

# What do we know about the natural history of severe symptomatic aortic valve stenosis?

Aortic valve stenosis (AS) is increasingly observed in the clinic. Although at present surgical valve replacement is the gold standard in patients with severe symptomatic AS, elderly patients experience higher morbidity and mortality compared with younger patients. The emergence of transcatheter aortic valve implantation offers an alternative for high-risk or inoperable patients. However, mortality and morbidity is high and long-term outcomes, particularly with respect to device durability, are not yet available. The life expectancy of patients with severe symptomatic AS who are not operated upon is reduced. Most of the reported data, however, date back to the presurgical and precatheterization era. The aim of this article is to outline the evidence of natural history with medical treatment to assist in optimal clinical decision making in the high-risk elderly population with severe symptomatic AS.

**KEYWORDS:** aortic valve stenosis • medical treatment • severe • symptomatic

After hypertension and coronary artery disease, aortic valve stenosis (AS) is the most frequent cardiovascular disease. AS is increasingly observed in octogenarians and even in nonagenarians. The prevalence of AS is currently reported to be 2.5% at the age of 75 years and almost 8% at 85 years [1].

Angina pectoris, syncope and congestive heart failure are the classic manifestations of severe symptomatic AS. However, severe symptomatic AS may manifest clinically in earlier stages with more subtle symptoms, such as decrease in exercise tolerance, fatigue or exertional dyspnea. The onset of symptoms is a critical point for making treatment decisions. It has been reported that only 50% of patients who present with angina survive for 5 years or more, whereas the average survival is 3 years for patients who present with syncope and 2 years in patients with congestive heart failure [2].

At present, surgical aortic valve replacement is the gold standard for treatment of severe symptomatic AS and numerous reports document the safety and efficacy of this approach even in elderly patients. However, elderly patients experience higher morbidity and mortality compared with younger patients, with mortality rates ranging from 5.7 to 13% (TABLE 1) [3–9]. Although consensus exists regarding the utility of aortic valve replacement for severe symptomatic AS, the decision to offer surgery to the elderly high-risk population is much more complex. Some patients are physically unfit for surgery, or surgery is denied because of a treatment preference of either the patient or the physician. Certain

comorbid factors, such as preoperative cerebrovascular accident, respiratory insufficiency, renal failure and reduced left ventricular function, are independent predictors of in-hospital mortality in octogenarians [3,5,6].

At present, patients who are high-risk candidates for surgical valve replacement may be offered transcatheter aortic valve implantation (TAVI). Although promising, periprocedural complications and mortality rate are significant (TABLE 2). The prognosis is influenced by increased age (patient's life expectancy) and various comorbidities. In this setting, the cardiologist and surgeons have to balance the mortality and morbidity associated with surgery or TAVI against the expected duration and quality of life with medical treatment, as the life expectancy of elderly people is short, regardless of whether or not the patient has severe symptomatic AS (FIGURE 1). The benefit of surgery or alternative treatment methods such as TAVI is uncertain because the majority of information about the outcome of medical treatment dates back to the presurgical and precatheterization era [2]. Therefore, the aim of this article is to outline the evidence of natural history with medical treatment to assist in optimal clinical decision-making in the high-risk elderly population with severe symptomatic AS.

## Natural history: the evidence

The first report presenting survival data of patients treated conservatively for severe symptomatic AS was published in 1954. Bergeron *et al.* described the natural history outcome of 82

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Table 1. Outcome of surgical aortic valve replacement in octogenarians.

Author	Year	n	Patient characteristics	Mortality (%)	Morbidity			5-year survival (%)	Ref.
					CVA (%)	MI (%)	Respiratory failure (%)		
Thourani <i>et al.</i>	2008	88	≥80 years (isolated AVR)	5.7	3	0	–	61	[3]
de Vincentiis <i>et al.</i>	2008	345	≥80 years (70% CABG)	7.5	–	–	5	61	[5]
Filsoufi <i>et al.</i>	2008	231	≥80 years (48% CABG)	5.2	4	1	13	66	[6]
Melby <i>et al.</i>	2007	245	≥80 years (57% CABG)	9.0	3	1	22	56	[7]
Kolh <i>et al.</i>	2007	220	≥80 years (26% CABG)	13.0	2	4	21	75	[8]
Bose <i>et al.</i>	2007	68	≥80 years (46% CABG)	13.0	3	–	–	78 (at 2 years)	[4]
Chiappini <i>et al.</i>	2004	115	≥80 years (38% CABG)	8.5	1	4	5	69	[9]

