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Progression Rate of Severity of Aortic Stenosis in Patients With Rheumatoid Arthritis^a

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Abstract

Objective—Valvular heart disease is common in patients with rheumatoid arthritis (RA). However, there is uncertainty about how often to perform echocardiographic surveillance in this population. The objective of this study was to assess the progression rate of mild and moderate AS in patients with RA.

Methods—A population-based cohort of patients with RA and either mild (2.0–2.9 m/s) or moderate (3.0–3.9 m/s) AS was identified. Demographic, clinical, and echocardiographic data were collected. Annual progression rate of AS was then calculated for the study cohort and the impact of pertinent RA variables on progression rate determined.

Results—Sixty-eight patients with RA and mild or moderate AS met the inclusion requirements. Peak aortic valve (AV) velocity and mean AV gradient increased during the study period, whereas AV area decreased, consistent with progression of AS ($P<.001$). Mean (SD) annual increase in peak AV jet velocity was 0.05 m/s (0.01) and in mean AV gradient was 1.0 mm Hg (0.18). Mean annual decrease in AV area was 0.04 (0.01) cm². The progression rate of AS was higher in patients with increased erythrocyte sedimentation rates (ESR) ($P=.001$).

Conclusions—The rate of AS progression in the RA population was higher in patients with increased ESR but less than that of the reported rate of AS progression in the general population. Although the cause for this finding is uncertain, these results suggest that patients with RA who have mild or moderate AS should undergo echocardiographic surveillance for disease progression similar to that of the general population.

Keywords

aortic stenosis; echocardiography; rheumatoid arthritis

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Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune condition resulting in systemic inflammation (1). Predominantly affecting females, RA has a lifetime risk of 3.6% in females and 1.7% in males, and the risk increases with age (2). Prior investigations have described the detrimental effect of RA on the various components of the cardiovascular system. For instance, the increased mortality in the RA population is primarily due to accelerated coronary atherosclerosis and resultant ischemic heart disease (3) that cannot be attributed to traditional risk factors alone (4). Indeed, the frequency of myocardial infarction in the RA population is increased 2-fold compared with that in age-matched persons (5). Also, RA is associated with an increased risk of congestive heart failure (6), the specific pathophysiologic mechanism for this finding remaining elusive. Along with the coronary vasculature and the myocardium, the pericardium also seems to be affected by the presence of RA in that studies have shown higher rates of pericardial effusions in these patients (7). Activation of the inflammatory cascade via tumor necrosis factor may both accelerate atherosclerosis and induce myocardial or pericardial damage (8) and therefore be responsible for the increased rates of cardiovascular disease in the RA population. As a result, anti-tumor necrosis factor therapies have been investigated in this population and have resulted in lower rates of both cardiovascular events and overall mortality (9).

Valvular heart disease (VHD) in patients with RA was initially thought to be rare (7,10,11); however, recent analyses have found that the RA population has a higher incidence of VHD than the general population in that 30% of patients with RA have valvulopathy (12). However, the impact of RA on the progression on VHD, specifically aortic stenosis (AS), is not well established. AS is common in the elderly population, affecting nearly 1 in 10 patients (13), and can result in considerable sequelae, including sudden cardiac death (14). Prior investigations have determined the average annual rate of progression of severity of AS in the general patient population (15). These findings have informed our current national guidelines for recommendation of subsequent surveillance imaging. Specifically, for patients with mild AS, serial echocardiographic studies are recommended every 3 to 5 years, whereas for patients with moderate AS, echocardiographic assessment is recommended every 1 to 2 years (14). Unfortunately, such guidelines are lacking in the RA population because of the paucity of studies assessing the rate of AS progression in these patients. Given the aforementioned effects of RA on the cardiovascular system, the inflammatory burden of RA may accelerate the rate of progression of AS in these patients. Therefore, the primary objective of this study was to determine the rate of progression of AS in patients with RA.

