Atheromatosis of the Thoracic Aorta as Predictor of Cardiovascular Mortality and Cerebrovascular and Coronary Events

HECTOR ALFREDO DESCHLE [MTSAC 1]; PABLO OBERTI [MTSAC 2]; JORGE LOWENSTEIN [MTSAC 3]; CARLOS RODRÍGUEZ CORREA [* 4]; GASTÓN LANTERNIER [5]; SALVADOR SPINA [* 6]; MARIANO FALCONI [MTSAC 2]; EDUARDO GUEVARA [MTSAC 4]; SILVIA MAKHOUL [* 7]; MARÍA ELENA ADANIYA [MTSAC 9]. COUNCIL ON DOPPLER ECHOCARDIOGRAPHY OF THE ARGENTINE SOCIETY OF CARDIOLOGY.

SUMMARY

Objective
To evaluate the severity of atheromatosis of the thoracic aorta and its relation with mortality and cerebrovascular and coronary events.

Material and Methods
Between 2005 and 2007, 601 patients (ps) were referred for evaluation with transesophageal echocardiography (TEE).
Age: 64.53±13.61 years.
Male gender: 337ps.
The following variables were included:
  Reason for ordering the study: embolic source (37.7%), endocarditis (22.1%), previous to cardioversion (11.5%), mitral valve disease (9.8%), other reasons (18.95%).
  Risk factors: diabetes, smoking habits, hypertension, dyslipemia.
  Presence of atrial fibrillation.
The patients were divided into two groups:
  With uncomplicated aortic plaques < 4 mm: ps = 465.
  With complex aortic atheromatosis (CAA): aortic plaques ≥ 4 mm, with ulcers, thrombi or aortic debris: ps = 36.
Follow-up: 1596 days (mean: 759 days). A total of 520 ps (86.52%) were contacted; the following events were considered: transient ischemic attack or stroke, AMI, angina, revascularization and/or cause of mortality during that period. Multivariate analysis was used to identify independent predictors. A p value < 0.01 was considered statistically significant.

Results
Cardiovascular mortality: 3.2% (13/407 ps) in group a and 18.6% (21/113 ps) in group b (p<0.01). Combined vascular events: 91/407 ps (22.4%) in group a and 45/113 ps (39.8%) in group b (p<0.01). Multivariate analysis showed that CAA was an independent predictor of cardiovascular mortality (OR 4.54, 95% CI 1.52-13.58, p<0.01) and of cerebrovascular and/or coronary events (OR 3.33, 95% CI 1.66-6.67, p<0.01).

Conclusions
In this population, CAA was an independent predictor of cardiovascular mortality and combined vascular events.

REV ARGENT CARDIOL 2011;79:231-237.

Key words > Echocardiography – Atherosclerosis -Aorta

BACKGROUND

Several retrospective studies have demonstrated a relationship between aortic atheromatosis and the occurrence of coronary or cerebrovascular events. In some cases it is considered a marker for generalized atherosclerosis1 while, in others, it is a potential source of embolic events (even retrograde embolism) from a fragment of an atheromatous plaque or, probably, from a thrombus superimposed to an ulcerated plaque.2-4However, the only two population-based studies published up to the present have failed to demonstrate any association, probably because they were conducted on relatively healthy and small populations for the number of events expected.5,6

We think that the extent and aggressiveness of the atherosclerotic disease should not be minimized in a sick population with greater incidence of events.

Patients referred for transesophageal echocardiography (TEE) due to any cause constitute a population who is sicker than the general population and in whom we can perform a very carefully the proximal aorta looking for manifestations of atherosclerotic disease.

The goal of the present study was to establish in a prospective fashion the relationship between the presence, complexity and extent of aortic atheromatosis with cardiovascular mortality and cerebrovascular and coronary hard events.

MATERIAL AND METHODS

From November 2004 to August 2207 601 consecutive patients > 21 years and referred for TEE were enrolled. All the patients signed an informed consent form and accepted to provide the result of the study for further analysis. Duplicate cases (more than one study in the same patient), terminally ill patients and those who refused to participate or provide the information to be contacted were excluded from the study.

