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REVIEW

Use of anticoagulant therapy and cerebral microbleeds: a systematic review and meta-analysis

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Abstract

Background Anticoagulant therapy increases the risk that cerebral microbleeds (CMBs) progress to intracerebral hemorrhage, but whether the therapy increases risk of CMB occurrence is unclear. We performed a systematic review and meta-analysis to investigate the potential association between anticoagulant use and CMB occurrence in stroke and stroke-free individuals.

Methods We searched observational studies in PubMed, Ovid EMBASE, and Cochrane Library from their inception until September 2019. We calculated the pooled odds ratio (OR) and 95% confidence interval (CI) for the prevalence and incidence of CMBs in anticoagulant users relative to non-anticoagulant users.

Results Forty-seven studies with 25,245 participants were included. The pooled analysis showed that anticoagulant use was associated with CMB prevalence (OR 1.54, 95% CI 1.26–1.88). The association was observed in subgroups stratified by type of participants: stroke-free, OR 1.86, 95% CI 1.25–2.77; ischemic stroke/transient ischemic attack, OR 1.33, 95% CI 1.06–1.67; and intracerebral hemorrhage, OR 2.26, 95% CI 1.06–4.83. Anticoagulant use was associated with increased prevalence of strictly lobar CMBs (OR 1.68, 95% CI 1.22–2.32) but not deep/infratentorial CMBs. Warfarin was associated with increased CMB prevalence (OR 1.64, 95% CI 1.23–2.18), but novel oral anticoagulants were not. Anticoagulant users showed higher incidence of CMBs during long-term follow-up (OR 1.72, 95% CI 1.22–2.44).

Conclusion Anticoagulant use is associated with higher prevalence and incidence of CMBs. This association appears to depend on location of CMBs and type of anticoagulants. More longitudinal investigations with adjustment for confounders are required to establish the causality.

Keywords Anticoagulants · Cerebral microbleeds · Intracerebral hemorrhage · Prevalence · Incidence · Meta-analysis

Introduction

Cerebral microbleeds (CMBs) are recognized as small rounded foci of signal void on T2*-weighted gradient-recalled echo (GRE) or susceptibility-weighted imaging (SWI) [1]. Histopathologically, CMBs correspond to hemosiderin deposits leaked from damaged small vessels affected by hemorrhage-prone angiopathy [1, 2]. CMBs are common in the elderly population [3] and they are associated with increased risk of intracerebral hemorrhage (ICH) [4].

Anticoagulant therapy is widely used to treat patients with atrial fibrillation or thromboembolic diseases, but it carries a risk of major bleeding and even ICH. Large longitudinal studies suggest that the presence of CMBs is a strong predictor of anticoagulant-related ICH, leading to concerns about the safety of prescribing anticoagulant drugs in patients with CMBs [5–8]. Hence, it is important

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to investigate the possible links among anticoagulants, CMB development and future ICH for risk stratification of patients receiving anticoagulation therapy.

Given the shared pathophysiology of CMBs and ICH, anticoagulant exposure might contribute to the development of subclinical hemorrhages before symptomatic ICH occurs. Several observational studies have linked anticoagulant use to CMB occurrence, but the results have been inconsistent [9–13]. A previous meta-analysis showed an association between warfarin use and CMB presence in 1460 patients with ICH, but not in 3817 patients with ischemic stroke (IS) or transient ischemic attack (TIA) [11]. However, the number of studies included in that meta-analysis was small, and several new studies became available on the association between anticoagulant use and CMB presence in patients with IS or TIA [12], as well as in the general population [13]. Also unclear is whether the relationship between anticoagulant use and CMB occurrence depends on the location of CMBs and the type of anticoagulants. CMBs in strictly lobar areas originate from distinct underlying microangiopathy than CMBs in deep/infratentorial areas and may be associated with different risk of ICH [1]. Novel oral anticoagulants (NOACs) have been associated with a lower risk of ICH than warfarin [14], and whether the same is true for risk of CMBs is unknown.

In view of these questions, we conducted a comprehensive systematic review and meta-analysis to explore: (1) the association between anticoagulant use and prevalence of preexisting CMBs in stroke and stroke-free individuals (2) whether the association varies by location of CMBs and type of anticoagulant therapy, and (3) whether anticoagulant use is associated with the incidence of new CMBs.

Methods

We performed the meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [15] and prospectively registered the study protocol in the PROSPERO International Prospective Register of Ongoing Systematic Reviews (CRD42019118378).

Search strategy

We searched PubMed, Ovid EMBASE and the Cochrane Library databases from their inception to 11 November 2018 and updated search on 1 September 2019 using the follow keywords: 'microbleed*', 'microh(a)emorrhage', 'cerebral' and 'brain'. We checked the reference lists of the identified articles and reviews for additional eligible studies.

Study selection

Two reviewers (YC and KQ) screened titles and abstracts to identify relevant articles for further full-text assessment. Any disagreement was resolved by consensus with the help of a third reviewer (ML). We included studies that met the following criteria: (1) prospective or retrospective cohort, case–control or cross-sectional study design; (2) stroke (IS, TIA or ICH) or stroke-free population; (3) used T2*-GRE or SWI sequences to detect CMBs; (4) reported the association between anticoagulant therapy and presence of CMBs. Only articles in English were included. We excluded studies that solely reported the antithrombotic effect on CMBs without a specific analysis of anticoagulants. Reviews, editorials, letters, conference abstracts, case reports, protocols, and animal studies were also excluded. When two or more publications analyzed the same study cohort, we retained only the one with the most complete data or with the largest sample.

Data extraction and quality assessment

Three authors (YC, YW and QS) independently performed data extraction and quality assessment. The uncertainties were resolved by discussion among the three reviewers. We used a predefined spreadsheet to extract the following data from each publication: first author; year of publication; country of origin; study design; type and number of participants; baseline characteristics of participants such as age, sex; prevalence of hypertension; imaging parameters; prevalence (or incidence) and distribution of CMBs (strictly lobar or deep/infratentorial); type and frequency of anticoagulant therapy (warfarin or NOACs); incident ICH; and follow-up period. The Newcastle–Ottawa Scale (NOS) was used to assess the quality of case–control and cohort studies (maximum score of 9) [16]. The Agency for Healthcare Research and Quality (AHRQ) scale was used to assess the quality of cross-sectional studies (maximum score of 11) [17].

