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Coronary artery calcium score as a predictor for incident stroke: Systematic review and meta-analysis☆

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ABSTRACT

Background: Coronary artery calcium score (CACS) is a well-established test for risk stratifying asymptomatic patients for overall cardiovascular or coronary events. However; the prognostic value for incident stroke remains controversial. The objective of this study was to investigate the predictive value of CACS obtained by non-contrast electrocardiogram-gated computed tomography for incident stroke.

Methods: We searched PubMed, EMBASE, Cochrane databases for prospective longitudinal studies of CACS which reported the incidence of stroke. Incidence of stroke was compared in patients with and without coronary calcification.

Results: Three studies evaluated 13,262 asymptomatic patients (mean age = 60 years, 50% men) without apparent cardiovascular diseases. During a follow-up of 7.2 years (median 5 years, range 4.4–9.5 years, 95,434 patient-years), the overall pooled incidence of stroke was 0.26%/year. The pooled risk ratio of CACS > 0 for incident stroke was 2.95 (95% CI: 2.18–4.01, $p < 0.001$) compared to CACS = 0. The heterogeneity among studies was low ($I^2 = 0\%$). The pooled incidence rate of stroke categorized by CACS was 0.12%/year for CACS 0, 0.26%/year for CACS 1–99, 0.41%/year for CACS 100–399 and 0.70%/year for CACS ≥400.

Conclusions: In asymptomatic patients without apparent cardiovascular diseases, the incidence of stroke was overall low. The presence and severity of coronary artery calcification were associated with incident stroke over mid-long term follow-up.

1. Introduction

Atherosclerosis is a systemic disease that often coincides in multiple vascular territories [1]. Well established subclinical atherosclerosis surrogates include coronary artery calcium score (CACS) for coronary artery disease (CAD) [2], carotid intimal media thickness for cerebrovascular disease [3] and ankle brachial index for peripheral arteries of the leg [4,5]. A recent study demonstrated that subclinical stages of the disease often coexist in multiple vascular territories simultaneously [6]. Furthermore, CACS has been shown to be associated with stroke in retrospective studies or in cohorts that included patients with prior cardiovascular events [7–9]. However, current evidence of relationship between CACS and incident stroke in asymptomatic population without apparent cardiovascular disease remains controversial with a mixture of negative [10] and positive [11,12] studies and underpowered due to the low event rates [10–12].

Hence, the objective of this systemic review and meta-analysis was to evaluate the prognostic value of CACS for predicting incident stroke in asymptomatic patients without apparent cardiovascular diseases.

2. Methods

2.1. Data sources

Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines were followed for the conduct of the current systematic review and meta-analysis [13]. We searched MEDLINE, EMBASE and Cochrane library database for studies assessing prognostic value of CACS by computed tomography (CT). We used the text words and related Medical Subject Headings (MeSH) for cardiac, calcification, computed tomography, prognosis, and stroke. Our search query was (coronary calcification OR calcium score) AND (stroke OR cerebrovascular disease OR neurological). The initial search results were further investigated manually as described below. The last search was performed on October 8th, 2016.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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2.2. Study selection

We initially reviewed the title and abstracts of retrieved citations. Then full texts of those citations considered relevant were assessed for eligibility for inclusion. Inclusion criteria included the following:

1. Prospective cohort studies that involved asymptomatic patients who underwent CACS testing. Studies with mixed populations (symptomatic and asymptomatic) could be included into our meta-analysis if the studies explicitly mentioned CACS and incident stroke in the subgroup of the asymptomatic patients. Studies with cross-sectional or retrospective designs were not included in our meta-analysis.
2. CACS that was performed by computed tomography (CT), either multidetector CT or electron-beam CT, and quantified using the Agatston method. CACS testing could be either isolated CACS assessment or CACS assessment performed prior to contrast-enhanced coronary CT angiography studies.
3. Studies that reported incident stroke.
   We did not include case reports, non-English studies, review articles without systematic approach and meta-analysis data or conference abstracts. Two physician investigators (K.C. and H.Y.J.) independently assessed studies for eligibility. Discrepancy was resolved by consensus determined by additional investigator (physician investigator G.P.S.S).

2.3. Data extraction and quality assessment

Two coauthors (physician investigator K.C. and physician investigator H.Y.J.) independently extracted data from the included full-text citations. The following information was abstracted: the last name of the first author; publication year; country where the study was performed; total participants in the study; number of male participants; baseline cardiovascular risk profile (mean age, mean body mass index, percentage with diabetes mellitus, hypertension, dyslipidemia, smoking, atrial fibrillation (AF), statin therapy, mean blood pressure, mean low-density lipoprotein level); type of CT scanner; CACS results; and incident stroke with median follow-up duration. For studies that reported adjusted measures of association with stroke (CACS = 0 compared with CACS > 0), the variables that were adjusted in these analyses were abstracted. We assessed quality of included studies using the Newcastle-Ottawa Quality Assessment Scale for cohort studies. Studies with ≥5 stars were considered to be high quality.

