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Coronary artery calcium score and its association with stroke: A systematic review and meta-analysis

Short running title: Coronary artery calcium score and stroke

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Abstract

Background: The relationship between coronary artery calcium (CAC) score and incident stroke is controversial.

Methods: We conducted a systematic review of the literature evaluating CAC score and incident stroke. A search of MEDLINE and EMBASE was performed, and data were extracted from relevant studies. Statistical pooling with random-effects meta-analysis was undertaken to evaluate the risk of incident stroke with any CAC vs no CAC, 1-100 CAC vs no CAC and >100 CAC vs no CAC.

Results: Data from 9 different cohort studies from the United States and Europe with a total of 61,096 patients were included in this review. The mean age of patients in the studies ranged from 44 to 69 years and follow up duration ranged from a median of 5.5 years to 12.3 years. The crude stroke event varied from 1.6% to 9.5%. Meta-analysis of risk of incident stroke with any vs no CAC (RR 1.70 95%CI 0.87-3.31, I^2=95%) and for CAC 1-100 vs no CAC (RR 1.54 95%CI 0.75-3.17, I^2=93% was not statistically significant. For CAC >100, the risk of incident stroke was significantly higher compared to no CAC (RR 2.61 95%CI 1.51-4.52, I^2=89%). When the one study which included only young adults was excluded, there was significant increase in risk of incident stroke with all categories of CAC.

Conclusions: There is an association between high CAC score and incident stroke, but more studies are needed to determine how patients with incidental CAC should be managed from the perspective of stroke prevention.

Keywords: Coronary artery calcium; stroke; meta-analysis

Introduction

Coronary artery calcium (CAC) is a marker of coronary atherosclerosis burden in an individual.[1] While it can be detected incidentally on non-gated chest computed tomography,[2] the most wildly used method of evaluation and quantification is the Agatston score or CAC score which uses the weighted sum of lesions with a density above 130 Hounsfield units and multiplying the area of calcium by a factor related to the maximum plaque attenuation.[3] The determination of CAC score is important because extent of CAC can predict cardiac events in asymptomatic and symptomatic patients.[4] In view of the evidence, the 2018 American College of Cardiology/American Heart Association Cholesterol Guidelines suggested that CAC testing may be considered in adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥70 mg/dl-189 mg/dl at intermediate risk of 10-year atherosclerotic cardiovascular disease if a decision about statin therapy is uncertain.[5] One recent review suggests that CAC is associated with increased risk of cardiovascular outcomes including stroke.[6] Whether or not CAC has value in predicting the risk of stroke is uncertain as use of CAC is not incorporated into guidelines for stroke prevention.

Indeed, the possible association between CAC and stroke is less consistent compared to its association with coronary artery disease. The most recent evaluation from the Multi-Ethnic Study of Atherosclerosis suggests that high CAC was associated with stroke but adding CAC to traditional risk factors does not improve risk discrimination.[7] The Walter Reed Study of young adults reported a significant increase in incident stroke for patients with CAC >100 compared to those without CAC.[8] Furthermore, data from the Jackson Heart Study suggests that CAC is associated with increased odds of incident stroke but this was not statistically significant.[9] The only meta-analysis on CAC and incident stroke to date included 3 studies which followed up patients for 7.2 years and found that the presence and severity of CAC was associated with incident stroke over mid-long term follow up.[10] In addition to newer studies

being published, the main limitation of this review was that the study pooled crude risk ratios and they did not consider different cut-offs for CAC score.

In view of the new literature and limitations of the previous review, we performed an updated systematic review and meta-analysis of CAC and its association with incident stroke, with considerations for adjusted estimates and different cutoffs for CAC score.

Methods

We conducted a systematic review of the literature evaluating CAC score and incident stroke. This manuscript was prepared in according to the recommendations of the MOOSE statement.[11]

Literature search

A search was performed by CSK on OVID of the databases MEDLINE and EMBASE on 10 June 2022 to identify studies of coronary artery calcium and stroke. The exact search terms were: (coronary artery calcium score OR coronary artery calcium OR Agatston) AND (stroke OR cerebrovascular disease OR cerebrovascular accident).

