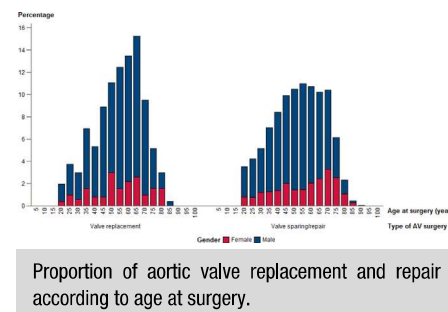


# Aortic Valve Surgery in Nonelderly Patients: Insights Gained From AVIATOR

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Aortic valve surgery in non-elderly patients represents a very challenging patient population. The younger the patient is at the point of aortic valve intervention, the longer their anticipated life expectancy will be, with longer exposure to valve-related complications and risk for re-operation. Although the latest international guidelines recommend aortic valve repair in patients with aortic valve insufficiency, what we see in the real world is that the vast majority of these aortic valves are replaced. However, current prosthetic valves has now been shown to lead to significant loss of life expectancy for non-elderly patients up to 50% for patients in their 40s undergoing mechanical aortic valve replacement. Bioprostheses carry an even worse long-term



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survival, with higher rates of re-intervention. The promise of trans-catheter valve-in-valve technology is accentuating the trend of bioprosthetic implantation in younger patients, without yet the appropriate evidence. In contrast, aortic valve repair has shown excellent outcomes in terms of quality of life, freedom from re-operation and freedom from major adverse valve-related events with similar life expectancy to general population as it is also found for the Ross procedure, the only available living valve substitute. We are at a time when the paradigm of aortic valve surgery needs to change for the better. To better serve our patients, we must acquire high quality real-world evidence from multiple centers globally — this is the vision of the AVIATOR registry and our common responsibility.

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### Central Message

Treatment of aortic valve pathology in the non-elderly population remains a challenge. Long-term outcomes of mechanical valves and bioprostheses show significantly impaired survival and reduction of life expectancy, with emerging evidence favoring aortic valve repair, the Ross procedure, and the need for “living” valve implants. To better serve our patients, we must acquire high-quality real-world evidence from multiple centers globally—this is the vision of the AVIATOR registry and our common responsibility.

We are currently in an era of change in management and shared decision-making for heart valve disease. Aortic valve (AV) surgery in nonelderly patients represents a very challenging patient population. Their high level of physical activity places hemodynamic demands on the valve. Their postoperative quality of life is extremely important and must be compatible with their professional and personal lifestyle. More importantly, the younger the patient is at the point of AV intervention, the longer their anticipated life expectancy will be. This fact alone poses the biggest challenge to any AV procedure—that is, longer anticipated life expectancy means longer exposure to valve-related complications such as degeneration, need for reoperation, bleeding, and thromboembolism. Unlike what is found in older patients, aortic insufficiency (AI) is very common in the younger AV patients. More than 50% of AI cases are in patients under the age of 50 years, and these patients with AI have an impaired survival compared to those with aortic stenosis.<sup>1</sup>

Although the latest international guidelines<sup>2</sup> recommend AV repair in patients with AV insufficiency, what we see in the real world is that the vast majority of these AVs are replaced. There is a push to promote the lowering of the age of implantation of bioprosthetic valves—yet on the other hand, little investment is made into the development of AV repair. A lot of media attention has turned recently to the worldwide lack of assessment of medical implants.<sup>3</sup> The surgical and interventional community now more than ever needs to take responsibility for the long-term assessment of patients' outcomes and the devices we implant into them. Furthermore, in order to make a truly shared decision with our patients about the type of AV surgery they are going to embark on, we need to be able to understand the evidence and convey this to them appropriately.