Data synthesis and statistical analysis

Data were analyzed using Review Manager 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) and Stata version 15 (StataCorp LP, College Station, TX, USA). Unadjusted odds ratio (OR) and 95% confidence intervals (CI) were calculated for the presence of CMBs in anticoagulant users relative to non-anticoagulant users. We performed a separate analysis in terms of prevalent or incident CMBs. Given the likely heterogeneity across studies, we pooled estimates from eligible studies using random-effects models with inverse-variance weighting. Between-study heterogeneity was assessed using the

Cochrane Q statistic, with $P < 0.1$ indicating significant heterogeneity; and the I^2 statistic, with 25%, 50%, and 75% indicating low, moderate or high heterogeneity, respectively. Sources of heterogeneity were explored using subgroup analyses and meta-regression. Pre-defined stratified analyses were based on the type of participant, type of anticoagulant therapy, location of CMBs, study design (cohort versus case–control/cross-sectional), imaging modality (T2*-GRE versus SWI), and study location (Asian versus Western). Publication bias was evaluated using funnel plots and the Egger and Begg asymmetry tests, where $P < 0.05$ was considered statistically significant. The impact of potential publication bias on pooled estimates was explored using the 'trim-and-fill' method. Sensitivity analysis was performed to test the influence of each study on the pooled results by omitting one study at a time.

Post hoc analysis

We conducted a post hoc analysis of prospective longitudinal studies to further clarify the association between baseline CMBs and future risk of ICH in patients taking oral anticoagulants. A random-effects model was used to calculated pooled OR of incident ICH among anticoagulant users with CMBs relative to those without CMBs.

Results

Study selection

The flowchart of the study selection process is illustrated in Fig. 1. We initially identified 3757 non-duplicated articles and excluded 2627 of them after review of titles and abstracts. The full-text of the remaining 1130 articles was examined in detail, and we eliminated 1087 publications that did not meet our eligibility criteria: case reports ($n = 28$); editorials ($n = 22$); letters ($n = 24$); reviews ($n = 11$); animal experiments ($n = 2$); conference abstracts ($n = 482$); studies of CMBs on Alzheimer's disease, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) or Parkinson's disease ($n = 105$); no relevant data ($n = 408$); and overlapping populations ($n = 5$). We updated our search in September 2019 and retrieved four new articles [6, 7, 18, 19]. Ultimately, 47 studies were included in the meta-analysis [5–7, 12, 13, 18–59]. Forty-two studies provided data on the association between anticoagulant use and CMB occurrence and were included in the main analysis [6, 12, 13, 18–53, 57–59]. Eight studies reported the risk of incident ICH in anticoagulant users with CMBs relative to those without CMBs and were selected for post hoc analysis [5–7, 25, 49, 54–56].

Study characteristics

The characteristics and quality of the studies included in the main analysis are summarized in Tables 1 and 2. Eighteen studies were cohort studies ($n = 12{,}582$), 21 were cross-sectional ($n = 9419$), and 3 had a case–control design ($n = 573$). Twenty-three studies were conducted in Asia ($n = 10{,}196$), 11 in Europe ($n = 9254$), 7 in North America ($n = 3108$), and 1 in Australia ($n = 16$). Twenty-five studies focused on IS or TIA patients ($n = 9421$), 7 included ICH patients ($n = 751$), and 10 included stroke-free participants ($n = 12{,}178$), while 1 study included mixed patients of IS, TIA or ICH ($n = 224$). CMBs were assessed through T2* GRE in 32 studies ($n = 19{,}004$), through SWI in 9 studies ($n = 3020$), and through either T2* GRE or SWI in one study ($n = 134$). All the included studies showed moderate to high quality, with NOS or AHRQ scores ranging from 6 to 10.

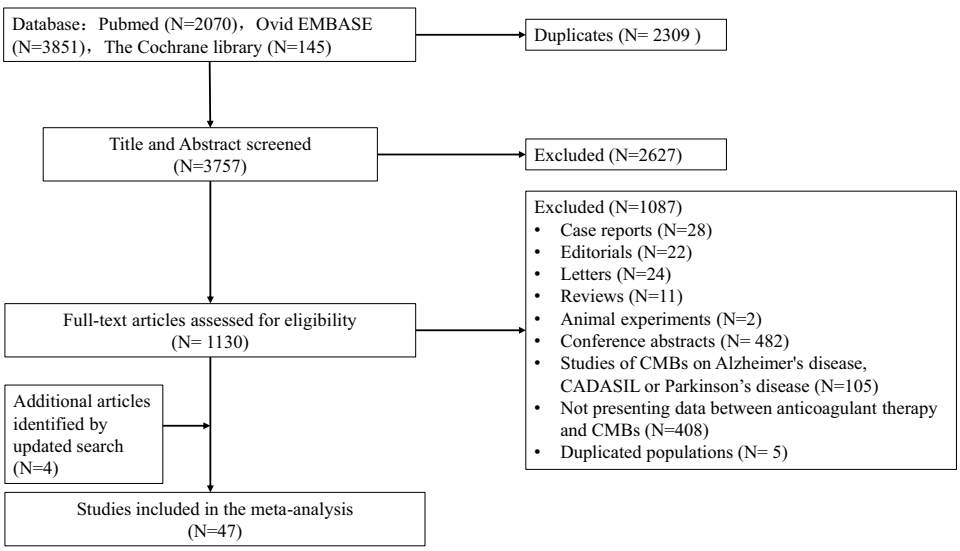

Fig. 1 Flow chart of literature search and selection. *CADASIL*, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy

