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Background

Ascending aorta (ASC) dilatation (AAD) is a common finding in arterial hypertension, affecting about 15% of hypertensive patients. AAD is associated with an increase in cardiac and vascular hypertension-related organ damage, but its prognostic role is unknown. The aim of the study was to evaluate the prognostic value of AAD as predictor of cardiovascular events in essential hypertensive patients.

Methods

Recruited patients underwent two-dimensional transthoracic echocardiography from 2007 to 2013 and followed-up for cardiovascular events until November 2018 by phone call and hospital information system check. ASC diameter and AAD were defined using both absolute and scaled definitions. Four hundred and twenty-three hypertensive patients were included in our study.

Results

During a median follow-up of 7.4 years (interquartile range 5.6–9.1 years), 52 events were observed. After adjusting for age, sex and BSA, both ASC diameter and AAD definition, according to ARGO-SIIA project, resulted associated with a greater risk of cardiovascular event (both $P < 0.010$), even after adjusting for major confounders (both $P < 0.010$). Moreover, we observed that the assessment of ASC improves risk stratification compared with pulse wave velocity alone, and that in absence of AAD, sinus of valsalva dilatation lost any prognostic value (P ¼ 0.262).

Conclusions

ASC diameter and AAD are both associated with a greater risk of cardiovascular events. ASC should be

assessed to optimize risk stratification in hypertensive patients and its dilatation may be considered as a surrogate for vascular organ damage.

Keywords: arterial hypertension, ascending aorta, ascending aorta dilatation, prognosis, transthoracic echocardiography.

Abbreviations: AADa, ascending aorta dilatation according to ARGO-SIIA project; ASC, ascending aorta; ASCh0.5, ascending aorta diameter/height0.5; ASCi0.4, ascending aorta diameter/BSA0.4; eGFR, estimated glomerular filtration rate; ICD, implanted cardioverter defibrillator; LVH, left ventricular hypertrophy; LVMi, left ventricular mass index; PWV, pulse wave velocity; SOV, sinus of Valsalva diameter; SVD, sinus of Valsalva dilatation according to z-score; TIA, transient ischemic attack; TTE, transthoracic echocardiography.

Introduction

The ascending aorta (ASC), the aortic segment between sinotubular junction and the aortic arch, is frequently found dilated in patients with hypertension: about 15% of hypertensive patients present this condition [1]. Ascending aorta dilatation (AAD) has been associated with hypertension mediated organ damage (HMOD) hypertensive patients with AAD have an increased arterial stiffness (as measured by carotid– femoral pulse wave velocity, PWV) [1] and a three times greater prevalence of left ventricular (LV) hypertrophy (LVH) compared with individuals without this condition [1]. The dilatation of the first tract of the proximal aorta, sinuses of Valsalva diameter (SOV), has so far received more attention: it has recently been observed that the dilatation of SOV (SVD) has prognostic value both in patients with hypertension [2] and in patients with LVH [3]. Conversely, the predictive value of AAD in terms of cardiovascular events has not yet been assessed. Therefore, in this study we aimed to evaluate the prognostic role of AAD in predicting the risk of cardiovascular events in a population of hypertensive patients.

Methods

Patients evaluated for cardiovascular damage at the tertiary Hypertension Unit of the University of Turin between December 2007 and November 2013 were prospectively enrolled; and the assessment of cardiovascular damage was carried out through standard clinical evaluation, transthoracic echocardiography (TTE) and arterial stiffness assessment with carotid– femoral PWV. Patients aged at least 18, free of previous myocardial infarction (MI), significant valvular disease (more than mild regurgitation/stenosis), primary cardiomyopathies, atrial fibrillation, bicuspid aortic valve, medical history indicative of connective tissue disease or secondary hypertension were considered for the study. We recruited individuals for whom ASC obtained by TTE on first visit was available. The study was approved by our local ethic committee (Comitato Etico Interaziendale A.O.U. Città della Salute e della Scienza di Torino – A.O. Ordine Mauriziano – A.S.L. CDT – CEI/330) and all patients provided written informed consent to participate in this study. All patients underwent blood pressure (BP) measurements according to the recommendations of the European Society of Hypertension/European Society of Cardiology [4]. All BP measurements were performed using a validated semiautomatic sphygmomanometer (Omron Matsusaka, Kyoto, Japan) with an appropriately sized cuff after 5 min in a quiet room. The average of three consecutive measurements was used in the analysis. Estimated glomerular filtration rate (eGFR) was calculated by Cockroft–Gault formula [5]. Patients have been split into three groups according to pharmacotherapy: no drugs, group A (up to three drugs none of which diuretic or up to two drugs including a diuretic) and group B (three drugs, including a diuretic, or more).

