



Association of thoracic aorta calcium and non cardiac vascular events in cardiac disease-free individuals[☆]



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ABSTRACT

Objective: Thoracic aorta calcium (TAC) is measurable on the same computed tomography (CT) scan as coronary artery calcium (CAC) but has still unclear clinical value. We assessed TAC and CAC relations with non-cardiac vascular events history in a cohort of subjects at risk for cardiovascular disease.

Methods: We analyzed retrospectively 1000 consecutive subjects having undergone CAC detection by non-contrast multi-slice CT with measurement field longer than usual in order to measure total TAC including aortic arch calcium. We also determined partial TAC restricted to ascending and descending thoracic aorta sites by removing arch calcium from total TAC. Calcium deposits were measured with a custom made software using Agatston score.

Results: Compared with the rest of the cohort, the 30 subjects with non-cardiac vascular event history had higher median values [95% CI] of total TAC (282 [28–1809] vs 39 [0–333], $p < 0.01$) and partial TAC (4 [0–284] vs 0 [0–5], $p < 0.01$) but no different value of CAC (73 [0–284] vs 16 [0–148]). Odds ratio [95% CI] of having non-cardiac vascular event per 1-SD increase in log-transformed calcium value was significant for total TAC but not for CAC, if total TAC and CAC were entered separately (1.56 [1.12–2.24], $p < 0.01$ and 1.13 [0.86–1.50], respectively) or together (1.57 [1.10–2.32], $p < 0.01$ and 0.98 [0.73–1.32], respectively) in the logistic adjusted model.

Conclusion: TAC assessment simultaneous with CAC detection provides complementary information on the extra coronary component of cardiovascular risk beyond CAC's coronary risk prediction. Further studies are required to prospectively confirm this result.

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1. Introduction

The detection of coronary artery calcium (CAC) by new generation low-dose non-contrast computed tomography (CT) has become a recognized and robust strategy to improve coronary risk stratification [1–3]. Indeed, it is well established that CAC predicts future coronary events beyond traditional risk factors prediction [4–8]. Interestingly, the CT that measures CAC can simultaneously quantify thoracic aorta calcium (TAC) on the same scan [9].

However, the clinical relevance and complementarity of TAC detection as regards CAC prognostic information have to be clarified. Some studies suggest that TAC detection does not provide incremental information beyond CAC prediction [4,10]. Conversely, other studies suggest that TAC may relate to, or predict non-cardiac vascular events better than CAC [11–13], especially when calcium deposit is assessed in the aortic arch [14]. This latter result merits attention because the CT assessment of TAC concomitantly with CAC detection uses traditionally a field of measurement that does not visualize aortic arch [15,16] so raising the question whether the lack of assessment of aortic arch calcium may attenuate the prognostic performance of TAC.

To address these issues, we performed a retrospective analysis of a cohort of 1000 consecutive subjects at risk for cardiovascular disease, having undergone a non-contrast multi-slice computed tomography (MSCT) scan in the framework of routine care. The

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length of the CT field of measurement was more extended than usual in order to include the aortic arch in view of detecting early aortic dilatation [17,18] in the entire thoracic aorta. This complete thoracic aortic scan allowed detecting and quantifying total TAC including aortic arch calcium. To analyze the incremental information of aortic arch calcium, we also calculated partial TAC, defined as excluding the arch from aorta calcium measurement [4,16]. Our main objective was to assess and compare the relations of total TAC, partial TAC, and CAC with history of non-cardiac vascular event. We also evaluated the association of total TAC with non-cardiac vascular events compared to partial TAC.

2. Methods

2.1. Subjects

Participants were recruited as part of a cardiovascular risk stratification program between 2010 and 2012. They were consecutively included in our study if they had undergone a non-contrast MSCT scan in view of a double screening: (i) estimation of calcified coronary atherosclerosis burden and (ii) detection of early aortic dilatation in all thoracic aortal sites including ascending aorta, arch and descending aorta. Such scan allowed measuring total TAC, i.e. the amount of calcium deposit in the entire thoracic aorta. Exploration was performed during a one-day hospitalization and was accompanied by concomitant measurements of traditional risk factors according to a procedure previously described in detail [19]. The presence or the absence of history of non-cardiac vascular disease, including cerebrovascular and peripheral vascular events, was documented in each subject from their clinical examination and medical records. The exclusion criteria were history of coronary heart disease in whom CAC detection is not recommended [20] and cardiac arrhythmia because this condition is incompatible with optimal CT-gating image acquisition. Finally, this retrospective study allowed us to analyze 1000 consecutive subjects.

