ARTICLE

MRI predicts intracranial hemorrhage in patients who receive long-term oral anticoagulation

Joan Martí-Fàbregas, MD, PhD, Santiago Medrano-Martorell, MD, Elisa Merino, MD, Luis Prats-Sánchez, MD, Rebeca Marín, RN, Raquel Delgado-Mederos, MD, PhD, Alejandro Martínez-Domeño, MD, Pol Camps-Renom, MD, Elena Jiménez-Xarrié, PhD, Mariluisa Zedde, MD, Manuel Gómez-Choco, MD, PhD, Lidia Lara, MD, Amèlia Boix, MD, Ana Calleja, MD, Ana María De Arce-Borda, MD, Yolanda Bravo, MD, PhD, Blanca Fuentes, MD, PhD, María Hernández-Pérez, MD, PhD, David Cánovas, MD, PhD, Laura Llull, MD, PhD, Beatriz Zandio, MD, Marimar Freijo, MD, Ignacio Casado-Naranjo, MD, Jordi Sanahuja, MD, Dolores Cocho, MD, PhD, Jerzy Krupinski, MD, PhD, Ana Rodríguez-Campello, MD, PhD, Ernest Palomeras, MD, PhD, Alicia De Felipe, MD, Marta Serrano, MD, Elena Zapata-Arriaza, MD, Josep Zaragoza-Brunet, MD, Inmaculada Díaz-Maroto, MD, Jessica Fernández-Domínguez, MD, PhD, Aida Lago, MD, José Maestre, MD, Manuel Rodríguez-Yáñez, MD, PhD, and Ignasi Gich, MD, PhD, for the HERO study investigators

Correspondence
Prof. Martí-Fàbregas
jmarti@santpau.cat

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Abstract

Objective

We tested the hypothesis that the risk of intracranial hemorrhage (ICH) in patients with cardioembolic ischemic stroke who are treated with oral anticoagulants (OAs) can be predicted by evaluating surrogate markers of hemorrhagic-prone cerebral angiopathies using a baseline MRI.

Methods

Patients were participants in a multicenter and prospective observational study. They were older than 64 years, had a recent cardioembolic ischemic stroke, and were new users of OAs. They underwent a baseline MRI analysis to evaluate microbleeds, white matter hyperintensities, and cortical superficial siderosis. We collected demographic variables, clinical characteristics, risk scores, and therapeutic data. The primary endpoint was ICH that occurred during follow-up. We performed bivariate and multivariate Cox regression analyses.

Results

We recruited 937 patients (aged 77.6 ± 6.5 years; 47.9% were men). Microbleeds were detected in 207 patients (22.5%), moderate/severe white matter hyperintensities in 419 (45.1%), and superficial siderosis in 28 patients (3%). After a mean follow-up of 23.1 ± 6.8 months, 18 patients (1.9%) experienced an ICH. In multivariable analysis, microbleeds (hazard ratio 2.7, 95% confidence interval [CI] 1.1–7, $p = 0.034$) and moderate/severe white matter hyperintensities (hazard ratio 5.7, 95% CI 1.6–20, $p = 0.006$) were associated with ICH (C index 0.76, 95% CI 0.66–0.85). Rate of ICH was highest in patients with both microbleed and moderate/severe WMH (3.76 per 100 patient-years, 95% CI 1.62–7.4).

Conclusion

Patients taking OAs who have advanced cerebral small vessel disease, evidenced by microbleeds and moderate to severe white matter hyperintensities, had an increased risk of ICH. Our results should help to determine the risk of prescribing OA for a patient with cardioembolic stroke.

ClinicalTrials.gov identifier

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Page 981

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HERO coinvestigators are listed in appendix 2.

Glossary

AF = atrial fibrillation; **CAA** = cerebral amyloid angiopathy; **CHA** = cerebral hypertensive angiopathy; **CHA_2DS_2-VASc** = congestive heart failure (or left ventricular systolic dysfunction), hypertension: blood pressure consistently above 140/90 mm Hg (or treated hypertension on medication), age ≥75 years, diabetes mellitus, prior stroke or TIA or thromboembolism, vascular disease (e.g., peripheral artery disease, myocardial infarction, aortic plaque), age 65–74 years, sex category (i.e., female sex); **CI** = confidence interval; **CROMIS-2** = Clinical Relevance of Microbleeds in Stroke–2; **cSS** = cortical superficial siderosis; **DOAC** = direct oral anticoagulant; **FLAIR** = fluid-attenuated inversion recovery; **GRE** = gradient-recalled echo; **HAS-BLED** = hypertension, abnormal renal and liver function, stroke, bleeding, labile INR, elderly, drugs or alcohol; **HERO** = Hemorrhage Predicted by Resonance in Patients Receiving Oral Anticoagulants; **HR** = hazard ratio; **ICH** = intracranial hemorrhage; **INR** = international normalized ratio; **MB** = microbleed; **OA** = oral anticoagulant; **SS** = superficial siderosis; **SWI** = susceptibility-weighted imaging; **VKA** = vitamin K antagonist; **WMH** = white matter hyperintensity; **WML** = white matter lesion.

Long-term treatment with oral anticoagulants (OAs) is very effective for the secondary prevention of ischemic stroke and systemic embolism in patients who had a cardioembolic stroke.[1,2] However, the possibility of major bleeding, and particularly intracranial hemorrhage (ICH), is a major concern and accounts for the underuse of OAs,[3] especially in elderly patients, in whom ICH risk is much greater than in young patients.[4] Therefore, there is a need to improve the data to help select patients who are suitable for safe OA treatment.

One explanation for the increased ICH risk associated with aging is the existence of an underlying cerebral hemorrhagic–prone angiopathy, either amyloid or hypertensive.[5] Currently, MRI can detect surrogate markers of these angiopathies.[3,6,7] Strictly lobar microbleeds (MBs) and cortical superficial siderosis (cSS) are surrogate markers of cerebral amyloid angiopathy (CAA). Deep MBs are markers of cerebral hypertensive angiopathy (CHA), and white matter hyperintensities (WMH) are a marker of both CAA and CHA. Studies in patients with ischemic stroke[8–10] consistently showed that MBs are associated with an increased risk of hemorrhagic stroke during follow-up, and in some studies, even with ischemic stroke. Likewise, WMH[11–13] and cSS[14,15] are associated also with ICH.

The risk of an intracranial bleeding may be too high with the administration of OAs in a patient with ischemic stroke and with an underlying cerebral hemorrhagic–prone angiopathy.[16–20] One study[21] of patients with an acute cardioembolic stroke treated with OAs reported that MBs were independently associated with ICH risk (hazard ratio [HR] = 3.67). Additional cohorts are needed to investigate whether the risk associated with OA therapy is greater than the benefit in patients with MBs, WMH, or SS.