The reason of the study, patient's personal data, patient's phone number and that of a close relative were recorded. Patients were asked about the presence of history of coronary artery disease (documented myocardial infarction or hospitalization due to acute coronary syndrome; previous coronary angiography with stenosis >70% of any of the main branches or > 50% of the left main coronary artery), previous stroke (clinical or radiological neurological deficits and/or hospitalization due to transient ischemic attack [TIA]), diabetes (DBT), hypertension (HT) and/or hypercholesterolemia (defined by the results of the laboratory tests or in case of treatment with insulin, hypoglycemic drugs, lipid-lowering agents and/or antihypertensive agents), current smoking, atrial fibrillation (AF) and medication taken. According to smoking habits, patients were divided into three categories: a) non smokers; b) those who had quit smoking more than one year before; and c) those who had been smoking during the last year

The study was conventionally performed using Omni Plane TEE transducers, with frequencies between 3.7 to 7 Mhz. The three segments of the aorta (ascending aorta, aortic arch and descending aorta) were examined in the transverse plane to determine the presence of atheromatous plaques. The following characteristics of the plaques were recorded: location, type (lipid or calcic plaque), size (plaque protruding in the arterial lumen from the intima-media border) and presence of ulcers, thrombus or debris (Figure 1). Both carotid arteries were examined with a 7 MHz linear transducer to measure the intima-media thickness (IMT) or determine the presence of atheromatous plaques. Atheromatous plaque was defined by an IMT > 1.5 mm.7

The patients were divided into two groups: a) patients without atherosclerotic plaques or with uncomplicated aortic plaques with lesions < 4 mm (p = 465), and, b) patients with plaques > 4mm with ulcers, thrombi or aortic debris (complex aortic atheromatosis [CAA]) (p = 136) according to the levels of risk defined by Amarenci et al. 8
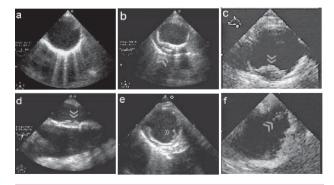
Statistical Analysis

Qualitative variables are expressed as percentages, and compared using chi square test. Quantitative variables are expressed as mean ± standard deviation and compared with Student's t test or by non-parametric methods if required.
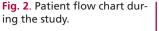
All calculations were performed using Epi-Info software package. Univariate and multivariate analyses were performed to identify predictors of mortality and combined (cerebrovascular and coronary) vascular events. The variables "age" and "gender", and those related with the development of events in the univariate analysis were included in the multivariate model. The variable smoking habits with three options was represented by a dummy variable for logistic regression analysis. The association of the variables with the development of events is expressed as odds ratio with its corresponding 95% confidence interval (CI) and statistical significance. Kaplan-Meier survival curves were used. A p value < 0.05 was considered statistically significant.
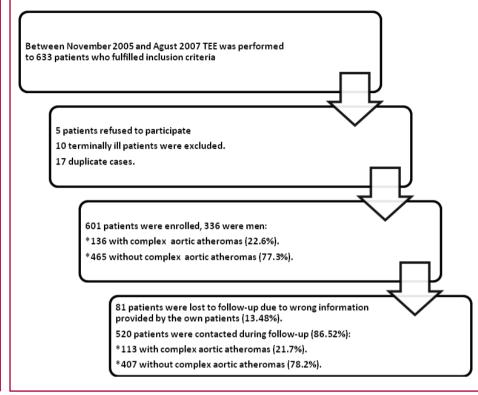
RESULTS

Eighty-one patients were lost during follow-up (81/601, 13.47%). The follow-up period was 1596 days (mean: 759 days; interquartile range: 661 days). During this period, 520 patients (86.52%) or their close relatives were contacted by the principal investigator of each center (Fig. 2). The subjects were asked to answer a previously printed questionnaire about the clinical conditions defined at the moment of enrollment: development of new cerebrovascular events (stroke or transient ischemic attack [TIA]) or coronary events (AMI, hospitalization due to angina, coronary artery bypass graft surgery [CABGS] or percutaneous coronary intervention [PCI]) mortality and its causes. Mean age was 64.53±13.61 years; 337 patients were men. The reasons to order TEE were: detection of an

Fig. 1. Different levels of complexity or aortic atheromatosis. **a** normal aorta; **b** aorta with diffuse atheromatosis; **c** large lipid plaque; **d** long-axis view of an atherosclerotic aortic ulcer; **e** small aortic debris; **f** ulceration of a plaque with aortic debris.

