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Transcatheter Aortic Valve Replacement with Self- Versus Balloon-Expandable Bioprostheses for the Treatment of Bicuspid Aortic Valve Stenosis.

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SUMMARY

AORTIC VALVE STENOSIS

Aortic valve stenosis is the most common primary heart valve disease in developed countries accounting for approximately 45% of cases and affecting approximately 2.8-3.4% of subjects aged ≥ 75 years.(1-4) In contemporary registries, aortic valve stenosis leads to greater morbidity and mortality than other cardiac valve diseases.(2, 5-7) In the 1999-2009 decades, it has been estimated that 146304 deaths for aortic valve disease occurred in the United States. Of these, 82.7% were attributed to aortic stenosis, 4.0% to aortic insufficiency, and 0.6% to aortic stenosis with insufficiency, whereas 11.9% were unspecified or coded as attributed to other aortic valve disease.(8)

Normal aortic valve is made up of three cusps of equal size, arranged to produce an even distribution of mechanical stress to the valve ring and the aorta.(9) Cusps appear smooth, < 1 mm thin, and opalescent, and are composed of four tissue layers: the endothelium, fibrosa, spongiosa, and ventricularis.(10) At their base, cusps are attached to a dense collagenous network (annulus) connected to the aortic root.(10)

The most common causes of aortic valve stenosis are calcific degenerative disease, bicuspid aortic valve, and rheumatic valve disease. Calcification of a tricuspid aortic valve is most prominent in the central part of each cusp and commissural fusion is absent, while rheumatic aortic valve stenosis is characterized by commissural fusion with thickening and calcification most prominent along the edges of the cusps.(11) A bicuspid valve results from fusion of two cusps, it could be stenotic without extensive calcification or due to superimposed calcific changes, which often obscures the number of cusps, making its identification as bicuspid or tricuspid valve difficult.(11)

Epidemiology

Since the 1950s, the predominance of valvular disease has shifted from a rheumatic to a degenerative aetiology in developed countries, leading to important changes in patient characteristics

and in the distribution of the type of valvular lesions.(12) Today, aortic valve stenosis presents primarily as degenerative valve disease in elderly patients as a result of the consistent and significant association with age as observed in a number of registries and population-based cohort studies.(4, 6, 13)

Severe aortic stenosis begins with leaflet thickening and sclerosis without hemodynamically significant narrowing.(14, 15) Degenerative changes of aortic valve are observed in 20% of the patients aged 65-76 years, 35% in those aged 75-85 years, and 48% in those aged more than 85 years.(16) According to a recent meta-analysis, the rate of progression to significant aortic stenosis in individuals with degenerative aortic sclerosis is 1.8–1.9% per year.(17)

In Europe and the United States, the prevalence of significant aortic stenosis markedly increases in subjects older than 65 years.(2, 4, 18) In Europe, a large-scale, contemporary registry conducted across 28 countries showed for aortic valve stenosis a median age at diagnosis of 76 years and a proportion of 37.6% of patients older 80 years or more suffering from this valve disease.(7) In the United States, the estimated prevalence of aortic stenosis is 0.4% in the general population, 1.3% in the population aged from 65 to 74 years, and 2.8% in the population aged ≥ 75 years.(4) For individuals aged ≥ 75 years, a pooled analysis of available epidemiologic data in developed countries produced an estimated severe aortic stenosis prevalence of 3.4%, with more than 75% of patients presenting with symptoms.(1) However, smaller studies with random selection of patients have identified aortic valve stenosis even in 5% of patients aged ≥ 75 years.(15)

The burden of calcific aortic valve stenosis in the community is expected to increase over the next decades owing to population aging and the current lack of strategies that significantly prevent disease development or reduce disease progression.(19) Estimates based on current prevalence rates predict that in developed countries the number of patients with degenerative aortic stenosis aged over 75 years will increase 2- to 3-fold over the next 50 years due to population aging.(3, 20) In addition, according to a Bayesian predictive analysis based on the information accrued in recent years, the expected annual incidence of severe aortic stenosis in patients older than 65 years is expected to be

4.4% and 79.9% of these patients will have low surgical risk, as defined by a Society of Thoracic Surgeons – Predicted Risk of Mortality (STS-PROM) < 4%.(21)

Natural history

The natural history of aortic stenosis involves a prolonged latent period (**Figure 1**), during which the progressive valve obstruction leads to left ventricle hypertrophy, myocardial fibrosis, and propensity to systolic and diastolic dysfunction, and a subsequent symptomatic period characterized by shorter duration due to high rates of death.(22-27) Indeed, the risk of sudden cardiac death in patients with asymptomatic severe aortic valve stenosis managed conservatively was estimated to be approximately 1% per year and occurs without preceding symptoms in 70% of cases, while following symptoms onset up to 50% of patients die in the first 1-2 years and 90% at 5 years.(22-25, 28-32) Recent data indicates a decline in aortic valve stenosis mortality as a possible result of advances in medical therapy and increased performance of early aortic valve replacement as well as the extension of interventions to patients with more advanced age and higher comorbidity burden.(33)

As the aortic valve area becomes less than 1.5 cm^2, a measurable pressure gradient between the left ventricle and ascending aorta may be detected on echocardiography or by direct measurement at cardiac catheterization, though the magnitude is small.(5) The presence of an increased pressure afterload due to aortic stenosis translates into increased left ventricular wall stress requiring compensatory left ventricular hypertrophy to maintain adequate contractility and systemic pressures (**Figure 2**).(10, 34, 35) The diastolic dysfunction and increased resistance to left ventricular filling in the asymptomatic period are balanced by left atrial and ventricular contractility enhancement and increased preload to maintain an adequate stroke volume and normalise afterload (**Figure 2**).(5, 10, 34-36) Left ventricular hypertrophy, however, weakly correlates with aortic stenosis severity and can become maladaptive over time. Indeed, aortic stenosis patients display marked variations in the

magnitude of their hypertrophic response and increasing hypertrophy, fibrosis, and contractility dysfunction have been associated with progression to heart failure.(37-39)

As aortic valve stenosis worsens and aortic valve area decreases to 1 cm^2 or less, compensatory changes in left ventricular anatomy and function can become no longer adequate to overcome the outflow obstruction and maintain a normal stroke volume.(5) The resulting impairment in systolic function, alone or combined with diastolic dysfunction, can lead to symptoms appearance and clinical heart failure (**Figure 2**).(10, 40) The transition from hypertrophy to heart failure expresses the beginning of the stage when the left ventricle fails in the face of an increased pressure afterload and is no longer able to maintain an adequate flow through the aortic valve.(5) This heralds the onset of symptoms, adverse events, and a poor prognosis.(5, 41)

Progression to left ventricular dilatation and systolic dysfunction has been associated with increased myocyte apoptosis and fibrosis due to chronic afterload increase and high oxygen demand.(10, 40) Repetitive myocardial ischaemia related to the exhaustion of coronary flow reserve leads to apoptosis of myocytes and myocardial tissue is replaced by fibrosis.(19) This type of fibrosis occurs predominantly in the subendocardial and mid-wall layers of the left ventricle wall and is generally not reversible following relief of left ventricle pressure overload by aortic valve replacement.(19) End-stage aortic valve stenosis pathophysiology includes severely decreased diastolic compliance, subendocardial ischaemia, exhausted myocardial contractile reserve followed by irreversible myocardial fibrosis, and baroreceptor-activated vasodilation.(42)

Causes

Main causes of aortic stenosis in adults are the following (**Figure3**):(3, 5, 7)

1. Degenerative disease of cusps with development of thickening and calcifications.
2. Bicuspid or unicuspid valve with early dysfunction and regional asymmetric calcification.

3. Rheumatic fever sequalae with distortion of cusps margins and fusion of commissures.

However, nowadays in developed countries rheumatic fever aetiology is rare and it is expected to further decrease in the next decades.(5, 43) Indeed, according to the Euro Heart Survey on Valvular Heart Disease, degenerative aetiology is predominant (81.9%), followed by rheumatic origin (11.2%) and congenital bicuspid aortic valve dysfunction (5.4%).(3) Endocarditis complications account for 0.8% of the cases, while other uncommon causes are observed in 0.6% of the patients.(3)

Predictors and possible mediators associated with degenerative calcific aortic valve stenosis largely overlap those of atherosclerosis and coronary artery disease (**Figure 4**).(5, 10, 19, 44-46) Old age, male sex, diabetes, hypertension, hyperlipidaemia, smoking, metabolic syndrome, evidence of active inflammation, advanced chronic kidney disease, and disorders of mineral metabolism have been related to calcified aortic stenosis development and progression.(5, 10, 19, 27, 47-49) (**Figure 4**) The compresence of similar risk conditions is also corroborated by the finding of an estimated prevalence of significant coronary disease in up to 60% of patients with aortic valve stenosis.(50) However, there is an inverse relationship between individual patient risk and coronary artery disease prevalence and proportions of significant coronary artery disease in the low surgical risk setting are definitely lower, below 30%.(51)

In general, the rate of progression of aortic valve stenosis is highly variable with uncertain prediction in individual patients and no medical therapy against modifiable risk conditions in common with atherosclerosis have proved to be effective in delaying disease onset.(19, 27, 52-54) Genetic predisposition to aortic valve stenosis development may be relevant in the understanding of disease mechanisms. Genetic variation in the lipoprotein a locus was associated with both aortic valve calcification across multiple ethnic groups and incident clinical aortic stenosis.(44, 55)

Degenerative calcific aortic valve stenosis development and progression is linked to the activation of lipid accumulation, inflammation, and calcification (**Figure 3**).(10, 19) Mechanical stress (e.g., elevated stretch and shear stress) on aortic valve leads to valvular endothelial dysfunction,

followed by lipoprotein deposition, oxidative stress, inflammatory cells infiltrate, including T-lymphocytes and macrophages, valvular interstitial cells osteoblastic transformation, and active calcification.(10, 19, 56) Lipid deposition on disrupted endothelium causes oxidative modifications and chronic inflammation that seem to be the link across stages of aortic valve disease structural changes by steadily promoting fibrosis and calcification.(57, 58) Cytokines, such as interleukin 1 and tumour necrosis factor α, are markedly elevated in stenotic valves, as well as angiotensin-converting enzyme and angiotensin I.(45, 59-61) Other mediators, such vascular endothelial growth factor A and transforming growth factor-β have been related to fibrosis, angiogenesis, and structural remodelling progression of aortic valve disease.(10, 62) Microscopic areas of mineralization can be observed early at the level of lipid deposition and inflammatory infiltrates.(10) Several extracellular matrix proteins typically found in bones, for example osteocalcin, osteopontin, osteonectin, bone morphogenetic protein, and metalloproteinases, are observed in aortic valve calcification sites.(10, 63) End-stage aortic stenosis presents ossification in a manner similar to mature bone and histologic examination reveals expression of bone morphogenic proteins 2 and 4, angiogenesis, and frequently osteoblastic/osteoclastic activity consistent with active bone remodelling.(5, 10, 19)

Under a functional point of view, disease progression due gradual fibro-calcific remodelling of aortic valve results in increased leaflets thickness, stiffening and calcification with consequent impairment of normal motion.(5, 15) Aortic valve calcification is relatively common in elderly patients, often designated as valve sclerosis on echocardiography, with an estimated rate of 14%.(15) Over the years, the disease evolves towards more diffuse and severe valve calcifications, markedly reduced motion of cusps, and significant obstruction to blood outflow from left ventricle.(5)

Diagnosis

The classic symptoms of aortic stenosis are angina, syncope, and dyspnoea due to congestive heart failure.(22, 64) The reported prevalence of angina in patients with severe aortic valve stenosis

without significant coronary artery disease ranges from 52% to 61%.(65, 66) Angina does seem to strongly correlate with valve obstruction severity and diastolic filling time.(67) Angina develops in aortic stenosis in part because of reduced coronary flow reserve and diastolic filling and in part because of increased myocardial oxygen demand and subendocardial wall stress caused by high afterload and left ventricular hypertrophy.(68-72) Moreover, in contrast to physiological hypertrophy, a greater density of the coronary capillary network remains insufficient in relation to myocardial tissue and oxygen demand, small penetrating arteries and thinned vessel susceptible to mechanical stress perfuse subendocardium, epicardial vessels are preferentially perfused due to systolic blood backflow from subendocardium, and coronary flow reserve is impaired.(72-77) In addition, as aortic stenosis becomes severe, cardiac output no longer increases with exercise, thus angina can be triggered by reduced coronary perfusion, especially when significant coronary artery disease coexists and left ventricular ejection fraction is impaired.(78)

Exertional syncope in aortic stenosis is another traditional symptom of severe aortic stenosis.(22, 64) Syncope seems to result from an exercise-induced drop in total peripheral resistance inadequately counterbalanced by cardiac output due to the presence of a significantly stenotic aortic valve.(79) A precipitation of a vasodepressor response may also play a role in the development of hypotension and syncope.(80)

Dyspnoea is a typical symptom, usually progressively worsening over time, sometimes adduced to other cardiac and extra-cardiac conditions when simultaneous comorbidity exist, related to systolic dysfunction, insufficient stroke volume, increased diastolic filling pressure, and postcapillary pulmonary hypertension pulmonary.(22, 64)

The most common sign of aortic stenosis is a systolic ejection murmur, heard best in the aortic area, radiating to the neck.(64) The murmur that often disappears over the sternum and then reappears in the apical area, mimicking mitral regurgitation (Gallivardin's phenomenon).(64) In mild aortic stenosis, the murmur usually peaks early in systole, it is often associated with a thrill, and the carotid upstrokes are preserved.(64) As the severity of stenosis increases, the murmur peaks progressively

later in systole, it may become softer as cardiac function is abnormal, and carotid upstrokes become diminished in amplitude and delayed in time (parvus et tardus).(64) The second heart sound may become single as the aortic closing component is lost, or S2 may paradoxically split because of delay in left ventricular emptying.(64)

Echocardiography is key to confirming the diagnosis and severity of aortic stenosis, assessing valve morphology and calcification, left ventricle function and wall thickness, detecting other valve disease or aortic pathology, and providing prognostic information.(5, 81)

In some cases, aortic stenosis is first recognized on echocardiography requested for other indications and about 5–10% of patients are not diagnosed with aortic stenosis until late in the disease course.(19)

The severity of valve calcification can be graded semi-quantitatively, as mild, when few areas of dense echogenicity with little acoustic shadowing are observed, moderate, when, multiple larger areas of dense echogenicity are present, or severe, when cusps show extensive thickening and increased echogenicity with a prominent acoustic shadow.(81) The degree of valve calcification correlates with aortic stenosis severity, disease progression, clinical conditions, and adverse events.(26, 82, 83)

In Europe and United States, echocardiography guidelines define severe aortic stenosis as a mean gradient greater than 40 mm Hg, peak aortic jet velocity greater 4.0 m/sec, and aortic valve area smaller than 1 cm^2 or aortic valve area index less than 0.6 cm^2/m^2.(84, 85) Around 20% of patients with severe aortic stenosis present with low left ventricular stroke volume and low gradients.(84, 85)

Four broad categories of aortic stenosis can be defined according to current guidelines of the European Society of Cardiology and American College of Cardiology / American Heart Association:(84, 85)

1) <u>High-gradient</u>

- Mean gradient ≥ 40 mm Hg
- Peak velocity ≥ 4.0 m/s,
- Valve area ≤ 1 cm^2 (or ≤ 0.6 cm^2/m^2)

Severe aortic stenosis can be assumed irrespective of left ventricular ejection fraction function and flow conditions.(84, 85)

2) Low-flow, low-gradient with reduced ejection fraction

- Mean gradient < 40 mm Hg
- Valve area ≤ 1 cm^2
- Left ventricular ejection fraction < 50%
- Stroke volume ≤ 35 mL/m^2

Low-dose dobutamine stress echocardiography is recommended to distinguish between true severe and pseudo-severe aortic stenosis by assessing whether during valve area become < 1.0 cm^2 and flow increases with a peak systolic velocity ≥ 4 m/sec and identifying patients with no flow or contractile reserve.(84, 85)

3) Low-flow, low-gradient with preserved ejection fraction

- Mean gradient < 40 mm Hg
- Valve area ≤ 1 cm^2
- Left ventricular ejection fraction ≥ 50%
- Stroke volume ≤ 35 mL/m^2

Typically encountered in hypertensive elderly subjects with small LV size and marked hypertrophy, but this scenario may also result from conditions associated with low stroke volume including moderate to severe mitral regurgitation, severe tricuspid regurgitation,

severe mitral stenosis, and large ventricular septal defect and severe right ventricle dysfunction.(84, 85)

Diagnosis of low-flow low-gradient severe aortic stenosis is challenging and requires exclusion of measurement errors, other explanations for the echocardiographic findings, the presence of typical symptoms with no other explanation, left ventricle hypertrophy, especially in the absence of coexistent significant hypertension history, or reduced left ventricle longitudinal strain without more likely other cause. Computed tomography assessment of the degree of valve calcification provides important additional information by grading disease extent for severe aortic stenosis in Agatston units: men > 3000, women > 1600 = highly likely; men > 2000, women > 1200 = likely; men < 1600, women < 800 = unlikely.(86-90)

4) Normal-flow, low-gradient aortic stenosis with preserved ejection fraction:

- Mean gradient < 40 mm Hg,
- Valve area ≤ 1 cm^2
- Left ventricular ejection fraction ≥ 50%
- Stroke volume > 35 mL/m^2

These patients usually have only moderate aortic stenosis.(84)

Transoesophageal echocardiography is appropriate when assessment of aortic valve is limited by insufficient transthoracic acoustic windows and concomitant mitral valve disease requires appropriate evaluation.(91) Transoesophageal echocardiography is helpful as periprocedural imaging technique during surgical aortic valve replacement, but nowadays the use for transcatheter aortic valve implantation is very uncommon.(91) Left ventricular global longitudinal strain, and, as previously mentioned,(88, 92) abnormal biomarker levels, especially natriuretic peptides and

troponin are predictors of adverse outcomes and should be considered in the global assessment of aortic valve stenosis, in particular in asymptomatic patients.(84, 85, 93-95)

Exercise testing can be helpful to uncover symptoms in seemingly asymptomatic patients and exercise echocardiography provides prognostic information by assessing the increase in mean pressure gradient and changes in left ventricle function.(84, 85, 96) Aortic valve replacement is recommended in patients with severe aortic stenosis who have abnormal blood pressure responses during exercise and those with left ventricular systolic dysfunction, in whom reduced contractility is presumed to represent severe afterload excess.(84, 85, 96)

Left heart catheterisation is no longer a primary diagnostic test for aortic stenosis, but can be very useful to clarify severity when echocardiography is non-definitive. However, coronary angiography is generally performed to delineate concomitant coronary disease before aortic valve replacement and right heart catheterisation can be helpful in identifying the presence of pulmonary hypertension.(84, 85)

Computed tomography imaging is a highly valuable diagnostic tool in the workup of patients who are being considered for transcatheter aortic valve replacement since it provides accurate and reliable information on aortic valve anatomy, annular size and shape, extent and distribution of valve and vascular calcification, risk of coronary ostial obstruction, aortic root dimensions, optimal fluoroscopic projections for valve deployment, and feasibility of vascular access (transfemoral, transsubclavian, transaxillary, transcarotid, transcaval, transaortic, or transapical).(84, 85, 97, 98)

The assessment of myocardial fibrosis using cardiac magnetic resonance offers incremental prognostic information in patients with aortic stenosis. Cardiac magnetic resonance detects ventricular decompensation in aortic stenosis through the identification of myocardial extracellular expansion and replacement fibrosis.(99) Clinical implementation of this technique to optimise the timing of aortic valve intervention in asymptomatic patients is currently tested in a randomised trial.(100)

Treatment

Untreated symptomatic severe aortic stenosis has poor prognosis.(22) Early intervention is strongly recommended in all patients presenting with symptoms associated with valve dysfunction, unless valve replacement is unlikely to improve quality of life or survival due to severe comorbidities or there are concomitant conditions associated with survival < 1 year.(84, 101)