Table 1 Characteristics of included studies on prevalent cerebral microbleeds

Author, year	Country	Design	Type of participant	Sample size (% male)	Mean/ median age	HTN (%)	MRI	CMBs (%)	Strictly lobar (%)	Deep / infratentorial (%)	Type of anticoagulants	Anticoagulant users (%)	Quality score
Akoudad 2014 [13]	Netherlands	Cohort	Free-stroke	4945 (44.9)	64 ± 11	34.3	1.5 T T2*GRE	957 (19.4)	629 (12.7)	328 (6.6)	Coumarin	8.6	9[a]
Alemany 2006 [43]	Sweden	Case–control	ICH	45 (NA)	NA	71.1	1.5 T T2*GRE	29 (64.4)	NA	NA	NA	6.7	7[a]
Charidimou 2016 [25]	Japan	Cohort	IS	119 (61.3)	76 (68–82)	71.4	1.5 T T2*GRE	26 (21.8)	2 (1.7)	24 (20.1)	Warfarin/ NOACs	22.7	9[a]
Chatzikonstantinou 2011 [22]	Germany	Cross-sectional	IS	132 (50.8)	74.1 ± 9.8	81.1	1.5 T T2*GRE	9 (6.8)	NA	NA	NA	19.7	6[b]
Cheng 2019 [18]	China	Cross-sectional	IS	160 (42.5)	71 (59–78)	40	1.5/3.0 T SWI	90 (56.3)	37 (23.1)	53 (33.1)	Warfarin	11.3	9[b]
Copenhaver 2008 [47]	USA	Cross-sectional	ICH	87 (46.0)	NA	77	1.5/3.0 T T2*GRE	50 (57.5)	NA	NA	NA	9.2	8[b]
Day 2011 [48]	USA	Cross-sectional	IS/TIA	300 (58.7)	71 ± 10.3	NA	1.5/3.0 T T2*GRE	70 (23)	35 (11.7)	35 (11.7)	Warfarin	7.7	9[b]
Gregoire 2010 [46]	UK	Cohort	IS/TIA	21 (61.9)	NA	76.2	1.5 T T2*GRE	8 (38.1)	NA	NA	NA	4.8	8[a]
Gustavsson 2015 [42]	Sweden	Cross-sectional	Free-stroke	207 (40.6)	71 ± 4.8	41.1	3.0 T T2*GRE	25 (12.1)	NA	NA	Warfarin	4.3	6[b]
Haji 2016 [49]	USA	Cohort	IS/TIA	134 (53.0)	NA	85.1	1.5/3.0 T T2*GRE/ SWI	37 (27.6)	NA	NA	NA	22.4	9[a]
Horstmann 2015 [12]	Germany	Cross-sectional	IS/TIA	785 (62.5)	63.9 ± 14.2	76.2	3.0 T SWI	186 (23.7)	68 (8.7)	118 (15.0)	NA	6.2	9[b]
Imaizumi 2015 [29]	Japan	Cohort	ICH	231 (60.2)	68 ± 12	74.9	1.5 T T2*GRE	149 (64.5)	NA	149 (64.5)	Warfarin	4.3	9[a]
Imaizumi 2015 [29]	Japan	Cohort	IS	309 (54.7)	70.7 ± 11.7	59.2	1.5 T T2*GRE	126 (40.8)	NA	126 (40.8)	NA	5.5	9[a]
Jeong 2004 [32]	Korea	Cross-sectional	ICH	107 (55.9)	62.4 ± 12.8	67.3	1.5 T T2*GRE	75 (70.1)	NA	NA	NA	2.8	9[b]
Karayiannis 2016 [53]	Australia	Cross-sectional	ICH	16 (NA)	NA	NA	SWI	9 (56.3)	NA	NA	NA	68.8	8[b]
Kim 2011 [37]	Korea	Cross-sectional	IS	182 (55)	67.5 ± 11.2	64.8	1.5 T T2*GRE	43 (23.6)	NA	NA	NA	3.8	9[b]
Kim 2012 [35]	Korea	Cross-sectional	Free-stroke	1251 (57.6)	69.7	49.4	1.5 T T2*GRE	120 (9.6)	29 (2.3)	91 (7.3)	Warfarin	6.2	10[b]

Table 1 (continued)

Author, year	Country	Design	Type of participant	Sample size (% male)	Mean/ median age	HTN (%)	MRI	CMBs (%)	Strictly lobar (%)	Deep / infratentorial (%)	Type of anticoagulants	Anticoagulant users (%)	Quality score
Kim 2014 [36]	Korea	Cohort	IS	225 (54.7)	67.6 ± 13.7	62.7	3 T T2*GRE	87 (38.7)	NA	NA	NA	1.8	8[a]
Kim 2016 [34]	Korea	Cross-sectional	IS	1033 (60.3)	NA	75.5	1.5 T/3.0 T T2*GRE	328 (31.8)	75(7.3)	253 (24.5)	NA	6.5	8[b]
Laible 2015 [23]	Germany	Cross-sectional	ICH	97 (55.7)	65.9 ± 13.9	76.3	3.0 T SWI	56 (57.7)	18 (18.6)	38 (39.2)	Vitamin K antagonists	14.4	8[b]
Lau 2017 [58]	China	Cohort	IS	1003 (59.9)	69.0 ± 12.0	65.5	3.0 T SWI	450 (44.9)	161 (16.1)	289 (28.8)	Warfarin/ NOACs	2.3	9[a]
Lei 2018 [19]	China	Cross-sectional	IS	161 (57.1)	NA	73.9	SWI	80 (49.7)	40 (24.8)	60 (37.3)	NA	1.7	8[b]
Miwa 2011 [26]	Japan	Cross-sectional	Free-stroke	431 (52)	69.3 ± 8.6	71	1.5 T T2*GRE	65 (15.1)	30 (7.0)	35 (8.1)	Warfarin	3	10[b]
Oh 2014 [38]	Korea	Cross-sectional	IS	683 (63.4)	66.6 ± 12.3	50.2	1.5 T T2*GRE	189 (27.7)	54 (7.9)	135 (19.8)	Warfarin	5	9[b]
Orken 2009 [45]	Turkey	Case–control	IS	246 (57.3)	NA	76.8	1.5 T T2*GRE	48 (19.5)	NA	NA	Warfarin	57.3	6[a]
Ovbiagele 2006 [50]	USA	Cross-sectional	IS/TIA	164 (48.2)	71	67.1	1.5 T T2*GRE	57 (34.8)	NA	NA	Warfarin	6.1	9[b]
Potigumjon 2017 [44]	Thailand	Cross-sectional	IS	200 (63.0)	61 (19–90)	61	1.5 T T2*GRE	39 (19.5)	9 (4.5)	30 (15.0)	Warfarin/ NOACs	21	6[b]
Romero 2014 [51]	USA	Cross-sectional	Free-stroke	1965 (46.0)	66.5 ± 11.0	56	1.5 T T2*GRE	173 (8.8)	109 (5.5)	64 (3.3)	NA	4.4	10[b]
Saito 2015 [27]	Japan	Cohort	Free-stroke	69 (71)	> 45	59.4	1.5 T T2*GRE	27 (39.1)	NA	NA	Warfarin/ NOACs	76.8	9[a]
Schonewille 2005 [52]	USA	Cross-sectional	IS	42 (NA)	NA	88.1	1.5 T T2*GRE	21 (50.0)	NA	NA	Warfarin	11.9	7[b]
Song 2014a [40]	Korea	Cross-sectional	IS	1137 (62.3)	65 ± 12	77.7	3.0 T T2*GRE	350 (30.8)	36 (3.2)	314 (27.6)	NA	1.1	9[b]
Song 2014b [41]	Korea	Cohort	IS	504 (57.1)	70 ± 11	77.8	3.0 T T2*GRE	155 (30.8)	41 (8.1)	114 (22.6)	NA	24.2	9[a]
Soo 2008 [59]	China	Cohort	IS	908 (57.7)	NA	68.1	1.5 T T2*GRE	252 (27.8)	44 (4.8)	208 (22.9)	Coumarin	2.5	9[a]
Soo 2018 [20]	China	Case–control	Free-stroke	282 (50.7)	NA	85.1	3.0 T SWI	103 (36.5)	NA	NA	NOACs	44	8[a]
Soo 2019 [6]	China	Cohort	Free-stroke	237 (51.3)	74.3 ± 8.9	NA	3.0 T SWI	84 (35.4)	NA	NA	Warfarin	78.1	9[a]

