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Stroke Risk and Antithrombotic Treatment During Follow-up of Patients With Ischemic Stroke and Cortical Superficial Siderosis

Author(s):
Joan Martí-Fàbregas, MD, PhD[1]; Pol Camps-Renom, MD, PhD[1]; Jonathan G Best, MD[2]; Anna Ramos-Pachon, MD[1]; Marina Guasch-Jiménez, MD[1]; Alejandro Martinez-Domeño, MD[1]; Daniel Guisado-Alonso, MD[1]; Beatriz M Gómez-Ansón, MD, PhD[3]; Gareth Ambler, PhD[4]; Duncan Wilson, PhD[2]; Keon-Joo Lee, MD[5]; Jae-Sung Lim, M.D., Ph.D[6]; Hee-Joon Bae, MD[5]; Masayuki Shiozawa, MD[7]; Masatoshi Koga, M.D., Ph.D.[7]; Kazunori Toyoda, M.D., Ph.D.[7]; Michael G. Hennerici, MD[8]; Hugues Chabriat, PD, PhD[9]; Eric Jouvent, MD PhD[9]; Debbie Yuen Kwun Wong, MSc[10]; Henry Mak, MD[10]; Kui Kai Lau, DPhil[10]; Young Dae Kim, MD PhD[11]; Tae-Jin Song, MD, PhD[11]; Ji-Hoe Heo, MD[11]; Sebastian Eppinger, MD[12]; Thomas Gattringer, MD[12]; Ender Uysal, MD[13]; Derya Selçuk Demirelli, MD[13]; Natan Bornstein, MD[14]; Einor Ben Assayag, PhD[14]; Hen Hallevi, MD[14]; Jeremy A. Molad, MD[14]; Masashi Nishihara, MD[15]; Jun Tanaka, MD[15]; Hideo Hara, PhD[15]; Yusuke Yakushiji, PhD[15]; Shelagh B. Coutts, MD[16]; Eric Smith, MD MPH[16]; Alexandros A Polymeris, MD[17]; Benjamin Wagner, MD[17]; David Seiffge[17]; Philippe A. Lyrer, MD[17]; Nils Peters, MD[17]; Stefan T. Engelter, MD[17]; Rustam Al-Shahi Salman, MD PhD[18]; Hans Rudolf Jäger, MD[19]; Gregory Y H Lip, FRCP[20]; Martina Goeldlin, MD[21]; Leonidas Panos, MD[21]; Christopher Charles Karayiannis, MD[22]; Thanh G Phan, MBBS FRACP PhD[22]; Velandai K Srikanth, MD, PhD[22]; Nicolas Christ, MD[23]; Sarah Gunkel, MD[23]; Felix Fluri, MD[23]; Thomas W Leung, MD[24]; Yannie O.Y. Soo, MD[24]; Winnie Chu, MD[24]; Jill Abrigo, MD[24]; Carmen Barbato, MD[2]; Simone Browning, BsC[2]; Robert Simister, MD[2]; Anne-Marie Mendyk, RN[25]; Régis Bordet, MD[25]; Saima Hilal, MD/PhD[26]; Bibek Gyanwali, MD[26]; Christopher Chen, MD[26]; Simon Jung, MD[21]; Dilek Necioglu Orken, MD[27]; David Werring, FRCP, PhD[2]; Luis Prats-Sanchez, MD, PhD[1] on behalf of and Microbleeds International Collaborative Network (MICON)

Corresponding Author:
Joan Martí-Fàbregas, jmarti@santpau.cat

Affiliation Information for All Authors: 1. Department of Neurology, Hospital de la Santa Creu i Sant Pau, Biomedical Research Institute Sant Pau; 2. UCL Stroke Research Centre, Department of Brain Repair and Rehabilitation, University College London Queen Square, Institute of Neurology; 3. Neuroradiology Unit, Department of Radiology, Hospital de la Santa Creu i Sant Pau, Biomedical Research Institute Sant Pau; 4. Department of Statistical Science, University College London; 5. Seoul National University College of Medicine Cerebrovascular Disease Center; 6. Department of Neurology, Asan Medical Center University of Ulsan College of Medicine; 7. Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Centre; 8. Federation Universitätsmedizin Mannheim, University of Heidelberg; 9. Assistance Publique Hôpitaux de Paris, Lariboisière Hospital, Translational Neurovascular Centre and Department of Neurology; 10. Division of Neurology, Department of Medicine and Department of Diagnostic Radiology, The University of Hong Kong; 11.Department of Neurology, Yonsei University College of Medicine; 12. Department of Neurology, Medical University of Graz; 13. Department of Neurology, Saglık Bilimleri University, Hamidiye Etfal Education and Research Hospital; 14. Department of Neurology, Tel-Aviv Sourasky Medical Center; 15. Department of Radiology and Division of Neurology, Department of Internal Medicine, Saga University Faculty of Medicine; 16. Calgary Stroke Program, Department of Clinical Neurosciences, Radiology and Community Health Sciences, Hotchkiss Brain Institute, University of Calgary; 17. Department of Neurology and Stroke Centre, University Hospital Basel and University of Basel; 18. . Centre for Clinical Brain Sciences, School of Clinical Sciences, University of Edinburgh; 19. Lysholm Department of Neuroradiology and the Neuroradiological Academic Unit, Department of Brain Repair and Rehabilitation, University College London Institute of Neurology and the National Hospital for Neurology and Neurosurgery; 20. Liverpool Centre for Cardiovascular Science, University of Liverpool; 21. Department of Neurology, Inselspital, Bern University Hospital and University of Bern; 22. Peninsula Clinical School, Peninsula Health and Stroke and Ageing Research Group, School of Clinical Sciences at Monash Health, Monash University; 23. Department of Neurology, University Hospital of Würzburg; 24. Department of Medicine and Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong; 25. Univ Lille, Inserm, CHU de Lille. Lille Neuroscience & Cognition; 26. Memory Aging & Cognition Centre, Yong Loo Lin School of Medicine, National University of Singapore; 27. Istanbul Arel University, Department of Neurology

Equal Author Contribution:
Joan Martí-Fàbregas and Pol Camps-Renom contributed equally to this work as first authors

