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Patterns of Infarction on MRI in Patients With Acute Ischemic Stroke and Cardio-Embolism: A Systematic Review and Meta-Analysis

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Background: Cardioembolic strokes are common however atrial fibrillation, the most common cause, is often asymptomatic and difficult to detect. There is evidence that infarct topography and volume on magnetic resonance imaging may be associated with specific stroke etiologies.

Aim: A systematic review and meta-analysis were undertaken to summarize the available evidence on the association between stroke etiology, infarct topography, and volume.

Methods: A systematic review was conducted using Medline (OVID), Embase (OVID), and PubMed databases. Hand searches of the gray literature and of reference lists in relevant articles were also performed. A quality assessment was undertaken, based on the STROBE checklist. For each study, the number of patients with and without a CE source of stroke and infarct topography was collected and outcomes presented as odds ratios (OR) with 95% CI and *p*-values.

Results: Four thousand eight hundred and seventy-three patients with ischemic stroke were included, of whom 1,559 were determined to have a CE source. Bilateral infarcts (OR 3.41; 95% CI 2.20–5.29; *p* < 0.0001) and multiple territory infarcts (OR 1.57; 95% CI 1.12–2.21; *p* = 0.009) were more common in patients with a CE source of stroke, than patients without a CE source. Lacunar infarcts (OR 0.49; 95% CI 0.31–0.80; *p* = 0.004) were more likely to occur in patients without a CE source. No significant difference between the frequency of multiple infarcts (OR 0.96; 95% CI 0.57–1.61; *p* = 0.87) anterior circulation (OR 1.45; 95% CI 0.83–2.53; *p* = 0.19) or posterior circulation infarcts (OR 1.06; 95% CI 0.72–1.57; *p* = 0.75), between the two groups were identified. Three out of four studies examining volume, found a significant association between increased infarct volume and CE source of stroke. A sensitivity analysis with cryptogenic and undetermined stroke sources assumed to be cardioembolic, did not alter the associations observed.

Conclusion: The findings of this systematic review and meta-analysis are broadly consistent with previous literature and provide more robust evidence on the association between infarct topography, volume and stroke etiology. Our findings may assist with refining cardiac investigations for patients with cryptogenic stroke, based on infarct topography.

Keywords: stroke, cardio-embolism, magnetic resonance imaging, topography, volume

INTRODUCTION

Ischemic stroke is a common cause of morbidity globally, with over 116 million years of healthy life lost each year due to stroke related death and disability (1). Cardioembolic (CE) sources form the underlying etiology in 20–25% of cases (2). Atrial fibrillation (AF), a common cause of CE stroke, may be asymptomatic in one third of patients and hence may go undetected (3). This has major implications for management, given the proven benefit of anticoagulation (4, 5). Current diagnostic techniques for AF detection are limited by low detection rate, particularly with non-invasive techniques such as Holter monitoring and wearable devices (6). Cost effectiveness is also a factor. The test with the highest detection rate, an implantable cardiac monitor (ICM), is not cost-effective with the incremental cost-effectiveness ratio (ICER) at £17,175 per quality of life year (QALY) gained, compared to 24-h cardiac telemetry (7).

Previous studies have examined factors, which predict the presence of AF in patients with ischemic stroke. Older age, atrial cardiopathy (8), and a prolonged PR interval on ECG, are independently associated with increased incidence of AF (9–11). Serum biomarkers, such as brain natriuretic peptide, have been associated with future development of paroxysmal AF in patients with ischemic stroke (12, 13). Thrombus histopathology has also been associated with stroke etiology, with CE source strokes more likely to be fibrin rich and erythrocyte poor (14, 15). In addition to findings from cardiac and pathology testing, there is evidence to suggest that a CE stroke etiology may be associated with topographical infarct patterns on magnetic resonance imaging (MRI).

Multi-territory MRI-DWI lesion topography is a common finding in CE strokes (16–18). In a large study by Chung et al. (17), multi-territory infarction was more prevalent amongst those with a CE etiology (representing 44.2% of all multi-territory infarctions). A number of other studies have demonstrated that a large proportion of patients with multi-territory infarction will have a CE source (19, 20). Akhtar et al. (19), in a systematic review of simultaneous infarcts in multiple territories, revealed that simultaneous infarcts in the anterior and posterior circulation, are more likely to be associated with AF than other etiologies such as large artery atherosclerosis (LAA). Such infarcts had an underlying CE source in two-thirds of cases.