### AV REPAIR

AV repair is now recognized as a good alternative to prosthetic valve replacement in selected patients with AI or proximal aorta aneurysm. Several pioneering cohorts with single-center experience have achieved long-term results (up to 20 years), showing excellent outcomes of 96% freedom from reoperation,

low rates of valve-related events, and an improved quality of life compared to valve replacement.<sup>4</sup> A propensity score analysis comparing AV repair vs replacement showed an improved survival at 9 years of 87% for AV repair vs 60% for AV replacement ( $P=0.007$ ).<sup>5</sup> A meta-analysis of 31 studies involving 4777 patients (mean age  $51 \pm 14.7$  years) undergoing valve-sparing root replacement described an early mortality of 2%, late mortality 1.5%/y (10-year survival 85%), and reoperation on the AV 1.3%/y.<sup>6</sup> The safety of valve-sparing root replacement has been confirmed by the multicenter CAVIAR trial showing similar 30 days' mortality compared to a mechanical composite valve and graft (Bentall procedure) with a trend toward more major adverse valve-related events in the Bentall group (odds ratio 2.52,  $P=0.09$ ).<sup>7</sup> Moreover, active ongoing research has led to several significant improvements in the AV repair techniques, such as better repair stabilization using circumferential annuloplasty and systematic assessment of valve configuration using the effective height caliper.<sup>8,9</sup>

The latest 2017 European Association for Cardio-Thoracic Surgeons (EACTS)/European Society of Cardiology (ESC) guidelines for heart valve disease recommend a “heart team discussion” for selected patients “with pliable, non-calcified tricuspid or bicuspid” AV insufficiency “in whom aortic valve repair may be a feasible alternative to valve replacement” (class I C indication).<sup>10</sup> According to Euro Heart Survey for valvular heart disease, two-third of cases have a tricuspid or bicuspid dystrophic AI representing good candidates for AV repair, while only 1.7% had their valve repaired at that time.<sup>11</sup> Recent STS database analysis showed a slight improvement with 14% of patients who underwent aortic root surgery receiving a valve-sparing procedure (20% of low-risk and 6% of high-risk patients), but still leaving over 80% of root procedures for AI as composite valve and graft replacement (Bentall).<sup>12</sup> However, in recent years, there has been a trend toward valve repair. As they have accumulated experience, the main schools of AV repair have standardized approaches and techniques to enhance the reproducibility and dissemination of AV repair. Furthermore, the high-volume AV repair centers have combined their experience by the creation of a dedicated scientific

meeting (Aortic Valve Repair Summit) and a common data base (AVIATOR registry [<http://heartvalvesociety.org/AVIATOR/>]) aiming to improve the level of medical evidence.

Several issues have limited the widespread use of AV repair, such as the commonly held belief that mechanical valve replacement is a life-long operation with almost no risk of reoperation, the lack of uptake of AV repair development by the valve industry, and importantly the lack of large multicenter comparisons of AV repair vs replacement on long-term outcomes.

### AV REPLACEMENT

Although being reproducible with short cross-clamp times, AV replacement with standard prosthetic valves has been shown to lead to potential significant loss of life expectancy. This has been recently published in a large cohort of 9942 patients from California state showing 30.6% (bioprosthesis) vs 26.4% (mechanical) ( $P < 0.03$ ) mortality rate at 15 years in the 45–54 years old group.<sup>13</sup> This finding strongly indicates the need to better evaluation of our practice and the urgent need to consider alternative treatments.

### MECHANICAL AVR

A meta-analysis of mechanical AVR in patients  $\leq 55$  years of age by Takkenberg et al (5728 patients, mean follow-up 5.7 years) showed an early mortality of 3.15%, with a late mortality 1.55%/y meaning a survival at 10 years of 84.5%.<sup>14</sup> They also carried out microsimulation to estimate life expectancy based on the age of the patient at surgery. Taking an example of a 45-year-old undergoing mechanical AVR, their estimated life expectancy was 19 years (survival to age 64), compared to a life expectancy of 34 years (survival to age 79) for the general population. This equates to almost a 50% drop in life expectancy postoperatively.