Contributions:
Joan Martí-Fàbregas: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data
Pol Camps-Renom: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data
Jonathan G Best: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Anna Ramos-Pachon: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Marina Guasch-Jiménez: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Alejandro Martinez-Domeño: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Daniel Guisado-Alonso: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Beatriz M Gómez-Ansón: Drafting/revision of the manuscript for content, including medical writing for

content; Major role in the acquisition of data; Analysis or interpretation of data
Gareth Ambler: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Duncan Wilson: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Keon-Joo Lee: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Jae-Sung Lim: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Hee-Joon Bae: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Masayuki Shiozawa: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Masatoshi Koga: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Kazunori Toyoda: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Michael G. Hennerici: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Hugues Chabriat: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Eric Jouvent: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Debbie Yuen Kwun Wong: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Henry Mak: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Kui Kai Lau: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Young Dae Kim: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Tae-Jin Song: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Ji-Hoe Heo: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Sebastian Eppinger: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Thomas Gattringer: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Ender Uysal: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Derya Selçuk Demirelli: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Natan Bornstein: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Einor Ben Assayag: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Hen Hallevi: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Jeremy A. Molad: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Masashi Nishihara: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Jun Tanaka: Drafting/revision of the manuscript for content, including medical writing for content;

Major role in the acquisition of data; Analysis or interpretation of data
Hideo Hara: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Yusuke Yakushiji: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Shelagh B. Coutts: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Eric Smith: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Alexandros A Polymeris: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Benjamin Wagner: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
David Seiffge: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Philippe A. Lyrer: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Nils Peters: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Stefan T. Engelter: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Rustam Al-Shahi Salman: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Hans Rudolf Jäger: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Gregory Y H Lip: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
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Christopher Charles Karayiannis: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Thanh G Phan: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Velandai K Srikanth: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Nicolas Christ: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Sarah Gunkel: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Felix Fluri: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Thomas W Leung: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Yannie O.Y. Soo: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Winnie Chu: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Jill Abrigo: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Carmen Barbato: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Simone Browning: Drafting/revision of the manuscript for content, including medical writing for

content; Major role in the acquisition of data; Analysis or interpretation of data
Robert Simister: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Anne-Marie Mendyk: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Régis Bordet: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Saima Hilal: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Bibek Gyanwali: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Christopher Chen: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Simon Jung: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
Dilek Necioglu Orken: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Analysis or interpretation of data
David Werring: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data
Luis Prats-Sanchez: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data; Additional contributions: -

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ABSTRACT

Background and objectives

In patients with ischemic stroke (IS) or TIA and cortical superficial siderosis (cSS), there are few data regarding the risk of future cerebrovascular events and also about the benefits and safety of antithrombotic drugs for secondary prevention. We investigated the associations of cSS and stroke risk in patients with recent IS or TIA.

Methods

We retrospectively analyzed the Microbleeds International Collaborative Network (MICON) database. We selected patients with IS or TIA from cohorts who had MRI-assessed cSS, available data on antithrombotic treatments, recurrent cerebrovascular events [Intracranial hemorrhage -ICrH-, IS, or any stroke (ICrH or IS)], and mortality. We calculated incidence rates (IR) and performed univariable and multivariable Cox regression analyses.

Results

Of 12.669 patients (mean age 70.4±12.3 years, 57.3% men), cSS was detected in 273 (2.2%) patients. During a mean follow-up of 24±17 months, IS was more frequent than ICrH in both cSS (IR 57.1 versus 14.6 per 1000 patient-years) and non-cSS groups (33.7 versus 6.3 per 1000 patient years). Compared to the non-CSS group, cSS was associated with any stroke on multivariable analysis [IR 83 versus 42 per 1000 patient-years, adjusted HR for cSS 1.62 (95%CI: 1.14-2.28; p=0.006)]. This association was not significant in subgroups of patients treated with antiplatelet drugs (n=6.554) or with anticoagulants (n=4.044). Patients with cSS who were treated with both antiplatelet drugs and anticoagulants (n=1.569) had a higher incidence of ICrH (IR 107.5 vs 4.9 per 1000 patient-years, adjusted HR 13.26; 95%CI: 2.90-

60.63; p=0.001) and of any stroke (IR 198.8 vs 34.7 per 1000 patient-years, adjusted HR 5.03; 95%CI: 2.03-12.44; p<0.001) compared to the non-CSS group.

Discussion

Patients with IS or TIA with cSS are at increased risk of stroke (ICrH or IS) during follow-up; the risk of IS exceeds that of ICrH for patients receiving antiplatelet or anticoagulant treatment alone, but the risk of ICrH exceeds that of IS in patients receiving both treatments. The findings suggest that either antiplatelet or anticoagulant treatment alone should not be avoided in patients with cSS, but combined antithrombotic therapy might be hazardous. Our findings need to be confirmed by randomized clinical trials.

INTRODUCTION

Cortical superficial siderosis (cSS) is an imaging abnormality with a characteristic appearance depicted by iron-sensitive magnetic resonance imaging (MRI) sequences.[1] cSS is regarded as the chronic stage of acute subarachnoid bleeding in the sulci of the cerebral hemispheric convexities.[2-4] Several lines of evidence, including pathological correlations,[5] demonstrate that cSS is part of the spectrum of advanced cerebral amyloid angiopathy (CAA) in elderly patients.

Cohort studies[6-10] and a meta-analysis[3] of patients with cSS have consistently reported that during follow-up, intracerebral hemorrhage (ICH) survivors with cSS are at a high risk of recurrent ICH; this risk is higher for disseminated cSS than for focal cSS.[8] Importantly, this increased risk is independent of age and lobar cerebral microbleeds (CMBs).

Because cSS is so infrequent,[1,11,12] available cohorts consist of relatively few patients. Leaving aside the increased ICH risk, the follow-up risk of ischemic cerebrovascular events

and death are unclear. Patients with cSS are usually elderly and so are frequently treated with antiplatelet or anticoagulant agents (sometimes in combination) for primary or secondary prevention of vascular diseases. However, it is unclear if there is any additional risk or benefit in prescribing antithrombotic agents to patients with cSS after ischemic stroke (IS) or TIA.[13]

To provide practical information that could guide therapeutic decisions, we reviewed the Microbleeds International Collaborative Network (MICON) database, containing data on a large number of patients with IS or TIA, baseline MRI, and long-term clinical follow-up. We compared the follow-up frequency of cerebrovascular events and death in patients with and without cSS, and investigated the risks associated with long-term antithrombotic treatment in patients with cSS.