Use of surgical and transcatheter aortic valve replacement has allowed substantial improvements in the overall number of patients with aortic stenosis undergoing intervention and long-term survival. The proportion of patients undergoing intervention, surgical or transcatheter, for aortic valve stenosis is increasing. Nowadays, in Europe almost 80% of patients with symptomatic aortic valve stenosis and a Class I indication for intervention had one performed or scheduled.(7) Twenty-years ago, surgery was considered in lower proportion symptomatic patients suffering from aortic stenosis and more frequently when age was not advanced, with at least one third of patients not referred for intervention.(102, 103) These results may be explained by the introduction of transcatheter aortic valve replacement that currently accounts for almost 40% of interventions for aortic valve stenosis.(7) Symptomatic patients with high-gradient aortic stenosis have indications for aortic valve replacement irrespective of baseline left ventricular ejection fraction, especially when peak systolic velocity is > 5.0 m/sec.(84, 101, 104) Low-flow, low-gradient without or with preserved ejection fraction patterns require additional examination by dobutamine echocardiography and it is necessary the complementation of the exams with conventional exercise stress test and computed tomography.(84, 101, 104) Recently, the results of the RECOVERY trial have suggested a potential prognostic advantage of early aortic valve replacement in patients with asymptomatic severe aortic valve stenosis.(105) In this trial among asymptomatic patients suffering from aortic stenosis with aortic valve area < 0.75 cm^2 associated with either an aortic jet velocity of ≥4.5 m/sec or a mean transaortic gradient of ≥ 50 mm Hg, the incidence of a composite endpoint including operative

mortality or death from cardiovascular causes was significantly lower in patients treated by early aortic valve replacement than in patients who received conservative care.(105)

Surgical aortic valve replacement

Surgical aortic valve replacement is the traditional treatment for symptomatic severe aortic valve stenosis, with the first intervention performed in 1960.(106) Over the past half century, tremendous advances in operative management, techniques and valve design have improved outcomes of patients with aortic valve stenosis.(107, 108) Surgical aortic valve replacement has shown to improve symptoms and survival, with benefits also in settings of patients at increased risk of death or severe complications compared to medical therapy and low risk of operative mortality in patients without significant coexistent conditions.(107-114) In the United States, there was a significant 44.7% reduction in 30-day postoperative mortality following surgical aortic valve replacement, from 7.6% in 1999 to 4.2% in 2011.(114) This trend was observed among all age ranges, with the most marked decrease (52.8%) among those aged 85 years or older.(114) Recent data from the Society of Thoracic Surgeons database and German Aortic Valve Registry showed that, following isolated surgical aortic valve replacement, current 30-day mortality rate is under 3%.(107, 115)

Surgical prosthetic aortic valves can be of two types: mechanical or biological. Mechanical prosthesis are made of different material and different shapes (caged-ball, monoleaflet and bileaflet), are structurally robust, more thrombogenic but more durable.(116) Surgical biological aortic valves are made of biological tissue that can be xenogenic (bovine or porcine) or allogenic (homograft), stented or stentless (manufactured from intact porcine aortic valves or from bovine pericardium). Although biological valves are less thrombogenic, they prone to structural valve deterioration caused mainly by calcification.(101, 117)

In the last decades, a substantial shift from mechanical valves towards bioprosthetic valves was observed, particularly in patients >65 years of age.(107) Increasingly, younger patients or those

with an active lifestyle opt for a bioprosthetic valve to avoid anticoagulation despite its shorter durability compared to a mechanical valve.(107)

A further evolution in surgical aortic valves is represented by biological sutureless and rapid deployment aortic valves that anchor within the aortic annulus with no more than three sutures. In a recent randomized study that enrolled 910 patients treated with sutureless (n = 453) or conventional stented valves (n = 457), with a mini-sternotomy approach in 50.4% and 47.3% respectively, the use of sutureless valves significantly reduced surgical times but resulted in a higher rate of pacemaker implantation (11.1% vs 3.6% at 1 year) while incidences of perivalvular and central leak were similar. At 1 year follow up, sutureless valves were noninferior to stented valves with respect to major adverse cerebral and cardiovascular events.(118)

Although surgical aortic valve replacement has been shown to improve symptoms and survival, yet older patients are at an increased risk of morbidity and mortality, making a less-invasive treatment strategy desirable in such patients.(119) Minimally invasive aortic valve replacement, first described in 1996 has been shown to reduce morbidity and decrease mortality in high-risk populations with outcomes equivalent or superior to those of conventional aortic valve replacement.(120-122) Although operative mortality for aortic valve replacement varies according to the skill and experience of the surgical team as well as hospital volume.(123)

Transcatheter aortic valve replacement

Successful implantation in a porcine model was reported in 1992 with a balloon expandable catheter mounted transcatheter aortic valve made of stainless steel surgical wires folded in loops with a porcine aortic valve sewn inside.(124) In 1993-1994, proof-of-concept benchmark testing demonstrated in 12 fresh specimens of calcific aortic stenosis that a 23 mm Palmaz stent could circularly increase valve area.(125) The ideal height of the stent was 14-16 mm above the aortic valve annulus to avoid obstruction of coronary ostia obstruction or interference with the intraventricular septum or the anterior mitral valve leaflet.(125) The stents were steadily anchored within the aortic

annulus and a high traction force was required to produce a dislodgement.(125) However, these promising experimental results did not produce enthusiasm and no company was interested in the development of a transcatheter heart valve since the risk of potential complications, including early dislodgement of the device, stroke, and mechanical damage of cardiac structures, was deemed unsuitable for the application in vivo.(125) Eventually, in 1999, a start-up company, was able to design the first models of balloon-expandable transcatheter heart valve, which consisted of a stainless steel stent integrating a tri-leaflet polyurethane valve.(125) In 2000, animal experiments on the sheep model produced favourable results on the feasibility of transcatheter aortic valve replacement and results aroused encouraging enthusiasm from the medical community.(125) After years of ex vivo testing and animal implantation of transcatheter heart valves, the first in-human transcatheter aortic valve replacement was finally performed by Cribier and colleagues in 2002.(126)

Transcatheter aortic valve implantation has become an established therapy, irrespective of perioperative surgical risk, that is preferred over surgery by increasing number of patients with severe calcific aortic stenosis amenable to both surgical and transcatheter approaches.(51, 127-132) In recent trials, the hemodynamic performance and clinical outcomes of the newer generation of bioprostheses demonstrated similar or improved outcomes compared with surgical outcomes in patients of similar risk.(51, 127-130, 132) Improved outcomes with transcatheter aortic valve replacement have to be also adduced to significant reduction in access site complications, stroke, and paravalvular leak occurrence.(132)

Today, a number of different commercially available transcatheter aortic valves are available.(131) After withdrawal of the most commonly used mechanical valve due to complexities associated with the delivery system and very high rates of post-intervention pacemaker implantation, commercially available transcatheter aortic valves can be broadly grouped according to deployment technology as balloon-expandable (Sapien, Sapien XT, Sapien 3, Sapient Ultra; Edwards Lifesciences) and self-expandable (CoreValve, Evolut R, Evolut PRO, and Evolut Pro+; Medtronic; Portico and Navitor, Abbott Vascular; Acurate neo and Acurate neo2, Boston Scientific).(131)

Balloon-expandable valves

Balloon expandable transcatheter heart valves have undergone considerable evolution over time. The original Cribier-Edwards valve (Edwards Lifesciences) was made of a stainless-steel frame with equine pericardium valve leaflets. This design was adapted to the Sapien transcatheter heart valve (**Figure 5**), with the modification of a sealing cuff, three bovine pericardial tissue leaflets and a polyethylene terephthalate fabric skirt. The fabric skirt was sewn on the inner portion of the bottom of the stent frame to help seal the aortic annulus. The Sapien transcatheter heart valve was available in two sizes, 23 mm and 26 mm, and was delivered through a 22F, 24F or a 26F catheter sheath depending on valve size and access (transfemoral or transapical) (**Figure 5**). The safety and effectiveness of the Sapien valve were evaluated in a randomized, controlled pivotal PARTNER trial.(31, 133)

The Sapien XT (Edwards Lifesciences) was the second-generation of transcatheter balloon-expandable heart valves (**Figure 5**). The valve was characterized by a frame made of cobalt-chromium instead of stainless steel which allowed covering expanded annular sizes and using smaller sheath sizes, with consequent amplification of the possible access routes. Four sizes of Sapien XT transcatheter heart valve were available: 20 mm, 23 mm, 26 mm, and 29 mm. When delivered using transfemoral access, a sheath size of either 16F, 18F, or 20F catheter was used. When delivered using transaortic or transapical access, a 24F catheter sheath for the 23 mm or 26 mm valve was used and a 26F catheter sheath for the 29 mm valve was used.(134-136)

The Sapien 3, the third- generation of Edwards Lifesciences valve, is a low-profile prosthesis with implementations aimed at reducing vascular complications and paravalvular regurgitation, while enhancing ease of positioning. It incorporates a different stent geometry and leaflet design that allows for crimping to a further reduced profile. A polyethylene terephthalate fabric outer skirt was added in addition to the fabric inner skirt to further seal the aortic annulus and further reduce the amount of

para valvular leak (**Figure 5**).(137) In patients with bicuspid anatomy the rates of paravalvular leak may be higher but newer generation transcatheter valve have shown improved sealing in bicuspid anatomy compared with earlier generation devices.(138, 139) The available valve size are the same of Sapien XT valve (20 mm, 23 mm, 26 mm, and 29 mm) but available delivery catheter sheaths for transfemoral, transaortic and transsubclavian access range from 14F to 16 F and from 18F to 21F for transapical access. Clinical trial results from the PARTNER 2 and 3 trials demonstrated favourable outcomes associated with the Sapien 3 transcatheter heart valve in patients with intermediate and low surgical risk.(51, 127, 140)

The latest generation of balloon expandable prosthesis is the Sapien 3 Ultra (Edwards Lifesciences) that has the enhanced feature of a 40% higher external skirt with the objective of further reducing paravalvular leak (**Figure 5**). A 14F expandable seamless sheath accommodates the 20 mm, 23 mm and 26 mm Sapien 3 Ultra valves, a 16F eSheath is available for the 29 mm Sapien 3 valve.(141) Last valve implementations have shown to reduce rates of paravalvular regurgitation compared with the previous Sapien 3 valve, especially mild paravalvular leak (10.8 vs 36.5%; $p < 0.0001$).(142-144)

Self-expandable valves

The CoreValve system (Medtronic) was the first-generation self-expandable valve introduced in 2003. The CoreValve is a self-expandable supra-annular transcatheter aortic prosthesis, composed by three porcine leaflets and an inner porcine skirt sutured to a self-expanding nitinol frame. It was characterized by a basal portion with high radial force to contrast calcification of native valve, the central part with the valve and the upper expanded portion to fixate and stabilize the valve in the ascending aorta. It was available in three sizes (26 mm, 29 mm, and 31 mm) using an 18F catheter sheath (**Figure 7**).

The second-generation transcatheter valve, CoreValve Evolut R (Medtronic), improved the nitinol frame allowing reduction of delivery catheter dimension, expanded sealing skirt to reduce the amount of paravalvular leak and become recapturable once partially deployed allowing repositioning within the annulus. It is available in four sizes (23 mm, 26 mm, 29 mm, and 34 mm) using a 14F or a 16F catheter sheath. Both the CoreValve and CoreValve Evolut R were delivered using transfemoral, trans-aortic and trans-subclavian access (**Figure 7**).

The Evolut Pro (Medtronic), the contemporary iteration of the family, is a self-expanding supra-annular bioprosthesis with an improved external porcine pericardial wrap over the lower cells of the valve intended to decrease paravalvular regurgitation.(145) It is available in the same size of the previous model, using a 14F or 18F delivery system. This new generation of bioprosthesis has shown decreased rates of pace-maker implantation and a relative increase of with no or minimal paravalvular regurgitation.(145)

The Acurate neo (Boston Scientific) is a self-expandable supra-annular transcatheter aortic prosthesis composed of porcine pericardial leaflets mounted on a self-expanding nitinol stent and is implanted in a top-down two-step release mechanism.(146) This deployment mechanism minimizes periprocedural outflow obstruction and allows for stable positioning without rapid ventricular stimulation. Three stabilization arches and the protruding upper crown further enhance co-axial deployment and device stabilization. In addition, the upper crown may deter the native leaflets from the coronary ostia and reduce the risk of coronary obstruction.(147) Currently, there are three sizes of the valve (S - 23 mm, M - 25 mm, L - 27 mm) and the delivery system is compatible with an 18-Fr sheath. Due to low radial strength pre-dilatation is required prior to valve implantation with lower need for permanent pacemaker implantation but at the expense of an increased risk of paravalvular aortic regurgitation compared to the Sapien 3 and Evolut R / Pro. (146, 148) The Acurate neo2 valve was developed to overcome the high rates of paravalvular leak observed.(148, 149) All available sizes (23 mm, 25 mm, and 27 mm) can be deployed via a transfemoral 18F sheath delivery system.(149)

Early clinical results with the Acurate neo2 were favourable with low rates of new permanent pacemaker implantation, paravalvular leak, and patient-prosthesis mismatch.(148, 149)

The Portico valve (Abbott Vascular) is a self-expandable aortic prosthesis composed of bovine pericardial leaflets mounted on a self-expanding nitinol stent and it is designed to be re-sheathable, repositionable, and retrievable.(150, 151) The in-flow portion has a large-cell frame and is made of porcine pericardium and functions as a sealing zone, this design features are intended to provide a better sealing of paravalvular leaks.(150) It is available in four sizes (23 mm, 25 mm, 27 mm, and 29 mm) using a 14F or a 16F catheter sheath. The Navitor (Abbott Vascular) is the newer iteration of this intra-annular self-expandable valve.(152) Main characteristics, such as a nitinol frame and bovine pericardium leaflets, and available sizes (23 mm, 25 mm, 27 mm, and 29 mm by 14F catheter sheath) has remained unchanged compared with the previous version, but the skirt was significantly enhanced.(152) Early use of this novel transcatheter heart valve has shown improved deliverability due to a new catheter capable of three-dimensional flexibility.(152)

Surgical versus transcatheter aortic valve replacement

Transcatheter aortic valve replacement has gradually become the leading technique for aortic valve replacement in symptomatic patients with severe aortic stenosis and is currently approved for all surgical risk categories (i.e., high-, intermediate-, and low-risk).(153) In the United States, transcatheter aortic valve replacement procedures exceeded surgical aortic valve replacement procedures (72991 vs. 57626, respectively) in 2019.(154) In Germany, more than 15000 transcatheter aortic valve replacement procedures were performed in 2016, a number more than 3 times than in 2011.(155) In contrast, isolated surgical aortic valve replacement remained relatively stable with approximately 10000 per year.(155) Surgical aortic valve replacement is performed now much less frequently than transcatheter aortic valve replacement and patients undergoing surgery are generally younger than 75 years, without left ventricular dysfunction or significant extra-cardiac disease, with

indications to treatment of other heart valve dysfunction, or presenting with unsuitable anatomy for transcatheter aortic valve replacement.(84) Aortic valve replacement involves a multidisciplinary team of interventional cardiologists, cardiothoracic surgeons, radiologists, echocardiographers, nurses, and social workers, named Heart Team, to determine the optimal strategy for managing each patient. Individual patients are examined and referred to treatment following collegial assessment of major conditions favouring a transcatheter or a surgical approach (**Table 1**). An objective decrease of physiologic reserve and ability to maintain homeostasis leading to an increased individual risk of morbidity and mortality after invasive interventions, commonly named as frailty, has traditionally resulted to be among factors favouring a transcatheter approach.(156, 157)In low-risk patients, including most of those with severe bicuspid aortic valve stenosis, frailty is underrepresented.(51, 127)

The PARTNER and US CoreValve High Risk trials, respectively testing balloon-expandable and self-expanding bioprostheses again surgical aortic valve replacement, respectively, have shown that transcatheter aortic valve replacement is overall not associated with significant differences in terms of both effectiveness and safety compared with surgical aortic valve replacement in patients at high operative risk of mortality.(133, 158) In the PARTNER trial, all-cause death occurred in 3.4% of patients assigned to transcatheter aortic valve replacement and in 6.5% of patients assigned to surgical aortic valve replacement (p=0.07).(133) At 1 year, 24.2% of patients assigned to transcatheter aortic valve replacement and 26.8% of patients assigned to surgical aortic valve replacement died (p=0.44, $p_{noninferiority}$=0.001).(133) The favourable results associated with transcatheter aortic valve replacement were confirmed at 5-year follow-up, when no significant difference in mortality between transcatheter and surgical aortic valve replacement (67.8% vs. 62.4%; HR 1.04, 95% CI 0.86–1.24; p=0.76) was observed.(159) The major secondary endpoints of stroke and hospital readmission were not significantly different between treatment groups.(159) In the US CoreValve High Risk trial, all-cause death was significantly lower in the transcatheter aortic valve

replacement than in the surgical transcatheter aortic valve replacement group (14.2% versus 19.1%), with an absolute reduction of 4.9% ($p_{noninferiority} < 0.001$; $p_{superiority} = 0.04$).(158) At 5-year follow-up, mortality between groups was not significantly different between transcatheter and surgical aortic valve replacement (55.3% vs 55.4%; HR 0.93, 95% CI 0.77-1.14; p=0.50).(160)

The PARTNER 2 and SURTAVI trials addressed the comparison between transcatheter versus surgical aortic valve replacement in patients at intermediate risk of perioperative death, defined as an STS score 4% to 8%. In the PARTNER 2 (cohort A) randomized trial, transcatheter aortic valve replacement using a balloon expandable valve system was compared with conventional surgery in patients with severe aortic stenosis and intermediate surgical risk profile.(130) In this cohort of 2032 intermediate-risk patients the estimated incidence of the primary composite endpoint of death attributable to any cause or disabling stroke at 2 years was 19.3% in the group transcatheter aortic valve replacement group and 21.1% in the surgical aortic valve replacement group (HR 0.89; 95% CI 0.73-1.09; p=0.25). At 5 years, the incidence of any-cause death or disabling stroke was 47.9% in the transfemoral transcatheter aortic valve replacement group and 43.4% in the surgical aortic valve replacement group (HR 1.09, 95% CI 0.95–1.25; p=0.21).(129) In the SURTAVI trial, testing transcatheter aortic valve replacement with supra-annular self-expandable bioprosthesis versus surgical aortic valve replacement, in a cohort of 1746 patients with severe aortic stenosis at intermediate surgical risk, the event rates of the same end point of PARTNER 2 were 12.6% in the transcatheter aortic valve replacement group and 14.0% in the surgical aortic valve replacement group (95% credible interval for difference, −5.2 to 2.3%; posterior probability of noninferiority > 0.999) at 24 months.(128) Overall, these findings demonstrate that transcatheter aortic valve replacement is a noninferior alternative to surgical aortic valve replacement in patients with severe aortic stenosis at intermediate surgical risk.(128-130)

The objectives of the PARTNER 3 and the Evolut Low Risk trials were to evaluate the safety and effectiveness of transcatheter aortic valve replacement with a balloon-expandable or a self-

expanding bioprosthesis, respectively, as compared with surgical aortic-valve replacement in patients deemed to have a low risk of death with surgery.(51)

The PARTNER 3 trial enrolled 1000 low-risk patients (patient's mean age was 73 years, and the mean STS-PROM score was 1.9%), the estimated incidence of the primary end point (death attributable to any cause or debilitating stroke) at 1 years was 8.5% in the transcatheter aortic valve replacement group (using a self-expanding device) and 15.1% in the surgical group (−6.6 percentage points; 95% confidence interval, −10.8 to −2.5; $p < 0.001$ for non-inferiority; hazard ratio, 0.54; 95% CI, 0.37 to 0.79; p=0.001 for superiority). These findings were sustained at 2 years (transcatheter aortic valve replacement 11.5% vs. surgical 17.4%; hazard ratio:0.63 [95% confidence interval: 0.45 to 0.88]; p=0.007) in the 96.5% of patients available for follow-up.(161). Differences in death and stroke favouring transcatheter aortic valve replacement at 1 year were not statistically significant at 2 years (death: transcatheter aortic valve replacement 2.4% vs. surgical 3.2%; p=0.47; stroke: transcatheter aortic valve replacement 2.4% vs. surgical aortic valve replacement 3.6%; p=0.28), although patient-level analysis of each event demonstrated that 4 of the 7 deaths occurring between 1- and 2-year follow-up in the transcatheter aortic valve replacement arm were of non-cardiac origin while only 3 of 6 strokes in the transcatheter aortic valve replacement arm were disabling and confirmed on cerebral imaging. Valve thrombosis was more frequent in transcatheter aortic valve replacement patients (13 events, 2.6% vs. 3 events, 0.7%; p=0.02), 63% of which presented between 1 and 2 years and the majority (75%) were asymptomatic.