Methods

RA Patient Population

A retrospective, population-based cohort (16) of Olmsted County, Minnesota, residents (age, 18 years) with incident or prevalent RA was previously identified (17). Patients were considered to have RA if they fulfilled the 1987 American College of Rheumatology criteria (18). Information on RA disease severity had been collected previously through medical record review (19). Disease severity measures included rheumatoid factor positivity,

presence of joint erosions or destructive changes, rheumatoid nodules, and severe extra-articular manifestations of RA (including pericarditis, pleuritis, Felty syndrome, glomerulonephritis, cutaneous vasculitis, peripheral neuropathy, scleritis, episcleritis, or retinal vasculitis). Data on inflammatory markers (C-reactive protein and erythrocyte sedimentation rate [ESR]) were also collected within 3 months of each echocardiogram. In accordance with local laboratory standard reference ranges, an increase in inflammatory marker was defined as a C-reactive protein value of more than 8 mg/L or an ESR value (determined with the Westergren method) of more than 22 mm/h for men and more than 29 mm/h for women. Data regarding the initiation and termination dates for use of systemic glucocorticoids (ie, oral, parental, or intraarticular forms of prednisone, prednisolone, methylprednisolone, hydrocortisone, and dexamethasone), disease-modifying antirheumatic drugs (ie, methotrexate, hydroxychloroquine, azathioprine, leflunomide, and sulfasalazine), and biologics (ie, etanercept, infliximab, adalimumab, abatacept, and rituximab) were collected on all patients. Information about the use of aspirin for RA (ie, >1,950 mg/day for at least 3 months) was also collected.

AS Patient Population

The RA cohort (16) was reviewed for patients who were clinically referred for echocardiographic assessment at our institution. Patients were included in the study if they 1) had either mild (2.0–2.9 m/s) or moderate (3.0–3.9 m/s) native valve AS (14) and 2) had at least 2 echocardiograms obtained at least 3 months apart after RA diagnosis. The first echocardiogram after RA diagnosis was considered the baseline (ie, study inclusion date). Systolic and diastolic blood pressure and heart rate were recorded at the commencement of echocardiography. Comprehensive transthoracic or transesophageal echocardiography was subsequently performed and interpreted by a staff cardiologist.

Aortic valve (AV) stenosis was assessed in accordance with recommended guidelines (20). Specifically, the AV was evaluated in both the long- and the short-axis planes to determine its morphologic features. The left ventricular outflow tract (LVOT) diameter was measured in the parasternal long-axis view. Continuous-wave Doppler assessment of the peak AV jet velocity was performed using both imaging- and nonimaging-guided transducers while interrogating multiple imaging windows (apical, suprasternal notch, right supraclavicular, or right parasternal notch). The imaging window with the highest obtained velocity was reported (or an average of 5 measurements if a patient was in an irregular rhythm), and the mean AV gradient was obtained from the continuous-wave Doppler signal. AV area was derived from the continuity equation, and the dimensionless index was derived as the ratio of LVOT/AV time velocity integral (20). Cardiac stroke volume was derived as the product of LVOT area and LVOT time velocity integral, and stroke volume index was obtained by dividing the stroke volume by the patient's body mass index (21). Cardiac output was derived from the product of stroke volume and heart rate, and cardiac index was obtained by dividing cardiac output by body mass index. Left ventricular ejection fraction (LVEF) was obtained with the biplane methods of disks (modified Simpson method) or linear dimensions (modified Quinones equation), or if neither method was feasible then the staff cardiologist estimated the LVEF (22). The severity of other valvular lesions was classified in accordance with recommended guidelines (14,23).

