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REVIEW ARTICLE

Viewpoint: The ENIGMAS Trial – When Should We Treat Patients with Moderate Aortic Stenosis?

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Aortic stenosis (AS) is the most frequent valvular heart disease encountered in our daily practice. Although there are clear guidelines for severe AS management, cardiologists often have few treatment options for patients with moderate AS; however, there is higher mortality in this patient subgroup versus an age-matched population. The authors reviewed all of the studies on moderate AS, summarized the factors that increase disease progression and discussed an ideal trial design to prospectively evaluate AS progression factors using modern cardiology tools such as strain and magnetic resonance imaging. (Echocardiography 2012;0:1-13)

Key words: ENIGMAS trial, magnetic resonance imaging, moderate aortic stenosis, outcome

Aortic stenosis (AS) is the most encountered valvular disease. According to the 2012 ESC guidelines,[1] moderate AS is defined as an aortic valve area of 1.0–1.5 cm^2 (0.6–0.9 cm^2/m^2), a peak velocity (PV) between 3 and 4 m/sec, or a mean gradient of 20–40 mmHg with normal flow. Cardiologists have a defined treatment course for severe AS patients, whether they are symptomatic or not. However, in moderate AS patients, there is not a clear agreement on how to reduce excess mortality, which is detailed in the text and tables below.[2–5]

Significance and Difficulty of the Problem Being Addressed:

The main question is why do these patients die and how can cardiologists reduce mortality rates in these patients? There are some progression factors that have been identified for the entire AS spectrum that could influence mortality in this patient subgroup, but none of the studies address moderate AS exclusively. Majority of these studies have major limitations and are not prospective. Some of these studies included mixed populations with variable degrees of AS, and the study parameters did not utilize all of the cardiologic investigational tools such as three-dimensional (3D) left ventricular (LV) ejection fraction (EF), strain and magnetic resonance imaging (MRI). Furthermore, several of these studies that include moderate AS contradict one another (Refs 6–10 vs. 11–13 and 12 vs. 14).

AS Incidence:

Degenerative aortic valve disease evolves slowly from aortic sclerosis to AS. Aortic sclerosis and stenosis are found in approximately 29% and 2–9% of adults older than 65 years, respectively.[4] Of the 5201 subjects that were enrolled in the Cardiovascular Health Study, aortic valve sclerosis was present in 26% and AS in 2% of the patients who were older than 65. In the subjects who were older than 75, sclerosis was present in 37% and stenosis in 2.6% of these patients.[15] In the 75- to 86-year-old group from another study, the prevalence of severe aortic valve stenosis was 2.9%.[16] In an observational study [17] that enrolled 953 subjects aged 25–74 years, the overall degenerative aortic valve disease prevalence was 28%, defined as the presence of valvular sclerosis, calcification, or thickening on echocardiographic examination. The prevalence of degenerative aortic valve disease was 7% in patients aged 35–44 years, 19% in patients aged 45–54 years, 30% in patients aged 55–64 years, 38% in patients aged 65–74 years, and 64% in patients aged 75–84 years. No significant differences were reported between men and women.

Death in Moderate AS:

The results of several studies proved suspicions that even mild aortic disease may increase

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mortality.[2] People with mild or moderate AS and aortic sclerosis have an increased death rate compared with an age-matched healthy population. In one study,[3] asymptomatic adults with moderate-to-severe AS were studied at baseline; the authors found a cardiovascular-associated death rate of 3.5% at a mean follow-up (FU) of 2.5 years (4 symptomatic patients died). In 1999, the results of a prospective study [4] with a 5-year FU were published; a cardiac-associated death rate of 6.1% was found in the general population with normal aortic valves, a 10.1% death rate was found in patients with aortic sclerosis, and a 19.6% death rate was found in AS patients. Although the mean age of study patients was 73 years and there was no reported aortic valve surgery (AVS), this study was relevant for the general population that has various risk factors and is also relevant to our review. There is a 4% increase in cardiac-associated death for aortic sclerosis patients and an additional 13.5% increase in cardiac-associated death for AS patients. In 2004, Rosenhek et al.[5] reported a cardiac death rate of 8.7% in a population with moderate AS and a mean age of 67 years at the initial examination. Nineteen percent of patients (n = 33) had AVS for severe AS at the 48-month FU. The largest study[11] evaluating medical treatment in moderate AS patients reported a cardiac death rate of 6.0%, which was similar to the general population; however, the authors considered this study to not be significant for death rate in moderate AS patients because a super-selected population was enrolled (among exclusion criteria were coronary artery disease (CAD) history, stroke, and diabetes mellitus). The exact death rates and event-free survival can be found in the tables below.

Trials Involving Patients with Moderate AS:

In this presentation, the authors will not review or discuss severe AS outcomes and will only discuss moderate AS patient outcomes.

