JAMA Cardiology | Original Investigation

Natural History of Asymptomatic Severe Aortic Stenosis and the Association of Early Intervention With Outcomes
A Systematic Review and Meta-Analysis

Brigitta Gahl, PhD; Mevlüt Çelik, MD; Stuart J. Head, MD, PhD; Jean-Louis Vanoverschelde, MD, PhD; Philippe Pibarot, DVM, PhD; Michael J. Reardon, MD; Nicolas M. van Mieghem, MD, PhD; A. Pieter Kappetein, MD, PhD; Peter Jüni, MD; Bruno R. da Costa, PhD

IMPORTANCE Whether intervention should be performed in patients with asymptomatic severe aortic stenosis (AS) remains debated.

OBJECTIVE To meta-analyze the natural history of asymptomatic severe AS and examine the association of early intervention with survival.

DATA SOURCES PubMed, Embase, and Cochrane databases were searched from inception to February 1, 2020.

STUDY SELECTION Observational studies of adult patients with asymptomatic severe AS.

DATA EXTRACTION AND SYNTHESIS Two investigators independently extracted study and patient characteristics, follow-up time, events, and prognostic indicators of events. Random-effects models were used to derive pooled estimates.

MAIN OUTCOMES AND MEASURES The meta-analysis on natural history was performed on the primary end point of all-cause death occurring during a conservative treatment period, with secondary end points consisting of cardiac death, death due to heart failure, sudden death, development of symptoms, development of an indication for aortic valve intervention, and aortic valve intervention. The primary end point for the meta-analysis of early intervention vs a conservative strategy was all-cause death during long-term follow-up. Finally, meta-analysis was performed on the association of prognostic indicators with the composite of death or aortic valve intervention found in multivariable models.

RESULTS A total of 29 studies with 4075 patients with 11 901 years of follow-up were included. Pooled rates per 100 patients per year were 4.8 (95% CI, 3.6-6.4) for all-cause death, 3.0 (95% CI, 2.2-4.1) for cardiac death, 2.0 (95% CI, 1.3-3.1) for death due to heart failure, 1.1 (95% CI, 0.6-2.1) for sudden death, 18.1 (95% CI, 12.8-25.4) for an indication for aortic valve intervention, 18.5 (95% CI, 13.4-25.5) for development of symptoms, and 19.2 (95% CI, 15.5-23.8) for aortic valve intervention. Early intervention was associated with a significant reduction in long-term mortality (hazard ratio, 0.38; 95% CI, 0.25-0.58). Factors associated with worse prognosis were severity of AS, low-flow AS, left ventricular damage, and atherosclerotic risk factors.

CONCLUSIONS AND RELEVANCE Data from observational studies and a recent randomized clinical trial suggest that many patients with asymptomatic severe AS develop an indication for aortic valve intervention, and their deaths are mostly cardiac but not only sudden. Other end points besides sudden death should be considered during the decision to perform early intervention that are associated with improved survival.

JAMA Cardiol. doi:10.1001/jamacardio.2020.2497
Published online July 8, 2020.

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Stuart J. Head, MD, PhD, Department of Cardiothoracic Surgery, Erasmus Medical Center, PO Box 2040, 3000 CA Rotterdam, the Netherlands (s.head@erasmusmc.nl).

Patients with symptomatic severe aortic stenosis (AS) have an indication for surgical aortic valve replacement (SAVR) or transcatheter aortic valve replacement. The role of intervention is less clear in patients with asymptomatic severe AS. North American and European guidelines agree on a class I indication for SAVR in patients with a reduced left ventricular (LV) ejection fraction (<50%) but are inconsistent for patients with other disease or comorbid factors.[1-3]

Studies suggest that as many as 50% of patients with asymptomatic severe AS progress to a symptomatic status and require surgery within the first 2 years of follow-up[4] and that this waiting period increases the risk of sudden cardiac death and congestive heart failure.[5,6] In light of these results, the concept of early intervention has raised increasing interest.[5,7] However, advocates of a conservative approach argue that the procedural risk does not balance against the potential benefits of early intervention and that many patients will never become symptomatic.[8] Such arguments come mainly from single-center observational studies with few patients and based on events that occur infrequently.[1]

The natural history should be better quantified to improve our understanding of potential benefits and harms of intervention vs conservative treatment. Moreover, risk factors of poor prognosis should be identified to evaluate which patients are at highest risk and may particularly benefit from early intervention. Therefore, we have performed a systematic review and meta-analysis of studies evaluating the natural history of patients with asymptomatic severe AS and determined whether early intervention improves long-term survival.

Key Points

Question What is the natural history of asymptomatic severe aortic stenosis, which variables predict prognosis, and can early intervention improve outcomes?

Findings In this systematic review and meta-analysis of 29 studies with 4075 patients with 11 901 years of follow-up, the rate of all-cause death was 5 per 100 conservatively treated patients per year, of which 3 and 1 were of cardiac and sudden cause, respectively. Twenty per 100 patients per year developed an indication for intervention; early intervention was significantly associated with improved survival.

Meaning Patients with asymptomatic severe aortic stenosis may develop indication for intervention and have deaths that are mostly cardiac but not only sudden.

Methods

Search Strategy and Study Inclusion

The PubMed, Embase, and Cochrane databases were searched from their inception to February 1, 2020, for full-length, English-language, observational studies that reported on patients with asymptomatic severe AS who were initially treated conservatively. We searched among titles and abstracts using the keywords *asymptomatic* AND *aortic* AND *stenosis*. No search software was used. Authors were not contacted for studies that did not fulfill inclusion criteria or if data were unclear. This study complies with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guideline.[9]

Two investigators (S.J.H. and M.Ç.) independently reviewed the search result in duplicate. In case of disagreement, consensus was reached through discussion. The title and abstract were reviewed during the first stage, after which the remaining articles were reviewed in depth during the second stage. Reference lists of potentially valid studies and review articles were checked to ensure no relevant studies were missed. Abstracts from meetings were not considered.

Studies were included if they fulfilled the following criteria: (1) the study included adult patients with severe AS quantified by at least an aortic valve area of less than 1.0 cm^2 or an indexed aortic valve area less than 0.6 cm^2/m^2, a jet velocity of more than 4.0 m/s, or a mean gradient of more than 40 mm Hg; (2) patients were considered to be asymptomatic if reported as such, which was left to the discretion of the physicians and investigators of the individual studies and performance of exercise testing was not considered mandatory to confirm absence of symptoms; and (3) at least the event of death during follow-up and the mean/median duration of follow-up was reported. Studies with a combined inclusion of patients with moderate and severe AS were excluded unless results were separately reported for patients with severe AS. In case there was overlap in the patient populations in different studies from the same center, we included only the study with the longest follow-up or largest patient cohort. A list of excluded articles is available on request.

Data Extraction

Two investigators (S.J.H. and M.Ç.) independently extracted and crosschecked clinically relevant data and data necessary for study inclusion and meta-analysis (eAppendix 1 in the Supplement). Inconsistencies were resolved by discussion.

End Points

For the meta-analysis on the natural history, the primary end point was all-cause death. Secondary end points consisted of cardiac death, sudden death, death due to congestive heart failure, the development of an indication for aortic valve intervention, the development of symptoms, and aortic valve intervention by either SAVR or transcatheter aortic valve replacement. For the meta-analysis of early intervention vs conservative treatment, the primary end point was all-cause death. For the meta-analysis of predictors, the primary end point consisted of the composite of all-cause death and aortic valve intervention (or development of symptoms) but allowing for studies to include hospitalization or congestive heart failure as additional end point in the composite.

Statistical Analyses

We calculated the log rate of events per 100 patients per year of observation time and the corresponding standard error within studies and then used a DerSimonian and Laird random-effects model to derive pooled estimates and corresponding limits of the 95% CI[10] and back-transformed pooled estimates and limits of the 95% CI to rates per 100 patient-years throughout. If the total amount of follow-up time was not reported, this was calculated by multiplying the number of patients by the mean follow-up time. In case of 0 events, we derived the upper end of the 95% CI of the rate as described by Hanley and Lippman-Hand, adding a continuity correction of 0.01 to the numerator, and a continuity correction of 0.01 multiplied by the mean follow-up time to the denominator to derive rates.[11] We explored heterogeneity across studies using the DerSimonian and Laird between-study variance τ^2 statistic[12] and calculated 95% prediction intervals for the pooled rates in addition to conventional CIs taking into account the between-study variance to reflect residual uncertainty.[13] Our analysis on the natural history consisted of pooling the studies that reported events occurring only during a period of time in which patients were asymptomatic and no aortic valve intervention took place. Prespecified subgroup analyses were restricted to the 26 studies with follow-up until aortic valve intervention, investigating heterogeneity by study design (prospective vs retrospective), year of initiation of patient recruitment (before 1999 vs 1999 or later), number of patients included in the study (<100 vs ≥100 patients), length of mean follow-up time (<2 vs ≥2 years), length of accumulated follow-up patient-time (<200 vs ≥200 patient-years), and whether or not good LV ejection fraction (defined as ≥50%, ≥55%, or normal) was an inclusion criterion of the study. Subgroup analyses were accompanied by a test for interaction from random-effects meta-regression.