The retrospective analysis of personal health data of study subjects had the authorization of the French CNIL (Commission Nationale de l'Informatique et des Libertés) and was in accordance with the Helsinki declaration. Patient's information was anonymized and de-identified prior to analysis.

2.2. Image acquisition

Cardiac and aortic images were obtained with non-contrast cardiac 64-slice MSCT (light-spaced VCT; GE Health care, Milwaukee, Wisconsin, USA) during an extended scan length acquisition, as previously described [21]. Briefly, images were acquired with prospective-ECG gating at 60% of R–R interval in the cranio-caudal direction from the top of the aortic arch to the level of the diaphragm. Measurements were taken with 2.5 mm axial slices, 120 kVp, 250-mA current, 250-ms exposure time, and average 250-mm field of view. The effective radiation dose assessed in a previous group of 200 subjects was 1.23 ± 0.14 mSv (range 0.92–2.1 mSv) [18].

Global amount of CAC and TAC deposits were measured using the Agatston score method [22], implemented in a custom made software previously described [21]. Total TAC was assessed from the apex of the heart until the top of the aortic arch, so including the entire thoracic aorta with the exception of the sinotubular junction (Fig. 1). Partial TAC restricted to ascending and descending thoracic aorta sites was calculated by removing aortic arch calcium amount from total TAC measurement (Fig. 1).

2.3. Statistical analysis

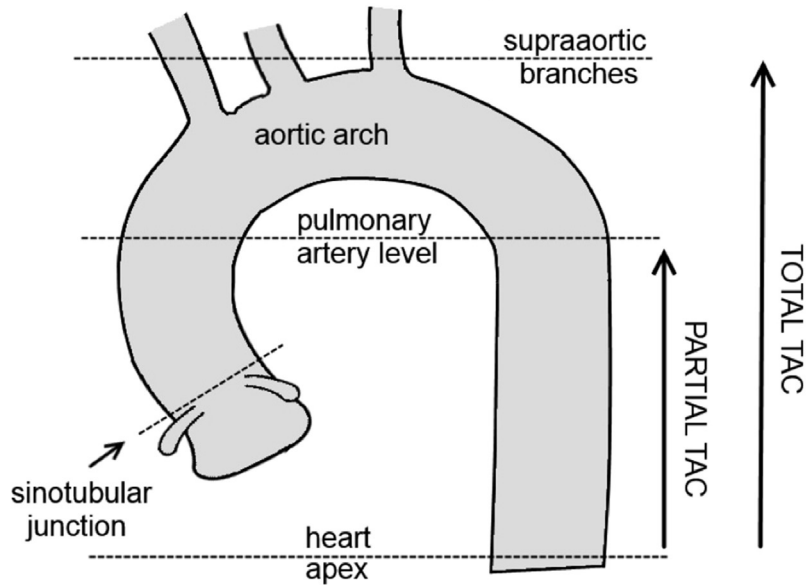
Normally distributed continuous variables were described by means (standard deviation), categorical variables were described as frequencies (percentages) and skewed variables were described by median [interquartiles]. CAC, total TAC, and partial TAC were expressed as raw values and log-transformed values (Log (raw value + 1)). The differences in study parameters were analyzed by presence or absence of history of non-cardiac vascular events using chi-square tests for categorical variables, student t-tests for variables with normal distribution, and non-parametric Mann–Whitney test for parameters with skewed distribution. The association of history of non-cardiac vascular events with CAC, total TAC and partial TAC taken separately were examined with three logistic regressions adjusted for age, gender, total cholesterol, systolic blood pressure, and statin and anti-hypertensive treatments. The odds ratio (OR) of having history of non-cardiac vascular events was determined per 1-SD increase in log-transformed CAC, total TAC and partial TAC. Such SD increase was calculated from nonzero values of total TAC, partial TAC or CAC. The associations of non-cardiac vascular events with CAC and total TAC taken together were determined with a logistic regression adjusted for age, gender, total cholesterol, systolic blood pressure, statin and anti-hypertensive treatments and the OR of having non cardiac vascular event was calculated for each parameter entered in the logistic model, using 1-SD increase for each quantitative parameters. All analyses were performed with JMP 8 software (SAS institute, Cary, NC).