Echocardiography

TTE was performed by experienced operator with a commercially available machine (IE33; Philips, Amsterdam, The Netherlands) equipped with a S5 probe for two-dimensional and Doppler acquisition. All patients underwent a complete echocardiographic evaluation by means of standard two-dimensional

acquisitions, particularly focused on the aortic root at the level of SOV and at the level of the ASC [6]. ASC diameter has been measured at level of the maximum identifiable dilatation point following the leading edge to leading edge convention. All echocardiographic measurements were performed following the current international recommendations [7]. For subsequent analysis ASC diameter was scaled by allometric indexes (height0.5 and BSA0.4). AAD was defined following three different methods: first, an ASC diameter more than 36 mm for female and 41 mm for male patients (AADa) [8]; second, an ASC diameter indexed to height0.5 (ASCh0.5) exceeding the 75th percentile of the population distribution; third, an ASC diameter indexed to BSA0.4 (ASCi0.5) exceeding the 75th percentile of the population distribution. In the last two methods the 75th percentile has been arbitrarily chosen as a threshold. Predicted SOV was obtained from age, sex and height as previously reported [9]. SOV diameter z-score (SOVz) was generated by the difference between observed SOV and predicted SOV, divided by sex specific SD of observed SOV. SOVz exceeding the 75th percentile of the population distribution was considered as SVD [2]. LVH was defined as LV mass (LVM) normalized for BSA [LVM index (LVMi)] more than 95 g/m2 in women or more than 115 g/m2 in men [7]. Left atrial enlargement (LAe) was defined as left atrial volume normalized for BSA (LAVi) more than 34 ml/m2 [7]. BSA was calculated using the Dubois & Dubois formula: BSA ¼ 0.20247 [weight 0.425 (height/100) 0.725] [10].

Aortic stiffness

Arterial stiffness was assessed using carotid– femoral PWV, which has been assessed by applanation at both carotid and femoral arteries, currently considered the gold standard method [11]. From the pulse wave profile acquired at the level of the radial artery, through pulse wave analysis the values of central SBP and central DBP were obtained. A validated instrument was used (SphygmoCor System; AtCor Medical, Sydney, New South Wales, Australia). PWV was considered normal if less than 10 m/s [12].

Outcome

The primary outcome of this study was a composite of first cardiovascular event, defined as: nonfatal MI, nonfatal stroke, sudden cardiac death, heart failure requiring hospitalization, transient ischemic attack (TIA), coronary revascularization, unstable angina (meant as typical symptoms and ECG changes without significant troponin movement, which underwent coronary angiography and possibly revascularization), need for surgery involving aorta or its major branches, implanted cardioverter defibrillator (ICD) implantation and arrhythmias (atrial fibrillation and major ventricular arrhythmias). The event identification occurred on November 2018 and was based on chart review from clinical documentation present on the electronic medical record within our hospital system (AOU Città della Salute e della Scienza di Torino, TrackCare, InterSystems Corporation, Milano, Italy), the Hypertension Centre of the University of Torino (HyperMacondo) and direct telephone contact with all the patients.

Statistical analysis

The analysis was performed by using a dedicated software (R: A Language and Environment for Statistical Computing, v4.0.0 for Mac OSX, R Core Team., Vienna, Austria). The normal distribution of variables was verified by graphical evaluation (histogram and Q–Q graph) and Shapiro–Wilk test. Data were presented as ‘mean ±SD’ or ‘median (interquartile range)’ and as ‘observations (percentage frequency)’ as appropriate. Continuous variables were compared by t test or Mann–Whitney test, while categoric ones by the x2 test. Allometric indexes to scale ASC diameter have been computed as follow: logarithmic transformation of the formula Y ¼ aXb was performed and scaling exponents obtained by linear regression. The equality of scaling exponents between sexes was assumed. The homoscedasticity and normality of residual variance were tested using the Breusch–Pagan/Cook–Weisberg tests and the Shapiro–Wilk tests, respectively. Univariate Cox regression analysis was performed for all clinical variables and penalized model has been performed for selecting variables to be included in the multivariate Cox model. Different AAD definitions have also been tested by correcting for age, sex and BSA. A P value less than 0.05 for two-tail tests was considered significant

in all statistical analysis.