Baseline Demographics and Comorbidities

Patient age and body surface area were documented at the time the initial echocardiogram was obtained. Smoking history and family history of premature coronary heart disease (defined as the presence of coronary heart disease in first-degree relatives at an age <65 years for females and <55 years for males) were determined at the time of RA diagnosis. Hypertension, hyperlipidemia, and diabetes mellitus were defined based on physician diagnosis, treatment, or standardized criteria, as previously described (19). Chronic obstructive pulmonary disease and obstructive sleep apnea were based on physician diagnosis. Reduced kidney function was defined as 2 consecutive estimated glomerular filtration rates less than 45 mL/min per 1.73 m² at least 90 days apart using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation (24). Atrial fibrillation or flutter was based on electrocardiographic findings. Coronary artery disease was defined as the presence of one of the following: angina pectoris, myocardial infarction (including silent events), or coronary revascularization procedures (ie, coronary artery bypass graft or percutaneous intervention). Myocardial infarction was defined using standardized epidemiologic criteria, as previously described. Silent myocardial infarction was considered present at the date a characteristic electrocardiogram was first documented or at the date a physician recorded the diagnosis for a patient who had no documented history of myocardial infarction. Heart failure was defined using the Framingham criteria (25). The Mayo Clinic Institutional Review Board and the Olmsted Medical Center Institutional Review Board approved the study.

Statistical Analysis

Descriptive statistics (eg, means, percentages) were used to summarize the data. Crude annual rates of change in echocardiographic measures were calculated as last available measure minus baseline measure divided by the time between measures. Generalized linear models with random intercepts per subject were used to estimate rate of progression over time adjusting for age and sex. Interactions between characteristics of interest and time since diagnosis of AS were considered to examine whether the characteristics influenced the rate of progression of AS. Kaplan-Meier methods were used to assess time from baseline to first progression (from mild to moderate or severe and from moderate to severe). Analyses were performed using SAS version 9.4 (SAS Institute, Inc) and R 3.2.3 (R Foundation for Statistical Computing).

Results

Baseline Demographics, Comorbidities, and Echocardiographic Data at Study Onset

Sixty-eight patients met the study's inclusion criteria. The majority of the study population was female (68%), and the mean age at first echocardiogram for all patients was 75 years. The most common comorbidities were hypertension (94%) and hyperlipidemia (88%) (Table 1). At the time of the initial echocardiographic assessment, the mean duration of RA in the study population was 13 years, and approximately two-thirds of the patients had been prescribed RA medications at that time (Table 1). At baseline, 49% of the patients were positive for rheumatoid factor, and serum inflammatory markers were within relatively normal range (Table 1). Mild AS was present in 88% of patients at baseline, whereas 12%

had moderate AS (associated specific AS variables listed in further detail in Table 2). The mean LVEF was 63%, and a minority (9%) of patients had an LVEF less than 50%. Mean stroke volume and stroke volume index were within normal limits (Table 2).

AS Progression

Mean duration of study follow-up (time between baseline and final echocardiogram) was 4.8 years. Peak AV velocity and mean AV gradient increased during the study period ($P<.001$), whereas AV area and AV dimensionless index decreased ($P<.001$), consistent with progression of AS (Table 3). The crude mean (95% CI for the mean) annual rate of change of peak AV velocity was 0.02 (−0.04 to 0.09) m/s, and the crude annual rate of change of the mean AV gradient was 1.4 (0.3 to 2.6) mm Hg. The annual decrease in AV area was 0.07 (+0.004 to −0.14) cm². Although age at time of echocardiography was associated with a greater rate of decrease in AV area and AV dimensionless index (interaction $P=.02$ and $P=.01$ respectively; Figure 1), ESR was associated with a greater rate of increase in mean AV valve gradient (interaction $P=.001$).

On the basis of this model, the estimated annual rates of change were 1.6 and 0.7 mm Hg for ESR values of 45 and 20 mm/h, respectively (Figure 1C). Biologic users experienced smaller increases in peak AV velocity and mean AV valve gradient over time than nonusers, but they had higher peak AV velocity and mean AV valve gradient at initial echocardiography than nonusers, which may indicate confounding by indication (interaction $P=.03$ and $P=.03$, respectively). Methotrexate use at echocardiography was associated with a greater rate of increase in mean AV valve gradient in users than in nonusers (interaction $P=.006$). Hydroxychloroquine use at echocardiography was associated with a greater rate of decrease in AV dimensionless index in users than in nonusers (interaction $P=.04$). On Kaplan-Meier estimates, 19% (95% CI, 6% to 30%) of the study population had progression from mild to moderate AS after 5 years (only 1 patient had progression from mild to severe during the course of the study), whereas 29% (95% CI, 0% to 55%) had progression from moderate to severe AS 5 years after initial echocardiography.