These findings were in keeping with Bouhout et al who studied 450 patients aged  $\leq 65$  years who had undergone mechanical AVR.<sup>15</sup> They found a 10-year survival of  $87\% \pm 1\%$ , with an actuarial survival free from reoperation at 10 years of  $82\% \pm 2\%$ . Kvidal et al showed that in patients aged  $\leq 50$  years, the observed/expected ratio (O/E) was 4.5 (31 observed deaths compared to 6.8 expected deaths), compared to an O/E ratio of 1.02 in the elderly group.<sup>1</sup>

Similar outcomes are observed after mechanical composite valve and graft replacement. A meta-analysis of 46 studies involving 7629 patients with a mean age of 50 years showed a pooled early mortality of 6%.<sup>16</sup> With a mean follow-up of 6 years, the annual late mortality was 2.0%/y, equating to a 10-year survival of 80%. The rate of aortic root reoperation was 0.5%/y, equating to 5% at 10 years, higher than would be expected for a mechanical valve.

### BIOPROSTHETIC AVR

Although several studies, both randomized and observational, have demonstrated superior outcomes with the use of mechanical valves vs bioprosthetic valves in young and

middle-aged adults, there has been a significant increase in the use of bioprostheses for AV replacement over the last 2 decades in this age group.<sup>13,17,18</sup> This has largely been to avoid long-term anticoagulation (with the inherent hemorrhage and neurologic risk), valve noise and to improve quality of life. The promise of transcatheter valve-in-valve therapy is accentuating this trend of implanting bioprosthetic valves in younger patients. However, as Mihaljevic et al studied on 3049 patients with bioprosthetic AVR, elderly patients had survival comparable to their age, sex, and race-matched cohorts, whereas younger patients had worse than expected survival.<sup>19</sup>

Comparable studies of pericardial bioprosthetic AVRs in nonelderly adults ( $n = 373$ ; mean age of 51) showed a linearized rate of mortality 2.6%/valve year, and an actuarial survival of 78.1% at 10 years.<sup>20</sup> Survival of patients aged  $\leq 60$  years was lower than the gender- and age-matched general population at all time points ( $48\% \pm 7\%$  at 20 years compared to 80% for the general population).<sup>21</sup>

The decision to use bioprosthetic valves in young patients should not be taken without consideration of the evidence for reoperation. The median time to reoperation for patients aged  $\leq 40$  years was 7.7 years, and 12.9 years for patients aged 40–60 years.<sup>22</sup> This was supported by a UK study which showed that in a young adult population, freedom from aortic reintervention after bioprosthetic AVR was 75.0% at 12 years.<sup>23</sup>

### PULMONARY AUTOGRAFT: THE ROSS PROCEDURE

The pulmonary autograft is the only “living substitute” available for AV replacement. Unlike standard prosthetic valves which hold an excess mortality in patients below the age of 60, the Ross procedure is the only valve replacement which has shown a long-term survival equal to that of the general population. It is clear now that some of the high reintervention rates initially reported for the Ross operation<sup>24</sup> are not consistent with the better long-term outcomes produced by large-volume Ross centers, and may have been related to technique. The Ross procedure is a more complex operation when compared to a standard AVR, and includes coronary reimplantation which holds a higher operative risk albeit for a long-term benefit. However, this higher operative risk does not translate into higher operative mortality in expert centers with high volume.

A randomized controlled trial comparing Ross to homograft root replacement support this evidence by showing a 10-year survival of 97% in the Ross group vs 83% in the homograft group, with a hazard ratio for death of 4.6 in the homograft group ( $P = 0.006$ ).<sup>25</sup> A meta-analysis of 13,129 patients (adults and children) showed a late mortality in adults of 0.6%/y, which equates to a 15-year survival of 91%.<sup>26</sup> They also reported left-sided valvular deterioration rates of 0.8%/y (with AI seen as a risk factor for deterioration) and right-sided valvular deterioration rates of 0.5%/y (Table 1). A large long-term cohort showed at 15–20 years a 93.6% survival rate (mean age  $34 \pm 9$  years) similar to the general population matched for age and sex.<sup>27</sup> Furthermore, propensity-matched analysis