Our aim was to prospectively follow up a large cohort of patients with acute cardioembolic stroke who were new users of OAs and who underwent a cerebral MRI at the start of OA treatment. We hypothesized that the presence of MRI-surrogate markers of hemorrhagic-prone angiopathies at baseline predicts an increased risk of ICH during follow-up.

Methods

Standard protocol approvals, registrations, and patient consents

We conducted our study at 29 centers (28 Spanish, 1 Italian). The local ethics committee approved the study at each center. Written informed consent was obtained from all participants or their legal representatives.

We used the acronym "HERO" to define our study. It stands for the risk of intracranial Hemorrhage Predicted by Resonance in Patients Receiving Oral Anticoagulants. The study was registered at ClinicalTrials.gov with the identifier NCT02238470.

Patients

Investigators at each center prospectively included patients fulfilling the following inclusion criteria: (1) age 65 years or older; (2) TIA or cerebral infarct attributed to a recent cardiac embolism and who were considered candidates by the local neurologist to start indefinite OA treatment for the secondary prevention of ischemic stroke. Patients with atrial fibrillation (AF) or with other high-risk cardioembolic sources diagnosed by routine clinical assessment from individual clinicians were acceptable, and TOAST (Trial of Org 10172 in Acute Stroke Treatment) criteria were suggested. The study did not recommend the use of one type of anticoagulant over another. The local researcher chose the anticoagulant (vitamin K antagonists [VKAs] or direct oral anticoagulants [DOACs]) that seemed most suitable for secondary prevention according to his/her preferences and the specific characteristics of the patient. Likewise, international normalized ratio (INR) monitoring was according to local protocols; (3) the patient is a new user of any OA; (4) the consent to participate is signed before performing MRI; (5) MRI is performed within 1 month of the index ischemic stroke; and (6) follow-up is possible by a face-to-face or a telephone interview with either the patient or a caregiver.

We excluded patients with a contraindication to perform an MRI, or in whom MRI was not done, or not uploaded to the website, or was technically not acceptable. Also, we excluded patients who used OAs for other reasons than the secondary

prevention of cardiac embolism and those with an absolute contraindication for OA treatment according to local protocols.

Clinical variables

We recorded the following: demographic data (age, sex); traditional vascular risk factors: previous cerebral infarct, TIA, intracerebral hemorrhage, hypertension, diabetes mellitus, hypercholesterolemia, hypertriglyceridemia, smoking, alcohol abuse, chronic renal insufficiency, ischemic heart disease, peripheral vascular disease, AF, valvular heart disease, cancer, advanced liver disease; the CHA_2DS_2-VASc score and the HAS-BLED score after the index stroke; prior Rankin Scale score and at discharge; type of stroke (TIA or cerebral infarct); and therapeutic data: pretreatment with antiplatelet drugs and statins, type of OA (VKA, DOAC), and concurrent treatment with antiplatelets.

Neuroradiologic evaluation

MRI was performed within 1 month from the onset of symptoms. MRI scans were performed at each site with the available equipment (1T, 1.5T, or 3T) and according to standard protocols. MRI included a T2*-weighted gradient-recalled echo (T2*-GRE) and/or susceptibility-weighted imaging (SWI) for assessment of MB and cSS, and a fluid-attenuated inversion recovery (FLAIR) sequence for assessment of WMH. The scans were uploaded to our website. Two neuroradiologists, who were blinded to the clinical data, evaluated the MRI scans. Standard definitions were used.[6] MB was defined as a rounded small hypointense lesion of up to 10 mm in diameter, as evidenced in T2*-GRE or SWI images and after having ruled out MB mimics. We assessed MB burden and distribution with the MARS (Microbleed Anatomical Rating Scale).[22] According to previous studies,[23] we grouped patients with deep or mixed MB as CHA. Brainstem and cerebellar MBs were considered deep MBs. WMH were defined as deep and periventricular white matter hyperintense lesions of presumed vascular origin detected on FLAIR sequences. Its severity was quantified by the Fazekas scale,[24] and the highest score at the periventricular or deep white matter was used. Patients with a score of 2 or 3 had moderate and severe WMH. cSS was defined as signal loss on T2*-GRE and SWI sequences in a curvilinear pattern following the gyral cortical surface.[14,15] It was classified as focal (restricted to ≤3 sulci) or disseminated (affecting 4 or more sulci).

Follow-up and outcomes

Follow-up data were obtained from the patient or a caregiver with a structured telephone interview in which questions were asked about vascular and nonvascular events and about the reason for any treatment modifications. Telephone interviews were performed at 3, 6, 9, 12, 15, 18, 21, and 24 months after inclusion, but longer follow-ups were accepted. Recruitment started in April 2012 and finished in September 2015; therefore, follow-up finished in September 2017. The local neurologist was contacted when important information (cause of death and details from patients with ICH and other important events) was missing or incomplete. The local neurologist gathered all the available information including medical reports and digitalized medical information stored in the health system.

The primary endpoint of our study was ICH (intracerebral, subdural, or subarachnoid), either spontaneous or traumatic during follow-up. We required a neuroimaging result of the acute intracranial bleeding. Secondary endpoints included the following: recurrent ischemic stroke; ischemic heart disease (acute myocardial infarction or angina); vascular events (ICH, recurrent ischemic stroke, ischemic heart disease, systemic embolism, pulmonary thromboembolism, and aortic dissection); major hemorrhages (according to the definition by the International Society on Thrombosis and Hemostasis[25]); death from any cause; and vascular death (a fatal vascular event and sudden death without explanation).

During follow-up, we recorded the definite stop of OA treatment, addition or cessation of antiplatelet therapy, and change from OA-VKA to DOACs and vice versa.

In addition to ICH and death, the follow-up was finished when there was withdrawal of consent, the inability to contact the patient or caregiver, or if we were unable to gather information from the local neurologist.

Statistical analysis

The statistical analysis was predefined before the start of recruitment. Based on previous observational studies,[26] we assumed an ICH frequency of 2% during the first year of follow-up and 1% during the second year. The sample size analysis was performed with a dichotomous predictive variable (MB vs no MB) and the dependent variable (ICH) by means of a logistic regression. We assumed that the frequency of ICH during 2 years of follow-up will be 3.5% in patients with MB compared to 0.5% in patients without MB. This would provide sufficient power (minimum of 80%) and would allow the conclusion that the difference is significant ($\alpha = 0.05$, bilateral approach), accepting a small percentage of losses (SamplePower, V2.0/event rates [IBM Corp., Armonk, NY], set at 0.035 vs 0.005). The total number of patients to be included in the study was 1,000 and at the end of follow-up, we calculated to diagnose about 30 patients with ICH compared with 970 without ICH.

