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Influence of metabolic syndrome and diabetes on progression of calcific aortic valve stenosis

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ABSTRACT

Background: Determinants of the progression of aortic stenosis (AS) remained unclear. Metabolic syndrome (MetS) and diabetes are suspected to play an active role but literature is scarce and results conflicting. We sought to assess their impact in an ongoing prospective cohort of asymptomatic patients with at least mild AS.
Methods: We enrolled 203 patients (73 ± 9 years, 75% men) with at least 2 years of follow-up. Risk-factors assessment was performed at baseline. Annual progression was calculated as [(final-baseline measurements)/follow-up duration] for both mean pressure gradient (MPG) and degree of aortic valve calcification (AVC) measurements.
Results: Ninety-nine patients (49%) had MetS and 50 (25%) had diabetes (including 39 with MetS). After a mean follow-up of 3.2 ± 1.2 years, AS progression was not different between patients with and without MetS either using MPG (+3 ± 3 vs. +4 ± 4 mm Hg/year, $p = 0.25$) or AVC (+211 ± 231 vs. +225 ± 222 AU/year, $p = 0.75$). Same results were obtained for patients with diabetes (3 ± 3 vs. 4 ± 4 mm Hg/year $p = 0.53$, 187 ± 140 vs. 229 ± 248 AU/year $p = 0.99$). MetS had no impact on AS progression in all tested subgroups based on age, statin prescription, valve anatomy and AS severity (all $p \geq 0.10$).
Conclusion: In our prospective cohort of AS patients, we found no impact of MetS or diabetes on AS progression. Although MetS and diabetes should be actively treated, no impact on AS progression should be expected. Our results support the theory that if cardiovascular risk-factors may play a role at the early phase of AS disease they have no or limited influence on AS progression.

1. Introduction

Degenerative aortic stenosis (AS) is a common valvular disorder, characterized by progressive calcification of aortic leaflets eventually leading to impaired valve opening and for which valve replacement is the only curative treatment [1,2]. In recent years our understanding of this disease has evolved from a purely passive and degenerative process to an active phenomenon involving inflammation and lipids deposition sharing important similarities with atherosclerosis.

Traditional cardiovascular risk factors, including diabetes and metabolic syndrome (MetS) are associated with a higher incidence of AS [3,4]. Metabolic syndrome is associated with an increased risk of cardiovascular disease [5] and with inflammation at the aortic valve level, supporting the hypothesis of MetS being a generator of oxidative stress and a potential accelerator of AS progression similar to atherosclerosis [6,7]. However, data regarding the impact of MetS and/or diabetes on AS progression are scarce and results contradictory [3,8–13].

Extensive research is ongoing to identify the determinants of AS occurrence and progression, which might lead to preventive therapeutic actions. In our own prospective cohort of asymptomatic patients with at least mild AS, we sought to assess the influence of MetS and diabetes on AS progression.

2. Methods

2.1. Study design

Our study population consisted of patients with degenerative AS, with at least 2 years of follow-up enrolled between November 2006 and September 2013 in our ongoing prospective cohort COFRASA/GENERAC (clinicalTrial.gov number NCT 00338676 and clinicalTrial.gov number NCT00647088) aiming at evaluating the determinants of AS occurrence and progression. Inclusion criteria were pure, at least mild (defined by a mean

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pressure gradient (MPG) ≥10 mm Hg and aortic valve structural changes (thickening/calcification)) asymptomatic AS (patients had to be free of dyspnea, angina and chest pain). Exclusion criteria were AS due to rheumatic disease or radiotherapy, previous infective endocarditis, more than mild coexisting aortic regurgitation (defined by a vena contracta width ≥ 3 mm or a regurgitant volume ≥ 30 mL) or associated valvular disease and severe renal insufficiency (creatinine clearance ≤30 mL/min). All participants underwent a comprehensive clinical, transthoracic echocardiography (TTE) and MSCT evaluation at study entry and yearly thereafter. Echocardiographic and MSCT measurements were performed blinded one of each other. Patients were contacted every 6 months and seen at our research center every year. Occurrence of AS related events (sudden death, congestive heart failure, or new onset of symptoms (dyspnea, angina or syncope)) was prospectively recorded. Our regional ethic committee approved the study and all patients gave a written informed consent.