**Table 1.** Linearized Occurrence Rates for Different AV Procedures

|                                  | Linearized Occurrence Rate %/y (+95% CI)                      |                                                                     |                                                          |                                                                   |                                                         |
|----------------------------------|---------------------------------------------------------------|---------------------------------------------------------------------|----------------------------------------------------------|-------------------------------------------------------------------|---------------------------------------------------------|
|                                  | Mechanical AVR<br>5728 pts <sup>14</sup><br>(Mean Age 48.0 y) | Bioprosthetic AVR<br>373 pts <sup>20</sup><br>(Mean Age 51 ± 9.2 y) | Ross<br>6892 pts <sup>26</sup><br>(Mean Age 42 ± 11.4 y) | Mechanical Bentall<br>7629 pts <sup>16</sup><br>(Mean Age 49.8 y) | VSRR<br>4777 pts <sup>6</sup><br>(Mean Age 51 ± 14.7 y) |
| Late mortality                   | 1.55 (1.25–1.92)                                              | 2.58 (2.07–3.17)                                                    | 0.59 (0.46–0.76)                                         | 2.02 (1.77–2.31)                                                  | 1.53 (1.19–1.96)                                        |
| Reoperation on aortic valve/root | 0.51 (0.37–0.71)                                              | 2.61 (2.10–3.20)                                                    | 1.20 (1.01–1.42)*                                        | 0.46 (0.36–0.59)                                                  | 1.32 (1.00–1.74)                                        |
| Bleeding                         | 0.85 (0.65–1.12)                                              | 0.21 (0.09–0.42)                                                    | 0.10 (0.01–0.67)                                         | 0.64 (0.47–0.87)                                                  | 0.23 (0.13–0.42)                                        |
| Thromboembolism                  | 0.90 (0.68–1.21)                                              | 0.49 (0.29–0.77)                                                    | 0.17 (0.11–0.27)                                         | 0.77 (0.60–1.00)                                                  | 0.41 (0.22–0.77)                                        |
| Endocarditis                     | 0.41 (0.29–0.57)                                              | 0.52 (0.31–0.81)                                                    | 0.27 (0.16–0.45)                                         | 0.39 (0.33–0.46)                                                  | 0.23 (0.11–0.51)                                        |
| MAVRE                            |                                                               |                                                                     |                                                          | 2.66 (2.17–3.24)                                                  | 1.66 (1.24–2.23)                                        |

MAVRE, major adverse valve-related event.

\*Combined for both autograft and RVOT.

shows a superior survival at 20 years after the Ross procedure (94%) compared to mechanical AVR (84%;  $P = 0.018$ ).<sup>28</sup>

### A “LIVING IMPLANT” – THE FORGOTTEN VISION

Up until the development of the newer valve technologies such as transcatheter devices, a large body of research was being carried out internationally in trying to develop an artificially “living” valve—the so-called holy grail that all major valve industry players were chasing. This was based largely on the notion (and evidence) that the best long-term outcomes would come from a valve which is dynamic and has the capacity to adapt to its complex biomechanical environment. This has been shown in part by the long-term outcomes of the Ross procedure. Almost 20 years of bench research was carried out by different institutions around the world, with the vision of a new generation of tissue-engineered “living” valve.<sup>29</sup> Unfortunately, most of the focus has shifted away from this vision, with resources being used for development of minimally invasive transcatheter technologies. To date, no tissue engineered valve is available for routine clinical practice aside from within specific trials. Some work has been carried out studying the transcatheter application of tissue-engineered valves,<sup>30</sup> but this is considerably in its infancy, given that the long-term results of transcatheter deployment devices are still unknown. We will know in time whether this change in our attention was too premature or not.

### AN INDUSTRIAL CONFLICT OF INTEREST

As for the mitral valve, AV repair has significant advantages for the patient compared to valve replacement. However, unlike the mitral valve, the development and innovation of AV repair techniques is limited by major industry’s lack of interest. Although AV repair is currently carried out by a small proportion of cardiac centers, its use represents potentially around 20% of AV surgery and even more below the age of 50 related to higher incidence of AI in younger patients.<sup>1</sup> Aside from the time and cost needed to train a surgeon in AV repair techniques, a further explanation is the potential conflict of interest (or industry bias) toward valve replacement with current mechanical and bioprosthetic implants. Since the introduction of transcatheter valves, this conflict of interest has become more apparent. The lower the age a bioprosthetic valve is implanted, the higher the likelihood the patient is going to undergo a second intervention with a valve-in-valve transcatheter valve replacement, with ever escalating costs. Emerging initiatives such as “The Valve for Life” launched by European Association of Percutaneous Cardiovascular Interventions are also stimulating the growth of the valve replacement market according to a recently published market research report.<sup>31,32</sup> Since 2016, the number of transcatheter AV interventions has surpassed surgical AVR in the United States. The US structural heart devices market is estimated at over \$1.2B for AV replacement devices (ie, SAVR plus TAVR). In contrast, given the considerably lower prices for surgical annuloplasty devices, the mitral repair (annuloplasty) market represents but a dwindling