The first step in our research was identifying all of the moderate AS studies. The large majority of studies included moderate AS among the AS patient spectrum of mild, moderate, and severe sclerosis, either alone or combined. For that reason, the authors of this review categorized studies by the baseline inclusion criteria. We found 4 major groups of enrolled patients as reviewed and discussed below. The 4 groups were patients with mild-to-moderate AS (Table I),[5,11,12,18–20] patients with moderate AS (Table II),[3,21,22] patients with mild, moderate, and severe AS (Table III) [14,23–29] and patients with moderate-to-severe AS (Table IV).[30–36] All of the tables reproduce the hallmark findings from each study, with emphasis on patient characteristics, AS progression, outcomes, survival, limitations, and conclusions.

Even though all of the essential moderate AS data can be easily read in the tables, the authors would like to briefly discuss the studies that refer to echocardiography as a tool for stratifying outcomes, and also to debate whether medical interventions had any impact in disease regression.

Monin et al. enrolled 107 patients with a baseline PV of 3.5–4.4 m/sec. Seventy-two percent of these patients had severe AS, of which 62 became symptomatic at 2 years.[35] He concluded that the female sex, PV, and brain natriuretic peptide (BNP) at baseline were correlated with AS progression and developed a score to best stratify outcomes in these patients. Twenty-month survival was 80% for the patients within the first score quartile versus 7% for the patients within the fourth score quartile. A landmark trial, the study of Marechaux et al.[36] included 135 patients with a mean age of 64 years with moderate or severe AS (mean PV of 3.8 $\pm$ 0.8 m/sec, 53% had severe AS) and with a normal stress test at the baseline, from which 67 had an event at 20 months. He found that an age of $\geq$65 years, diabetes, LV hypertrophy, resting mean gradient >35 mmHg, and an exercise-induced mean gradient increase of >20 mmHg (by multivariate analysis) were independent predictors of death and AVS. Increased progression was present in those patients with a resting mean gradient of >35 mmHg and an exercise-induced mean gradient increase of >20 mmHg. Although this was a remarkable study, it lacks strain analysis, 3D LVEF, twist and torsion; furthermore, an MRI was not performed for fibrosis evaluation. Moreover, the included population was not limited to moderate AS patients. A recent substudy from the SEAS trial that was not included in the tables described that increased left atrial systolic force is a marker of increased cardiovascular events at 4.3 years FU.[37] Although cardiologists become more and more familiar with strain techniques [38] with time, few studies clarified the role of strain in AS. One of the studies demonstrated that despite an unchanged LVEF, strain gradually decreased as AS severity increased; therefore, global longitudinal strain might be useful to assess subtle changes in LV function in mild, moderate, and severe AS patients.[26] However, there are important limitations: this was a nonprospective investigation, only longitudinal strain was measured, there was a small sample size, the groups were nonheterogenic, and no progression was reported. The second study by Ng et al.[28] evaluated the systolic function of 420 patients with aortic sclerosis and stenosis with a mean age of 61 years and a normal EF. The author found that

TABLE I

Trials with Mild-to-Moderate AS as Baseline Inclusion Criteria

Author/Parameter	Patients	Age	Baseline Aortic Valve	FU	Progression (m/sec/year If Not Specified Otherwise)	Predictors of Outcome	Endpoint	Limitations	Conclusions, Survival
Ngo et al.[18]	87 Patients, 81% men	70.7 ± 10 years	61% with mild and 31% with moderate AS	2.5 years	6.3 ± 13 mm Hg/year mean rate of progression	Independent clinical factors associated with a progression of 5 mm Hg/year or greater: history of smoking and increased BMI	To identify clinical predictors of progression of AS	Retrospective	BMI and a history of smoking are independent predictors of significant progression of AS, defined as >5 mmHg/year
Rosenhek et al.[5]	176 Asymptomatic patients (73 women) with mild-to-moderate AS (mean PV of 3.13 ± 0.39 m/sec) divided into no events and events group	58 ± 19 years	No events group (n = 67, PV of 3.06 ± 0.38 m/sec) Events group (n = 109, PV of 3.25 ± 0.37 m/sec)	48 ± 19 months	0.24 ± 0.30 (overall population) 0.14 ± 0.18 vs. 0.45 ± 0.38 (no event vs. event) 0.16 ± 0.19 vs. 0.35 ± 0.31 (grade 3–4 calcif. vs. grade 1–2) 0.18 ± 0.19 vs. 0.34 ± 0.42 (no CAD vs. CAD) 0.10 ± 0.14 vs. 0.30 ± 0.33 (<50 years vs. >50 years of age)	Moderate to severe aortic valve calcification, CAD and peak jet velocity were independent predictors of outcome (MA)	Death (n = 34) or AVR (n = 33)	Retrospective Lack of onset of symptoms as endpoint Not all had echo FU	Rapid progression in those with events, with grade 3–4 calcifications, with CAD, with baseline PV > 3 m/sec and age >50 years Event free survival was 95 ± 2%, 75 ± 3% and 60 ± 4% at 1, 3 and 5 years. Mortality was 80% higher than in the general population
Kume et al.[19]	19 Patients >80 years and 21 patients <80 years (mean age of 84 vs. 66 years)	75 years	Mild-to-moderate		Rate of AVA degression: −0.05 ± 0.06 cm^2/year (group >80 years) −0.10 ± 0.08 cm^2/year (group <80 years)	Age	NA	NA	Progression of mild and moderate AS in patients aged 80 years and older was more rapid than that in those aged younger than 80 years
Rossebo et al. (SEAS trial)[11] Prospective.	1873 Patients with mild-to-moderate, asymptomatic AS (mean AVA of 1.28 cm^2) randomized to 40 mg of simvastatin + 10 mg of ezetimibe or placebo.	58 ± 19 years	Placebo group (n = 929, PV of 3.1 ± 0.54 m/sec) Simvastatin + Ezetimibe group (n = 944, PV of 3.09 ± 0.55 m/sec)	52.2 months	0.15 ± 0.01 (placebo group) 0.16 ± 0.01 (Simvastatin + Ezetimibe group)	Simvastatin and ezetimibe reduced the incidence of ischemic cardiovascular events, but not events related to aortic-valve stenosis	The primary outcome was a composite of MACE Similar percentages of deaths and AVR	High incidence of cancer in active arm, low-risk patients enrolled (known CAD, stroke, DM excluded)	Simvastatin and ezetimibe reduced the incidence of ischemic cardiovascular events, but not events related to