3. Results

Clinical characteristics of the study population are shown in Table 1. Half had hypertension (45% with anti-hypertensive treatment), 82% had hypercholesterolemia (53% with statin treatment), 20% were current smokers and 8% had diabetes. Thirty subjects (3% of the cohort) had documented history of non-cardiac vascular events including 17 patients with cerebrovascular event (12 with stroke and 5 with transient ischemic attack) and 13 patients with peripheral vascular disease.

Raw and log-transformed values of total TAC, partial TAC, aortic arch TAC and CAC are shown in Table 1. Medians [interquartile] were 41 [0–242], 0 [0–6], 34 [0–290] and 17 [0–149], respectively. The distributions of log-transformed total TAC, partial TAC and CAC are shown in Fig. 2. Distributions of nonzero values of log-transformed total TAC and CAC were approximately normal but the frequency of total TAC and CAC equal to zero were high, 36% and 28% respectively. The distribution of nonzero values of log-transformed partial TAC had a non-normal shape that reflects a truncated phenomenon due to the lack of aortic arch calcium measurement resulting in a very high frequency of zero partial TAC (69%). Additionally, Fig. 2 shows that the number of patients with total TAC, partial TAC and CAC above 100 were 402 (40%), 141 (14%) and 301 (30%), respectively. Thus, the number of participants detected as having aortic calcium was 50% lesser if the measures excluded aortic arch, resulting in a lack of sensitivity for partial TAC, as compared with total TAC assessment.

The comparison of subjects with and without history of non-cardiac vascular event showed that age and gender did not differ (Table 1). Comparison of traditional risk factors showed that hypertension, anti-hypertensive and statin treatment were more frequent ($p < 0.05$, $p < 0.01$, $p < 0.05$), lifelong smoking dose was greater ($p < 0.001$) and total cholesterol was lower ($p < 0.01$) in the group with history of non-cardiac vascular events than in the group without (Table 1). Lastly, total TAC, partial TAC and aortic arch TAC were higher in subjects with history of non-cardiac vascular events



Total TAC includes calcifications from the apex of the heart to the top of the aortic arch. Partial TAC is measured from the apex of the heart until the axial slice that passes through the level of the pulmonary artery bifurcation. Calcifications in the aortic root (below the sinotubular junction) are excluded.

Fig. 1. Definition of total and partial thoracic aorta calcium (TAC).

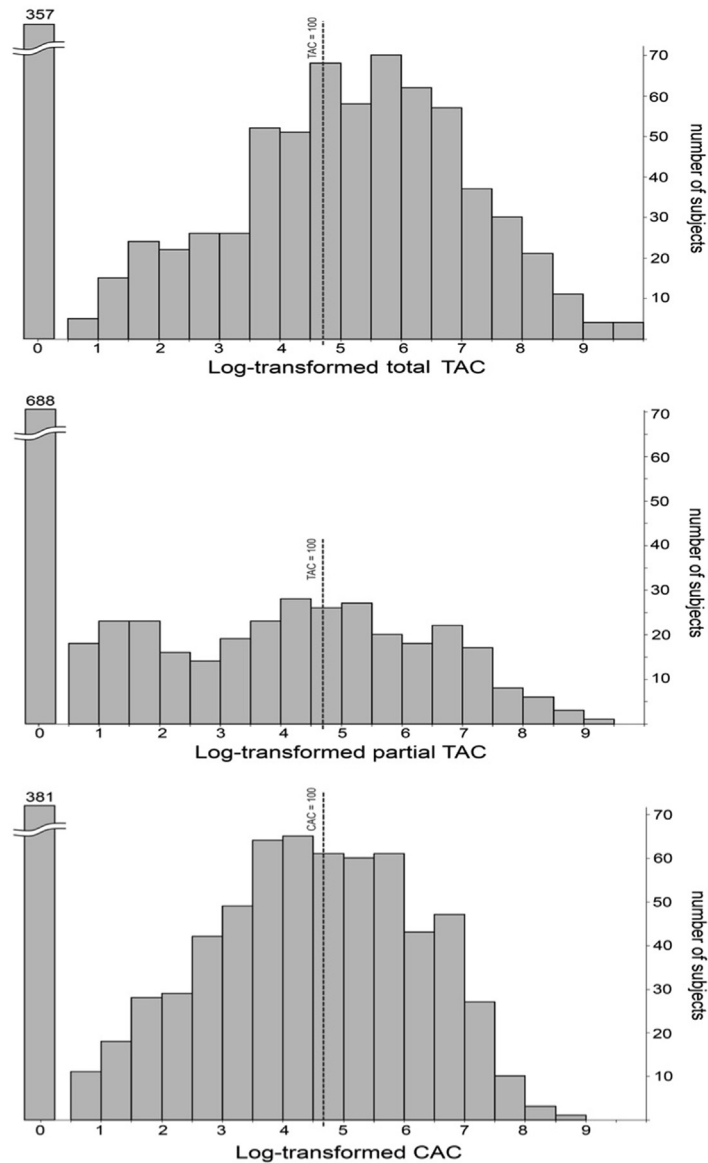
Table 1
Clinical characteristics of the study population.

