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Research Article

Association of Subclinical Coronary Artery Disease and Ischemic Stroke Caused by Cervical or Intracranial Atherosclerosis

Ana Luíza Vieira de Araújo[1], Raul Dias dos Santos Filho[2], Marcio Sommer Bittencourt[3], Roberto Nery Dantas Junior[4], Carlos André Oshiro[5], Cesar Higa Nomura[4], Edson Bor-Seng Shu[5], Marcelo de Lima Oliveira[5], Claudia da Costa Leite[6], Maria da Graça Morais Martin[6], Maramelia Miranda Alves[7], Gisele Sampaio Silva[8], Victor Marinho Silva[5], Adriana Bastos Conforto[1*]

[1]Department of Neurology, Clinical Hospital, University of Sao Paulo, Neurology Clinical Division, Hospital Israelita Albert Einstein, Instituto Israelita de Ensino e Pesquisa, Sao Paulo, Brazil

[2]Heart Institute, University of Sao Paulo, Medical School Hospital, Hospital Israelita Albert Einstein, Academic Research Organization, Sao Paulo, Brazil

[3]Center for clinical and epidemiological research, University Hospital, University of Sao Paulo, Sao Paulo, Brazil

[4]Heart Institute, University of Sao Paulo, Medical School Hospital, Sao Paulo, Brazil

[5]Department of Neurology, Clinical Hospital, University of Sao Paulo, Neurology Clinical Division, Sao Paulo, Brazil

[6]Department of Radiology, Clinical Hospital, University of Sao Paulo, Sao Paulo, Brazil

[7]Department of Neurology and Neurosurgery, Federal University of Sao Paulo, Sao Paulo, Brazil

[8]Department of Neurology and Neurosurgery, Federal University of Sao Paulo, Hospital Israelita Albert Einstein, Academic Research Organization, Sao Paulo, Brazil

***Corresponding author:** Adriana Bastos Conforto, Clinical Hospital, University of Sao Paulo, Neurology Clinical Division, Hospital Israelita Albert Einstein, Instituto Israelita de Ensino e Pesquisa, Sao Paulo, Brazil, Tel: +5511988140907, E-mail: adriana.conforto@gmail.com

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Abstract

Background: Coronary calcium score (CAC) is a marker of coronary atherosclerosis. We compared CAC scores in patients with ischemic stroke (IS) caused by large-artery atherosclerosis ($Group_{athero}$) to a control group ($Group_{control}$), in multiethnic subjects without history of symptomatic coronary artery disease (CAD).

Methods: In this cross-sectional study, subjects in $Group_{athero}$ (n=80) had at least one symptomatic stenosis ≥ 50% in the carotid or vertebrobasilar territories. $Group_{athero}$ included two subgroups: stenosis in either cervical *or* intracranial arteries ($Group_{ExtraorIntra}$), and in at least one cervical *and* one intracranial artery ($Group_{Extra\&Intra}$). Subjects in $Group_{control}$ (n=40) had no history of stroke or stenosis ≥ 50% in cervical or intracranial arteries. Frequencies of CAC ≥ 100 and CAC > 0 were compared between the groups and subgroups by bivariate logistic regressions. Multivariate analyses were also performed.

Results: Rates of CAC ≥ 100 were not significantly different between $Group_{athero}$ and $Group_{control}$ but were significantly greater in $Group_{Extra\&Intra}$ when compared to $Group_{control}$ (OR 4.67; 1.21-18.04; p = 0.025). CAC > 0 was significantly more frequent in $Group_{athero}$ (85%) than $Group_{control}$ (OR, 4.19; 1.74-10.07; p = 0,001). In multivariate analyses, "$Group_{athero}$" and "$Group_{Extra\&Intra}$" was significantly and independently associated with CAC.

Conclusions: The frequency of coronary calcification was higher in subjects with atherothrombotic stroke without symptoms of coronary disease than in controls with similar vascular risk factors. In patients with stroke, the burden of subclinical CAD was significantly higher in those with cervical and intracranial atherosclerosis.

