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Silent cerebral infarcts in patients with atrial fibrillation: Clinical implications of an imaging-adjusted CHA_2DS_2-VASc score

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Abstract

Background: The CHA_2DS_2-VASc score does not include silent infarcts on neuroimaging in stroke risk estimation for patients with atrial fibrillation (AF). The inclusion of silent infarcts into CHA_2DS_2-VASc scoring and its impact on stroke prophylaxis recommendations in patients with AF has not been previously studied. The present study sought to quantify the prevalence of silent infarcts in patients with AF and describe potential changes in management based on magnetic resonance imaging (MRI) findings.

Methods: Participants from the Mayo Clinic Study of Aging with AF and brain MRI were included. Silent infarcts were identified. “Standard” CHA_2DS_2-VASc scores were calculated for each subject based on clinical history alone and “imaging-adjusted” CHA_2DS_2-VASc scores based on evidence of cerebral infarction on MRI. Standard and imaging-adjusted scores were compared.

Results: 147 participants (average age 77, 28% female) were identified with AF, MRI, and no clinical history of stroke. Overall, 41 (28%) patients had silent infarcts on MRI, corresponding with a 2-point increase in CHA_2DS_2-VASc score. Of these participants, only 39% (16/41) with silent infarct were on anticoagulation despite that standard CHA_2DS_2-VASc scores supportive of anticoagulation. After incorporating silent infarcts, 13% (19/147) would have an indication for periprocedural bridging compared to 0.6% (1/147) at baseline.

Conclusions: Incorporation of silent infarcts into the CHA_2DS_2-VASc score may change the risk-benefit ratio of anticoagulation. It may also increase the number of patients who would benefit from periprocedural bridging. Future research should examine whether an anticoagulation strategy based on imaging-adjusted CHA_2DS_2-VASc scores could result in a greater reduction of stroke and cognitive decline.

Key words: anticoagulation, atrial fibrillation, bridging, magnetic resonance imaging, silent infarct

Introduction

In the United States alone, over 5.2 million people have a diagnosis of atrial fibrillation (AF), and this number is expected to triple over the next three decades [1]. AF increases the risk of ischemic stroke, and antithrombotic agents are recommended for high-risk patients. The 2019 American College of Cardiology/American Heart Association (ACC/AHA) AF guidelines recommend using the CHA_2DS_2-VASc score to estimate annual stroke risk and to determine the need for anticoagulation. Anticoagulation is a class IA recommendation for men with a score of ≥ 2, and women with a score ≥ 3. Anticoagulation is a class IIb recommendation for a score of 1 in men and 2 in women [2].

The CHA_2DS_2-VASc scoring system is based on studies that define stroke clinically (sudden onset neurologic deficit lasting > 24 h diagnosed by a neurologist for stroke or < 24 h for transient ischemic attack [TIA]) [3]. However, it is also recognized that there are patients with computed tomography (CT) or magnetic resonance imaging (MRI) evidence of cerebral infarction without any previous clinical manifestations. These are termed “silent infarcts” and are not accounted for in current stroke risk estimation criteria. The prevalence of silent infarct in AF is estimated to be between 14% [4, 5] and 30% [6, 7] and is higher in patients with AF compared

to those without [8, 9]. Silent infarction is associated with future clinical infarction and cognitive impairment [6, 10–12].

The impact of including silent infarcts on neuroimaging into the CHA_2DS_2-VASc scoring system and stroke prophylaxis recommendations in patients with AF has not been previously studied. To evaluate the clinical implications, a cohort was utilized from the population-based Mayo Clinic Study of Aging (MCSA). This database is uniquely suited to study this question due to the routine use of brain MRI. In this study, it was sought to quantify the prevalence of silent infarcts in patients with AF and describe potential changes in management based on MRI findings.

Methods

Study design

Participants were enrolled in the MCSA, a prospective, longitudinal, population-based study of aging and cognitive decline that began enrolling patients in 2004. The MCSA study design has been previously published [13]. In the MCSA, residents of Olmsted County, Minnesota were identified and randomly sampled in an age- and sex-stratified manner using the Rochester Epidemiology Project medical records-linkage system [14]. Participants without contraindications (i.e., pacemaker or other implanted devices) were invited to undergo brain MRI imaging at the time of enrollment and at various points throughout the study. For the present study, the first MRI available for each participant was used. The MCSA and associated studies were approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Boards. Written informed consent was obtained from all participants prior to study enrollment.