A study by Yushan et al. (16) using MRI–DWI imaging demonstrated that 30% of patients with detected AF had bilateral infarcts at presentation, significantly higher than the 5.5% of the control cohort. Studies looking at anterior circulation infarcts did not show a clear predilection for CE stroke as opposed to other

stroke etiologies (21–23). A study by Rizos et al., utilizing lesion mapping techniques, showed a higher probability of CE infarcts in the right insula compared to other regions (24).

A number of studies (25–27) examining infarct patterns in the posterior circulation revealed LAA was the most likely etiology, however CE etiologies were implicated in 20–30% of cases. In contrast, Chung et al. (17) showed that 60% of superior cerebellar artery infarcts have an underlying CE source. Schiphorst et al. (28), however, showed that small obliquely oriented cortical cerebellar infarcts have a higher risk of future diagnosis of AF, compared to other cerebellar infarct subsets.

Larger infarct volumes have been associated with CE source of stroke, in multiple studies (24, 29–31). In addition to infarct size, subsequent infarct growth, and hemorrhagic transformation are also strongly predictive of underlying CE source. In a secondary analysis of the EPITHET trial by Tu et al. (29), patients with definite AF had significantly greater infarct growth, larger infarcts, more frequent parenchymal hematoma grade hemorrhagic transformation, worse functional outcomes and higher mortality compared to patients with no AF. An analysis of infarct volume by Rizos et al. (24) likewise showed larger volumes in patients with both new and established AF.

Hypothesis/Study Question

In patients with acute ischemic stroke, infarct pattern and volume on MRI will differ between patients with and without a CE source.

METHODS

Literature Search

A systematic review was performed according to PRISMA guidelines (32) and registered with the PROSPERO register of systematic reviews (Registration ID CRD42020169479). The search strategy (**Supplementary Material 1**) included a combination of controlled synonyms and vocabularies from Medical Subject Headings (MeSH) and EmTree covering stroke, infarction, pattern, topography, distribution, atrial fibrillation, cardioembolism, magnetic resonance imaging, and diffusion weighted imaging. The search was conducted using Medline (OVID), Embase (OVID), and PubMed databases using a combination of truncations and Boolean operators. Hand searches of the gray literature and of reference lists in relevant articles were also performed. Two co-authors reviewed the abstracts and selected the included studies (AS, BY). The literature search excluded reviews, editorials, and conference abstracts. The search strategy is summarized in **Figure 1**.