AVR: Aortic valve replacement; CABG: Coronary artery bypass grafting; CVA: Cerebrovascular accident; MI: Myocardial infarction.

patients, mean age of 69 years, with severe symptomatic AS who had been followed up over an 11-year period [10]. All patients were examined at necropsy at which severe AS was described as “an aortic valve admitting at most the tip of a finger”. In their analysis, 3-year survival was 45% in patients presenting with angina, 45% in patients with syncope and 35% in patients with congestive heart failure (TABLE 3). In line with these observations, the next important contribution to the understanding of the natural history of severe symptomatic AS was also in 1954 by Mitchell *et al.* [11]. Over a 39-year period, they investigated the natural history outcome in 122 patients with severe symptomatic AS. Aortic stenosis was proven at autopsy, or the diagnosis was made clinically and verified by the demonstration of calcium in the region of the aortic valve by x-ray and fluoroscopic study. Mean survival in patients presenting with angina, syncope and congestive heart failure was 4.1, 3.0 and 2.0 years, respectively.

In 1968, still before the era of hemodynamic assessment of AS severity, Ross and Braunwald summarized data from seven postmortem studies on the natural history of severe symptomatic AS [2]. Most of these studies were retrospective and published before 1955. Based on their analysis, they observed that the average life expectancy after the onset of angina pectoris, syncope and congestive heart failure was 5, 3 and 2 years, respectively. Ever since, these data have become commonly used to describe the natural history of severe symptomatic AS.

In the decade after this report, two studies assessed the hemodynamic consequence of valvular obstruction in severe symptomatic patients with AS [12,13]. In a report by Frank *et al.* comprising 15 patients, the 5- and 10-year survival rates were 48 and 10%, respectively [12]. Among the 23 patients reported by Chizner *et al.*, 26% were deceased 1 year after the onset of symptoms and 64% by 5 years [13]. Not surprisingly, a prospective study examining the natural history of

Table 2. Success and outcome of transcatheter aortic valve implantation.

Authors	Year	n	Approach	Procedure success (%)	30-day mortality (%)	30-day MACCE (%)	Ref.
<b>Edwards-Sapien™ valve</b>							
Cribier <i>et al.</i>	2006	34	Antegrade Retrograde	74	17	26	[24]
Webb <i>et al.</i>	2006	18	Retrograde	78	11	–	[39]
Webb <i>et al.</i>	2007	50	Retrograde	86	12	16	[40]
Eltchaninoff <i>et al.</i> (global update)	2008	>270	Retrograde	86	12	–	[41]
Ye <i>et al.</i>	2007	26	Transapical	100	23	31	[25]
Thomas <i>et al.</i> (SOURCE Registry)	2010	1038	Transfemoral Transapical	94	9	30	[42]
Walther <i>et al.</i>	2007	59	Transapical	90	14	–	[43]
<b>Core valve</b>							
Grube <i>et al.</i>	2006	25	Retrograde	84	20	32	[26]
Grube <i>et al.</i>	2007	86	Retrograde	88	12	22	[44]
Grube <i>et al.</i> (global update)	2008	175	Retrograde	92	15	–	[45]

MACCE: Major adverse cardiac and cerebrovascular event.

severe symptomatic AS has not been conducted since the introduction of aortic valve replacement. Because of the limited number of patients who were not operated on for severe symptomatic AS, some studies retrospectively identified the natural history of patients who refused or were denied aortic valve replacement [12–17]. The natural history of this small subset of highly selected patients probably does not represent the natural history of all patients with severe symptomatic AS.