Table 1 (continued)

Author, year	Country	Design	Type of participant	Sample size (% male)	Mean/ median age	HTN (%)	MRI	CMBs (%)	Strictly lobar (%)	Deep / infratentorial (%)	Type of anticoagulants	Anticoagulant users (%)	Quality score
Watanabe 2016 [28]	Japan	Cross-sectional	Free-stroke	279 (67.7)	70.0 ± 6.1	52	1.5 T SWI	73 (26.2)	20 (7.2)	53 (20.0)	NA	3.9	8[b]
Zerna 2016 [57]	Canada	Cohort	IS/TIA	416 (64.9)	67.0 ± 14.1	54.3	1.5/3.0 T T2*GRE	65 (15.6)	39 (9.4)	26 (6.3)	Warfarin	3.8	7[a]

HTN hypertension, *CMBs* cerebral microbleeds, *IS* ischemic stroke, *TIA* transient ischemic attack, *ICH* intracerebral hemorrhage, *MRI* magnetic resonance imaging, *GRE* gradient-recalled echo, *SWI* susceptibility-weighted imaging, *NOACs* novel oral anticoagulants, *NA* not available

[a]Newcastle–Ottawa Scale (NOS)

[b]Agency for Healthcare Research and Quality (AHRQ)

Anticoagulant use and risk of prevalent CMBs

Overall, 35 studies ($n = 18{,}825$) were pooled to estimate the association between anticoagulant use and prevalent CMBs (Table 1). The pooled analysis showed that anticoagulant therapy was associated with increased risk of prevalent CMBs (OR 1.54, 95% CI 1.26–1.88; $I^2 = 40\%$; Fig. 2). The pooled estimates remained stable after each study was omitted sequentially from the meta-analysis. The funnel plot seemed to be asymmetric and one statistical test showed marginal significance (Egger test, $P = 0.932$; Begg test, $P = 0.048$), indicating potential publication bias (Supplementary Fig. 1). We tested the impact of publication bias on the effect estimate using the 'trim-and-fill' method. After eight studies were 'filled', the pooled estimate was not significantly altered (OR 1.38, 95% CI 1.12–1.70; Supplementary Fig. 1).

When stratified by type of participants, CMBs were more frequent in anticoagulant users than in non-users for all the following pre-defined groups (Fig. 2): stroke-free population (OR 1.86, 95% CI 1.25–2.77; $I^2 = 62\%$), IS/TIA (OR 1.33, 95% CI 1.06–1.67; $I^2 = 21\%$), and ICH (OR 2.26, 95% CI 1.06–4.83; $I^2 = 0\%$). Regarding the type of anticoagulant therapy, 17 studies ($n = 10{,}727$) found an association between warfarin use and prevalent CMBs (OR 1.64, 95% CI 1.23–2.18; $I^2 = 41\%$), while we found no association in three studies ($n = 521$) reporting on NOACs (OR 0.82, 95% CI 0.51–1.33; $I^2 = 0\%$; Fig. 3). In terms of CMB location, the pooled OR of strictly lobar CMBs was 1.68 (95% CI 1.22–2.32; $I^2 = 24\%$) for anticoagulant users versus non-users, while the pooled OR of deep/infratentorial CMBs did not reveal any association (OR 1.50, 95% CI 0.89–2.55; $I^2 = 79\%$; Fig. 4).

The results of univariate meta-regression analyses are shown in Table 3. Age, prevalence of hypertension, publication year, study design or imaging modality did not modify the association between anticoagulation and prevalent CMBs (all $P > 0.05$). However, the study location did modify this association ($P < 0.001$): anticoagulant use was associated with increased risk of CMBs in Western populations (OR 2.15, 95% CI 1.82–2.54; $I^2 = 0\%$) but not in Asian populations (OR 1.18, 95% CI 0.94–1.47; $I^2 = 18\%$; Supplementary Fig. 2).

Anticoagulant use and risk of incident CMBs

Eight studies ($n = 6451$) with follow-up data were included to analyze the association between anticoagulant use and risk of incident CMBs (Table 2). Overall, we found a trend for the association between anticoagulant use and increased risk of incident CMBs (OR 1.46, 95% CI 0.98–2.19; $I^2 = 39\%$). Considering the highly variable follow-up period (1 week in two studies, over 1 year in