(continued)

Table I (continued)

Author/Parameter	Patients	Age	Baseline Aortic Valve	FU	Progression (m/sec/year If Not Specified Otherwise)	Predictors of Outcome	Endpoint	Limitations	Conclusions, Survival
									aortic-valve stenosis in patients with mild-to-moderate AS Similar percentages of MACE, deaths, and AVR (35.3% vs. 38.2%, 10.8% vs. 11.1%, and 29.9% vs. 28.3%) in the placebo vs. active group
Jassal et al. (ASTRONOMER study)[20]	168 Patients	56 ± 13 years	Group I: 2.5–3.0 m/sec; Group II: 3.1–3.5 m/sec; Group III: 3.6–4.0 m/sec, placebo vs. rosuvastatin in all	3.5 years	No difference in progression for placebo vs. rosuvastatin: Group 1: 2.8 ± 0.1 at baseline vs. 3.3 ± 0.7 m/sec at FU Group 2: 3.2 ± 0.1 at baseline vs. 3.9 ± 0.7 m/sec at FU Group 3: 3.7 ± 0.2 at baseline vs. 4.4 ± 0.5 m/sec at FU.	NA	NA	Observational Small sample size Medial TDI, LA volumes, strain, strain rate, and Vp were not available TDI is angle dependent.	Rosuvastatin did not attenuate the progression of diastolic dysfunction
Chan et al. (ASTRONOMER study)[12]	250 Patients randomized double-blind, placebo vs. Rosuvastatin 40 mg.	57 years	Mild-to-moderate AS (mean 3.1 m/sec, range 2.5–4.0 m/sec)	3.5 years	Progression of AS was not different between patients treated with rosuvastatin and those treated with placebo in all tertiles of CRP	PV predicted AS progression (MA). Age, female gender, BMI, and low high-density lipoprotein cholesterol were associated with elevated CRP.	To examine the role of high-sensitivity CRP and its interaction with rosuvastatin on the progression of AS.	Observational	Treatment with rosuvastatin reduces CRP levels, but has no effect on the progression and clinical events of AS. CRP does not predict severity, progression, and prognosis in patients with mild-to-moderate AS

BMI = body mass index; PV = peak velocity; CAD = coronary artery disease; AVA = aortic valve area; NA = nonavailable; AVR = aortic valve replacement; FU = follow-up; DM = diabetes mellitus; AS = aortic stenosis; CRP = C-reactive protein; MACE = major adverse cardiovascular events; MA = multivariate analysis; TDI = tissue Doppler imaging; LA = left atrium; Vp = propagation speed into left ventricle.

longitudinal, radial, and circumferential strain as well as strain rate deteriorated with aortic valve disease progression. Several limitations may be noted: the study was not prospective; thus, there were no progression numbers, the time to symptoms was not specified, twist or torsion were not evaluated, clinical variables were not evaluated, and the measurements were performed on different instruments.

Strain was already utilized in severe AS patients; however, those patients are not our target group.

Until April 2012, there were no MRI studies on moderate AS patients.