2.2. Definition of metabolic syndrome and diabetes

Cardiovascular risk factors and presence of metabolic syndrome were recorded at inclusion. Height, weight, abdominal circumference, fasting glucose, lipid profile, and therapy for diabetes, high blood pressure or dyslipidemia were recorded during inclusion visit. MetS was defined as 3 or more out of the 5 following criteria: waist circumference (male (M) >102 cm/female (F) >88 cm), hypertension (≥130/85 mm Hg, or treated), triglycerides (≥1.7 mmol/L, or treated), fasting glucose (≥5.6 mmol/L, or treated), HDL-cholesterol (M < 1.03 mmol/L/F < 1.29 mmol/L, or treated) as defined by AHA/NHLBI [5]. Patients under anti-diabetic therapy at inclusion constituted our diabetic population. Of note according to this definition, diabetic patients were included in the MetS group if two other criteria were met.

2.3. Echocardiography

AS severity was evaluated based on peak velocity (PV), mean pressure gradient (MPG) and calculation of the aortic valve area (AVA) using the continuity equation as recommended by current guidelines [14]. The AVA was indexed (*AVA*i) to body surface area (BSA). Mild AS was defined by a MPG < 20 mm Hg, moderate AS was defined by a MPG between 20 and 40 mm Hg, and severe AS by a MPG > 40 mm Hg. All the echocardiographies were performed by a single experienced operator (last author).

2.4. MSCT measurements

MSCT was performed the same day than TTE using a Philips scanner (MX 8000 IDT 16, Phillips Medical Systems, Andover, MA, USA) or a General Electric scanner (Light speed VCTTM, General Electric Company, Fairfield, Connecticut, USA). A scan run consisted of a prospective acquisition of 43-mm thick contiguous transverse slices. Acquisition time was 0.5 s/slice ECG triggered at 75% of the RR interval. No contrast enhancement was needed nor was a beta-blocker administered for the purpose of the examination. Measurements were performed using dedicated semi-automatic software (Heart Beat Calcium Scoring, Philips Medical Systems or SmartScore, General Electric Medical Systems). Calcification was defined as four adjacent pixels with density >130 Hounsfield units. The degree of AVC was quantitatively assessed according to the Agatston method (calcium score) expressed in AU. AVC was defined as calcification within the valve leaflets, aortic annulus, or aortic wall immediately adjacent to leaflet or annular calcification. Two MSCT runs were performed sequentially with 1 or 2 mm initial interval. Each run was independently scored and the two scores were averaged. Radiation exposure was typically between 2 and 3 mSV.

2.5. Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD), median [percentile 25 and 75] and categorical variable as number of patients (percent). Log transformation was performed when values were not normally distributed. Annualized progression was calculated as [(final measurement - baseline measurement)/follow-up duration] for hemodynamic (MPG) and anatomic (AVC score) measurements. Linear regressions in univariate analysis and in bivariate analysis after adjustment for age, statin therapy, valve anatomy (bicuspid or trileaflet aortic valve), baseline AS severity (as a continuous variable) or diabetes were used to assess the impact of MetS or diabetes on AS anatomic or hemodynamic progression. Event-free survival (composite endpoint of AS-related events defined as occurrence of sudden death, congestive heart failure, or new onset of symptoms (dyspnea, angina or syncope) and of performance of aortic valve replacement (AVR)) was assessed using the Kaplan-Meier analysis. Comparison of event-free survival according to presence of MetS, diabetes or combination of MetS and diabetes was performed by means of log-rank test. Cox proportional-hazard analyses evaluated the predictive value of MetS, diabetes and combination of MetS and diabetes for event-free survival after adjustment for age, valve anatomy (bicuspid or trileaflet

Table 1
Characteristics of the population, values expressed as mean (± standard deviation) or number of patients (percentage).