Discussion

To our knowledge, this is the only study that has investigated the rate of progression of AS in the RA population. Given the increasing incidence of both AS (13) and RA (2) in the elderly population and current national demographic trends, the prevalence of patients with RA who present with AS will likely continue to increase. Therefore, it is critical to ascertain the rate of progression of AS in this unique population and thereby inform the appropriate timing of subsequent imaging surveillance.

The rate of progression of AS in the general population (including patients with mild and moderate AS) has been reported to range from a peak AV velocity annual increase between 0.18 and 0.33 m/s, a mean gradient increase between 6 and 8 mm Hg a year, and a decrease in AV area between 0.08 and 0.4 cm² a year (15,26–29). Our study found that patients with RA have a less marked rate of progression of AS than does the general population (an annual increase in peak AV velocity of 0.02 m/s and mean gradient of 1.4 mm Hg) despite a similar annual decrease in AV area of 0.07 cm².

This finding initially seems counterintuitive given the presumption that calcific AS is, in part, driven by an inflammatory process and RA induces systemic inflammation. Specifically, the current understanding of the pathophysiologic mechanism underlying the development of calcific AS is that the development of AS begins with an initial inflammatory phase characterized by low-density lipoprotein accumulation and oxidation (30,31) and increased interleukin-1 β and transforming growth factor-1 β signaling (32,33) with resultant macrophage and lymphocyte aortic tissue infiltration (34,35). However, although this inflammatory model may be the mechanism for the development of AS, a distinct pathophysiologic mechanism has been postulated to be responsible for the actual progression of AS and is predicated on pathologic and imaging studies finding that pro-calcific pathways induce the accumulation of cartilage and bone on the AV.

This model, in which inflammation leads to development of calcific AS but a separate pathophysiologic pathway involved with bone formation leads to progression of AS, may help to elucidate the findings of both prior RA and VHD studies and our study. For example, studies (12,36) have found a high incidence of VHD in the RA population, and this could be due to the increased inflammatory state present in these patients. However, the progression of AS, which is dependent on cartilage and bone formation, may be uniquely inhibited in the RA population because of the presence of tumor necrosis factor and interleukin-1, which incite osteoclast activation and ultimately bone resorption (37). More detailed molecular studies and further understanding of the pathophysiologic mechanism underpinning the progression of AS in the RA population are needed to more fully understand the disease process.

A potential alternative explanation to our finding that progression of AS in patients with RA is less than that in the general population may be the use of immunosuppressive therapy in our study population. If inflammation at least drives the initial phases of AS, then the use of systemic anti-inflammatory agents in the RA population may actually serve to limit AS progression more so than in the general population, who are less likely to be receiving immunosuppressive therapy. This hypothesis is supported by our finding that the rate of AS progression was higher in patients who had an increased ESR.

Limitations

The population-based design of the study with extensive follow-up and the use of complete (inpatient and outpatient) contemporary medical record documentation strengthens our work by providing complete ascertainment of study outcomes. However, echocardiography was completed as part of routine clinical practice and, as a result, patients with subclinical disease may not have been identified. Although we did not have a comparison group, we compared the results of our study with the known AS progression rates described in the general population (15,26–29). Whether any of these studies included patients with RA was not reported, but, if present, their percentage of the total study population is likely small. Our study focused on mild and moderate AS given that we wanted to understand the rate of progression of AS in these patients so as to inform clinical decision making about when repeat surveillance imaging might be warranted. Assessment of the rate of progression of severe AS in the RA population would be of interest in future studies. The trials assessing

AS progression in the general population have ranged from including patients with only moderate or greater AS (15) to including the entire spectrum of AS (mild, moderate, and severe) (29). Finally, this study evaluated patients who were being treated or evaluated for RA who had relatively normal levels of systemic inflammatory markers throughout the duration of the study and, therefore, the impact of untreated disease on AS progression cannot be derived from our study cohort.