AS Progression:

There is a wide variability in AS progression, and each study reported differing AS progression rates depending on the FU interval, comorbidities, and patient age (see Tables I–IV). For example, peak jet velocity rates were as low as 0.15 ± 0.01 m/sec per year in the population without cardiovascular risk factors,[11] and increased to 0.61 ± 0.32 m/sec per year in primary care patients.[29]

High progressors had at least one of the following:

1. Echocardiography parameters: increased baseline jet velocity,[3,5,12,22,25,29,35] increased baseline peak gradient,[33] increased mean gradient,[3] high rate of increase in jet velocity,[3,29] moderate-to-severe aortic valve calcification on echo,[5,22] LV hypertrophy,[36] resting mean gradient >35 mmHg,[36] exercise-induced mean gradient increase >20 mmHg,[36] increased E velocity,[25] bicuspid aortic valve.[25]
2. Clinical parameters: CAD,[5,30] age (>80 years[19, 22, 27, 29], >64 years[30], >65 years[36]), diabetes,[23,36] metabolic syndrome,[33] dialysis,[39,40] increased body mass index (BMI),[18] functional status,[3] history of smoking,[15,18] systolic blood pressure (SBP),[15,27] male gender,[15,33] female gender[35];
3. Biological parameters: increased parathyroid hormone levels,[27] increased baseline BNP,[35] increased C-reactive protein levels (>0.15 mg/dL),[14] high lipoprotein(a) and low-density lipoprotein cholesterol levels.[15]

Treatment with simvastatin and ezetimibe,[11] eplerenone [34] rosuvastatin,[20] or other statins [23] had no influence on AS progression.

Slower AS progression was observed in patients with osteoporosis [21] or bisphosphonate treatment,[24,41] but these studies were too small, retrospective,[21,24] or biased.[21]

The authors of the above study did not discuss very old studies or very small series of AS patients' studies (most of these are found in Ref. 30). Their capability to address this subject was limited by a retrospective design in most cases, potential selection bias, and limited clinical, functional, or exercise data.

AS Pathophysiology:

Aortic stenosis often progresses slowly over a period of years. During this period of pressure overload, the LV adapts by sarcomere replication. This remodeling leads to development of concentric hypertrophy and an increase in LV wall thickness with normal chamber volume. This is enough to counterbalance the increased LV pressure and thus preserve LVEF in the initial stages.[42] Once these physiological mechanisms are surpassed, chronic pressure overload develops and leads to a depressed LVEF because of improper ventricular hypertrophy in response to high LV pressure. Depressed LVEF may also occur because of true myocardial contractility depression, which is explained by alterations in myocardial perfusion in the absence of CAD [43] and ischemia due to increased LV mass. Finally, depressed LVEF may occur because of a prolonged ejection period and fibrosis, which often begins in the subendocardium.[44,45]

Future Directions:

The question in the title is not rhetorical. Because the mortality rate in moderate AS patients is increased, there should be a specific treatment window when medical or surgical interventions for these valvular heart disease patients would be of benefit. Cardiologists should not wait until moderate AS becomes severe, but should aim to nullify the effects of factors that increase mortality and determine whether these patients improve after targeted medical treatment or surgery. Although some progression factors in all AS spectrums may influence mortality, none of the previous studies addressed moderate AS exclusively. Most of these previous studies have major limitations. Because the mortality rate is double or nearly triple in older AS patients compared with an age-matched population, future studies must clearly identify and stratify progression risk factors in moderate AS patients for appropriate treatment.

A more integrated approach in moderate AS patient management would be to develop a risk score by identifying the clinical parameters, echocardiographic parameters (3D, strain, strain rate, twist or torsion at rest and during stress), and MRI parameters (fibrosis extent, LV mass, EF, etc.

TABLE II

Trials with Moderate AS as Baseline Inclusion Criteria

Author/Parameter	Patients	Age	Baseline Aortic Valve	FU	Progression (m/sec/year If Not Specified Otherwise)	Predictors of Outcome	Endpoint	Limitations	Conclusions, Survival
Otto et al.[3] Prospective	123 Asymptomatic moderate AS patients, 70% males, mean PV of 3.6 ± 0.6 m/sec, mean AVA of 1.3 ± 0.5 cm^2	63 ± 16 years	No events group -asymptomatic -AS (n = 67, PV of 3.3 ± 0.5 m/sec) Events groups AS (n = 56, PV of 3.9 ± 0.5 m/sec)	2.5 ± 1.4 years	0.23 ± 0.22 m/sec (no events group) 0.45 ± 0.42 m/sec (events group) 0.32 ± 0.34 m/sec (overall)	Jet velocity at baseline, the rate of change in jet velocity, and functional status score (MA)	Death (n = 3.5) or AVR (n = 39)	Nonrandomized, mixed population, substantial overlap	In adults with asymptomatic moderate AS at baseline, the rate of hemodynamic progression and clinical outcome are predicted by jet PV, rate of change in jet velocity and functional status Survival for overall population was 93 ± 5% at 1 year, 67 ± 10% at 2 years and 34 ± 15% at 3 years
Skolnick et al.[21]	18 Patients on OT and 37 patients not on OT	82 years	Mean baseline AVA was 1.33 cm^2 (1.29 ± 0.46 cm^2-OT group vs. 1.39 ± 0.42 cm^2-controls)	2.4 ± 1.0 years	AVA regression was: −0.22 ± 0.22 cm^2 in those not on OT −0.10 ± 0.18 cm^2 in patients on OT	OT associated with AS progression (MA)	NA	Biased Retrospective	OT is strongly and independently associated with decreased progression of AS
Seo et al.[22]	153 Asymptomatic Korean patients, 31 males	62.1 ± 11.9 years	Mild AS (peak aortic jet velocity ≥2.0 and <3.0 m/sec)	6.0 years	2.6 ± 0.3 (fast progressors) 2.2 ± 0.3 (slow progressors)	Baseline PV and incidence of moderate-to -severe AV calcification related to progression	Progression and cardiac events (death or AVR)	NA	The progression of AS was slower than expected and it was related to age, the baseline PV, and AV calcifications Event-free survival rate at FU: 87.5 ± 8.3% vs. 100%, respectively, for fast vs. slow progressors