	Overall $N = 203$	MetS $N = 99$	No MetS $N = 104$	P
Age, years	73 ± 9	72 ± 9	74 ± 9	0.03
Male gender	152 (75%)	76 (77%)	76 (73%)	0.54
Sinus rhythm	190 (94%)	91 (92%)	99 (95%)	0.34
Diabetes	50 (25%)	39 (39%)	11 (11%)	<0.0001
Hypertension	139 (69%)	76 (77%)	63 (61%)	0.01
Smoker	105 (57%)	58 (59%)	47 (45%)	0.05
Hypercholesterolemia	130 (64%)	69 (70%)	61 (59%)	0.10
Peripheral artery disease	18 (8%)	12 (12%)	6 (6%)	0.11
Height, m	1.67 ± 9	1.67 ± 9	1.66 ± 9	0.44
Weight, kg	79 ± 16	87 ± 15	72 ± 13	<0.0001
Body mass index, kg/m^2	29 ± 5	31 ± 5	26 ± 4	<0.0001
Waist circumference, cm	102 ± 15	109 ± 11	96 ± 15	<0.0001
Statins therapy	133 (66%)	70 (70%)	63 (61%)	0.13
Total cholesterol, mmol/L	4.7 ± 1.1	4.5 ± 1.1	4.9 ± 1.1	0.013
Triglycerides	1.3 ± 0.8	1.7 ± 0.9	1.0 ± 0.4	<0.0001
HDL-cholesterol, mmol/L	1.5 ± 0.4	1.3 ± 0.4	1.6 ± 0.4	<0.0001
Low-density lipoprotein cholesterol, mmol/L	2.7 ± 0.9	2.5 ± 0.9	2.8 ± 0.9	0.017
Fasting glucose, mmol/L	6.2 ± 1.8	6.7 ± 1.9	5.7 ± 1.6	<0.0001
Serum creatinine, μmol/L	92 ± 28	96 ± 33	88 ± 21	0.12
Bicuspid aortic valve	40 (20%)	17 (17%)	23 (22%)	0.40
Ejection fraction, %	63 ± 5	64 ± 4	63 ± 5	0.10
Left ventricular mass index, g/m^2	114 ± 27	117 ± 28	112 ± 26	0.16
Left ventricular hypertrophy, %	112 (55%)	57 (58%)	55 (53%)	0.16
AS severity				0.62
- Mild AS	96 (47%)	50 (51%)	46 (44%)	
- Moderate AS	89 (44%)	40 (40%)	49 (47%)	
- Severe AS	18 (9%)	9 (9%)	9 (9%)	
Baseline mean pressure gradient, mm Hg	22 ± 11	22 ± 11	23 ± 11	0.54
Baseline peak velocity, cm/s	303 ± 65	302 ± 64	304 ± 66	0.60
Baseline aortic valve area, cm^2	1.2 ± 0.4	1.2 ± 0.4	1.1 ± 0.4	0.09
Baseline indexed aortic valve area, cm^2/m^2	0.73 ± 0.19	0.71 ± 0.18	0.75 ± 0.19	0.14
Baseline aortic valve calcification score, AU	1168 ± 984	1081 ± 924	1250 ± 1035	0.31
Mean pressure gradient increase, mm Hg/year	3 ± 4	3 ± 3	4 ± 4	0.24
Mean peak velocity increase, cm/s/year	17 ± 16	15 ± 13	19 ± 18	0.19
Mean aortic valve area decrease, cm^2/year	−0.08 ± 0.07	−0.08 ± 0.08	−0.08 ± 0.07	0.46
Mean indexed aortic valve area decrease, cm^2/m^2/year	−0.04 ± 0.04	−0.04 ± 0.04	−0.05 ± 0.04	0.12
Mean aortic valve calcification increase, AU/year	218 ± 226	211 ± 231	225 ± 222	0.75

aortic valve) and baseline AS severity. Data were analyzed with JMP (version 9.0) and a p value <0.05 was considered statistically significant.

3. Results

3.1. Characteristics of the population

A total of 203 patients with at least 2 years of follow-up constituted our population. Patient characteristics are summarized in Table 1. Mean age was 73 ± 9 years, and 152 (75%) were men. At inclusion, MPG was 23 ± 11 mm Hg (median 20 mm Hg [15-28]). Ninety-six patients (47%) had mild AS, 89 (44%) moderate AS, and 18 (9%) severe AS. Mean AVC score was 1168 ± 984 AU (median 897, [550-1561]). Fifty patients (25%) had diabetes (all type II diabetes), 139 (69%) had hypertension, mean BMI was 29 ± 5 kg/m^2 and 133 (66%) received statin therapy.

Overall, 99 patients (49%) corresponded to the definition of MetS; five patients (5%) fulfilled the 5 criteria, 31 (31%) 4 criteria, and 63 (64%) 3 criteria. When compared to patients without MetS, patients with MetS were younger ($p = 0.03$), and as expected presented with larger body mass index (BMI) ($p < 0.001$) and were more likely to have hypertension and diabetes ($p = 0.01$ and <0.001, respectively). Patients with MetS had higher triglycerides and fasting glucose levels ($p < 0.001$) but lower total-cholesterol ($p = 0.01$), LDL-cholesterol ($p = 0.02$) and HDL-cholesterol levels ($p < 0.001$). Sex and AS severity were similarly distributed ($p = 0.54$ and 0.62 respectively). Among the 50 diabetic patients, 39 patients (78%) also fulfilled criteria for MetS.