RESULTS

Overall population

Out of 627 hypertensive patients evaluated, 493 (78.6%) had available ASC diameter and met inclusion/exclusion criteria. The drop out was 8.5% and follow-up data were available for 423 patients. PWV data were available in only 360 individuals due to the exclusion of patients with low quality acquisition or noncompliance to the exam. Demographic features of the study population divided by presence of AADa is summarized in Table 1. AADa was found in 16.1% of study population. Patients with AADa were older [62.2 ± 10.9 vs. 51.2 ± 12.5 years] than the ones without AADa and presented a longer history of hypertension [6.00 (2.00–12.5) vs. 11.0 (5.00–19.0) years, P < 0.001], a worse eGFR [90.6 ± 26.8 ml/min vs. 103.4 ± 29.6 ml/min, P ¼ 0.004], and higher cardiovascular risk, obtained by both Systemic Coronary Risk Evaluation [13] and Framingham [14] scores. No differences were found between AADa groups with regard to peripheral or central BP, but patients with AADa showed higher aortic augmentation index (23.0 ± 11.5 vs. 28.5 ± 10.0%, P < 0.0.001). Table 2 displays echocardiographic features in different AADa groups. Patients with AADa presented a greater prevalence of LVH, particularly with concentric geometry, LAe, SVD, PWV more than 10 m/s and higher values of mean E/tdiE (P < 0.050 for all). No differences in ejection fraction were observed.

Survival analysis

During a median follow-up of 7.4 years (5.6–9.1 years) 52 events occurred: 19 among patients with AADa and 33 among patients without AADa (27.9 vs. 9.3%, P < 0.001). In particular we observed 16 atrial fibrillations (30.8%), 13 MIs (25.0%), six coronary revascularizations (11.5%), six surgeries involving aorta or its major branches (11.5%), four ICD implants (7.6%), three strokes (5.7%), three TIA (5.7%), one unstable angina (1.9%) (Supplementary Table A, http://links.lww.com/HJH/ B535). In univariate Cox regression and after adjusting for age, sex and BSA, the increasing of ASC diameter, as well as ASCh0.5 and ASCi0.4, resulted related to a greater risk of event (P < 0.001 for all) [Fig. 1a, Supplementary Table B(a) and (b), http://links.lww.com/HJH/B536]. Similar outcomes were obtained for the presence of AAD defined according to different criteria (ARGO-SIIA project, height0.5 and BSA0.4) (P < 0.05 for all). Univariate Cox regression was performed for all demographic and echocardiographic variables investigated (Supplementary Tables C and D, http://links.lww.com/HJH/ B537, http://links.lww.com/HJH/B538): variables which showed to be associated with event (age, hypertension duration, wash-out from antihypertensive drugs, pharmacotherapy group A, eGFR, LAVi, PWV, ASC diameter, Framingham score risk) were included in a penalized regression to perform variables selection. As shown in Table 3, selected variables have been hypertension duration, eGFR and PWV in the case of ASC [hazard ratio ¼ 1.13 (1.04–1.23), P ¼ 0.005], and hypertension duration, eGFR and PWV more than 10 m/s in the case of AADa [hazard ratio ¼ 2.58 (1.47–4.54), P ¼ 0.001]. Both ASC diameter and AADa (Fig. 1b) resulted associated with greater risk of event after correction for these variables. Similar results were obtained for all others diameter indexation and for all AAD definitions considered (Supplementary Tables E(a)–(b), http://links.lww.com/HJH/B539). Adding LVMi and mean E/tdiE to confounders didn't affect ASC significance in predicting cardiovascular events (data not shown). In Fig. 2 survival curves of a first model including AADa and PWV more than 10 m/s are displayed. In Kaplan–Meier analysis presenting AADa alone (AADa +/ PWV–) (P = 0.024) conferred a higher risk of event compared with patients with no AADa nor PWV more than 10 m/s (AADa–/ PWV–). Furthermore, the presence of both conditions (AADa+/PWV+) was associated with a greater risk of event than both AADa and PWV more than 10 m/s alone (P= 0.036 and 0.006, respectively). Survival curves of a second model including AADa and SVD are show in Fig. 3. Presence of AADa (with or without SVD) resulted in a greater risk of event than no dilatation on either levels (AADa–/SVD–) (P < 0.001) and SVD alone (AADa–/SVD+) (P= 0.026).