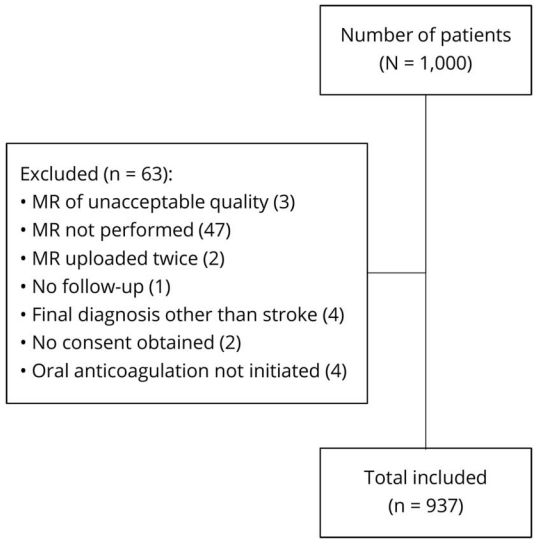
The results are expressed as percentages for categorical variables, as mean and standard deviation for continuous variables, and as median (interquartile range) for ordinal variables. The comparison of clinical and neuroimaging variables from patients with or without ICH was performed using Cox-regression analyses and with calculations of the HRs. In addition, we performed a multivariate Cox-regression analysis with variables that had a $p < 0.1$ in the bivariate analysis and calculated the Harrell C index. We repeated the analysis adjusted for age, because age is a risk factor for ICH. We assessed the proportional hazards assumption of factors included in the model, with log-log plots of the log cumulative.

Figures were obtained with Kaplan-Meier cumulative incidence curves. The following Cox-regression analyses were planned also to evaluate the risk of ICH: the distribution of MB (lobar vs deep/mixed), the amount of MB (by comparing ICH risk in patients with no MB, patients with 1 MB, and patients with 2 or more MBs). Interrater percentage of agreement on MB, WMH, and cSS diagnosis was calculated for a sample of 50 patients. When a value was missing, numbers and percentages were given with the actual denominator. No patients with ICH had missing values. No missing imputations were done. All the analyses were performed using the statistical package IBM-SPSS (V25).

Data availability

The database containing information of deidentified patients enrolled in the HERO study and the statistical analysis plan will be shared at formal request by a qualified investigator who wants to replicate procedures and results. The request should be addressed to the corresponding author.

Figure 1 Participant flowchart



Results

We recruited 1,000 patients. For analyses, we included 937 patients with clinical and MRI data, as shown in figure 1. Their mean age was 77.6 ± 6.5 years and 449 patients (47.9%) were men. Deviations from the inclusion and exclusion criteria were noted: 2 patients had received OA previously, consent was obtained after MRI in 1 patient, and MRI was performed after 1 month in 4 patients.

Clinical characteristics are detailed in table 1. Of note, about half of the patients had a previously known AF but were not receiving OA. A high percentage of patients (46%) were treated currently with antiplatelet drugs. CHA_2DS_2-VASc (5 [4–6]) and HAS-BLED (2 [2–2]) scores were typical of a stroke population. Two-thirds of patients were started on VKA whereas one-third were on DOACs. During follow-up, OA was discontinued at some time point in 42 (4.5%); antiplatelet treatment was added to 21 (2.2%) and discontinued in 3 patients (0.3%); 37 patients (3.9%) changed from VKA to DOAC and 9 (1%) changed from DOAC to VKA therapy.

MRI results

Table 2 shows the details of the MRI results. FLAIR sequences were available in 929 of the patients (99.1%) while SWI (n = 450) and/or GRE (n = 833) sequences were available in 919 (98%). Information from both SWI/GRE and FLAIR sequences were available in 911 (97.2%).

In patients with MB, median MB number was 2 (interquartile range 1–3), and 207 patients (22.5%) had at least 1 MB. The majority of patients with MB had only 1 (47%) or 2 MBs (25%) and only a small portion of patients had ≥5 MBs (16.5%). A total of 419 (45%) had moderate/severe WMH and 0.4% had disseminated cSS. A total of 121 patients (13%) had both MB and moderate/severe WMH. Percentage of agreement between both neuroradiologists was 90.5% for MB, 75.6% for WMH, and 95.2% per cSS.

Outcomes

During a mean follow-up of 23.1 ± 6.8 months, 18 patients experienced an ICH, which was intracerebral in 15 of them. This is a rate of 1.01 per 100 patient-years (95% confidence interval [CI] 0.6–1.59). The ICH rate/100 patient-years according to the presence of MB, moderate/severe WMH, or both are provided in table 3. ICH occurred in 9 patients with MB and 9 patients without MB, and the rate for patients with MB was 2.33 per 100 patient-years (95% CI 1.06–4.41). ICH occurred in 3 patients with no/mild WMH but 15 with moderate/severe WMH, and the rate for patients with moderate/severe WMH was 1.96 per 100 patient-years (95% CI 1.1–3.23). Both MB and moderate/severe WMH were present in 8 patients with ICH and the rate in this subgroup of patients was 3.76 per 100 patient-years (95% CI 1.62–7.4).

Table 4 shows bivariate comparison of clinical and radiologic variables associated with the risk of ICH. Presence of MB (HR = 3.51, 95% CI 1.39–8.85, p = 0.008; figure 2A) and moderate/severe WMH (HR = 6.58, 95% CI 1.90–22.7, p = 0.003; figure 2B) was associated with the rate of ICH (figure 2), while CHA_2DS_2-VASc score was not different in patients with or without ICH. Of note, age, cSS, or HAS-BLED was not associated with the ICH rate. The multivariate Cox regression analysis showed that MB (HR = 2.7, 95% CI 1.1–7, p = 0.031) and WMH (HR = 5.7, 95% 1.6–20, p = 0.006) were associated with the rate of ICH, and the C index was 0.76 (95% CI 0.66–0.85). After adjusting for age, we obtained almost identical values (HR = 2.7 for MB and HR = 5.8 for WMH). Type of OA was not associated with ICH rate. The ICH risk according to the amount of MB was assessed by a Cox regression analysis in 3 groups of patients: patients without MB, patients with 1 MB, and patients with more than

Table 1 Clinical characteristics of the patients (n = 937)