In 2004, Bouma *et al.* reported on a cohort of 280 elderly patients with severe symptomatic AS of which 120 were operated upon and 160 were treated conservatively [18]. The overall 1-year survival of these 160 patients was 60% and the 5-year survival was 28%. They found no difference in survival among patients  $\geq 80$  years with severe symptomatic AS and without cardiac comorbidity. One of the most recent series was published by Varadarajan *et al.* in 2006 [19]. In this study, the authors screened their echocardiographic database over a 10-year period for patients with severe AS (Doppler estimated aortic valve area [AVA] of 0.8 cm<sup>2</sup> or less). Seven hundred and forty patients were identified, of whom 453 had no aortic valve replacement through follow-up. These patients had a 1-, 5- and 10-year survival of 62, 32 and 18%, respectively. In a recent series, van Geldorp *et al.* also screened the Erasmus MC echocardiographic database over a 3.5-year period for patients with severe symptomatic AS [20]. One hundred and seventy seven patients were identified, of whom 101 were treated conservatively. These patients had a 1- and 2-year survival of 77 and 69%, respectively.

The most recent series was published in 2010 by Rajani *et al.* [21]. The authors published a series of 85 patients who were screened for TAVI. Of these patients, 38 received TAVI and 47 patients (55%) were managed medically as these patients were deemed not suitable for a TAVI procedure. Survival was better for the TAVI group compared with the medically managed group. However, as medically treated patients were deemed not suitable for TAVI, these results are biased owing to selection bias.

## Discussion

Successful cardiac surgical therapy in octogenarians and nonagenarians is increasingly performed and the number of procedures will increase even further over the coming years as healthcare in general improves and the population ages. Despite the high risk, surgical valve

replacement is still the gold standard in those patients who are medically fit and have severe symptomatic AS. The decision to proceed with aortic valve replacement depends on many factors, including the patient's wishes and expectations. However, some patients are at high risk due to several reasons and some will refuse surgery, even with a clear understanding of the risks and benefits.

The development of TAVI offers a viable option for patients at high surgical risk. Recent studies have highlighted the underuse of aortic valve replacement, ranging from 30 to 60% of elderly patients with severe symptomatic AS [22,23]. As a result of the emergence of TAVI, some high-risk patients are now being referred because the strategy of the cardiologists is changing. The feasibility and immediate efficacy of the percutaneous devices have been demonstrated, while its long-term outcomes, particularly with respect to device durability, remains to be proven. However, the rates of periprocedural complications and major adverse cardiac and cerebrovascular event rates within 30 days are of concern and need further improvement [24–26].

The hand drawn survival figure, based on data from seven postmortem studies on the natural history of AS, published by Ross and Braunwald in 1968 is still being used in current clinical practice as the accepted clinical view regarding the natural history of severe symptomatic AS [2]. However, the natural history studies described in this article have significant limitations when extrapolating findings to current clinical decision-making. Studies in

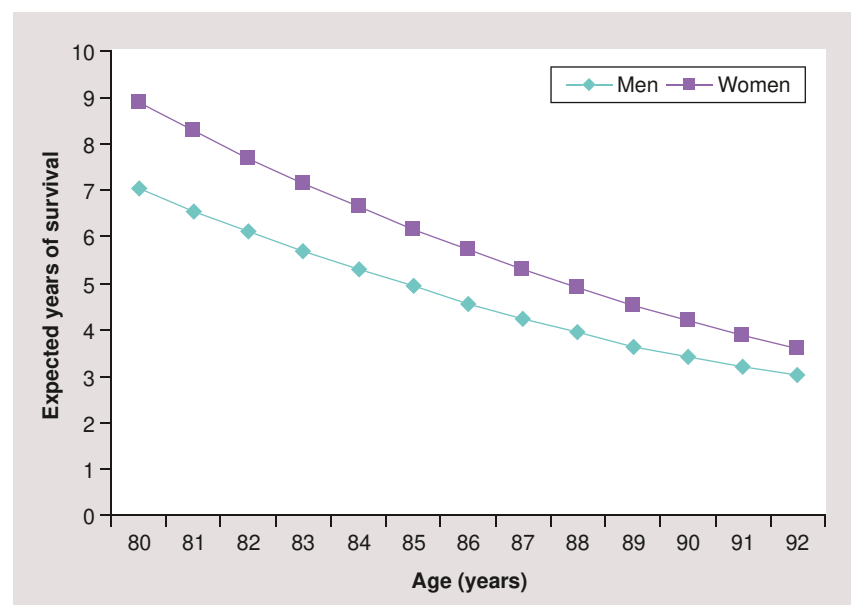


Figure 1. Expected gender-specific survival for octogenarians.