Keywords: Atherosclerotic ischemic stroke; Coronary calcium score; Subclinical coronary artery disease; Coronary atherosclerosis; Cervicocephalic atherosclerosis

1. Introduction

Unlike myocardial infarction that is caused by atherosclerosis in more than 90% of the cases [1], only about 25% of ischemic strokes (IS) are attributable to atherosclerosis [2-4]. Classification systems based on results of clinical, neuroimaging and laboratory tests aim to determine the most likely etiology of stroke or whether the cause cannot be determined. A diagnosis of "evident large-artery atherosclerosis" can be made if severity of the stenosis is ≥ 50% in intracranial or cervical arteries that supply the territory affected by the stroke and other causes of stroke are excluded [5]. In addition to affecting different segments of arteries that supply the brain, atherosclerosis can involve different vascular beds. Patients with IS may have polyvascular disease with concomitant coronary (20%) or peripheral artery disease (22%) [6-8]. Asymptomatic coronary artery stenosis ≥ 50% was reported in 18-20% of French patients with noncardioembolic IS and associated with increased risk of death [9, 10].

Besides the presence of stenosis or plaques, atherosclerosis in coronary arteries can be indirectly estimated by the coronary calcium score (CAC). Large prospective studies have established CAC as an excellent noninvasive predictor of atherosclerotic cardiovascular risk currently available [11-13]. CAC is a surrogate of atherosclerosis plaque burden and is independently associated with the risk of myocardial

infarction or mortality [14-16]. In a meta-analysis that included 27,622 patients with no previous manifestation of cardiovascular disease, the presence of CAC > 0 indicated a relative risk of 4.3 of major coronary events [17]. In the MESA study, the annual frequencies of cardiovascular events in asymptomatic subjects were: CAC zero, 0.4%; CAC 1-100, 0.8% and CAC > 100, 2.4% [18]. Detrano et al. 2008 reported (n=6,722) that CAC scores between 101 and 300 were associated with an 8-fold increase in the risk of any coronary event. The risk was increased almost 10-fold in those with CAC above 300 [16]. Until now, no studies about subclinical coronary artery disease (CAD) assessed with CAC were performed in patients with IS specifically attributed to atherosclerosis.

The main goal of this study was to evaluate CAC scores in subjects with IS caused by atherosclerosis ($Group_{athero}$) compared to controls ($Group_{control}$) in multiethnic subjects in Brazil. We hypothesized that the frequency of CAC ≥ 100 and > 0, as well as absolute CAC scores would be higher in $Group_{athero}$ than in $Group_{control}$. In addition, we expected that patients with symptomatic cervical and intracranial stenosis ≥ 50% due to atherosclerosis ($Group_{Extra\&Intra}$) would have a greater extent of subclinical CAD than patients with symptomatic, exclusively cervical *or* intracranial stenosis ≥ 50% ($Group_{ExtraorIntra}$).

2. Methods

2.1 Study design and participants

In this cross-sectional study, patients were recruited from two outpatient stroke clinics at Hospital das Clínicas/São Paulo University and São Paulo Hospital/São Paulo Federal University between September 2015 and March 2018. Controls with comparable age and sex distribution were recruited from non-consanguineous companions of patients. The protocol was approved by the Institutional Review Board (protocol number 1.175.113) and all patients provided written informed consent.

2.2 Eligibility criteria

Subjects aged 45 to 80 years were included. History of coronary heart disease or pathologic Q waves on the electrocardiogram were exclusion criteria. Specific criteria for patients with atherosclerosis *(*$Group_{athero}$) and controls ($Group_{control}$) are listed below.

2.3 Atherosclerosis group ($Group_{athero}$)

2.3.1 Inclusion criteria: IS in the internal carotid artery or vertebrobasilar territory in the past 15 years, confirmed by computerized tomography (CT) or magnetic resonance imaging; stenosis ≥ 50% in cervical, intracranial, or both segments of these arteries, diagnosed by computed tomography angiography, magnetic resonance angiography (MRA) or digital subtraction angiography within 6 months post-stroke.

2.3.2 Exclusion criteria: High- or medium-risk source of cardiac embolism according to the Causative Classification System of Ischemic Stroke (CCS) [5, 19]; stroke etiology other than atherosclerosis according to CCS; another IS in a large-artery territory, in the absence of ≥ 50% stenosis in an artery supplying that territory.