DISCUSSION

The current study is to the best of our knowledge the first one to evaluate the prognostic value of AAD in hypertensive patients. Our main findings can be summarized as follows: first, in our population of hypertensive patients, increasing ASC diameter and AAD according to ARGO-SIIA definition resulted associated with a greater risk of cardiovascular events; second, AADa seemed to be able to stratify cardiovascular risk in patients without PWV more than 10 m/s; third, the prognostic value of proximal aorta dilatation could depend on the presence of AAD, since in its absence, SVD seemed to not be able to predict patients' risk of cardiovascular events in our population. Ageing has been proven to cause an alteration in physiological elastic property of aortic vessel, which may occur in the form of aortic remodelling and dilatation [1,15]. In agreement with this evidence, in our study patients who presented AADa were on average 10 years older and with a longer arterial hypertension history than patients without aortic enlargement. Our work seems to confirm the marginal role, among hypertensive patients, of both peripheral and central BP on aortic remodelling, as previously reported in literature [1,16]. On the other hands surrogates of arterial stiffness are reported to be significant determinant of aortic remodelling [1], and our results seem to support this hypothesis. Patients with AADa showed a higher rate of established cardiovascular risk factors, such as LVH, LAe and PWV more than 10 m/s, supporting previous evidences of a role of AAD in cardiovascular risk stratification [1,8]. In particular LVMi, arterial stiffness (in terms of PWV) and ASC dimension could be considered as three different anatomical expression of the same adaptive phenomenon. Hypertension, such as ageing, are associated with an increase in arterial stiffness (in form of PWV) [17], affecting the summation between incident and reflexed pulse pressure waves at aortic root level [18,19]. This complex interplay leads to a mismatch between cardiac output and vascular impedance with consequent LVH and AAD, as recently suggested [8,20]. Nevertheless, the prognostic value of the AAD has never been specifically studied. In our population ASC dimension showed a significant prognostic value, even when corrected for main diameter itself (Table 3a), but even for ASC ASCi0.4 and ASCh0.5 (Supplementary Tables E(a)–(b), http://links.lww.com/HJH/B539), providing a strong evidence that ASC dimensions have a significant role in cardiovascular risk stratification. In this perspective, AAD definition proposed by ARGO-SIIA project resulted clinically effective in identifying at-risk patients, and the same was true for dilatation of the ASC as defined based on other criteria (AAD according to height0.5 and ASCi0.4). Although aortic dimensions and PWV, as previously discussed, can be thought of two different ways to describe the same phenomenon, the information they provide is not necessarily equivalent, as proven by the fact that the presence of both AADa and PWV more than 10 m/s is a more powerful predictor of cardiovascular events compared with the presence of either one alone. Moreover, since AADa alone resulted able to stratify cardiovascular risk in patients with both presence or absence of PWV more than 10 m/s, combined with greater availability of TTE technology, relatively short time needed for ASC diameters acquisitions and measurements compared with the dedicated instrument for PWV assessment, suggests that ascending aortic dimensions should be considered as marker for vascular organ damage in routine evaluation of cardiovascular risk. The prognostic role of the proximal aorta dilatation has already been proven in several studies at the level of SOV. SVD has been shown to be an additional risk factor in patients with LVH [3] and an independent cardiovascular risk factor in patients without LVH [2] and older than 65 years [21]. In our population SVD resulted effective in cardiovascular risk stratification only when associated with AADa as well (Fig. 3), suggesting ASC enlargement to be the main determinant in prognostic value of aortic root dilatation. The pathophysiological basis of these findings is not yet completely understood, although differences in microscopic structure and mechanical characteristics between ASC and SOV has been proven. Biomechanical experiments proved that ASC has a greater compliance, with more gradual variation after mechanical stretching compared with SOV [22]. Also morphometric and hemodynamic determinants exert a different role in determining the diameters of these different sectors of the aorta [23]: for example, males tend to have larger SOV than females, whereas the BSA-indexed diameter of the ASC is not influenced by sex and in some studies was found to be even larger in female patients [9,24,25]. On the other hand, age seems to influence the ASC more than SOV [9,24]. It is therefore evident that these two segments of the aorta are two distinct units able to influence and be influenced in a different way by the hemodynamic of the individual. So, our results suggest that during the risk stratification process of hypertensive patients, ASC diameter may be evaluated, as well as other HMODs such as LAVi and LVMi. Indeed, AADa showed to be able to stratify, independently from the other HMODs, the cardiovascular

risk of hypertensive patients.

Limitations of the study

The current study had some limitations. First of all, it was an observational study, in a highly selected population. Hence, although important data and hypothesis can be generated from our observation, we are unable to establish a direct causal link between aortic dilatation and cardiovascular events. Moreover, evaluating patients referred to a Tertiary hypertension unit, we would be cautious generalizing our results to a less selected population – of note, our patients were mostly male, with well controlled BP values. The hypertensive patients referred to a tertiary hypertension unit, hence the relatively small sample size could lead to a type 1 error, although this limitation strengthened the data about the goodness of the AAD as a cardiovascular risk marker. The limited number of events also did not allow for a more accurate analysis of the impact of AAD on single cardiovascular endpoints, for which further studies will be needed.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Milan A, Tosello F, Naso D, Avenatti E, Leone D, Magnino C, Veglio F. Ascending aortic dilatation, arterial stiffness and cardiac organ damage in essential hypertension. J Hypertens 2013; 31:109–116.

2. Canciello G, Mancusi C, Losi MA, Izzo R, Trimarco B, de Simone G, De Luca N. Aortic root dilatation is associated with incident cardiovascular events in a population of treated hypertensive patients: the Campania Salute Network. Am J Hypertens 2018; 31:1317–1323.