Table 3. Studies of the natural history of symptomatic patients with severe aortic valve stenosis.

Author	Year	Period of study	Design	n	Age (years)	Survival (years)	Definition of severe stenosis	Ref.
Bergeron et al.	1954	1943–1952	Retrospective Autopsy	82	Mean: 69	Angina: – 3 year: 45% – 5 year: 15% Syncope: – 3 year: 45% – 5 year: 25% CHF: – 3 year: 35% – 5 year: 10%	Aortic valve admitting at most the tip of a finger	[10]
Mitchell et al.	1954	1913–1952	Retrospective Autopsy/follow-up	122	Mean: 65	Angina: mean 4.1 Syncope: mean 3.0 CHF: mean 2.0	Clinical findings or autopsy	[11]
Olesen et al.	1958	1933–1949	Retrospective Autopsy/follow-up	42	Mean: 53	Angina: mean 4.7 Syncope: mean 3.2	Clinical findings or autopsy	[29]
Anderson et al.	1961	–	Retrospective Autopsy	49	Mean: 63	Angina: mean 3.5 CHF: mean 2.2	Not described	[46]
Takeda et al.	1963	1948–1959	Retrospective Follow-up	60	Mean: 57	Overall: mean 6.1 Angina: mean 6.3 Syncope: mean 6.4 CHF: mean 3.6	Not described	[27]
Ross and Braunwald	1968	Review 1968	Retrospective Autopsy	–	Not described	Angina: mean 5.0 Syncope: mean 3.0 CHF: mean 2.0	Not described	[2]
Frank et al.	1973	1954	Retrospective Follow-up	15	Range: 32–59	Overall: – 3 year: 64% – 5 year: 48%	Aortic valve area index $\leq 0.7$ cm <sup>2</sup> or maximum peak gradient $\geq 50$ mmHg	[12]
Chizner et al.	1980	1966–1971	Retrospective Follow-up	23	Mean: 56	Overall: – 3 year: 43% – 5 year: 36%	Aortic valve area $\leq 1.1$ cm <sup>2</sup> or maximum peak gradient $\geq 40$ mmHg	[13]
Schwarz et al.	1982	1975–1980	Retrospective Follow-up	19	Mean: 56	Overall: – 3 year: 21%	Clinical findings and maximum peak gradient $\geq 45$ mmHg	[30]
O’Keefe et al.	1987	1978–1985	Retrospective Follow-up	50	Mean: 77	Overall: – 1 year: 57% – 2 year: 37% – 3 year: 25%	Clinical findings	[31]
Horstkotte and Loogen	1988	1968–1976	Retrospective Follow-up	35	Not described	Angina: mean 4.5 Syncope: mean 2.6 CHF: mean 1.0	Aortic valve area $\leq 0.8$ cm <sup>2</sup>	[16]

CHF: Chronic heart failure.

Table 3. Studies of the natural history of symptomatic patients with severe aortic valve stenosis (cont.).