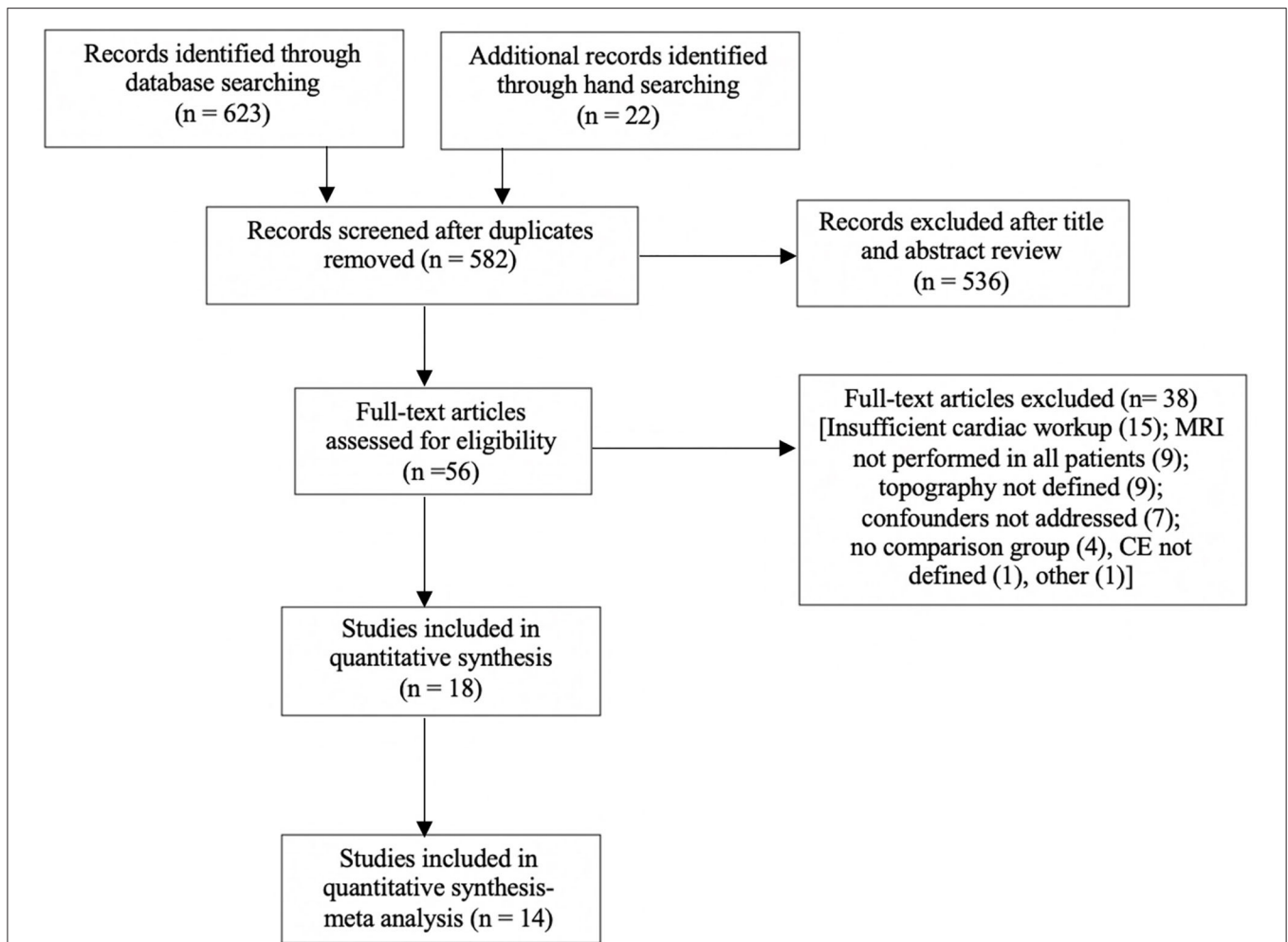


FIGURE 1 | Search strategy for meta-analysis. Full text articles analyzed, may have more than one reason for exclusion. Eighteen articles were included, with four excluded from the meta-analysis due to analysis of volume only.

Inclusion Criteria

A quality assessment of all full text articles selected was undertaken (**Supplementary Table 1** in **Supplementary Material 2**) based on The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist and Joanna Briggs Institute checklists for cross-sectional studies (33, 34). To be included in the meta-analysis, all studies were required to meet the following minimum criteria:

1. All patients had an MRI with diffusion weighted imaging (DWI) sequence performed.
2. Infarct topography is clearly defined.
3. The criteria for a stroke categorized as cardio-embolic is clearly defined. For example, using the TOAST criteria (35).
4. All included patients have been investigated for cardio-embolic sources, at a minimum with baseline ECG and 24 h of cardiac telemetry plus echocardiography if no cause found.
5. A comparison group is available, i.e., cardioembolic vs. non-cardioembolic strokes.

6. Background and objectives are clearly delineated.
7. Participant selection criteria are outlined.
8. Appropriate synthesis, outcome measures, methodology, and statistics.
9. Confounders and limitations are addressed.

Data Extraction

For each study, the total number of patients with CE stroke, the total number of stroke patients, the breakdown of stroke etiologies and topographical infarct patterns on MRI, were collected. Stroke etiology was dichotomized as being either CE or non-CE source. Where etiology was undetermined, the cause was assumed to be non-CE. A sensitivity analysis with the opposite assumption, with undetermined etiology assumed to be CE, was therefore performed which revealed no difference in the results (**Supplementary Material 3**). Topographical patterns analyzed were bilateral infarcts, multiple infarcts, multiple vascular territory infarcts, lacunar, anterior circulation, posterior

circulation, internal watershed, and external watershed infarcts. Papers mentioning infarct volume, were also analyzed.