2.4. Statistical analysis

We performed an analysis for unadjusted risk ratios for incident stroke. We combined data using the Der Simonian and Laird random-effects model with inverse variance weighting considering the clinical and statistical heterogeneity between studies. Effect estimate was estimated as relative risk (RR) comparing CACS = 0 vs CACS > 0, with 95% confidence intervals (CIs). Differences were considered statistically significant based on 2 tailed analysis with $p < 0.05$. Heterogeneity across studies was assessed with the Cochran Q statistic (χ^2) and with the I^2 test. We considered Q statistic $p < 0.10$ and an $I^2 > 50\%$ suggestive of statistically significant inter-study heterogeneity. If heterogeneity was present, meta-regression was performed to investigate the sources of heterogeneity in the included studies. Pooled incidence of stroke was compared among each CACS category using a chi square test.

Publication bias was assessed using the Egger linear regression test and visual inspection of funnel plots. The trim-and-fill method was used to adjust for publication bias if present. All the analyses were performed using Revman v5.3, Comprehensive Meta Analysis v3. A $p < 0.05$ was considered statistically significant.

3. Results

3.1. Literature search (Supplemental Fig. 1)

From a total of 1510 unique citations identified, 34 full text articles were assessed for eligibility and 31 were excluded. Out of 1510 unique studies, 1508 studies (1505 excluded and 3 included) were in agreement for inclusion/exclusion between both investigators. There were 2 studies (eventually not included into the meta-analysis) that we involved the third investigator for consensus. The inter-rater reliability was good (weight kappa 0.75; 95% CI 0.41–1.00). Three studies [10–12] were included for qualitative synthesis. All 3 studies were also included in the meta-analysis for defining relative risks of incident stroke.

3.2. Study characteristics (Table 1)

Included studies were conducted in the United States [10,11] and Germany [12] from 1991 and 2000. The included were of good quality. Of these 3 studies, 2 used only electron beam CT [10,12] to assess CACS and another study used both electron beam CT and multidetector CT [11]. Although it is well established that there are some differences between electron beam CT and multi-detector CT [14], both CT scanner types have been shown to have equivalent reproducibility for measuring coronary artery calcium [15]. The CACS scanning, post-processing and interpretation protocols are the same as originally described by Agatston et al. [16].

3.3. Participant characteristics in the included studies

A total of 13,262 asymptomatic patients without apparent cardiovascular diseases were evaluated with CACS (pooled mean age 60 years; 95% CI 56–62 years, 50% men; 95% CI 47–62%). Other relevant baseline patient characteristics are shown in Table 1. Pooled prevalence of CACS = 0 was 55% (7287/13262) (95% CI 47–68%). Studies which provided comparisons between baseline patient characteristics and incident stroke reported overall higher markers of comorbidity in patients who developed stroke versus those who did not (Table 2).

3.4. Incident stroke

During a follow-up of 7.2 years (median 5 years, range 4.4–9.5 years, 95,434 patient-years), there were 250 incident stroke reported. Patients with CACS > 0 had a significantly higher risk of incident stroke than those with CACS > 0 (RR 2.95; 95% CI: 2.18–4.01, $p < 0.001$). The heterogeneity among studies was low with an $I^2 = 0\%$ (Fig. 1). Pooled adjusted risk ratio of CACS for incident stroke could not be performed because there was only one study that reported the adjusted risk ratio [12].

The overall pooled incident stroke rate was 0.26%/year (0.26 stroke per 100 patient-years or 250 events in 95,434 patient-years). Patients with CACS present had significantly higher incidence of stroke than those with CACS absent (0.37%/year; 0.37 stroke per 100 patient-years or 197 events in 52,848 patient-years vs 0.12%/year; 0.12 stroke per 100 patient-years or 53 events in 42,638 patient-years, $p < 0.001$). The higher CACS groups had significantly higher incidence of stroke compared to the lower CACS groups as shown in Fig. 2.

Table 1
Patient characteristics of included studies.

Studies	*N*	Population	Age, year	Men, %	BMI, kg/m^2	HTN, %	SBP, mm Hg	DM, %	LDL, mg/dL	Cig, %	AF, %	F/U, year	CT	Prevalence of CACS, %			
														0	1–99	100–399	400+
Wong 2009 (USA)	2303	Asymptomatic patients without CVD referred who had CACS assessment	56	62	27	NA	133	7	NA	7	0	4.4	EBCT	53	27	12	8
Hermann 2013 (Germany)	4180	*Heinz Nixdorf Recall Study* Prospective population-based cohort study without CVA, CAD	59	47	27.8	38	129	7	147	56	1.4	5	EBCT	32	41	17	10
Gibson 2014 (USA)	6779	*Multi-Ethnic Study of Atherosclerosis* Prospective population-based cohort study without CVD	62	47	28.3	33	126	12	117	50	5.6	9.5	MDCT	50	26	14	10
Total	13,262		60	50		NA	128	10	NA	44	3.3	7.2		45	31	14	10

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