Similar results were obtained in the Evolut Low Risk trial using a self-expandable prosthesis in a cohort of 1403 patients with severe aortic stenosis at low surgical risk, the event rates of the composite death or disabling stroke was 5.3% in the transcatheter aortic valve replacement group and 6.7% in the surgery group (difference, −1.4 percentage points; 95% Bayesian credible interval for difference, −4.9 to 2.1; posterior probability of noninferiority > 0.999) at 24 months.(127)

Noninferiority of transcatheter aortic valve replacement (with a self-expanding prosthesis) versus surgical aortic valve replacement in low-surgical-risk patients with severe aortic stenosis was

confirmed at the 5-year follow-up in the European NOTION trial although more transcatheter aortic valve replacement patients had moderate/severe total aortic regurgitation (8.2% versus 0.0%, $p < 0.001$) and a new pacemaker (43.7% versus 8.7%, $p < 0.001$).(162)

Although the results of the PARTNER 3, Evolut Low Risk, and NOTION trial were favourable, patients with bicuspid aortic valves, low-flow aortic stenosis, severe coronary artery disease, concomitant valve disease, peripheral vascular disease precluding transfemoral access, or high-risk anatomy for either transcatheter or surgical aortic valve replacement were excluded, thus primary conclusions of these trials may be not extendable to these cohorts.(163)

BICUSPID AORTIC VALVE

Bicuspid aortic valve is a common congenital heart defect characterized by the presence of an aortic valve with two cusps instead of the usual three as a result of varying degrees of malformation from the complete absence of raphe and a third sinus to two mildly asymmetric cusps with partial raphe (**Figure 7**).(164-166) The bicuspid aortic valve was first described by Leonardo da Vinci over five-hundred years ago but its association with a higher propensity to develop disease was brought to attention by Paget in 1844 and Peacock in 1858.(167-169) Later, Osler described a predilection of bicuspid aortic valve for infective endocarditis in 1886, while clinical aortopathy recognized only in 1927 by Abbott.(168) Subsequently, between 1970 and 1990, anatomic-pathology studies corroborated a clear association between bicuspid aortic and aortic dissection.(170-172) In more contemporary times, with the advent of imaging, clinical studies indicate that aortic valve dysfunction and dilatation of the ascending aorta are the most common complications associated with bicuspid phenotype.(173, 174) Although absolute rates are very low, aortic dissection remains the most feared complication of bicuspid aortic valve and presents a significantly higher incidence compared with general population.(173, 174)

The congenital condition of bicuspid aortic valve needs to be more properly considered as a valvulo-aortopathy due to the significant relationship between abnormal valve anatomy and aortic disorders. significant heterogeneity in valvular and aortic phenotypic expressions, associated disorders and complications, need for treatment, and long-term prognosis.(174-176) Structural abnormalities related to bicuspid aortic valve are extremely heterogeneous leading to the development of a broad spectrum of clinical conditions, ranging from non-progressive lifelong silent conditions incidentally detected by imaging to complex valvulo-aorthopathy associated with significant dysfunction and concomitant disorders. Non- or mildly-progressive variants are generally detected in elderly subjects undergoing examination for other reasons or post-mortem, while complex valvulo-arthopathy with accelerated progression and early dysfunction are commonly diagnosed in the paediatric, adolescent, and young adult patient.(175, 177)

However, although bicuspid aortic valve is associated with normal valve function in the majority of young adults, it exposes these individuals to an increased risk of developing significant aortic valve dysfunction, primarily stenosis, later in life owing to superimposed degenerative valve remodelling.(176, 178, 179) Because bicuspid aortic valve is a disease of both the valve and the aorta, surgical decision making is more complicated, and many undergoing aortic valve replacement will also need aortic root surgery. With or without surgery, patients with bicuspid aortic valve require continued surveillance.

Epidemiology

Bicuspid aortic valve is affecting 0.5% to 2.0% of adults, with an yearly incidence of 13 cases per 1000 live births and a 2:1 to 3:1 male to female ratio.(180-183) This condition is associated with a higher incidence of cardiovascular complications to patients with tricuspid aortic valve patients as a result of the marked propensity to accelerated valve degeneration and thoracic aorta enlargement.(178, 179) Cardiovascular complications requiring intervention include aortic valve stenosis, aortic valve regurgitation, ascending aorta dilation, ascending aorta dissection, and infective endocarditis, with possible combined presentations.(166) Patient with bicuspid aortic valve stenosis require treatment at a younger age compared with those with tricuspid aortic valve stenosis.(179) Large registries of operatively excised stenotic aortic valves show that patients with bicuspid pattern generally require surgery 10 years earlier than patient with tricuspid aortic valve, with the highest rate in the sixth decade.(179, 182) However, approximately 30-40% of patients with bicuspid aortic valve stenosis undergo surgery later and in a more contemporary analysis octogenarians accounted for 22% of patients.(179, 184)

The most common complication of the bicuspid aortic valve in adults is valve dysfunction that necessitates surgical aortic valve replacement or repair, and it is strongly determined by the development of aortic stenosis. Degenerative bicuspid aortic valve dysfunction is also a common

cause of significant aortic regurgitation in developed countries, accounting for approximately two-thirds of cases.(7)

In recent times, survival rates in asymptomatic patients with bicuspid aortic stenosis are comparable to those in age-and sex-matched control patients, likely as a result of the significant of proportion of patients undergoing intervention.(176) Despite the higher risk of cardiovascular complications, two large studies have demonstrated that life expectancy in adults with bicuspid aortic valve disease is comparable to that of general population.(176, 178, 185) In asymptomatic adults with dysfunctional bicuspid aortic valve, the 10-year survival was 96.1%, and in asymptomatic adults with bicuspid aortic valve without significant valve dysfunction, the 20-year survival was 90.3%.(176, 178, 185)

Causes

Cardiac and valve morphogenesis occur early in embryogenic development. Initially, the extracellular matrix thickens and develops in the endocardial cushion that subsequently turn into the 4 cardiac valves. Embryological mechanisms leading to abnormal valve genesis with formation of a bicuspid aortic valve are not known.(186-188) Some theories involve cell migration, signalling pathways, and genetic susceptibility.(186-188) Abnormal neural crest migration resulting in fusion of valve cushions has been suggested as a possible explanation.(186-189) Aortic, cervico-cephalic, and intracranial aneurysms present neural crest origin and are consistently reported in the bicuspid aortic valve population.(190, 191) Additional mechanism that have been suggested include the key role in valve formation of extracellular matrix proteins and endothelial nitric oxide.(192)

In some studies, the heritability of bicuspid aortic valve has been resulted in high proportions which may suggests that many cases are familial.(180) linked to specific gene mutations, such as NOTCH1, GATA5, and more recently GATA4.(193, 194) Other reports on familial clustering of bicuspid aortic valve disease reported a prevalence of 24% in families with more than 1 person with

aortic disease, suggesting a Mendelian pattern of inheritance.(195, 196) However, heritability of aortic dilatation in first-degree relatives of probands with bicuspid aortic is less evident and more recent studies have demonstrated that bicuspid aortic valve disease is likely due to mutations in different genes with dissimilar patterns of inheritance.(180, 197)

The development of complications related to bicuspid aortic valve seems to be associated with turbulent ejection flow stress and chronic injury.(198-200) These disturbances lead to valve damage, scarring, thickening, calcification, and resultant valve dysfunction.(198-200) Turbulent flow into the ascending aorta combines with genetic variant-induced aortic medial abnormalities likely contribute to progressive dilatation and enhanced odds of aneurism, thrombosis, rupture or dissection.(198-200) Accelerated progressive calcification and restricted leaflet motility contribute to the development of severe aortic stenosis.(198-200)

Whereas some changes are likely consequence of turbulent, abnormal flow dynamics, aortic dilatation in bicuspid aortic valve seems to depend also on structural abnormalities at the cellular level, independent of the hemodynamic lesions.(201-204) In 1972, McKusick first reported on the association between bicuspid aortic valve and Erdheim cystic medical necrosis.(205) Later, several studies showed in thoracic aorta of subjects with bicuspid aortic stenosis decreased amounts of fibrillin, elastin fragmentation, increased matrix metalloproteinases, and increased apoptosis, resulting in smooth muscle cell detachment, matrix disruption, and cell death.(206-208)

Anatomy

Early pathology studies documented three characteristics of bicuspid aortic valve: inequality of cusp size, presence of a central raphe (ridge), usually in the middle of the larger of the two cusps, and smooth cusp margins.(209) Later, a growing number of studies on gross examination of valves excised during surgery and cardiovascular imaging have revealed that aortic valve phenotypes include all possible combinations and degrees of cusps fusion, with or without the presence of a fibrous raphe.(164-166) Less common patterns include two cups of equal size without raphe.(164-166)

Pathologic examination of the raphe has revealed the absence of valve tissues.(210) Calcification increases with age and predominantly confined to the raphe and the base of the cusps leading to asymmetric patterns.(81) Most bicuspid valve results from fusion of the right and left coronary cusps, resulting in a larger anterior and smaller posterior cusp with both coronary arteries arising from the anterior cusp.(211, 212) Fusion of the right and non-coronary cusps resulting in larger right than left cusp, with one coronary artery arising from each cusp is less common.(211, 212) Proper bicuspid aortic valve stenosis phenotype can be challenging in degenerative and heavily calcified valves.

Three critical anatomical aspects require careful assessment in patients with bicuspid aortic valve stenosis: 1) size and shape of cusps, characteristics of the raphe when observable, calcification distribution and extent, and degree of valve orifice asymmetry; 2) valve dysfunction type and dysfunction grading, if function is abnormal; 3) presence and phenotype of aortic dilatation and presence of aortic coarctation.(166)

Several classifications elaborated and refined these anatomic variants in recent decades.(164, 165, 213) Among these the classification provided by Sievers and Schmidt have found large use.(164) This classification was obtained from operative reports of 304 patients with a diseased bicuspid aortic valve and is based on three characteristics (**Figure 8**): 1) number of raphes, 2) spatial position of cusps or raphes, and 3) functional status of the valve.(164) The number of raphes is the major characteristic and termed as "type".(164) Three types are possible: type 0, no raphe; type 1, one raphe; and, type 2, two raphes.(164) In type 0, the valve is purely bicuspid; in type 2, the valve is functionally unicuspid.(164) The secondary characteristic related to spatial relationships serves to subclassify types: in type 0, the free edge of cusps can be defined as antero-posterior or lateral; in type 1, the position of raphe can be considered as expression left and right cusps fusion, right and non-coronary cusps, and non-coronary and left cusps; in type 2, the valve is functionally unicuspid due to the presence of two raphes usually placed between left and right cusps and between right and non-coronary cusps, though raphe between right and non-coronary cusps and non-coronary and left cusps, and between non-coronary and left cusps and left and right cusps may be possible.(164, 214) The

other secondary characteristic provides information on functional status: predominant insufficiency, predominant stenosis, balanced insufficiency and stenosis, or no insufficiency and stenosis.(164)

A novel transcatheter aortic valve replacement-oriented and simplified non-numerical classifications based on the number of commissures and the presence of a raphe has been proposed (**Figure 8**).(213) Have been identified 3 types of bicuspid aortic valve morphologies: tricommissural, corresponding to three cusps with an incomplete raphe or an acquired fusion of two cusps near the commissure; bicomissural raphe type, corresponding to a fusion of two cusps by a complete raphe, and bicommissural non-raphe type, with a fusion of 2 cusps but with neither a raphe nor a third commissure. This classification takes into account the interaction between the transcatheter heart valve frame and the atrioventricular complex which may have important implications with regards to the transcatheter aortic valve expansion and orientation, as well as the postprocedural outcomes.(215)

Recently, an international consensus statement of experts has proposed a novel classification system for bicuspid aortic valve disease and associated aorthopathy with the aim of overcoming some limitation of previous classifications, mainly the counterintuitive language, the lack of evaluation of the symmetry of the bicuspid aortic valve, and the absence of integrated recognition of aortopathy phenotypes.(166) According to this classification there are three major types of bicuspid aortic valve with specific phenotype (**Figure 9**): 1) fused-valve; 2) two-sinus valve; and partial-fusion valve (forme fruste).(166) The fused-valve phenotype is the most common (90-95%) and includes valves characterized by the fusion of two of the three cusps resulting in two functional cusps of unequal size and shape, and commonly a raphe, though it may not be clearly visible; the fused-valve phenotypes is associated with three distinguishable aortic sinuses.(166, 174) Non-fused cusp commissural angles present varying degrees.(166) Symmetry of fused-valve type is defined by the angle between the commissures of the non-fused cusp and represents a critical aspect in the planning and performance of bicuspid aortic valve repair for pure aortic regurgitation.(216) The possible patterns are the following: right-left cusps fusion (70-80%), right-non-coronary cusps fusion (20-30%), left-non-coronary cusps fusion (3-6%), and indeterminate phenotypes.(166, 174) The two-sinus phenotype (5-

7%) includes valves with two cusps of equal size and shape, each one occupying 180° of the annular circumference, two 180°-angle commissures, and two aortic sinuses.(166) The orientation is frequently latero-lateral and less commonly anteroposterior.(166) Partial-fusion bicuspid aortic valve is associated to the presence of a small, incomplete raphe resulting in a partial, less than 50% cusps fusion at the base of a commissure.(166) The remaining structures are comparable to those of typical tricuspid aortic valve with three symmetrical cusps with a systolic triangular opening and commissural angles of 120°.(166)

Clinical patterns

Clinical presentation of bicuspid aortic valve disease is extremely heterogeneous ranging from an incidental echocardiography diagnosis in otherwise healthy subjects to severe or life-threatening conditions such as acute pulmonary oedema due to left ventricular dysfunction and aortic dissection complicating a thoracic aortic aneurysm.(176, 178)

Bicuspid aortic valve subjects to turbulent ejection-flow stresses and vibration that lead to valve damage, scarring, thickening, calcification, and resultant aortic stenosis and regurgitation.(199) Turbulent flow into the ascending aorta combines with genetic variant-induced aortic medial abnormalities contributes to progressive dilatation and enhanced odds of aneurism, thrombosis, rupture or dissection.(217)

The most common complication of the bicuspid aortic valve condition in adults is valve dysfunction necessitating aortic valve replacement, and it is driven by development of aortic stenosis. It is estimated that the risk of aortic valve replacement 25-years following bicuspid aortic valve diagnosis is 53%.(174) Patients with early degeneration have a 70% risk of aortic valve replacement at 12 years versus 8% in those without degeneration.(178). Bicuspid aortic valve regurgitation is significantly less common than bicuspid aortic valve stenosis (30% vs 70%) and the most important mechanisms are cusp prolapse, annular dilatation and root / sinotubular junction dilatation.(174, 216,

218) Echocardiography plays a critical role in determining repairability of the regurgitant bicuspid aortic valve, which is attained more frequently in bicuspid aortic valve than tricuspid aortic valves and has a cumulative reoperation incidence of 20% at 15 years when combined with root remodelling.(219) Left ventricular remodelling in response to bicuspid aortic valve is associated with pressure and volume overload, leading to hypertrophy, and accentuated subendocardial ischemia leading to myocardial hypoperfusion, angina and even risk of sudden cardiac death during exercise. Even asymptomatic bicuspid aortic valve patients with preserved ejection fraction may have significantly impaired left ventricular diastolic function.(220, 221)

Aortic dilatations occur commonly with bicuspid aortic valve, even in absence of aortic stenosis or regurgitation, associated with cystic medial degeneration. In patients with bicuspid aortic valve the ascending aorta has been reported to gradually dilate on average by 0.9 mm/year, and the risk of dissection is several times higher than the general population.(222) The root phenotype has been associated with faster tubular-ascending-aorta dilatation and aortic regurgitation is in turn related to faster root dilatation.(223, 224) Exclusion of concomitant aortic coarctation is critical in bicuspid aortic valve patients as it affects up to 10–15% of them.(225)

It is recommended to periodically examine the entire thoracic aorta of bicuspid aortic valve patients, since aortic dissections can involve both the ascending and the descending trunks. For interval monitoring, a critical premise is that it applies equally to native bicuspid aortic valve patients or post-AVR if the aorta has not been replaced, because the aorta may begin or continue to dilate after AVR.(226)

The incidence of bicuspid aortic valve endocarditis has been reported in 2% of most bicuspid aortic valve contemporary cohorts(174) which represents 16 times that of the general population, and it is more common than aortic dissection in bicuspid aortic valve patients.(227)

Diagnosis

Bicuspid aortic valve patients are at increased risk of valve dysfunction and ascending aorta aneurysm. Imaging techniques are essential to establish diagnosis, identify complications and indicate surgical treatment.(228)

Echocardiography is the first-line imaging modality in the diagnosis of bicuspid aortic valve to assess valve function and aortic dilatation,(81, 84, 101, 166) although cardiac magnetic resonance and computed tomography, using multiplanar reconstructions, are better at assessing aortic diameters. However, transthoracic echocardiography is affected by lower sensitivity than other imaging methodologies and, in some studies, it resulted to be unable to properly define bicuspid aortic valve in high proportion of elderly patients referred for transcatheter aortic valve replacement. When valvular phenotyping and functional assessment by transthoracic echocardiography is uncertain or inconclusive or image quality is suboptimal, transoesophageal echocardiography and 3-dimensional echocardiography implementation can be helpful. Echocardiographic criteria of bicuspid aortic valve include elliptical or slit-like orifice during ventricular systole in parasternal short-axis view, cusps doming during ventricular systole with pronounced bending strain in the parasternal long-axis view, asymmetrical closure line in the parasternal long-axis view, high stress in the raphe area, and uneven systolic flow patterns.(81, 84, 101, 166) In children, adolescents and young adults, a bicuspid valve may be stenotic without extensive calcification, but, in most adults, stenosis of a bicuspid aortic valve typically results from superimposed calcific changes often obscuring the number of cusps.(81, 101) Calcification of a bicuspid aortic valve is often more asymmetric than tricuspid aortic valve and frequently involving the raphe area.(179, 182) In these cases, indirect signs of bicuspid aortic valve may be provided from the analysis of aortic root and ascending aorta geometry and dilatation.(81, 84, 101, 166)

Adequate echocardiographic images are highly accurate for the diagnosis and classification of the bicuspid aortic valve morphotype in 80–90% of cases, with estimated sensitivity, specificity and accuracy of 78%, 96%, and 93%.(173) When valvular phenotyping and functional assessment by transthoracic echocardiography is uncertain or inconclusive or image quality is suboptimal,

transoesophageal echocardiography and 3-dimensional echocardiography implementation can be helpful; however, it is a semi-invasive procedure and limited to assess the upper part of the ascending aorta and proximal arch.