3.2. Overall progression and clinical events

Mean follow-up duration was 3.2 ± 1.2 years. Final MPG was 33 ± 17 mm Hg (median 28, [20-42]), with a mean yearly progression of 3 ± 4 mm Hg/year (median 2, [1-5]). Final AVC score was 1852 ± 1502 AU (median 1437, [2451-908]), with a mean yearly increase of 218 ± 226 AU/year (median 145, [67-273]). A total of 41 cardiovascular AS-related events occurred during the follow-up period; 34 presented with dyspnea, 5 with angina, one with syncope and one experienced a sudden death. An AVR was performed in 34 patients (31 of who experienced symptoms and 3 patients who underwent a prophylactic surgery).

3.3. Influence of metabolic syndrome on progression

Mean follow-up duration was similar between patients with and those without MetS (3.2 ± 1.1 vs. 3.3 ± 1.3 years, $p = 0.56$). AS hemodynamic and anatomic progression were not different between patients with and without MetS (mean MPG progression 3 ± 3 mm Hg (median 2, [1-4]) vs. 4 ± 4 mm Hg (median 2, [1-6]), $p = 0.25$) and (211 ± 231 AU (median 137, [65-285]), vs. 225 ± 222 AU (median

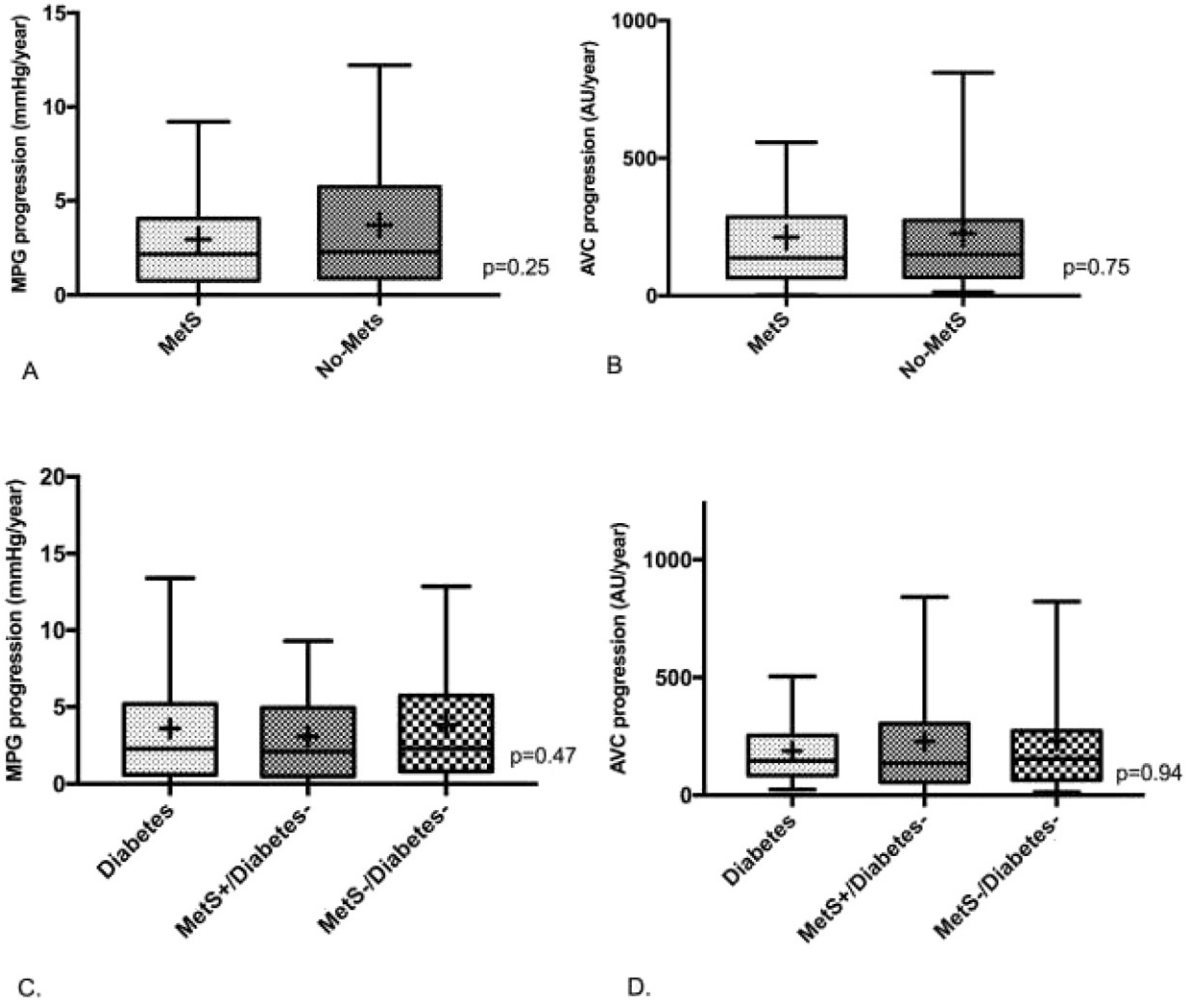

Fig. 1. Yearly hemodynamic (mean pressure gradient (MPG), mm Hg) (A and C) and anatomic (aortic valve calcification score (AVC), arbitrary units) (B and D) progression of aortic valve stenosis according to presence or absence of metabolic syndrome (MetS) (A and B) or according to presence of diabetes, presence of MetS but no diabetes and absence of both of diabetes and MetS. The box defines the interquartile range with the mean indicated by the crossbar and the median indicated by the line. The whiskers indicate the 5th and the 95th percentile.

150, [67-273]), $p = 0.75$) (Fig. 1A + B) respectively. Similar results were obtained when hemodynamic progression was defined based on PV (14 ± 2 vs. 19 ± 2 cm/s, $p = 0.19$) or AVA (−0.08 ± 0.08 vs. −0.08 ± 0.08 cm^2, $p = 0.46$).