fraction of this aortic replacement market (>20 times inferior). Although transcatheter valves are a highly successful innovation for the elderly population, one of the side effects to their development has been the slowdown of research and development of a true “living” implant for young patients. Aside from AV repair, a living implant would be the true alternative to current prosthetic valves and the Ross procedure.

### A SCIENTIFIC AND SOCIETAL RESPONSIBILITY TO EVALUATE OUR PRACTICE

Analysis of long-term outcomes remains difficult because of the heterogeneity and/or inadequate description of the populations studied, with limited follow-up that rarely exceeds 5–10 years. As a result, patients are treated according to guidelines on the basis of 30-year-old evidence. To achieve a real breakthrough in the treatment of AI, a joint collaboration of cardiologists and surgeons is needed to include the complete time span of AI from diagnosis through intervention until death. This longitudinal cohort is essential to investigate key epidemiologic questions. From here starts the Aortic Valve repair InternATIOnal Registry (AVIATOR) initiative from the Heart Valve Society.<sup>33</sup> The main objectives are to enhance uniform scientific reporting, to optimize multidisciplinary patient care, to assess quality of care, and to update and improve guidelines.

The AVIATOR initiative is a longitudinal observational cohort study enrolling patients with ascending aorta aneurysm and/or AI. It is open to any center willing to participate (<http://heartvalvesociety.org/AVIATOR/>). Organization and preliminary analysis are detailed in the reference paper.<sup>34</sup> The registry contains 2 separate entities: (1) AVIATOR medical registry to evaluate the natural history of nonoperated patients; and (2) AVIATOR surgical registry to evaluate long-term outcomes after surgical treatment

AVIATOR

Free Open Prospective Multicenter Registry

### Isolated AI and/or Ascending Aorta Aneurysm

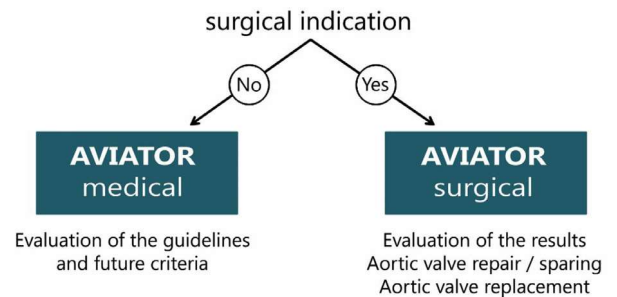


Figure 2. Organization of the AVIATOR registry.

(repair or replacement). Both registries will have an adult and a pediatric counterpart (AVIATOR-kids) (Fig. 1).

The adult surgical database currently has 58 centers which enroll patients into the registry, with a total of 4896 patients in the database. Mean age is  $52 \pm 16$  years (Fig. 2). European centers provide 89.5% of the patients, and North American centers 9.3%. Both valve repair (89%) and valve replacement (11%) operations are reported in the registry. From the repair group, 28% are isolated valve repair, 22% partial root or tubular ascending aorta replacement plus valve repair, and 49% valve-sparing root replacements. Early mortality was 0.5% for isolated AV repair compared to 1.0% for AVR. Partial root and tubular ascending aorta replacement plus valve repair shows an early mortality of 1.7% and 2.6%, respectively. Valve-sparing root replacement and the Bentall procedure have 1.2% and 2.0% early mortality, respectively.<sup>34</sup>