Cardiac magnetic resonance and cardiac tomography overcome the limitations of transthoracic echocardiography in the diagnosis and evaluation of the aortic valve morphology (i.e., heavily calcified valves), and can readily assess the planimetry of the valve area and the aortic diameters.(173) Furthermore, computed tomography is able to quantify the degree of valve calcification, which is very useful for determining the severity of the valve stenosis in doubtful cases and with prognostic implications in terms of survival.(90) Cardiac magnetic resonance provides functional information on the severity of aortic valve disease and the left ventricular function.(90)

Echocardiographic quantification of aortic valve stenosis and regurgitation are based on similar hemodynamic parameters to tricuspid valves. However, owing to the eccentricity of the ascending aorta jet, interrogation via the right parasternal window may yield the highest gradients.(225) Careful assessment of valve morphology allows identification of the mechanisms of regurgitant bicuspid aortic valve: cusp prolapse, annular dilatation and root / sinotubular junction dilatation. Eccentric jets are very common, making severity more difficult to assess. When eccentric jets are difficult to be quantified and left ventricle dilation is disproportionate to the degree of aortic valve regurgitation, cardiac magnetic resonance may provide a superior method to quantify aortic regurgitation and left ventricle volumes.(173)

Aorta dilation is a common finding in patients with bicuspid aortic valve. The gold standard for measuring the thoracic aorta is electrocardiography-gated computed tomography or magnetic resonance angiography because these imaging modalities guarantee measurement of the true largest diameters and truly perpendicular to aortic blood flow. Nonetheless, transthoracic echocardiography continues to be the initial modality of assessment. The echocardiographic aorta measurement method should be from leading edge-to-leading edge at end-diastole which correlates best with computed

tomography and magnetic resonance angiography diastolic inner wall-to-inner wall measurement.(226)

Current evidence on treatment

Current European and North American guidelines favour surgical approaches for the treatment of isolated bicuspid aortic valve stenosis.(84, 85) Surgical aortic valve replacement remains particularly appropriate in patients with bicuspid aortic valve stenosis with associated disease (e.g. aortic root dilatation, complex coronary disease, or severe mitral regurgitation) requiring treatment. However, although still not clearly endorsed for the absence of a dedicated randomized clinical trial, in real-world practice treatment of bicuspid aortic valve stenosis by transcatheter aortic valve replacement is considered to be an acceptable alternative to surgery when the intervention is technically feasible, age is advanced, surgical risk is intermediate-to-high due to significant comorbidity or unfavourable settings, correction of other anatomic and functional cardiac and aortic conditions is not required, and the patient is inclined to a less invasive treatment modality.(84, 85)

Most of the uncertainty related to the feasibility of transcatheter aortic valve replacement for bicuspid aortic valve stenosis depends on the paucity of available data and the systematic exclusion of this setting from randomized clinical trials because of several anatomic features that could increase the risk procedural complications or long-term failure.(215) Indeed, early pivotal trials aimed at demonstrating the favourable performance and safety of transcatheter aortic valve replacement as compared with traditional surgical approaches in high surgical risk, while more recent trials were designed to substantially expand transcatheter aortic valve replacement indications to the intermediate and low surgical risk population by proving the comparability of long-term outcomes between surgical and transcatheter aortic valve replacement.(51, 127-129, 159, 160) The inclusion of bicuspid aortic valve among eligibility criteria was deemed to be dangerous for the achievement of these main objectives. Finally, concerns related to the bicuspid aortic valve setting were not

compelling in the past due to lower proportions of potential candidates to transcatheter aortic valve replacement in relation to the guideline-approved surgical risk. In contrast, the recent expansion of the indication to the low-risk and substantial, steady growing of the number of transcatheter aortic valve replacement procedures have drawn the attention on the increasingly common setting of bicuspid aortic valve stenosis.(51, 127-129)

Bicuspid vs. tricuspid aortic valve

The first question on transcatheter aortic valve replacement for bicuspid aortic valve stenosis relates the comparative efficacy and safety with the setting of tricuspid aortic valve. Although available evidence on this aspect of the matter still warrants further analyses based on more contemporary transcatheter heart valves and prolonged follow-up, recently a growing amount of data on transcatheter aortic valve replacement for bicuspid aortic valve stenosis focused on the differential performance with transcatheter aortic valve replacement for tricuspid aortic valve stenosis.(138)

In a retrospective study, 546 propensity score matched pairs of patients with bicuspid and tricuspid were analysed.(138) Although bicuspid aortic valve group experienced more frequent conversion to surgery (2.0% vs. 0.2%, p=0.006) and less frequent device success (85.3% vs. 91.4%, p=0.002)(138) patients treated with early-generation balloon-expandable valve had more frequent aortic root injury (4.5% vs. 0%, p=0.015), while those treated with early-generation self-expandable valve had more frequent moderate-to-severe paravalvular leak (19.4% vs. 10.5%, p=0.02).(138). In patients treated with new-generation bioprostheses, there was no significant difference between bicuspid and tricuspid aortic valve groups.(138) The cumulative incidence of all-cause death at 2 years was not significantly different (17.2% vs. 19.4%, p=0.28).(138)

More recently, 2691 propensity score matched pairs of patients with bicuspid and tricuspid aortic valve stenosis included in the Society of Thoracic Surgeons / Transcatheter Valve Therapies registry were analysed.(229) The mean result of the study was the observation of comparable rates of

mortality at 30 days (2.6% vs 2.5%, HR 1.04, 95% CI 0.74-1.47) and 1 year (10.5% vs 12.0%; HR 0.90, 95% CI 0.73-1.10) between bicuspid and tricuspid groups. Although 30-day stroke rate was significantly higher for bicuspid vs tricuspid aortic stenosis (2.5% vs 1.6%; HR 1.57, 95% CI 1.06-2.33) and bicuspid aortic valve group experienced more frequent conversion to surgery (0.9% vs 0.4%, respectively; absolute risk difference, 0.5%, 95% CI 0%-0.9%). There were no significant differences in valve hemodynamic, in moderate or severe paravalvular leak at 30 days (2.0% vs 2.4%; absolute risk difference, 0.3%, 95% CI -1.3% to 0.7%]) and 1 year (3.2% vs 2.5%; absolute RD, 0.7%, 95% CI -1.3% to 2.7%).

Forrest and colleagues recently reported clinical and hemodynamic data from the nation-wide Society of Thoracic Surgeons / Transcatheter Valve Therapies registry including of 932 patients with bicuspid aortic valve stenosis undergoing transcatheter aortic valve replacement with the self-expanding Evolut R valve or Evolut PRO valve that were compared with a group of 26,154 patients with tricuspid aortic stenosis who underwent transcatheter aortic valve replacement during that same time period account for intrinsic differences among the two groups was applied a propensity score model.(230) Within the 929 matched pairs, all-cause mortality, stroke, and valve hemodynamic did not differ at 30 days or 1 year between patient groups. Rates of all-cause mortality at 30 days (2.6% vs. 1.7%; p = 0.18) and 1 year (10.4% vs. 12.1%; p =0.63), rate of stroke at 30 days (3.4% vs. 2.7%; p =0.41) and 1 year (3.9% vs. 4.4%; p = 0.93).

Surgical versus transcatheter aortic valve replacement

The second question on transcatheter aortic valve replacement for bicuspid aortic valve stenosis relates the comparison with surgical aortic valve replacement. Uncertainty related to the comparability of transcatheter aortic valve replacement with surgery for bicuspid aortic valve stenosis is high due to the absence of dedicated randomized clinical trials. By considering the younger age at presentation, the low proportions of patients with severe bicuspid aortic valve stenosis with high

surgical risk deemed preferentially suitable for transcatheter aortic valve replacement have not prioritized the inspection of differential effectiveness and safety with surgery.(133, 231) The favourable results of transcatheter aortic valve replacement observed in clinical trials, the expansion of indications to the broader population of patients with intermediate surgical risk, and the exponential growth of the number of procedures worldwide with inclusion of off-label settings have drawn the attention to the problem.(51, 127-130) Finally, the approval of transcatheter aortic valve replacement for low surgical risk patients, which includes substantial proportions of patients with isolated bicuspid aortic valve stenosis, has made more evident the absence of randomized trials and high-quality studies with adequate follow-up and promoted the debate on the treatment of bicuspid aortic valve stenosis by transcatheter approach.

A large-scale randomized clinical trial investigating transcatheter aortic valve replacement for the treatment of bicuspid aortic valve stenosis should face the following argumentations. First, surgery for bicuspid aortic valve stenosis is an established treatment associated with low in-hospital mortality and good very long-term outcomes.(232, 233) Second, studies on surgical strategies have mainly reported outcomes in young patients at very low operative risk and included heterogeneous patterns of bicuspid aortic valve dysfunction treated with biological or mechanical valves, with or without concomitant aortic intervention. In contrast there is paucity of studies on isolated surgical aortic valve replacement in patients with higher surgical risk. Indirect or historical comparative analyses with transcatheter aortic valve replacement have limited value and the few contemporary observational studies on the topic are affected by significant limitations that preclude significant conclusions. Finally, questions on transcatheter aortic valves durability have become central following extension of transcatheter aortic valve replacement to patients with low surgical risk since this subset has longer life expectancy those of patients with intermediate or high surgical risk.(234) Durability of transcatheter aortic valves in challenging anatomic patterns of bicuspid aortic valves may be reduced and the open debate related to long-term durability of transcatheter aortic valve

replacement currently limits a systematic use of this type of approach for bicuspid aortic valve stenosis while, in contrast, surgical aortic valve replacement is supported by long-term data.(234)

Self- vs. balloon-expandable bioprosthesis

The third question on transcatheter aortic valve replacement for bicuspid aortic valve stenosis related the comparison between main transcatheter aortic valve technologies, self- or balloon-expandable. Currently, there is a paucity of information on the comparative performance and safety of self- and balloon expandable valves for bicuspid aortic valve stenosis. Mangieri and collaborators recently evaluated 353 patients with bicuspid aortic valve who underwent transcatheter aortic valve replacement with the Sapien 3 (n=242) and Evolut R / Pro (n=111) valve systems.(235) The two valves type groups were compared overall and after a propensity matching analysis (77 patients in each group). Device success was similar between Sapien 3 and Evolut R / Pro also after propensity score matching (85.7% versus 84.4%; p=0.821) although patients treated with balloon-expandable valve had a higher rate of annular rupture.(235) On the other hand, the Evolut R / Pro group showed a higher rate of moderate-severe paravalvular aortic regurgitation at 1-year follow-up in the matched cohort. At 1-year follow-up, the rate of overall death and cardiovascular death were similar between the 2 groups.(235)

STUDY -Transcatheter Aortic Valve Replacement with Self- vs. Balloon-Expandable Bioprosthesis for Bicuspid Aortic Valve Stenosis

The study presented is the object of this thesis. The study needs to be considered ongoing since data extraction is still ongoing at five high-volume centres for a total of about 300 patients. The results here presented are therefore preliminary to completion of the study.

Introduction

The excellent results associated with transcatheter aortic valve replacement observed in the PARTNER 3 and Evolut Low Risk trials have produced a shift toward the treatment of patients with low surgical risk and an increasing involvement of patients with severe bicuspid aortic valve stenosis.(127, 236) In recent years, proportions of potential candidates for transcatheter aortic valve replacement with bicuspid phenotypes have dramatically increase up to approximately 9.0% at some high-volume centres.(237)

In the United States, data from the Society of Thoracic Surgeons / Transcatheter Valve Therapy registry before approval of transcatheter aortic valve replacement for low surgical risk patients, have defined that nonemergent interventions for severe aortic stenosis of native valves with defined morphology occurred in almost 3.5% of patients.(229, 230) The analysis of early and long-term outcomes in high- or intermediate-risk patients have shown similar survival between patients with bicuspid and tricuspid aortic valves, though some concerns remained due to an excess of early stroke events with balloon-expandable bioprostheses and increased postprocedural rates of significant aortic regurgitation and higher postprocedural transvalvular mean gradient with self-expandable bioprostheses.(229, 230) More recently, single-arm feasibility studies evaluating transcatheter aortic valve replacement in low-risk patients with bicuspid aortic valve stenosis have shown a favourable safety profile.(238, 239) A recent meta-analysis of thirteen studies explored outcomes after transcatheter aortic valve replacement according to bicuspid or tricuspid aortic valve

morphology.(240) The study concluded that 30-day and 1-year mortality, stroke, and new pacemaker implantation are not significantly different between treatment strategies, though bicuspid aortic valve was associated with higher risk of moderate-to-severe paravalvular leak and conversion to surgery, mostly with earlier iterations of transcatheter heart valves.(240)

Large-scale observational analyses and randomized clinical trials comparing efficacy and safety between self- and balloon-expandable transcatheter heart valves in bicuspid aortic stenosis are lacking. Thus far, only a small propensity score matching-based study including a matched cohort of 154 patients have tried to face unaddressed questions related to the differential performance of the two major technologies of transcatheter heart valves.(235) This study concluded that self-expandable bioprostheses were associated with higher occurrence of postprocedural moderate-to-severe aortic regurgitation but lower transvalvular mean gradient.(235) However, at 1-year follow-up survival and stroke were not statistically significant between treatment groups.(235)

Against this background of high uncertainty, we sought to conduct a multicentre, international, collaborative studies to define early, mid-term and long-term outcomes following transcatheter aortic valve replacement with self- versus balloon-expandable transcatheter aortic valves for the treatment of bicuspid aortic stenosis. It was prespecified the performance of sensitivity analyses to explore the impact of valve generation, differences between self-expandable bioprostheses, and variations over time.

Methods

The study was approved by the institutional ethics committee and all patients provided written informed consent to the intervention.

Design

This is a collaborative, international, retrospective study including consecutive patients with computed tomography-defined bicuspid aortic valve stenosis who underwent transcatheter aortic

valve replacement with self- or balloon-expandable bioprosthesis performed by experiences operators at 23 high-volume centres in Europe, United States, and Canada with established structural heart valves interventions program and systematic follow-up.

Bicuspid aortic valve

Bicuspid aortic valve phenotype was classified according to Sievers and Schmidtke classification primarily considering the number of raphes: type 0 identifies purely bicuspid aortic valve characterized by two cusps of equal size and shape, without evidence of a raphe and with two 180°-angle commissures; type 1 identifies bicuspid aortic valves with two cusps of unequal size and the presence of one raphe within the fused, underdeveloped cusp; and type 2 identifies bicuspid aortic valves with two cusps of unequal size and the presence of two raphes causing significant asymmetric in valve orifice.(164) The secondary characteristic related to spatial relationships serves to subclassify types: in type 0, the free edge of cusps can be defined as antero-posterior (0.1) or latero-lateral (0.2); in type 1, the position of raphe can be considered as expression left and right cusps fusion (1.1), right and non-coronary cusps (1.2), and non-coronary and left cusps (1.3); in type 2, the valve is functionally unicuspid due to the presence of two raphes usually placed between left and right cusps and between right and non-coronary cusps, though raphe between right and non-coronary cusps and non-coronary and left cusps, and between non-coronary and left cusps and left and right cusps may be possible.(164, 214) The diagnosis of bicuspid aortic valve was based on preoperative multi-slice computed tomography scan analysis , defined by multidisciplinary evaluation of local heart team before transcatheter aortic valve replacement, and confirmed by retrospective review during data extraction. Patients originally defined to have bicuspid aortic valve that eventually resulted to have tricuspid or morphologically-uncertain aortic valve were discarded.

Data extraction

Anonymized main baseline clinical and procedural characteristics, information on bicuspid aortic valve and possible related aortopathy, and major in-hospital, early, and long-term cardiovascular outcomes were extracted at each centre. Data were pooled at the coordinating centre and statistical analysis was performed.

Transcatheter heart valves

Commercially-available self- and balloon-expandable transcatheter aortic valves were allowed. Valves deployed by mechanically-expandable or other mechanism were excluded from this study.

Although the use of new-generation bioprostheses in both treatment groups was predominant, as discussed more in details in the following sections, sensitivity analyses with exclusion of early-generation iterations and self-expandable valves that have resulted to be less performant in recent randomized clinical trials of patients with tricuspid aortic valve stenosis were prespecified.(146, 148, 241)

The balloon-expandable group included only bovine pericardial trileaflet valves within a cobal-chromium frame deployed by balloon inflation during transient high-rate pacing (Sapien, Sapien XT, Sapien 3, Sapien 3 Ultra). Differences in polyethylene terephthalate fabric seal differentiated valve iterations, with newer valves presenting enhanced inner and outer covers and textured materials. Balloon-expandable valves were deployed by different delivery systems and sheats, mainly 3-dimensional coaxial positioning catheter. Self-expandable valves included main repositionable nitinol-frame self-expandable bioprostheses (CoreValve, Evolut R, Evolut Pro, Acurate neo, Portico).

Definitions

Bicuspid aortic valve needed to be defined by multidetector computed tomography that was routinely performed before each intervention at each participating centre. Cases with doubt bicuspid morphology at computed tomography recordings review were excluded. Bicuspid aortic valve morphology was classified according to Sievers and Schmidt.(164) In this classification, the number of raphes defines three major variants: type 0, no raphe; type 1, one raphe; and, type 2, two raphes.(164) In type 0, the valve is purely bicuspid; in type 2, the valve is functionally unicuspid.(164)

Diabetes and hypertension were defined according to current definitions. Chronic kidney disease was defined as estimated glomerular filtration rate < 60 mL/min/1.73 m^2 or serum creatinine > 1.5 mg/mL. Peripheral artery disease was defined as any known stenosis > 50% in lower limb artery segments. Functional class status at presentation was graded according to the New York Heart Association scale. Aortic, mitral, and tricuspid valve regurgitation was graded by transthoracic or transoesophageal echocardiography. Early generation transcatheter heart valves included: Sapien XT, CoreValve, Acurate neo, and Portico. New-generation transcatheter aortic valves included: Sapien 3 and Sapien Ultra.

Endpoints

Death was classified as cardiac or non-cardiac according to the cause; generally, when a clear non-cardiac cause could not be established, the event was considered as cardiac. Myocardial infarction was defined peri-procedural (≤ 72 h) or spontaneous (> 72h) based on the onset time of new ischemic symptoms or electrocardiographic changes and elevated biomarkers (consisting of at least one sample post-procedure with a peak value exceeding 15× as the upper reference limit for troponin or 5× for CK-MB) as defined elsewhere.(242)

Stroke was defined as an acute episode of a focal or global neurological deficit ≥ 24 h or < 24 h if available neuroimaging documents a new haemorrhage or infarct or the neurological deficit results in death. It was labelled as haemorrhage or ischaemic or ‘un- determined’ if there is

insufficient information to allow the categorization as ischaemic or haemorrhagic.; and disabling or non-disabling according to modified Rankin Scale (mRS).(242)

Bleeding was defined according to Bleeding Academic Research Consortium criteria as life-threatening (fatal bleeding or bleeding in critical organ or causing hypovolemic shock or severe hypotension with drop of haemoglobin = or > 5g/dl or requiring transfusion of >4units of whole blood), major bleeding (causing drop of haemoglobin at least 3 g/dL and requiring transfusion of 2-3 units of whole blood) and minor bleeding (any bleeding worthy of clinical mention that does not qualify as life-threatening, disabling, or major).(243)

Acute kidney injury was defined until 7 days after intervention according to Acute Kidney Injury Network system in 3 stage according to increased serum creatinine compared to baseline (to 150–199% or ≥ 0.3 mg/dL for stage 1, to 200-299% for stage 2, ≥ 300% or ≥ 4.0 mg/dL for stage 3) or the urine output (< 0.5 ml/kg/h for > 6 but < 12 h, < 0.5 mL/kg/h for >12 but < 24 h, < 0.3 mL/kg/h for ≥ 24 h or anuria for ≥ 12 h respectively for stage 1, 2 and 3).(244)

Vascular complications were recorded as either access or non-access site-related and defined according to Valve Academic Research Consortium-2 criteria in major vascular complications (aortic dissection, aortic rupture, annulus rupture, or access site or access-related vascular injury leading to death, life-threatening or major bleeding, visceral ischaemia, or neurological impairment, or distal embolization requiring surgery or unplanned endovascular or unplanned surgical intervention associated with death, major bleeding, visceral ischaemia or neurological impairment) and minor vascular complications (access site or access-related vascular injury not leading to death, life-threatening or major bleeding, visceral ischaemia, or neurological impairment; distal embolization treated with thrombectomy or any unplanned endovascular stenting or unplanned surgical intervention not meeting the criteria for a major vascular complication or percutaneous closure device failure).(242)

Secondary end-points were need for a new pacemaker, coronary obstruction, aortic valve reintervention both surgical and percutaneous, aortic valve endocarditis, valve disfunction and valve

thrombosis. Valve thrombosis was defined according to Valve Academic Research Consortium 2 criteria: thrombus associated with an implanted valve that interferes with valve function or warrants treatment (anticoagulation or explantation).(242) Echocardiography or 3-dimensional computed tomography imaging needed to be performed to diagnose valve-related thrombus and restricted leaflet motion however no prospective follow u was pre-specified and detection of events was expected to be incidental or clinically driven. Valve disfunction was defined according to multiparametric echocardiographic approach following current guidelines.(245)

Statistical analysis

Categorical variables were summarized as counts and proportions. Continuous variables were summarized as mean and standard deviation or median and interquartile range according to the distribution as assessed by Shapiro-Wilk test. However, in the presence of non-normal, mean and standard deviations were also supplemented for comparative purposes with previous literature. Baseline characteristics distribution between treatment groups was primarily assessed by standardized mean difference and Kolmogorov-Smirnov statistics as recommended in observational studies based on propensity score weighting and matching methods. These analyses were complemented by variate ratios and empirical cumulative density functions. Formal comparison of categorical and continuous variables by Pearson's Chi square or Fisher exact test and Student t or Wilcoxon-Mann-Whitney U test, as appropriate, was provided as supplementary material.