3. Cuspidi C, Facchetti R, Bombelli M, Re A, Cairoa M, Sala C, et al. Aortic root diameter and risk of cardiovascular events in a general population: data from the PAMELA study. J Hypertens 2014; 32:1879–1887.

4. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J 2018; 4:18014.

5. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16:31–41.

6. Leone D, Tosello F, Faletti R, Schivazappa G, Bruno G, Avenatti E, et al. Accuracy of transthoracic echocardiography in the assessment of proximal aortic diameter in hypertensive patients: comparison with cardiac magnetic resonance. J Hypertens 2017; 35:1626–1634.

7. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac

chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Hear J Cardiovasc Imaging 2015; 16:233–271.

8. Milan A, Degli Esposti D, Salvetti M, Izzo R, Moreo A, Pucci G, et al. Prevalence of proximal ascending aorta and target organ damage in hypertensive patients: the multicentric ARGO-SIIA project (Aortic RemodellinG in hypertensiOn ofthe Italian Society of Hypertension). J Hypertens 2019; 37:57–64.

9. Devereux RB, de Simone G, Arnett DK, Best LG, Boerwinkle E, Howard BV, et al. Normal limits in relation to age, body size and gender of two-dimensional echocardiographic aortic root dimensions in persons ≥15 years of age. Am J Cardiol 2012; 110:1189–1194.

10. Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. Nutrition 1916; 5:303–311.

11. Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur Heart J 2006; 27:2588–2605.

12. Van Bortel LM, Laurent S, Boutouyrie P, Chowienczyk P, Cruickshank JK, De Backer T, et al. Expert consensus document on the measurement of aortic stiffness in daily practice using carotid– femoral pulse wave velocity. J Hypertens 2012; 30:445–448.

13. Conroy RM, Pyo¨ra¨la¨ K, Fitzgerald AP, Sans S, Menotti A, De Backer G, et al., SCORE Project Group. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J 2003; 24:987–1003.

14. D'Agostino RB, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB. General cardiovascular risk profile for use in primary care: the Framingham heart study. Circulation 2008; 117:743–753.

15. Lakatta EG. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: Part III: Cellular and molecular clues to heart and arterial aging. Circulation 2003; 107:490–497.

16. Covella M, Milan A, Totaro S, Cuspidi C, Re A, Rabbia F, Veglio F. Echocardiographic aortic root dilatation in hypertensive patients: a systematic review and meta-analysis. J Hypertens 2014; 32:1928–1935.

17. O'Rourke MF, Nichols WW. Aortic diameter, aortic stiffness, and wave reflection increase with age and isolated systolic hypertension. Hypertension 2005; 45 (4 Suppl):652–658.

18. Taylor MG. Wave transmission through an assembly of randomly branching elastic tubes. Biophys J 1966; 6:697–716.

19. London GM, Pannier B. Arterial functions: how to interpret the complex physiology. Nephrol Dial Transplant 2010; 25:3815–3823.

20. Sabia L, Avenatti E, Cesareo M, Leone D, Tosello F, Veglio F, Milan A. Evaluation of aortic stiffness by a new simplified 2D speckle tracking analysis. Int J Cardiovasc Imaging 2018; 34:1753–1760.

21. Gardin JM, Arnold AM, Polak J, Jackson S, Smith V, Gottdiener J. Usefulness of aortic root dimension in persons ≥ 65 years of age in predicting heart failure, stroke, cardiovascular mortality, all-cause mortality and acute myocardial infarction (from the Cardiovascular Health Study). Am J Cardiol 2006; 22:270–275.

22. Azadani AN, Chitsaz S, Matthews PB, Jaussaud N, Leung J, Tsinman T, et al. Comparison of mechanical properties of human ascending aorta and aortic sinuses. Ann Thorac Surg 2012; 93:87–94.

23. Tosello F, Leone D, Laurent S, Veglio F, Milan A. Out of proportion proximal aortic remodeling: a subclinical marker of early vascular ageing? A systematic review. Int J Cardiol 2016; 223:999–1006.

24. Biaggi P, Matthews F, Braun J, Rousson V, Kaufmann PA, Jenni R. Gender, age, and body surface area are the major determinants of ascending aorta dimensions in subjects with apparently normal echocardiograms. J Am Soc Echocardiogr 2009; 22:720–725.

25. Muraru D, Maffessanti F, Kocabay G, Peluso D, Bianco LD, Piasentini E, et al. Ascending aorta diameters measured by echocardiography using both leading edge-to-leading edge and inner edge-to-inner edge conventions in healthy volunteers. Eur Heart J Cardiovasc Imaging 2014; 15:415–422.