Statistical Analysis

Review Manager (RevMan) version 5.3 (Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2014) was used to perform a meta-analysis of observational studies fulfilling the above criteria. The event rate for individual topographical patterns and 95% confidence intervals (CI) were determined from each study. Each topographical pattern was analyzed separately. Outcomes are presented as odds ratios (OR) with 95% CI and *p*-values. We used the Mantel-Haenszel implementation of the DerSimonian and Laird random-effect method implemented in RevMan (36). This implementation estimates the amount of between-study variation by comparing each study's result with a Mantel-Haenszel fixed-effect meta-analysis result (36). Heterogeneity of treatment effect across studies was evaluated by using the I^2 statistic, in which $I^2 > 50\%$ suggests substantial heterogeneity, as per the guide for interpretation of thresholds for I^2 from the Cochrane handbook chapter 10 (36). A $p < 0.05$ was treated as indicative of statistical significance. Funnel plot asymmetry and Egger's test was used to illustrate the extent of small study publication bias (Supplementary Material 4).

RESULTS

The literature search yielded 632 articles. Following review of titles, abstracts, exclusion of conference abstracts, and review articles, 45 full text papers were considered for inclusion. Fourteen papers exploring topography fulfilled all inclusion criteria (16, 18, 26, 37–47) and were included in a meta-analysis.

A total of 4,873 patients with ischemic stroke were included, of whom 1,559 were determined to have a CE source. Bilateral infarcts (OR 3.41; 95% CI 2.20–5.29; $p < 0.0001$) and multiple territory infarcts (OR 1.57; 95% CI 1.12–2.21; $p = 0.009$) were more common in patients with a CE source of stroke, than patients without a CE source. Lacunar infarcts (OR 0.49; 95% CI 0.31–0.80; $p = 0.004$) were more likely to occur in patients without a CE source. No significant difference between the frequency of multiple infarcts (OR 0.96; 95% CI 0.57–1.61; $p = 0.87$) anterior circulation (OR 1.45; 95% CI 0.83–2.53; $p = 0.19$) or posterior circulation infarcts (OR 1.06; 95% CI 0.72–1.57; $p = 0.75$), between the two groups were identified (Figures 2A–F). No significant heterogeneity was detected in the bilateral and multiple territory subgroups; however, the other subgroups did display significant heterogeneity between the included studies. Egger's test did not reveal any evidence of publication bias. Only one paper (39) analyzed watershed infarcts. Of 43 patients with watershed infarcts, 27 were classified as external watershed and 16 as internal watershed. In both cases, a non-CE etiology was more common than a CE etiology. Volume was not included in the meta-analysis, due to the low number of studies included and non-uniform reporting methods.

A sub-analysis of multiple territory and bilateral infarcts was performed on papers which also reported chronic infarcts in these territories. Only one paper reported on the presence of

concurrent chronic infarcts (44). There were numerically more chronic multi-territory infarcts seen in the non-AF population (15/83, 18%) than the AF population (2/21, 9.5%), although this did not reach statistical significance.

Infarct Volume

Four papers meeting inclusion criteria also analyzed infarct volume (2, 4, 29–31). The median baseline volume in CE ranged from 8.3 ml in Kim et al. (30) to 22.5 ml in Tu et al. (29) and the non-CE ranged from 3.0 ml in Kim et al. (30) to 4.2 ml in Tu et al. (29). In two out of three studies (29, 30), the baseline infarct volume with statistically significantly higher in CE compared to non-CE stroke. Rizos et al. (24) reported a mean baseline infarct volume of 41.2 ml, which was likewise significantly higher than patients with non-CE source of stroke (15.1 ml).

DISCUSSION

We set out to determine differences between infarct pattern and volume, in patients with and without a CE source of stroke. The findings of our study indicate that larger infarct volumes and certain topographical patterns, including multiple territory and bilateral infarcts in any arterial territory, occur more commonly in patients with a CE source of stroke. Lacunar infarcts are more likely to be associated with a non-CE source. These findings support previous studies in which a correlation between a CE source and infarcts in multiple territories, including bilateral infarcts (16–20) was found. This association to CE stroke may be explained by atrial thrombus fragmentation, leading to infarcts in different arterial territories (46).

Although the causes of multi-territory infarcts do include non-CE etiologies (44), the association of non-CE etiologies with other patterns in our meta-analysis, particularly lacunar, would support the notion that non-CE source infarct topography is less likely to be multi-territory compared to CE source strokes.