Conclusion

The progression of AS in the RA population has not previously been investigated. This study found that the rate of progression of AS in patients with RA is less than that in the general population. The exact mechanism for this finding is uncertain. Regardless of potential cause, the finding that AS progression in the RA population is no more severe than that in the general population indicates that adherence to current recommended echocardiographic surveillance guidelines for mild AS (every 3–5 years) and moderate AS (every 1–2 years) (14) is reasonable in the patient with RA who has AS.

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Abbreviations

AS	aortic stenosis
AV	aortic valve
ESR	erythrocyte sedimentation rate
LVEF	left ventricular ejection fraction
LVOT	left ventricular outflow tract
RA	rheumatoid arthritis
VHD	valvular heart disease

References

1. Lawrence RC, Helmick CG, Arnett FC, Deyo RA, Felson DT, Giannini EH, et al. Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. *Arthritis Rheum.* 1998 May; 41(5):778–99. [PubMed: 9588729]
2. Crowson CS, Matteson EL, Myasoedova E, Michet CJ, Ernste FC, Warrington KJ, et al. The lifetime risk of adult-onset rheumatoid arthritis and other inflammatory autoimmune rheumatic diseases. *Arthritis Rheum.* 2011 Mar; 63(3):633–9. [PubMed: 21360492]
3. Wolfe F, Mitchell DM, Sibley JT, Fries JF, Bloch DA, Williams CA, et al. The mortality of rheumatoid arthritis. *Arthritis Rheum.* 1994 Apr; 37(4):481–94. [PubMed: 8147925]