Study inclusion criteria

We included studies which evaluated CAC and incident stroke events. There was no restriction on whether the type of stroke or any restriction based on language of publication. Studies were excluded if the study: did not use CAC score as the exposure variable, did not have stroke as an outcome variable, was not prospective in design and the study only evaluated patients with stroke. Case reports and protocols were excluded but conference abstracts were considered for inclusion.

Study selection, data extraction and study quality assessment

Screening was performed independently by two reviewers (CSK and SB). Data were collected by two reviewers (CSK and SB) on study design, country, year, number of patients,

mean age, proportion that were male and study inclusion criteria. Additional data were collected on the follow-up, rate of stroke events in the study and results. Results were extracted were the estimates that most adjusted for potential confounders or crude events when no adjusted estimates were available. Study quality assessment was performed using the Ottawa-Newcastle Scale for cohort studies.[12]

Data synthesis

We used RevMan 5.4 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) in order to calculate odds ratios using the Mantel-Haenszel method for crude event rates data and the inverse variance method to perform random-effects meta-analysis. The statistical pooling was performed for: any CAC vs no CAC, 1-100 CAC vs no CAC and >100 CAC vs no CAC. Statistical heterogeneity was assessed using the I^2 statistic where I^2 values of 30%-60% represent moderate degree of heterogeneity.[13] We planned to conduct asymmetry testing for publication bias if there were more than ten studies in the meta-analysis and statistical heterogeneity was less than 50%.[14] Sensitivity analyses were performed to identify sources of statistical heterogeneity.

Sensitivity analysis

As CAC score has been shown to be associated with age, we carried out one sensitivity analysis excluding the Walter Reed Study[8] as the average age of the participants was 44 years. Another sensitivity analysis was performed excluding the study Singh 2021[15] because this study did not adjust for potential confounders.

Results

A total of 5 publications[7-9,15,16] were included in this review after exclusion of studies that did not meet the inclusion criteria (Figure 1). Thus, this review included 61,096 patients (the 4,838 patients from the MESA study in Mehta 2022[7] was not included as MESA study was included in the Yano 2017 study[16]). Data were derived from 9 different cohorts in the United States and Europe. The mean age of the participants ranged from 44 years in the Walter Reed Study[8] of asymptomatic patients aged 30 to 49 years, to 69 years in the collective evaluation of the MESA, Cardiovascular Health Study (CHS), Framingham Heart Study (FHS), Rotterdam Study (RS) and Heinz Nixdoff Recall Study (HNRS).[16] The proportion of male patients in the cohorts ranged from 45% to 77%.

The study quality assessment is shown in Supplementary Table 1. Two studies were from specific cohort that were not generalizable to a general adult population (one only included participants with African American ethnicity and the other only included of young adults). The study by Singh et al[15] did not report adjusted outcomes. Collectively the study quality was good which ranged from 7 to 9 stars out of 9 on the Ottawa-Newcastle Scale.

The follow up, stroke events and results are shown in Table 3. There was a wide range of follow up duration for studies which was as low as a median of 5.5 years to a median of 12.3 years. The crude stroke event varied considerably from 1.6% in the Walter Reed Study cohort[8] to 9.5% in the HNRS.[16] A meta-analysis of risk of incident stroke with any vs no CAC (RR 1.70 95%CI 0.87-3.31, I^2=95%) and for CAC 1-100 vs no CAC (RR 1.54 95%CI 0.75-3.17, I^2=93% was not statistically significant. For CAC >100 the risk of incident stroke was significantly higher compared to no CAC (RR 2.61 95%CI 1.51-4.52, I^2=89%).

As there was significant statistical heterogeneity sensitivity analysis was performed (Table 3). Exclusion of Singh 2021[15] which reported crude results only, showed a similar trend as the overall result pooled results where there was only significant increase in incident stroke

with CAC >100 but there were significant reductions in statistical heterogeneity. When the Walter Reed Study[8] of young adults was removed there was significant increase in risk of incident stroke with all categories of CAC (Supplementary Figure 1).