Table 2 Characteristics of included studies on incident cerebral microbleeds

Author, year	Country	Design	Type of participant	Sample size (% male)	Mean/ median age)	MRI	CMBs (%)	Strictly lobar (%)	Deep/ infratentorial (%)	Type of anticoagulants	Anticoagulant users (%)	Follow-up time	NOS Score
Akoudad 2014 [13]	Netherlands	Cohort	Free-stroke	3069 (46.0)	59.7 ± 8.1	1.5 T T2*GRE	213 (6.9)	150 (4.9)	63 (2.1)	Coumarin	5.9	3.9 ± 0.5 years	9
Ding 2015 [21]	Iceland	Cohort	Free-stroke	2512 (41.5)	74.6 ± 4.8	1.5 T T2*GRE	463 (18.4)	292 (11.6)	171 (6.8)	NA	5.5	5.2 years	8
Jeon 2009 [24]	Korea	Cohort	IS	237 (59.9)	64.0 ± 12.8	1.5 T T2*GRE	30 ((12.7)	NA	NA	NA	48.9	4 days	8
Kimura 2013 [30]	Japan	Cohort	IS	224 (54.0)	76.2 ± 10.6	1.5 T T2*GRE	11 (4.9)	NA	NA	Warfarin	10.3	24 h	9
Klarenbeek 2013 [31]	Netherlands	Cohort	IS	96 (59.4)	64.5 ± 11.1	1.5/3.0 T T2*GRE	17 (17.7)	NA	NA	NA	2.1	2 years	8
Lee 2011 [33]	Korea	Cohort	Stroke	224 (66.1)	64.6 ± 11.3	1.5 T T2*GRE	86 (38.4)	NA	NA	NA	5.4	27.5 ± 12.3 months	8
Pasquini 2016 [39]	France	Cohort	ICH	168 (NA)	64 (53–76)	1.5 T T2*GRE	80 (47.6)	18 (23.7)	58 (76.3)	NA	14.9	3.4 years	7
Saito 2015 [27]	Japan	Cohort	Free-stroke	69 (71)	> 45	1.5 T T2*GRE	9 (13.0)	6 (8.7)	3 (4.3)	Warfarin/ NOACs	76.8	1 year	9

CMBs cerebral microbleeds, *IS* ischemic stroke, *ICH* intracerebral hemorrhage, *MRI* magnetic resonance imaging, *GRE* gradient-recalled echo, *NOACs* novel oral anticoagulants, *NOS* Newcastle–Ottawa Scale, *NA* not available

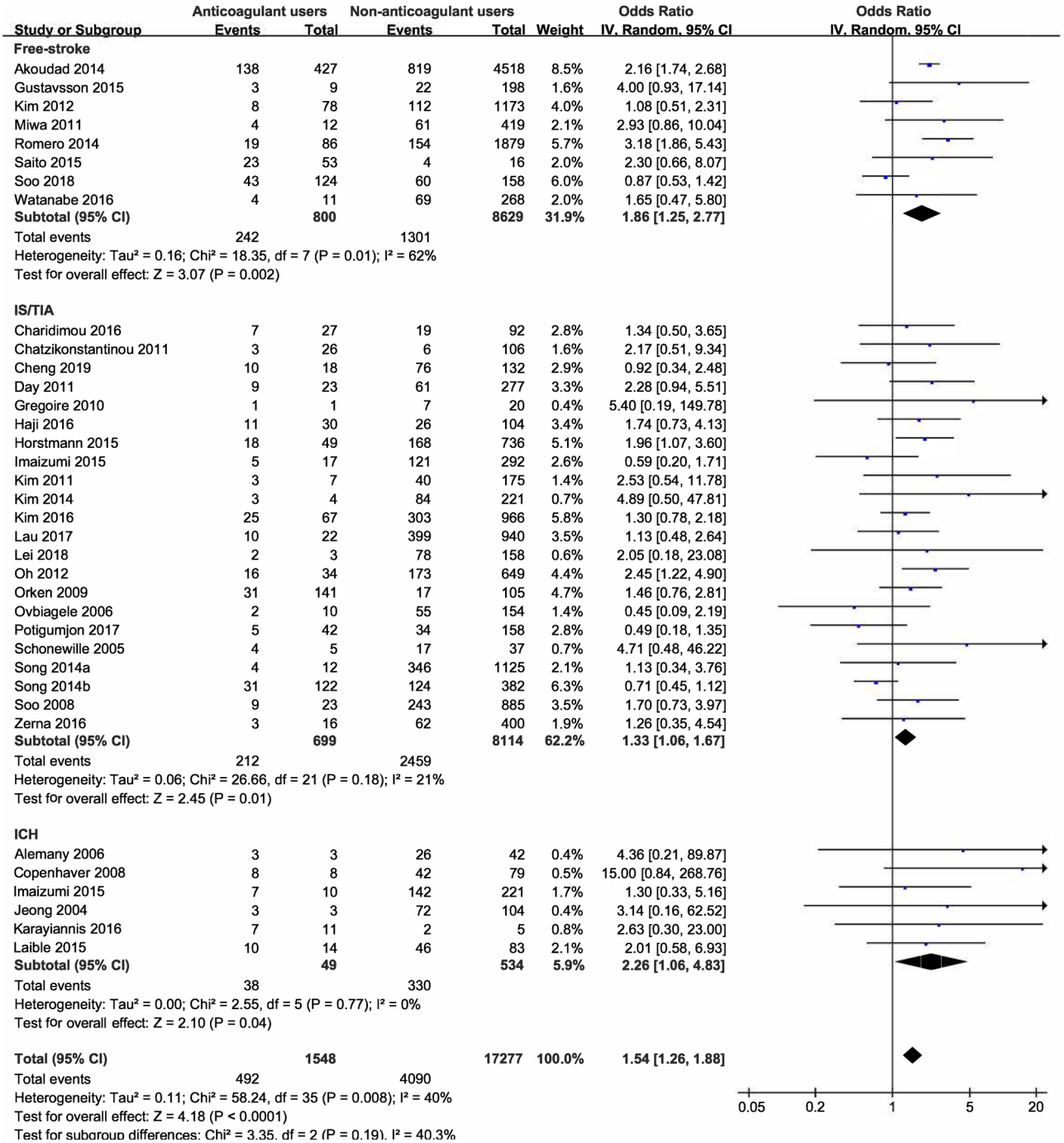

Fig. 2 Forest plot of the prevalence of cerebral microbleeds (CMBs) in anticoagulant users relative to non-anticoagulant users, stratified by type of participants. *IS* ischemic stroke, *TIA* transient ischemic attack, *ICH* intracerebral hemorrhage

the other six), we performed a subgroup analysis and the pooled estimate was significant in studies with follow-up longer than 1 year (OR 1.72, 95% CI 1.22–2.44; $I^2 = 19\%$) but not in studies with follow-up within 1 week (OR 0.68, 95% CI 0.33–1.42; $I^2 = 0\%$; Fig. 5).