Age, y, mean (SD)	77.6 (6.5)
Sex	
Men	449 (47.9)
Women	488 (52.1)
Previous cerebral infarct	246 (26.2)
Previous TIA	82 (8.7)
Previous intracerebral hemorrhage	8 (0.8)
Arterial hypertension	694 (74.3)
Diabetes mellitus	231 (22.8)
Hypercholesterolemia	444 (47.5)
Hypertriglyceridemia	84 (9.2)
Smoking habit	74 (7.9)
Alcohol abuse	50 (5.4)
Chronic renal insufficiency	67 (7.2)
Ischemic heart disease	146 (15.6)
Congestive heart failure	72 (7.7)
Peripheral vascular disease	53 (5.7)
Previous atrial fibrillation	468 (50.2)
Valvular heart disease	39 (4.2)
Other high-risk cardioembolic sources	37 (4)
Cancer	101 (10.8)
Advanced liver disease	15 (1.6)
Prior treatment with antiplatelet drugs	431 (46.4)
Prior treatment with statins	373 (40.1)
CHA_2DS_2-VASc score at inclusion	5 (4–6)
HAS-BLED score at inclusion	2 (2–2)
Previous Rankin Scale score	0 (0–1)
Rankin Scale score at discharge	2 (0–3)
Type of stroke	
TIA	197 (21.3)
Cerebral infarct	728 (78.7)
Cardioembolic source	
Atrial fibrillation and flutter	840 (89.6)
Other high-risk cardioembolic sources	97 (10.3)
Type of OA	
VKA	625 (66.8)
DOAC	310 (33.1)
Dabigatran	93
Apixaban	98
Rivaroxaban	118
Antiplatelet added to OA at discharge	78 (8.4)
Statins at discharge	594 (63.4)

Abbreviations: DOAC = direct oral anticoagulant; OA = oral anticoagulant; VKA = vitamin K antagonist.
Data expressed as n (%), mean (SD), and values for CHA_2DS_2-VASc and HAS-BLED scores are given in median (interquartile range).

1 MB; table 4). The HR was different among groups (p = 0.026). Taking the "no-MB" group as a reference, patients from the group "1 MB" had a higher risk than the reference group (HR 3.33, 95% CI 1.02–10.82, p = 0.045), and patients from the group "more than 1 MB" had a higher risk than the reference group (HR 3.77, 95% CI 1.26–11.25, p = 0.017). Therefore, HR and the 95% CI in patients with 1 MB and patients with more than 1 MB were similar.

Regarding MB location, in patients with MB and ICH (n = 9), deeply or mixed MB localization (n = 7) were more frequent in patients with ICH than with lobar MB (n = 2), although this was not strictly significant (HR 4.7, 95% CI 0.99–23, p = 0.051). When accounting for MB amount, the results of ICH risk according to MB location were still not significant (p = 0.066). Table 5 shows the frequency of other secondary endpoints. MB was not associated with the rate of recurrent ischemic stroke (HR 1.72, p = 0.14, 95% CI 0.83–3.54). We found no association between the Fazekas score and the risk of recurrent ischemic stroke (p = 0.065). However, when dividing patients according to the white matter lesion (WML) grade, a moderate/severe WML score was associated with an increased risk of ischemic stroke recurrence (HR 2.43, 95% CI 1.18–5.02, p = 0.016) and the association was attributable to the severe score group (p = 0.041 compared with the no-WML group) but not the moderate (p = 0.14) or the mild group (p = 0.58).

Discussion

We conducted an observational study of an inception cohort of patients with an acute cardioembolic stroke who had never received OA before the stroke and who had a baseline MRI at the start of OA treatment. After a follow-up of approximately 2 years, we observed an increased risk of ICH in patients in whom MBs and/or moderate to severe WMH were detected. Presence of at least 1 MB was associated with a 2.7-fold increase in the risk of ICH. Also, moderate to severe grade of WMH was associated with a 5.7-fold increase in the risk of ICH.

We found the frequency of ICH to be about 2% in 2 years, with a rate of 1.01 per 100 patient-years. This is in line with

Table 2 Details of MRI findings

Variable	No. (%)
MRI field	
1T	81 (8.6)
1.5T	706 (75.3)
3T	150 (16)
MRI sequences	
SWI/GRE	919 (98)
FLAIR	929 (99.1)
Microbleeds number	
No microbleeds	712 (77.5)
1 or more	207 (22.5)
5 or more	33 (3.5)
Microbleeds distribution	
Strictly cortical/subcortical	112 (54.1)
Deep	53 (25.6)
Mixed	42 (20.3)
Cortical superficial siderosis	
Focal	24 (2.6)
Disseminated	4 (0.4)
White matter hyperintensities	
No	180 (19.4)
Mild	330 (35.5)
Moderate	227 (24.4)
Severe	192 (20.7)

Abbreviations: FLAIR = fluid-attenuated inversion recovery; GRE = gradient-recalled echo; SWI = susceptibility-weighted imaging.

Table 3 Rate of intracranial hemorrhage per 100 patient-years (95% CI) according to MRI findings

	Rate	95% CI
All patients	1.01 per 100 patient-years	0.6–1.59
Patients without MB	0.66 per 100 patient-years	0.3–1.25
Patients with MB	2.33 per 100 patient-years	1.06–4.41
Patients with only 1 MB	2.19 per 100 patient-years	0.6–5.6
Patients with >1 MB	2.53 per 100 patient-years	0.82–5.89
Patients with no/mild WMH	0.3 per 100 patient-years	0.06–0.87
Patients with moderate/severe WMH	1.96 per 100 patient-years	1.1–3.23
Patients with MB and moderate/severe WMH	3.76 per 100 patient-years	1.62–7.4

Abbreviations: CI = confidence interval; MB = microbleed; WMH = white matter hyperintensity.

results from recent studies. For example, the annual ICH frequency for patients with stroke recruited in the ROCKET study[27] was 0.80% in the warfarin group and 0.59% in the rivaroxaban group. Observational studies[26] have reported an annual frequency of up to 2.5% in patients treated with warfarin. Because age is a risk factor for ICH in patients taking OA, we maximized the number of ICH outcomes by including those whose age was 65 or older.

MBs are small foci of blood that, according to histopathologic examinations,[28] are markers of hemorrhage-prone angiopathies, either CHA or CAA, and they are indicative of cerebral small vessel disease. The frequency of MB in patients with ischemic stroke was 23% in a systematic review[29] of patients with a first-ever ischemic stroke, in line with the MB frequency of 22.5% in our study. We found that the ICH risk for patients with MB was almost triple compared to patients without MB. The Clinical Relevance of Microbleeds in Stroke–2 (CROMIS-2) study[21] design was similar to ours and found that MB was associated with a 3.6 risk increase (compared to HR = 2.7 in our study). Also, a recently published meta-analysis[30] of different small heterogeneous observational studies that included 1,522 patients with stroke and AF concluded that MB was associated with ICH (odds ratio = 2.68). Because observational studies suggested that patients with stroke who were receiving VKA-OA before stroke had a higher frequency of MB compared to those patients not receiving OA,[20,31] we enrolled patients who had never taken OA. Thus, we avoided the possibility that MB could be attributed to previous OA treatment. In addition, we excluded "warfarin survivors," i.e., patients who tolerate chronic treatment with OA.