For the comparison of all-cause mortality following early intervention vs conservative treatment, we included studies that did not censor patients at the time of intervention and evaluated long-term mortality. We pooled studies using the study-level hazard ratios (HRs) in a random-effects model with Knapp-Hartung modification of the variance as the number of cohort studies that reported HRs for this comparison was low.

For the pooling of the effect of prognostic indicators on events, whenever 2 or more studies reported the HRs of the association between prognostic indicators and events during follow-up, we pooled them across studies using a random-effects bayesian meta-analysis. Details are provided in eAppendix 2 in the Supplement. Analyses were performed in Stata version 14.2 (StataCorp) and WinBUGS version 14 (Medical Research Council Biostatistics Unit).

Results

Study Inclusion

The literature search yielded 2370 studies that were potentially relevant for inclusion in the meta-analysis, and 29 studies were included in the meta-analysis on the natural history (eFigure in the Supplement). All studies were observational. A total of 4075 patients with a median (interquartile range [IQR]) follow-up of 2.3 (1.6-3.3) years were included in the natural history analysis (**Table 1**). In addition, 9 studies were included in the meta-analysis comparing an early surgical treatment strategy with watchful waiting, of which 1 was a randomized clinical trial (eFigure in the Supplement). A total of 3904 patients with a median (IQR) follow-up of 5.0 (3.7-5.7) years were included in our analyses comparing an early surgical treatment strategy with watchful waiting (Table 1).

Meta-analysis on Natural History

The rate of all-cause death was 4.8 (95% CI, 3.6-6.4) per 100 patients per year in 21 studies with 3041 patients with a median (IQR) follow-up of 2.3 (1.7-3.4) years (**Figure 1**A). Cardiac death occurred at a rate of 3.0 (95% CI, 2.2-4.1) per 100 patients per year in 18 studies with 2813 patients with a median (IQR) follow-up of 2.1 (1.4-2.9) years (Figure 1B). The rate of death due to congestive heart failure was 2.0 (95% CI, 1.3-3.1) per 100 patients per year in 11 studies with 1809 patients with a median (IQR) follow-up of 2.3 (1.9-2.9) years (Figure 1C). Sudden death occurred at a rate of 1.1 (95% CI, 0.6-2.1) per 100 patients per year in 12 studies with 1767 patients with a median (IQR) follow-up of 2.3 (1.7-3.1) years (Figure 1D).

Progression to Aortic Valve Intervention

An indication for aortic valve intervention was reported in 11 studies with 1754 patients with a median (IQR) follow-up of 2.3 (1.8-3.2) years and occurred in 18.1 (95% CI, 12.8-25.4) per 100 patients per year (**Figure 2**A). There were 16 studies with 2234 patients and median (IQR) follow-up of 1.9 (1.3-3.1) years that reported the number of patients that developed symptoms, with a pooled rate of 18.5 (95% CI, 13.4-25.5) per 100 patients per year (Figure 2B). Aortic valve intervention was performed in 19.2 (95% CI, 15.5-23.8) per 100 patients per year (21 studies with 3494 patients with a median [IQR] follow-up of 2.3 [1.7-3.0] years) (Figure 2C).

Subgroup Analyses

eTable 1 in the Supplement shows results of subgroup analyses. Studies with shorter total follow-up were associated with higher rates of all-cause death. Studies with shorter mean and total follow-up were associated with higher rates of symptom development and aortic valve interventions. Rates of an indication for aortic valve intervention (21.0 [95% CI, 15.8-28.0] vs 10.6 [95% CI, 9.6-11.6] per 100 patients per year; $P = .02$) and development of symptoms (21.2 [95% CI, 16.2-27.6] vs 8.7 [95% CI, 7.9-9.7] per 100 patients per year; $P = .007$) were markedly higher in prospective vs retrospective studies. There were no interactions with subgroups by LV ejection fraction.

Adverse Events

Fifteen studies performed a multivariable analysis on the composite of death or aortic valve intervention. Outcomes were largely associated with measurements of the severity of AS and LV dysfunction, with clinical factors being limited to atherosclerotic risk factors (eTable 2 in the Supplement). There was inconsistency in how variables and cutoffs were used in multivariable models, but pooling consistent variables with 2 or more results in multivariable analyses resulted in a set of independent variables (**Table 2**). Heterogeneity was low for all pooled analyses. Results were consistent in sensitivity analyses using different assumptions for the prior distribution of τ (eTable 3 in the Supplement).

Table 1. Study Characteristics

Source	Design	Patient inclusion	AS criteria	LVEF criteria, %	Mean (SD) LVEF, %	Stress test	No. of patients	Mean (SD) age, y	Abnormal stress test, %[a]	Mean follow-up, y	Total patient-years of follow-up
Censored at aortic valve intervention											
Suzuki et al,[14] 2018	Retrospective	2006-2015	AVA <1.0 cm^2	>50	68 (8)	No	63	87 (5)	NA	2.2	138.6
Wu et al,[15] 2018	Prospective	2012-2013	iAVA <0.6 cm^2/m^2	≥50	60 (6)	No	124	80 (9)	NA	0.6	78.5
González Gómez et al,[16] 2017	Retrospective	2012-2015	iAVA <0.6 cm^2/m^2	≥50	70.0[b]	No	442	80 (11)	NA	1.7	755.1
Christensen et al,[17] 2017	Prospective	2014-2016	AVA <1.0 cm^2 or maximum velocity >3.5 m/s	>50	62 (7)	Yes	92	74 (8)	0	1	90.5
Zilberszac et al,[18] 2017	Prospective	1999-2009	Maximum velocity ≥4.0 m/s	≥55	61.0 (5.9)	No	103	77.3 (4.8)	NA	1.6	166.5
Nishimura et al,[19] 2016	Retrospective	1994-2013	AVA ≤1.0 cm^2	≥50	70.2 (10.0)	No	140	73.6 (8.6)	NA	3.9	548.3
Maréchaux et al,[20] 2016	Retrospective	2000-2012	AVA ≤1.0 cm^2	≥50	65 (58-71)[c]	Yes	199	69 (14)	0	4	796
Shibayama et al,[21] 2016	Retrospective	2000-2012	AVA <1.0 cm^2 or maximum velocity >4.0 m/s	≥50	67 (10)	No	230	72 (11)	NA	2.8	632.5
Todaro et al,[22] 2016	Prospective	2009-2014	AVA ≤1.0 cm^2	≥50	60 (5)	Yes	82	73 (10)	0	1.3	109.3
Nagata et al,[23] 2015	Prospective	2011-2014	iAVA <0.6 cm^2/m^2	>50	60 (5)	No	104	78 (10)	NA	1	106.6
Jander et al,[24] 2014	Prospective	2001-2004	AVA <1.0 cm^2 and maximum velocity ≥2.5-≤4.0 m/s and mean gradient ≤40 mm Hg	≥55	66.6 (6)	No	435	69.8 (9)	NA	3.5	1522.5
Zuern et al,[25] 2014	Prospective	2009-2012	AVA <1.0 cm^2 or maximum velocity >4.0 m/s or mean gradient >40 mm Hg	None	55.0[b]	No	71	74[d]	NA	1.2	85.2
Levy et al,[26] 2014	Prospective	NA	AVA <1.0 cm^2 or iAVA ≤0.6 cm^2/m^2	>50	62 (7)	Yes	43	69 (13)	28	2.3	100.3
Cho et al,[27] 2013	Prospective	2007-2012	AVA <1.0 cm^2 or maximum velocity >4.0 m/s or mean gradient >40 mm Hg	>50	65.8[b]	Yes	31	62 (11)	0	1.7	51.7
Yingchoncharoen et al,[28] 2012	Prospective	2004-2010	AVA <1.0 cm^2 or maximum velocity >4.0 m/s	≥50	63.4 (7.9)	No	79	77 (12)	NA	1.9	151.4
Saito et al,[29] 2012	Retrospective	2001-2007	AVA <1.0 cm^2	None	60.0 (9.6)	No	103	72 (11)	NA	3	309
Lancellotti et al,[30] 2012	Prospective	NA	AVA <1.0 cm^2	≥55	66.6 (7.6)	Yes	150	69.7 (8.0)	0	2.3	337.5
Perera et al,[31] 2011	Retrospective	2005-2009	AVA ≤1.0 cm^2 or maximum velocity >4.0 m/s or mean gradient >40 mm Hg	None	NA	No	25	81.7 (14.4)	NA	2.9	72.9
Kitai et al,[32] 2011	Retrospective	1999-2009	AVA <1.0 cm^2 or mean gradient >40 mm Hg	≥50	65 (8)	No	76	70 (11)	NA	5.5	418
Cioffi et al,[33] 2011	Prospective	2003-2008	AVA <1.0 cm^2 or mean gradient ≥50 mm Hg	None	59.2 (10.4)	No	218	75 (11)	NA	1.8	399.7
Rosenhek et al,[34] 2010	Prospective	1995-2008	Maximum velocity ≥5.0 m/s	None	NA	No	116	67 (15)	NA	3.4	396.3