2.3.3 $Group_{athero}$ was divided in two subgroups: $Group_{ExtraorIntra}$ (stenosis ≥ 50% in either a cervical *or* an intracranial artery supplying the territory affected by IS) and $Group_{Extra\&Intra}$: Stenosis ≥ 50% in at least one cervical *and* at least one intracranial artery.

2.4 Controls ($Group_{control}$)

2.4.1 Inclusion criteria: Age and sex comparable to those of subjects in $Group_{athero}$.

2.4.2 Exclusion criteria: History of transient ischemic attack (TIA) or stroke; stenosis ≥ 50% in a cervical or intracranial artery diagnosed by MRA or transcranial Doppler and cervical Doppler.

2.5 Characteristics of the subjects

Demographic data, history of hypertension, diabetes, hypercholesterolemia, Ankle-brachial Index < 0.9, smoking and metabolic syndrome were assessed. Definitions are shown in Supplementary File 1. Use of antihypertensive, antidiabetic, antiplatelet drugs and statins was also registered. Results of routine laboratory exams from $Group_{athero}$ were retrieved from electronic records. Tests were ordered for controls and patients if no blood work-up had been performed within 6 months prior to enrollment.

Cardiovascular risk was estimated by the Pooled Cohort Equations (PCE), a well-established, global measure of vascular risk, according to the 2013 ACC/AHA recommendations [20]. This quantitative risk assessment method predicts the 10-year risk of developing a first cardiovascular event, defined as nonfatal myocardial infarction, death from CAD, or fatal or nonfatal stroke among people with no cardiovascular disease [21, 22]. Severity of neurological impairments caused by stroke was defined by scores in the National Institutes of Health Stroke Scale (NIHSS) [23-25] and severity of disability, by the Modified Rankin Scale [24, 26].

2.6 Outcomes

The primary outcome was CAC ≥ 100 in the two main groups ($Group_{athero}$ and $Group_{control}$). The secondary outcomes were CAC > 0 and CAC absolute values in the main groups; CAC ≥ 100, CAC > 0 and absolute CAC values in subgroups ($Group_{ExtraorIntra}$ and $Group_{Extra\&Intra}$); independent associated factors of CAC ≥ 100, CAC > 0 and CAC absolute values.

2.7 CAC

CAC was acquired by a 320-detector row CT scanner (Aquilion ONE, Canon Medical System Corporation, Otawara, Japan) at the Heart Institute (InCor)/University of São Paulo Medical School, São Paulo, Brazil. The protocol consisted of a prospective acquisition in inspiratory apnea, under electrocardiographic gating with the tube voltage of 120 kV, and current adjusted according to the patient's body mass index. The collimation pattern of the apparatus was 320 x 0.5 mm and the rotation speed, 0.35 s. Sequential slices with 3.0 mm spacing were obtained, which is the standard method in clinical practice, as previously described [14]. The effective radiation dose (in mSv) was calculated and controlled in all cases.

2.8 CT image analysis

The images were fully analyzed through a dedicated workstation (Aquarius, Intuition Edition, TeraRecon Inc., Version 4.4.11, California, USA) by a single experienced cardiologist (RD) blinded to clinical data using the scoring system previously described by Agatston et al [14]. All subjects were categorized in CAC ≥ 100 or <100, as well as in CAC=0 or > 0.

2.9 Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD), whereas categorical variables are presented as frequencies. Between-group comparisons of baseline characteristics were performed with unpaired t -tests, Mann-Whitney tests, likelihood test, chi-square tests or Fisher´s exact tests, according to the nature and distribution of the data. Frequencies of CAC=0 or > 0 and CAC <100 or ≥ 100 between $Group_{athero}$ and $Group_{control}$, as well as

between subroups $Group_{ExtraorIntra}$ or $Group_{Extra\&Intra}$ and $Group_{control}$, were compared with bivariate logistic regression. Odds Ratios (OR) and 95% confidence intervals (95%CI) were calculated.