Small proportions of missing values that could further reduce effective sample size after propensity score weighting and matching were handled by using chained equation multiple imputation techniques with generation of 10 datasets under the assumption of missingness at random. Subsequently, the propensity score was estimated within each dataset by using nonparsimonious multivariable logistic regression models including the bioprosthesis technology (self- vs. balloon-expandable) as dependent variable and baseline pre-exposure characteristics that were deemed to be potential cause of selection bias and significant confounders associated with outcomes as independent

variables. Propensity score estimation analyses were performed with respect to the average treatment effect on the treated.

Propensity score was used to weight each patient by the inverse probability of treatment weighting and produce an adjusted cohort. Early and long-term outcomes were estimated by mixed-effects generalized linear models and mixed-effects Cox proportional hazards regression models with random intercept and random slope to account for heterogeneity and effect variations across participating centres. These models included also intra-procedural characteristics that could have influenced the outcomes and valve-generation as covariates.

Greedy nearest neighbour matching without replacement was used as complementary analysis to match 1:1 the patients who received balloon-expandable valve with those who received self-expandable valve according to a conservative caliper of 0.1 standard deviations of logit of propensity score. Early and long-term outcomes were estimated as described for inverse probability of treatment weighting.

Proportional hazard assumption was assessed by using the Schoenfeld residual plot and Grambsh-Therneau test. In case of significant violation of proportional hazard assumption time-varying coefficient was used for the treatment indicator variable.

Results

A total of 1176 patients were identified at 23 centres by retrospective review of institutional archives since structural heart valve program inception (**Figure 10**). Of these, 71 patients were excluded due to implantation of a bioprosthesis with deployment mechanism other than self- or balloon-expandable, 11 patients had not clear bicuspid morphology at computed tomography recordings review, and 12 patients had not retrievable medical history, procedural information, and follow-up. The remaining 1082 patients, of whom 651 underwent transcatheter aortic valve

replacement with balloon-expandable bioprosthesis and 431 with self-expandable bioprosthesis, were included in the study.

Baseline characteristics are reported in **Table 2** and **Table 3**. The median Society of Thoracic Surgeons score for 30-day mortality was overall low (3.4 [2.1-5.2]), without significant difference between balloon- and self-expandable groups. The cohort comprised of patients with median age of 79 years, more frequently men (59.5%), with high proportions of hypertension (80.4%) and chronic kidney disease (43.7%). Most of patients showed bicuspid aortic valve morphology pattern type 1 (86.1%), followed by smaller proportions of valves type 0 (12.5%) and type 2 (1.4%), without significant imbalance between groups. Approximately half of patients underwent transcatheter aortic valve replacement in the time period from 2017 to 2021, following the presentation of the results of randomized clinical trials on intermediate surgical risk patients, receiving more frequently a self-expandable bioprosthesis, while the remaining half of patients underwent transcatheter aortic valve replacement from 2007 to 2016, more frequently by balloon-expandable bioprosthesis. Functional status at presentation was more frequently New York Heart Association class 3 in 61.4%. Left ventricular ejection fraction was generally normal or mildly decreased (56 [45-60] %), and transaortic mean gradient (46 [37-58] mmHg) and aortic valve area (0.7 [0.6-0.8] cm^2) were generally consistent with high-gradient severe aortic valve stenosis, without significant imbalance between treatment groups. Ascending aorta diameter as assessed by computed tomography was generally only mildly increased (37 [33-41] mm), but significantly larger in patients who received balloon-expandable bioprosthesis.

Mean absolute standardized differences following inverse probability of treatment weighting based on propensity score (**Table 2**, **Figure 11** and **Figure 12**) and nearest neighbour propensity score matching (**Table 2**, **Figure 13** and **Figure 14**) on datasets (n=10) generated by multiple imputation and outcomes assessment by mixed-effects models accounting for differences across centres and between valve generations showed the achievement of a good balance for each covariate included. An average of 389 matched pairs of patients was achieved by propensity score matching.

Periprocedural and in-hospital events are reported in **Table 4**. There was no significant unadjusted and adjusted difference in procedural and in-hospital death (OR 0.49, 95% CI 0.10-2.25; OR_{IPTW} 0.74, OR 95% 0.21-2.58; OR_{PSM} 0.74, 95% CI 0.22-2.53]) between groups between balloon- and self-expandable valve groups. Non-significant unadjusted differences in coronary obstruction, annulus rupture, major vascular complications, and conversion to surgery between treatment group appeared to be largely mitigated after propensity score weighting and matching. Consistently, major or life-threatening bleeding, myocardial infarction, stroke, and acute kidney injury were not significantly different between treatment groups, without significant variations after adjustment. However, patients in the balloon-expandable bioprosthesis group resulted to be associated with less frequent valve malposition and significant unadjusted and adjusted risk reductions in additional valve implantation (OR 0.20, 95% CI 0.08-0.43; OR_{IPTW} 0.37, 95% CI 0.16-0.82; OR_{PSM} 0.32, 95% CI 0.11-0.91) and moderate-to-severe postprocedural aortic regurgitation (OR 0.22, 95% CI 0.13-0.37; OR_{IPTW} 0.32, 95% CI 0.17-0.61; OR_{PSM} 0.38, 95% CI 0.19-0.75) compared with those in the self-expandable group. Finally, balloon-expandable valve was associated with a significant reduction in the need for permanent pacemaker implantation (OR 0.53, 95% CI 0.37-0.77; OR_{IPTW} 0.47, 95% CI 0.30-0.74; OR_{PSM} 0.50, 95% CI 0.29-0.85) compared with self-expandable valve.

Outcomes at 30-day are reported in **Table 5**. Despite some significant periprocedural differences, at 30-day follow-up there were no significant unadjusted and adjusted differences in major individual and composite clinical endpoints between groups, with the exception of reduced risk of pacemaker implantation associated with balloon-expandable bioprosthesis compared with self-expandable bioprosthesis (HR 0.55, 95% 0.42-0.79; HR_{IPTW} 0.58, 0.38-0.89; HR_{PSW} 0.56, 95% CI 0.35-0.90). More in details the composite endpoints of death, stroke, repeat aortic replacement, or valve dysfunction (HR 0.65, 95% CI 0.42-1.01; HR_{IPTW} 1.05, 95% CI 0.57-1.90; HR_{PSM} 0.99, 95% CI 0.48-2.05) and death, stroke, or repeat hospitalization (HR 0.80, 95% CI 0.50-1.27; HR_{IPTW} 0.96, 95% CI 0.50-1.81; HR_{PSM} 1.02, 95% CI 0.47-2.23) due to valve-related reasons were not significantly different between groups and results remained unchanged after both propensity score weighting and

matching. Consistently, the risk of death or stroke (HR 0.78, 95% CI 0.47-1.30; HR_{IPTW} 0.94, 95% CI 0.48-1.86; HR_{PSM} 0.97, 95% CI 0.41-2.30), the individual components of the endpoint, and the major individual endpoints of cardiac death, stroke, valve dysfunction, and repeat aortic valve replacement were similar between groups, regardless of the type of adjustment applied.

Mean follow-up was 516 and 491 days in the balloon- and self-expandable transcatheter heart valve group, respectively (p=0.287). At 3-year follow-up, balloon- and self-expandable valves were associated with similar incidences of major cardiovascular outcomes (**Table 6**). Composite endpoints such as death or stroke (HR 0.86, 95% CI 0.62-1.20; HR_{IPTW} 1.00, 95% CI 0.64-1.56; HR_{PSM} 1.04, 95% CI 0.63-1.73; **Figure 15**) and death, stroke, repeat aortic valve replacement, or valve dysfunction (HR 0.81, 95% CI 0.61-1.09; HR_{IPTW} 1.08, 95% CI 0.71-1.63; HR_{PSM} 1.06, 95% CI 0.63-1.76: **Figure 16**) were similar between treatment groups. At 3-year follow-up, the individual endpoints of death (HR 0.97, 95% CI 0.66-1.43; HR_{IPTW} 1.14, 95% CI 0.67-1.93; HR_{PSM} 1.17, 95% CI 0.67-2.07; **Figure 17**), cardiac death, stroke (HR 0.60, 95% CI 0.34-1.08; HR_{IPTW} 0.63, 95% CI 0.29-1.37; HR_{PSM} 0.65, 95% CI 0.27-1.56; **Figure 18**) were not significantly different before and after propensity score weighting and matching. In the unadjusted cohort, a numerical trend towards a significant risk reduction in death, stroke, or repeat hospitalization due to valve-related reasons was observed in patients who received a balloon-expandable valve as compared with those who received a self-expandable valve was observed, essentially as a result of a significant reduction in valve-related rehospitalization (HR 0.51, 95% CI 0.32-0.81). New York Heart Association class 3 or 4 over 3-year follow-up was also significantly less common in the balloon-expandable valve group compared with the self-expandable valve group (HR 0.57, 95% CI 0.34-0,95). However, both these findings were no longer significant after propensity score weighting and propensity score matching (valve-related repeat hospitalization: HR_{IPTW} 1.06, 95% CI 0.24-1.04; HR_{PSM} 1.45, 95% CI 0.55-1.38; New York Heart Association class 3 or 4: HR_{IPTW} 0.50, 95% CI 0.24-1.04; HR_{PSM} 0.55, 95% CI 0.24-1.26). Finally, the significant reduction in the incidence of pacemaker implantation associated with balloon-expandable valve implantation as compared with self-expandable valve implantation was confirmed

at 3-year follow-up (HR 0.57, 95% 0.40-0.80; HR_{IPTW} 0.57, 95% CI 0.38-0.87; HR_{PSM} 0.57, 95% CI 0.36-0.90), mainly due to early between-group differences (**Figure 19**). In a subgroup analysis, treatment groups were compared according to baseline functional status (**Table 7**) without detection of inconsistent findings and significant treatment-by-subgroup interaction.

Discussion

The main results of this study are the following:

1) Early and long-term composite and individual outcomes including major endpoints death, stroke, repeat aortic valve replacement, and valve dysfunction are not significantly different between self- and balloon-expandable valve groups, before and after inverse probability of treatment weighting based on the propensity score and nearest neighbour propensity score matching followed by mixed-effects models accounting for differences across centres and between valve generations;

2) Balloon-expandable bioprosthesis is associated with lower periprocedural rates of malposition, additional valve implantation, and significant aortic regurgitation compared with self-expandable bioprosthesis, before and after adjustment;

3) Early differences between bioprostheses did not translate in clear functional differences at long-term follow-up since significant unadjusted reductions in 3-year valve-related rehospitalization and New York Heart Association class 3 or 4 were no longer detectable after both propensity score weighting and propensity score matching followed by mixed-effects models;

4) A significant advantage of balloon-expandable valve use for the treatment of bicuspid aortic valve stenosis is a 40-45% relative risk reduction in permanent pacemaker implantation compared with self-expandable valve use, with results consistent in magnitude between unadjusted and adjusted analyses;

5) Treatment of bicuspid aortic valve stenosis in patients without significant aortic dilatation (isolated valvular pattern) and low surgical risk by transcatheter aortic valve replacement is feasible and

acceptable in terms of long-term safety, though rates of major cardiovascular events are higher than those observed in clinical trials.

Transcatheter aortic valve replacement is an established intervention for severe trileaflet aortic valve stenosis and nowadays represents the main treatment strategy for higher surgical risk clinical settings.(84, 85) The favourable safety profile and effectiveness of transcatheter aortic valve replacement is supported by exponentially increasing numbers of procedures per year worldwide and currently in some development countries more patients with aortic valve stenosis are treated by transcatheter aortic valve replacement than surgery.(154, 155) With the recent expansion of the indications for transcatheter aortic valve replacement to the low surgical risk subset of patients, significant proportions of patients with bicuspid aortic valve stenosis requiring treatment have become potentially eligible for a transcatheter approach. Indeed, it is estimated that up to 2% of general population have bicuspid aortic valve, in longitudinal studies more than 50% of subjects with bicuspid aortic valve requires aortic valve replacement within 25 years since initial diagnosis mainly due to isolated aortic valve stenosis, and in more recent analyses the proportions of patients with severe bicuspid aortic valve stenosis have older age and higher comorbidity burden than previously considered.(166, 174, 178, 179, 184)

However, current European and North American guidelines still recommend surgery as preferential approach for most bicuspid aortic valve patients due to the absence of randomized clinical trials comparing transcatheter versus surgical aortic valve replacement and a paucity of observational studies on this off-label setting as a result of the higher valve disease complexity characterized by cusps fusion, asymmetric calcification and valvular orifice, and larger ascending aorta.(84, 85)

Beyond the absence of comparisons with surgery, two main questions on transcatheter aortic valve replacement for bicuspid aortic valve stenosis still need to be addressed. The first question relates the differential performance of transcatheter aortic valve replacement between bicuspid and tricuspid aortic valve settings. In recent years, some large-scale analyses have provided promising

conclusions, with generally similar comparative feasibility and safety of transcatheter aortic valve replacement between bicuspid and tricuspid settings. The second question relates the differential performance of available transcatheter heart valve technology in light of the challenging and frequently atypical anatomy of bicuspid aortic valve stenosis. Thus far, only the observational study by Mangieri and colleagues, including 353 patients that eventually turned into pairs of 77 patients after propensity score matching, tried to provide answers.(235) The study concluded that second-generation supra-annular self-expandable valves were more likely associated with aortic regurgitation compared with second-generation balloon-expandable valves, though clinical outcomes explored were not significant different. However, results could not be considered statistical to be conclusive since statistical power was very low and outcomes were assessed at 1 year.(235)

In the present large, international, collaborative, observational study, we sought to address at 3-year follow-up whether transcatheter aortic valve replacement with self- and balloon-expandable bioprostheses are comparable in terms of efficacy and safety. With respect to in-hospital outcomes, despite the inclusion of different types of self-expandable valves, we found results partially consistent with the study by Mangieri and colleagues.(235) Indeed, we observed increased proportions of valve malposition, need for implantation of an additional valve, and moderate-to-severe aortic regurgitation. Unadjusted findings remained quite consistent following both propensity score weighting and matching followed by mixed-effects model accounting for difference across participating centres and valve generation. An increased rate of paravalvular leak associated with self-expandable valve as compared with balloon-expandable valve was also identified in previous studies on trileaflet aortic valve stenosis.(246) Notwithstanding, at 30 days and 3 years we did not observe significant differences in composite outcomes, such as death or stroke, death, stroke, repeat aortic valve intervention, or valve dysfunction, and death, stroke, or valve-related rehospitalization as well as major individual endpoints including stroke. Of note, with respect to annulus rupture and stroke, in an anatomical setting characterized by complex and asymmetrically calcified valves, the

risk of stroke associated with balloon-expandable valve, which has more aggressive deployment, was comparable to that associated with self-expandable valve.

Rates observed in our study are consistent with those reported in other reports on transcatheter aortic valve replacement for bicuspid aortic stenosis.(138, 229, 238, 239) However, by considering the low surgical risk of our cohort, long-term incidences of major endpoints were significantly higher than those reported in recent trials of low surgical risk trileaflets aortic valve patients and were more consistent with intermediate surgical risk trials.(127-129, 161) These findings warrant further analysis.

With respect to 3-year follow-up, at unadjusted analysis we observed significant reductions in repeat hospitalization due to valve-related cause and New York Heart Association class 3 or 4 associated with balloon-expandable valve used compared with self-expandable valve use. These findings may be consistent with the observation of increased proportions of moderate-to-severe aortic valve regurgitation in the self-expandable valve group. Significant paravalvular leak has been associated in previous investigations with increased mortality and poor outcomes. However, differences were no longer significant after propensity score weighting and matching followed by mixed-effect models accounting for differences across centres, valve generation, and procedural characteristics. The influence of confounders, centre-specific variation, and selection bias are likely the reasons for these observation in the unadjusted cohort, though definitive conclusions require additional studies.

Finally, we found a significant advantage of balloon-expandable valve over self-expandable valve for bicuspid aortic valve stenosis in terms of permanent pacemaker implantation following transcatheter aortic valve replacement. Importantly, estimates were quite consistent in magnitude and direction between unadjusted and adjusted analyses. This finding has been previously described in some investigations on tricuspid aortic valve stenosis as possible negative interaction between the taller frame of self-expandable valves and the heart conduction system structures.(247, 248) However, other studies in the same setting did not show consistent conclusions and no study in the

setting of bicuspid aortic valve stenosis has provided thus far this between-bioprosthesis technology comparative result.(249)

Conclusions

Transcatheter aortic valve replacement with balloon-expandable valves for the treatment of bicuspid aortic valve is associated with lower rates of valve malposition, additional valve implantation, and moderate-to-severe aortic regurgitation compared with self-expandable valves. These periprocedural findings however did not translate in significant differences in major clinical and individual endpoints in-hospital, at 30 days, and at 3 years and unadjusted higher incidence of valve-related rehospitalization at long-term follow-up associated with self-expandable valve was no longer detectable after propensity score weighting or matching. Finally, a consistent advantage from balloon-expandable valve was a 40-45% relative risk reduction in pacemaker implantation compared with self-expandable valve.

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TABLES

Table 1. Indications for transcatheter versus surgical aortic valve replacement.

	Favours transcatheter aortic valve replacement	Favours surgical aortic valve replacement
Clinical characteristics		
Lower surgical risk	−	+
Higher surgical risk	+	−
Younger age	−	+
Older age	+	−
Previous cardiac surgery (particularly intact coronary artery bypass grafts at risk of injury during repeat sternotomy)	+	−
Severe frailty	+	−
Active or suspected endocarditis	−	+
Anatomical and procedural factors		
TAVI feasible via transfemoral approach	+	−
Transfemoral access challenging or impossible and surgical aortic valve replacement feasible transfemoral access challenging or impossible and surgical aortic valve replacement inadvisable	− +	+ −
Sequelae of chest radiation	+	−
Porcelain aorta	−	+
High likelihood of severe patient–prosthesis mismatch (aortic valve area <0.65 cm^2/m^2 body surface are)	+	−
Severe chest deformation or scoliosis	+	−

	Favours transcatheter aortic valve replacement	Favours surgical aortic valve replacement
Aortic annular dimensions unsuitable for available transcatheter aortic valve replacement devices	−	+
Valve morphology unfavourable for transcatheter aortic valve replacement (e.g., high risk of coronary obstruction due to low coronary ostia or heavy leaflet/left ventricle outflow tract calcification)	−	+
Thrombus in aorta or left ventricle	−	+
Concomitant cardiac conditions requiring intervention		
Significant multi-vessel coronary artery disease requiring surgical revascularization	−	+
Severe primary mitral valve disease	−	+
Severe tricuspid valve disease	−	+
Significant dilatation/aneurysm of the aortic root and/or ascending aorta	−	+
Septal hypertrophy requiring myectomy	−	+

Table 2. Baseline characteristics.