The lack of association with either a CE or non-CE etiology in anterior circulation and posterior circulation strokes, may be due to the influence of multiple vascular risk factors, such as diabetes and ischemic heart disease influencing infarct location (48). One question that remains unanswered however is whether or not a CE source, such as AF, is more likely to determine topography, when two or more etiologies are considered equally likely. The results of our sensitivity analysis, which showed no difference in patterns, would suggest that intercurrent CE sources offer no additional weighting to the topography of the infarct.

Studies analyzing volume, all indicated that larger infarct volumes are more likely to be associated with a cardio-embolic source. This finding supports the findings of Tu (49), who postulated that larger infarct volumes were the result of poorer collateral circulation in patients with AF.

Strengths of our study include the definitions of topography and volume based on MRI alone, rather than CT, and the inclusion of a large number of patients (4,873), which reduces the likelihood that topographical associations were due to chance alone. The comparison to other possible stroke sources and the criteria for minimum cardiac investigations, reduces the likelihood of a missed CE source.

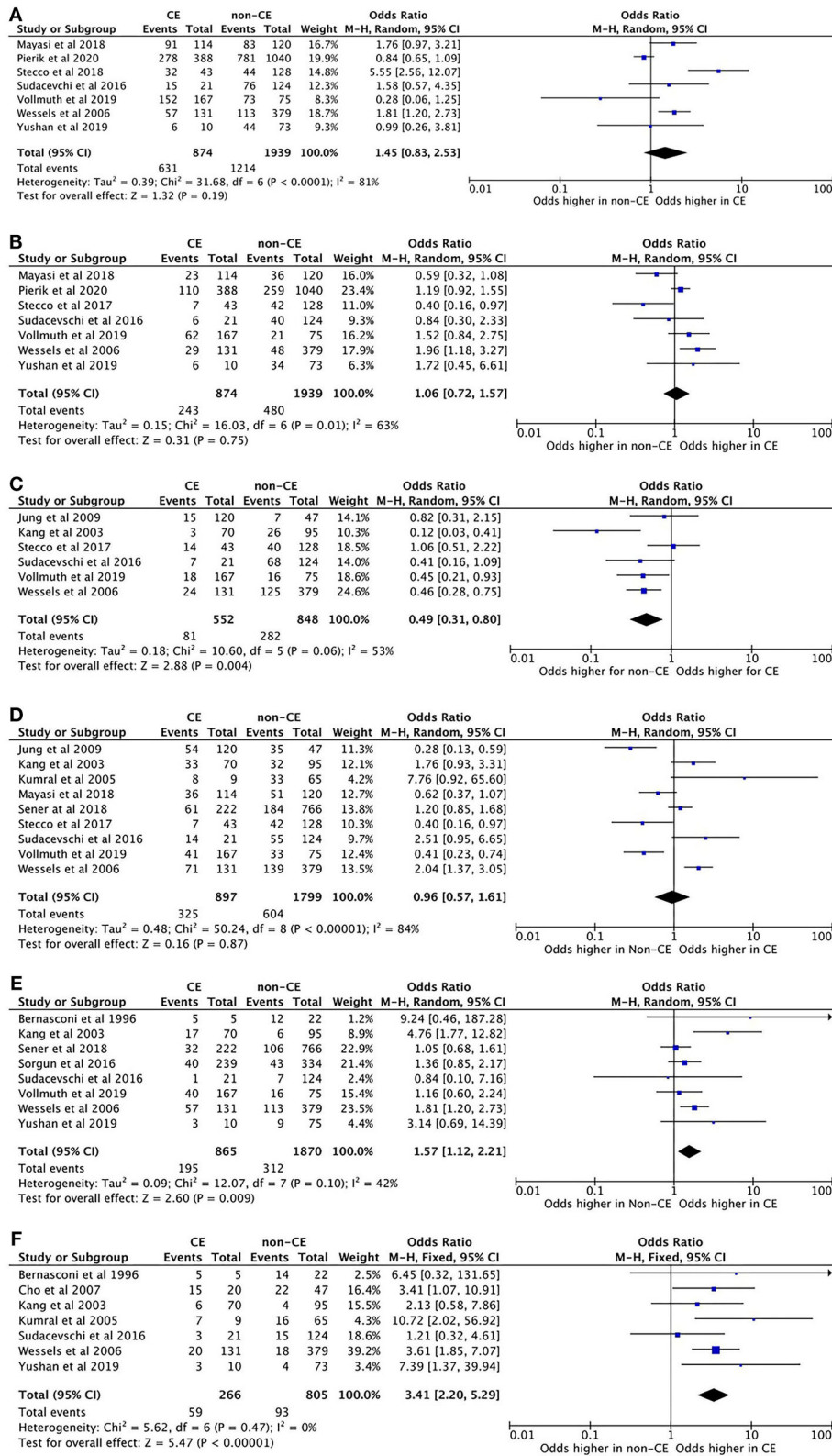


FIGURE 2 | (A) Forest plot showing the odds ratio of anterior circulation infarct topography in CE stroke, compared to non-CE stroke. **(B)** Forest plot showing the odds ratio of posterior circulation infarct topography in CE stroke, compared to non-CE stroke. **(C)** Forest plot showing the odds ratio of lacunar infarct topography in CE stroke, compared to non-CE stroke. **(D)** Forest plot showing the odds ratio of multiple infarcts in one or more arterial territories in CE stroke, compared to non-CE stroke. **(E)** Forest plot showing the odds ratio of infarcts in multiple large artery territories in CE stroke, compared to non-CE stroke. **(F)** Forest plot showing the odds ratio of bilateral hemisphere infarcts in CE stroke, compared to non-CE stroke.

An urgent need exists for rapid, non-invasive, accurate tests for AF detection. There is an unanswered question regarding anticoagulation for cryptogenic stroke, particularly those with embolic stroke of undetermined source (ESUS). The findings of our study are pertinent given negative studies for anticoagulation in ESUS so far (50, 51). The results of our analysis suggest the cryptogenic source strokes offer no additional weighting to infarct source based on MRI topography. In line with recent literature (52, 53), this may in turn indicate that a large portion of cryptogenic strokes may actually be non-cardioembolic and therefore will not benefit from anticoagulation.

LIMITATIONS