METHODS

In this multicenter study, we retrospectively analyzed the MICON database[14], which has pooled individual-patient data (n=20.322) for 38 hospital-based prospective cohorts from 18 countries in Europe, the Middle East Asia, Australasia, and North America. The database includes clinical and neuroimaging variables collected by local investigators. Patients were included if they had had a TIA or IS, MRI had been performed and cSS had been evaluated (using gradient echo T2* and/or susceptibility weighted imaging) . We also required that ntithrombotic treatment, cerebrovascular events, and mortality data during follow-up were available. According to these criteria we included patients from 21 cohorts. Variables were analyzed as follows:

(1) Demographic data (age, sex)

(2) Stroke etiology according to the TOAST criteria[15]

(3) Traditional vascular risk factors: atrial fibrillation, hypertension, previous IS, previous ICH, ischemic heart disease, hyperlipidemia, diabetes, smoking, alcohol abuse

(4) Antithrombotic treatment in the six months before hospitalization and during follow-up: antiplatelet agents, direct oral anticoagulants (DOACs), vitamin K antagonists (VKAs)

(5) MRI markers of hemorrhagic-prone cerebral angiopathies as assessed and rated locally according to consensus criteria:[16] CMBs (presence, burden, distribution), white matter hyperintensities (presence, grading according to the Fazekas score[17]), and cSS, classified as focal or disseminated (involvement of up to 3 sulci or of 4 or more sulci, respectively[8])

(6) Major vascular events during follow-up as assessed by local investigators: IS, intracranial hemorrhage (ICrH), any stroke (IS or ICrH), and all-cause mortality.

Standard protocol approvals, registrations, and patient consents

Ethical approval was obtained for all cohorts as required by local regulations to allow data sharing. All data reviewed in this study has been fully anonymized.

Statistical analyses

Results are expressed as number and percentage for categorical variables, as mean and standard deviation for continuous variables, and as median (and interquartile range) for ordinal variables. Clinical and neuroimaging variables from patients with and without cSS were compared using the Student t-test, χ^2 test with Fisher test, or Mann Whitney U test, as appropriate. For missing values, we report numbers and percentages with the actual denominator. No missing data were imputed.

For patients with and without cSS we calculated the incidence rates (IR) per 1000 patient-years of each event (ICrH, IS, any stroke, death) and the incidence rate ratio (IRR).

To estimate the significance of the association between cSS and each event we performed univariable and multivariable Cox regression analyses, calculating the hazard ratio (HR) with 95% confidence interval (CI) for each event for all variables that proved significant ($p<0.05$) in the univariable analyses. Variables with more than 10% of missing values were excluded from the multivariable Cox regression analyses. We also performed Kaplan-Meier survival curves. Finally, we analyzed event occurrence by subgroups of patients with and without cSS stratified by antithrombotic treatments: antiplatelets, oral anticoagulants, or both.

Data availability

For purposes of replicating procedures and results, requests for anonymized data not provided in the article because of space limitations will be considered from qualified investigator.

RESULTS

We studied 12.669 patients for whom cSS had been evaluated. Clinical data and MR results are provided in Table 1. Mean age was 70.4±12.3 years, and 57.3% were men. Frequency of arterial hypertension was 70.8% and 45% of patients had atrial fibrillation. Treatment with antithrombotic agents prior to the index event was frequent: 543 patients (6.4 %) were on oral anticoagulants, 3.163 (37.9 %) on antiplatelet agents, and 79 (0.9%) were on both antithrombotic treatments. A total of 3.925 patients (31%) had at least 1 CMB. While data regarding white matter hyperintensities were lacking for many patients, 29% for whom a total Fazekas score (deep plus periventricular, score 0-6) was available scored more than 3. cSS was detected in 273 patients (2.2%), most (n=194; 71%) with a focal distribution, 13 (4.7%) with a disseminated distribution, and the remaining 66 (24.1%) unclassified. On discharge, antiplatelets were prescribed to 6.554 (51.7%), oral anticoagulants to 4.044 (31.9%) and both antiplatelets and oral anticoagulants to1.569 (12.3%), while 502 (3.9%) either received no

treatment or their therapy was unknown. Patients were followed-up for a mean of 24±17 months (range 6-60).

Comparison between cSS and non-cSS groups

Univariable comparisons between the cSS and non-CSS groups are summarized in Table 2. Age and sex distributions were equivalent. The frequency of several vascular risk factors, including hypertension and previous stroke (ischemic or hemorrhagic) was greater in the cSS group, while atrial fibrillation and heavy alcohol use were less common in the cSS group. Similar proportions of patients in both groups were on antithrombotic treatment either before the index event or during follow-up, except that oral anticoagulants (DOACs or VKAs) were prescribed less often in the cSS group. Both the frequency (48%) of 1 or more CMBs (lobar, deep, or mixed) and white matter hyperintensity severity were greater in patients with cSS.

Cerebrovascular events and death during follow-up (see Figures 1, 2, and 3):

For all patients studied, regardless of whether or not they had cSS, the incidence of IS (34.2 per 1000 patient-years) was substantially higher than that of ICrH (IR 6.5 per 1000 patient-years). The analysis of events according to the presence or absence of cSS showed the following results:

1. Ischaemic Stroke

A total of 9314 patients were followed-up, of whom 621 experienced IS during follow-up. The IR in the cSS group was 57.1 per 1000 patient-years, compared to 33.7 per 1000 patient-years in the non-cSS group, reflecting an IRR of 1.69 (95% CI: 1.07-2.57; p=0.020). Univariable Cox regression analysis indicated that IS was more frequent in the cSS group than in the non-cSS group (HR 1.67, 95% CI 1.10-2.54, p=0.015; Figure 3A), that IS frequency increased with age, hypertension, ischemic heart disease, atrial fibrillation,

diabetes, any previous stroke, alcohol abuse, antiplatelet treatment, white matter hyperintensity severity, and CMB presence, and that IS frequency decreased for treatment with VKAs, DOACs, or any oral anticoagulant.

Multivariable Cox regression analysis with the available sample of 8565 patients showed that cSS was not significantly associated with IS risk (adjusted HR 1.39, 95% CI 0.89-2.15, p=0.138). Age, any previous stroke, ischemic heart disease, diabetes,and CMB presence were independent risk factors, whereas treatment with oral anticoagulants was protective.

2. Intracranial Haemorrhage

Of 9314 followed-up patients, 220 (2.4%) had cSS. A total of 119 experienced ICrH. ICrH subtypes were ICH (n=92), subdural hemorrhage (n=25) and subarachnoid hemorrhage (n=2). The IR for the cSS group was 14.6 per 1000 patient-years, compared to 6.3 per 1000 patient-years for the non-cSS group, an IRR of 2.32 (95% CI: 0.83-5.22; p=0.07).