Among the 41 events recorded during the follow-up, 19 occurred in the MetS group, and 22 in the no-MetS group. There was no significant difference in outcome between the two groups (Fig. 2) ($p = 0.78$). This remained true after adjustment for age, valve anatomy and baseline AS severity ($p = 0.38$). Using AVR instead of AS-related as endpoint, similar results were obtained with no impact of MetS ($p = 0.67$).

3.4. Influence of diabetes on AS progression

Diabetes also had no impact on AS hemodynamic (3 ± 3 mm Hg vs. 4 ± 4 mm Hg respectively, $p = 0.53$) or anatomic progression (187 ± 140 vs. 229 ± 248 AU $p = 0.99$).

We then divided our population was into 3 groups, the 50 diabetic patients, 49 patients with MetS but no diabetes and the 104 patients free of diabetes and MetS. Both hemodynamic (3 ± 3 mm Hg vs. 3 ± 3 mm Hg vs 4 ± 4 mm Hg respectively, $p = 0.47$) and anatomic progression (187 ± 140 vs. 228 ± 275 vs 229 ± 220 AU respectively, $p = 0.94$) were not different between the three groups (Fig. 1C and D) and event free survival was also not different ($p = 0.89$) (Fig. 2B).

3.5. Subgroup analysis

3.5.1. Interaction with age

Metabolic syndrome had no impact on AS hemodynamic or anatomic progression in the 51 patients of the youngest quartile (≤67 years) (mean MPG progression 2 ± 2 mm Hg with MetS vs. 4 ± 3 mm Hg without MetS, $p = 0.34$, and 186 ± 198 vs. 292 ± 263 AU, $p = 0.14$) as well as in the rest of the cohort (mean MPG progression 3 ± 3 vs. 4 ± 4 mm Hg, $p = 0.60$, and 223 ± 245 vs. 209 ± 210 AU, $p = 0.53$) (Fig. 3) or in patients aged 73 or below (median age of the cohort) (3 ± 4 mm Hg vs. 4 ± 4 mm Hg, $p = 0.29$, and 206 ± 268 vs. 233 ± 237 AU respectively, $p = 0.48$) or above 73 years (3 ± 2 vs. 4 ± 4 mm Hg, $p = 0.61$, and 218 ± 174 vs. 219 ± 212 AU respectively, $p = 0.51$). After adjustment for age (as a continuous variable), MetS was not predictive of either AS hemodynamic ($p = 0.14$) or anatomic progression ($p = 0.59$).