	Total (n=1082)	Balloon-Expandable (n=650)	Self-Expandable (n=432)	SMD	SMD_{MI}	SMD_{IPTW}	SMD_{PSM}
Age	79.0 [73.0-83.6] 77.7 ± 8.5	78.4 [72.0-83.0] 77.0 ± 8.8	80.0 [75.1-84-1] 78.7 ± 7.9	0.225	0.225	-0.011	-0.002
Men	644 (59.5)	421 (64.7)	223 (51.7)	-0.259	-0.259	-0.017	-0.026
Body Mass Index	25.8 [23.1-29.4] 26.7 ± 5.5	25.8 [23.2-29.7] 27.0 ± 5.8	25.5 [22.9-29.0] 26.3 ± 5.2	-0.140	-0.137	0.021	0.002
STS-PROM	3.4 [2.1-5.2] 4.3 ± 4.0	3.4 [2.1-5.3] 4.4 ± 4.5	3.3 [2.2-5.1] 4.2 ± 3.2	-0.056	–	–	–
Period of transcatheter aortic valve replacement				0.229	0.250	-0.007	0.020
2007-2016	492 (47.1)	320 (50.6)	128 (31.1)				
2017-2021	552 (52.9)	306 (48.4)	246 (59.7)				
Bicuspid Morphology							
Type 0	107 (12.5)	59 (12.0)	48 (13.2)	0.036	-0.021	0.018	-0.011
Type 1	734 (86.0)	423 (86.3)	311 (85.7)	-0.019	0.086	-0.017	0.014
Type 2	12 (1.4)	8 (1.6)	4 (1.1)	-0.051	-0.171	0	-0.010
Diabetes	259 (23.9)	162 (24.9)	97 (22.5)	-0.054	-0.052	0.007	0.013
Hypertension	870 (80.4)	527 (81.0)	343 (79.6)	-0.027	-0.029	0.042	0.020
Coronary Artery Disease	456 (42.1)	292 (44.9)	164 (42.1)	-0.143	-0.147	0.032	0.014
Chronic Kidney Disease	409 (43.7)	263 (44.9)	146 (41.8)	-0.062	-0.136	-0.037	-0.013
Peripheral Artery Disease	151 (14)	99 (15.2)	52 (12.1)	-0.072	-0.001	0.016	0.010
Prior Pacemaker	99 (9.1)	55 (8.4)	44 (10.2)	0.059	0.062	0.005	-0.014
Prior Myocardial Infarction	147 (13.6)	88 (13.5)	59 (13.7)	0.008	0.010	-0.010	-0.012
Prior PCI	291 (26.9)	188 (28.9)	103 (23.9)	-0.113	-0.111	-0.015	0.009
Prior Stroke	97 (9.6)	64 (10.2)	33 (8.6)	-0.059	-0.022	-0.003	0.018
Prior CABG	110 (10.2)	68 (10.4)	42 (9.7)	-0.021	-0.021	0.008	0.034

NYHA							
0-2	295 (27.3)	179 (27.5)	116 (26.9)	-0.010	-0.011	0.009	-0.018
3	668 (61.7)	390 (59.9)	278 (64.5)	0.103	0.102	-0.018	0.003
4	112 (10.4)	79 (12.1)	33 (7.7)	-0.167	-0.163	0.016	0.020
LVEF	56 [45-60] 51.5 ± 13.7	55 [43-60] 50.6 ± 14.1	58 [45-60] 53.1 ± 13.0]	0.186	0.183	0.007	
Aortic Valve Area	0.70 [0.55-0.80] 0.70 ± 0.24	0.70 [0.57-0.80] 0.70 ± 0.22	0.70 [0.53-0.80] 0.68 ± 0.22	-0.080	-0.087	-0.010	
Mean Gradient	46 [37-58] 48 ± 17	46 [37-57] 48 ± 17	46 [37-58] 48 ± 17	0.026	0.019	-0.001	
Peak Systolic Velocity	4.3 [3.9-4.8] 4.3 ± 0.9	4.3 [3.9-4.8] 4.3 ± 0.8	4.3 [3.9-4.8] 4.3 ± 0.8	0.010	-0.014	0.028	
Ascending aorta diameter	37 [33-41] 37 ± 6	38 [34-42] 38 ± 6	36 [33-40] 37 ± 6	-0.275	-0.293	-0.001	
Aortic Regurgitation							
None or Mild	859 (81.4)	517 (81.2)	342 (81.8)	0.017	0.019	0.004	-0.023
Moderate	144 (13.6)	87 (13.7)	57 (13.6)	-0.001	-0.004	-0.005	0.040
Severe	52 (4.9)	33 (3.1)	19 (4.5)	-0.031	-0.028	0	-0.021
Mitral Regurgitation							
None or Mild	791 (75.3)	465 (73.9)	326 (77.3)	0.079	0.081	-0.017	-0.037
Moderate	201 (19.1)	125 (19.9)	76 (18.0)	-0.049	-0.051	-0.001	0.035
Severe	59 (5.6)	39 (6.2)	20 (4.7)	-0.069	-0.069	0.036	0.008
Tricuspid Regurgitation							
None or Mild	826 (87.9)	515 (87.9)	311 (87.9)	-0.001	-0.041	-0.026	-0.002
Moderate	97 (10.3)	62 (10.6)	35 (9.9)	0.023	0.019	0.028	0.004
Severe	17 (1.8)	9 (1.5)	8 (2.3)	-0.049	0.047	0.003	-0.001
General Anesthesia	341 (31.5)	214 (32.9)	127 (29.5)	-0.066	-0.070	-0.033	0.026
Predilation	688 (63.6)	398 (61.1)	290 (67.3)	-0.178	–	–	–
Postdilation	338 (31.2)	134 (20.6)	204 (47.3)	-0.705	–	–	–
Valve Generation				-0.614	–	–	–

Early	250 (23.1)	72 (11.1)	178 (41.3)
New	832 (76.9)	579 (88.9)	253 (58.7)

CABG=Coronary artery bypass grafting; LVEF=Left ventricular ejection fraction; NYHA=New York Heart Association; PCI=Percutaneous coronary intervention; SMD=Standardized mean difference of unadjusted dataset; SMD_{MI}=Mean standardized mean difference following multiple imputation by chained equations (10 datasets); SMD_{IPTW}=Mean standardized mean difference following inverse probability of treatment weighting on datasets generated by multiple imputation; SMD_{PSM}=Mean standardized mean difference following 1:1 nearest neighbour propensity score matching on datasets generated by multiple imputation; STS-PROM= Society of Thoracic Surgeons score to predict 30 days mortality; transcatheter aortic valve replacement=Transcatheter aortic valve replacement.

Age is expressed as years, body mass index as kg/m^2, estimated glomerular filtration rate as $mL/min/1.73\ m^2$, left ventricular ejection fraction as percentage, aortic valve area as cm^2, mean transaortic gradient ad mm Hg, and peak systolic velocity as cm/sec.
STS-PROM was not included in the propensity score model due to collinearity with several covariates used to the derive the score. Valve generation, predilation, and postdilation variables were not included in the propensity score estimation model since they could not properly be considered as pre-exposure conditions and intrinsically related to the deployment technology. However, given the large differences observed at baseline and the potential confounding effect on outcomes, these conditions were included in as covariate in the multivariable mixed-effects models used to estimate outcomes. In addition, prespecified analysis were performed to assess the influence of valve generation.
Early generation transcatheter heart valves included: Sapien XT, CoreValve, Acurate neo, and Portico. New-generation transcatheter aortic valves included: Sapien 3 and Sapien Ultra.

Table 3. Transcatheter heart valve implanted in the study.

Balloon-Expandable (n=651)	Self-Expandable (n=431)
Sapien XT (72, 11.1%)	Acurate neo (62, 14.4%)
Sapien 3 (562, 86.3%)	Allegra (1, 0.2%)
Sapien Ultra (17, 2.6%)	Centera (5, 1.2%)
	CoreValve (110, 25.5%)
	Evolut Pro (64, 14.8%)
	Evolut R (166, 38.5%)
	Portico (23, 5.3%)

Table 4. Unadjusted, inverse probability of treatment weighting-adjusted, and propensity score matching-based in-hospital outcomes.

	Total Population (n=1082)	Balloon-Expandable (n=651)	Self-Expandable (n=431)	p	OR [95% CI]	OR_{IPTW} [95% CI]	OR_{PSM} [95% CI]
Procedural Death	7 (0.6)	3 (0.5)	4 (0.9)	0.446	0.49 [0.10-2.25]	0.67 [0.04-12.08]	—
In-Hospital Death	22 (2.0)	11 (1.7)	11 (2.6)	0.325	0.66 [0.28-1.55]	0.74 [0.21-2.58]	0.74 [0.22-2.53]
Major Vascular Complications	53 (4.9)	26 (4.0)	27 (6.3)	0.090	0.62 [0.36-1.08]	0.78 [0.19-3.26]	1.02 [0.37-2.81]
Annulus Rupture	14 (1.4)	11 (1.8)	3 (0.7)	0.145	2.51 [0.78-11.17]	5.73 [0.41-80.55]	—
Cardiac Tamponade	12 (1.2)	8 (1.3)	4 (1.0)	0.771	1.36 [0.43-5.13]	3.76 [0.41-34.81]	2.56 [0.38-17.13]
Valve Malposition	24 (2.3)	8 (1.3)	16 (4.1)	0.004	0.16 [0.00-1.11]	0.41 [0.18-0.91]	0.47 [0.18-1.18]
Additional Valve	32 (3.1)	8 (1.3)	24 (6.1)	<0.001	0.20 [0.08-0.43]	0.37 [0.16-0.82]	0.32 [0.11-0.91]
Moderate or Severe Aortic Regurgitation	72 (7.5)	21 (3.5)	51 (14.2)	<0.001	0.22 [0.13-0.37]	0.32 [0.17-0.61]	0.38 [0.19-0.75]
Conversion to Surgery	6 (0.6)	2 (0.3)	4 (1.0)	0.212	0.31 [0.04-1.60]	0.75 [0.17-3.24]	0.52 [0.12-2.22]
Major or Life-Threatening In-Hospital Bleeding	100 (9.2%)	55 (8.4%)	45 (10.4)	0.268	0.79 [0.52-1.20]	0.66 [0.38-1.15]	0.85 [0.47-1.54]
Coronary Obstruction	5 (0.5)	2 (0.3)	3 (0.5)	0.393	0.44 [0.06-2.66]	0.77 [0.09-6.63]	—
Myocardial Infarction	7 (0.6)	2 (0.3)	5 (1.2)	0.122	0.26 [0.04-1.22]	0.35 [0.06-1.99]	—
In-Hospital Stroke	34 (3.1)	19 (2.9)	15 (3.5)	0.604	0.83 [0.42-1.68]		
Pacemaker Implantation[a]	148 (13.7)	71 (10.9)	77 (17.0)	0.001	0.53 [0.37-0.77]	0.47 [0.30-0.74]	0.50 [0.29-0.85]
Acute Kidney Injury	51 (4.7)	26 (4.0)	25 (5.8)	0.172	0.68 [0.38-1.19]	1.06 [0.52-2.17]	0.72 [0.35-1.48]

[a] After exclusion of patients with pacemaker prior to transcatheter aortic valve replacement, 584 patients were included in the Balloon-Expandable group and 377 in the Self-Expandable group.

Values are counts and proportions. P value refers to the Person χ^2 or Fisher exact test, as appropriate.

CI = Confidence Interval; OR = Odds Ratio from logistic regression on the unadjusted cohort; OR_{IPTW} = Odds Ratio from multivariable mixed-effects models accounting for effect variations across participating centres and valve generation after inverse probability of treatment weighting on datasets produced by

multiple imputation; HR_{PSM} = Hazard ratios from multivariable mixed-effects models accounting for effect variations across participating centres and differences in procedural characteristics after propensity score matching on datasets produced by multiple imputation.

Table 5. Unadjusted, inverse probability of treatment weighting-adjusted, and propensity score matching-based 30-day clinical outcomes

	Total Population (n=1082)	Balloon-Expandable (n=651)	Self-Expandable (n=431)	p	HR [95% CI]	HR_{IPTW} [95% CI]	HR_{PSM} [95% CI]
Death or Stroke	59 (5.5)	32 (5.0)	27 (6.3)	0.338	0.78 [0.47-1.30]	0.94 [0.48-1.86]	0.97 [0.41-2.30]
Death, Stroke, or Repeat Aortic Valve Replacement	61 (5.7)	33 (5.2)	28 (6.6)	0.317	0.78 [0.47-1.28]	0.93 [0.48-1.81]	0.97 [0.43-2.18]
Death, Stroke, or Repeat Aortic Valve Replacement, or Valve Dysfunction	78 (7.3)	39 (6.1)	39 (9.1)	0.055	0.65 [0.42-1.01]	1.05 [0.57-1.90]	0.99 [0.48-2.05]
Death, Stroke, or Repeat Hospitalization	73 (6.9)	40 (6.3)	33 (7.9)	0.337	0.80 [0.50-1.27]	0.96 [0.50-1.81]	1.02 [0.47-2.23]
Death	23 (2.2)	12 (1.9)	11 (2.6)	0.437	0.72 [0.32-1.64]	0.67 [0.19-2.39]	0.80 [0.22-2.94]
Cardiac Death	17 (1.6)	7 (1.1)	10 (2.4)	0.111	0.47 [0.18-1.22]	1.06 [0.50-2.23]	0.73 [0.17-3.13]
Stroke	39 (3.6)	21 (3.2)	18 (4.2)	0.403	0.77 [0.41-1.44]	0.93 [0.40-2.19]	0.90 [0.32-2.55]
Valve Dysfunction	16 (1.5)	6 (0.9)	10 (2.3)	0.062	0.39 [0.14-1.08]	2.70 [0.64-11.45]	2.42 [0.44-13.19]
Valve Thrombosis	3 (0.3)	2 (0.3)	1 (0.3)	0.815	1.33 [0.12-14.68]	1.46 [0.09-23.35]	1.68 [0.10-27.22]
Repeat Aortic Valve Replacement	5 (0.5)	2 (0.3)	3 (0.7)	0.359	0.44 [0.07-2.65]	0.40 [0.03-5.09]	0.56 [0.00-257.90]
Pacemaker Implantation[a]	157 (16.5)	75 (12.9)	82 (21.8)	<0.001	0.55 [0.42-0.79]	0.58 [0.38-0.89]	0.56 [0.35-0.90]
Valve-Related Rehospitalization	20 (2.0)	9 (1.5)	11 (2.7)	0.164	0.54 [0.22-1.30]	1.13 [0.24-5.24]	1.26 [0.16-10.07]
Myocardial Infarction	3 (0.3)	2 (0.3)	1 (0.2)	0.817	1.32 [0.12-14.62]	1.52 [0.12-19.58]	–

Percutaneous Coronary Intervention	1 (0.1)	1 (0.2)	0	0.415	–	–	–

[a] After exclusion of patients with pacemaker prior to transcatheter aortic valve replacement, 584 patients were included in the Balloon-Expandable group and 377 in the Self-Expandable group.

Values are counts and incidences by Kaplan-Meier method in the unadjusted cohort. P value refers to the log-rank test.

CI = Confidence Interval; HR = Hazard Ratio from standard proportional hazard regression models; HR_{IPTW} = Hazard ratios from multivariable mixed-effects models accounting for effect variations across participating centres, valve generation, and differences in procedural characteristics after inverse probability of treatment weighting on datasets produced by multiple imputation; HR_{PSM} = Hazard ratios from multivariable mixed-effects models accounting for effect variations across participating centres, valve generation, and differences in procedural characteristics after propensity score matching on datasets produced by multiple imputation.

Table 6. Unadjusted, inverse probability of treatment weighting-adjusted, and propensity score matching-based 3-year clinical outcomes.

	Total Population (n=1082)	Balloon-Expandable (n=651)	Self-Expandable (n=431)	p	HR [95% CI]	HR_{IPTW} [95% CI]	HR_{PSM} [95% CI]
Death or Stroke	142 (22.3)	80 (21.1)	62 (24.0)	0.384	0.86 [0.62-1.20]	1.00 [0.64-1.56]	1.04 [0.63-1.73]
Death, Stroke, or Repeat Aortic Valve Replacement	149 (23.1)	83 (21.7)	66 (25.2)	0.274	0.84 [0.60-1.15]	0.98 [0.64-1.50]	1.03 [0.64-1.65]
Death, Stroke, or Repeat Aortic Valve Replacement, or Valve Dysfunction	186 (27.2)	103 (25.3)	83 (29.8)	0.160	0.81 [0.61-1.09]	1.08 [0.71-1.63]	1.06 [0.63-1.76]
Death, Stroke, or Repeat Hospitalization	198 (30.7)	107 (27.6)	91 (35.0)	0.062	0.77 [0.58-1.02]	1.09 [0.73-1.64]	1.21 [0.77-1.92]
Death	106 (19.2)	62 (19.1)	44 (19.4)	0.870	0.97 [0.66-1.43]	1.14 [0.67-1.93]	1.17 [0.67-2.07]
Cardiac Death	54 (9.2)	28 (7.8)	26 (11.3)	0.242	0.73 [0.43-1.25]	1.06 [0.50-2.23]	1.15 [0.50-2.61]
Stroke	46 (5.1)	22 (3.4)	24 (7.7)	0.082	0.60 [0.34-1.08]	0.63 [0.29-1.37]	0.65 [0.27-1.56]
Valve Dysfunction	44 (5.9)	25 (6.4)	19 (5.3)	0.670	0.88 [0.48-1.59]	1.50 [0.39-5.80]	1.25 [0.12-12.71]
Valve Thrombosis	7 (1.5)	6 (2.5)	1 (0.3)	0.146	4.24 [0.51-35.20]	3.23 [0.24-43.38]	3.08 [0.22-42.61]
Repeat Aortic Valve Replacement	11 (1.5)	4 (0.9)	7 (2.2)	0.111	0.38 [0.11-1.31]	0.87 [0.12-6.11]	0.42 [0.06-2.90]
Pacemaker Implantation[a]	168 (19.0)	82 (15.3)	86 (24.9)	<0.001	0.57 [0.40-0.80]	0.57 [0.38-0.87]	0.57 [0.36-0.90]
Endocarditis	6 (180)	4 (1.1)	2 (0.9)	0.738	1.33 [0.24-7.28]	2.08 [0.22-19.84]	2.06 [0.15-27.64]
NYHA 3-4 class	59 (11.1)	27 (9.5)	32 (13.7)	0.028	0.57 [0.34-0.95]	0.50 [0.24-1.04]	0.55 [0.24-1.26]
Repeat	73 (11.9)	32 (9.2)	41 (15.9)	0.004	0.51 [0.32-0.81]	1.06 [0.51-2.20]	1.45 [0.55-3.81]

Rehospitalization							
Myocardial Infarction	12 (3.4)	6 (2.7)	6 (4.4)	0.538	0.70 [0.23-2.18]	0.81 [0.17-3.84]	0.89 [0.14-5.70]
Percutaneous Coronary Intervention	14 (3.2)	10 (3.3)	4 (3.0)	0.354	1.72 [0.54-5.49]	0.74 [0.18-3.10]	1.02 [0.20-5.22]

[a] After exclusion of patients with pacemaker prior to transcatheter aortic valve replacement, 584 patients were included in the Balloon-Expandable group and 377 in the Self-Expandable group.

Values are counts and incidences by Kaplan-Meier method in the unadjusted cohort. P value refers to the log-rank test.