(continued)

Table 1. Study Characteristics (continued)

Source	Design	Patient inclusion	AS criteria	LVEF criteria, %	Mean (SD) LVEF, %	Stress test	No. of patients	Mean (SD) age, y	Abnormal stress test, %[a]	Mean follow-up, y	Total patient-years of follow-up
Hristova-Antova et al,[35] 2009	Prospective	2004	AVA ≤1.0 cm² and maximum velocity >4.0 m/s and mean gradient >60 mm Hg	>50	69.9 (5.5)	No	49	59 (13)	NA	1.8	89.8
Lafitte et al,[36] 2009	Prospective	NA	AVA <1.0 cm²	>55	64 (7)	Yes	60	70 (12)	65	1	60
Weisenberg, et al,[37] 2008	Retrospective	2001-2005	AVA <1.0 cm² or mean gradient ≥50 mm Hg	Normal	NA	Yes	101	69 (10)	68	2.9	294.6
Avakian et al,[38] 2008	Prospective	NA	Mean gradient ≥60 mm Hg	Normal	72.7 (6.0)	No	133	66.2 (13.6)	NA	3.3	438.9
Le Tourneau et al,[39] 2010 and Pellikka et al,[40] 2005[e]	Retrospective	1984-1995	Maximum velocity ≥4.0 m/s	None	64.3 (7.3)	No	622	72 (11)	NA	5.4	3358.8
Amato et al,[6] 2001	Prospective	1987-1992	AVA ≤1.0 cm²	None	NA	Yes	66	49.7 (14.9)	67	1.2	81.4
Pierri et al,[41] 2000	Prospective	1981-1993	AVA <0.9 cm² or mean gradient >50 mm Hg	None	NA	No	12	81.1	NA	6	72
Rosenhek et al,[42] 2000	Prospective	1994	Maximum velocity ≥4.0 m/s	None	NA	No	106	57 (19)	NA	2.3	238.5
Watchful waiting vs intervention											
Kang et al,[43] 2020	Prospective	2010-2015	AVA ≤0.75 cm² and (jet velocity ≥4.5 m/s or mean gradient ≥50 mm Hg)	≥50	64.8 (4.1)	No	72	63.4 (10.7)	NA	5.8	4998.7
Kim et al,[44] 2019	Retrospective	2000-2015	AVA ≤1.0 cm² or iAVA ≤0.6 cm²/m² or maximum velocity ≥4.0 m/s or mean gradient ≥40 mm Hg	≥50	63.1 (5.1)	No	247	67.1 (13.1)	NA	5.1	1253.5
Campo et al,[45] 2019	Retrospective	2005-2013	AVA ≤1.0 cm² or maximum velocity ≥4.0 m/s or mean gradient ≥40 mm Hg	None	61 (8.1)	Yes	161	73.0 (12.6)	18	NA	NA
Bohbot et al,[46] 2018	Retrospective	2000-2015	Mean gradient ≥40 mm Hg	≥50	NA	Yes	247	NA	64	3.5	864.5
Masri et al,[47] 2016	Prospective	2001-2012	iAVA ≤0.6 cm²/m²	≥50	58 (4)	Yes	533	66 (13)	44	6.9	3677.7
Taniguchi et al,[5] 2015	Retrospective	2003-2011	AVA <1.0 cm² or maximum velocity >4.0 m/s or mean gradient >40 mm Hg	None	65.7 (11.1)	No	1517	77.8 (9.4)	NA	3.7	5650.8
Le Tourneau et al,[39] 2010	Retrospective	1994-1995	Maximum velocity ≥4.0 m/s	None	64 (7)	No	694	71 (11)	NA	5.5	3817
Kang et al,[48] 2010	Prospective	1996-2006	AVA ≤0.75 cm² and maximum velocity >4.5 m/s or mean gradient ≥50 mm Hg	≥50	63 (7)	No	95	63 (12)	NA	4.8	460
Pai et al,[49] 2006	Retrospective	1993-2003	AVA ≤0.8 cm²	None	59 (17)	No	338	71 (15)	NA	3.5	1183

Abbreviations: AS, aortic stenosis; AVA, aortic valve area; iAVA, indexed aortic valve area; LVEF, left ventricular ejection fraction; NA, not applicable.

[a] Occurrence of symptoms, abnormal blood pressure response, ST-segment depression, or ventricular arrhythmia.

[b] Mean is reported.

[c] Median (interquartile ranges) is reported.

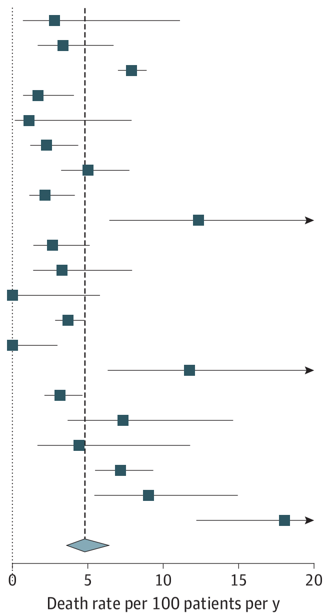
[d] Median is reported.

[e] There is overlap between the studies by Pellikka et al[40] and Le Tourneau et al.[39] The study characteristics in this Table are from Pellikka et al.[40] The study by Le Tourneau et al[39] was used for the comparison of conservative treatment vs early surgery.

Figure 1. Meta-analysis of Studies on Death

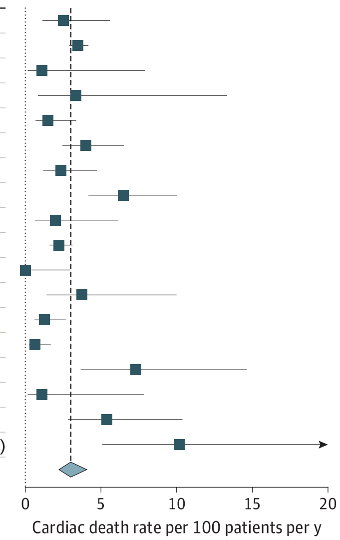
A All-cause death

Source	No. of deaths/ No. of patients	Death rate
Pierri et al,[41] 2000	2/72	2.8 (0.7-11.1)
Rosenhek et al,[42] 2000	8/239	3.4 (1.7-6.7)
Pellikka et al,[50] 2005	265/3359	7.9 (7.0-8.9)
Weisenberg et al,[37] 2008	5/295	1.7 (0.7-4.1)
Hristova-Antova et al,[35] 2009	1/90	1.1 (0.2-7.9)
Rosenhek et al,[34] 2010	9/396	2.3 (1.2-4.4)
Cioffi et al,[33] 2011	20/400	5.0 (3.2-7.8)
Kitai et al,[32] 2011	9/418	2.2 (1.1-4.1)
Perera et al,[31] 2011	9/73	12.3 (6.4-23.7)
Lancellotti et al,[30] 2012	9/338	2.7 (1.4-5.1)
Yingchoncharoen et al,[28] 2012	5/151	3.3 (1.4-7.9)
Cho et al,[27] 2013	0/52	0 (0-5.8)
Jander et al,[24] 2014	56/1523	3.7 (2.8-4.8)
Levy et al,[26] 2014	0/100	0 (0-3.0)
Zuern et al,[25] 2014	10/85	11.7 (6.3-21.8)
Maréchaux et al,[20] 2016	25/796	3.1 (2.1-4.6)
Todaro et al,[22] 2016	8/109	7.3 (3.7-14.6)
Christensen et al,[17] 2017	4/90	4.4 (1.7-11.8)
González Gómez et al,[16] 2017	54/755	7.2 (5.5-9.3)
Zilberszac et al,[18] 2017	15/167	9.0 (5.4-14.9)
Suzuki et al,[14] 2018	25/139	18.0 (12.2-26.7)
Overall: τ^2 = 0.29; 95% PI, 1.5-15.5		4.8 (3.6-6.4)