3.5.2. Interaction with statin therapy

MetS had no impact on AS hemodynamic or anatomic progression in the 133 patients (66%) on statins (3 ± 3 mm Hg vs. 4 ± 4 mm Hg, $p = 0.12$, and 202 ± 230 vs. 213 ± 214 AU respectively, $p = 0.59$), nor in the 70 patients free of statins (3 ± 3 vs. 3 ± 3 mm Hg, $p = 0.94$, and 235 ± 235 vs. 243 ± 237 AU respectively, $p = 0.92$) (Fig. 3). After adjustment, for statin therapy MetS was not a predictor of AS hemodynamic ($p = 0.11$) or anatomic ($p = 0.74$) progression.

3.5.3. Interaction with valve anatomy

MetS had also no impact on hemodynamic or anatomic progression in the 40 patients (20%) with bicuspid aortic valve (4 ± 4 mm Hg vs. 5 ± 5 mm Hg $p = 0.48$, 338 ± 406 vs. 322 ± 287 AU respectively, $p = 0.71$) or in patients with tricuspid aortic valve (3 ± 3 vs. 3 ± 4 mm Hg $p = 0.35$, 184 ± 160 vs. 198 ± 194 AU respectively, $p = 0.94$). After adjustment for valve anatomy, MetS was not a predictor of AS progression (hemodynamic $p = 0.17$, anatomic $p = 0.82$).

3.5.4. Interaction with AS severity

Baseline AS severity was equally distributed between patients with and without MetS ($p = 0.62$). MetS did not impact on AS hemodynamic progression in patients with mild AS (2 ± 2 mm Hg vs. 2 ± 2 mm Hg in patients with MetS and without respectively, $p = 0.10$), moderate AS (3 ± 3 vs. 5 ± 4 mm Hg $p = 0.06$), severe AS (5 ± 5 vs. 8 ± 5 mm Hg $p = 0.21$) or in patients with mild and moderate AS (3 ± 3 vs. 3 ± 4 mm Hg $p = 0.47$). Finally after adjustment for baseline MPG or AVC, MetS was not a predictor of either hemodynamic ($p = 0.13$) or anatomic progression ($p = 0.70$).

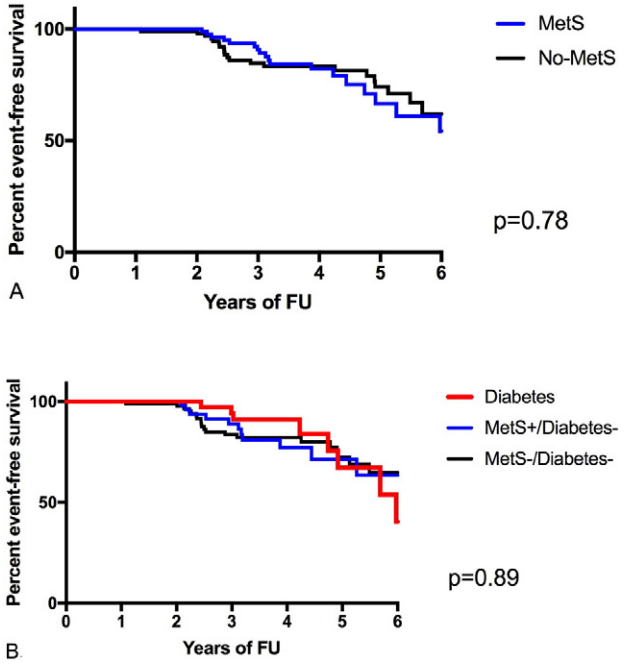

Fig. 2. Survival free of aortic valve stenosis (AS) related events (sudden death, congestive heart failure, or new AS related onset of symptoms (dyspnea, angina or syncope)) according to (A) presence or absence of metabolic syndrome (MetS) and (B) presence of diabetes, presence of MetS but no diabetes and absence of both of diabetes and MetS.

4. Discussion

The main observation of the present prospective observational study is the lack of association between MetS and/or diabetes and AS progression (and consequently AS-related events), overall and in every subgroup studied defined based on age, statin prescription, valve anatomy or AS baseline severity.

In recent years, metabolic syndrome and diabetes have been proposed as a risk factor for AS progression. Histological and animal studies supported the theory that AS disease share similarities with atherosclerosis, and a faster progression in mice with abdominal obesity has been reported [6,15]. Faster AS progression among patients with metabolic syndrome was also observed in one retrospective study [10]. In a large prospective study, which aimed at identifying factors influencing cardiovascular disease in healthy individuals using CT calcium scoring, Katz et al. indeed found higher incidence of aortic valve calcifications in patients with MetS or diabetes [3], but no difference on AS progression [9]. In contrast, in a substudy of ASTRONOMER [16], Capoulade et al. recently showed a faster AS progression among patients with MetS [11]. Diabetes was also linked to AS progression in a previous retrospective study [8]. As the role of MetS and diabetes on AS progression remained unclear, we sought to evaluate its influence in our own prospective cohort of AS patents.