It is reasonable to expect a higher ICH risk with a higher MB load, likely revealing a more advanced vasculopathy. Previous studies[21,30] found a dose-response effect. However, we did not find a relationship between MB number and ICH risk. On the contrary, the CROMIS-2 study[21] reported that the risk of ICH increased with increasing MB burden in the adjusted Cox regression analysis. In patients with MBs, the number of MBs is usually skewed[32] and the majority of patients have only 1 or 2 MBs and only a small portion of patients have ≥5 MBs. Thus, our analysis is limited by the relatively small number of outcomes (ICH) in patients with more than 2 MBs. Multicenter collaboration with a combination of large databases will be necessary to know unequivocally the influence of the amount of MB on ICH risk.

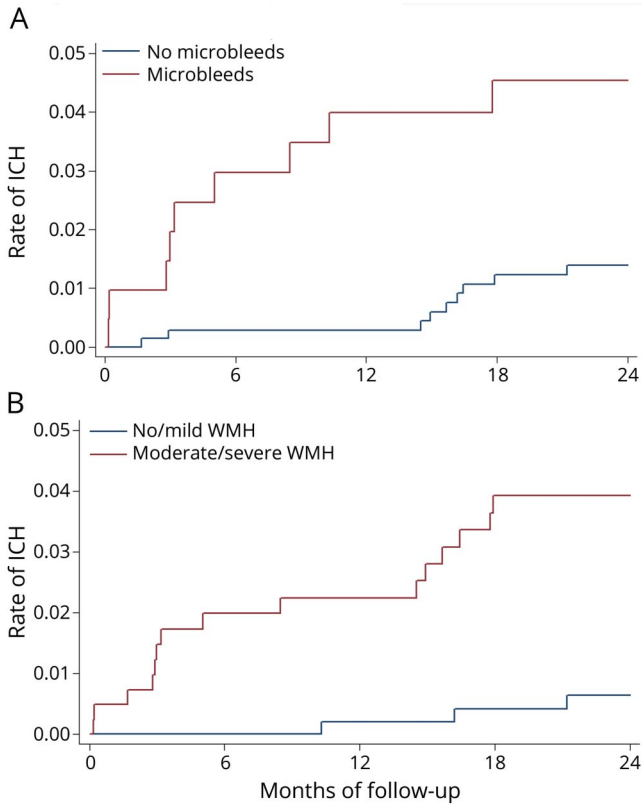
The location of the MB differs depending on the underlying angiopathy, as lobar location is ascribed to CAA whereas deep location is assumed secondary to CHA.[7] We found that more than half of our patients had a lobar location, whereas the remaining patients were classified as deep or mixed location.

Table 4 Bivariate analysis of variables associated with ICH (n = 18) vs non-ICH (n = 919)

	HR (95% CI)	*p* Value
Age	1.02 (0.95–1.09)	0.55
Sex, women	0.71 (0.28–1.8)	0.47
Previous cerebral infarct	1.83 (0.71–4.73)	0.20
Previous TIA	1.34 (0.3–5.85)	0.69
Previous intracerebral hemorrhage	6.83 (0.9–51.3)	0.06
Arterial hypertension	2.86 (0.65–12.4)	0.16
Diabetes mellitus	1.03 (0.34–3.14)	0.95
Hypercholesterolemia	2.23 (0.83–5.94)	0.10
Hypertriglyceridemia	2.07 (0.59–7.14)	0.25
Smoking habit	0.72 (0.09–5.44)	0.75
Alcohol abuse	2.27 (0.52–9.9)	0.27
Chronic renal insufficiency	2.73 (0.79–9.43)	0.11
Ischemic heart disease	1.60 (0.52–4.86)	0.40
Peripheral vascular disease	0.04 (0.00–424.3)	0.50
Atrial fibrillation	0.49 (0.18–1.31)	0.15
Valvular heart disease	1.39 (0.18–10.49)	0.74
Cancer	1.66 (0.48–5.75)	0.41
Advanced liver disease	3.73 (0.49–28.09)	0.20
CHA_2DS_2-VASc score	1.39 (0.96–2.01)	0.07
HAS-BLED score	0.87 (0.42–1.80)	0.66
Rankin Scale score at discharge	1.22 (0.89–1.69)	0.21
Type of stroke, TIA vs cerebral infarct	0.71 (0.25–1.99)	0.51
Type of OA, VKA vs DOAC	0.56 (0.18–1.72)	0.32
Antiplatelet added to OA at discharge	1.41 (0.32–6.17)	0.64
Statins added to OA at discharge	2.01 (0.66–6.12)	0.21
Microbleeds		
≥1 vs none	3.51 (1.39–8.85)	0.026
1 vs none	3.33 (1.02–10.8)	0.045
>1 vs none	3.77 (1.26–11.25)	0.017
Microbleeds distribution		
Deep/mixed vs lobar	4.7 (0.99–23)	0.051
White matter hyperintensities		
Moderate/severe vs no/mild	6.58 (1.90–22.7)	0.003
Cortical superficial siderosis	0.51 (0.06–3.87)	0.51

Abbreviations: CI = confidence interval; DOAC = direct oral anticoagulant; HR = hazard ratio; ICH = intracranial hemorrhage; OA = oral anticoagulant; VKA = vitamin K antagonist.

Figure 2 Probability of ICH according to the presence of MB and the degree of WMH



Kaplan-Meier cumulative incidence curves reflecting (A) the probability of ICH according to the presence/absence of MB; and (B) the probability of ICH according to the degree of WMH. ICH = intracranial hemorrhage; MB = microbleeds; WMH = white matter hyperintensities.

Deeply or mixed distributed MB had more risk of ICH compared to the risk when the location was lobar, although the difference was not strictly significant ($p = 0.051$). In our study, 74% of our patients were hypertensive, and together with aging, hypertension is the most consistent risk factor for MB.[7] No reliable data regarding the importance of MB distribution were reported in the CROMIS-2[21] study because of few events within each category.

We found that the type of OA had no influence on ICH risk, and the same was reported by the CROMIS-2 study.[21] The consistent reduced risk of ICH associated with DOAC vs VKA treatment[2] in patients with FA was not replicated. The influence of OA type will have to be analyzed in studies with more patients.