Clinical data retrieval

Clinical data were abstracted by a nurse from the detailed medical records included in the medical records–linkage system from the Rochester Epidemiology Project [14]. Diagnosis of AF was based on physician diagnosis, electrocardiographic evidence of AF, and/or treatment for AF. Using this method, patients with postoperative AF were included. Infarcts were graded on two-dimensional FLAIR MRI that was co-registered with magnetization-prepared rapid gradient-echo T1 MRI. The full details of infarct grading have been previously published [15]. All

possible infarcts were initially identified by trained image analysts and subsequently confirmed by a vascular neurologist (J.G.R.) who was blinded to all clinical information [15].

Outcomes

For the main analysis, CHA_2DS_2-VASc scores were calculated for each participant as per the usual method, only counting points for clinical history of stroke ("standard" CHA_2DS_2-VASc). For this study, a second "imaging-adjusted" CHA_2DS_2-VASc score was also calculated, for which stroke was defined as evidence of infarct on MRI regardless of clinical diagnosis (i.e., including radiologically documented infarctions that may have been clinically silent or not previously clinically diagnosed).

Standard and imaging-adjusted scores were compared for outcomes of interest. Patients with an increase in score from their standard to imaging-adjusted score were identified. The 2019 ACC/AHA AF guidelines were used to determine if a change in management would be indicated for patients based on their imaging-adjusted CHA_2DS_2-VASc score [2]. The 2017 ACC periprocedural anticoagulation guidelines were used to determine if a change in bridging anticoagulation would be indicated based on imaging-adjusted scores [16]. Bridging anticoagulation was defined as the periprocedural use of full-dose parenteral anticoagulants.

Statistical analysis

Descriptive statistics were used to calculate central tendencies, measures of spread, and prevalence for the current cohort. Mean age with standard deviation, and prevalence of each of the CHA_2DS_2-VASc criteria (age, sex, congestive heart failure, hypertension, stroke/TIA, vascular disease, and diabetes mellitus) were calculated. The prevalence of silent infarcts for each standard CHA_2DS_2-VASc score was determined. Lastly, the number of participants on anticoagulation, acetylsalicylic acid, and dual antiplatelets was quantified. Data analysis was performed using BlueSky Statistics Version 7.20 (BlueSky Statistics, Chicago, Illinois).

Results

Baseline characteristics and antithrombotic regimen of the study cohorts

The present cohort was developed by including all MCSA participants with AF, brain MRI at the time of enrollment, and sufficient data available for CHA_2DS_2-VASc score

calculation. Those with a history of clinically apparent stroke were excluded so that those with silent stroke could be identified. Overall, 147 patients were included in the study. Baseline characteristics of the initial cohort are summarized in Table 1. The cohort was separated into two groups — those with silent infarct (n = 41) and those without silent infarct (n = 106). This design is visually depicted in Figure 1. Among the 147 participants, 41 (28%) had evidence of silent infarct on MRI, which resulted in an increase of their CHA_2DS_2-VASc scores by 2 points. CHA_2DS_2-VASc scores prior to and after imaging adjustment is visually depicted in Figure 2. The rate of anticoagulation was 35% (51/147), which is 37% (51/137) of those with a standard CHA_2DS_2-VASc score high enough for anticoagulation. Antiplatelet use included aspirin alone in 47%, dual antiplatelet therapy in 7%, and 11% were on neither anticoagulation nor antiplatelet agents. Of the 52 participants on anticoagulation, 50 were on warfarin, 1 was on a heparin product, and 1 was on an unspecified anticoagulant.

Impact on stroke prophylaxis management in patients with silent infarcts

None of the patients with silent infarct (n = 41) had a standard CHA_2DS_2-VASc < 2. Thus, after adjustment for imaging findings, no patients would have had a new indication for anticoagulation based on current AF management guidelines. However, among the 41 patients with silent brain infarction, only 39% (16/41) were anticoagulated despite all of them having a standard CHA_2DS_2-VASc score supporting anticoagulation. This rate of anticoagulation was no different than those without silent infarct (36/106, 34%, p = 0.58).