Univariable Cox regression analysis showed that ICrH was more frequent in the cSS group than in the non-cSS group (HR 2.33, 95% CI 1.02-5.31, p=0.043; Figure 3B), and also that ICrH risk increased with age, hypertension, any previous stroke, VKA treatment, white matter hyperintensity severity, and CMB presence. Multivariable Cox regression analysis with the available sample of 9052 patients indicated that cSS was not significantly associated with ICrH risk (adjusted HR 1.93, 95% CI 0.85-4.41, p=0.11). Age, any previous stroke, and CMB presence were the only independent risk factors.

3. Any stroke

Of 12474 followed-up patients, 906 experienced stroke (ischemic or hemorrhagic) during follow-up. Stroke IR in the cSS group was 82.9 per 1000 patient-years, compared to 42 per 1000 patient-years in the non-cSS group, for an IRR of 1.97 (95% CI: 1.38-2.74; p<0.001).

Univariable Cox regression analysis (eTable 1) showed that stroke frequency was greater in the cSS group than in the non-cSS group (HR 1.98, 95% CI 1.42-2.75, p<0.001; Figure 3C).

Multivariable Cox regression analysis (Table 3) with the available sample of 11911 patients showed that cSS was associated with an increased risk of any stroke (HR 1.62; 95% CI: 1.14-2.28; p=0.006). Additional risk factors were age, any previous stroke, ischemic heart disease, and presence of CMBs, while treatment with any oral anticoagulant decreased stroke risk.

4. Death.

A total of 11928 patients were followed-up, of whom 1553 died during follow-up. Mortality IR in the cSS group was 95.5 per 1000 patient-years, compared to 73.6 per 1000 patient-years in the non-cSS group, an IRR of 1.29 (95% CI: 0.94-1.75; p=0.09). Univariable Cox regression analysis showed that cSS was not significantly associated with mortality (HR 1.29, 95% CI 0.95-1.74, p=0.093, Figure 3D), that mortality increased with age, female sex, atrial fibrillation, hypertension, previous stroke, ischemic heart disease, treatment with VKA or any oral anticoagulant, the presence of 1 or more CMBs, and white matter hyperintensity severity, and that mortality decreased with hyperlipidemia, smoking, alcohol abuse, and antiplatelet treatment.

Sensitivity analyses

1. Antiplatelet agent only (see Figure 1 and 2 for IR)

A total of 6554 patients were treated only with an antiplatelet agent during follow-up. IS risk was evaluated in 3843 followed-up patients, of whom 333 experienced IS. For the cSS group, IS risk was not significantly increased (HR 1.55, 95% CI 0.92-2.61, p=0.091). Of 3910 patients followed-up for ICrH risk, 47 experienced ICrH. Cox regression analysis showed that ICrH risk was not significantly different between the cSS group and the non-cSS group (HR 2.31, 95% CI 0.71-7.44, p=0.149). The risk of any stroke during follow-up was evaluated in 6115 patients, of whom 500 had an ischemic or hemorrhagic stroke. Stroke risk was significantly increased in the cSS group in the unadjusted (HR 1.83; 95% CI: 1.2-2.78;

p=0.005) but not in the adjusted (HR 1.54; 95% CI 0.99-2.39; p=0.052) analyses. Finally, mortality risk was evaluated in 6110 patients, of whom 542 died during follow-up. cSS increased the risk of death in both the unadjusted (HR 1.51; 95% CI: 1.01-2.26; p=0.041) and adjusted (HR 1.74; 95% CI: 1.15-2.65; p=0.009) analyses (eTable 2). IR was 108.4 versus 65.8 per 1000 patient-years, with an IRR of 1.65 (1.11-2.38), p=0.01.

2. Oral anticoagulants (see Figure 1 and 2 for IR)

A total of 4044 patients were treated only with any oral anticoagulant during follow-up. IS risk was evaluated in 3836 patients of whom 195 experienced IS, and this risk was no greater in the cSS group (HR 1.52; 95% CI: 0.67-3.44; p=0.30).A total of 3835 were followed-up for ICrH risk, which was diagnosed in 56. Cox regression analysis showed that ICrH risk was similar in the cSS and non-cSS groups (HR 0.84; 95% CI: 0.11-6.06; p=0.86). The risk of any stroke during follow-up was evaluated in 4001 patients, of whom 254 experienced stroke. The risk of any stroke risk was not significantly different in the cSS and non-cSS groups (HR 1.34; 95% CI: 0.63-2.84; p=0.44). Finally, of 4000 patients evaluated for mortality during follow-up, 641 patients died. Cox regression analysis (HR 0.87; 95% CI: 0.49-1.55; p=0.65) indicated no significantly increased risk of death in the cSS group.

3. Combined antiplatelets and oral anticoagulants (see Figure 1 and 2 for IR).

Of 1569 patients on both antiplatelets and oral anticoagulants at baseline, 1103 were followed-up. Overall characteristics of this subgroup of patients are detailed in eTable 3. IS risk during follow-up, evaluated in 1103 patients, was not significantly greater in the cSS group (HR 2.04, 95% CI 0.28-14.76, p=0.47). Cox regression analysis showed that ICrH risk was greater in the cSS group in both unadjusted (HR 22.88; 95% CI: 5.11-102.36; p<0.001) and adjusted (HR 13.26; 95% CI: 2.90-60.63; p=0.001) analyses (eTable 4). IR was 107.5 versus 4.9 per 1000 patient-years with an IRR of 22.06 (2-40-99.11), p=0.005. The risk of any stroke during follow-up, evaluated in 1563 patients, was greater in the cSS group in both

the unadjusted (HR 5.50; 95% CI: 2.23-13.54; p<0.001) and adjusted (HR 5.03; 95% CI: 2.03-12.44; p<0.001) analyses (eTable 5) IR was 198.8. versus 34.7 per 1000 patient-years, with an IRR of 5.74 (1.82-13.85), p=0.003. Finally, mortality risk during follow-up, evaluated in 1563 patients, was not significantly greater in either the unadjusted or adjusted analyses (HR 0.58, 95% CI 0.08-4.14, p=0.58).