Author	Year	Period of study	Design	n	Age (years)	Survival (years)	Definition of severe stenosis	Ref.
Bouma <i>et al.</i>	2004	1991–1994	Retrospective Follow-up	157	Range: 70–93	Overall: – 1 year: 60% – 5 year: 28%	Aortic valve area $\leq 1.0$ cm <sup>2</sup> or maximum peak gradient $\geq 50$ mmHg	[18]
lung <i>et al.</i>	2005	2001	Retrospective Follow-up	72	Mean: 82	Overall: – 1 year: 85%	Aortic valve area index $\leq 0.6$ cm <sup>2</sup> /m <sup>2</sup> or mean gradient $\geq 50$ mmHg	[23]
Charlson <i>et al.</i>	2006	1995–1997	Retrospective Follow-up	75	Mean: 85	Overall: – 1 year: 55% – 3 year: 23% – 5 year: 15%	Aortic valve area $\leq 0.8$ cm <sup>2</sup> or mean gradient $\geq 50$ mmHg	[47]
Varadarajan <i>et al.</i>	2006	1993–2003	Retrospective Follow-up	453	Mean: 75	Overall: – 1 year: 62% – 5 year: 32% – 10 year: 18%	Aortic valve area $\leq 0.8$ cm <sup>2</sup>	[19]
van Geldorp <i>et al.</i>	2009	2004–2007	Retrospective Follow-up	101	Mean: 73	Overall: – 1 year: 77% – 2 year: 69%	Aortic valve area $< 1.0$ cm <sup>2</sup> or maximum aortic jet velocity $> 4.0$ m/s or peak aortic gradient $> 64$ mmHg or mean aortic gradient $> 40$ mmHg	[20]
Bakaeen <i>et al.</i>	2010	1997–2008	Retrospective Follow-up	140	Mean: 76	Overall: – 1 year: 65% – 3 year: 29% – 5 year: 16%	Aortic valve area $< 1.0$ cm <sup>2</sup>	[48]

CHF: Chronic heart failure.

which prognosis is based only on postmortem cases are biased, because prognosis will appear better if living patients with symptoms are also included. For example, Takeda *et al.* reported an average survival of 4.4, 3.8 and 2.8 years after angina, syncope and congestive heart failure, respectively [27]. However, they excluded living patients in their calculation. If living patients were included, mean survival calculations would be 6.3, 6.4 and 3.6 years after angina, syncope and congestive heart failure, respectively.

A problem that has arisen in clinical practice is the definition of 'severe' AS. Over recent years, echocardiography has evolved to become the major tool for evaluating patients with valvular AS. At present, severe AS is defined by the American College of Cardiology/American Heart Association Practice Guidelines as an AVA less than 1.0 cm<sup>2</sup>, mean gradient greater than 40 mmHg or jet velocity greater than 4.0 m/s [28]. In the past, the severity of AS was based on clinical examination [11,27,29–31]. As cardiac catheterization evolved and provided an objective measurement of the severity of AS by means of the AVA, the criterion for severe AS was first set as an AVA less than 0.7 cm<sup>2</sup> [32]. However, the precise hemodynamic criterion for 'severe' AS has varied in the past (TABLE 3). As a consequence, the validity (patient generalizability) of earlier studies must be questioned.

Coronary angiography was not performed in most of the published series, although the presence of coronary artery disease is clearly a major risk factor for mortality. In a study by Turina *et al.*, 50% of patients with severe symptomatic AS with additional coronary artery disease died within the first year of follow-up, while only 16% of patients without coronary artery disease died [33]. Therefore, survival and symptoms may even be improved if medically treated patients undergo percutaneous coronary intervention of significant coronary lesions.

Furthermore, treatment decisions made in the past differ greatly from those of today. For example, today an impaired left ventricular function would be an indication for operation [34], whereas in the past it would be considered a relative contraindication. In addition, the etiology of AS and the characteristics of the patient population have changed markedly over the past decades, and it can be questioned whether the course of AS in middle-aged patients of the 1960s should guide the management of today's octogenarians and nonagenarians with severe symptomatic AS. Moreover, studies have

involved few elderly patients and have reported on combined end points (e.g., a combination of death and cardiac surgery), which makes their results difficult to interpret [16,35,36].