ATHEROMATOSIS OF THE THORACIC AORTA AS PREDICTOR OF CARDIOVASCULAR MORTALITY / Hector Alfredo Deschle et al.

233

embolic source (37.7%), endocarditis (22.1%), before indicating cardioversion (11.5%), mitral valve disease (9.8%) and other conditions (18.95%).

Complex aortic atheromatous plaques were identified in 136 patients (22.6%). Thirty-six patients had CAA in the ascending aorta (26.47%), 79 in the aortic arch (58.08%) and 88 in the descending aorta (64.70%). Table 1 summarizes the characteristics of the population according to the severity of aortic atheromatosis. Table 2 shows the distribution of the aortic atheromatous plaques. There were no significant differences between patients contacted and those lost during follow-up.

Global mortality during follow-up was 13.3% (n =69): 10,8% (44/407) in the group of patients with simple or uncomplicated plaques or with absence of plaques and del 22.1% (25/113) in the group with CAA (OR 2.41, 95% CI 1.38-4.19 p=0.0018). Cardiovascular mortality was 3.2% (13/407) in the group of patients with simple or uncomplicated plaques or with absence of plaques and 18.6% (21/113) in the group with CAA (p<0.01). These differences were statistically significant at univariate and multivariate analysis (OR 4.54, 95% CI 1.52-13.58 p=0.0067). There were 136 combined cardiovascular and/or coronary events; 91 in the group without CAA (91/407; 22.4%) and 45 in the group with CAA (45/113; 39.8%) (p<0.01). This difference was also significant at univariate and multivariate analysis (OR 3.33, 95% CI 1.66-6.67 p=0.0007) (Figure 3 and Table 3).

CAA was an independent predictor of cardiovascular mortality and combined vascular events.

The presence of CAA in the descending aorta also predicted combined vascular events and cardiovascular mortality compared to CAA in the other aortic segments.

The analysis was also performed excluding those patients referred for detection of an embolic source and in the subgroup of patients with suspected endocarditis. In both cases, the presence of CAA was an independent predictor of cardiovascular mortality and combined vascular events (Table 4).
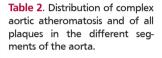
DISCUSSION

The Framingham study had previously reported that the presence of calcic plaques in the thoracic aorta (visualized at the chest-X ray) was associated with increased cardiovascular mortality, even after considering other risk factors.9 Transesophageal echocardiography opened the way to a thorough study of aortic atheromatosis and its characteristics.10-12 Since then, several publications have associated the presence of aortic atheromatous plaques with coronary artery disease13 and combined cardiovascular events.14,15 TEE allowed to differentiate plaques < 4 mm from protruding plaques with intima thickness > 4mm, with ulcers or thrombosis. The latter are specially associated with vascular events.16-19 In our environment, Pérez E. et al. evaluated the presence of diffuse atheromatosis in a study20 and intima-media thickness in other,21finding a greater incidence or events among those with more severe lesions. The limitations of these studies were that they were retrospective and included only patients who had previously suffered an event. Only the last study21

	Absence of plaque or plaque < 4 mm (n = 465)	Complex aortic atheromatosis (n=136)	P
Age	62.6±13.9	70.9±10.0	0.001
Male gender	256 (55.1%)	80 (58.8%)	0.436
Previous stroke	70 (15.1%)	36 (26.5%)	0.002
DBT	53 (11.4%)	30 (22.1%)	0.002
DLP	198 (42.6%)	63 (46.3%)	0.439
Receiving statins	140 (30.1%)	47 (34.6%)	0.324
SH	49 (10.5%)	14 (10.3%)	0.740
CAD	81 (17.4%)	38 (27.9%)	0.007
HT	293 (63.0%)	109 (80.1%)	0.001
Recieving antihypertensive agents	256 (55.1%)	93 (68.4%)	0.006
AF	106 (22.8%)	19 (14.0%)	0.026
Receiving anticoagulant agents	128 (27.1%)	28 (20.6%)	0.105
Receiving antiplatelet therapy	212 (45.6%)	71 (52.2%)	0.174

Table 1. Characteristics of the population according to the severity of aortic atheromatosis.