There were additional results which could not be statistically pooled. The data from the Jackson Heart Study[9] suggests that there was an increase in incident stroke with CAC but this was not statistically significant (adjusted hazard ratio (aHR) 1.18 95%CI 0.54-2.58). The predictive value of CAC and stroke had an area-under-the-curve of 0.694 in the study by Singh et al.[15] The confirmation studies which used European data from the RS and HNRS found minor reductions in incident stroke prediction comparing age as a predictor to CAC score.[16]

Discussion

The principal findings from this systematic review are as follows: (i) prospective observational studies suggest that there is an association between CAC score and incident stroke; (ii) the increase in risk of stroke is more significant among patients with CAC score >100; (iii) the predictive risk of incident stroke with CAC score is dependent on age of the population evaluated as low CAC scores (<100) may not be predictive of incident stroke. These findings suggest that there is an association between high CAC score and incident stroke among studies with long term follow up, but more studies are needed to determine what actions should be taken when elevated CAC is detected in terms of stroke prevention.

Atherosclerosis is the pathological process which links CAC and stroke. Atherosclerosis is a chronic inflammatory condition was originally thought to be the result of passive lipid accumulation in the vascular walls, but more recent investigations suggest that the condition begins with the formation of calcified plaque which causes narrowing of the vessels.[17] While there is established evidence of an association between vascular calcification and increased cardiovascular morbidity and mortality,[18] an unresolved question is potential

mechanistic relationship between CAC and stroke. One possibility is that CAC can directly result in cerebral infarction. This may be the case for calcium in the ostia of the left main coronary artery and right coronary artery where calcium can embolise and cause cerebral infarction. However, coronary calcium is frequently present in other parts of the coronary vessels and the direction of the blood flow will push any calcium that dislodges in most cases down the coronary vessel potentially compromising flow to the myocardium rather than retrograde into the aorta and then to the cerebral circulation. In addition, the presence and extent of coronary artery disease has been shown to be associated with incremental risk of ischemic stroke.[19] Coronary artery disease and CAC could indirectly increase risk of stroke by having shared risk factors for atherosclerosis such as hypertension, hyperlipidaemia and tobacco use. Hypertension is the single most important risk factor for all types of stroke and epidemiological studies show that good control of hypertension reduces risk of stroke.[20] Hyperlipidaemia is a major risk factors for cardiovascular disease and cerebrovascular disease which has synergistic interactions with hypertension and statin use to control blood lipids plays an important role in stroke prevention.[21] Cigarette smoking is a well-established preventable risk factor for stroke, which increases risk of stroke by three to fourfold.[22] Furthermore, atherosclerosis is also linked to atrial fibrillation[23] and atrial fibrillation increases the risk of stroke by five-fold.[24] The main pathophysiology for coronary heart disease and coronary calcium formation is atherosclerosis, but for cerebrovascular events have a more heterogeneous pathophysiology which includes atherosclerosis as well as haemorrhage, small vessel lacunar stroke and ischaemia.[25]

The event rates of stroke in the studies together with follow up in the studies that evaluate CAC score and incident stroke merit consideration. A population with low event rates makes it more challenging to show a statistical difference between groups with and without CAC because larger sample size is needed. The event rate was variable in the included studies which was lowest in the cohort of young adults and much higher in other studies. This is

important as it is possible that CAC may not be predictive of stroke in patients of younger age because the studies did not have enough patients as strokes are rare events in young people. In addition, a longer follow up may increase event rate but the problem is that with prolonged follow up there may be the development of other cardiovascular risk factors or comorbid illnesses that increase the propensity for stroke. To increase the event rate, it is possible to restrict the cohort to elderly patients as was done by Yano et al[16] which only included patients who were greater than 60 years old. However, in the case of elderly cohort there is also the issue of competing risk as patients may die for other reasons such as cancer or coronary heart disease before developing stroke and there is the complexity of the need to adjust for cardiovascular risk factors and comorbidities.

A question remains about the clinical utility of CAC score and how it impacts clinical practice. As CAC is a marker of atherosclerosis, it is a marker of adverse cardiovascular outcome. Studies consistently show that CAC scoring improves risk stratification in cardiovascular disease when added to traditional risk factors.[26] Hoff et al showed CAC in the population varies with age and sex with increasing calcium in older patients.[27] Atherosclerosis is also a disease of aging[28] so the important consideration is whether the additional consideration of CAC adds value to the predictive value of age. Among patients aged 60-years and over the in validation European cohorts of the study by Yano et al,[16] age alone appears to be a better predictor of incident stroke compared to CAC score. This is different from the findings of the pooled results which was restricted to studies which adjusted for potential confounders including age which shows that CAC scores >100 are associated with incident stroke compared to patients with CAC.