There were a number of limitations to this study. First and foremost, in all studies, the etiology of ischemic stroke could not be determined with absolute certainty, as this would necessitate screening for all potential stroke risk factors in all patients. Although PRISMA guidelines were adhered to, there is a risk of selection and reporting bias, as all studies are observational and the majority retrospective in nature. Not all included studies, reported on all topographical patterns, hence comparison was made on available data. Infarct patterns were often common to multiple groups; for example, patients with multi-territory infarcts also had anterior or posterior circulation infarcts recorded. It was often not possible to determine the proportion of isolated infarcts in different circulations, as this was often not explicitly stated (with the exception of lacunar infarcts). Other confounders, such as anticoagulant and statin use, could not be accounted for. There was significant heterogeneity in a number of subgroups, likely reflecting the inclusion of studies with low patient numbers.

CONCLUSIONS AND FUTURE DIRECTIONS

This study has provided further evidence for associations between infarct volume, topography and CE stroke. Further large, long term prospective studies, with low cardiovascular risk

populations, are needed to demonstrate this link. The use of more sensitive methods for determining infarct topography and volume than human visual analysis, such as machine learning, may also improve our understanding of infarct etiology in future. The use of machine learning in stroke neuroimaging is already well-established, being utilized for determination of ischemic penumbra and large vessel occlusions (54). Emerging applications include the prediction of stroke onset time, functional outcomes following stroke, neurological deterioration, and hemorrhagic transformation (55). Future studies utilizing machine learning in infarct topography may offer additional, more accurate diagnostic tools for determination of stroke etiology. This may in turn lead to future anticoagulation trials in patients with high risk cardioembolic patterns, looking for stroke recurrence.

In the interim, this study may assist with refining cardiac investigations for patients with cryptogenic stroke, based on infarct topography.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Materials**, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

AS conceptualized the project and was responsible for primary writing of the text. LC and AS performed the statistical analysis and co-wrote the article methods. AS and BY selected and critically appraised included articles. SD, GD, LC, MP, and BY provided critical appraisal and editing of the manuscript. All authors approved the final version of the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fneur.2020.606521/full#supplementary-material>

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The handling Editor declared a past co-authorship with one of the authors LC.

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