PV = peak velocity; AVA = aortic valve area; AVR = aortic valve replacement; FU = follow-up; AS = aortic stenosis; NA = nonavailable; OT = osteoporosis treatment (bisphosphonates, calcitonin, or estrogen receptor modulators); MA = multivariate analysis.

TABLE III

Trials with Mild, Moderate and Severe AS as Baseline Inclusion Criteria

Author/Parameter	Patients	Age	Baseline Aortic Valve	FU	Progression (m/sec/year If Not Specified Otherwise)	Predictors of Outcome	Endpoint	Limitations	Conclusions, Survival
Imai et al.[14]	135 Patients	76 years	Mild AS (n = 18, 71 ± 10 years), Moderate AS (n = 57, 77 ± 9), Severe AS (n = 60, 78 ± 8)	23 ± 11 months	Degression of AVA <0.15 cm^2/year-slow progressors (n = 25), Degression of AVA >0.15 cm^2/year-fast progressors (n = 22)	CRP (>0.15 mg/dL) was an independent predictor of severe AS CRP higher in the rapid progression group	Assess whether CRP influences AS	Retrospective	CRP predicts severity, progression, and prognosis in patients with asymptomatic AS Survival was lower in the high CRP group (33 deaths (−23 cardiac), 25 hospitalization due to congestive heart failure, and 13 AVR)
Kamalesh et al.[23]	166 Patients with calcific AS, of which 72 (43%) had DM	70 ± 9 years	Calcific AS was mild in 66 subjects, moderate in 75 and severe in 25 patients.	Mild AS: 2.93 years Moderate AS: 2.40 years Severe AS: 1.69 years	Progression in moderate AS group: −0.14 ± 0.13 cm^2/year in non-DM group −0.25 ± 0.20 cm^2/year in DM group	Diabetes predicts calcific AS severity	NA	Retrospective	Calcific AS severity progresses faster in DM than in non-DM subjects with moderate calcific AS at baseline. Statins do not affect progression of calcific AS
Sterbakova et al.[24]	103 Patients with preserved renal function 57 had mild AS and 46 moderate-to -severe AS	68 ± 10 years	Bisphosphonates group (n = 28), of whom 22 had mild and 6 moderate-to -severe AS	29 ± 13 months	0.1 ± 3.3 mmHg/year – biophosphonates group 2.8 ± 3.3 mm Hg/year controls	Progression inversely correlated with biophosphonates treatment	AS progression	Retrospective	Bisphosphonate treatment was independently associated with slower progression of mild AS in patients with preserved renal function
Ryu et al.[25]	325 Korean patients	67 ± 13 years	Mild AS in 207 (64%), moderate AS in 81 (25%), and severe AS in 37 patients (11%)	Retrospective, 2003–2008	0.12 ± 0.23 (mean progression rate) 0.28 ± 0.36 m/sec/year (severe AS) 0.14 ± 0.26 (moderate AS) 0.09 ± 0.18 (mild AS) 0.23 ± 0.35 vs. 0.11 ± 0.20 in bicuspid vs. tricuspid AS	Baseline PV, bicuspid aortic valve, and E velocity (MA)	NA	Retrospective	The progression rate of AS in Korean patients is slower than that reported in Western population
Miyazaki et al.[26]	113 Patients, 38% males Mild AS (n = 49), Moderate AS (n = 25), Severe AS (n = 39)	73.3 ± 8.8 years	Mild (PV of 2.7 ± 0.3 m/sec), moderate (PV of 3.7 ± 0.4 m/sec), and severe	No FU, observational	GLS showed significant differences among the 3 groups (mild: 17.1 ± 3.0%,	GLS was significantly correlated with AVA, LVEF, E', LV mass	NA	Observational. Only long. strain measured. Small size,	Despite unchanged LVEF, GLS gradually decreased as severity of AS

(continued)

Table III (continued)