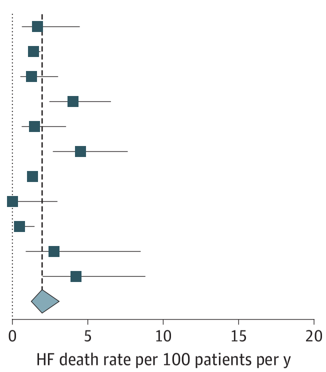
B Cardiac death

Source	No. of cardiac deaths/No. of patients	Death rate
Rosenhek et al,[42] 2000	6/239	2.5 (1.1-5.6)
Pellikka et al,[40] 2005	117/3359	3.5 (2.9-4.2)
Hristova-Antova et al,[35] 2009	1/90	1.1 (0.2-7.9)
Lafitte et al,[36] 2009	2/60	3.3 (0.8-13.3)
Rosenhek et al,[34] 2010	6/396	1.5 (0.7-3.4)
Cioffi et al,[33] 2011	16/400	4.0 (2.5-6.5)
Lancellotti et al,[30] 2012	8/338	2.4 (1.2-4.7)
Saito et al,[29] 2012	20/309	6.5 (4.2-10.0)
Yingchoncharoen et al,[28] 2012	3/151	2.0 (0.6-6.1)
Jander et al,[24] 2014	34/1523	2.2 (1.6-3.1)
Levy et al,[26] 2014	0/100	0 (0-3.0)
Nagata et al,[23] 2015	4/107	3.8 (1.4-10.0)
Nishimura et al,[19] 2016	7/548	1.3 (0.6-2.7)
Shibayama et al,[21] 2016	4/633	0.6 (0.2-1.7)
Todaro et al,[22] 2016	8/109	7.3 (3.7-14.6)
Christensen et al,[17] 2017	1/90	1.1 (0.2-7.8)
Zilberszac et al,[18] 2017	9/167	5.4 (2.8-10.4)
Wu et al,[15] 2018	8/79	10.2 (5.1-20.4)
Overall: τ^2 = 0.24; 95% PI, 1.0-8.8		3.0 (2.2-4.1)



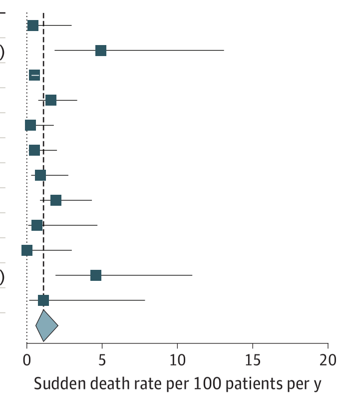
C HF death

Source	No. of HF deaths/ No. of patients	Death rate
Rosenhek et al,[42] 2000	4/239	1.7 (0.6-4.5)
Pellikka et al,[50] 2005	47/3359	1.4 (1.1-1.9)
Rosenhek et al,[34] 2010	5/396	1.3 (0.5-3.0)
Cioffi et al,[32] 2011	16/400	4.0 (2.5-6.5)
Lancellotti et al,[30] 2012	5/338	1.5 (0.6-3.6)
Saito et al,[29] 2012	14/309	4.5 (2.7-7.7)
Yingchoncharoen et al,[28] 2012	2/151	1.3 (0.3-5.3)
Levy et al,[26] 2014	0/100	0 (0-3.0)
Shibayama et al,[21] 2016	3/633	0.5 (0.2-1.5)
Todaro et al,[22] 2016	3/109	2.7 (0.9-8.5)
Zilberszac et al,[18] 2017	7/167	4.2 (2.0-8.8)
Overall: τ^2 = 0.36; 95% PI, 0.5-8.4		2.0 (1.3-3.1)



D Sudden death

Source	No. of sudden deaths/No. of patients	Death rate
Rosenhek et al,[42] 2000	1/239	0.4 (0.1-3.0)
Amato et al,[6] 2001	4/81	4.9 (1.8-13.1)
Pellikka et al,[50] 2005	17/3359	0.5 (0.3-0.8)
Avakian et al,[38] 2008	7/439	1.6 (0.8-3.3)
Rosenhek et al,[34] 2010	1/396	0.3 (0.0-1.8)
Cioffi et al,[33] 2011	2/400	0.5 (0.1-2.0)
Lancellotti et al,[30] 2012	3/338	0.9 (0.3-2.8)
Saito et al,[29] 2012	6/309	1.9 (0.9-4.3)
Yingchoncharoen et al,[28] 2012	1/151	0.7 (0.1-4.7)
Levy et al,[26] 2014	0/100	0 (0-3.0)
Todaro et al,[22] 2016	5/109	4.6 (1.9-11.0)
Christensen et al,[17] 2017	1/90	1.1 (0.2-7.8)
Overall: τ^2 = 0.73; 95% PI, 0.1-8.5		1.1 (0.6-2.1)

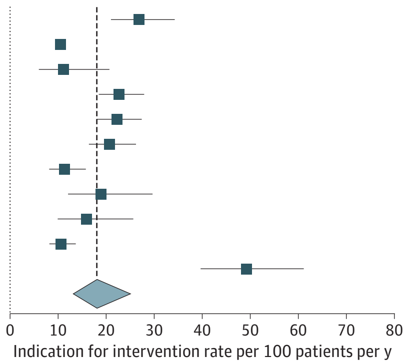


HF indicates heart failure; PI, prediction interval.

Figure 2. Meta-analysis of Studies on Progression to Aortic Valve Intervention

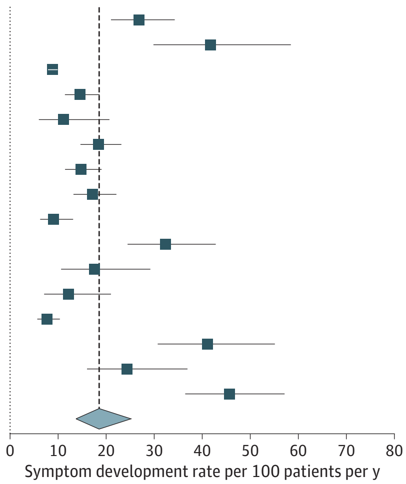
A Indication for aortic valve intervention

Source	Patients, No./total No.	Rate (95% CI)
Rosenhek et al,[42] 2000	64/239	26.8 (21.0-34.3)
Pellikka et al,[40] 2005	352/3359	10.5 (9.4-11.6)
Hristova-Antova et al,[35] 2009	10/90	11.1 (6.0-20.7)
Rosenhek et al,[34] 2010	90/396	22.7 (18.5-27.9)
Cioffi et al,[33] 2011	89/400	22.3 (18.1-27.4)
Lancellotti et al,[30] 2012	70/338	20.7 (16.4-26.2)
Saito et al,[29] 2012	35/309	11.3 (8.1-15.8)
Levy et al,[26] 2014	19/100	18.9 (12.1-29.7)
Nagata et al,[23] 2015	17/107	15.9 (9.9-25.7)
Nishimura et al,[19] 2016	58/548	10.6 (8.2-13.7)
Zilberszac et al,[18] 2017	82/167	49.2 (39.7-61.1)
Overall: τ^2 = 0.31; 95% PI, 4.9-66.9		18.1 (12.8-25.4)