DISCUSSION

We report three major findings for our analysis of clinical, MRI, and follow-up data obtained from a large database of patients with IS or TIA that included 273 patients with cSS (frequency of 2.2%). First, the risk of IS was higher than that of ICrH in both the cSS and the non-cSS groups. Second, cSS was associated with the risk of future cerebrovascular events (IS, ICrH, or any stroke) and death. However, after adjusting for confounders in multivariable analyses these associations no longer held, except for any stroke (IS plus ICrH), whose risk was higher in patients with cSS (adjusted HR 1.6). Third, patients with cSS receiving antiplatelet agents alone or oral anticoagulants alone were not at an increased risk of cerebrovascular events. However, in the antiplatelet plus anticoagulant subgroup, a marked increase in the risk of ICrH and of any stroke was noted in patients with cSS.

cSS is infrequent, detected in only 0.43% of 6049 community-dwelling older adults,[11] and in only 2.2% of our patients with IS. In a North-American population study of 1142 individuals, cSS was detected in 0.21% and 1.4% of individuals aged 50-69 years and older than 69 years, respectively.[12] The fact that cSS was detected in only 1% of patients with acute IS[18] and in 1% of patients treated with intravenous thrombolysis[19], but was reported in 60.5% of patients with histopathologically-proven CAA,[20] but in no controls with ICH non-related to CAA,[8] suggests that cSS is a marker of CAA. Because cSS is infrequent and because most

studies have focused on its consistent association with ICH risk, mainly in ICH survivors,[3] several uncertainties remain regarding its prognostic implications. Our additional data based on a relatively large sample may be useful to advance the understanding of prognostic and therapeutic aspects of cSS.

Patients with cSS in our study had a high burden of vascular risk factors, and, consequently, frequent vascular events during follow-up would be expected. Indeed, patients with cSS had a greater frequency of hypertension, and previous ischemic or hemorrhagic stroke than patients without cSS, but a lower frequency of atrial fibrillation. The finding that the former were less often prescribed anticoagulants is probably related to the prescribing physician's perceived risk of cerebral hemorrhage. Previous observational studies in patients with previous ICH have consistently demonstrated that cSS is strongly associated with a follow-up risk of recurrent ICH[3,6-10,20]. A meta-analysis of patients with symptomatic CAA followed up for three years reported annual ICH rates of 3.9% for patients without cSS, 9.1% for patients with focal cSS, and 12.5% for patients with disseminated cSS.[3] cSS is a progressive disease,[21] and ICH risk has been reported to be greater in patients with disseminated cSS[8] and multifocal cSS.[22] In our study, although cSS was associated with an increased absolute risk of cerebrovascular events, after adjusting for confounding factors, the association disappeared for ICrH and IS risk, and was attenuated for any stroke. Explanations for our finding regarding ICrH may be an underpowered analysis (due to a low frequency of events) or indication bias due to underuse of antithrombotic drugs (fueled by concerns about the risk of cerebral hemorrhage).

Of 38 cohorts participating in MICON, 21 contributed data to the current analysis. Lack of availability of cSS ratings, or resources to perform these ratings, were the main reasons for non-participation. However, cSS was an independent risk factor for any stroke, suggesting

that cSS is associated with both ischemic and hemorrhagic stroke risk, and that this risk is in addition to that of CMBs. In our study, it is possible that the greater IS and ICrH risks observed in the univariable analysis, but that disappeared after adjustment for confounding variables, are maintained when the outcome is the combined risk of any stroke, given that the number of events and the full sample is greater.

Since cSS is a marker of CAA, its independent contribution to vascular risk is difficult to ascertain if this risk is analyzed jointly with the risk of CMBs. CMBs are a well-known and more frequent CAA marker (frequency 31% in our series) that markedly increases the risk of both ischemic and hemorrhagic stroke.[14,23,24] The well-documented association between cSS and CMB presence[1] was corroborated in our study, in which around half of the patients with cSS also had CMBs. However, some authors advocate distinct vasculopathic mechanisms: cSS may be associated with preferentially leptomeningeal deposition and the APOE ε2 allele, while CMBs may be related to cortical deposition and the APOE ε4 allele.[25] Our findings of an independent contribution of CMBs and cSS to the risk of any stroke suggests that future therapeutic studies should consider both MR markers of CAA and patient genetics to personalize the safe use of antithrombotics.[2] Our recent MICON risk score study demonstrated that ICrH predictions for patients with IS taking antithrombotics improve markedly if CMB presence and burden is taken into account.[24] It is possible that considering cSS could further improve the predictive ability of the MICON risk score.

Literature on IS and mortality incidence during follow-up of patients with cSS is scant. A neuropathology study with postmortem brain 7.0 Tesla MR images showed that cSS was more often spatially related to an underlying cortical infarct than to a cortical bleed, thus suggesting that cSS is not exclusively observed in CAA, and also that cSS is associated with both hemorrhagic and ischemic lesions.[26] One study reported that, after a mean follow-up of

24 months, up to 57% of 21 patients with convexity subarachnoid hemorrhage (cSAH) – a precursor of cSS – had ischemic brain lesions,[27] while a recently published multicenter study, of cSAH associated with probable or possible CAA ,concluded that cSAH is associated with an increased risk of ICH during follow-up, but not of IS.[9] Another study reported that, while patients with cSS reached a composite endpoint of stroke or death more frequently than patients without cSS, ICH incidence accounted for the majority of primary endpoints, and that after multivariable regression, death and ICrH, but not IS, were associated with cSS.[28] Multicenter studies are needed to clarify whether the risk of IS recurrence or death is increased, since no specifically designed study exists with which we could compare our findings.

Regarding the influence of antithrombotic treatment, it is well known that CMB presence is associated with an increased risk of IS and ICrH, and that the risk of ICH is increased in patients receiving antithrombotic agents.[14,23] Because CMB presence and cSS – usually associated – are markers of CAA,[1] the benefits and risks associated with antithrombotic treatment in patients with cSS may be the same as in patients with CMBs but may differ if both abnormalities result from different mechanisms.[13,25]

We would like to highlight that the absolute risk of IS was consistently higher than that of ICrH, both in the cSS group (IR 57.1 versus 14.6 per 1000 patient-years, about 4 times more) and in the non-CSS group (33.7 versus 6.3 per 1000 patient-years, about 5 times more). It is therefore extremely important to know the risk associated with the secondary prevention treatments. On the basis of currently available information, it is uncertain whether these drugs, if indicated, should be started or resumed in patients with cSS. According to our findings, in patients with cSS, the adjusted risk of cerebrovascular events (ICrH, IS or any of

them), is not greater in patients who receive antiplatelet alone or anticoagulant alone, but it is markedly greater in patients receiving combined antiplatelet and oral anticoagulant treatment These findings suggest that the combination of antiplatelets and anticoagulants should be avoided if cSS is present. The adjusted risk of death was also greater in patients on antiplatelets and we need further studies to confirm this finding and to know the reasons for it. Those results are clinically important, since almost half of our patients were taking antithrombotic agents – mostly antiplatelet drugs – prior to stroke, and most of those patients need to start or resume antithrombotic treatment.