Impact on bridging anticoagulation management in patients with silent infarcts

Of the 147 patients analyzed for silent infarct, only one participant had an indication for bridging based on their standard CHA_2DS_2-VASc score. After calculation of imaging adjusted CHA_2DS_2-VASc scores, anticoagulation would have been indicated in 19/147 (13%) participants after imaging adjustment. This indication for bridging would have been a new indication for 18/147 (12%). In other words, for those participants with silent infarct on MRI, 44% (18/41) had a new indication for periprocedural bridging. All of the present findings are summarized in the Central illustration.

Discussion

Main findings

The impact of imaging-adjusted CHA_2DS_2-VASc scores on chronic and periprocedural anticoagulation recommendations was evaluated and it was found that: 1) 28% of participants with AF had evidence of cerebral infarct despite no clinical history of stroke, 2) only 39% of participants who had silent infarct were on anticoagulation despite all of them having a standard CHA_2DS_2-VASc score supporting the use of anticoagulation, and 3) use of image-adjusted CHA_2DS_2-VASc scores would have led to 12% of our cohort having a new indication for peri-procedural bridging.

Clinical relevance

Although silent infarcts may seem inconsequential due to lack of overt focal symptoms, silent infarcts are clinically important. Previous studies have demonstrated increased risk of dementia and future risk of clinically apparent strokes in patients with silent infarcts on imaging [6, 10–12]. Recognizing the clinical ramifications of these silent infarcts should affect clinical management. Yet, current scoring systems used to decide whether to prescribe anticoagulation do not take silent infarcts on neuroimaging into consideration.

Prevalence of silent infarct

Silent stroke is commonly encountered in the clinical setting as an incidental discovery when head imaging is obtained for other purposes. There is an increased prevalence of silent stroke in patients with AF when compared to the general population [8, 9]. In the current cohort, a substantial proportion (28%) of patients with AF had silent stroke on brain MRI. Other studies report varying prevalence of silent stroke in AF. Older studies such as the SPINAF trial (1995) and EAFT study group (1996) showed silent stroke prevalence of 14.7% and 14%, respectively based on CT findings [4, 5]. Other studies using MRI have estimated the risk of stroke to be similar to that herein, at 28.3% [7]. The differences are likely due to increased sensitivity of MRI over CT imaging in detecting small ischemic lesions [17, 18].

Impact on anticoagulation management

Given the high prevalence of silent stroke in patients with AF, the benefit of anticoagulation is likely underestimated by CHA_2DS_2-VASc scoring. If silent infarcts are

accounted for, 28% of the present study participants would saw an increase in their CHA_2DS_2-VASc scores by 2 points, increasing their estimated annual risk of stroke. Only 39% of those with silent infarct were on anticoagulation, and the rate of anticoagulation in those with a prior history of stroke was only 42%. However, these low rates are similar to previously reported rates of anticoagulation for patients with AF with an indication for anticoagulation [19].

The reason for low anticoagulation rates despite an indication for anticoagulation is unclear. It is possible that many patients had increased risk of bleeding, or some may have had a lower estimation of stroke risk based on the older $CHADS_2$ score. Regardless, if imaging-adjusted CHA_2DS_2-VASc scores are used, patients with silent infarcts would have a 2-point increase, shifting the risk-benefit ratio even further towards anticoagulation. In other words, while many patients in the present cohort had a baseline indication for anticoagulation by CHA_2DS_2-VASc score regardless of brain imaging, the presence of silent infarct on brain imaging may prompt further consideration of anticoagulation given the increased stroke risk from the presence of silent infarct.

Impact on bridging anticoagulation management

Bridging anticoagulation is an important management concern in those with AF, and the decision to bridge with heparin prior to procedures is guided by the CHA_2DS_2-VASc score as well. Per the 2017 ACC guidelines on periprocedural anticoagulation, bridging prior to or after procedures is dependent on the risk of thrombotic events. Patients are categorized into high, moderate, or low risk groups. High risk corresponds to a CHA_2DS_2-VASc of 7 or greater, moderate corresponds to a score of 5–6, and low risk is a score of 4 or less [16]. Using the imaging-adjusted CHA_2DS_2-VASc score, bridging anticoagulation in the periprocedural period would have been indicated for 18/147 (12%) participants who would not have met the 2017 ACC guidelines criteria for bridging based on their standard CHA_2DS_2-VASc score. In other words, 18 of the 41 participants (44%) with silent infarct had a new indication for bridging.