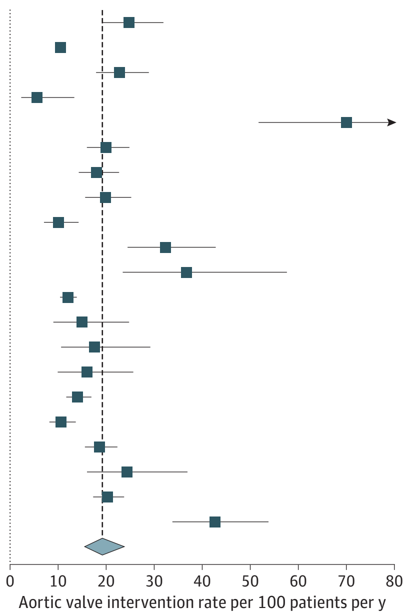
B Development of symptoms

Source	Patients, No./total No.	Rate (95% CI)
Rosenhek et al,[42] 2000	64/239	26.8 (21.0-34.3)
Amato et al,[6] 2001	34/81	41.8 (29.8-58.5)
Pellikka et al,[40] 2005	297/3359	8.8 (7.9-9.9)
Avakian et al,[38] 2008	64/439	14.6 (11.4-18.6)
Hristova-Antova et al,[35] 2009	10/90	11.1 (6.0-20.7)
Rosenhek et al,[34] 2010	73/396	18.4 (14.6-23.2)
Cioffi et al,[33] 2011	59/400	14.8 (11.4-19.1)
Lancellotti et al,[30] 2012	58/338	17.2 (13.3-22.2)
Saito et al,[29] 2012	28/309	9.1 (6.3-13.1)
Yingchoncharoen et al,[28] 2012	49/151	32.4 (24.5-42.8)
Zuern et al,[25] 2014	15/85	17.6 (10.6-29.2)
Nagata et al,[23] 2015	13/107	12.2 (7.1-21.0)
Nishimura et al,[19] 2016	42/548	7.7 (5.7-10.4)
Todaro et al,[22] 2016	45/109	41.2 (30.7-55.1)
Christensen et al,[17] 2017	22/90	24.3 (16.0-36.9)
Zilberszac et al,[18] 2017	76/167	45.6 (36.5-57.1)
Overall: τ^2 = 0.40; 95% PI, 4.6-74.9		18.5 (13.4-25.5)



C Aortic valve intervention

Source	Patients, No./total No.	Rate (95% CI)
Rosenhek et al,[42] 2000	59/239	24.7 (19.2-31.9)
Pellikka et al,[40] 2005	352/3359	10.5 (9.4-11.6)
Weisenberg et al,[37] 2008	67/295	22.7 (17.9-28.9)
Hristova-Antova et al,[35] 2009	5/90	5.6 (2.3-13.4)
Lafitte et al,[36] 009	42/60	70.0 (51.7-94.7)
Rosenhek et al,[34] 2010	79/396	19.9 (16.0-24.9)
Cioffi et al,[33] 2011	72/400	18.0 (14.3-22.7)
Lancellotti et al,[30] 2012	67/338	19.9 (15.6-25.2)
Saito et al,[29] 2012	31/309	10.0 (7.1-14.3)
Yingchoncharoen et al,[28] 2012	49/151	32.4 (24.5-42.8)
Cho et al,[27] 2013	19/52	36.8 (23.4-57.6)
Jander et al,[24] 2014	183/1523	12.0 (10.4-13.9)
Levy et al,[26] 2014	15/100	14.9 (9.0-24.8)
Zuern et al,[25] 2014	15/85	17.6 (10.6-29.2)
Nagata et al,[23] 2015	17/107	15.9 (9.9-25.7)
Maréchaux et al,[20] 2016	112/796	14.1 (11.7-16.9)
Nishimura et al,[19] 2016	58/548	10.6 (8.2-13.7)
Shibayama et al,[21] 2016	118/633	18.7 (15.6-22.3)
Christensen et al,[17] 2017	22/90	24.3 (16.0-36.9)
González Gómez et al,[16] 2017	153/755	20.3 (17.3-23.7)
Zilberszac et al,[18] 2017	71/167	42.6 (33.8-53.8)
Overall: τ^2 = 0.22; 95% PI, 7.0-52.5		19.2 (15.5-23.8)



PI indicates prediction interval.

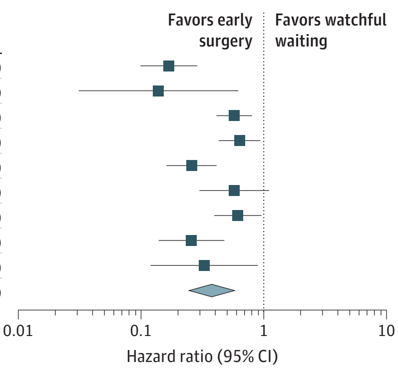
Table 2. Factors Associated With Death or Aortic Valve Intervention

Characteristic	HR (95% CrI)	τ^2 (95% CrI)	Source
Peak pressure gradient, per 10 mm Hg	1.22 (1.03-1.44)	0.002 (0-0.067)	Yingchoncharoen et al, 2012[28]; Cioffi et al, 2011[33]
Peak aortic jet velocity ≥4.0 m/s	1.93 (1.17-3.18)	0.006 (0-0.131)	Nishimura et al, 2016[19]; Saito et al, 2012[29]
Aortic valve area ≤0.6 cm^2	1.68 (1.13-2.53)	0.010 (0-0.146)	Maréchaux et al, 2016[20]; Rosenhek et al, 2010[34]
Aortic valve calcification ≥ grade 3	2.65 (1.71-4.25)	0.006 (0-0.115)	Yingchoncharoen et al, 2012[28]; Nishimura et al, 2016[19]; Rosenhek et al, 2000[42]
Female	0.97 (0.72-1.33)	0.006 (0-0.113)	Rosenhek et al, 2010[34]; Rosenhek et al, 2000[42]
Hypertension	0.66 (0.48-0.93)	0.005 (0-0.089)	Zilberszac et al, 2017[18]; Rosenhek et al, 2010[21]; Rosenhek et al, 2000[42]
Dyslipidemia	1.45 (1.09-1.93)	0.006 (0-0.097)	Zilberszac et al, 2017[18]; Nishimura et al, 2016[19]; Rosenhek et al, 2010[34]; Rosenhek et al, 2000[42]
Diabetes	1.64 (1.09-2.41)	0.044 (0-0.272)	Cioffi et al, 2011[33]; Zilberszac et al, 2017[18]; Rosenhek et al, 2010[34]; Rosenhek et al, 2000[42]
Coronary artery disease	1.32 (0.90-1.91)	0.012 (0-0.161)	Zilberszac et al, 2017[18]; Rosenhek et al, 2010[34]; Rosenhek et al, 2000[42]
Global longitudinal strain on speckle	1.12 (1.02-1.28)	0.002 (0-0.049)	Yingchoncharoen et al, 2012[28]; Todaro et al, 2016[22]; Lancellotti et al, 2012[30]
Valvulo-arterial impedance	1.35 (1.03-1.76)	0.005 (0-0.100)	Yingchoncharoen et al, 2012[28]; Todaro et al, 2016[22]
Left ventricular mass Index, per 10 units	1.1 (0.87-1.39)	0.004 (0-0.089)	Nagata et al, 2015[23]; Cioffi et al, 2011[33]

Abbreviations: CrI, credible interval; HR, hazard ratio.

Figure 3. Meta-analysis on All-Cause Mortality of Surgery vs an Initial Conservative Treatment Strategy

Source	Hazard ratio (95% CI)	*P* Value
Pai et al,[49] 2006	0.17 (0.10-0.29)	<.001
Kang et al,[48] 2010	0.14 (0.03-0.63)	.008
Le Tourneau et al,[39] 2010	0.58 (0.42-0.81)	<.001
Taniguchi et al,[5] 2015	0.64 (0.43-0.95)	.02
Masri et al,[47] 2016	0.26 (0.16-0.42)	<.001
Bohbot et al,[46] 2018	0.58 (0.30-1.12)	<.001
Kim et al,[44] 2019	0.62 (0.40-0.97)	.04
Campo et al,[45] 2019	0.26 (0.14-0.48)	.10
Kang et al,[43] 2020	0.33 (0.12-0.90)	.03
Overall: τ^2 = 0.21	0.38 (0.25-0.58)	



Meta-analysis on the Association of Early Intervention With Outcomes

There were 9 studies that compared patients who underwent early intervention vs an initial conservative treatment strategy, which included a combined 3904 patients with a median (IQR) follow-up of 5.0 (3.7-5.7) years (eTable 4 in the Supplement).[5,39,43,47-49] All but 1 randomized clinical trial used either propensity-score matching or multivariable models to adjust for differences in baseline characteristics between treatment groups. Intervention consisted of surgery in most cases. Our meta-analysis indicates that intervention was associated with a significant reduction in all-cause mortality during follow-up (HR, 0.38; 95% CI, 0.25-0.58), with moderate heterogeneity (τ^2 = 0.21) (**Figure 3**).