CI = Confidence Interval; HR = Hazard Ratio from standard proportional hazard regression models; HR_{IPTW} = Hazard ratios from multivariable mixed-effects models accounting for effect variations across participating centres, valve generation, and differences in procedural characteristics after inverse probability of treatment weighting on datasets produced by multiple imputation; HR_{PSM} = Hazard ratios from multivariable mixed-effects models accounting for effect variations across participating centres, valve generation, and differences in procedural characteristics after propensity score matching on datasets produced by multiple imputation.

Table 7. Key endpoints according to functional class at baseline.

	Balloon-Expandable	Self-Expandable	p	HR [95% CI]	p_{int}	HR_{IPTW} [95% CI]	p_{int}	HR_{PSM} [95% CI]	p_{int}
30 days									
Death or Stroke									
NYHA 0-2	4 (2.2)	5 (4.4)	0.611	0.51 [0.14-1.90]	0.360	0.29 [0.03-2.57]	0.149	0.47 [0.05-4.82]	0.236
NYHA 3-4	28 (6.1)	19 (6.3)	0.920	0.98 [0.54-1.79]		1.20 [0.56-2.58]		1.15 [0.47-2.84]	
Death, Stroke, or Repeat Aortic Valve Replacement									
NYHA 0-2	4 (2.2)	5 (4.4)	0.554	0.51 [0.14-1.90]	0.370	0.29 [0.03-2.57]	0.158	0.47 [0.05-4.82]	0.247
NYHA 3-4	29 (6.3)	20 (6.6)	0.872	0.97 [0.54-1.75]		1.15 [0.54-2.43]		1.10 [0.46-2.65]	
Death, Stroke, or Valve Dysfunction									
NYHA 0-2	6 (3.4)	10 (8.7)	0.144	0.47 [0.15-1.45]	0.233	0.47 [0.08-2.72]	0.072	0.45 [0.04-4.77]	0.147
NYHA 3-4	33 (7.2)	26 (8.5)	0.626	0.85 [0.50-1.44]		1.08 [0.56-2.08]		1.01 [0.47-2.14]	
Death, Stroke, or Repeat Hospitalization									
NYHA 0-2	6 (3.5)	7 (6.2)	0.532	0.36 [0.08-1.53]	0.293	0.37 [0.06-2.34]	0.160	0.43 [0.04-4.38]	
NYHA 3-4	34 (7.4)	23 (7.7)	0.935	1.08 [0.61-1.90]		1.28 [0.62-2.66]		1.24 [0.53-2.92]	
3 years									
Death or Stroke									
NYHA 0-2	12 (11.1)	9 (15.1)	0.688	0.70 [0.25-1.96]	0.846	0.72 [0.21-2.46]	0.363	0.58 [0.06-5.24]	0.456
NYHA 3-4	68 (24.5)	53 (27.1)	0.578	0.92 [0.63-1.34]		1.18 [0.72-1.93]		1.10 [0.63-1.89]	
Death, Stroke, or Repeat Aortic Valve Replacement									
NYHA 0-2	12 (11.1)	9 (15.1)	0.688	0.70 [0.25-1.96]	0.924	0.77 [0.23-2.52]	0.430	0.58 [0.06-5.27]	0.524
NYHA 3-4	71 (25.3)	57 (28.7)	0.411	0.87 [0.61-1.25]		1.14 [0.71-1.83]		1.05 [0.62-1.79]	
Death, Stroke, or Valve Dysfunction									
NYHA 0-2	19 (16.5)	18 (28.5)	0.364	0.80 [0.29-2.18]	0.575	0.83 [0.28-2.40]	0.270	0.99 [0.19-5.05]	0.406
NYHA 3-4	84 (28.4)	65 (31.3)	0.503	0.89 [0.63-1.28]		1.24 [0.78-1.95]		1.04 [0.63-1.70]	
Death, Stroke, or Repeat Hospitalization									
NYHA 0-2	18 (15.5)	16 (26.1)	0.347	0.57 [0.27-1.23]	0.379	0.57 [0.27-1.23]	0.152	0.58 [0.10-3.42]	0.310
NYHA 3-4	89 (31.7)	75 (37.9)	0.205	1.08 [0.76-1.53]		1.13 [0.73-1.78]		1.22 [0.74-2.03]	

CI=Confidence interval; HR = Hazard ratio; NYHA = New York Heart Association; IPTW = Inverse probability of treatment weighting; p_{int} = P value of interaction testing; PSM = Propensity score matching.

Values between treatment groups are counts and incidences as estimated by Kaplan-Meier method. Log-rank test p values for pairwise comparisons were adjusted for multiplicity by Benjamini-Hochman method. Hazard ratios and 95% confidence intervals were estimated by mixed-effects Cox proportional hazards regression accounting for heterogeneity across collaborating centres before and after inverse probability of treatment weighting based on propensity score and propensity score matching.

FIGURES

Figure 1. Temporal trends in the incidence and prognosis of aortic valve stenosis.

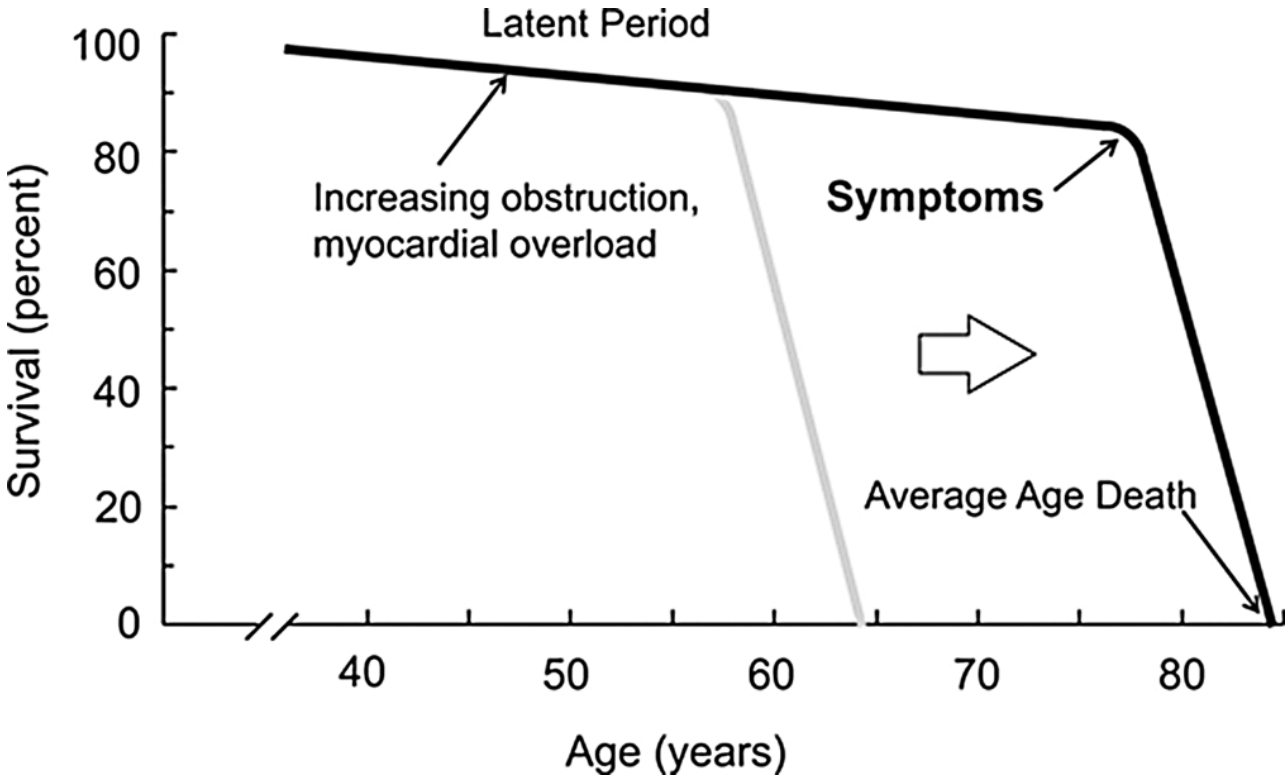


Figure 2. Aortic valve stenosis natural history.

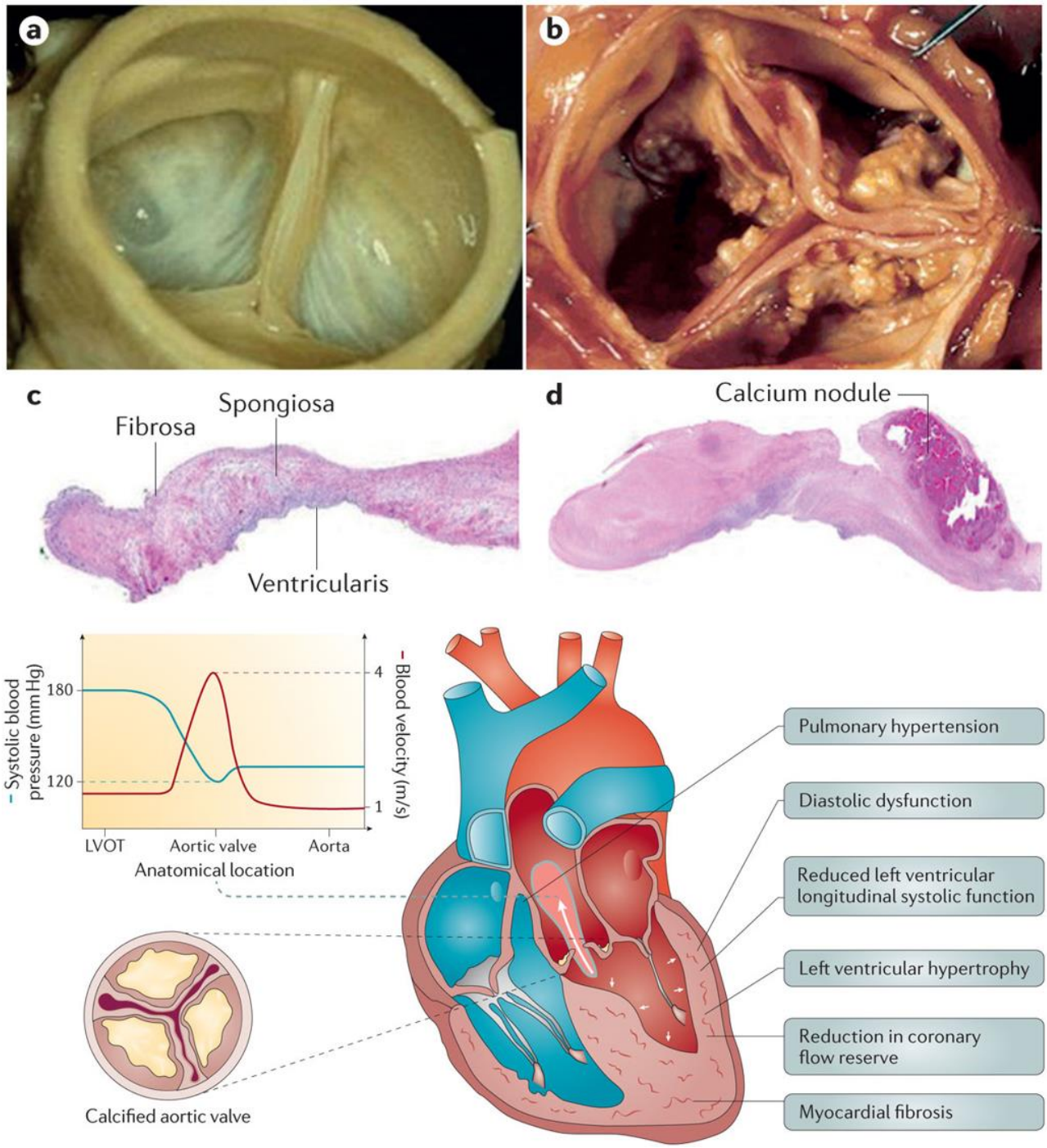


Figure 3. Main types of aortic valve stenosis.

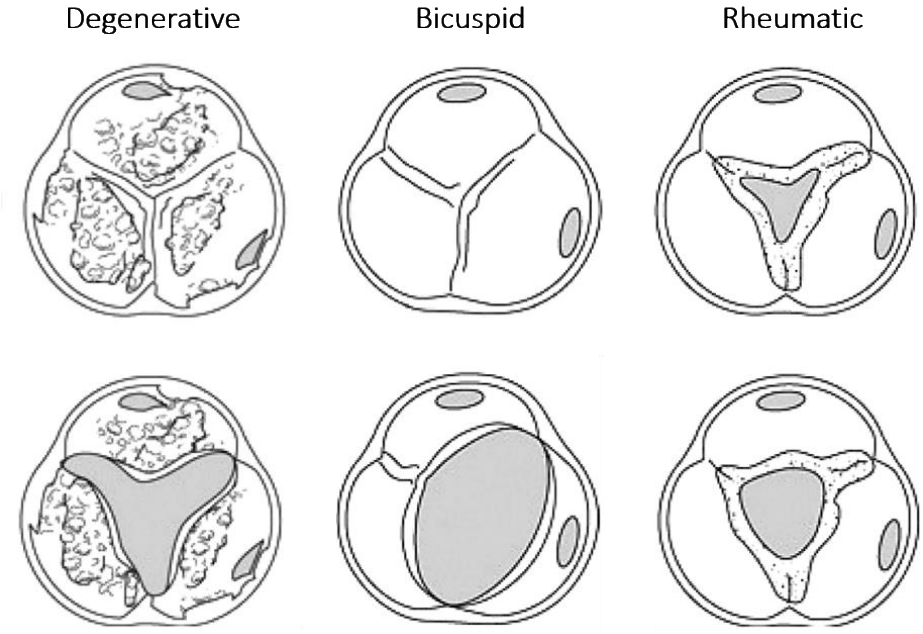


Figure 4. Predictors and possible mediators associated with degenerative calcific aortic valve stenosis.

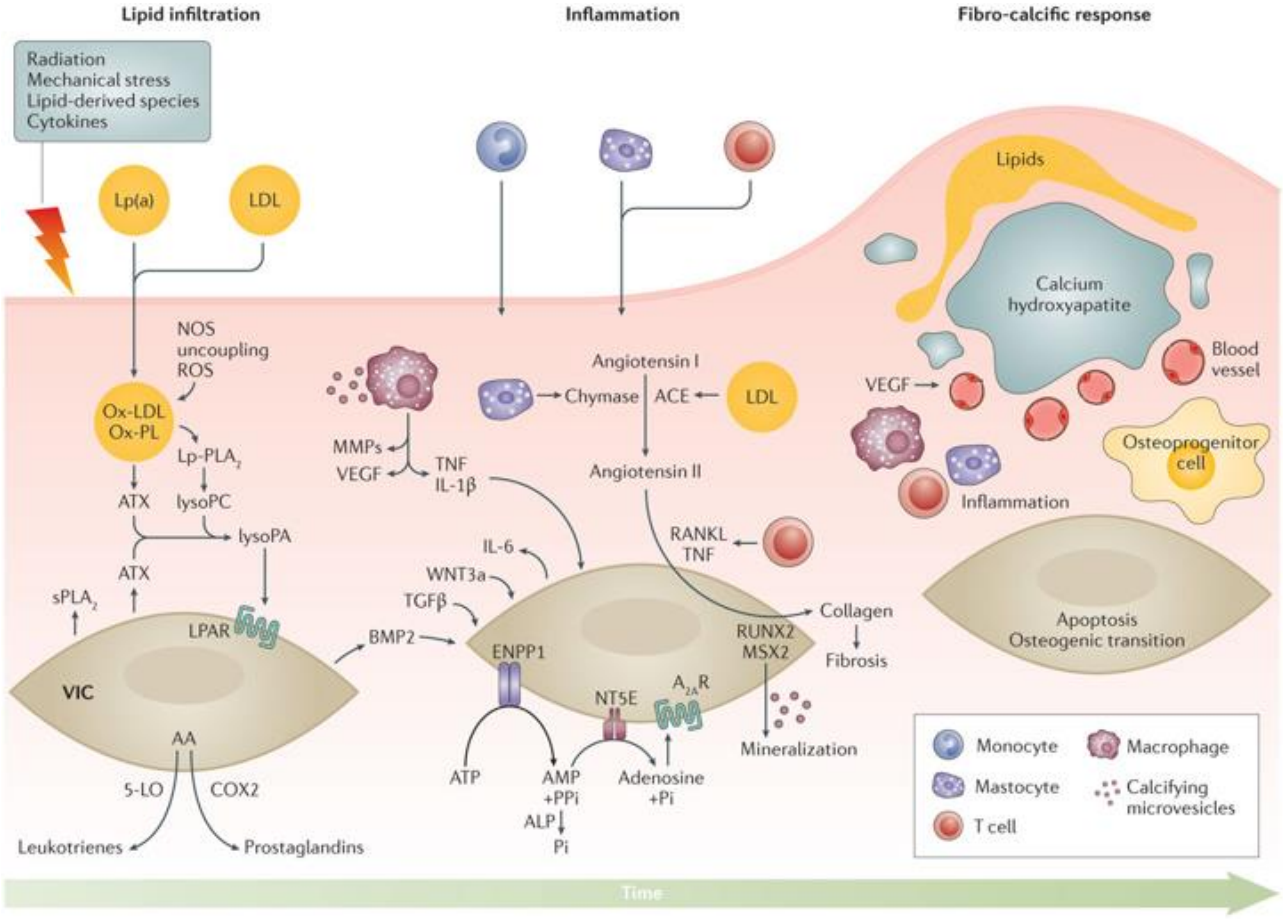
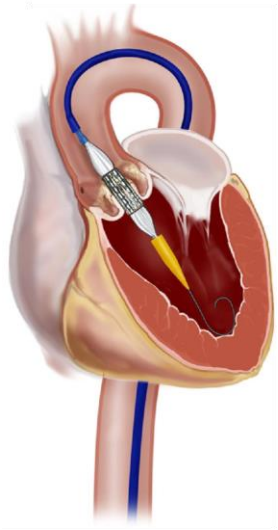
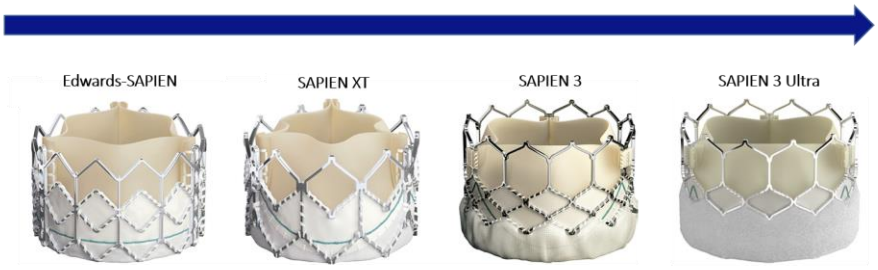


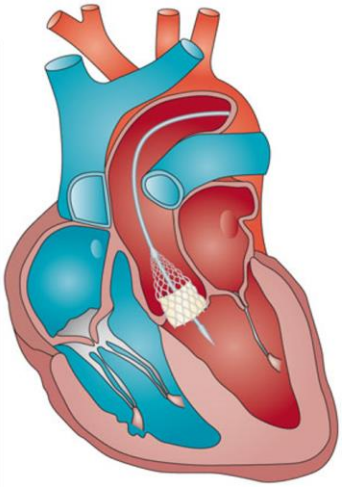
Figure 5. Transcatheter balloon expandable prosthesis





	Edwards-SAPIEN	SAPIEN XT	SAPIEN 3	SAPIEN 3 Ultra
Size	23 mm - 26 mm	20 mm - 23 mm - 26 mm - 29 mm	20 mm - 23 mm - 26 mm - 29 mm	20 mm - 23 mm - 26 mm - 29 mm
Leaflets	Bovine pericardium	Bovine pericardium	Bovine pericardium	Bovine pericardium
Frame	Stainless-steel	Cobalt-chromium	Cobalt-chromium	Cobalt-chromium
Crimped profile	8.3 mm	8.0 mm	8.0 mm	7.0 mm
Frame height*	16.1 mm - 18.1 mm	17.2 mm - 20.1 mm	20.0 mm - 28.0 mm	20.0 mm - 28.0 mm
Frame shortening	2 mm	2.9 mm	8 mm	8 mm
Skirt	–	Polyethylene terephthalate	Polyethylene terephthalate	Textured polyethylene terephthalate
Skirt height*			7.0 mm - 10.2 mm	?? - 10.2 mm
Delivery system	RetroFlex3	NovaFlex+	Commander	Commander
Sheat*	Retroflex (24 Fr)	eSheath (18 Fr)	eSheath (14 Fr - 16 Fr)	eSheath (14 Fr) - Axela (14 Fr)
Sheat size*	7.9 mm - 9.2 mm	6.5 mm - 7.5 mm - 8.9 mm	4.7 mm - 6.0 mm - 8.0 mm	4.7 mm - 6.0 mm - 8.0 mm

Figure 6. Transcatheter self- expandable prosthesis



	CoreValve™	CoreValve Evolut R™	CoreValve Evolut Pro™
			
Size	26mm - 29 mm - 31 mm	23 mm - 26 mm - 29 mm - 34 mm	23 mm - 26 mm - 29 mm
Leaflets	Bovine pericardium	Porcine pericardium	Porcine pericardium
Frame	Nickel-titanium alloy	Nickel-titanium alloy	Nickel-titanium alloy
Frame height*	55mm - 53 mm - 52 mm	45mm	45mm
Skirt	–	Porcine pericardium	Porcine pericardium
Delivery system	AccuTrack	AccuTrack	AccuTrack
Sheat*	18/20 Fr	14/16 Fr	16 Fr
Minimum vessel diameter	6.0 mm	5.0 mm	5.5 mm

Figure 7. Bicuspid aortic valve.