WMH of presumed vascular origin are a surrogate marker of cerebral small vessel disease. Several large studies[3,8,16,29] clearly demonstrated that severe WMH are more prevalent in patients with MB than in those without, and that, just like what happens with MB, are a risk factor for ICH in patients with[11,12] or without[13] OA therapy. In our study, patients with moderate to severe WMH had a 6-fold risk of ICH, independently of the risk

Table 5 Relevant vascular or nonvascular events during follow-up (n = 937 patients)

Variable	No. (%)
Recurrent cerebral infarct	33 (3.6)
Angina pectoris or acute myocardial infarction	26 (2.8)
Pulmonary thromboembolism	4 (0.4)
Acute aortic dissection	1 (0.2)
Systemic embolism	4 (0.4)
Noncerebral major hemorrhage	38 (4.1)
Intracranial hemorrhage	18 (1.9)
Intracerebral hemorrhage	15
Subdural hemorrhage	2
Subarachnoid hemorrhage	1
Death	
Vascular death	49 (5.3)
Nonvascular death or cause unknown	65 (7)
Death from any cause	114 (12.3)

associated with MB. Of importance, in 121 patients (13%), MB and significant WMH coexisted and this coincidence increased the risk of ICH reaching a rate of 3.76 per 100 patient-years. One reasonable explanation is that the association of both markers indicates a more advanced stage of cerebral small vessel disease. However, in the CROMIS-2 study[21] and other small studies,[33] MB but not WMH was a risk factor for ICH. In the CROMIS-2 study, WMH were also more frequent in patients with MB compared to patients without MB, and the degree of WMH was higher in patients who experienced ICH compared with patients without ICH, although the difference was not significant. Results from both studies are not comparable since a different scoring system to assess WMH was used. Although age in both studies was similar, we recruited a higher number of patients with hypertension (74% vs 63%), diabetes (23% vs 17%), and previous ischemic stroke (26% vs 10%) compared to the CROMIS-2 study, and these are well-known risk factors for WMH. We found moderate to severe WMH in 45% of patients compared with 29% in the CROMIS-2 study. Thus, patients in our study had more severe white matter involvement, probably because of a higher risk factor profile. This may explain our different results.

cSS may be identified in 1% of patients with acute ischemic stroke.[34] cSS is associated with a high risk of subsequent intracerebral hemorrhage and is considered a highly specific finding of CAA.[14,15] We found cSS in 3% of our patients but only 4 had a disseminated cSS, the subtype with the highest risk of intracerebral hemorrhage. Contrary to what we expected, only 1 of 28 patients with cSS had an ICH during follow-up. The same was reported in the CROMIS-2 study.[21] According to some studies,[35] cSS is not associated with a higher count of MB and therefore CAA-related cSS and MBs may arise from different mechanisms. Hence, despite no firm results, the risk associated with cSS does not increase with OA treatment. Therefore, OA should be used, at least with focal cSS. Again, more data are needed to clarify this point.

Lastly, the relevant question is: Should we withhold OA therapy in patients with MB and/or moderate to severe WMH? No studies have used randomized patients with cardioembolic stroke who receive OA depending on the presence or absence of CAA and CHA markers. Therefore, our study and the CROMIS-2 study[21] together provide the best evidence on the safety of OA in these patients. However, we do not know whether ICH is caused by OA, the underlying cerebral angiopathy, or the interaction between both. It is interesting that in patients with MB who are not treated with OA,[9] the odds ratio for ICH risk is similar to that obtained by our study and the CROMIS-2 study. Therefore, it seems reasonable that advanced small vessel disease can trigger ICH without any influence of the OA. Alternatively, the underlying angiopathy could cause an MB instead of an ICH in the absence of OA treatment. Thus, we think that in those patients who have a relatively low risk of ischemic stroke and a high risk of ICH, the decision to prescribe continuous OA therapy requires a careful evaluation of risk and benefit. Also important is to avoid concomitant antiplatelet therapy, maintain strict control of blood pressure and INR, and to consider the alternative of left atrial appendage occlusion. About 13% of our patients had a high ICH risk, thus this is a frequent dilemma. We must keep in mind that OAs are very effective for the secondary prevention of cardioembolic stroke.[1,2] The prevention may occur even if there are MBs and moderate to severe WMH. ICH risk scores such as the HAS-BLED score were not specifically developed to predict ICH risk, and at best, its predictive value is modest.[36] Therefore, the HAS-BLED score is not a useful guide for OA treatment.[3,36] Because of the rarity of ICH, multicenter collaboration with pooled analyses is necessary to validate new risk scores that should incorporate MRI abnormalities.[3] However, contrary to our results, current guidelines[37] do not recommend a screening by MRI to decide to start OA treatment.

Our study has some limitations. ICH infraestimation may have occurred. It is likely that ICH was the cause in some patients in whom the cause of death was unknown. The need for a CT scan for a reliable ICH diagnosis is an obvious limitation, which is shared by all observational and clinical trials. Moreover, the assessment of endpoints by a telephone interview may be a source of mistakes in the adjudication of events. To minimize this limitation, we contacted the local neurologist and medical records were checked to obtain additional and more reliable information. Selection bias may have occurred since only patients suitable to undergo an MRI were enrolled. Moreover, although we asked the participating investigators to enroll consecutive patients, a screening log was not kept by all centers and therefore investigators may

have enrolled only those patients they considered best candidates for indefinite anticoagulation. We tried to minimize this selection bias by requiring a signature of consent to participate before having the MRI.

Although we report a large cohort of patients, the number of ICH events was relatively small and thus our study may have insufficient power to definitely establish the ICH risk associated with MRI abnormalities. Multinational collaboration and meta-analysis with other studies should help to yield more reliable results, build new risk scores, and analyze subgroups of patients.

Also, the absence of information of time-in-range in patients on VKA-OA prevents us from knowing what the results would have been in case of better or worse control of OA use. Therefore, our result should be considered a reflection of real-world conditions, including the degree of INR control in patients on VKA.

The fact that imaging was not uniform is important. The analysis of the MRIs uploaded from different institutions is a source of heterogeneity in evaluating the results because of different protocols and field strengths. Infraestimation is likely with the use of 1T and 1.5T vs 3T and with GRE vs SWI sequences.[8] Since we did not calculate Cohen κ coefficient, our evaluation of the MRIs is not totally reliable.

Finally, our study is not a randomized clinical trial; therefore, despite our instructions to the participating centers for the consecutive inclusion of patients, there may be some inclusion bias. To avoid an influence of the knowledge of MB on the prescription of OA, consent was signed before the MRI was performed.

The burden of small vessel disease measured by MB and moderate to severe WMH in patients with cardioembolic stroke who were naive for OA was associated with an increase in ICH risk. It seems prudent to avoid OA in patients with an estimated ICH risk that is equal or higher than the estimated benefit. However, to refine the balance between harm and benefit, we need to pool analyses of large cohorts. In the absence of randomized clinical trials, this will help the physician to select the best strategy for secondary prevention and will allow the design of new risk scores and the definition of the importance of relevant variables such as MB amount, MB location, WMH degree, and OA type. Meanwhile, we recommend incorporating MRI results to help decide whether or not to start long-term OA therapy.