Author/Parameter	Patients	Age	Baseline Aortic Valve	FU	Progression (m/sec/year If Not Specified Otherwise)	Predictors of Outcome	Endpoint	Limitations	Conclusions, Survival
			(PV of 4.9 ± 0.5 m/sec) AS with mean AVA of 1.0 ± 0.3 cm^2		moderate: 16.4 ± 3.0%, and severe: 14.5 ± 3.9%, P = 0.003)	index, and MPG, LVEF, and hypertension were independently associated with GLS (MA)		nonheterogenic. Blood pressure not measured, obtained from records	increased. GLS might be useful to assess subtle changes in LV function in AS patients
Iwata et al.[27]	34 Chronic hemodialysis patients	69 ± 8 years	Mild (n = 9), moderate (n = 20), and severe AS (n = 5); AVA of 1.31 ± 0.31 cm^2 and mean PV of 2.7 ± 0.56 m/sec	20 ± 9 months (rapid progressors) 26 ± 8 months (slow progressors)	AVA reduction of: 0.29 ± 0.19 cm^2/year (rapid progression group, 20 patients) 0.03 ± 0.02 cm^2/year (slow progression group, 14 patients)	PTH level and SBP (MA) associated with AS progression	To define risk factors affecting AS progression in chronic hemodialysis patients	Retrospective	AS progression was accelerated in the presence of high PTH and SBP in patients with chronic hemodialysis
Ng et al.[28]	420 Patients, 60.7% men with aortic sclerosis and AS had multidirectional strain and SR imaging performed	66.1 ± 14.5 years	Aortic sclerosis (n = 118), mild AS (n = 81), moderate AS (n = 109), severe AS (n = 112) Symptoms in 58.7% of moderate and severe AS	No FU	Strain (%) decreased for the 4 groups as following (from sclerosis /mild/moderate to severe AS): Long. strain: −20.3 ± 1.9, −18.0 ± 1.7, −17.1 ± 2.0, −15.1 ± 2.4 Circ. strain: −22.2 ± 3.3, −21.1 ± 3.7, −19.7 ± 3.3, −17.9 ± 4.0 Radial strain: 53.7 ± 14.8, 50.3 ± 17.5, 47.4 ± 13.2, 41.1 ± 15.7	NA	Identify changes in multidirectional strain and SR in patients with AS	Not prospective, not randomized, no progression reported, patients with WMA or history of MI excluded, no twist/ torsion/time to symptoms	In aortic valve disease patients with normal LVEF, there is a myocardial dysfunction that appears to start in the subendocardium and progresses to transmural dysfunction with increasing AS severity (by strain). Symptomatic moderate and severe AS patients had a decreased strain compared with asymptomatic patients
Nistri et al.[29]	153 Asymptomatic patients, 65% men	77 ± 9 years	135 patients with mean PV of 3.2 ± 0.6 m/sec 64 patients (42%) had mild, 71 (46%) moderate, and 18 (12%) severe AS	4.9 ± 2.7 years	0.61 ± 0.32 (fast progression, 49 patients [32%]) 0.10 ± 0.16 (slow progression, 104 patients [68%])	The independent predictors of mortality were the yearly change in PV and age (MA); The predictors of the composite endpoint of death and AVR were the yearly change in PV and PV on the initial echo	All-cause mortality and a composite of all-cause mortality and AVR 40 died and 48 underwent AVR	Retrospective	Primary care patients with asymptomatic AS are usually elderly and frequently develop rapid hemodynamic progression, which independently predicts, not only AVR, but also overall mortality

(continued)

Table III (continued)

Author/Parameter	Patients	Age	Baseline Aortic Valve	FU	Progression (m/sec/year If Not Specified Otherwise)	Predictors of Outcome	Endpoint	Limitations	Conclusions, Survival
									Survival worse in patients with mild-to-moderate AS at baseline and rapid hemodynamic progression and in patients with severe AS. Similar event-free survival

PV = peak velocity; AVA = aortic valve area; AVR = aortic valve replacement; FU = follow-up; DM = diabetes mellitus; AS = aortic stenosis; CRP = C reactive protein; MACE = major adverse cardiovascular events; GLS = global longitudinal strain; LVEF = left ventricular ejection fraction; MPG = mean peak gradient; WMA = wall-motion abnormalities; MI = myocardial infarction; MA = multivariate analysis; SBP, systolic blood pressure.

at rest and stress) that expose a portion of fast-progressing moderate AS patients to a higher rate of events than the slow-progressing moderate AS patients.

The ENIGMAS trial, a prospective study focused on identification of clinical, biological and imagistic parameters in rapid-progression subgroup patients with moderate aortic stenosis, is divided into a prospective observational study and a prospective interventional study, and seems to be an ideal trial for patient evaluation (ClinicalTrials.gov no. NCT01575249). The study protocol is highlighted in Fig. 1. The ENIGMAS trial will start enrolling patients in July 2012, will last for 3 years, and will include only moderate AS patients. It will include symptomatic and asymptomatic moderate AS patients and will add new evaluation techniques such as newer echo parameters, strain and twist, and MRI. Mild AS patients with an initial PV of 2.8–3.1 m/sec will be divided into 2 groups. The first (observational) group will have 160 patients with a negative exercise stress echo for symptoms/ECG/wall-motion abnormalities (WMA), a negative spirometry test for pulmonary disease, no known CAD or other valvular diseases, and an in-sinus rhythm and an LVEF > 55%. The second group (medical/surgery group) will also have 160 patients with symptomatic AS as determined by negative pulmonary tests but positive stress echo, prior CAD or other valvular diseases, and an LVEF > 55%). One major difference of this study from other studies is that the echo exams will be performed on identical echo instruments because strain is instrument dependent. Patients will be followed every 6 months for 3 years with clinical, biological, and stress echo exams. MRI will also be included at each FU to evaluate LV mass, LVEF, WMA, calcifications, and fibrosis so that this moderate AS patient subgroup will have complete cardiologic data for evaluation. The primary endpoint will be the occurrence of major adverse cardiac events defined by the following: death and AVS. The secondary endpoint will be the time that it takes to develop stress symptoms such as angina, dyspnea, or syncope in the first group. The tertiary endpoint will be the time that it takes to develop altered stress-related hemodynamic parameters in both groups such as strain decrease, EF decrease, ventricular arrhythmia, SBP decrease, and pathological stress gradients. The role of fibrosis and other MRI manifestations of pathological changes in moderate AS patients will also be clarified. Investigators will also differentiate patient outcomes with mean gradients between 40 and 50 mmHg, which is the gray AS zone, because currently there is a discrepancy between the American and European guidelines for the severe AS cutoff.[1,46]