Limited information is available in the form of previous studies with which to compare our findings. In a series of 49 patients with cSS who were followed-up for a mean of 6.4 years, ICH recurrence increased in patients treated with antiplatelets or anticoagulants, but this association disappeared in the multivariable analysis; IS and mortality were not analyzed, however.[7] In the RESTART study,[29] the presence of focal or disseminated cSS did not influence the risk of IS or ICH recurrence in a subgroup of MRI-assessed patients with ICH. In a recent study of 248 patients who experienced transient focal neurologic events attributable to CAA that included 156 (62.9%) patients with cSS and 38 patients on antiplatelet or anticoagulant treatment, it was reported that antithrombotic use, but not cSS, was associated with greater ICH incidence, while cSS was associated with a greater risk of death.[30] In another recent study, neither antiplatelet nor anticoagulant use after cSAH were associated with ICH, IS, or death during follow-up.[31]

Our findings together with the limited data available in the literature should be viewed as hypothesis-generating, as a definitive answer on the benefits and risks of antithrombotic treatment in patients with cSS can only be obtained from randomized clinical trials, which

may be difficult to conduct given the rarity of cSS and the established use of antithrombotic drugs after IS or TIA. In the meantime, our findings provide some reassurance for cases where anticoagulation or antiplatelet treatment is clearly indicated, but would suggest that combined antithrombotic treatment should be carefully assessed, given the increased risk of cerebrovascular complications and mortality.

Strengths and Limitations

The strength of our study is the large number of included MRI-assessed stroke patients followed up in the various participating centers. However, we highlight several limitations of our study. The number of patients with cSS was relatively small, due to cSS being a very infrequent abnormality. There was a risk of inclusion bias, as investigators may have preferentially included patients in better general and neurological condition or younger patients, and may also have reserved antithrombotic treatment for patients with a lower perceived risk of bleeding complications. MR images were not evaluated centrally, sequences were not standardized, and the field strength of the MRI devices was not homogeneous. The fact that many patients with cSS were not classified according to focal or disseminated variants meant that the relative risk could not be estimated for disseminated cSS, which has been reported to be more dangerous than focal cSS.[8] No data was provided on factors that may influence the risk of vascular events, such as cognitive impairment, APOE alleles, race, degree of control of anticoagulant treatment, adherence to antithrombotics, treatment interruptions and changes, the reasons for the individualized decision of the neurologist in charge about the specific antithrombotic treatment prescribed and blood pressure control. We do not know if some patients underwent left atrial appendage occlusion, which could be an alternative to anticoagulants in patients at excessive risk of ICrH. Indeed, our findings are exploratory and need to be confirmed by randomized clinical trials to clarify the best

approach to secondary prevention of ischemic stroke in patients with cSS. Finally, missing patient data for some variables complicated multivariable analyses, as several variables had to be discarded.

In conclusion, our study suggests that patients with cSS are at a high risk of stroke during follow-up, while cerebrovascular events (particularly ICrH) are even more frequent in patients with cSS treated with antiplatelets combined with oral anticoagulants. Care should therefore be taken when prescribing these drugs in combination.

http://links.lww.com/WNL/C546

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Table 1. Overall demographic, clinical, and neuroimaging characteristics. *

Age, mean (SD) y, n=12651	70.4 (12.3)
Sex (men), n (%), n=12669	7269 (57.3)
Race, n (%), n=10552	
Caucasian	4427 (41.9)
Asian	6059 (57.4)
Black	66 (0.62)
Index event, n=12658	
TIA, n (%)	1489 (11.7)
Ischemic stroke, n (%)	11169 (88.2)
Etiology (TOAST), n (%), n=8063	
Large-artery atherosclerosis	2329 (18.3)
Cardioembolism	3382 (26.7)
Small vessel occlusion	1494 (11.7)
Other determined mechanism	713 (5.6)
Undetermined etiology	1457 (11.5)
Atrial fibrillation, n (%), n=12575	5703 (45.3)
Hypertension, n (%), n=12632	8974 (71)
Previous stroke, n (%), n=12637	1858 (14.7)
Previous ICH, n (%)n =12251	174 (1.4)
Any previous stroke, n (%), n=12648	1990 (15.7)

Ischemic heart disease, n (%), n=12244	1637 (13.3)
Hyperlipidemia, n (%), n=12636	5062 (40.1)
Diabetes, n (%), n =12649	3218 (25.4)
Smoking, n (%), n=11124	2008 (18.1)
Alcohol >8 U/week, n (%), n=5234	719 (13.7)
Antiplatelets previous 6 months, n (%), n=8334	3163 (37.9)
Anticoagulants previous 6 months, n (%), n=8359	543 (6.4)
Antiplatelet+any oral anticoagulant previous 6 months, n (%), n=8334	79 (0.9)
VKAs at baseline, n (%), n=12667	2532 (19.9)
DOACs at baseline, n (%), n=12668	1534 (12.1)
Any oral anticoagulant at baseline, n (%), n=12666	4044 (31.9)
Antiplatelets at baseline, n (%), n=12660	6554 (51.7)
Antiplatelet+oral anticoagulant at baseline, n (%), n=12660	1564 (12.3)
MRI sequence, n (%), n=12669 Gradient echo Susceptibility weighted imaging	 9750 (76.9) 2919 (23)

Number of microbleeds, n=12669	
None	8744 (69)
1	1688 (13.3)
2-4	1396 (11)
5 or more	841 (6.6)
Presence of 1 or more microbleeds, n (%)	3925 (30.9)
Presence of non-lobar microbleeds, n (%)	2635 (20.8)
Presence of lobar microbleeds, n (%)	2519 (19.8)
Presence of mixed microbleeds, n (%)	1229 (9.7)
Fazekas total score, n=7975	
Fazekas grade 0	853 (10.7)
Fazekas grade 1	1236 (15.5)
Fazekas grade 2	2186 (27.4)
Fazekas grade 3	1394 (17.5)
Fazekas grade 4	1094 (13.7)
Fazekas grade 5	715 (9)
Fazekas grade 6	498 (6.2)
Cortical superficial siderosis, n=12669	273 (2.2)
Focal	194
Disseminated	13
Unclassified	66

*For each variable we provide the exact number of patients for whom data are available.

