ICH volume. Lastly, in several patients, we do not know the functional prognosis or prophylaxis prescribed.

In summary, we found that the incidence of OAC-induced ICH is greater than that described elsewhere and that it has tended to rise in recent years in Spain, although with slightly lower mortality. Hematoma volume and the frequency of ICH-related death were lower in patients who had previously received treatment with DOACs; therefore, the results of our study indicate that these drugs are the safest option in patients with nonvalvular AF and a high risk of hemorrhage.

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Statement of Ethics

As this was a noninterventional retrospective study in which patients' personal data were not collected, informed consent was not necessary. The study was approved by the Ethics Committee of Hospital Universitario de La Princesa, Madrid, Spain, and a request for the study to be classified was made to the Spanish Agency of Medicinal Products and Medical Devices, which approved the classification of postauthorization study.

Disclosure Statement

The authors declare that they have no conflicts of interest.

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Appendix

Study Investigators

Autonomous Community	Hospital	Investigator(s)
Andalucía	Virgen del Rocío, Sevilla	Francisco Moniche, Blanca Pardo-Galiana, Irene Escudero
Aragón	Clínico Universitario Lozano Blesa, Zaragoza	Carlos Tejero
Asturias	Central de Oviedo, Asturias	Sergio Calleja, Lorena Benavente
Balearic Islands	Son Espases, Balears	Carmen Jiménez Martínez, María Moragues
Castilla La Mancha	Complejo Hospitalario General Universitario de Albacete	Eva Fernández Díaz, Ana López, Tomás Segura
	Hospital General La Mancha Centro, Ciudad Real	Enrique Botia, Pablo del Saz, Rafael García Ruiz
	Complejo Hospitalario de Toledo	Carlos Marsal, Francisco Muñoz
Catalonia	Hospital del Mar, Barcelona	Jaume Roquer, Alejandra Gomez Gonzalez
	Hospital Universitari Clínic de Barcelona	Angel Chamorro, Blanca Llull
	Hospital Universitari de Bellvitge, L'Hospitalet de Llobregat	Pere Cardona
	Santa Creu i Sant Pau, Barcelona	Joan Martí Fabregas, Alejandro Martínez Domeño
	Arnau de Vilanova, Lleida	Francisco Purroy
	Dr. Josep Trueta. Girona	Joaquín Serena
Galicia	Complejo Hospitalario Universitario A Coruña	Mar Castellanos, Alexia Roel García, María Feal Painceiras.
	Hospital Clínico Universitario de Santiago de Compostela	Manuel Rodríguez Yáñez
	Complejo Hospitalario Universitario de Vigo	José Maciñeiras, Pablo Vicente Alba
Canary Islands	Hospital Ntra. Sra. De la Candelaria, Tenerife	Antonio Medina
	Hospital Universitario de Gran Canaria Dr Negrín, Las Palmas de Gran Canaria	Juan Carlos López Fernández, Diana Ramos Rodríguez
Madrid	Clínico Universitario San Carlos, Madrid	José Egidio
	Universitario de La Princesa, Madrid	Gustavo Zapata Wainberg, Sonia Quintas Gutiérrez, Álvaro Ximénez-Carrillo, José Vivancos
	Universitario La Paz, Madrid	Blanca Fuentes
	Universitario Ramón y Cajal, Madrid	Jaime Masjuán
	General Universitario Gregorio Marañón, Madrid	Andres García Pastor, Sergio López Anguita, Ana Saldaña Díaz
	Universitario 12 de Octubre, Madrid	Jaime Díaz Guzmán
Murcia	Universitario Virgen de la Arrixaca, Murcia	Laura Albert
Basque Country	Basurto, Bilbao	Mar Freijó
	Universitario de Donosti	Maite Martínez, Amaia Muñoz Lopetegui
Valencia	Universitario y Politécnico La Fe, Valencia	Aida Lago
	Clínico Universitario de Valencia	José Miguel Láinez, Anna Ramos