TABLE IV

Trials with Moderate-to-Severe AS as Baseline Inclusion Criteria

Author/Parameter	Patients	Age	Baseline Aortic Valve	FU	Progression (m/sec/year If Not Specified Otherwise)	Predictors of Outcome	Endpoint	Limitations	Conclusions, Survival
Peter et al.[30]	49 Patients, 29 males, 21 were rapid progressors at FU	58 ± 16 years	38 ± 15 mmHg	32 ± 16 months	19 ± 12 mmHg increase/year (rapid progressors, n = 21), 4 ± 3 mmHg increase/year (slow progressors, n = 28)	Increased progression in older patients (64 vs. 53 years) and with CAD (38% vs. 7%)	Symptoms, AVR (n = 9 vs. n = 4), death (n = 3 vs. n = 1) in rapid vs. slow progress	Small study	Nearly half the patients with initially moderate to severe AS reveal a progression of ≥10 mm Hg per year. Mean progression/year of 10.6 ± 11.0 mmHg
Alborino et al.[31]	30 Asymptomatic patients	62 ± 14 years	Moderate (n = 20) and severe (n = 10) AS	36 months	There was no statistically significant difference in AV area, maximal, and MG between patients with normal and abnormal exercise tests	Exercise-limiting symptoms. At FU, 10 patients with a normal exercise ST and 4 with an abnormal ST did not require AVR as they remained asymptomatic (PPV of 78%)	AVR (n = 16)	–	An abnormal test may reveal symptoms or identify a population for closer FU
Das et al.[32]	125 Patients, from which 36 developed spontaneous symptoms at FU	65 years	AVA < 1.4 cm^2, more than 42% had severe AS	12 months	NA Patients with endpoint versus patients with no end-point had a PV of 4.1 ± 0.6 m/sec versus 3.7 ± 0.8 m/sec	Exercise-limiting symptoms	Development of spontaneous exertional symptoms (n = 36) or cardiovascular death (n = 0) at FU	AS not correctly defined (severe AS: AVA < 0.8 cm^2)	The PPV for exercise-induced symptoms was 57% in the whole population and 79% for patients aged <70 in Specific Activity Scale Class I. The NPV was 87% in the whole population and 86% in the subgroup. Symptom -free survival at 12 months: 49% for symptomatic patients on exercise testing versus 89% for those asymptomatic. There was no AVR.
Briand et al.[33]	105 Patients, from which 38% had MS, 64 men	69 ± 12 years	Baseline PV: 3.2 ± 0.6 m/sec, baseline AVA: 1.08 ± 0.24 cm^2, 40% had severe AS	28 ± 13 months	0.19 ± 0.27 (all population), 0.28 ± 0.30 m/sec/year and −0.14 ± 0.13 cm^2/year (MS patients) 0.13 ± 0.24 m/sec/year	MS, males and baseline peak gradient were independent predictors of progression and event-free survival (MA)	Death (n = 5 cardiac, n = 3 noncardiac) and AVR (n = 45)	Retrospective.	MS is associated with a faster disease progression and worse outcome in patients with AS

(continued)

Table IV (continued)