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Disclosure

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Appendix 1 Authors

Name	Location	Role	Contribution
Joan Martí-Fàbregas, MD, PhD	Hospital de la Santa Creu i Sant Pau, Barcelona, Spain	Author	Designed and conceptualized the study, analyzed the data, drafted the manuscript for intellectual content
Santiago Medrano-Martorell, MD	Hospital del Mar, Barcelona, Spain	Author	Designed and conceptualized the study, analyzed the data, revised the manuscript for intellectual content
Elisa Merino, MD	Hospital Germans Trias i Pujol, Badalona, Spain	Author	Designed and conceptualized the study, analyzed the data, revised the manuscript for intellectual content
Luis Prats-Sánchez, MD	Hospital de la Santa Creu i Sant Pau, Barcelona, Spain	Author	Designed and conceptualized the study, major role in the acquisition of data, revised the manuscript for intellectual content
Rebeca Marín, RN	Hospital de la Santa Creu i Sant Pau, Barcelona, Spain	Author	Major role in the acquisition of data, revised the manuscript for intellectual content
Raquel Delgado-Mederos, MD, PhD	Hospital de la Santa Creu i Sant Pau, Barcelona, Spain	Author	Designed and conceptualized the study, major role in the acquisition of data, revised the manuscript for intellectual content
Alejandro Martínez-Domeño, MD	Hospital de la Santa Creu i Sant Pau, Barcelona, Spain	Author	Designed and conceptualized the study, major role in the acquisition of data, revised the manuscript for intellectual content
Pol Camps-Renom, MD	Hospital de la Santa Creu i Sant Pau, Barcelona, Spain	Author	Designed and conceptualized the study, major role in the acquisition of data, revised the manuscript for intellectual content
Elena Jiménez-Xarrié, PhD	Hospital de la Santa Creu i Sant Pau, Barcelona, Spain	Author	Major role in the acquisition of data, revised the manuscript for intellectual content

Appendix 1 *(continued)*

Name	Location	Role	Contribution
Marialuisa Zedde, MD	Arcispedale Santa Maria Nuova IRCCS, Reggio Emilia, Italy	Author	Major role in the acquisition of data, revised the manuscript for intellectual content
Manuel Gómez-Choco, MD, PhD	Hospital Moises Broggi, Sant Joan Despí, Spain	Author	Major role in the acquisition of data, revised the manuscript for intellectual content
Lidia Lara, MD	Hospital de León, León, Spain	Author	Major role in the acquisition of data, revised the manuscript for intellectual content
Amèlia Boix, MD	Hospital Universitari Son Espases, Palma de Mallorca, Spain	Author	Major role in the acquisition of data, revised the manuscript for intellectual content
Ana Calleja, MD	Hospital de Valladolid, Valladolid, Spain	Author	Major role in the acquisition of data, revised the manuscript for intellectual content
Ana María De Arce-Borda, MD	Hospital de Donostia, Spain	Author	Major role in the acquisition of data, revised the manuscript for intellectual content
Yolanda Bravo, MD PhD	Hospital de Burgos, Spain	Author	Major role in the acquisition of data, revised the manuscript for intellectual content
Blanca Fuentes, MD, PhD	Hospital Universitario La Paz, Madrid, Spain	Author	Major role in the acquisition of data, revised the manuscript for intellectual content
María Hernández-Pérez, MD, PhD	Hospital Germans Trias I Pujol, Badalona, Spain	Author	Major role in the acquisition of data, revised the manuscript for intellectual content
David Cánovas, MD, PhD	Hospital Parc Taulí, Sabadell, Spain	Author	Major role in the acquisition of data, revised the manuscript for intellectual content
Laura Llull, MD, PhD	Hospital Clínic, Barcelona, Spain	Author	Major role in the acquisition of data, revised the manuscript for intellectual content
Beatriz Zandio, MD	Hospital de Navarra, Pamplona, Spain	Author	Major role in the acquisition of data, revised the manuscript for intellectual content
Marimar Freijo, MD	Hospital de Basurto, Bilbao, Spain	Author	Major role in the acquisition of data, revised the manuscript for intellectual content
Ignacio Casado-Naranjo, MD	Hospital San Pedro de Alcántara, Cáceres, Spain	Author	Major role in the acquisition of data, revised the manuscript for intellectual content
Jordi Sanahuja, MD	Hospital Arnau de Vilanova, Lleida, Spain	Author	Major role in the acquisition of data, revised the manuscript for intellectual content

Appendix 1 *(continued)*

Name	Location	Role	Contribution
Dolores Cocho, MD, PhD	Hospital de Granollers, Granollers, Spain	Author	Major role in the acquisition of data, revised the manuscript for intellectual content
Jerzy Krupinski, MD, PhD	Mutua de Terrassa, Spain	Author	Major role in the acquisition of data, revised the manuscript for intellectual content
Ana Rodríguez-Campello, MD, PhD	Hospital del Mar, Barcelona, Spain	Author	Major role in the acquisition of data, revised the manuscript for intellectual content
Ernest Palomeras, MD, PhD	Hospital de Mataró, Spain	Author	Major role in the acquisition of data, revised the manuscript for intellectual content
Alicia de Felipe, MD	Hospital Dr. Gregorio Marañón, Madrid, Spain	Author	Major role in the acquisition of data, revised the manuscript for intellectual content
Marta Serrano, MD	Hospital La Rioja, Logroño, Spain	Author	Major role in the acquisition of data, revised the manuscript for intellectual content
Elena Zapata-Arriaza, MD	Hospital Virgen del Rocío, Sevilla, Spain	Author	Major role in the acquisition of data, revised the manuscript for intellectual content
Josep Zaragoza-Brunet, MD	Hospital Verge de la Cinta, Tortosa, Spain	Author	Major role in the acquisition of data, revised the manuscript for intellectual content
Inmaculada Díaz-Maroto, MD	Hospital de Albacete, Spain	Author	Major role in the acquisition of data, revised the manuscript for intellectual content
Jessica Fernández-Domínguez, MD, PhD	Centro Médico Asturias, Oviedo, Spain	Author	Major role in the acquisition of data, revised the manuscript for intellectual content
Aida Lago, MD, PhD	Hospital La Fe, Valencia, Spain	Author	Major role in the acquisition of data, revised the manuscript for intellectual content
José Maestre, MD	Hospital Virgen de las Nieves, Granada, Spain	Author	Major role in the acquisition of data, revised the manuscript for intellectual content
Manuel Rodríguez-Yáñez, MD	Hospital Santiago de Compostela, Santiago de Compostela, Spain	Author	Major role in the acquisition of data, revised the manuscript for intellectual content
Ignasi Gich, MD, PhD	Hospital de la Santa Creu i Sant Pau, Barcelona, Spain	Author	Designed and conceptualized the study, analyzed the data, revised the manuscript for intellectual content