References

- 1 van Nieuwenhuizen KM, van der Worp HB, Algra A, et al: Apixaban versus antiplatelet drugs or no antithrombotic drugs after anticoagulation-associated intracerebral haemorrhage in patients with Atrial Fibrillation (APACHE-AF): study protocol for a randomised controlled trial. *Trials* 2015;16:393.
- 2 Milling TJ, Spyropoulos AC: Re-initiation of dabigatran and direct factor Xa antagonists after a major bleed. *Am J Med* 2016;129:S54–S63.
- 3 Zapata-Wainberg G, Ximénez-Carrillo Rico Á, Benavente Fernández L, et al: Epidemiology of intracranial haemorrhages associated with vitamin K antagonist oral anticoagulants in Spain: TAC Registry. *Interv Neurol* 2015;4:52–58.
- 4 Wilson D, Charidimou A, Shakeshaft C, et al: Volume and functional outcome of intracerebral hemorrhage according to oral anticoagulant type. *Neurology* 2015;86:360–366.
- 5 Flaherty ML, Tao H, Haverbusch M, et al: Warfarin use leads to larger intracerebral hematomas. *Neurology* 2008;71:1084–1089.
- 6 Steiner T, Rosand J, Diringer M: Intracerebral hemorrhage associated with oral anticoagulant therapy: current practices and unresolved questions. *Stroke* 2006;37:256–262.
- 7 Sjöblom L, Hårdemark HG, Lindgren A, et al: Management and prognostic features of intracerebral hemorrhage during anticoagulant therapy: a Swedish multicenter study. *Stroke* 2001;32:2567–2574.
- 8 Connolly SJ, Ezekowitz MD, Yusuf S, et al: Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;361:1139–1151.
- 9 Patel MR, Mahaffey KW, Garg J, et al: Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;365:883–891.
- 10 Granger CB, Alexander JH, McMurray JJ, et al: Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;365:981–992.
- 11 Giugliano RP, Ruff CT, Braunwald E, et al: Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013;369:2093–2104.
- 12 Flaker GC, Eikelboom JW, Shestakovska, et al: Bleeding during treatment with aspirin versus apixaban in patients with atrial fibrillation unsuitable for warfarin: the apixaban versus acetylsalicylic acid to prevent stroke in atrial fibrillation patients who have failed or are unsuitable for vitamin K antagonist treatment (AVERROES) trial. *Stroke* 2012;43:3291–3297.
- 13 Ellis MH, Neuman T, Bitterman H, et al: Bleeding in patients with atrial fibrillation treated with dabigatran, rivaroxaban or warfarin: a retrospective population-based cohort study. *Eur J Intern Med* 2016;33:55–59.
- 14 Chatterjee S, Sardar P, Biondi-Zoccai G, Kumbhani DJ: New oral anticoagulants and the risk of intracranial hemorrhage: traditional and Bayesian meta-analysis and mixed treatment comparison of randomized trials of new oral anticoagulants in atrial fibrillation. *JAMA Neurol* 2013;70:1486–1490.
- 15 Zapata Wainberg G, Ximénez-Carrillo Rico A, Vivancos Mora J: Manejo clínico de los nuevos anticoagulantes. *Neurología* 2012;27:33–38.
- 16 R Development Core Team. R: a Language and Environment for Statistical Computing. Vienna, R Foundation for Statistical Computing, 2008.
- 17 Sullivan KM, Dean A, Soe MM: OpenEpi: a web-based epidemiologic and statistical calculator for public health. *Public Health Rep* 1989;124:471–474.
- 18 Arias-Rivas S, Vivancos J, Castillo J, et al: Epidemiología de los subtipos de ictus en pacientes hospitalizados atendidos por neurólogos; resultados del registro EPICES (I). *Rev Neurol* 2012;54:385–393.
- 19 An SJ, Kim TJ, Yoon B: Epidemiology, risk factors, and clinical features of intracerebral hemorrhage: an update. *J Stroke* 2017;19:3–10.
- 20 Gómez-Doblas JJ, Muñoz J, Martín JJ, et al: Prevalence of atrial fibrillation in Spain. OFRECE study results. *Rev Esp Cardiol (Engl Ed)* 2014;67:259–269.
- 21 Hagii J, Tomita H, Metoki N, et al: Characteristics of intracerebral hemorrhage during rivaroxaban treatment: comparison with those during warfarin. *Stroke* 2014;45:2805–2807.
- 22 Marques-Matos C, Alves JN, Marto JP, et al: POST-NOAC: Portuguese observational study of intracranial hemorrhage on non-vitamin K antagonist oral anticoagulants. *Int J Stroke* 2017;12:623–627.
- 23 Pisters R, Lane DA, Nieuwlaar R, de Vos CB, Crijns HJ, Lip GY: A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest* 2010;138:1093–1100.
- 24 Dowlatshahi D, Butcher KS, Asdaghi N, et al: Poor prognosis in warfarin-associated intracranial hemorrhage despite anticoagulation reversal. *Stroke* 2012;43:1812–1817.
- 25 Parry-Jones AR, Di Napoli M, Goldstein JN, et al: Reversal strategies for vitamin K antagonists in acute intracerebral hemorrhage. *Ann Neurol* 2015;78:54–62.
- 26 Pollack CV Jr, Reilly PA, Eikelboom J, et al: Idarucizumab for dabigatran reversal. *N Engl J Med* 2015;373:511–520.
- 27 Connolly SJ, Milling TJ Jr, Eikelboom JW, et al: Andexanet alfa for acute major bleeding associated with factor Xa inhibitors. *N Engl J Med* 2016;375:1131–1141.
- 28 Hemphill JC 3rd, Bonovich DC, Besmertis L, Manley GT, Johnston SC: The ICH score: a simple, reliable grading scale for intracerebral hemorrhage. *Stroke* 2001;32:891–897.