Discussion

In this systematic review and meta-analysis of 29 studies on the natural history of patients with asymptomatic severe AS, we found that there were overall 5 deaths per 100 patients per year during a conservative treatment strategy, with a high rate of progressing to a symptomatic state and developing an indication for aortic valve intervention. Particularly patients with more severe AS, abnormal LV characteristics, and atherosclerotic clinical factors were at a higher risk of death or an indication for intervention. Moreover, among another 9 studies that investigated performing early intervention, consisting of surgery in the majority of cases within these studies, early intervention was associated with a significant reduction in all-cause death during follow-up. While it has been argued that many patients do not develop an indication for intervention and that the risk of death is low during conservative treatment, the results of the current meta-analysis suggest otherwise. Indeed, most studies focus on sudden death, but this meta-analysis demonstrates that sudden death accounts for only part of cardiac deaths that occur in asymptomatic patients with severe AS and that the risk of death may therefore be underestimated. These data suggest that early intervention may need to be considered in a greater proportion of patients with asymptomatic severe AS.

Currently, the largest and only available randomized clinical trial on asymptomatic patients with severe AS analyzed 145 patients and found that initial surgery vs an initial conservative treatment significantly reduced the all-cause death and operative or cardiovascular death, even when 74% of patients in the conservative group required SAVR during follow-up.[43] This study is pivotal in the debate on treating asymptomatic patients, but it only provides a perspective on patients with very severe AS, applying inclusion criteria of an aortic valve area of 0.75 cm^2 or less with either a jet velocity of 4.5 m/s or more or a mean gradient of 50 mm Hg or more, while lacking evidence on the much broader patient population with asymptomatic AS. Further data from observational studies as summarized in the current meta-analysis provide these additional insights. The largest available observational study analyzed 291 propensity-matched pairs and found that early surgery vs an initial conservative treatment significantly reduced the 5-year rates of all-cause death and hospitalization for heart failure, even when 41% of patients in the conservative group required SAVR during follow-up.[5] When pooling multiple studies on the effect of intervention on survival, we found that intervention vs conservative treatment was associated with significantly improved survival with an HR of 0.38. While this may be a true effect, considering the high rates of death and progression to an indication for aortic valve intervention (eg, symptoms or LV dysfunction) among conservatively treated patients in this meta-analysis, most of the observational studies may be biased because physicians could have opted for a conservative treatment strategy for patients owing to a high risk for surgery, as was often the case before the introduction of transcatheter aortic valve replacement, when most of these studies were performed.[50] Moreover, not all studies specifically evaluated the effect of intervention within a short (eg, 3 months) period after the diagnosis of severe AS. Patients who went on to have intervention at a later follow-up time are inherently a selected group with a better prognosis because the highest-risk patients may have died within the early follow-up period. Indeed, Le Tourneau and coauthors[39] found that the point estimate of the HR in favor of surgery was much larger if conservative treatment was compared with surgery being performed within 1 year of presentation as opposed to surgery at any time during follow-up (HR, 0.58 vs HR, 0.39). Data from the RECOVERY trial are consistent with that of these observational studies,[43] but additional results from ongoing randomized clinical trials comparing an early interventional treatment strategy and a conservative strategy in asymptomatic patients with severe AS will add significant knowledge and provide important insight to substantiate the role of early intervention (eTable 5 in the Supplement).

The decision to undergo early intervention should depend on a critical assessment of symptoms and careful and individualized consideration of potential benefits and harms. Cardiac magnetic resonance to detect LV damage furthermore helps identify patients that may benefit from early intervention.[51] Apart from LV dysfunction as an indication to perform SAVR in patients with asymptomatic severe AS, current clinical guidelines provide several additional recommendations to consider intervention in patients with asymptomatic severe AS.[1] Our meta-analysis of variables associated with mortality-related outcomes indicates that prognosis is significantly worse if global longitudinal strain or valvulo-arterial impedance is present even with a preserved LV function,[22,23,28,33] if AS is more severe as measured by higher valve gradient and lower valve area, and if atherosclerotic risk factors, such as dyslipidemia or diabetes, are present. These additional diseases and comorbid characteristics are not considered in current guidelines or are inconsistently recognized in North American and European guidelines. Therefore, we suggest that cardiologists and surgeons take these additional factors into account when deciding to perform early intervention or initiate a conservative treatment strategy. Of note, our subgroup analysis could not confirm that lower LV ejection fraction was associated with worse outcomes, which is most likely related to the criteria used in the individual articles; almost all studies included patients with preserved LV ejection fraction.

Strengths and Limitations

An important strength is that a large number of studies could be pooled in a random-effects model with moderate statistical heterogeneity, increasing the validity of the results. The included studies consisted exclusively of patients with asymptomatic severe AS, unlike many other studies and reviews that have not stratified results according to the severity of AS in asymptomatic patients.[7,52] Lastly, using bayesian methods for meta-analyses of a low number of studies allowed a more reliable estimation of between-trial variance and its uncertainty to identify particular disease and patient factors that affect the prognosis of asymptomatic severe AS. This resulted in identifying several variables that are currently not included in clinical guidelines.

This is a meta-analysis of observational studies, which is dependent on the quality of the individual studies that were included. Many of the studies were single center and retrospective, and it may therefore have been difficult to adjudicate events related to the development of symptoms and indications for intervention during follow-up. Second, only a few studies routinely performed stress testing in patients with asymptomatic severe AS, and we were therefore not able to determine whether all patients in these studies were truly asymptomatic. In addition, studies mainly reported that patients with severe AS referred to their clinic were included but did not clarify whether patients already had severe AS a certain time before primarily being evaluated in the clinic (eg, prevalent cases) or had mild or moderate AS when primarily being evaluated and progressed to severe AS just before a later check (eg, incident cases). Nevertheless, there was considerable heterogeneity in our meta-analyses of event rates. Although subgroup analyses to detect heterogeneity within meta-analyses of observational studies should be interpreted with caution, our subgroup analyses revealed that the type of study (prospective vs retrospective) and the duration of follow-up (short vs long mean and total follow-up time) were associated with differences in event rates. This may have been the result of more closely monitoring patients who were prospectively followed, with earlier recognition of symptoms and timely referral for intervention, as opposed to a less strict follow-up regimen in retrospective studies. Moreover, the higher rates of symptom development, (an indication for) aortic valve intervention, all-cause death, and sudden death in studies with a shorter mean and total length of follow-up of a conservative strategy are most likely related to shorter follow-up due to the occurrence of these events, and publication bias may also play a role. Lastly, the effect of the associations between variables from multivariable analysis of several studies could not be pooled due to different definitions or cutoffs used in the models. Initiatives like the Valve Academic Research Consortium can further standardize studies to improve meta-analyses.[53]

Conclusions

In this meta-analysis, asymptomatic severe AS was associated with a high rate of developing an indication for aortic valve intervention, while all-cause, cardiac, and sudden death occurred in 4.8, 3.0, and 1.1, respectively, of 100 patients per year during a conservative strategy. Therefore, it is important to consider not only sudden death but also cardiac death due to heart failure or other causes. Patients with higher severity of AS, low-flow AS, evidence of LV damage, and atherosclerotic risk factors are at particular high risk of death or requiring intervention. Moreover, our meta-analysis suggested that surgery vs an initial conservative treatment strategy is associated with better long-term survival. Although existing guidelines provide some guidance on when to perform SAVR in patients with asymptomatic severe AS, this meta-analysis provides additional data to support a recommendation to consider early intervention in patients at high risk of adverse events. Further results from the ongoing randomized clinical trials are required to substantiate the role of early intervention in patients with asymptomatic severe AS.

ARTICLE INFORMATION

Accepted for Publication: May 19, 2020.