Author/Parameter	Patients	Age	Baseline Aortic Valve	FU	Progression (m/sec/year If Not Specified Otherwise)	Predictors of Outcome	Endpoint	Limitations	Conclusions, Survival
					and -0.08 ± 0.08 cm^2/year (controls)				Survival lower ($44 \pm 8\%$ vs. $69 \pm 6\%$) among patients with MS
Stewart et al.[34]	65 Asymptomatic patients randomized double-blind to elprenone or placebo	67.5 years	Eplerenone group 100 mg daily (n = 33) baseline PV of 3.85 m /sec or placebo (n = 32) baseline PV of 3.92 m/sec	19 months	Similar decrease of AVA (-0.11 ± 0.22 vs -0.18 ± 0.24 cm^2/year for elprenone vs. placebo group, P = ns)	None	Eplerenone effect on delay of LV systolic dysfunction or LV hypertrophy in asymptomatic patients with moderate to severe AS	Study too small for clinical outcomes	In asymptomatic patients with moderate-to-severe aortic stenosis, eplerenone did not slow the onset of LV systolic or diastolic dysfunction, decrease LV mass, or reduce progression of valve stenosis.
Monin et al.[35] Prospective	107 Asymptomatic AS, from which 62 became symptomatic at FU	72 years	3.5–4.4 m/sec, mean 4.1 m/sec	24 months	0.2 m/sec in asymptomatic, 0.4 m/sec in symptomatic patients	Female sex, PV and BNP at baseline	Death (n = 3) or AVR (n = 58) due to symptoms or positive ST, 1 patient refused surgery	72% had severe AS, 22.1% had CAD	Similar survival Authors developed a risk score based on independent predictors of outcome Survival after 20 months: 80% for patients within the first score quartile vs. 7% for the fourth quartile
Marechaux et al.[36] Prospective	135 Patients with at least moderate AS, with normal ST, from which 67 had an event at FU	64 ± 15 years	Mean PV of 3.8 ± 0.8 m /sec, 53% had severe AS	20 ± 14 months	Increased progression in those with resting MG >35 mmHg and exercise-induced increase in mean gradient >20 mmHg	Age $\geq$65, diabetes, LV hypertrophy, resting MG >35 mmHg, and exercise -induced increase in mean gradient >20 mmHg (MA)	Death (n = 3) or AVR (n = 59) due to symptoms or LV dysfunction	No BNP measurements, no strain	Hemodynamic indices measured by ESE, but not indices of maximum exercise capacity are associated with outcome in patients with true asymptomatic AS

AS = aortic stenosis; PV = peak velocity; AVA = aortic valve area; AVR = aortic valve replacement; FU = follow-up; CAD = coronary artery disease; NA = not available; MS = metabolic syndrome; MA = multivariate analysis; LV = left ventricle; ST = stress test; ESE = exercise stress echocardiography; MG = mean gradient; PPV = positive predictive value; NPV = negative predictive value.

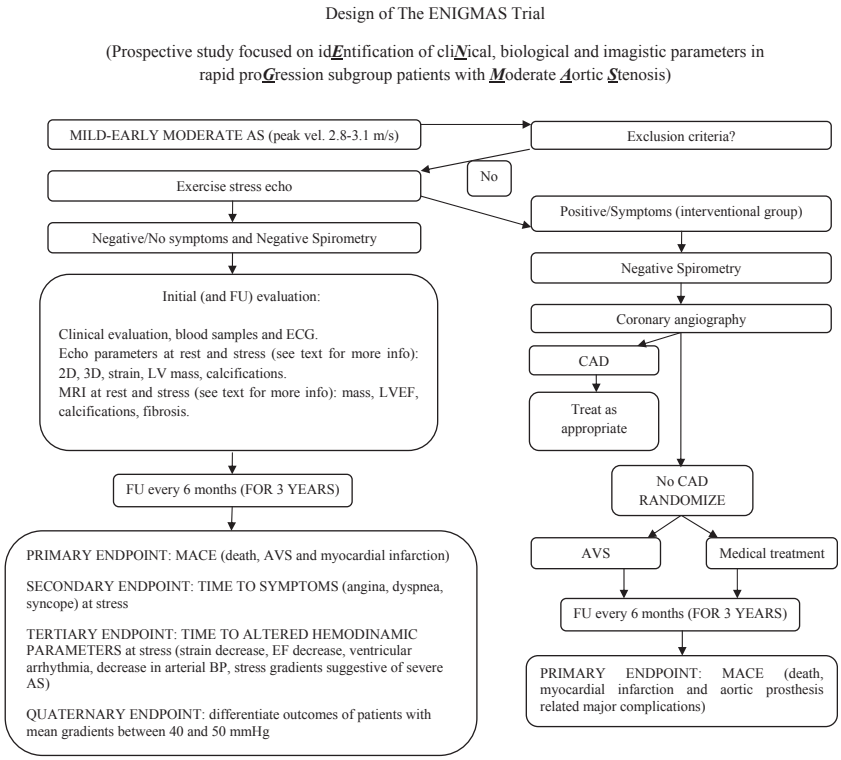

Figure 1. Design of The ENIGMAS Trial. AS = aortic stenosis; AVS = aortic valve surgery; BP = blood pressure; CAD = coronary artery disease; EF = ejection fraction; FU = follow-up; LV = left ventricle; MACE = major adverse cardiac events; MRI = magnetic resonance imaging.

Conclusions:

Moderate AS patients have poorer health compared with the healthy population. With the use of newly available investigational techniques, finding the parameters that accelerate moderate-to-severe AS will translate into proper medical care or treatment interventions to reduce AS progression, resulting in reduced mortality rates. The ENIGMAS trial is designed to highlight disease progression factors, and perhaps it will provide a substantial benefit to not only patients but also the medical community. In addition, investigators hope to reach a consensus regarding the severe AS cutoff values.

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