Metabolic syndrome, defined as an association of 3 out of 5 criteria, confers an increased cardiovascular risk. Definition of MetS has changed over the last 15 years, and according to the last statement, includes patients treated for type 2 diabetes fulfilling two other criteria for MetS [5]. While it is appropriate to consider these type 2 diabetes patients as having MetS according to the definition, diabetic patients are considered at higher cardiovascular risk than those with MetS free of diabetes. This being said, we found no influence of MetS or diabetes on AS progression.

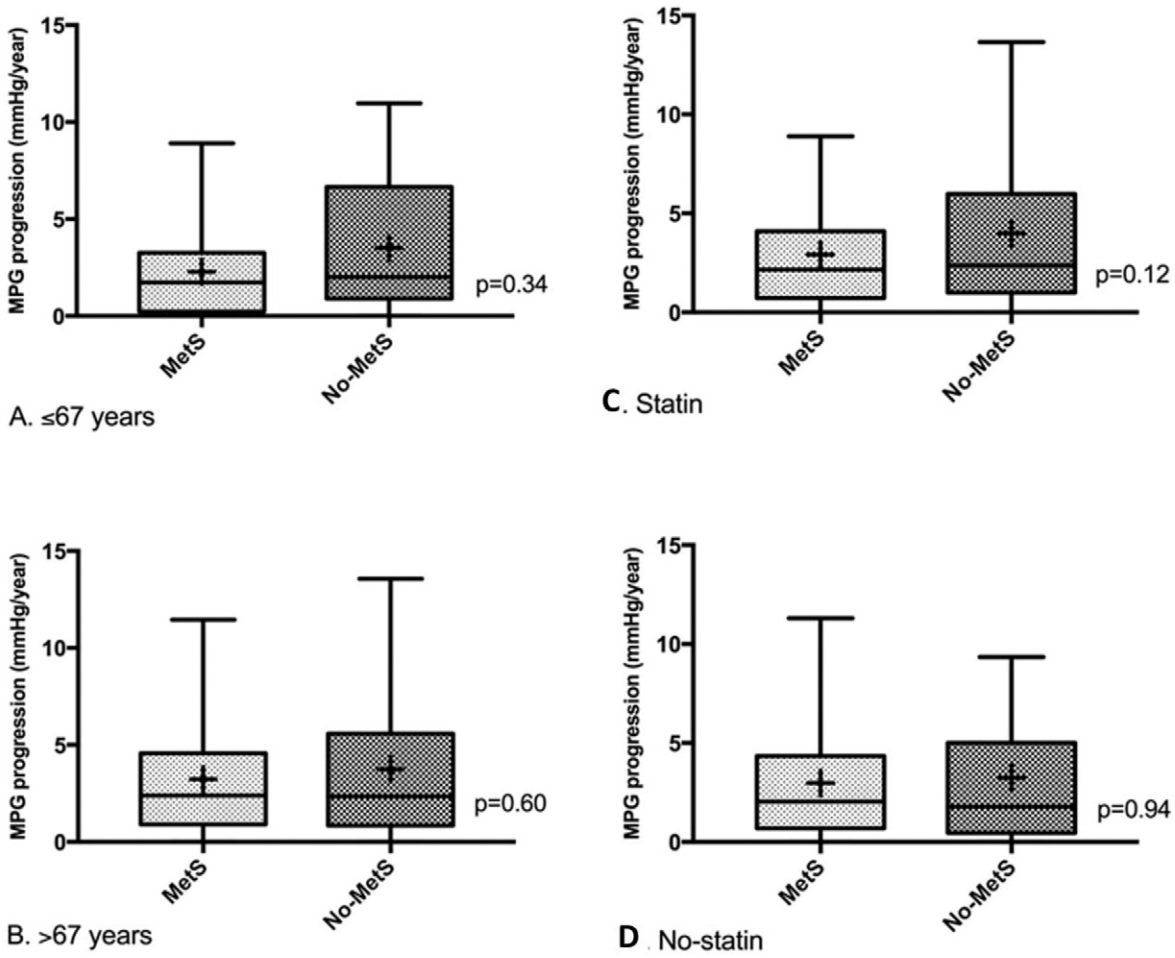

Fig. 3. Yearly hemodynamic (mean pressure gradient (MPG), mm Hg) progression of aortic valve stenosis according to presence or absence of metabolic syndrome (MetS), (A) in the 51 patients of the youngest quartile (≤67 years) and (B) in the remaining population, (C) in patients on statin therapy and (D) in patients not on statin therapy. The box defines the interquartile range with the mean indicated by the full crossbar and the median indicated by the dotted line. The whiskers indicate the 5th and the 95th percentile.