Parameter	All patients (n = 1000)	History of non-cardiac vascular events		p value (1 vs 2)
		Absence (1) (n = 970)	Presence (2) (n = 30)	
Age, years	57 ± 9	57 ± 9	59 ± 10	NS
Male gender, n (%)	776 (78)	754 (78)	22 (73)	NS
Body mass index, kg/m ²	26 ± 4	26 ± 4	26 ± 4	NS
Hypertension, n (%)	497 (50)	476 (49)	21 (70)	<0.05
Anti-hypertensive treatment, n (%)	446 (45)	425 (44)	21 (70)	<0.01
Systolic pressure, mmHg	124 ± 13	124 ± 13	127 ± 14	NS
Diastolic pressure, mmHg	73 ± 9	73 ± 9	75 ± 10	NS
Hypercholesterolemia, n (%)	823 (82)	796 (82)	27 (90)	NS
Statin treatment, n (%)	527 (53)	506 (52)	21 (70)	<0.05
Total cholesterol, mmol/l	5.19 ± 1.17	5.21 ± 1–17	4.62 ± 1.15	<0.01
Current smoker, n (%)	204 (20)	198 (20)	6 (20)	NS
Lifelong smoking dose, pack yrs	10 [0–25]†	10 [0–25]	30 [15–40]	<0.001
Blood glucose, mmol/l	5.55 ± 1.04	5.55 ± 1.05	5.42 ± 0.66	NS
Diabetes, n (%)	84 (8)	83 (9)	1 (3)	NS
Type of non-cardiac vascular events				
– Cerebrovascular disease, n	17	0	17	
– Peripheral vascular disease, n	13	0	13	
Total TAC value				
– Raw	41 [0–342]	39 [0–333]	282 [28–1809]	<0.01
– Log-transformed	3.33 ± 2.91	3.28 ± 2.89	5.05 ± 2.91	<0.001
Partial TAC value				
– Raw	0 [0–6]	0 [0–5]	4 [0–284]	<0.01
– Log-transformed	1.33 ± 2.30	1.28 ± 2.26	2.84 ± 3.09	<0.001
Aortic arch TAC value				
– Raw	34 [0–290]	33 [0–269]	253 [20–1242]	<0.01
– Log-transformed	3.16 ± 2.83	3.11 ± 2.82	4.77 ± 2.91	<0.001
CAC value				
– Raw	17 [0–149]	16 [0–148]	73 [0–284]	NS
– Log-transformed	2.79 ± 2.57	2.77 ± 2.56	3.57 ± 2.67	NS

Values are number of subjects, n (%) or mean ± SD with range or median [interquartile range]. CAC, coronary artery calcium; NS, non-significant; TAC, thoracic aorta calcium.

than in those without ($p < 0.01$ for raw values and $p < 0.001$ for log-transformed values) but CAC did not differ between both groups (Table 1).

Table 2 shows that the adjusted OR of having a history of non-cardiac vascular events per 1-SD increase in log-transformed calcium value was significant and similar for total TAC (OR [95%



TAC, thoracic aorta calcium; CAC, coronary artery calcium. The raw score threshold of 100 is indicated with a dotted line.