TABLE 1. Demographic characteristics at baseline by groups of 'ascending aorta dilatation according to ARGO-SIIA project'

	Population, *N* = 423 AADa			***P* value**
		No, *N* = 355	**Yes, *N* = 68**	
Age (years)	52.9 ± 12.9	51.2 ± 12.5	62.2 ± 10.9	**<0.001**
Males, *n* (%)	330 (78.0%)	283 (79.7%)	47 (69.1%)	0.076
BMI (kg/m^2)	26.7 ± 3.26	26.6 ± 3.32	27.3 ± 2.85	0.054
BMI over 25, *n* (%)	283 (66.9%)	232 (65.4%)	51 (75.0%)	0.159
BSA (m^2)	1.93 ± 0.19	1.93 ± 0.19	1.95 ± 0.21	0.508
pSBP (mmHg)	138.3 ± 15.2	138.2 ± 14.8	139.0 ± 17.0	0.725
pDBP (mmHg)	82.0 ± 10.2	81.8 ± 9.86	83.3 ± 11.8	0.321
pPP (mmHg)	56.3 ± 11.8	56.4 ± 11.5	55.6 ± 13.4	0.620
cSBP (mmHg)	126.25 ± 14.8	125.7 ± 14.5	129.0 ± 16.1	0.093
cDBP (mmHg)	83.34 ± 10.2	83.1 ± 9.9	84.8 ± 11.5	0.210
cPP (mmHg)	42.91 ± 10.96	42.66 ± 10.75	44.26 ± 12.04	0.274
Augmentation index (%)	23.9 ± 11.4	23.0 ± 11.5	28.5 ± 10.0	**<0.001**
HR (bpm)	71.0 ± 11.1	71.5 ± 10.8	67.9 ± 12.1	**0.034**
Smoke, *n* (%)	122 (29.0)	107 (30.1)	15 (22.7)	0.223
Diabetes, *n* (%)	16 (3.8%)	12 (4.3%)	4 (5.9%)	0.303
Hypertension duration (years)	6.50 (2.00–14.0)	6.00 (2.00–12.5)	11.0 (5.00–19.0)	**<0.001**
Blood tests				
Total cholesterol (mg/dl)	212 ± 41.6	213 ± 42.2	209 ± 38.1	0.561
HDL cholesterol (mg/dl)	53.4 ± 15.5	53.1 ± 15.3	54.9 ± 16.4	0.497
LDL cholesterol (mg/dl)	133.2 ± 35.9	134.1 ± 36.5	128.1 ± 32.5	0.283
Triglycerides (mg/dl)	106 (75.0–163)	105 (74.8–165)	109 (76.0–152)	0.913

	Population, *N* = 423 AADa			*P* value
		No, *N* = 355	Yes, *N* = 68	
eGFR (ml/min)	101.3 ± 30.0	103.4 ± 29.6	90.6 ± 26.8	**0.004**
Drugs at echo time				
No drugs, *n* (%)	102 (24.1%)	97 (27.3%)	5 (7.4%)	**0.001**
Group A, *n* (%)	251 (59.3%)	202 (56.9%)	48 (70.5%)	0.058
Group B, *n* (%)	70 (16.5%)	55 (15.5)	15 (22.1%)	**0.026**
SCORE risk (%)	1.40 (0.50–3.40)	1.20 (0.45–2.70)	3.25 (1.17–6.03)	**<0.001**
Framingham (%)	17.4 (9.10–30.0)	16.4 (8.60–27.9)	26.7 (15.0–30.0)	**<0.001**
Events, *n* (%)	52 (12.3%)	33 (9.3%)	19 (27.9%)	**<0.001**

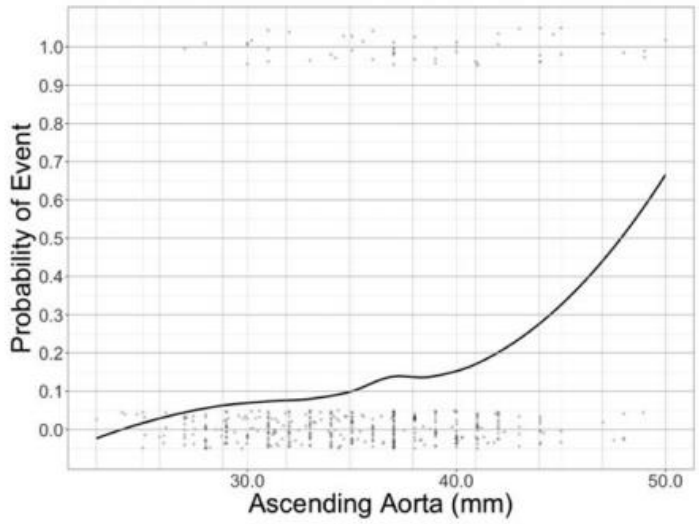
Significant P results between AADa and not AADa are reported by boldface. Group A: up to 3 drugs none of which diuretic or up to 2 drugs including a diuretic; Group B: 3 (including a diuretic) or more drugs. AADa, ascending aorta dilatation according to ARGO-SIIA project; cDBP, central DBP; cPP, central pulse pressure; cSBP, central SBP; eGFR, estimated glomerular filtration rate; HR, heart rate; pDBP, peripheral DBP; pPP, peripheral pulse pressure; pSBP, peripheral SBP.