Limitations of the study

This study is limited since a database with previously extracted data was used. Therefore, there was limited insight into details such as the rationale for choice of anticoagulant, decision not to anticoagulate, and the chronicity of the AF. The average age of the cohort was 77 years,

and 28% were female. Although previous studies have demonstrated higher prevalence of AF with increasing age and higher prevalence in men compared to women in all age groups, the ratio of women to men appears to be lower than what other population-based studies estimate [20]. The advanced age of the present cohort determined that many patients had a standard CHA_2DS_2-VASc score of 2 based on age alone. Thus, the clinical implications of using an imaging-adjusted CHA_2DS_2-VASc score may be greater in a younger cohort, because more individuals would start with a lower standard CHA_2DS_2-VASc score and cross the threshold for indication of anticoagulation after imaging adjustment. Additionally, while the study was population-based, the population was predominantly white and, therefore, future studies with more diverse populations are needed. Another limitation is that some patients with difficult-to-control AF undergo atrioventricular nodal ablation with pacemaker placement, which may predispose to stroke. However, this population was unable to be captured in the current study due to the incompatibility with MRI.

Conclusions

In this population-based cross-sectional study, 28% of patients with AF had evidence of infarct on MRI despite not having clinical history of stroke (referred to as silent infarct). Only 39% of the patients with silent infarct were on anticoagulation, despite already having a baseline CHA_2DS_2-VASc score ≥ 2 points. If silent brain infarct was included in the definition of stroke, a significant subset of patients would have a 2-point increase in their CHA_2DS_2-VASc score. Such an adjustment would substantially increase their estimated annual stroke risk and would more strongly support the use of anticoagulation as the risk-benefit ratio shifts in favor of anticoagulation. Similarly, use of imaging-adjusted CHA_2DS_2-VASc scores would have major implications on which patients receive periprocedural bridging. Based on the present findings, the value of anticoagulation based on imaging-adjusted CHA_2DS_2-VASc scores should be formally examined in future longitudinal studies.

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Conflict of interest: Michelle M. Mielke has consulted for Biogen and Brain Protection Company. Dr. Knopman serves on a Data Safety Monitoring Board for the DIAN study. He serves on a Data Safety monitoring Board for a tau therapeutic for Biogen but receives no personal compensation. He is an investigator in clinical trials sponsored by Biogen, Lilly Pharmaceuticals and the University of Southern California. He has served as a consultant for Roche, Samus Therapeutics, Third Rock and Alzeca Biosciences but receives no personal compensation. He receives funding from the NIH. Prashanthi Vemuri is funded by NIH and received speaking fees from Miller Medical Communications Inc. Clifford R. Jack Jr. serves on an independent data monitoring board for Roche, has served as a speaker for Eisai, and consulted for Biogen, but he receives no personal compensation from any commercial entity. He receives research support from NIH, the GHR Foundation and the Alexander Family Alzheimer's Disease Research Professorship of the Mayo Clinic. The remaining authors have nothing to disclose.

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Table 1. Baseline characteristics.

CHA_2DS_2-VASc criteria	**Overall cohort (n = 147)**	**Silent infarct Present (n = 41)**	**Silent infarct Absent (n = 106)**
Age, mean ± SD	77 ± 10	82 ± 6	75 ± 10

Female	41 (28%)	9 (22%)	32 (30%)
CHF	39 (27%)	16 (39%)	23 (22%)
Hypertension	121 (82%)	39 (95%)	82 (77%)
Stroke	0 (0%)	0 (0%)	0 (0%)
TIA	13 (9%)	0 (%)	13 (12%)
CAD	71 (48%)	31 (76%)	40 (38%)
PAD	14 (10%)	2 (5%)	12 (11%)
Diabetes mellitus	34 (23%)	8 (20%)	26 (25%)

CAD — coronary artery disease; CHF — congestive heart failure; PAD — peripheral arterial disease; SD — standard deviation; TIA — transient ischemic attack

