1.a. **Full Title:** Silent Brain Infarcts (SBI) and risk for ischemic stroke: should we give points to SBI when calculating CHADS2 & CHA2DS2-VASC scores?

b. **Abbreviated Title (Length 26 characters):** Silent strokes & CHA2DS2-VASC

2. **Writing Group:** Silent Brain infraction Collaborative Investigators Group
   
   **Writing group members:** George Ntaios, Vasileios Papavasileiou, Konstantinos Vemmos, Thomas H. Mosley, B. Gwen Windham, Kaori Miwa, Sudha Seshadri, Marco Di Tullio, Ralph Sacco, Mitchel Elkind, Toshitaka Umemura, Kazuomi Kario, Gregory Lip.

   I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. GN [please confirm with your initials electronically or in writing]

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   **ARIC author** to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

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3. **Timeline:** 6-12 months.

4. **Rationale**
   
   The CHADS2 & CHA2DS2-VASC scores are two widely used prognostic scores which predict reliably the risk of stroke both in patients with and without atrial fibrillation and are valuable tools for treatment decisions in patients with atrial fibrillation. These scores are derived from several risk factors which are given points when present.

<table>
<thead>
<tr>
<th>CHADS2</th>
<th>CHA2DS2-VASC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk factors</td>
<td>Points</td>
</tr>
<tr>
<td>CHF</td>
<td>1</td>
</tr>
<tr>
<td>HTN</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥ 75</td>
<td>1</td>
</tr>
<tr>
<td>DM</td>
<td>1</td>
</tr>
<tr>
<td>Stroke/TIA/Embolism</td>
<td>2</td>
</tr>
<tr>
<td>Max 6</td>
<td></td>
</tr>
<tr>
<td>Vascular disease (prior MI, PAD, or aortic plaque)</td>
<td></td>
</tr>
<tr>
<td>Age 65-74 years</td>
<td>1</td>
</tr>
<tr>
<td>Sex category (Female)</td>
<td>1</td>
</tr>
</tbody>
</table>

One of the parameters included in both scores is previous Stroke (S). However, it is not known whether the existence of a Silent Brain Infarct (SBI, or else silent stroke) should be also given points when
calculating a patient’s score, or rather only clinically evident strokes should be given points. To address this question, we aim to perform an individual patient-data meta-analysis aiming to investigate whether SBI should be scored when calculating a patient’s CHADS2 & CHA2DS2-VASC scores.

5. Main Hypothesis/Study Questions
The hypothesis of the study is that SBI should be given points (qualifying as stroke) when calculating a patient’s CHADS2 & CHA2DS2-VASC scores.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).
This will be an individual patient data retrospective multicenter analysis aiming to investigate whether the existence of a SBI should be given points (qualifying as score) when calculating a patient’s CHADS2 & CHA2DS2-VASC score.

Inclusion criteria include patients with SBI (by default, no clinical stroke history at the time of the MRI) who have available information about their CHADS2 & CHA2DS2-VASC scores as well as follow-up information about stroke.

The primary outcome will be ischemic stroke during follow-up, whereas the secondary outcome will be overall/cardiovascular mortality during follow-up.

This multicenter analysis will include several datasets which were already identified and the corresponding principle investigators were contacted and agreed to collaborate. Datasets from ARIC, the Northern Manhattan Study, the Osaka Follow-Up Study for Carotid Atherosclerosis, and two clinical populations of Japanese adults will be merged together and analyzed by the coordinating center (Larissa, Greece). The list of parameters which are necessary for the analysis and are requested are presented below.

Firstly, we will assess the prognostic value of the CHADS2 & CHA2DS2-VASC scores (in their current form, i.e. not giving points for SBI) to predict ischemic stroke, or else we will assess the discriminatory power of the two scores (i.e. the degree to which the scores enable the discrimination between patients with ischemic stroke during follow-up and patients without ischemic stroke during follow-up) by calculating the area under the receiver operating characteristics curve (AUC).

Then, we will assess the prognostic value of the CHADS2 & CHA2DS2-VASC scores (in a modified form, i.e. giving points for SBI) to predict ischemic stroke during follow-up, or else we will assess the discriminatory power of the two scores (i.e. the degree to which the scores enable the discrimination between patients with ischemic stroke during follow-up and patients without ischemic stroke during follow-up) by calculating the area under the receiver operating characteristics curve (AUC).

Then, we will compare the AUCs of the models to assess whether the models which give points for SBI show a better prognostic accuracy than the models which do not give points for SBI.

Finally, if the hypothesis is confirmed, we will perform Multivariate Cox proportional Hazards analysis and Kaplan-Meier analysis to provide further information about the association between the updated models (which give points for SBI) and ischemic stroke during follow-up.

7.a. Will the data be used for non-CVD analysis in this manuscript? No

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = “CVD Research” for non-DNA analysis, and for DNA analysis RES_DNA = “CVD Research” would be used? N/A
8.a. Will the DNA data be used in this manuscript? No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = “No use/storage DNA”? No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscc.unc.edu/ARIC/search.php

Yes

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? X Yes

11.b. If yes, is the proposal
   ___ A. primarily the result of an ancillary study (list number* __________  __________  __________  __________)
   ___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* __________  __________  __________)

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is your responsibility to upload manuscripts to PUBMED Central whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript X No.
List of requested variables:

1. At visit 3 (1993-5)
   - Age of patient
   - Sex of patient
   - History of congestive heart failure
   - History of hypertension
   - History of diabetes mellitus
   - History of previous clinically evident stroke
   - History of previous transient ischaemic attack
   - History of previous thromboembolism
   - History of vascular disease (e.g. peripheral artery disease, myocardial infarction or aortic plaque)
   - Smoking
   - History of Dyslipidemia
   - History of Atrial fibrillation
   - If silent brain infarct (SBI) present at brain MRI:
     - Type of SBI (i.e. lacunar or non-lacunar)
     - Number of SBIs
   - Antithrombotic treatment that patient was receiving during visit (i.e. antiplatelet or anticoagulant)
   - Statin treatment that patient was receiving during visit
   - Antihypertensive treatment that patient was receiving during visit

2. At Ancillary study visit (2004-6)
   - Occurrence of clinically evident ischemic stroke since visit 3 (yes/no)
     - If yes, please provide the time length between the occurrence of stroke and visit 3
   - Death
     - If yes, please provide the time length between death and visit 3