Fig. 2. Distribution of log-transformed total TAC, partial TAC and CAC in the overall study population.

Table 2

Separate logistic regressions of the presence of non-cardiac vascular events on log-transformed calcium values.

Log-transformed parameter	OR	95% CI
Total TAC	1.56†	1.12–2.24
Partial TAC	1.58†	1.12–2.25
Aortic arch TAC	1.47*	1.08–2.06
CAC	1.13	0.86–1.50

Each logistic regression was adjusted for age, gender, total cholesterol, systolic blood pressure, anti-hypertensive and statin treatment. 1-SD increments for log-transformed total TAC, partial TAC, aortic arch TAC and CAC were 1.89, 1.13, 1.79 and 1.71, respectively.

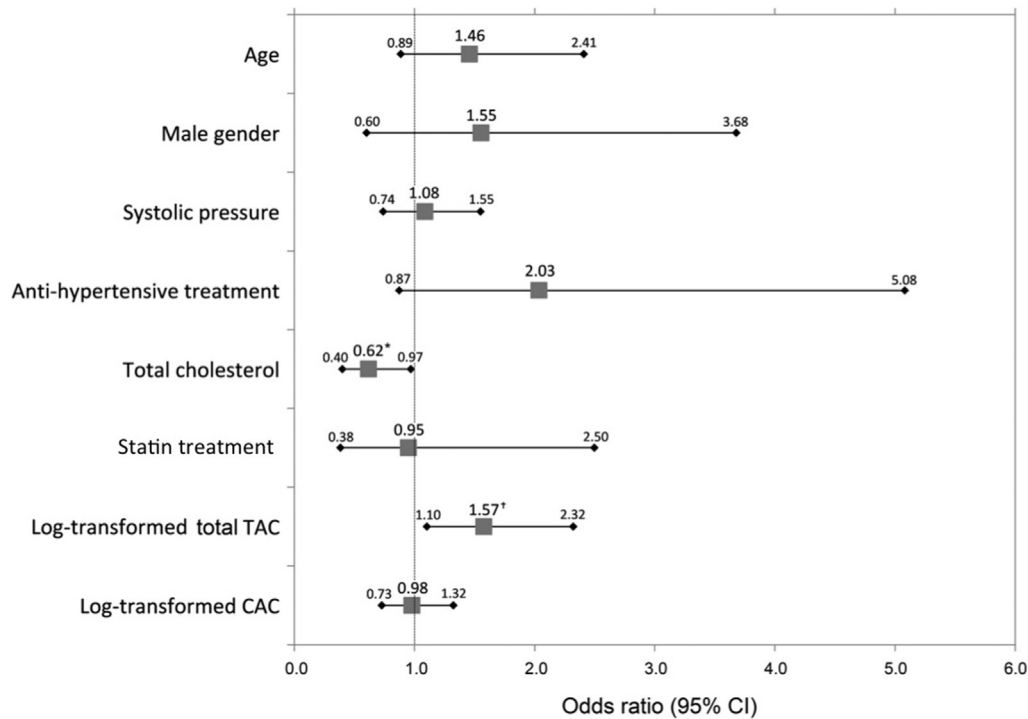
†, $p < 0.01$; *, $p < 0.05$; CAC, coronary artery calcium; CI, confidence interval; SD, standard deviation; TAC, thoracic aorta calcium.

CI] = 1.56 [1.12–2.24], $p < 0.01$), partial TAC (1.58 [1.12–2.25], $p < 0.01$), aortic arch TAC (1.47 [1.08–2.06], $p < 0.05$) but not for CAC (1.13 [0.86–1.50]).

Fig. 3 shows the OR of having history of non-cardiac vascular events by 1-SD increase in each parameter when entering total TAC and CAC together in the logistic regression as well as risk factors. Of all covariates, OR were significant only for total TAC (1.57 [1.10–2.32], $p < 0.01$) and negatively for cholesterol (0.62 [0.40–0.97], $p < 0.05$).

4. Discussion

Our study used an original MSCT-based method that allows determining the amount of calcium in the entire thoracic aorta including aortic arch, concomitantly with the CAC detection



Odds ratios of having non-cardiac vascular events calculated from a logistic regression that included both total TAC and CAC and adjusted for age, gender, total cholesterol, systolic blood pressure and anti-hypertensive and statin medication. Odds ratios were calculated per 1 standard deviation increase of age (9.2 years), systolic pressure (13.5 mmHg), total cholesterol (1.17 mmol/l) and log-transformed TAC and CAC (1.89 and 1.71, respectively).