TIA: Transient Ischemic attack; ICH: intracerebral hemorrhage; VKA: Vitamin K antagonists; DOACs: Direct oral anticoagulants

Table 2. Univariable comparison of variables for patients in the cortical superficial siderosis (cSS) and non-cSS groups*

	cSS (n=273)	Non-cSS (n=12396)	p
Age, mean (SD) y	71.2 (10.59)	70.42 (12.34)	0.194
Sex (men), n (%)	168 (61.5)	7101 (57.3)	0.174
Race, n (%) n (available)	211	10341	
Caucasian	119 (56.4)	4308 (41.7)	
Asian	86 (40.8)	5973 (57.8)	<0.001
Black	6 (2.8)	60 (0.6)	
Index event, n (available)	272	12386	
TIA, n (%)	15 (5.5)	1474 (11.9)	0.001
Ischemic stroke, n (%)	257 (94.5)	10912 (88.1)	
Etiology (TOAST), n (available)	187	9188	
Large-artery atherosclerosis	67 (35.8)	2262 (24.6)	
Cardioembolism	41 (21.9)	3341 (36.4)	<0.001
Small vessel occlusion	26 (13.9)	1468 (16)	
Other determined mechanism	25 (13.4)	688 (7.5)	
Undetermined etiology	28 (15)	1429 (15.6)	
Atrial fibrillation, n (%), n=268/12307	105 (39.2)	5598 (45.5)	0.041

Hypertension, n (%), n=273/12359	211 (77.3)	8763 (70.9)	0.023
Previous stroke, n (%), n=271/12366	63 (23.2)	1795 (14.5)	<0.001
Previous ICH, n (%), n=257/11994	10 (3.9)	164 (1.4)	0.004
Any previous stroke, n (%), n=271/12377	70 (25.8)	1920 (15.5)	<0.001
Ischemic heart disease, n (%), 260/11984	44 (16.9)	1593 (13.3)	0.093
Hyperlipidemia, n (%), n=271/12365	130 (48)	4932 (39.9)	0.008
Diabetes, n (%), n=271/12378	76 (28)	3142 (25.4)	0.32
Smoking habit, n (%), 230/10894	51 (22.2)	1957 (18)	0.098
Alcohol abuse, n (%), 109/5125	8 (7.3)	711 (13.9)	0.049
Antiplatelet (previous 6 months, n (%), n=189/8145	86 (45.5)	3156 (38.7)	0.070
Anticoagulant (previous 6 months, n (%), n=190/8169	16 (8.4)	606 (7.4)	0.575
VKAs at baseline, n (%), n=273/12394	70 (25.6)	3625 (29.2)	0.203
DOACs at baseline, n (%), n=273/12395	34 (12.5)	1927 (15.5)	0.179
Any oral anticoagulant at baseline, n (%), n=203/12393	103 (37.7)	5513 (44.5)	0.027
Antiplatelet at baseline, n (%), n=272/12388	171 (62.9)	7950 (64.2)	0.657
Number of microbleeds, n (available)	273	12396	
None	142 (52)	8602 (69.4)	
1	34 (12.5)	1654 (13.3)	<0.001
2-4	50 (18.3)	1346 (10.9)	
5 or more	47 (17.2)	794 (6.4)	

Presence of 1 or more microbleeds, n (%)	131 (48)	3794 (30.6)	<0.001
Presence of non-lobar microbleeds, n (%)	87 (31.9)	2548 (20.6)	<0.001
Presence of lobar microbleeds, n (%)	103 (37.7)	2416 (19.5)	<0.001
Presence of mixed microbleeds, n (%)	59 (21.6)	1170 (9.4)	<0.001
Fazekas total score, n=available	113	7862	
Fazekas grade 0	5 (4.4)	848 (10.8)	
Fazekas grade 1	7 (6.2)	1229 (15.6)	
Fazekas grade 2	31 (27.4)	2155 (27.4)	
Fazekas grade 3	16 (14.2)	1378 (17.5)	<0.001
Fazekas grade 4	23 (20.4)	1070 (13.6)	
Fazekas grade 5	14 (12.4)	701 (8.9)	
Fazekas grade 6	17 (15)	481 (6.1)	

*Percentage obtained from the number of patients available for each variable.

TIA: Transient Ischemic attack; ICH: intracerebral hemorrhage; VKA: Vitamin K antagonists; DOACs: Direct oral anticoagulants

Table 3. Multivariable Cox regression analysis of the risk of any stroke during follow-up.

Variable	HR	95% CI	p
Cortical Superficial Siderosis	1.61	1.14-2.27	0.006
Age (per 1 year)	1.01	1.00-1.01	<0.001
Any previous stroke	1.99	1.71-2.32	<0.001
Ischemic heart disease	1.31	1.09-1.57	0.003
Any oral anticoagulant	0.63	0.54-0.73	<0.001
1 or more microbleeds	1.35	1.17-1.54	<0.001

Figure legends

Figure 1. Incidence rate per 1000 patient-years, stratified by cSS and by antithrombotic treatment.