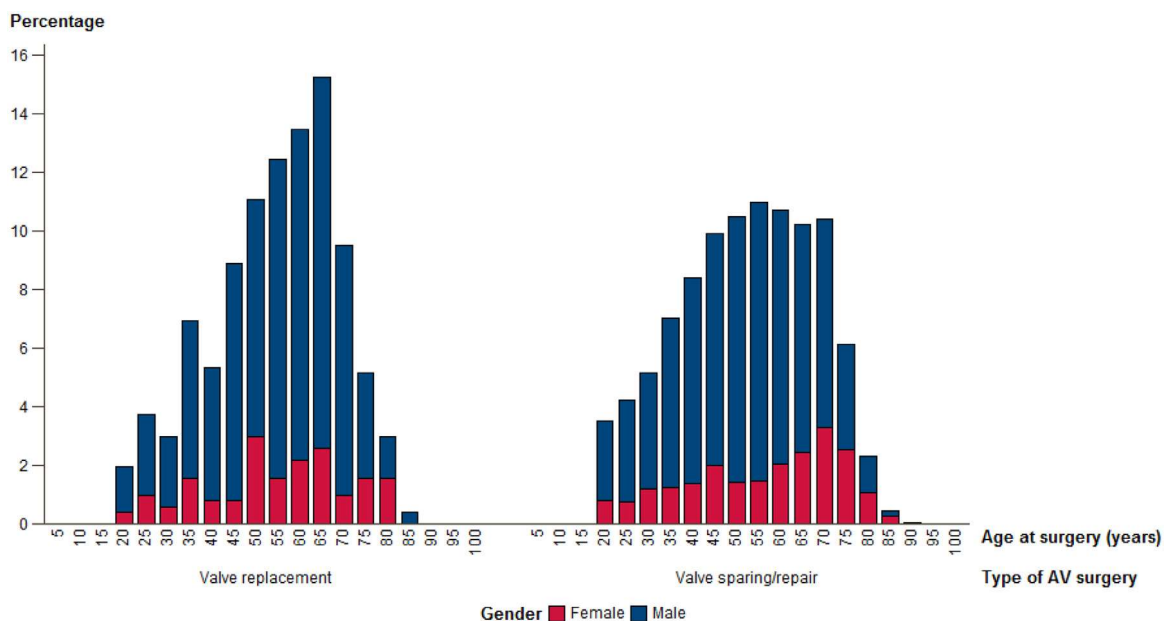


Figure 1. Proportion of aortic valve replacement and repair according to age at surgery.

The challenges for the coming years are evident and it is our scientific and societal responsibility as a surgical and medical community to improve the level of medical evidence on current therapy. There is a need to focus on data completeness and data quality. Global standards to evaluate aortic stenosis and insufficiency as well as surgical and percutaneous technology on the same database platform need to be established. Evaluation of AV repair is currently underway with the AVIATOR database. Soon a new valve research network from the Heart Valve Society on AV replacement in nonelderly patients (LEOPARD) will go live and aim to complete the evaluation of AV surgery on the same platform. By combining surgical experience from multiple centers, and applying uniform definitions of echocardiographic and outcome parameters, it should become possible to provide a solid evidence base to clarify and standardize the place of repair vs replacement in AV surgery. This will provide an evidence base for tailored treatment for each individual patient.

## CONCLUSION

Treatment of regurgitant AV pathology in the nonelderly remains a challenge for surgery. Ideally, the heart team discussion should first evaluate reparability of the valve. If the valve is not repairable, a shared decision-making process should be conducted with the patient in order help choose the appropriate valve substitute. The challenge for every team, including expert centers, is to adapt to what the patient needs, and not to our surgical practice or interest.

We do not yet have a perfect solution for these patients. The preservation of the complex functions of the valve determines the outcomes after AV intervention: survival, valve-related complications, quality of life. These factors play a role in why the long-term outcomes of our gold standard procedures such as AV replacement and Bentall root replacement are no longer seen as acceptable. They are also the same factors that lead the way for development of techniques of valve repair and alternatives to glutaraldehyde bioprosthetic or mechanical valves which need to be supported by major industry. We are at a time when the paradigm of AV surgery needs to change for the better. But to achieve this, it requires the search for high-quality real-world evidence from multiple sources—this is the vision of the AVIATOR registry and our common responsibility.

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