The finding of the current review that high coronary calcium score is associated with incident stroke may suggest the need for ultrasound evaluation of the carotid artery to identify stenosis and plaque burden in patients who are found to have high coronary calcium score. This

is potentially important as plaques in the carotid may be a source of embolic stroke and imaging may also be needed for the aortic arch. Whether it is of benefit and cost effective for these patients who have high calcium score to have routine imaging of the carotids and aortic arch for risk stratification is an area of investigation for further studies.

The value of the CAC score is in the patients is likely in line with guidelines which suggest that it should be considered in patients with intermediate risk ie. neither young age with few traditional cardiovascular risk factors or the elderly with one or more cardiovascular risk factors. The other consideration is if CAC is found even via computed tomography of the thorax what should be done? It is likely that symptoms of angina should be assessed but should stroke risk be evaluated and testing be considered such as carotid doppler, atrial fibrillation screening and cerebral imaging? The resources required for investigations of stroke risk could result in significant burden to health services and it needs to be clear that it would be of patient benefit. This will require future studies before any recommendations could be made.

Limitations

This systematic review and meta-analysis has several limitations. Two of the studies were only available in conference abstract format so detailed assessment of methodology was not possible. Variable degrees of adjustments for confounders in the pooled studies. The Walter Reed study[8] only adjusted for age, sex, tobacco use, hypertension, hyperlipidaemia and diabetes while Yano et al[16] further adjusted for race, study site and medications and the Mehta et al[7] evaluation also adjusted for family history of myocardial infarction and educational attainment. Consideration of potential confounders is important if the aim is to determine if CAC has predictive value about age or other established stroke risk factors alone. In addition, there was high degrees of statistical heterogeneity in several of the pooled estimates, this statistical heterogeneity could be reduced by exclusion of the study Singh et al which reported unadjusted

estimates that were higher risks of stroke events with narrow confidence intervals compared to the other studies. Nevertheless, it is important to recognize the methodological heterogeneity present in the included studies which contribute to statistical heterogeneity as the mean age of the participants and proportion of participants who are male differ among the included studies and one of these studies only included African American patients while another only included patients aged 30 to 49 years. Also, another limitation was that the way the studies pooled individual cohorts and reported overall variables precluded meta-regression to examine the impact of age and sex on pooled estimates of CAC score and risk of stroke. Finally, the findings are primarily those from American healthcare settings and may not be generalizable to other countries.

In conclusion, CAC score appears to be associated with increased risk of incident stroke in studies with long term follow up. The patients at highest risk are those who are elderly and those with CAC scores >100. Further studies are needed to determine how best to manage patients who are incidentally found to have CAC in terms of stroke risk.

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Table 1: Study design, participants and inclusion criteria

Study ID	Study design; Country; Year	No. of patients	Mean age	% male	Inclusion criteria
Effoe 2018[9]	Prospective cohort study; United States; Unclear.	2,641	62±10	63%	Patients who are African-American in the Jackson Heart Study.
Javaid 2021[8]	Prospective cohort study; United States; 1997 to 2009.	13,397	44	77%	Patients were asymptomatic and aged between 30 to 49 years old in the Walter Reed Study.
Mehta 2022[7]	Prospective cohort studies; United States; Baseline 2000.	7,042 - 4,838 (MESA), 2,204 DHS	57±13	46%	Patients were in the MESA and DHS.
Singh 2021[15]	Prospective cohort study; United States; 2008 to 2019.	33,086	-	46%	Patients with age ≥18 years with heart screen done between November 2008 and February 2019.
Yano 2017[16]	Prospective cohort studies; United States and Europe; Baseline 1997 Rotterdam Study.	9,768 - 4,778 (MESA, CHS, FHS), 4990 (RS, HNRS).	69	45%	Patients with age ≥60 years in the MESA, FHS, CHS, HNRS and RS.

MESA = Multi-Ethnic Study of Atherosclerosis Study, DHS = Dallas Heart Study, FHS = Framingham Heart Study, CHS = Cardiovascular Heart Study, HNRS = Heinz Nixdorf Recall Study, RS = Rotterdam Study.