The sample size was not formally estimated because no preliminary data were available. Multiple logistic regression was performed to identify independent associated factors of CAC ≥ 100 or CAC > 0. In Model 1, the independent variables were Pooled Cohort Equations (PCE) and $Group_{athero}$ (Model 1). In addition, in Model 2, we calculated "$PCE_{without\ statin\ use}$" for statin users by estimating the likely LDL-C level in the absence of statin use as previously described [LDL-C level+(30% x LDL-C level)] [27]. This analysis was performed because there is evidence that statin therapy may influence CAC development [28]. The independent variables were $PCE_{without\ statin\ use}$ and $Group_{athero}$.

Comparisons of absolute CAC values between groups were performed with the Mann-Whitney test and between $Group_{ExtraorIntra}$, $Group_{Extra\&Intra}$ and $Group_{control}$, with the Kruskal-Wallis test. Post hoc analyses were made with Dunn's multiple comparisons. We also evaluated absolute calcium scores as a continuous variable, using the base-10 logarithm of the sum of the coronary calcium score plus 1 (log10 [CAC+1]). The addition of 1 to the calcium score before logarithmic transformation was performed so that patients with a calcium score of zero could be included in the analysis as previously described [16]. A *p*-value <0.05 was considered statistically significant. The tests were performed using SPSS for Windows version 22.0.

3. Results

3.1 Characteristics of the subjects

Figure 1 shows the flowchart of inclusion. Table 1 shows the baseline characteristics of the subjects in $Group_{athero}$ (n=80) and in $Group_{control}$ (n=40). In $Group_{athero,}$ the median modified Rankin score was 2 (range, 0-5); the median NIHSS at the time of inclusion, 1.5 (0-16) and the median time from stroke onset, 2 years (0-11.5). More than half (55%) of the patients were assessed within the first-year post-stroke and 32.5%, within 2-5 years. There were no significant differences between groups in relation to age, sex, diagnoses of hypertension, diabetes mellitus, smoking, metabolic syndrome or estimated cardiovascular risk according to PCE. Hyperlipidemia, family history of stroke, abnormal ankle-brachial index, use of antiplatelet drugs, statins, antidiabetic and antihypertensive drugs were more frequent in $Group_{athero}$ than in $Group_{control.}$

3.2 Outcomes

3.2.1 Primary outcome: 3.2.1.1 CAC ≥ 100 in main groups CAC ≥ 100 was present in 46.3% (n= 37) subjects in $Group_{athero}$ and 32.5% (n= 13) in $Group_{control}$ (OR, 1.79; 95%CI 0.81-3.96; *p*=0.152). Table 2 shows results of univariate subgroup analyses. CAC ≥ 100 were significantly more frequent in $Group_{Extra\&Intra}$ than in patients in $Group_{control}$. There were no differences between proportions of CAC ≥ 100 in $Group_{Extra\&Intra}$ and in $Group_{ExtraorIntra}$.

3.2.2 Secondary outcomes: 3.2.2.1 CAC > 0 in main groups and in subgroups CAC > 0 was found in 85% (n= 68) subjects in $Group_{athero}$ and 57.5% (n=23) in $Group_{control}$ (OR, 4.19; 95% CI 1.74-10.07; *p*=0.001). Table 2 shows results of subgroup analyses. CAC > 0 was significantly more frequent in $Group_{ExtraorIntra}$ or $Group_{Extra\&Intra}$ than in$Group_{control}$.

3.2.2.2 Absolute CAC values in main groups and in subgroups

CAC scores were significantly higher in $Group_{athero}$ (median, 75.4; range: 0-2766.1) compared to $Group_{control}$ (median, 11.7; range: 0-2153.7) (p=0.024). CAC absolute values were significantly greater in $Group_{Extra\&Intra}$ (median 109.51; range: 0-2766) and in $Group_{ExtraorIntra}$ (median 56.26; range: 0-1817) than in $Group_{control}$ (p=0.028), but post-hoc analysis did not show significant differences between $Group_{ExtraorIntra}$ and $Group_{control}$ (p=0.194), $Group_{Extra\&Intra}$ and $Group_{control}$ (p=0.075) or $Group_{ExtraorIntra}$ compared to $Group_{Extra\&Intra}$ (p=0.308).