	Plaques	Age	CAA	Age
Ascending Ao	24p (4.0%)	68.2±12.0	14p (2.3%)	70.3±9.9
Aortic arch	25p (4.2%)	63.1±10.3	31p (5.2%)	68.2±11.4
Descending Ao	61p (10.1%)	65.3±10.9	36p (6.0%)	70.3±10.1
Ascending Ao + aortic arch	15p (2.5%)	65.8±8.6	3p (0.5%)	76.0±7.5
Ascending Ao +descending Ao.	33p (5.5%)	71.9±7.8	7p (1.2%)	73.9±10.0
Aortic arch + descending Ao	107p (17.8%)	69.6±11.1	33p (5.5%)	71.5±9.3
Ascending Ao + aortic arch + descending Ao	124p (20.6%)	72.7±9.6	12p (2.0%)	76.6±6.8

Table 2. Distribution of complex aortic atheromatosis and of all plaques in the different segments of the aorta.
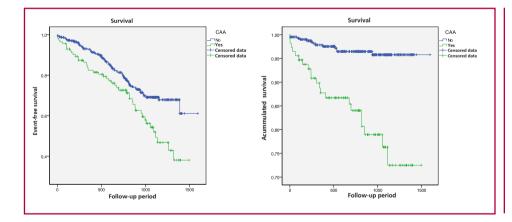

Fig. 3. Cardiovascular mortality and vascular event-free survival based on the presence or absence of CAA in both graphs.

prospectively included 25% of the patients analyzed. In 2004, Meisnner I. et al. published a population-based study of 585 persons with a mean follow-up of 5 years, and found a significant association between the presence of complex plaques and cardiac or cerebrovascular events after correcting by risk factors.5 This study deserves to be praised as it was the first performed in the general population including a large number of participants (it is not easy to enroll people from the general population to undergo a TEE).

However, this study has few limitations. Firstly, as Tunick P. reported in a letter from the readers,22 they did not report the aortic segment with atheromatous lesions. As the lesions are most common in the descending aorta, and those in the ascending aorta or aortic arch are more probable responsible for embolic stroke, the study has less reliability. Secondly, and although the number of participants is high considering the study was conducted on the general population, most of them were healthy subjects with a

Table 3. Analysis of cardiovascular mortality and combined cerebrovascular and coronary events. Those variables with statistical significance are underlined.

Variable	Cardiovascular mortality				Combined events			
	OR	95%	CI	P	OR	95%	CI	P
CAA	4.5477	1.5221	13.5877	0.0067	3.3336	1.6647	6.6754	0.0007
Carotid atheromatosis	1.2158	0.3325	4.4459	0.7677	0.9014	0.4350	1.8677	0.7800
DBT	1.1023	0.3033	4.0059	0.8824	1.0863	0.4738	2.4904	0.8450
DLP	0.5165	0.1327	2.0103	0.3407	1.0319	0.4327	2.4608	0.9436
HT	1.3995	0.4115	4.7596	0.5904	1.3440	0.6113	2.9549	0.4621
More than 1 year without smoking	0.8166	0.2587	2.5773	0.7297	0.9574	0.4544	2.0170	0.9088

Table 4. Analysis of cardiovascular mortality and combined cerebrovascular and coronary events excluding patients referred to detect embolic source and in those with suspected endocarditis. Those variables with statistical significance are underlined.

	Events according to indication of the study							
	Excluding patients referred to detect embolic source				Patients referred with suspected endocarditis			
	Cardiovascular mortality		Combined events		Cardiovascular mortality		Combined events	
Variable	OR	P	OR	P	OR	P	OR	P
CAA	7.1	0.0082	5.4	0.0019	51.0	0.0062	10.2	0.0042
DBT	1.0	0.9621	0.7	0.557	0.7	0.7976	1.9	0.5371
DLP	0.5	0.4555	0.6	0.4418	7.0	0.2004	1.6	0.6565
HT	0.6	0.5521	0.9	0.7699	1.2	0.9161	2.1	0.4791
More than 1 year without smoking	0.8	0.752	1.0	0.974	1.0	0.9858	0.5	0.4181

low probability of events.