Table 2: Follow up, stroke event rates and results

Study	Follow up	Stroke event rate	Results
Effoe 2018 (Jackson Heart Study)[9]	Median 5.5 years.	Not reported.	CAC and incident stroke: aHR 1.18 95%CI 0.54-2.58.
Javiad 2021 (Walter Reed Study)[8]	Mean 11.1 years.	210/13,397 (1.6%).	Any CAC vs no CAC and stroke: aHR 0.97 95%CI 0.7-1.4. CAC 1-10 vs no CAC and stroke: aHR 0.76 95%CI 0.42-1.37. CAC 11-100 vs no CAC and stroke: aHR 0.83 95%CI 0.52-1.34. CAC >100 vs no CAC and stroke: aHR 1.73 95%CI 1.01-2.97.
Mehta 2022 (MESA study)[7]	Median 12.3 years.	241/7,042 (3.4%) (combined with DHS study).	Any CAC vs no CAC and stroke: aHR 1.32 95%CI 1.05-1.83. CAC 1-99 vs no CAC and stroke: aHR 1.21 95%CI 0.84-1.76. CAC ≥100 vs no CAC and stroke: aHR 1.45 95%CI 1.00-2.12.
Mehta 2022 (DHS study)[7]	Median 12.3 years.	241/7,042 (3.4%) (combined with MESA study).	Any CAC vs no CAC and stroke: aHR 2.13 95%CI 0.94-4.81. CAC 1-99 vs no CAC and stroke: aHR 1.81 95%CI 0.63-5.23. CAC ≥100 vs no CAC and stroke: aHR 2.19 95%CI 0.96-4.97.
Singh 2021[15]	Days to event 1450 days.	1,989/33,086 (6.0%).	Any CAC vs no CAC and stroke: 1,423/15,635 vs 546/17,451. CAC 1-100 vs no CAC and stroke: 557/8,919 vs 546/17,451. CAC ≥100 vs no CAC and stroke: 866/6,716 vs 546/17,451. Predictive value of CAC and stroke: 0.694.
Yano 2017 (Combined MESA Study, Cardiovascular Heart Study, Framingham Heart Study, Heinz Nixdorf Study, Rotterdam Study)[16]	Median 10.7 years.	MESA, Cardiovascular Heart Study, Framingham Study: 228/4,778 (4.8%). Rotterdam study: 77/3,089 (2.5%). Heinz Nixdorf Study: 180/1,901 (9.5%).	Data from MESA, Cardiovascular Heart Study and Framingham Study: CAC 1-100 vs no CAC and stroke: aHR 1.41 95%CI 0.92-2.16. CAC 100-299 vs no CAC and stroke: aHR 2.20 95%CI 1.40-3.45. CAC ≥300 vs no CAC and stroke: aHR 2.62 95%CI 1.70-4.03. Data from Rotterdam Study: Age performed better at predicting stroke as AUC for age 0.711, CAC categorical -0.099 (-0.0179 to -0.19), CAC continuous -0.069 (-0.154 to 0.017). Data from Heinz Nixdorf Study: Age performed better at predicting stroke as AUC for age 0.699, CAC categorical -0.020 (-0.062 to 0.017), CAC continuous -0.002 (-0.066 to 0.025).

MESA = Multi-Ethnic Study of Atherosclerosis, DHS = Dallas Heart Study, CAC = coronary artery calcium, aHR = adjusted hazard ratio

Table 3: Sensitivity analysis

Analysis	Any CAC vs no CAC	CAC 1-100 vs no CAC	CAC >100 vs no CAC
All studies	RR 1.70 95%CI 0.87-3.31, I^2=95% 4 studies	RR 1.54 95%CI 0.75-3.17, I^2=93% 6 studies	RR 2.61 95%CI 1.51-4.52, I^2=89% 6 studies
Exclusion of Singh 2021 because it was an unadjusted	RR 1.24 95%CI 0.90-1.72, I^2=47% 3 studies	RR 1.14 95%CI 0.71-1.85, I^2=59% 5 studies	RR 2.19 95%CI 1.68-2.85, I^2=0% 5 studies
Exclusion of Walter Reed Study low risk cohort as age 30 to 49 years.	RR 2.07 95%CI 1.05-4.08, I^2=94% 3 studies	RR 2.02 95%CI 1.16-3.51, I^2=79% 5 studies	RR 3.03 95%CI 1.70-5.38, I^2=88% 5 studies