4. Solomon DH, Karlson EW, Rimm EB, Cannuscio CC, Mandl LA, Manson JE, et al. Cardiovascular morbidity and mortality in women diagnosed with rheumatoid arthritis. *Circulation*. 2003 Mar 11; 107(9):1303–7. [PubMed: 12628952]
5. Hollan I, Meroni PL, Ahearn JM, Cohen Tervaert JW, Curran S, Goodyear CS, et al. Cardiovascular disease in autoimmune rheumatic diseases. *Autoimmun Rev*. 2013 Aug; 12(10):1004–15. Epub 2013 Mar 27. [PubMed: 23541482]
6. Wolfe F, Michaud K. Heart failure in rheumatoid arthritis: rates, predictors, and the effect of anti-tumor necrosis factor therapy. *Am J Med*. 2004 Mar 1; 116(5):305–11. [PubMed: 14984815]
7. Guedes C, Bianchi-Fior P, Cormier B, Barthelemy B, Rat AC, Boissier MC. Cardiac manifestations of rheumatoid arthritis: a case-control transesophageal echocardiography study in 30 patients. *Arthritis Rheum*. 2001 Apr; 45(2):129–35. [PubMed: 11324775]
8. Bartoloni E, Shoenfeld Y, Gerli R. Inflammatory and autoimmune mechanisms in the induction of atherosclerotic damage in systemic rheumatic diseases: two faces of the same coin. *Arthritis Care Res (Hoboken)*. 2011 Feb; 63(2):178–83. [PubMed: 20740611]
9. Jacobsson LT, Turesson C, Gulfe A, Kapetanovic MC, Petersson IF, Saxne T, et al. Treatment with tumor necrosis factor blockers is associated with a lower incidence of first cardiovascular events in patients with rheumatoid arthritis. *J Rheumatol*. 2005 Jul; 32(7):1213–8. [PubMed: 15996054]
10. Montecucco C, Gobbi G, Perlini S, Rossi S, Grandi AM, Caporali R, et al. Impaired diastolic function in active rheumatoid arthritis: relationship with disease duration. *Clin Exp Rheumatol*. 1999 Jul-Aug; 17(4):407–12. [PubMed: 10464549]
11. Mody GM, Stevens JE, Meyers OL. The heart in rheumatoid arthritis: a clinical and echocardiographic study. *Q J Med*. 1987 Nov; 65(247):921–8. [PubMed: 3455547]
12. Kitas G, Banks MJ, Bacon PA. Cardiac involvement in rheumatoid disease. *Clin Med (Lond)*. 1(1): 2001–Feb. 18–21.
13. Faggiano P, Antonini-Canterin F, Baldessin F, Lorusso R, D'Aloia A, Cas LD. Epidemiology and cardiovascular risk factors of aortic stenosis. *Cardiovasc Ultrasound*. 2006 Jul 1; 4:27. [PubMed: 16813661]
14. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Guyton RA, et al. ACC/AHA Task Force Members. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014 Jun 10; 129(23):2440–92. Epub 2014 Mar 3. Erratum in: *Circulation*. 2014 Jun 10; 129(23):e650. [PubMed: 24589852]
15. Otto CM, Burwash IG, Legget ME, Munt BI, Fujioka M, Healy NL, et al. Prospective study of asymptomatic valvular aortic stenosis: clinical, echocardiographic, and exercise predictors of outcome. *Circulation*. 1997 May 6; 95(9):2262–70. [PubMed: 9142003]
16. Maradit Kremers H, Crowson CS, Gabriel SE. Rochester Epidemiology Project: a unique resource for research in the rheumatic diseases. *Rheum Dis Clin North Am*. 2004 Nov; 30(4):819–34. vii. [PubMed: 15488695]
17. Myasoedova E, Crowson CS, Kremers HM, Therneau TM, Gabriel SE. Is the incidence of rheumatoid arthritis rising? Results from Olmsted County, Minnesota, 1955–2007. *Arthritis Rheum*. 2010 Jun; 62(6):1576–82. [PubMed: 20191579]
18. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum*. 1988 Mar; 31(3):315–24. [PubMed: 3358796]
19. Myasoedova E, Crowson CS, Nicola PJ, Maradit-Kremers H, Davis JM 3rd, Roger VL, et al. The influence of rheumatoid arthritis disease characteristics on heart failure. *J Rheumatol*. 2011 Aug; 38(8):1601–6. Epub 2011 May 15. [PubMed: 21572155]
20. Baumgartner H, Hung J, Bermejo J, Chambers JB, Evangelista A, Griffin BP, et al. American Society of Echocardiography; European Association of Echocardiography. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. *J Am Soc Echocardiogr*. 2009 Jan; 22(1):1–23. Erratum in: *J Am Soc Echocardiogr*. 2009 May; 22(5):442. [PubMed: 19130998]
21. Quinones MA, Otto CM, Stoddard M, Waggoner A, Zoghbi WA. Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of

Echocardiography. Recommendations for quantification of Doppler echocardiography: a report from the Doppler Quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography. *J Am Soc Echocardiogr*. 2002 Feb; 15(2):167–84. [PubMed: 11836492]

22. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Chamber Quantification Writing Group; American Society of Echocardiography's Guidelines and Standards Committee; European Association of Echocardiography. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr*. 2005 Dec; 18(12):1440–63. [PubMed: 16376782]
23. Bonow RO, Carabello BA, Kanu C, de Leon AC Jr, Faxon DP, Freed MD, et al. American College of Cardiology/American Heart Association Task Force on Practice Guidelines; Society of Cardiovascular Anesthesiologists; Society for Cardiovascular Angiography and Interventions; Society of Thoracic Surgeons. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease): developed in collaboration with the Society of Cardiovascular Anesthesiologists: endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. *Circulation*. 2006 Aug 1; 114(5):e84–231. Errata in: *Circulation*. 2007 Apr 17; 115(15):e409. *Circulation*. 2010 Jun 15; 121(23):e443. [PubMed: 16880336]
24. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al. CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009 May 5; 150(9):604–12. Erratum in: *Ann Intern Med* 2011 Sep 20; 155(6):408. [PubMed: 19414839]
25. Ho KK, Pinsky JL, Kannel WB, Levy D. The epidemiology of heart failure: the Framingham Study. *J Am Coll Cardiol*. 1993 Oct; 22(4 Suppl A):6A–13A. [PubMed: 8509564]
26. Brener SJ, Duffy CI, Thomas JD, Stewart WJ. Progression of aortic stenosis in 394 patients: relation to changes in myocardial and mitral valve dysfunction. *J Am Coll Cardiol*. 1995 Feb; 25(2):305–10. [PubMed: 7829781]
27. Rosenhek R, Rader F, Loho N, Gabriel H, Heger M, Klaar U, et al. Statins but not angiotensin-converting enzyme inhibitors delay progression of aortic stenosis. *Circulation*. 2004 Sep 7; 110(10):1291–5. Epub 2004 Aug 30. [PubMed: 15337704]
28. Roger VL, Tajik AJ, Bailey KR, Oh JK, Taylor CL, Seward JB. Progression of aortic stenosis in adults: new appraisal using Doppler echocardiography. *Am Heart J*. 1990 Feb; 119(2 Pt 1):331–8. [PubMed: 2301222]
29. Nassimiha D, Aronow WS, Ahn C, Goldman ME. Rate of progression of valvular aortic stenosis in patients > or = 60 years of age. *Am J Cardiol*. 2001 Mar 15; 87(6):807–9. A9. [PubMed: 11249913]
30. Otto CM, Kuusisto J, Reichenbach DD, Gown AM, O'Brien KD. Characterization of the early lesion of 'degenerative' valvular aortic stenosis: histological and immunohistochemical studies. *Circulation*. 1994 Aug; 90(2):844–53. [PubMed: 7519131]
31. Olsson M, Thyberg J, Nilsson J. Presence of oxidized low density lipoprotein in nonrheumatic stenotic aortic valves. *Arterioscler Thromb Vasc Biol*. 1999 May; 19(5):1218–22. [PubMed: 10323772]
32. Kaden JJ, Dempfle CE, Grobholz R, Tran HT, Kilic R, Sarikoc A, et al. Interleukin-1 beta promotes matrix metalloproteinase expression and cell proliferation in calcific aortic valve stenosis. *Atherosclerosis*. 2003 Oct; 170(2):205–11. [PubMed: 14612199]
33. Jian B, Narula N, Li QY, Mohler ER 3rd, Levy RJ. Progression of aortic valve stenosis: TGF-beta1 is present in calcified aortic valve cusps and promotes aortic valve interstitial cell calcification via apoptosis. *Ann Thorac Surg*. 2003 Feb; 75(2):457–65. [PubMed: 12607654]
34. Wallby L, Janerot-Sjöberg B, Steffensen T, Broqvist M. T lymphocyte infiltration in non-rheumatic aortic stenosis: a comparative descriptive study between tricuspid and bicuspid aortic valves. *Heart*. 2002 Oct; 88(4):348–51. [PubMed: 12231589]

35. Olsson M, Rosenqvist M, Nilsson J. Expression of HLA-DR antigen and smooth muscle cell differentiation markers by valvular fibroblasts in degenerative aortic stenosis. *J Am Coll Cardiol*. 1994 Dec; 24(7):1664–71. [PubMed: 7963113]
36. Prasad M, Hermann J, Gabriel SE, Weyand CM, Mulvagh S, Mankad R, et al. Cardiorheumatology: cardiac involvement in systemic rheumatic disease. *Nat Rev Cardiol*. 2015 Mar; 12(3):168–76. Epub 2014 Dec 23. [PubMed: 25533796]
37. Deal C. Bone loss in rheumatoid arthritis: systemic, periarticular, and focal. *Curr Rheumatol Rep*. 2012 Jun; 14(3):231–7. [PubMed: 22527950]

Figure 1.

Rate of Progression of Aortic Stenosis According to Age and Erythrocyte Sedimentation Rate (ESR). A and B, Association of aortic valve (AV) area and dimensionless index with age in years. C, Association of mean AV gradient with ESR (mm/h).