- 29 Wang X, Arima H, Al-Shahi Salman R, et al: Clinical prediction algorithm (BRAIN) to determine risk of hematoma growth in acute intracerebral hemorrhage. *Stroke* 2015;46:376–381.
- 30 Takahashi H, Jimbo Y, Takano H, et al: Intracerebral hematoma occurring during warfarin versus non-vitamin K antagonist oral anticoagulant therapy. *Am J Cardiol* 2016;118:222–225.
- 31 Nielsen PB, Larsen TB, Skjøth F, Lip GYH: Outcomes associated with resuming warfarin treatment after hemorrhagic stroke or traumatic intracranial hemorrhage in patients with atrial fibrillation. *JAMA Intern Med* 2017;177:1–7.
- 32 Kuramatsu JB, Gerner ST, Schellinger PD, et al: Anticoagulant reversal, blood pressure levels, and anticoagulant resumption in patients with anticoagulation-related intracerebral hemorrhage. *JAMA* 2015;313:824–836.
- 33 Yung D, Kapral MK, Asllani E, Fang J, Lee DS; Investigators of the Registry of the Canadian Stroke Network: Reinitiation of anticoagulation after warfarin-associated intracranial hemorrhage and mortality risk: the Best Practice for Reinitiating Anticoagulation Therapy after Intracranial Bleeding (BRAIN) Study. *Can J Cardiol* 2012;28:33–39.
- 34 Kirchhof P, Benussi S, Kotecha D, et al: 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur J Cardiothorac Surg* 2016;50:e1–e88.
- 35 Yoon CH, Park YK, Kim SJ, et al: Eligibility and preference of new oral anticoagulants in patients with atrial fibrillation: comparison between patients with versus without stroke. *Stroke* 2014;45:2983–2988.
- 36 Majeed A, Kim YK, Roberts RS, Holmström M, Schulman S: Optimal timing of resumption of warfarin after intracranial hemorrhage. *Stroke* 2010;41:2860–2866.