Published Online: July 8, 2020. doi:10.1001/jamacardio.2020.2497

Author Affiliations: Clinical Trial Unit Bern, University of Bern, Bern, Switzerland (Gahl); Department of Cardiothoracic Surgery, Erasmus Medical Center, Rotterdam, the Netherlands (Çelik, Head, Kappetein); Medtronic, Maastricht, the Netherlands (Head); Pôle de Recherche Cardiovasculaire, Institut de Recherche Expérimentale et Clinique, Université Catholique de Louvain, Brussels, Belgium (Vanoverschelde); Division of Cardiology, Cliniques Universitaires Saint-Luc, Brussels, Belgium (Vanoverschelde); Québec Heart and Lung Institute, Laval University, Quebec City, Quebec, Canada (Pibarot); Department of Cardiovascular Surgery, Houston Methodist DeBakey Heart & Vascular Center, Houston Methodist Hospital, Houston, Texas (Reardon); Department of Cardiology, Erasmus Medical Center, Rotterdam, the Netherlands (van Mieghem); Department of Medicine and Institute of Health Policy, Management and Evaluation, Applied Health Research Centre (AHRC), Li Ka Shing Knowledge Institute of St. Michael's Hospital, University of Toronto, Toronto, Ontario, Canada (Jüni); Institute of Health Policy, Management and Evaluation, Applied Health Research Centre (AHRC) , Li Ka Shing Knowledge Institute of St. Michael's Hospital, University of Toronto, Toronto, Ontario, Canada (da Costa); Institute of Primary Health Care (BIHAM), University of Bern, Bern, Switzerland (da Costa).

Author Contributions: Drs Head and Gahl had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Gahl and Çelik contributed equally as first authors; Drs Jüni and da Costa contributed equally as last authors.
Concept and design: Çelik, Head, Pibarot, Reardon, Van Mieghem, Kappetein, Jüni, da Costa.
Acquisition, analysis, or interpretation of data: Gahl, Çelik, Head, Vanoverschelde, Jüni, da Costa.
Drafting of the manuscript: Gahl, Çelik, Head, Vanoverschelde, Reardon, Jüni, da Costa.
Critical revision of the manuscript for important intellectual content: Çelik, Vanoverschelde, Pibarot, Reardon, Van Mieghem, Kappetein, Jüni, da Costa.
Statistical analysis: Gahl, Head, Kappetein, Jüni, da Costa.
Administrative, technical, or material support: Çelik.
Supervision: Head, Vanoverschelde, Reardon, Van Mieghem, Jüni, da Costa.

Conflict of Interest Disclosures: Dr Pibarot reports grants from Edwards Lifesciences and Medtronic outside the submitted work. Dr Reardon reports consulting for Medtronic. Dr Van Mieghem reports research grants support by Medtronic, Edwards Lifesciences, Boston Scientific, Abbott, and PulseCath and serves on the advisory board for PulseCath and Ancora. Dr Kappetein reports personal fees from Medtronic during the conduct of the study and outside the submitted work. Dr Juni reports grants from AstraZeneca, Biotronik, Biosensors, Eli Lilly and Company, and The Medicines Company outside the submitted work and serves as unpaid member of the steering group of trials funded by AstraZeneca, Biotronik, Biosensors, St. Jude Medical, and The Medicines Company. No other disclosures were reported.

REFERENCES

1. Falk V, Baumgartner H, Bax JJ, et al; ESC Scientific Document Group. 2017 ESC/EACTS guidelines for the management of valvular heart disease. *Eur J Cardiothorac Surg*. 2017;52(4):616-664. doi:10.1093/ejcts/ezx324

2. Nishimura RA, Otto CM, Bonow RO, et al; ACC/AHA Task Force Members. 2014 AHA/ACC guideline 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. *Circulation*. 2014; 129(23):e521-e643. doi:10.1161/CIR.0000000000000031

3. Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2017;135(25):e1159-e1195. doi:10.1161/CIR.0000000000000503

4. Heuvelman HJ, van Geldorp MW, Kappetein AP, et al. Clinical course of patients diagnosed with severe aortic stenosis in the Rotterdam area: insights from the AVARIJN study. *Neth Heart J*. 2012;20(12): 487-493. doi:10.1007/s12471-012-0309-3

5. Taniguchi T, Morimoto T, Shiomi H, et al; CURRENT AS Registry Investigators. Initial surgical versus conservative strategies in patients with asymptomatic severe aortic stenosis. *J Am Coll Cardiol*. 2015;66(25):2827-2838. doi:10.1016/j.jacc.2015.10.001

6. Amato MC, Moffa PJ, Werner KE, Ramires JA. Treatment decision in asymptomatic aortic valve stenosis: role of exercise testing. *Heart*. 2001;86 (4):381-386. doi:10.1136/heart.86.4.381

7. Généreux P, Stone GW, O'Gara PT, et al. Natural history, diagnostic approaches, and therapeutic strategies for patients with asymptomatic severe aortic stenosis. *J Am Coll Cardiol*. 2016;67(19):2263-2288. doi:10.1016/j.jacc.2016.02.057

8. Owen A, Henein MY. Challenges in the management of severe asymptomatic aortic stenosis. *Eur J Cardiothorac Surg*. 2011;40(4):848-850. doi:10.1016/j.ejcts.2011.01.031

9. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting: Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA*. 2000;283 (15):2008-2012. doi:10.1001/jama.283.15.2008

10. Head SJ, da Costa BR, Beumer B, et al. Adverse events while awaiting myocardial revascularization: a systematic review and meta-analysis. *Eur J Cardiothorac Surg*. 2017;52(2):206-217. doi:10.1093/ejcts/ezx115

11. Hanley JA, Lippman-Hand A. If nothing goes wrong, is everything all right? interpreting zero numerators. *JAMA*. 1983;249(13):1743-1745. doi:10.1001/jama.1983.03330370053031

12. da Costa BR, Juni P. Systematic reviews and meta-analyses of randomized trials: principles and pitfalls. *Eur Heart J*. 2014;35(47):3336-3345. doi:10.1093/eurheartj/ehu424

13. Higgins JP, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis.

J R Stat Soc Ser A Stat Soc. 2009;172(1):137-159. doi:10.1111/j.1467-985X.2008.00552.x

14. Suzuki A, Tajiri K, Ishizu T, et al. Effect of asymptomatic severe aortic stenosis on outcomes of individuals aged 80 and older. *J Am Geriatr Soc*. 2018;66(9):1800-1804. doi:10.1111/jgs.15527

15. Wu VC, Takeuchi M, Nagata Y, et al. Prognostic value of area of calcified aortic valve by 2-dimensional echocardiography in asymptomatic severe aortic stenosis patients with preserved left ventricular ejection fraction. *Medicine (Baltimore)*. 2018;97(12):e0246. doi:10.1097/MD.0000000000010246

16. González Gómez A, Fernández-Golfín C, Monteagudo JM, et al. Severe aortic stenosis patients with preserved ejection fraction according to flow and gradient classification: prevalence and outcomes. *Int J Cardiol*. 2017;248:211-215. doi:10.1016/j.ijcard.2017.06.064

17. Christensen NL, Dahl JS, Carter-Storch R, et al. Relation of left atrial size, cardiac morphology, and clinical outcome in asymptomatic aortic stenosis. *Am J Cardiol*. 2017;120(10):1877-1883. doi:10.1016/j.amjcard.2017.07.101

18. Zilberszac R, Gabriel H, Schemper M, Laufer G, Maurer G, Rosenhek R. Asymptomatic severe aortic stenosis in the elderly. *JACC Cardiovasc Imaging*. 2017;10(1):43-50. doi:10.1016/j.jcmg.2016.05.015

19. Nishimura S, Izumi C, Nishiga M, et al. Predictors of rapid progression and clinical outcome of asymptomatic severe aortic stenosis. *Circ J*. 2016;80(8):1863-1869. doi:10.1253/circj.CJ-16-0333

20. Maréchaux S, Ringle A, Rusinaru D, Debry N, Bohbot Y, Tribouilloy C. Prognostic value of aortic valve area by doppler echocardiography in patients with severe asymptomatic aortic stenosis. *J Am Heart Assoc*. 2016;5(5):e003146. doi:10.1161/JAHA.115.003146

21. Shibayama K, Daimon M, Watanabe H, et al. Significance of coronary artery disease and left ventricular afterload in unoperated asymptomatic aortic stenosis. *Circ J*. 2016;80(2):519-525. doi:10.1253/circj.CJ-15-0876

22. Todaro MC, Carerj S, Khandheria B, et al. Usefulness of atrial function for risk stratification in asymptomatic severe aortic stenosis. *J Cardiol*. 2016;67(1):71-79. doi:10.1016/j.jjcc.2015.04.010