3.2.2.3 Independent associated factors of CAC ≥ 100, CAC > 0 and CAC absolute values

In multiple logistic regression, the variable "$Group_{athero}$" was independently associated with CAC > 0 and Log (CAC +1) (Table 3). Figure 2 shows subgroup analyses of CAC absolute values. Only $Group_{Extra\&Intra}$ was significantly associated with Log (CAC +1) (confidence interval, CI, 0.40-3.43; p=0.013). The results of Model 2 are shown in the Supplementary Table 1. The results of multivariate analyses, with calculated "$PCE_{without\ statin\ use}$" for statin users, were similar to those obtained in Model 1.

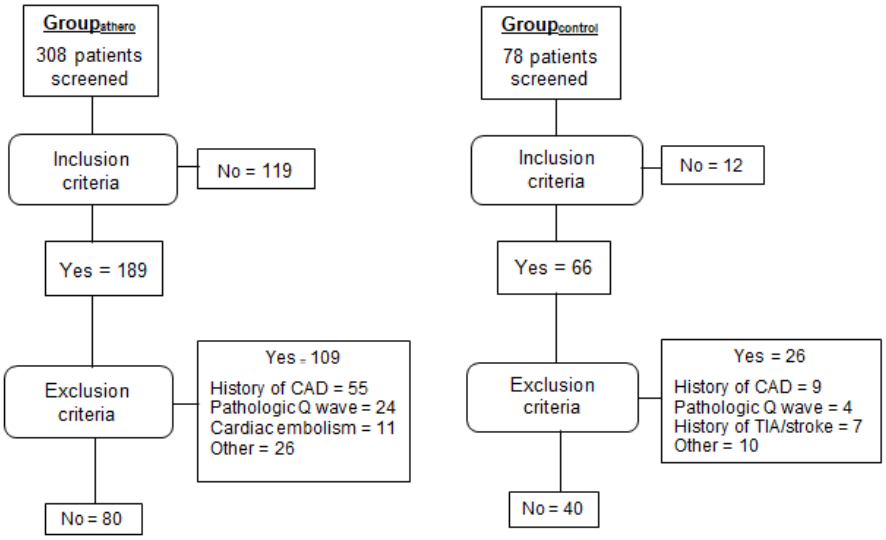

Figure 1: Flow diagram. CAD: coronary artery disease; TIA: transient ischemic attack.

Characteristic	$Group_{athero}$ (n=80)	$Group_{control}$ (n=40)	*p*-value
Age (y)	64.5 ± 7.6	64.2 ± 6.3	0.817[b]
Education (y)	6.8 ± 4.7	6.8 ± 4.9	0.766[c]
Male sex (%)	67.5	55	0.180[a]
Ethnic group (%)			
Black	44.4	47.5	0.302[d]
White	53.8	50	
Asian	3.8	2.5	
Hypertension (%)	87.5	75	0.083[a]
Diabetes (%)	45	42.5	0.795[a]
Hyperlipidemia (%)	100	70	<0.001[e]
Family history of stroke (%)	51.2	20	0.001[a]
Pooled Cohort Equations risk (%)	20.2 ± 16.3	22.1 ± 15.3	0.794[b]
Smoking (%)	15	12.5	0.923[a]
Ankle-brachial Index < 0.9 (%)	29	5	0.002[a]
Metabolic Syndrome (%)	47.5	50	0.796[a]
Antiplatelet agents (%)	92.5	17.5	< 0.001[a]
Statins (%)	97.5	40	< 0.001[a]
Anti-diabetic medications (%)	28.7	12.5	0.047[a]

Values represent mean ± SD (standard deviation); Y= years. aChi-square test, bTeste t-Student; cTeste Mann-Whitney, dLikelihood test, eFisher.

Table 1: Characteristics of the subjects.

Subgroups	CAC ≥ 100 n (%)	OR (95% CI)	*p*-value	CAC > 0 (n, %)	OR (95% CI)	*p*-value
$Group_{control}$	13 (32.5)	1		23 (57.5)	1	
$Group_{ExtraorIntra}$	28 (41.8)	1.49 (0.66-3.39)	0.34	56 (83.6)	3.76 (1.53-9.26)	0.004
$Group_{Extra\&Intra}$	9 (69.2)	4.67 (1.21-18.04)	0.025	12 (92.3)	8.87(1.05-74.95)	0.045

OR, odds ratio; CI, confidence interval; CAC, coronary artery calcification scores; OR calculated using bivariate logistic regression.