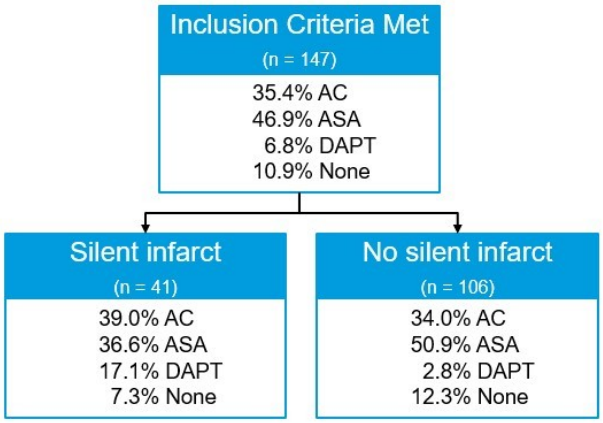


Figure 1. Study design and summary of results. 147 participants with atrial fibrillation, magnetic resonance imaging upon enrollment, and no clinical history of stroke were identified. 4/147 had silent infarct. Notably, only 39% were anticoagulated despite all having an indication for anticoagulation; AC — anticoagulation; ASA — acetylsalicylic acid; DAPT — dual antiplatelet therapy.

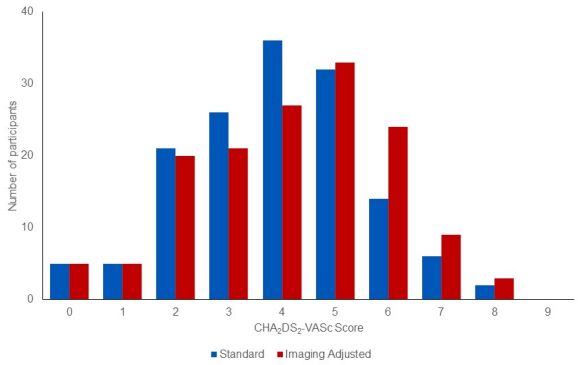
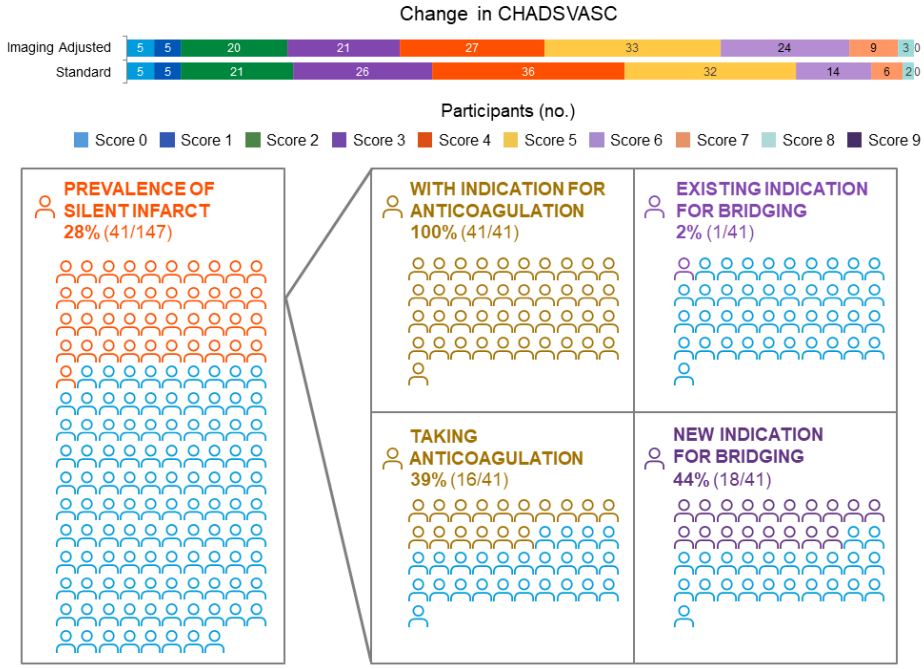


Figure 2. Change from standard to image adjusted CHA_2DS_2-VASc score. After incorporating imaging evidence of silent infarct, many participants had an increase in CHA_2DS_2-VASc score, causing a shift to the right.



Central illustration. The present study found that the prevalence of silent infarct in patients with atrial fibrillation is 28%. 39% of these participants were anticoagulated, despite all of them having an indication for anticoagulation. After incorporating silent infarct into stroke risk estimation, 44% of those with silent stroke had a new indication for periprocedural bridging. The top of the figure shows how CHA_2DS_2-VASc scores change after imaging adjustment.