†, $p < 0.01$; *, $p < 0.05$; CAC, coronary artery calcium; CI, confidence interval; TAC, thoracic aorta calcium.

Fig. 3. Independent association of total TAC with history of non-cardiac vascular events.

procedure.

A first result is the strong association of total TAC with history of non-cardiac vascular event, independently of age, gender and coexisting cardiovascular risk factors. A noteworthy exception to the lack of relation of total TAC with traditional risk factors is provided by total cholesterol found independently and negatively associated with non-cardiac event history. This latter finding likely results from the administration of more intensive statin treatment to patients with vascular events. Several prospective studies [4,10–13] previously showed that CT-assessed TAC predicted cardiovascular complications beyond coronary heart disease. However, most of these studies did not analyze specifically non-cardiac vascular events, but rather global cardiovascular morbidity or mortality, mixing cardiac and non-cardiac events [4,10]. In addition, a few studies pointed out the potential importance of aortic arch calcium in the association of TAC with non-cardiac vascular events. A prospective study in heavy smokers found that TAC was specifically related to the incidence of non-cardiac events including stroke and peripheral arterial disease, especially when calcium was measured in the aortic arch [12]. Another transversal study found specific associations between aortic arch calcium and cerebrovascular disease [14]. Mechanisms that may explain the associations of TAC and non-cardiac vascular events are different whether one considers cerebrovascular events or peripheral arterial disease. The role of atherosclerotic aortic arch plaque was demonstrated in ischemic stroke [23,24] as well as for predicting recurrent stroke [25]. The association of aorta calcium with peripheral arterial disease may involve the extension of thoracic aorta atherosclerosis to the abdominal aorta and its branches [26,27].

Our second finding was that CAC was not associated with non-cardiac vascular events, and the incorporation of CAC in the multivariable model did not attenuate the correlation of total TAC with non-cardiac events. Such findings may be due to that CAC is perhaps more a measure of localized than generalized atherosclerosis [12]. However, some previous studies in the literature showed that CAC predicted overall cardiovascular morbidity and mortality, better than TAC [4,10]. This is somewhat discrepant with our present findings and one explanation may be that these studies did analyze composite cardiovascular disease endpoints incorporating highly prevalent coronary heart disease that is strongly related to CAC. Also, the inferiority of TAC as regards CAC for predicting cardiovascular events in these studies may imply a field of measurement insufficiently long for detecting aortic arch calcium [4,10].

The exclusion of aortic arch calcium from TAC measurement may annihilate its association with cerebrovascular disease and consequently with non-cardiac vascular events, because plaques in the aortic arch were shown to play a major role in the incidence and prevalence of cerebrovascular disease [23–25]. To explore this possibility, we have analyzed whether incorporation or not of aortic arch calcium in the TAC measurement of our subjects had an impact on the association with non-cardiac events. Despite the potential lack of sensitivity of partial vs total TAC for calcium detection (Fig. 2), partial TAC was associated to non-cardiac vascular event with the same strength than total TAC. This finding suggests that measuring total TAC by including aortic arch calcium does not provide incremental information comparatively with partial TAC excluding arch calcium. However, the increased aortic arch calcification burden in patients with non-cardiac vascular events

enhances its potential relevance *per se*.

4.1. Study limitations

First, this study is retrospective and analyzed subjects at risk for cardiovascular disease from whom results cannot be extrapolated to the general population. Second, the radiation dose required by our enlarged field of measurement in order to incorporate aortic arch is greater than the radiation dose when measuring TAC during traditional CAC detection. However, this dose remains weaker than that delivered for a bilateral mammogram.

5. Conclusion

Our study suggests that the assessment of TAC simultaneous with CAC detection may provide complementary information on the extra coronary component of cardiovascular risk, beyond the coronary risk prediction of CAC. However, further studies are required to confirm prospectively this result, as well as to identify the biomarkers involved in the pathogenesis of TAC comparatively to CAC.

Disclosures

None.

Conflict of interest

Any of the authors have actual or potential conflict of interest.

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