Table 1**Baseline Characteristics of Study Population^a**

Characteristic	Study Population (N=68) ^b
Demographics	
Age, y	75±10
Female, No. (%)	46 (68)
Past medical history	
RA duration, y	13±11
CAD	25 (37)
HF	14 (21)
Hypertension	64 (94)
Hyperlipidemia	60 (88)
Smoking, current (n=62)	10 (16)
Smoking, previous (n=62)	27 (44)
Atrial fibrillation/atrial flutter	10 (15)
OSA	4 (6)
COPD	13 (19)
Diabetes mellitus	23 (34)
Reduced kidney function	20 (30)
Current RA medications	
Methotrexate	21 (31)
Hydroxychloroquine	17 (25)
Other DMARDs	7 (10)
Biologics	5 (7)
Glucocorticoids	30 (44)
Laboratory	
Rheumatoid factor positive	33 (49)
C-reactive protein, mg/L (n=20)	3.6 (1.6–7.9)
Erythrocyte sedimentation rate, mm/h (n=32)	29 (12–45)
RA disease characteristics	
Erosions/destructive changes	31 (46)
Severe extra-articular manifestations	7 (10)
Rheumatoid nodules	13 (19)

Abbreviations: CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; DMARDs, disease-modifying antirheumatic drugs; HF, heart failure; OSA, obstructive sleep apnea; RA, rheumatoid arthritis.

^a At time of initial echocardiography after diagnosis of RA, except for smoking variable, which was at time of diagnosis of RA.

^b Continuous variables are expressed as mean (SD), except for laboratory values, which are expressed as median (interquartile range). Categorical variables are expressed as count and percentage of patients.

Table 2**Baseline Echocardiographic Data of Study Population**

Variable	Study Population (N=68) ^a
Heart rate	69±14
Systolic blood pressure, mm Hg	133±22
Diastolic blood pressure, mm Hg	69±13
Body surface area, kg/m ² (n=55)	1.8±0.2
AS ^b	
Mild	60 (88)
Moderate	8 (12)
Peak AV velocity, m/s	2.4±0.4
Mean AV gradient, mm Hg	13±7
AV area, cm ² ^c	1.8±0.5
AV dimensionless index	0.5±0.1
Stroke volume, cc	92±22
Stroke volume index, cc/m ² , (n=34)	52±12
Cardiac output, L/min	6.2±1.6
Cardiac index, L/min per m ²	3.4±0.9
LVEF, %	63±10
LVEF<50%	6 (9)

Abbreviations: AS, aortic stenosis; AV, aortic valve; LVEF, left ventricular ejection fraction.

^aContinuous variables are expressed as mean (SD). Categorical variables are expressed as count and percentage of patients.

^bMild AS, peak jet velocity 2.0 to 2.9 m/s; moderate AS, 3.0 to 3.9 m/s.

^cCalculated by continuity equation.

Table 3

Annual Rate of Progression of Aortic Stenosis

Echocardiographic Variable	Mean (95% CI) at AS Diagnosis ^a	Mean (95% CI) at 5-Year Follow-Up ^a	Adjusted Annual Rate of Change (SE) ^a	Crude Mean Annual Rate of Change (SD/SE)
Peak AV velocity, m/s	2.3 (2.2, 2.5)	2.6 (2.4, 2.7)	0.05 (0.01)	0.02 (0.26/0.03)
Mean AV gradient, mm Hg	13 (11, 15)	18 (15, 20)	1.0 (0.18)	1.4 (4.6/0.59)
AV area, cm ² ^b	1.9 (1.8, 2.0)	1.7 (1.5, 1.8)	−0.04 (0.01)	−0.07 (0.29/0.04)
AV dimensionless index	0.6 (0.5, 0.6)	0.5 (0.4, 0.5)	−0.01 (0.003)	−0.01 (0.11/0.01)

Abbreviations: AS, aortic stenosis; AV, aortic valve.

^aAge and sex adjusted. Rate of change significantly different from zero ($P<.001$) for all 4 echocardiographic measurements.

^bCalculated by continuity equation.