This publication had a remarkable impact; yet other studies published later found that CAA is responsible for almost 82% of the recurrences of stroke of unknown origin.23,24 In 2006, a group from the Mayo Clinic reported that aortic debris is not a risk factor for cryptogenic ischemic stroke or transient ischemic attack but is a marker for generalized atherosclerosis and well-established atherosclerotic and cardioembolic mechanisms of cerebral ischemia.1In the same year, Ward R. et al. considered CAA as an independent predictor of cardiovascular mortality.25

More recently, several publications either agree26-30 or disagree 6about the predictive value of CAA.

Although our study was not population-based, it was prospective and included 601 patients referred to TEE due to diverse causes. However, the most common indication of TEE was detection of embolic source in 37.7% of patients, revealing the higher prevalence of disease in this subgroup.

Multivariate analysis demonstrated that the relationship between CAA and cardiovascular mortality was significantly high; it is also significant regarding the development of cerebrovascular and coronary events, yet a little lower. This significance persists even when patients referred for detection of embolic source are excluded or when only the

subgroup of patients with suspected endocarditis are analyzed. The latter finding reinforces our results.

We also analyzed separately CAA in the ascending aorta, aortic arch or descending aorta and found a relation between events and CAA in the latter segment. This might be due to less incidence of CAA in the first two segments, as CAA might be a marker of generalized atheromatosis rather than an embolic source, as we have previously mentioned.

In summary, we think that the discussion is still open; yet, in patients referred to TEE, the presence of CAA is a marker of risk for cardiovascular mortality and future vascular events. Further and more complex population-based studies including more number of subjects with longer follow-up periods are needed.

Study Limitations

Firstly, the fact that 13.48% of patients were lost to follow-up was a limitation, even though the characteristics of these patients were similar to those followed-up. In most cases the contact telephone number was wrong or non-existent. In this case, loss to follow-up can be considered eventful and, thus, there is a 90% of probability that the real OR is within the CI (with 86.5% of patients followed-up).31

Other limitation was that one third of patients were referred to detect embolic source, meaning that these patients were more prone to suffer events. However, the analyses performed excluding these patients or

those considering only subgroups still showed that CAA had predictive value for the events analyzed.

RESUMEN

Ateromatosis de la aorta torácica: su valor como predictora de mortalidad cardiovascular y eventos vasculares cerebrales y coronarios

Objetivo

Evaluar la gravedad de la ateromatosis de la aorta torácica y su relación con la mortalidad y los eventos vasculares cerebrales y coronarios.

Material y métodos

Entre 2005 y 2007 ingresaron prospectivamente 601 pacientes (p) enviados para ecocardiograma transesofágico (ETE).

Edad: 64,53±13,61 años.

Sexo masculino: 337 p.

Se registró:

Motivo del estudio: foco embolígeno (37,7%), endocarditis (22,1%), precardioversión (11,5%), valvulopatía mitral (9,8%), otros (18,95%).

Factores de riesgo: diabetes, tabaquismo, hipertensión arterial, dislipemia.

Presencia de fibrilación auricular.

Los p fueron agrupados en:

a. Con placas aórticas <4 mm y no complicadas: p = 465.

b. Con placas ≥ 4 mm y/o ulceradas, con trombos o debris (ateromatosis aórtica compleja [AAC]): p = 136.

Seguimiento: 1596 días (media: 759 días). Se contactaron 520 p (86,52%), considerándose los siguientes eventos: accidente cerebrovascular transitorio o permanente, IAM, angina, revascularización y/o causa de muerte en dicho período. Se utilizó el análisis multivariado para hallar predictores independientes. Se consideró significativa un p < de 0,01.

Resultados

Mortalidad cardiovascular: 3,2% (13/407 p) en el grupo a y 18,6% (21/113 p) en el grupo b (p < 0,01).