CMBs at baseline and risk of incident ICH in anticoagulant users

The characteristics and quality of studies in the post hoc analysis are presented in Supplementary Table 1. Eight cohort studies restricted to anticoagulant users were included

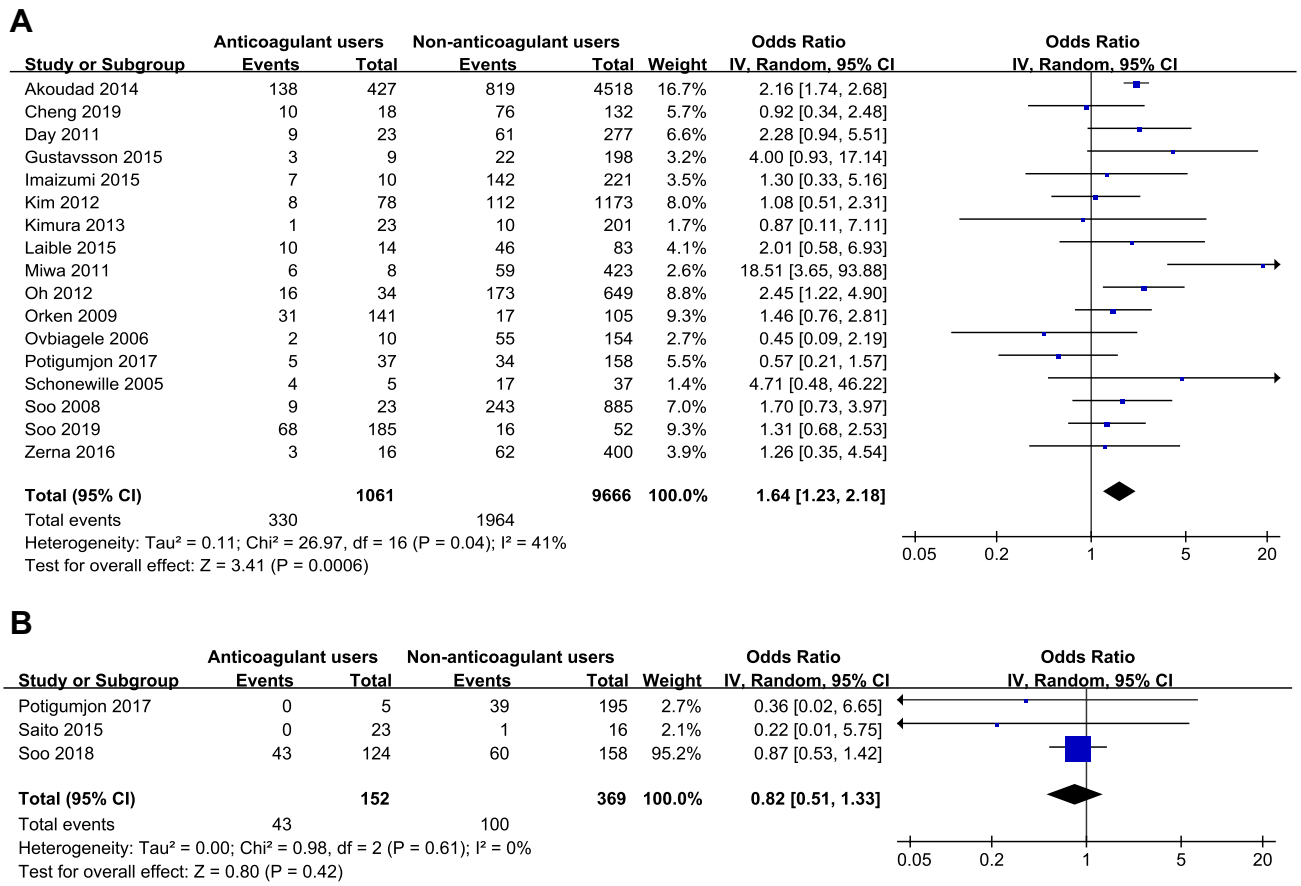

Fig. 3 Forest plot of the prevalence of cerebral microbleeds (CMBs) stratified by type of anticoagulants. **a** Warfarin users versus non-anticoagulant users; **b** NOAC users versus non-anticoagulant users. *NOAC* novel oral anticoagulant

($n = 3098$). A majority of the studies recruited patients with IS or TIA due to cardioembolism [5, 7, 25, 49, 54–56], and one study involved patients with atrial fibrillation without prior IS or TIA [6]. Among anticoagulant users, 27 out of 709 (3.8%) patients with baseline CMBs developed ICH, compared to 22 out of 2389 (0.9%) without baseline CMBs. The pooled OR of incident ICH in patients with CMBs relative to those without CMBs was 3.91 (95% CI 2.18–7.01; $I^2 = 0\%$; Supplementary Fig. 3).

Discussion

CMBs have been recognized as an indicator of subsequent ICH in patients receiving anticoagulant therapy [5–8], but whether anticoagulant drugs influence the risk of CMB occurrence remains uncertain. In this aggregate meta-analysis involving more than 25,000 participants, we provide up-to-date evidence that anticoagulants are associated with higher prevalence of CMBs among stroke patients and stroke-free individuals. In particular, warfarin but not NOACs appear to be associated with prevalent CMBs. Subgroup analysis suggests that the greater risk of CMBs applies to strictly lobar CMBs but not deep/infratentorial CMBs. Patients receiving anticoagulants are at greater risk of developing new CMBs after 1 year. These results are robust to potential influence of age, hypertension, publication year, study design, imaging modality and publication bias.