23. Nagata Y, Takeuchi M, Wu VC, et al. Prognostic value of LV deformation parameters using 2D and 3D speckle-tracking echocardiography in asymptomatic patients with severe aortic stenosis and preserved LV ejection fraction. *JACC Cardiovasc Imaging*. 2015;8(3):235-245. doi:10.1016/j.jcmg.2014.12.009

24. Jander N, Hochholzer W, Kaufmann BA, et al. Velocity ratio predicts outcomes in patients with low gradient severe aortic stenosis and preserved EF. *Heart*. 2014;100(24):1946-1953. doi:10.1136/heartjnl-2014-305763

25. Zuern CS, Rizas KD, Eick C, et al. Severe autonomic failure as a predictor of mortality in aortic valve stenosis. *Int J Cardiol*. 2014;176(3):782-787. doi:10.1016/j.ijcard.2014.07.088

26. Levy F, Fayad N, Jeu A, et al. The value of cardiopulmonary exercise testing in individuals with apparently asymptomatic severe aortic stenosis: a pilot study. *Arch Cardiovasc Dis*. 2014;107(10):519-528. doi:10.1016/j.acvd.2014.06.003

27. Cho EJ, Park SJ, Song JE, et al. What is the real practice of exercise echocardiographic testing in asymptomatic patients with severe aortic stenosis? *Chin Med J (Engl)*. 2013;126(24):4649-4654.

28. Yingchoncharoen T, Gibby C, Rodriguez LL, Grimm RA, Marwick TH. Association of myocardial deformation with outcome in asymptomatic aortic stenosis with normal ejection fraction. *Circ Cardiovasc Imaging*. 2012;5(6):719-725. doi:10.1161/CIRCIMAGING.112.977348

29. Saito T, Muro T, Takeda H, et al. Prognostic value of aortic valve area index in asymptomatic patients with severe aortic stenosis. *Am J Cardiol*. 2012;110(1):93-97. doi:10.1016/j.amjcard.2012.02.056

30. Lancellotti P, Magne J, Donal E, et al. Clinical outcome in asymptomatic severe aortic stenosis: insights from the new proposed aortic stenosis grading classification. *J Am Coll Cardiol*. 2012;59(3):235-243. doi:10.1016/j.jacc.2011.08.072

31. Perera S, Wijesinghe N, Ly E, Devlin G, Pasupati S. Outcomes of patients with untreated severe aortic stenosis in real-world practice. *N Z Med J*. 2011;124(1345):40-48.

32. Kitai T, Honda S, Okada Y, et al. Clinical outcomes in non-surgically managed patients with very severe versus severe aortic stenosis. *Heart*. 2011;97(24):2029-2032. doi:10.1136/heartjnl-2011-300137

33. Cioffi G, Faggiano P, Vizzardi E, et al. Prognostic effect of inappropriately high left ventricular mass in asymptomatic severe aortic stenosis. *Heart*. 2011;97(4):301-307. doi:10.1136/hrt.2010.192997

34. Rosenhek R, Zilberszac R, Schemper M, et al. Natural history of very severe aortic stenosis. *Circulation*. 2010;121(1):151-156. doi:10.1161/CIRCULATIONAHA.109.894170

35. Hristova-Antova E, Georgievska-Ismail Lj, Srbinovska E, Spiroska V, Hristova-Dimceva A, Zanteva-Naumoska M. Annual rate of progression of aortic-jet velocity and survival in cases of severe asymptomatic aortic stenosis. *Prilozi*. 2009;30(1):91-104.

36. Lafitte S, Perlant M, Reant P, et al. Impact of impaired myocardial deformations on exercise tolerance and prognosis in patients with asymptomatic aortic stenosis. *Eur J Echocardiogr*. 2009;10(3):414-419. doi:10.1093/ejechocard/jen299

37. Weisenberg D, Shapira Y, Vaturi M, et al. Does exercise echocardiography have an added value over exercise testing alone in asymptomatic patients with severe aortic stenosis? *J Heart Valve Dis*. 2008;17(4):376-380.

38. Avakian SD, Grinberg M, Ramires JA, Mansur AP. Outcome of adults with asymptomatic severe aortic stenosis. *Int J Cardiol*. 2008;123(3):322-327. doi:10.1016/j.ijcard.2006.12.019

39. Le Tourneau T, Pellikka PA, Brown ML, et al. Clinical outcome of asymptomatic severe aortic stenosis with medical and surgical management: importance of STS score at diagnosis. *Ann Thorac Surg*. 2010;90(6):1876-1883. doi:10.1016/j.athoracsur.2010.07.070

40. Pellikka PA, Sarano ME, Nishimura RA, et al. Outcome of 622 adults with asymptomatic, hemodynamically significant aortic stenosis during prolonged follow-up. *Circulation*. 2005;111(24):3290-3295. doi:10.1161/CIRCULATIONAHA.104.495903

41. Pierri H, Nussbacher A, Decourt LV, et al. Clinical predictors of prognosis in severe aortic stenosis in unoperated patients > or = 75 years of age. *Am J Cardiol*. 2000;86(7):801-804. doi:10.1016/s0002-9149(00)01088-2

42. Rosenhek R, Binder T, Porenta G, et al. Predictors of outcome in severe, asymptomatic aortic stenosis. *N Engl J Med*. 2000;343(9):611-617. doi:10.1056/NEJM200008313430903

43. Kang DH, Park SJ, Lee SA, et al. Early surgery or conservative care for asymptomatic aortic stenosis. *N Engl J Med*. 2020;382(2):111-119. doi:10.1056/NEJMoa1912846

44. Kim HJ, Kim JB, Kim HR, et al. Impact of valve replacement on long-term survival in asymptomatic patients with severe aortic stenosis. *Am J Cardiol*. 2019;123(8):1321-1328. doi:10.1016/j.amjcard.2019.01.035

45. Campo J, Tsoris A, Kruse J, et al. Prognosis of severe asymptomatic aortic stenosis with and without surgery. *Ann Thorac Surg*. 2019;108(1):74-79. doi:10.1016/j.athoracsur.2019.01.031

46. Bohbot Y, Pasquet A, Rusinaru D, et al. Asymptomatic severe aortic stenosis with preserved ejection fraction: early surgery versus conservative management. *J Am Coll Cardiol*. 2018;72(23 pt A):2938-2939. doi:10.1016/j.jacc.2018.09.049

47. Masri A, Goodman AL, Barr T, et al. Predictors of long-term outcomes in asymptomatic patients with severe aortic stenosis and preserved left ventricular systolic function undergoing exercise echocardiography. *Circ Cardiovasc Imaging*. 2016;9(7):e004689. doi:10.1161/CIRCIMAGING.116.004689

48. Kang DH, Park SJ, Rim JH, et al. Early surgery versus conventional treatment in asymptomatic very severe aortic stenosis. *Circulation*. 2010;121(13):1502-1509. doi:10.1161/CIRCULATIONAHA.109.909903

49. Pai RG, Kapoor N, Bansal RC, Varadarajan P. Malignant natural history of asymptomatic severe aortic stenosis: benefit of aortic valve replacement. *Ann Thorac Surg*. 2006;82(6):2116-2122. doi:10.1016/j.athoracsur.2006.07.043

50. Iung B, Baron G, Butchart EG, et al. A prospective survey of patients with valvular heart disease in Europe: the Euro Heart Survey on Valvular Heart Disease. *Eur Heart J*. 2003;24(13):1231-1243. doi:10.1016/S0195-668X(03)00201-X

51. Everett RJ, Tastet L, Clavel MA, et al. Progression of hypertrophy and myocardial fibrosis in aortic stenosis: a Multicenter Cardiac Magnetic Resonance Study. *Circ Cardiovasc Imaging*. 2018;11(6):e007451. doi:10.1161/CIRCIMAGING.117.007451

52. Lancellotti P, Magne J, Dulgheru R, et al. Outcomes of patients with asymptomatic aortic stenosis followed up in heart valve clinics. *JAMA Cardiol*. 2018;3(11):1060-1068. doi:10.1001/jamacardio.2018.3152

53. Kappetein AP, Head SJ, Généreux P, et al; Valve Academic Research Consortium (VARC)-2. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document (VARC-2). *Eur J Cardiothorac Surg*. 2012;42(5):S45-S60. doi:10.1093/ejcts/ezs533