Table 2: Comparisons in rates of coronary calcium scores (CAC) ≥ 100 or > 0 between $Group_{control}$, $Group_{ExtraorIntra}$ or $Group_{Extra\&Intra}$.

CAC ≥ 100[a]		
Model 1	**OR (95% CI)**	***p*-value**
PCE	1.026 (1.002-1.052)	0.035
$Group_{athero}$	1.769 (0.787-3.975)	0.167
CAC > 0[b]		
Model 1	**OR (95% CI)**	***p*-value**
PCE	1.026 (0.994-1.06)	0.108
$Group_{athero}$	4.229 (1.735 – 10.305)	0.002
Log (CAC +1)[c]		
Model 1	**Coefficient (95%CI)**	***p*-value**
PCE	0.039 (0.012-0.066)	0.005
$Group_{athero}$	1.021 (0.097-1.945)	0.030

[a]Multiple logistic regression: dependent variables, presence of coronary calcium scores (CAC) ≥ 100; Independent variables, scores in pooled cohort equations and group ($Group_{athero}$ or $Group_{control}$). [b]Multiple logistic regression: dependent variables, presence of coronary calcium scores (CAC) ≥ 0 Independent variables, scores in pooled cohort equations and group ($Group_{athero}$ or $Group_{control}$). [c]Linear regression: dependent variable, logarithm of sum (absolute coronary calcium scores + 1). Independent variables, scores in pooled cohort equations and group ($Group_{athero}$ or $Group_{control}$). OR, odds ratio. CI, confidence interval. CAC, coronary artery calcification scores. PCE, pooled cohort equations.

Table 3: Multivariate analyses.

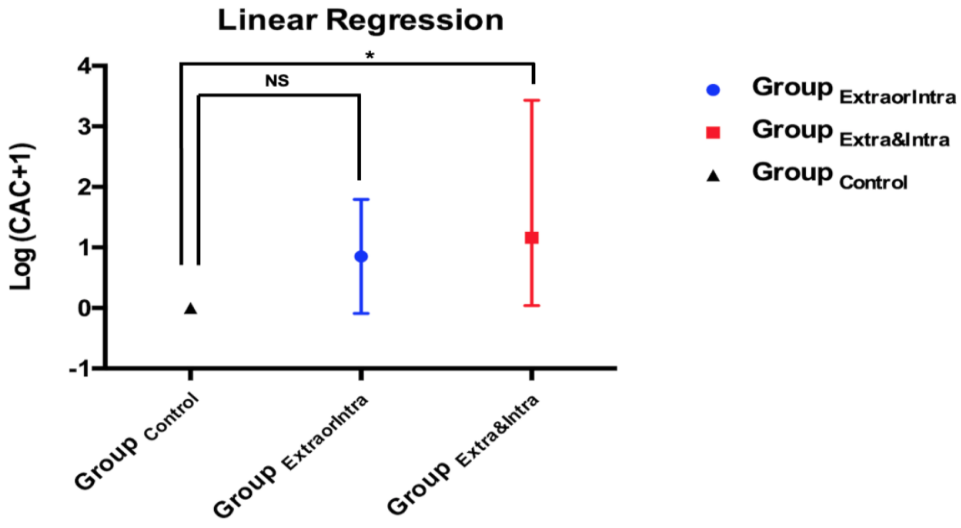

Figure 2: Linear Regression of log (CAC+1) between subgroups ($Group_{control,}$ $Group_{ExtraorIntra,}$ $Group_{Extra\&Intra}$). * indicates the statistically significant difference in reference to the control group. NS indicates non-statistically significant difference.