Figure 1: PRISMA flow diagram of study selection

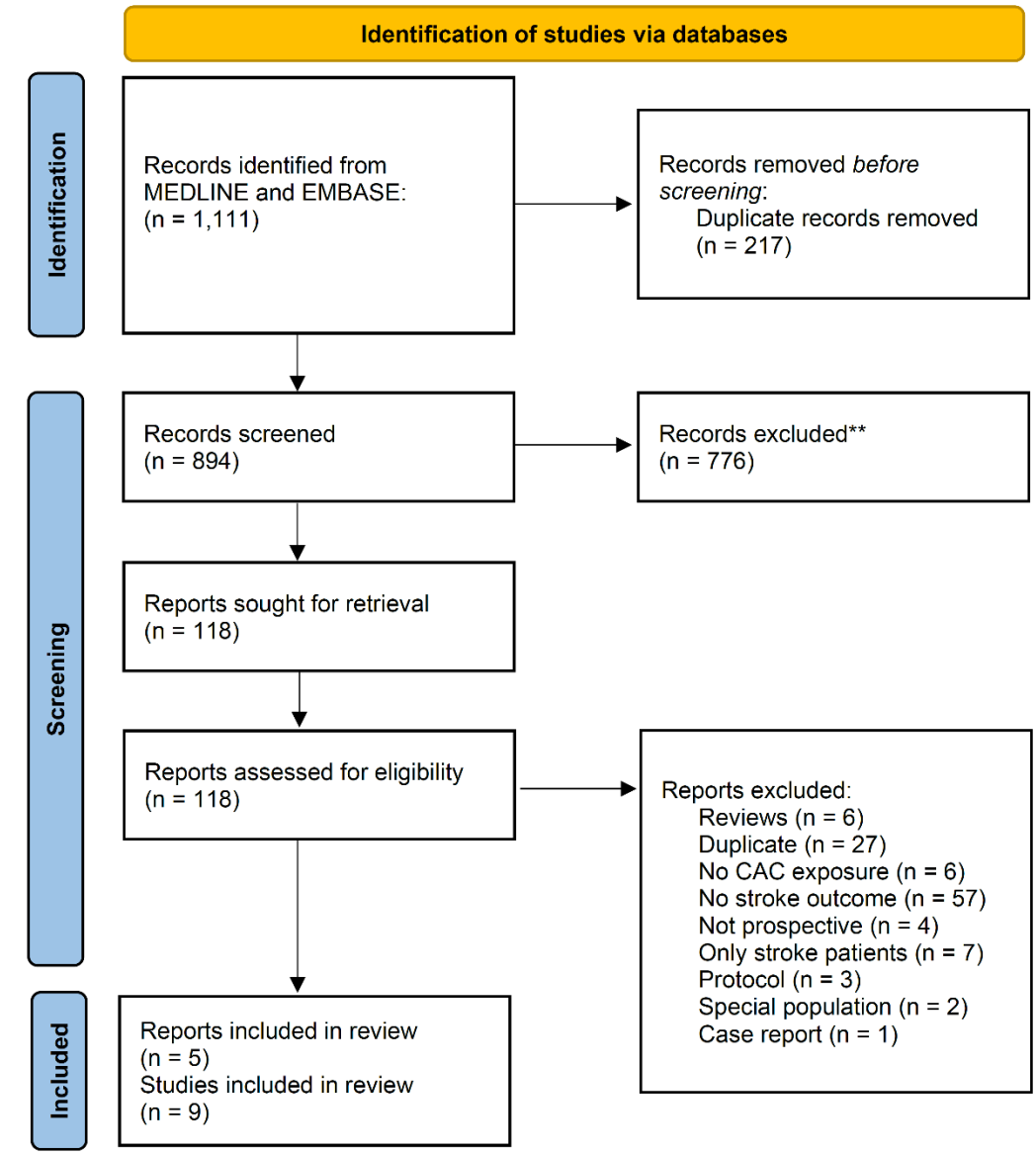

Figure 2: Forrest plot of the relationship between coronary artery calcium and stroke