This lack of impact was observed using two independent methods of assessment of AS progression, namely hemodynamic measurements performed using echocardiography and anatomic measurements (degree of aortic valve calcification) measured using CT. The absence of influence of MetS or diabetes on AS progression was further corroborated by the lack of impact of MetS or diabetes on outcome (AS related events or AVR) and thus further reinforces the robustness of our findings.

No impact of MetS on AS progression was observed in the overall population and in all tested subsets. Importantly, results of the substudy of ASTRONOMER suggested that AS progression might only be influenced by metabolic syndrome in youngest patients (below 57 years, median age of their population). It is worth noting that in ASTRONOMER, patients were >15 years younger than in the present study. Furthermore and parallel to the young age of the population, rate of bicuspid aortic valve was also markedly higher (51% vs. 20%). Nevertheless, we found no influence of MetS on AS progression in the youngest quartile of our population nor in the subset of patients with bicuspid aortic valve. However, in regard of the small sample size of these subsets, we cannot exclude determinants of AS progression may be different according to age subsets and that MetS may have an impact on AS progression in younger AS patients and/or in patients with bicuspid aortic valve deserving further studies. Inflammation induced by MetS may also not be a key factor for AS progression in the older population, so that its impact becomes less visible, or that other factors may counteract MetS' pro-inflammatory potential as age advances, such as for example fetuin-A [17]. Further researches are needed to explore these issues.

Current understanding of AS pathophysiology favors the role of inflammation at the early stage of the disease [2,18]. In the subsets of patients with mild or moderate AS, we also found no influence of MetS on AS progression. Dyslipidemia, a major actor of the metabolic syndrome, is also a target of research in the field of AS. The hypothesis of slower AS progression among patients taking statin therapy suggested by retrospective series and one prospective study [19,20] was refuted in large randomized trials [16,21,22]. Previous results from ASTRONOMER showed a paradoxical faster AS progression among patients taking statins, and presenting with MetS. In our cohort we found no interaction between MetS and statin therapy, and MetS had no influence of AS progression both in patients receiving statins and in patients free of statins. It is however important to underline that in our cohort, statins were introduced for primary or secondary prevention whereas in ASTRONOMER such patients were excluded. The potential deleterious influence of statin treatment in normocholesterolemic patients regarding AS progression or development of diabetes reminds us of the complex nature of glucose metabolism and insulin resistance, and its relation with lipid metabolism and inflammation [23].

Major strengths of our study are its prospective study design, the wide range of AS severity and the enrollment of a classical AS population, that is, elderly patients, with comorbidities. As we included patients already known for AS, we were not able to study influence of MetS or diabetes on AS incidence. The sample size of our cohort may be seen as a limitation to demonstrate a potential association between MetS or diabetes and AS progression, but they compare well to the literature and there was no trend suggesting that absence of impact of MetS

might be due to a small sample size or limited power. While definition of MetS is established, it is a binary variable (yes or no) and do not take into account neither the degree of severity of each of its components nor the number of components. Thus we could not exclude that a more severe presentation regading one or both of these aspect may have changed our conclusion. In addition, mean follow-up duration was approximately 3 years and although unlikely, we could not exclude that MetS would have influenced AS progression with a longer follow-up. Finally, although it is still debated if whether patients with diabetes should be excluded form MetS or not, our conclusion remained unchanged whether impact of MetS was assessed overall or excluding diabetic patients.

5. Conclusion

In a prospective cohort of AS patients with a wide range of AS severity, we found no impact of metabolic syndrome or diabetes on AS progression assessed using two complementary and independent methods in the overall population and in all subsets defined based on age, treatment, valve anatomy or baseline AS severity. Although MetS should be actively treated, no impact on AS progression should be expected. Our results support the theory that if cardiovascular risk factors including MetS and diabetes may play a role at the early phase of the disease they have no or a limited influence on AS progression.

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Conflict of interest

None of the authors has conflict of interest or disclosure related to the present paper.

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