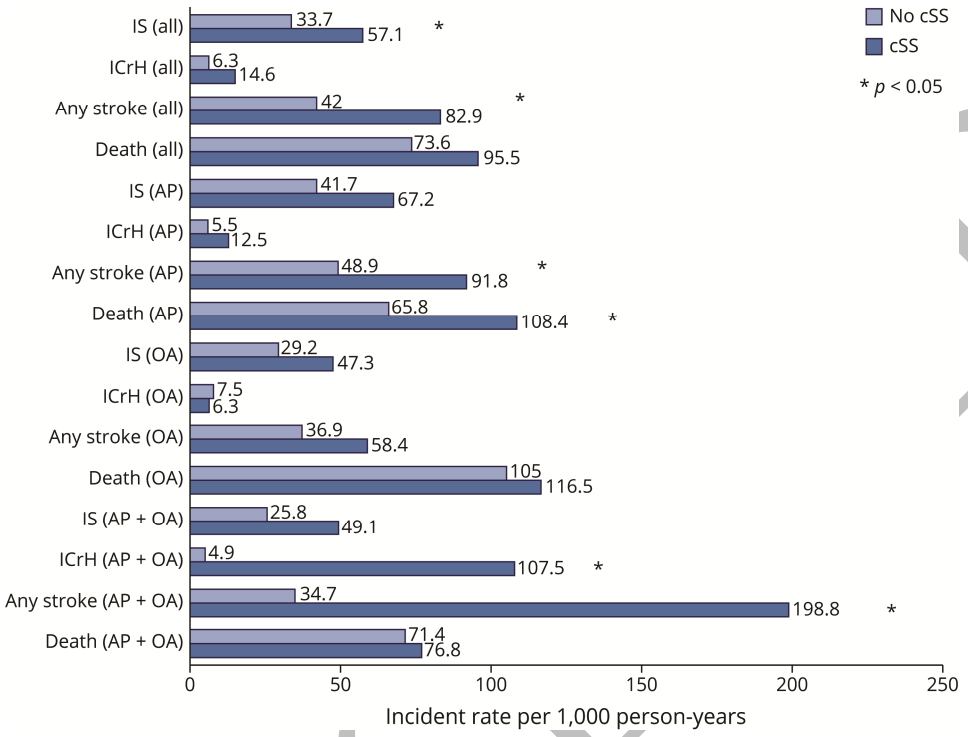


Figure 2. Results of the univariable and multivariable Cox regression analyses comparing cSS versus non-cSS groups.

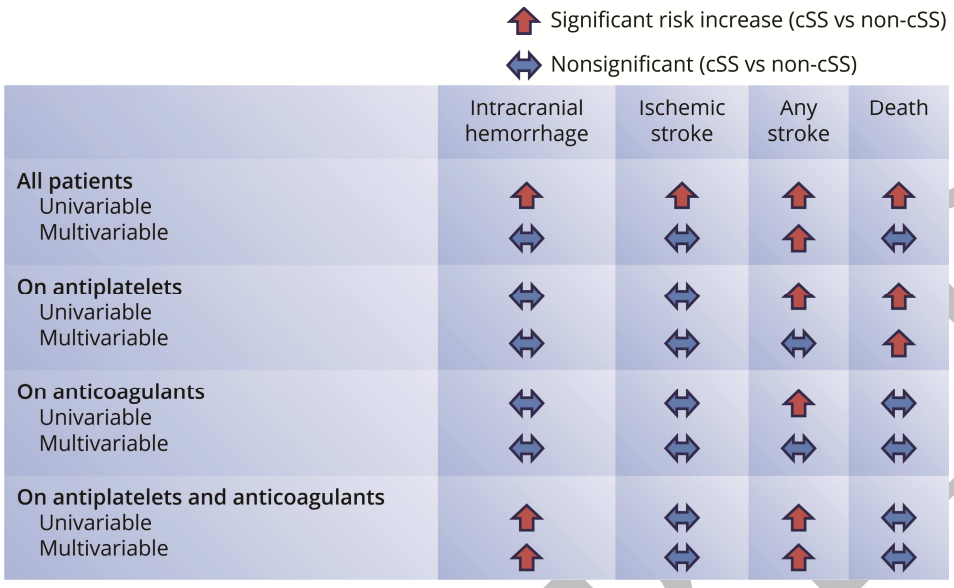
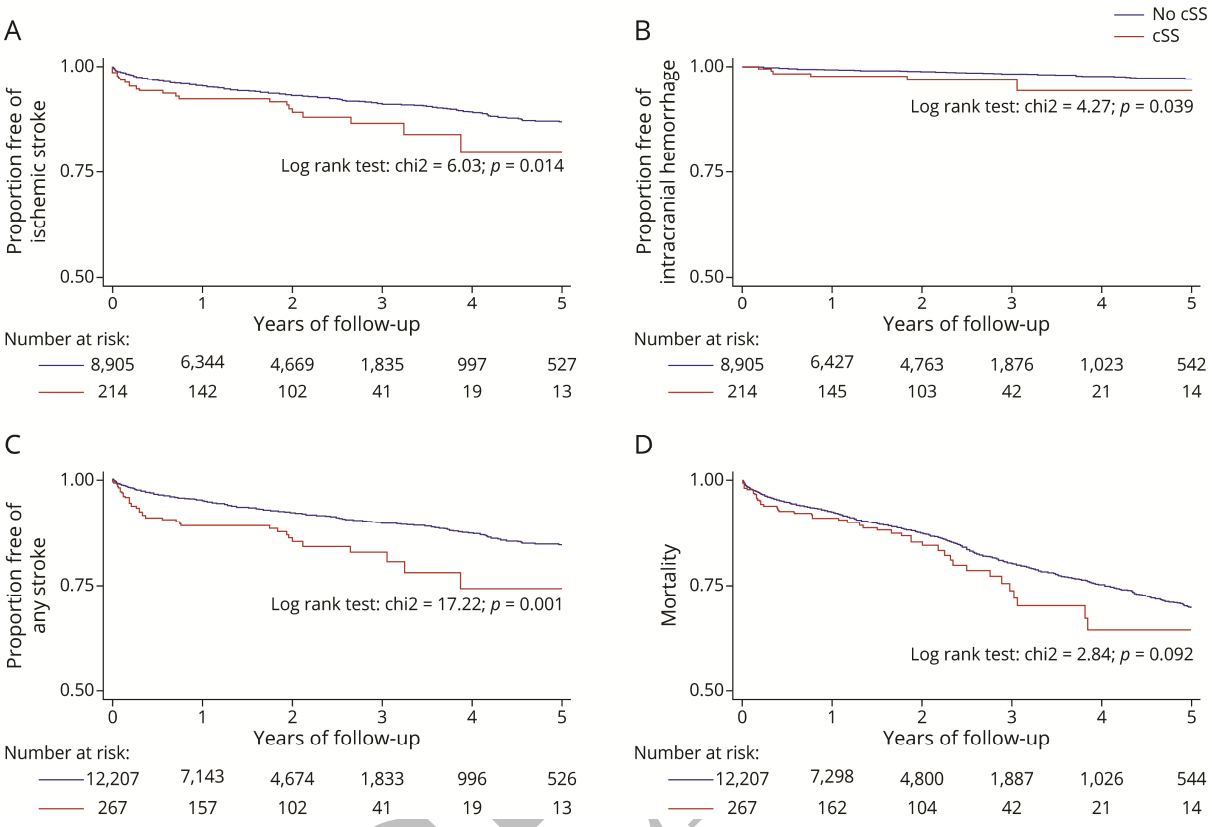


Figure 3. Kaplan-Meier survival curves for IS (a), ICrH (b), any stroke (c) and death (d) comparing the cSS and non-cSS groups.



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Joan Martí-Fàbregas, Pol Camps-Renom, Jonathan G Best, et al.

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