4. Discussion

We report, for the first time, a significantly greater presence and burden of subclinical coronary atherosclerosis in individuals with IS caused by cervicocephalic atherosclerosis than in controls. The frequency of more extensive CAC (CAC ≥ 100) was higher in $Group_{athero}$ than in $Group_{control}$ but this was not statistically significant. Interestingly, CAC ≥ 100 was significantly more frequent in the subgroup with a greater extension of atherosclerosis ($Group_{Extra\&Intra}$) but not in the subgroup with atherosclerosis restricted to intra- or extracranial arteries ($Group_{ExtraorIntra}$). We found that 85% of the patients in $Group_{athero}$ had CAC > 0 despite absence of CAD symptoms. CAC > 0 was significantly greater in either $Group_{ExtraorIntra}$ or $Group_{Extra\&Intra}$ than in controls. Therefore, IS due to atherosclerosis must be considered as a red flag to reinforce secondary prevention measures, not only to prevent IS recurrence but also to decrease global cardiovascular risk. Antiplatelet and statins are recommended to patients with IS caused by atherosclerosis according to current guidelines. Acknowledgment of a greater risk of death due to MI in these patients than subjects with similar risk factors without a history of IS, despite the absence of coronary symptoms, may strengthen the drive for adherence to treatment in patients with IS caused by atherosclerosis. Multivariate analysis showed an independent association of stroke caused by atherosclerosis ($Group_{athero}$) with higher values of CAC. This indicates that patients with IS caused by atherosclerosis have a greater risk of cardiovascular events or all-cause mortality than controls with comparable estimated vascular risk [17].

Multivariate analysis also showed an independent association of $Group_{Extra\&Intra}$ with higher values of CAC. Therefore patients with more extensive cervicocephalic atherosclerosis may be at greater risk of subclinical coronary atherosclerosis and therefore greater future risk of coronary events, compared with those with either cervical or intracranial atherosclerosis. This greater risk could point to a need for a more detailed assessment of these patients for CAD, since many patients after stroke have physical disabilities that could mask the onset of anginal symptoms related to mobility and delay the diagnosis of obstructive CAD [29, 30]. In addition, our results suggest the possibility of using more aggressive treatment measures for these very high-risk subgroups, such as the use of PSCK9 inhibitors in patients with stroke due to cervicocephalic atherosclerosis [31-34]. Future clinical trials are needed to confirm this hypothesis. To our knowledge, this is the first study that compared CAC in patients with IS caused specifically by large-artery atherosclerosis, without known CAD, and controls. Prior studies investigated rates of subclinical CAD with coronary computed tomography angiography (CCTA) in patients with IS of diverse etiologies [35, 36] or non-cardioembolic stroke [9, 10]. In Japanese patients with IS not caused by cardiac embolism or symptomatic carotid artery disease, without symptoms of CAD, absolute CAC scores were significantly higher than in controls, suggesting a greater risk of MI or death. Yet, other causes of stroke were not excluded in this study [37].

In the present study, the $Group_{control}$ included subjects recruited from non-consanguineous companions of patients in order to limit the difference between patients and controls to the “stroke” status rather than exposure to risk factors due to differences in lifestyle or access to health services. Of interest, controls were found to be at high risk of further atherosclerotic coronary events, comparable to those of patients,

according to PCE scores. Despite this high-risk profile, subjects in the control group were significantly less likely to use medications to treat hypertension, diabetes or dyslipidemia. This finding may reflect the poor control of risk factors likely caused by underdiagnosis of hypertension, diabetes and hyperlipidemia in asymptomatic subjects in low- and middle-income countries like Brazil [38].

This study has some limitations. It has limited power for the comparison of rates of CAC ≥ 100 between $Group_{athero}$ and controls. A multicenter study would be advisable to test the hypothesis that the rate of CAC ≥ 100 is significantly greater in $Group_{athero}$ than in controls, suggesting an even greater risk of cardiovascular events than CAC > 0. Also, inclusion of time from stroke in $Grupo_{athero}$, up to 15 years, might lead to bias. Over the years there might be progression of coronary calcification, as well as worsening of control of cardiovascular risk factors. However, it is unlikely that this may have biased our results because: first, more than half of the patients were assessed within the first year and less than 15%, more than five years post-stroke. Second, PCE scores were comparable between subjects with IS and controls. Third, the use of medications to control risk factors was found to be greater in the stroke group than in the control group. This could make the finding of greater CAC scores in the stroke group, compared to controls, less likely. Despite this, we found that the "stroke status" was an independent predictor of CAC > 0 and hence, greater cardiovascular risk. Fourth, multivariate analysis (Model 2), with "$PCE_{without\ statin\ use}$" for statin users (estimation of the likely LDL-C level in the absence of statin use) showed the same results compared to Model 1, in which the independent variables were PCE and $Group_{athero}$.