Appendix 2 Coinvestigators

Name	Location	Role	Contribution
Daniel Guisado-Alonso, MD	Hospital de la Santa Creu i Sant Pau, Barcelona, Spain	Coinvestigator	Coordinated communication among sites
Beatriz Gómez-Anson, MD, PhD	Hospital de la Santa Creu i Sant Pau, Barcelona, Spain	Coinvestigator	Coordinated imaging for site
Fidel Núñez, MD	Hospital de la Santa Creu i Sant Pau, Barcelona, Spain	Coinvestigator	Coordinated imaging for site
José Mateo, MD	Hospital de la Santa Creu i Sant Pau, Barcelona, Spain	Coinvestigator	Scientific advisor
Jaume Roquer, MD, PhD	Hospital del Mar, Barcelona, Spain	Coinvestigator	Coordinated communication among sites
Antonio Dávalos, MD, PhD	Hospital Germans Trias i Pujol, Badalona, Spain	Coinvestigator	Coordinated communication among sites
Rosario Pascarella, MD	Arcispedale Santa Maria Nuova IRCCS, Reggio Emilia, Italy	Coinvestigator	Coordinated imaging for site
Manuela Napoli, MD	Arcispedale Santa Maria Nuova IRCCS, Reggio Emilia, Italy	Coinvestigator	Coordinated imaging for site
Filippo Sassi, MD	Arcispedale Santa Maria Nuova IRCCS, Reggio Emilia, Italy	Coinvestigator	Coordinated imaging for site
Sonia María García-Sánchez, MD	Hospital Moises Broggi, Sant Joan Despí, Spain	Coinvestigator	Coordinated communication among sites
Laura Castrillo Salas, MD	Hospital Moises Broggi, Sant Joan Despí, Spain	Coinvestigator	Coordinated imaging for site
Javier Tejada, MD	Hospital de León, Spain	Coinvestigator	Coordinated communication among sites
Teresa Lorenzo Domínguez, MD	Hospital de León, Spain	Coinvestigator	Coordinated imaging for site
Carmen Jiménez, MD	Hospital Universitari Son Espases, Palma de Mallorca, Spain	Coinvestigator	Coordinated communication among sites
María José Torres, MD	Hospital Universitari Son Espases, Palma de Mallorca, Spain	Coinvestigator	Coordinated communication among sites

Appendix 2 *(continued)*

Name	Location	Role	Contribution
Juan F. Arenillas, MD, PhD	Hospital de Valladolid, Spain	Coinvestigator	Coordinated communication among sites
Elisa Cortijo, MD	Hospital de Valladolid, Spain	Coinvestigator	Coordinated communication among sites
Mercedes de Lera, MD	Hospital de Valladolid, Spain	Coinvestigator	Coordinated imaging for site
Margarita Rodríguez Velasco, MD	Hospital de Valladolid, Spain	Coinvestigator	Coordinated imaging for site
José Angel Larrea Peña, MD	Hospital de Donostia, Spain	Coinvestigator	Coordinated imaging for site
Maite Martínez Zabaleta, MD	Hospital de Donostia, Spain	Coinvestigator	Coordinated communication among sites
María Jesus Rubio Sanz, MD	Hospital de Burgos, Spain	Coinvestigator	Coordinated imaging for site
Exuperio Díez-Tejedor, MD, PhD	Hospital Universitario La Paz, Instituto de Investigación IdiPaz, Madrid, Spain	Coinvestigator	Coordinated communication among sites
Remedios Frutos, MD	Hospital Universitario La Paz, Instituto de Investigación IdiPaz, Madrid, Spain	Coinvestigator	Coordinated imaging for site
María del Carmen García Carreira, MD	Hospital Parc Taulí, Sabadell, Spain	Coinvestigator	Coordinated imaging for site
Angel Chamorro, MD, PhD	Hospital Clínic Barcelona, Spain	Coinvestigator	Coordinated communication among sites
Sebastián Capurro, MD	Hospital Clínic Barcelona, Spain	Coinvestigator	Coordinated imaging for site
Carmen Bacaicoa Saralegui, MD	Hospital de Navarra, Pamplona, Spain	Coinvestigator	Coordinated imaging for site
Juan Jose Gómez Muga, MD	Hospital de Basurto, Bilbao, Spain	Coinvestigator	Coordinated imaging for site
Cristina Pérez Calvo, MD	Hospital San Pedro de Alcántara, Cáceres, Spain	Coinvestigator	Coordinated imaging for site
Francisco Purroy, MD, PhD	Hospital Arnau de Vilanova, Lleida, Spain	Coinvestigator	Coordinated communication among sites
Ikram Benabdelhak, RN	Hospital Arnau de Vilanova, Lleida, Spain	Coinvestigator	Coordinated imaging for site

Appendix 2 *(continued)*

Name	Location	Role	Contribution
Miguel Cuadrado, MD	Hospital de Granollers, Spain	Coinvestigator	Coordinated imaging for site
Jessica Molina, MD	Mutua de Terrassa, Spain	Coinvestigator	Coordinated imaging for site
Israel Fernández-Cadenas, PhD	Mutua de Terrassa, Spain	Coinvestigator	Coordinated communication among sites
Jaime Masjuan, MD, PhD	Hospital Ramón y Cajal, Madrid, Spain	Coinvestigator	Coordinated communication among sites
Pilar Piñero, MD	Hospital Virgen del Rocío, Sevilla, Spain	Coinvestigator	Coordinated imaging for site
Francisco Moniche, MD	Hospital Virgen del Rocío, Sevilla, Spain	Coinvestigator	Coordinated communication among sites
Moises Garcés, MD	Hospital Verge de la Cinta, Tortosa, Spain	Coinvestigator	Coordinated imaging for site
Juanjo Baiges, MD	Hospital Verge de la Cinta, Tortosa, Spain	Coinvestigator	Coordinated communication among sites
Tomás Segura, MD, PhD	Hospital de Albacete, Spain	Coinvestigator	Coordinated communication among sites
Eva Fernández Díaz, MD	Hospital de Albacete, Spain	Coinvestigator	Coordinated imaging for site
Elena Lozano, MD	Hospital de Albacete, Spain	Coinvestigator	Coordinated imaging for site
Rafael Gómez Illán, MD	Centro Médico Asturias, Oviedo, Spain	Coinvestigator	Coordinated imaging for site
Fernando Aparici Robles, MD	Hospital La Fe, Valencia, Spain	Coinvestigator	Coordinated imaging for site
Victor Vázquez Añón, MD	Hospital La Fe, Valencia, Spain	Coinvestigator	Coordinated imaging for site
Jordi Delgado-Mengual, PhD	Port d'Informació Científica, Institut de Física d'Altes Energies, Campus UAB, Cerdanyola del Vallés, Spain	Coinvestigator	Coordinated imaging for site

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