Important 1-year data of the randomized trial in the USA, PARTNER-US, in which TAVI is compared with standard therapy in a group of patients unsuitable for surgical aortic valve replacement have recently been published [37]. At 1 year, the rate of death was 31% with TAVI, as compared with 50% with standard therapy ( $p < 0.001$ ). However, the incidence of major strokes at 30 days (5.0 vs 1.1%;  $p = 0.06$ ) and major vascular complications (16.2 vs 1.1%;  $p < 0.001$ ) was higher with TAVI as compared with standard therapy. These data must be interpreted with caution as patients in the TAVI group compared with the standard therapy group had a significantly lower incidence of prognostic factors that have an effect on outcome, such as a lower EuroSCORE, lower rate of chronic obstructive pulmonary disease and lower rate of atrial fibrillation. Moreover, only 12% of those patients considered not be suitable candidates for surgery were considered suitable for TAVI and underwent randomization. An important issue in the future will be the cost–benefit of TAVI versus medical therapy, since after 1 year 31% of the TAVI patients are dead and 20% have severe symptoms (New York Heart Association Class 3 or 4), resulting in a 1 year asymptomatic or mild symptomatic survival of only 50%. Nevertheless, recently Reynolds *et al.* showed that among selected inoperable patients with severe symptomatic AS, compared with standard therapy, TAVI resulted in significant improvements in health-related quality of life [38].

Management decision in elderly high-risk patients with severe symptomatic AS must be taken thoughtfully and should be made on an individual basis, taking into account patients' life expectancy and quality of life, patients' wishes and cardiac and noncardiac comorbid factors. Once coronary disease, other valvular heart disease, neurological deficits, renal failure and other comorbidities are added to the clinical setting, outcome worsens and these factors must be taken into consideration when deciding whether to correct AS in elderly patients. As life expectancy in the octogenarian is short and the main aim in the elderly is to improve quality of life rather than to increase the duration of life, surgeons and cardiologists have to question whether they do their patients a favor or a disservice with the chosen therapy. Based on the available data, TAVI promises significantly

improved 1-year survival when compared with medical management. Nevertheless, the technology of TAVI is still in its infancy and rigorous evaluation of transcatheter technology with adequate follow-up is needed. In addition, the natural history of medically managed patients with severe symptomatic AS in the modern era is still unclear, as most published data is outdated or biased. In this regard, much remains to be learned about the current natural history of severe symptomatic AS, especially in high-risk elderly patients.

### Future perspective

At present, surgical aortic valve replacement is still the gold standard for treatment of severe symptomatic AS. However, TAVI has been proven to be a feasible treatment option to treat high-risk inoperable elderly patients with severe symptomatic AS. An assessment of the durability and long-term clinical safety and effectiveness of the bioprosthetic valves will require more prolonged follow-up of patients who participate in clinical trials of TAVI.

The key issue in the future is to adequately select those elderly patients who will benefit

from TAVI and select those who will benefit from medical treatment. For example, treatment options could be different in an 85-year-old patient with severe AS, mild angina and comorbidity (medical treatment could be a better option) compared with an 85-year-old patient with severe AS, congestive heart failure and no further comorbidity (TAVI could be a better option). Additional randomized trials on specific patient populations with certain symptoms and comorbidity is necessary to determine the best treatment option in those groups of patients. In addition, a clinical course of patients who are denied TAVI (which was 88% in the PARTNER-US trial) should be documented.

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*The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.*

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### Executive summary

- Surgical aortic valve replacement is still the gold standard for treatment of severe symptomatic aortic valve stenosis.
- Patients who are inoperable or high-risk candidates may be offered transcatheter aortic valve implantation.
- The feasibility and immediate efficacy of transcatheter aortic valve implantation has been demonstrated, while its long-term outcome, particularly with respect to device durability, remains to be proven.
- The majority of published series describing the natural history of severe symptomatic aortic valve stenosis are biased because most reported series are postmortem studies and date back to the presurgical and precatheterization era, or are biased due to highly selected patient populations.
- The first randomized trial (PARTNER-US) comparing transcatheter aortic valve implantation with medical therapy in a group of inoperable patients with severe symptomatic aortic valve stenosis clearly demonstrates an improved 1-year survival in the transcatheter group. However, data cannot be extrapolated to all inoperable patients since the study population was highly selected (only 12% of inoperable patients were included in the study).
- The natural history of medically treated patients with severe symptomatic aortic valve stenosis in the modern era is still unclear. Additional randomized trials on specific patient populations with certain symptoms and comorbidity is necessary. The clinical course of patients who are denied transcatheter aortic valve implantation should be documented.

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