5. Conclusion

The frequency of coronary calcification was higher in subjects with atherothrombotic stroke without symptoms of coronary disease than in controls with similar vascular risk factors. In patients with stroke, the burden of subclinical CAD was significantly higher in those with cervical *and* intracranial atherosclerosis. Atherothrombotic stroke should be considered a red flag for subclinical coronary atherosclerosis.

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Conflicts of Interest

RDS has received honoraria related to consulting, research and or speaker activities from: Amgen, Aché, Astra Zeneca, Esperion, Kowa, Merck, Novo-Nordisk, PTC, Pfizer, and Sanofi/Regeneron.

MSB has received speaker fees from GE healthcare.

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Supplementary Material

Supplementary Document 1

Definitions of variables.

a) Hypertension: reported in the medical record or current use of antihypertensive, or physical examination, according to guidelines of the Brazilian Society of Cardiology. (http://departamentos.cardiol.br/dha/vidiretriz/06-cap02.pdf)

b) Diabetes mellitus or fasting hyperglycemia: reported in the medical record or current use of medications to control blood glucose or altered fasting glucose testes or two-hour tolerance test. (http://www.diabetes.org.br/images/2015/area-restrita/diretrizes-sbd-2015.pdf)

c) Dyslipidemia: diagnosis and current treatment or result of total cholesterol and fractions. (http://publicacoes.cardiol.br/consenso/2013/V_Diretriz_Brasileira_de_Dislipidemias.pdf)

d) Smoking: information written on the medical record or referred by the patient. Note how many packs / year (packs / day x years of smoking, remembering that 1 pack has 20 cigarettes).

e) Family history of stroke or coronary artery disease: written on the patient record or referred to by the patient.

f) Ankle / brachial index: quotient between the highest ankle systolic pressure and the brachial systolic pressure. The ankle / brachial index below 0.90 is indicative of peripheral obstructive arterial disease. (http://www.jvascbr.com.br/vol4_n4_supl4.pdf)

g) Metabolic syndrome: diagnosed when a patient has at least 3 of the following 5 conditions:

- Fasting glucose ≥100 mg/dL (or receiving drug therapy for hyperglycemia)
- Blood pressure ≥130 or ≥ 85 mm Hg (or receiving drug therapy for hypertension)
- Triglycerides ≥150 mg/dL (or receiving drug therapy for hypertriglyceridemia)
- HDL-C <40 mg/dL in men or <50 mg/dL in women Waist circumference ≥102 cm in men or ≥88 cm in women;

CAC ≥ 100[a]		
Model 2	**OR (CI)**	**P-value**
PCE without statin	1.025 (1.002 – 1.049)	**0.035**
$Group_{athero}$	1.754 (0.781 - 3.942)	0.174
CAC > 0[b]		
Model 2	**OR (CI)**	**P-value**
PCE without starting	1.029 (0.997 – 1.061)	0.074
$Group_{athero}$	4.203 (1.72 – 10.271)	**0.002**
Log (CAC +1)[c]		
Model 2	**Coefficient (CI)**	**P-value**
PCE without statin	0.039 (0.013-0.065)	**0.004**
$Group_{athero}$	1.006 (0.084-1.928)	**0.033**

[a]Multiple logistic regression: dependent variables, presence of coronary calcium scores (CAC) ≥ 100; Independent variables, scores in pooled cohort equations without statin and group ($Group_{athero}$ or $Group_{control}$). [b]Multiple logistic regression: dependent variables, presence of coronary calcium scores (CAC) ≥ 0 Independent variables, scores in pooled cohort equations and group ($Group_{athero}$ or $Group_{control}$). [c]Linear regression: dependent variable, logarithm of sum (absolute coronary calcium scores + 1). Independent variables, scores in pooled cohort equations and group ($Group_{athero}$ or $Group_{control}$). OR,odds ratio. CI, confidence interval. CAC, coronary artery calcification scores. PCE, pooled cohort equations.

Supplementary Table 1: Multivariate analyses with PCE without statin (Model 2).