TABLE 2. Echocardiographic data at baseline by groups of ' ascending aorta dilatation according to ARGO-SIIA project'

Population, *N* = 423	**AADa**		**P value**	
		No, *N* = 355	**Yes, *N* = 68**	
LVMi (g/m^2)	**89.9 ± 22.7**	**87.9 ± 20.9**	**100.0 ± 28.7**	**0.001**
LVH, *n* (%)	**70 (16.6%)**	**47 (13.3%)**	**23 (33.8%)**	**<0.001**
Normal, *n* (%)	**263 (62.2%)**	**230 (64.8%)**	**33 (48.5%)**	**0.017**
Concentric remodeling, *n* (%)	**90 (21.2%)**	**78 (21.9%)**	**12 (17.6%)**	**0.557**
Eccentric hypertrophy, *n* (%)	**41 (9.69%)**	**31 (8.73%)**	**10 (14.7%)**	**0.193**
Concentric hypertrophy, *n* (%)	**29 (6.86%)**	**16 (4.5%)**	**13 (19.1%)**	**<0.001**
EF (%)	**60.2 ± 4.4**	**60.3 ± 4.3**	**58.4 ± 4.6**	**0.157**
LAVI (ml/m^2)	**30.1 ± 9.09**	**29.8 ± 9.15**	**32.0 ± 8.62**	**0.093**
LAe, *n* (%)	**103 (28.4%)**	**80 (25.9%)**	**23 (42.6%)**	**0.019**
SOV (mm)	**36.5 ± 4.84**	**35.9 ± 4.51**	**40.0 ± 5.08**	**<0.001**
SVD, *n* (%)	**106 (25.1%)**	**72 (20.3%)**	**34 (50.0%)**	**<0.001**
ASC (mm)	**35.2 ± 5.31**	**33.7 ± 4.26**	**42.9 ± 3.22**	**<0.001**
E/A	**1.04 ± 0.35**	**1.08 ± 0.35**	**0.86 ± 0.26**	**<0.001**
Mean E/tdiE	**7.21 ± 2.33**	**7.07 ± 2.10**	**7.94 ± 3.26**	**0.042**
PWV (m/s)	**7.40 (6.50; 8.80)**	**7.20 (6.40; 8.50)**	**8.80 (7.20; 9.90)**	**<0.001**
PWV > 10 m/s, *n* (%)	**45 (12.5%)**	**31 (10.2%)**	**14 (25.5%)**	**0.003**

Significant P results between AADa and not AADa are reported by boldface. A, A wave on transmitralic Doppler; AADa, ascending aorta dilatation according to ARGO-SIIA project; ASC, ascending aorta; E, E wave on transmitralic Doppler; EF, ejection fraction; LAe, left atrial enlargement; LAVI, left atrial volume index; LVH, left ventricular hypertrophy; LVMi, left ventricular mass index; mean tdiE, tissutal Doppler E wave (Etdi mean); PWV, pulse wave velocity; SOV, sinuses of Valsalva; SVD, sinuses of Valsalva dilatation according to z-score.

A



B

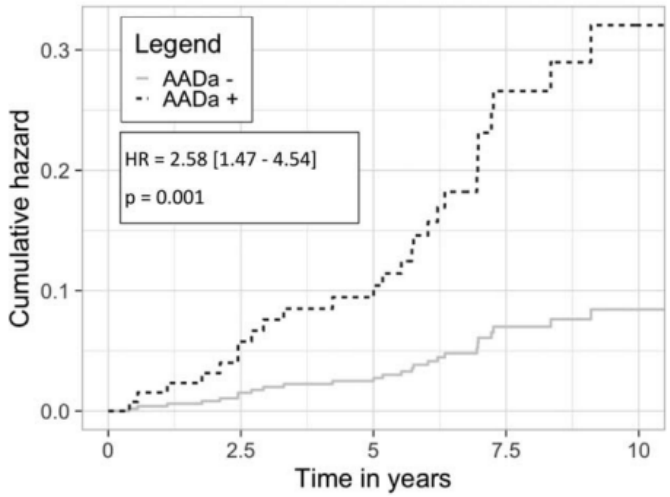
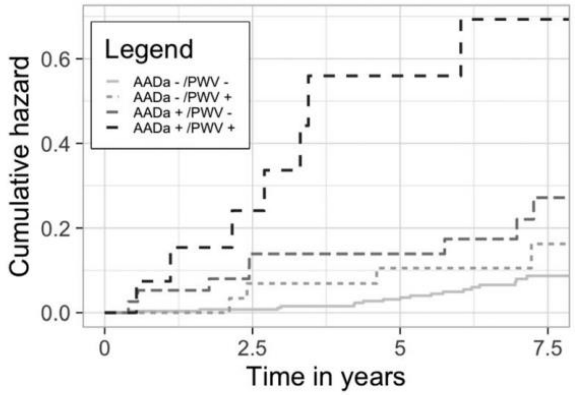