The current study is in line with a prior meta-analysis that demonstrated higher CMB presence in warfarin users with ICH than in non-users [11]. We also observed a positive association between anticoagulant use and CMBs in patients with IS/TIA and in stroke-free individuals. Because we included more studies with large sample size, our estimate might be more precise. Of note, the available evidence is consistent with the hypothesis that anticoagulation may promote the occurrence of CMBs. This is further supported by the pooled results showing an association between anticoagulant use and incident CMBs after long-term follow-up. How anticoagulant exposure contributes to CMBs is unclear. CMBs are considered small hemorrhages that have leaked from pathologically fragile small vessels [1] and, in most cases, such leakage is a self-limiting process controlled by

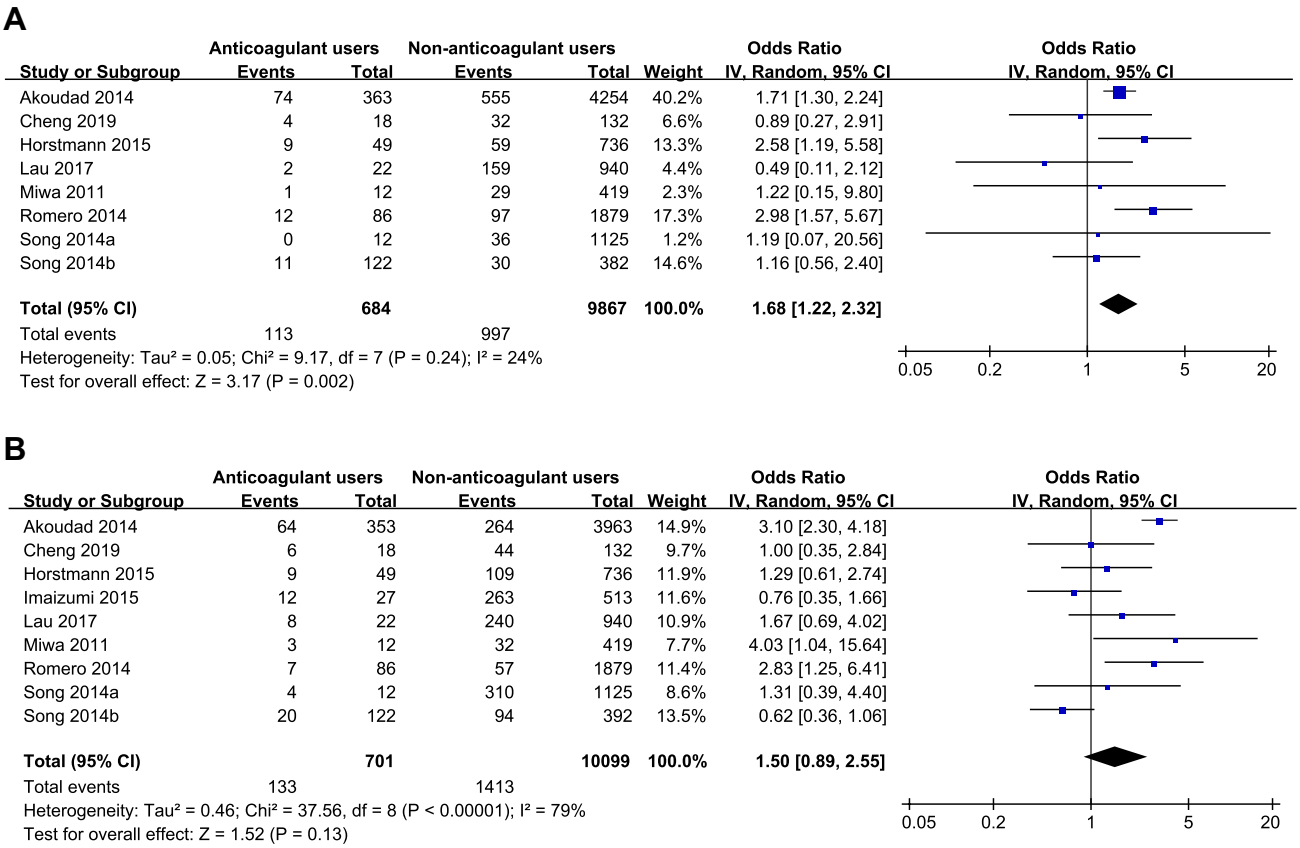

Fig. 4 Forest plot of the prevalence of cerebral microbleeds (CMBs) in anticoagulant users relative to non-anticoagulant users, stratified by location of CMBs. **a** Strictly lobar CMBs; **b** deep/infratentorial CMBs

Table 3 Results of the univariate meta-regression

Variable	No. of studies	Coefficient (95% CI)	*P* value
Mean age (per year increase)	24	−0.024 (−0.104, 0.056)	0.544
Prevalence of hypertension (%)	34	−0.008 (−0.021, 0.005)	0.222
Publication year	36	−0.061 (−0.129, 0.007)	0.077
Study design (cohort vs. other)	36	−0.162 (−0.604, 0.280)	0.462
Imaging modality (GRE vs. SWI)	36	−0.154 (−0.634, 0.327)	0.52
Study location (Asian vs. Western)	36	−0.603 (−0.928, −0.278)	<0.001

GRE gradient-recalled echo, *SWI* susceptibility-weighted imaging, *CI* confidence interval

hemostatic processes. When the hemostatic mechanism is impaired due to anticoagulation therapy, red blood cells are more likely to extravasate from the damaged vessels, which may accelerate formation of new CMBs [13, 60]. More studies are needed to understand the pathological process.

Our meta-analysis showed that anticoagulant use is associated with the prevalence of strictly lobar CMBs but not deep/infratentorial CMBs. We hypothesize that this region-specific association may in part reflect that a patient's underlying vasculopathy influences his or her response to anticoagulant drugs. Lobar CMBs are often attributed to cerebral amyloid angiopathy, whereas those in deep locations are associated with hypertensive vasculopathy [1]. Anticoagulants might exert a greater effect on cortical-subcortical vessels with cerebral amyloid angiopathy, an idea indirectly supported by the observation that anticoagulant-related bleeding occurs more frequently in lobar locations [61, 62]. Given that anticoagulant-related ICH shows a stronger association with lobar CMBs than with deep CMBs [4, 63], it is reasonable to recommend regular assessment of CMB progression and location in patients receiving anticoagulation therapy.