Eventos vasculares combinados: 91/407 p (22,4%) en el grupo a y 45/113 p (39,8%) en el grupo b (p < 0,01).

En el análisis multivariado, la AAC fue predictora independiente de mortalidad cardiovascular (OR 4,54, 95% IC 1,52-13,58 p < 0,01) y de eventos vasculares cerebrales y/o coronarios (OR 3,33, 95% IC 1,66-6,67 p < 0,01).

Conclusión

En esta población, la AAC fue predictora independiente de mortalidad cardiovascular y de eventos vasculares combinados.

Palabras clave > Ecocardiografia - Aterosclerosis - Aorta

BIBLIOGRAPHY

1. MPetty GW, Khandheria BK, Meissner I, Whisnant JP, Rocca WA, Sicks JD, et al. Population-based study of the relationship between atherosclerotic aortic debris and cerebrovascular ischemic events. Mayo Clin Proc 2006;81:609-14.

2. Casella G, Greco C, Perugini E, Pallotti MG, Pavesi PC, Di Pasquale G. Atheromatosis of the thoracic aorta and risk of stroke. G Ital Cardiol (Rome). 2006;7:309-16.

3. De Castro S, Rasura M, Di Angelantonio E, Beccia M, Passaseo I, Di Lisi F, et al. Distribution of potential cardiac sources of embolism in young and older stroke patients: implications for recurrent vascular events. J Cardiovasc Med (Hagerstown) 2006;7:191-6.

4. Kronzon I, Tunick PA. Aortic atherosclerotic disease and stroke. Circulation 2006;114:63-75.

5. Meissner I, Khandheria BK, Sheps SG, Schwartz GL, Wiebers DO, Whisnant JP, et al. Atherosclerosis of the aorta: risk factor, risk marker, or innocent bystander? A prospective population-based transesophageal echocardiography study. J Am Coll Cardiol. 2004;44:1018-24.

6. Russo C, Jin Z, Rundek T, Homma S, Sacco RL, Di Tullio MR. Atherosclerotic disease of the proximal aorta and the risk of vascular events in a population-based cohort: the Aortic Plaques and Risk of Ischemic Stroke (APRIS) study. Stroke 2009;40:2313-8.

7. Touboul PJ, Hennerici MG, Meairs S, Adams H, Amarenco P, Bornstein N, et al. Mannheim carotid intima-media thickness consensus (2004-2006). An update on behalf of the Advisory Board of the 3rd and 4th Watching the Risk Symposium, 13th and 15th European Stroke Conferences, Mannheim, Germany, 2004, and Brussels, Belgium, 2006. Cerebrovasc Dis 2007;23:75-80.

8. Amarenco P, Cohen A, Tzourio C, Bertrand B, Hommel M, Besson G, et al. Atherosclerotic disease of the aortic arch and the risk of ischemic stroke. N Engl J Med 1994;331:1474-9.

9. Witteman JC, Kannel WB, Wolf PA, Grobbee DE, Hofman A, D'Agostino RB, et al. Aortic calcified plaques and cardiovascular disease (the Framingham Study). Am J Cardiol 1990;66:1060-4.

10. Tunick PA, Kronzon I. The improved yield of transesophageal echocardiography over transthoracic echocardiography in patients with neurological events is largely due to the detection of aortic protruding atheromas. Echocardiography 1992;9:491-5.

11. Kutz SM, Lee VS, Tunick PA, Krinsky GA, Kronzon I. Atheromas of the thoracic aorta: A comparison of transesophageal echocardiography and breath-hold gadolinium-enhanced 3-dimensional magnetic resonance angiography. J Am Soc Echocardiogr 1999;12:853-8.

12. Reynolds HR, Tunick PA, Kronzon I. Role of transesophageal echocardiography in the evaluation of patients with stroke. Curr Opin Cardiol 2003;18:340-5.

13. Fazio GP, Redberg RF, Winslow T, Schiller NB. Transesophageal echocardiographically detected atherosclerotic aortic plaque is a marker for coronary artery disease. J Am Coll Cardiol 1993;21:144-50.