FIGURE 1 Ascending aorta risk curves. Probability of incurring an event as ascending aorta diameter increases (a) and curve risk of ascending aorta dilatation and not ascending aorta dilatation according to ARGO-SIIA project definition. AAD, ascending aorta dilatation; ASC, ascending aorta; HR, hazard ratio.

TABLE 3. Multivariate regressions table

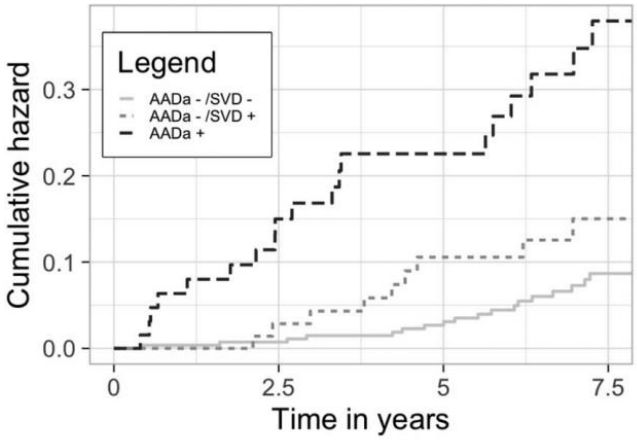
A	Beta	HR (95% CI for HR)	*P* value	B	Beta	HR (95% CI for HR)	*P* value
Hypertension duration (years)	0.02	1.02 (0.98–1.05)	0.391	Hypertension duration (years)	0.02	1.03 (0.98–1.06)	0.170
eGFR (ml/min)	−0.02	0.98 (0.98–0.99)	0.036	eGFR (ml/min)	−0.02	0.98 (0.97–1.01)	0.060
ASC (mm)	0.12	1.12 (1.04–1.22)	0.005	AADa	0.94	2.58 (1.47–4.54)	**0.001**
PWV (m/s)	0.70	1.07 (0.88–1.31)	0.494	PWV > 10 m/s	0.37	1.45 (0.75–2.82)	0.270

Risk of event after correction for the main confounders for ASC diameter (A column) and AADa (B column). Significant P results are reported by boldface. AADa, ascending aorta dilatation according to ARGO-SIIA project; ASC, ASC, ascending aorta; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; PWV, pulse wave velocity. a 243 Events, number of events¼ 26.



	Combined AAD and PWV>10m/s	AADa - / PWV -		AADa + / PWV +	
		Chi-squared	*p value*	Chi-squared	*p value*
Log-Rank	AADa - / PWV -			29.163	**<0.001**
	AADa - / PWV +	0.532	0.466	7.707	**0.006**
	AADa + /PWV -	5.068	**0.024**	4.353	**0.036**
	AADa + / PWV +	29.163	**<0.001**		

FIGURE 2 Kaplan–Meier curve of cardiovascular risk based on presence of ascending aorta dilatation and pulse wave velocity more than 10 m/s. Cumulative cardiovascular risk curve in relation to presence of ascending aorta dilatation according to ARGO-SIIA project and pulse wave velocity more than 10 m/s. AADa, ascending aorta dilatation according to ARGO-SIIA project; PWV, pulse wave velocity.



	Combined AAD and SVDz	AADa - / SVDz -		AADa +	
		Chi-squared	*p value*	Chi-squared	*p value*
Log-Rank	AADa - / SVDz -			20.625	**<0.001**
	AADa - / SVDz +	1.260	0.262	4.963	**0.026**
	AADa +	20.625	**<0.001**		

FIGURE 3 Kaplan–Meier curve of cardiovascular risk based on presence of ascending aorta dilatation and sinuses of valsalva dilatation. Cumulative cardiovascular risk curve in relation to presence of ascending aorta dilatation according to ARGO-SIIA project and sinuses of valsalva dilatation according to z-score. AADa, ascending aorta dilatation according to ARGO-SIIA project; SVD, sinuses of valsalva dilatation according to z-score