The relationship between anticoagulant use and CMBs is significant in Western cohorts, but not in Asian ones. This

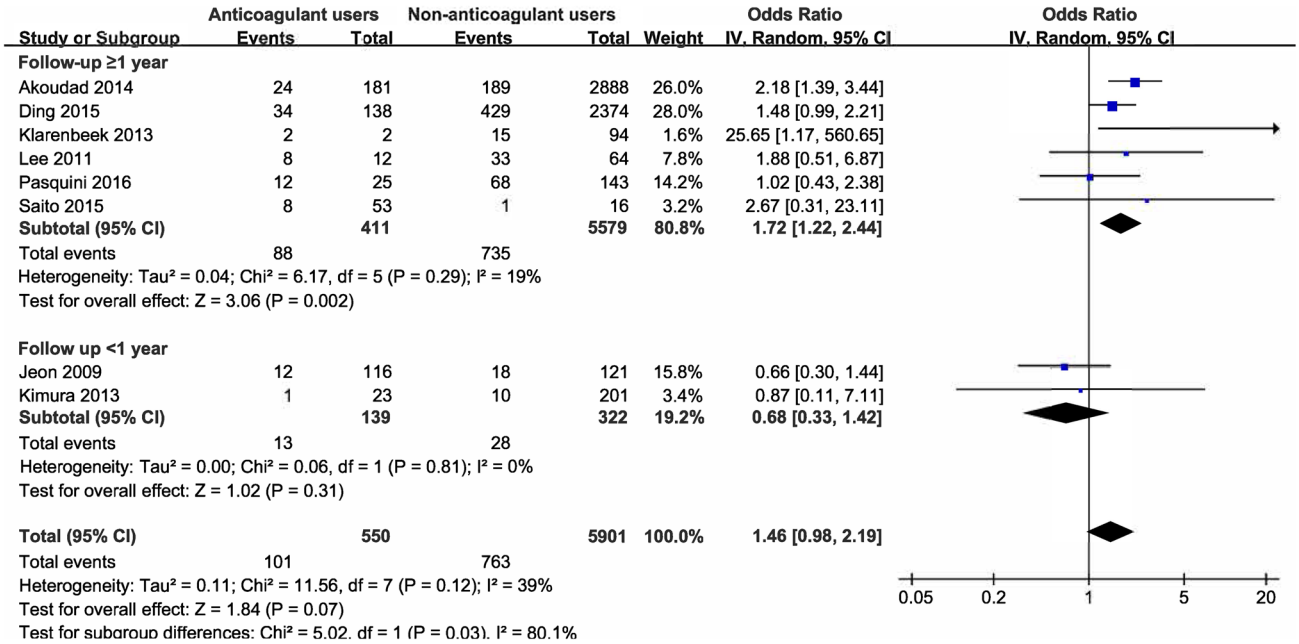

Fig. 5 Forest plot of the incidence of cerebral microbleeds (CMBs) stratified by follow-up period

might be explained by the different genetic backgrounds and patterns of small vessel disease in different populations. Patients in Western countries seem to have a higher prevalence of multiple strictly lobar CMBs [64], and anticoagulants favor the development of lobar CMBs [12]. Thus, the association between anticoagulant use and CMBs may be stronger in Western populations. Further studies and patient-level analyses are needed to verify this.

The available evidence suggests that presence of CMBs is related to warfarin exposure but not NOACs. However, we cannot conclude that NOACs are superior to warfarin due to the small number of studies in the NOACs group and the absence of direct comparisons between NOACs and warfarin. The recent prospective CMB-NOW study provides some preliminary results on this question [65]. This study recruited ischemic stroke patients with atrial fibrillation and at least one CMB, and compared the progression of CMBs after 12 months between patients receiving NOACs or warfarin. During the follow-up period, an increase in CMB number was less likely in NOAC users (16 out of 56 patients, 28.6%) than in warfarin users (4 out of 6 patients, 66.7%) [65]. Another retrospective study also provided evidence that the number of CMBs was lower in NOAC-associated ICH compared with that in warfarin-associated ICH [66]. However, these results should be interpreted with caution because of the small number of patients. Large multicenter studies are needed to verify these results.

Using pooled data of patients treated with anticoagulants, we confirmed the association between baseline CMBs and future risk of ICH that was shown in previous meta-analyses [67, 68]. Recently, a large collaborative pooled analysis of individual patient data showed that CMBs are associated with a greater risk of incident ICH in patients with IS or TIA under anticoagulant treatment [8]. Taken together, these findings have potential implications for clinical practice and future clinical trials. Anticoagulant use is associated with not only symptomatic ICH but also asymptomatic CMBs, suggesting that CMBs could be a surrogate marker to predict major bleedings [69]. Therefore, monitoring the progression of CMBs may help to identify high-risk individuals and guide the appropriate use of anticoagulants. Future clinical trials should focus on the efficacy of potential treatments, such as NOACs, on halting or slowing CMB incidence and preventing ICH. Large cohort studies are underway to provide further insights into this issue, such as the IPAAC-NOAC study [70].

Our study presents several limitations. First, in our meta-analysis the indication of anticoagulants is a confounder, since anticoagulants are more often prescribed to patients with vascular comorbidities, which are in turn related to the occurrence of CMBs [71]. We tried to minimize this confounding by adjusting for age and hypertension in the meta-regression, which are the two leading causes of CMBs. Reassuringly, these two factors did not seem to influence the association between anticoagulant therapy and CMBs. Second, different imaging parameters were used in the included studies, which may affect the detection of CMBs. However, in the stratified analysis by imaging modality, no significant difference was found between the studies that used SWI and those that used

GRE. Third, our pooled analysis could not fully adjust for several confounding factors, since few publications provided adjusted results or they used different multivariable models. Fourth, risk of selection bias was inevitable in the original studies, since not all participants were tolerant to magnetic resonance imaging. Fifth, there was a publication bias in the main analyses, although we used the 'trim-and-fill' approach to minimize its impact on the effect size. Such bias could arise, for example, because we included only full-text articles published in English. Finally, the inherent limitations of observational studies preclude any causal inferences. Future large longitudinal studies with long-term follow-up and adjusting for relevant confounders are required to establish cause–effect relationships. Despite these limitations, our meta-analysis offers the advantage of a large sample and relatively low heterogeneity among studies. In addition, we are able to analyze data on stroke-free populations and examine the relationship between anticoagulant use and CMBs in the short and long term, which has never been explored in previous meta-analyses.

Conclusions

Our meta-analysis suggests that anticoagulant use is consistently associated with prevalent CMBs in stroke patients and stroke-free individuals. This association is particularly evident in Western populations, among warfarin users, and among patients with lobar CMBs. Pooled results from longitudinal studies suggest a link between anticoagulation and incidence of CMBs. These findings reinforce the notion that CMBs may reflect subclinical bleeding complications of anticoagulation therapy, and may help to guide the appropriate use of these drugs and the design of clinical trials. Large, prospective studies with long-term follow-up are needed to confirm these results.

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical approval The manuscript does not contain clinical studies or patient data.

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