14. Tunick PA, Rosenzweig BP, Katz ES, Freedberg RS, Perez JL, Kronzon I. High risk for vascular events in patients with protruding aortic atheromas: a prospective study. J Am Coll Cardiol. 1994;23:1085-90.

15. Deschle H, Salazar A, Pissinis R, Carrascosa P, Carrascosa J. Ateromatosis de la aorta torácica: su valor como predictor de eventos coronarios y cerebrales. Rev Argent Cardiol 2004;72:133 (Abstract 83).

16. Mitusch R, Doherty C, Wucherpfennig H, Memmesheimer C, Tepe C, Stierle U, et al. Vascular events during follow-up in patients with aortic arch atherosclerosis. Stroke 1997;28:36-9.

17. Tunick PA, Kronzon I. Atheromas of the thoracic aorta: clinical and therapeutic update. J Am Coll Cardiol 2000;35:545-54.

18. Agmon Y, Khandheria BK, Meissner I, Schwartz GL, Petterson TM, O'Fallon WM, et al. Relation of coronary artery disease and cerebrovascular disease with atherosclerosis of the thoracic aorta in the general population. Am J Cardiol 2002; 89:262-7.

19. Macleod MR, Amarenco P, Davis SM, Donnan GA. Atheroma of the aortic arch: an important and poorly recognised factor in the aetiology of stroke. Lancet Neurol 2004;3:408-14.

20. Perez E, Hecht G, Harwicz P, Zimmerman E. Ateromatosis aortica: un indicador de riesgo cardiovascular. Rev Argent Cardiol 2000;68:255-61.

21. Perez D, Casas CH, Harwicz P, Zimmermam E, Hecht G. Cuantificación de la ateromatosis aórtica por eco transesofágico y su implicancia pronóstica. Rev Argent Cardiol 2004;72:30-5.

22. Tunick PA, Kronzon I. Atherosclerosis of the aorta: a risk factor, risk marker, or an innocent bystander? J Am Coll Cardiol 2005;45:1907.

23. Fujimoto S, Yasaka M, Otsubo R, Oe H, Nagatsuka K, Minematsu K. Aortic arch atherosclerotic lesions and the recurrence of ischemic stroke. Stroke 2004;35:1426-9.

24. Pujadas R, Arboix A, Anguera N, Oliveres M, Massons J, Comes E. Role of complex aortic atheroma plaques in the recurrence of

unexplained cerebral infarction. Rev Esp Cardiol 2005;58:34-40.

25. Ward RP, Don CW, Furlong KT, Lang RM. Predictors of long-term mortality in patients with ischemic stroke referred for transesophageal echocardiography. Stroke 2006;37:204-8.

26. Bugnicourt JM, Chillon JM, Tribouilloy C, Canaple S, Lamy C, Massy ZA, et al. Relation between intracranial artery calcifications and aortic atherosclerosis in ischemic stroke patients. J Neurol 2010;257:1338-43.

27. Harloff A, Simon J, Brendecke S, Assefa D, Helbing T, Frydrychowicz A, et al. Complex plaques in the proximal descending aorta: an underestimated embolic source of stroke. Stroke 2010;41:1145-50.

28. Gupta N, Lau C, Al-Dehneh A, Daoko J, Vazir A, Parikh R, et al. Importance of performing transesophageal echocardiography in acute stroke patients older than fifty. Echocardiography 2010;27:1086-92.

29. Harloff A, Strecker C, Dudler P, Nussbaumer A, Frydrychowicz A, Olschewski M, et al. Retrograde embolism from the descending aorta: visualization by multidirectional 3D velocity mapping in cryptogenic stroke. Stroke 2009;40: 1505-8.

30. Di Tullio MR, Russo C, Jin Z, Sacco RL, Mohr JP, Homma S; Patent Foramen Ovale in Cryptogenic Stroke Study Investigators. Aortic arch plaques and risk of recurrent stroke and death. Circulation 2009;119:2376-82.

31. Kristman V, Manno M, Côté P. Loss to follow-up in cohort studies: how much is too much? Eur J Epidemiol 2004;19:751-60.