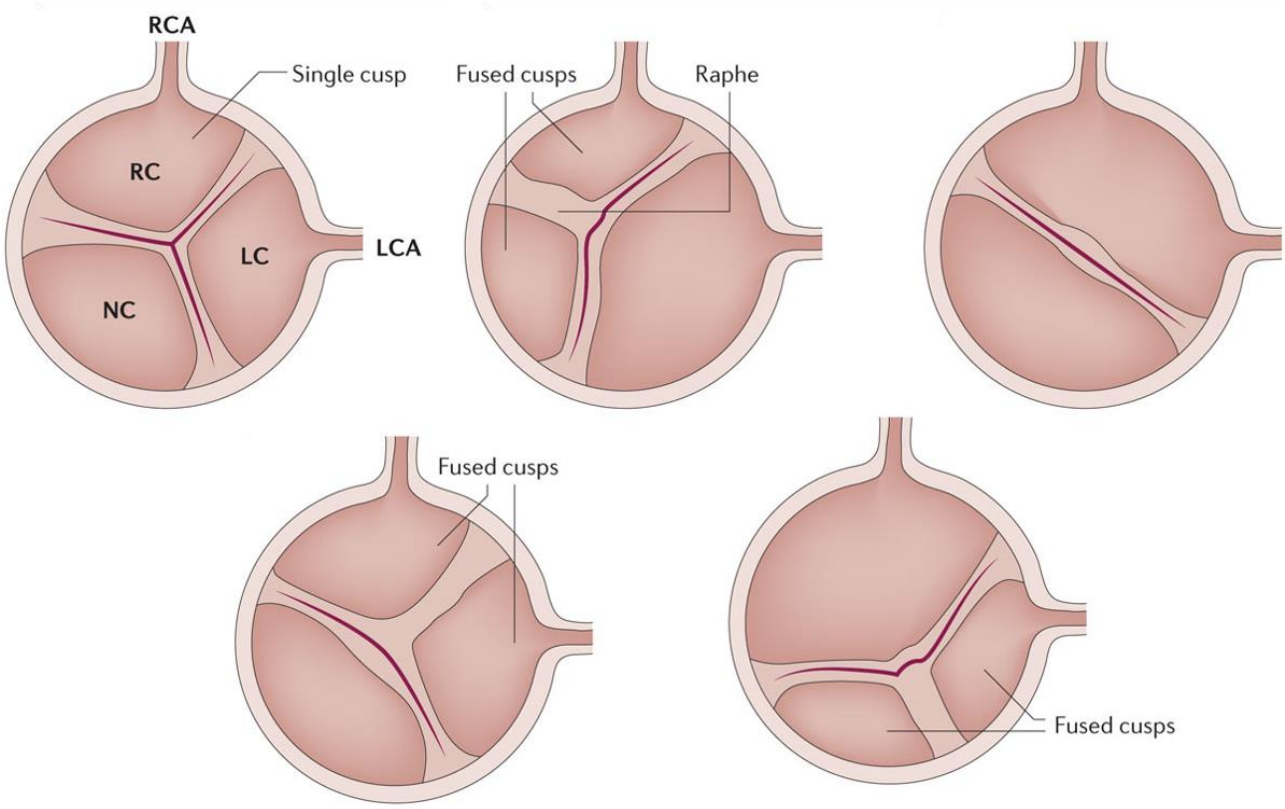


Figure 8. Bicuspid aortic valve classification according to Sievers HH (A) and Jilaihawi H(B)

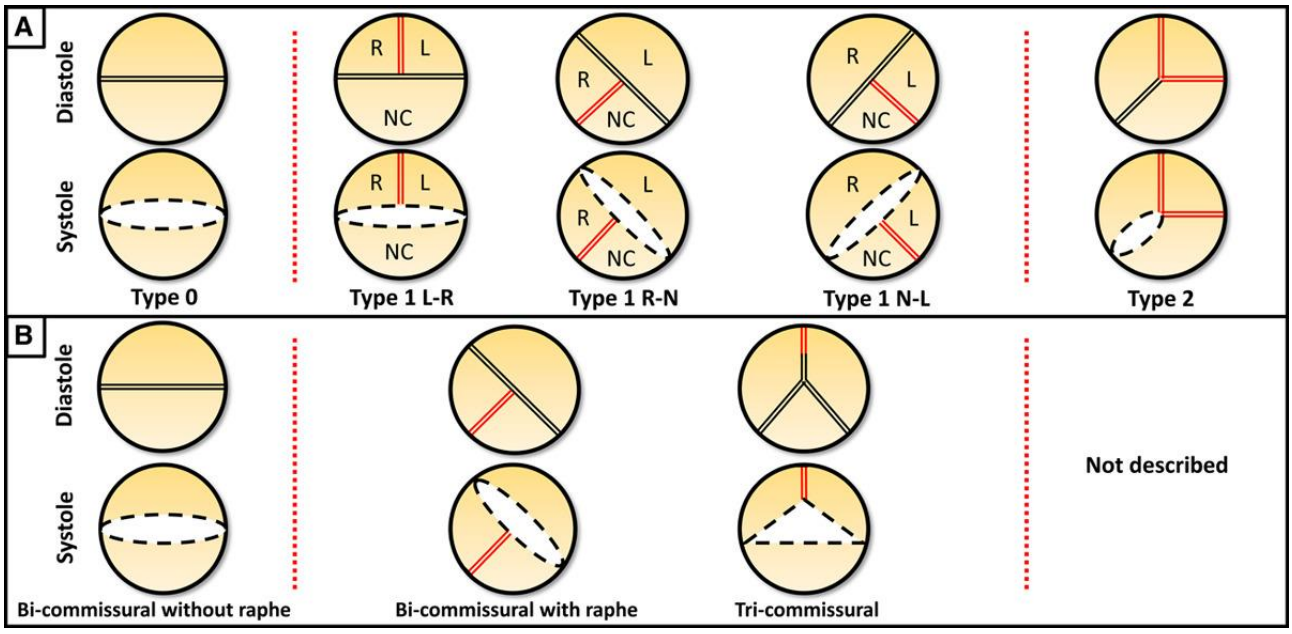


Figure 9. Bicuspid aortic valve classification according to the international consensus statement on nomenclature and classification of the congenital bicuspid aortic valve and its aortopathy

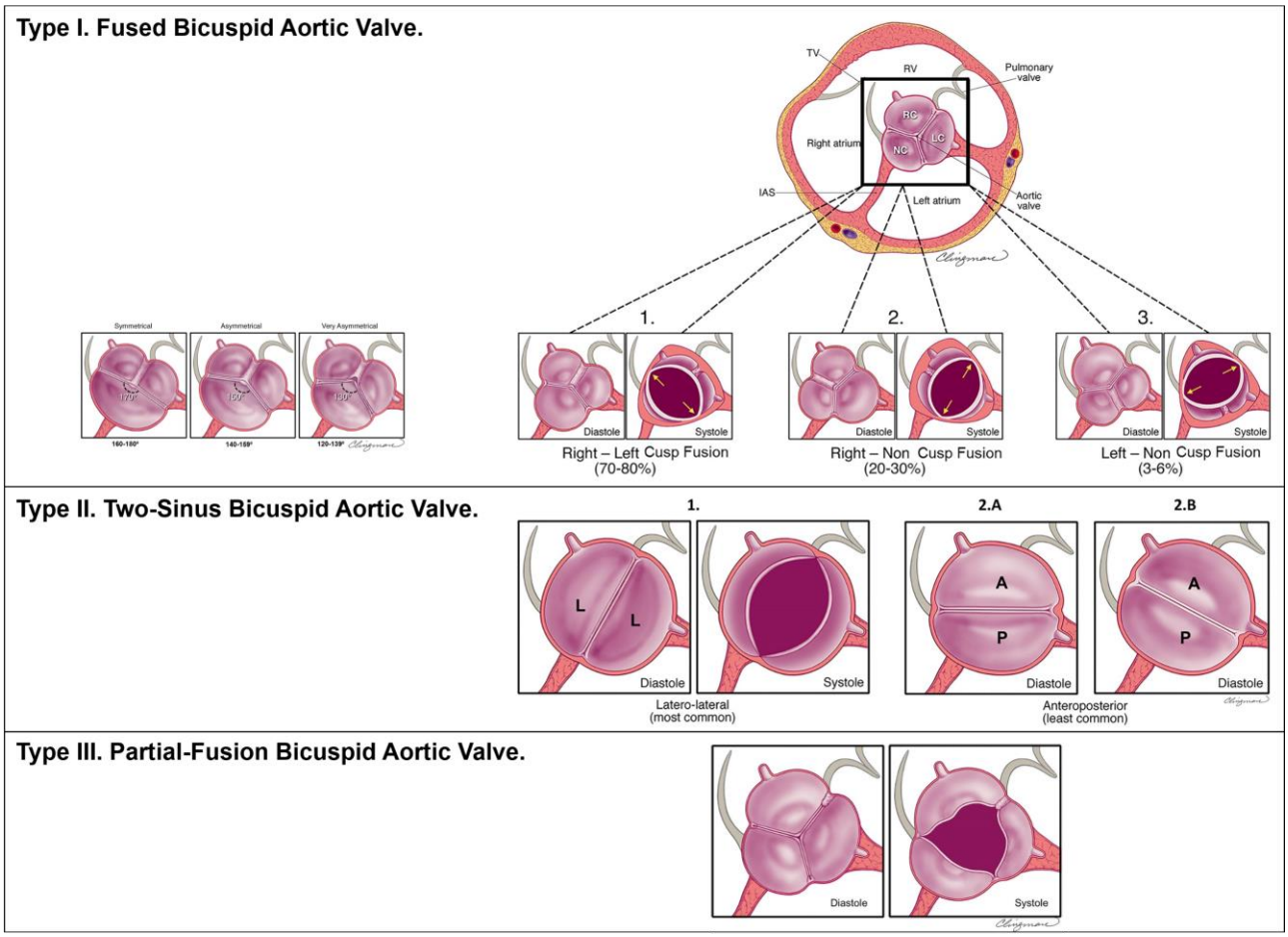


Figure 10. Collaborating centres.

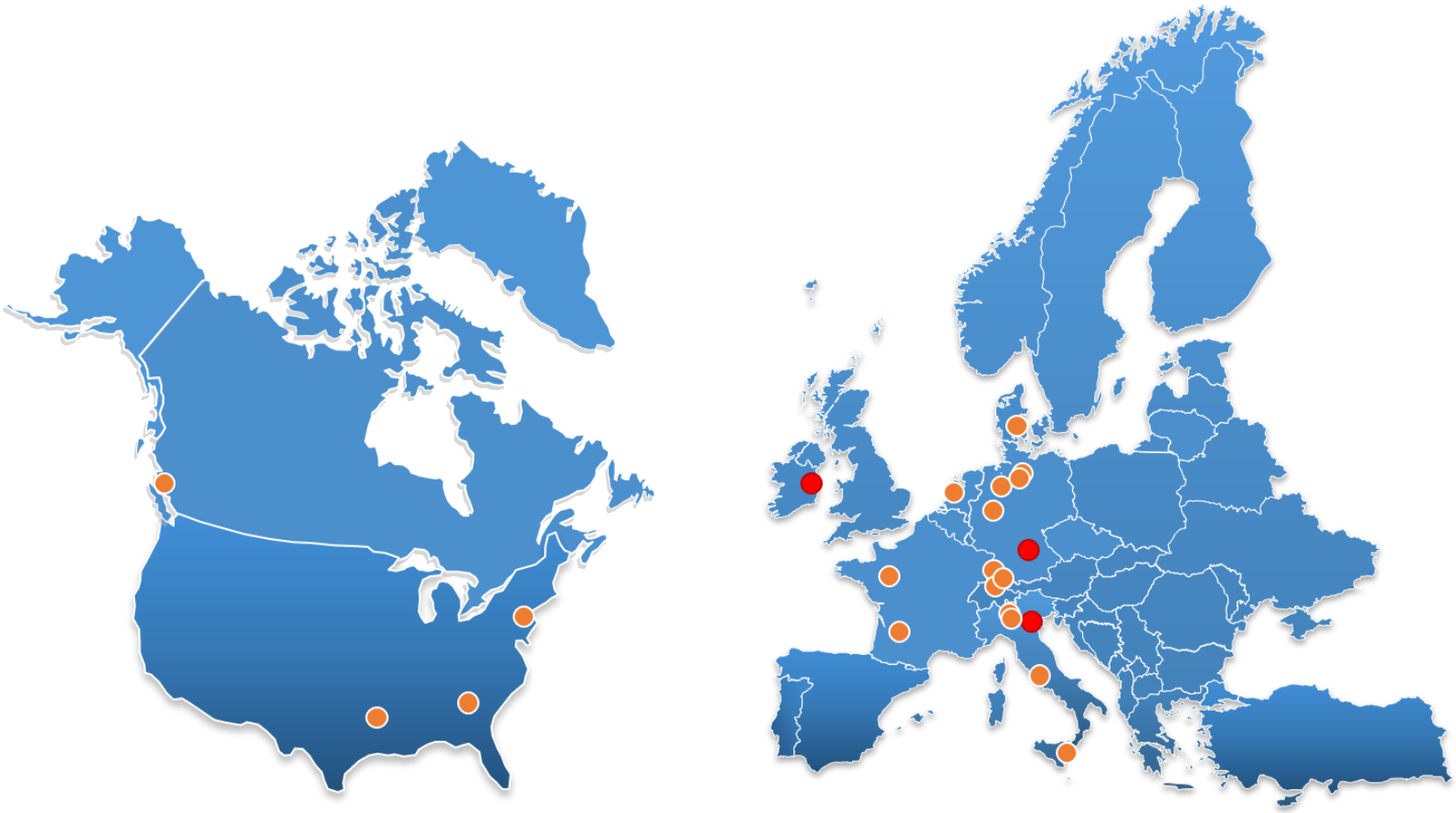
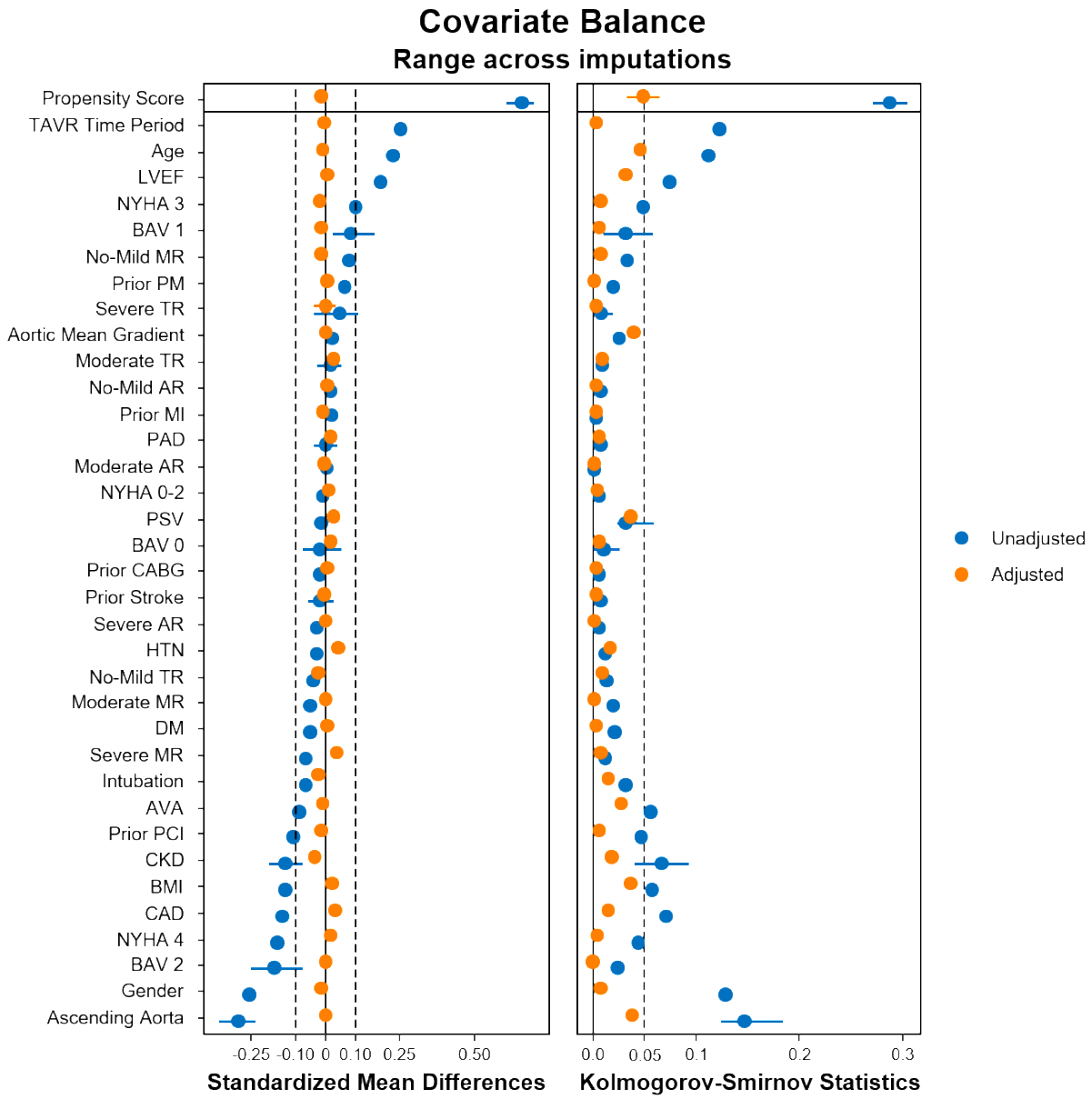


Figure 11. Balance between treatment groups before and after inverse probability of treatment weighting.



Balance statistics between treatment groups across 10 datasets generated by multiple imputation with chained equations before and after inverse probability of treatment weighting based on the propensity score. With respect to standardized mean difference the most commonly used conventional threshold to declare the achievement of a good balance between groups is 0.10. With respect to Kolmogorov-Smirnov statistics there is no strong consensus about the threshold to declare the achievement of a good balance. A very conservative 0.05 threshold was considered.

Figure 12. Distributional balance between treatment groups before and after inverse probability of treatment weighting.

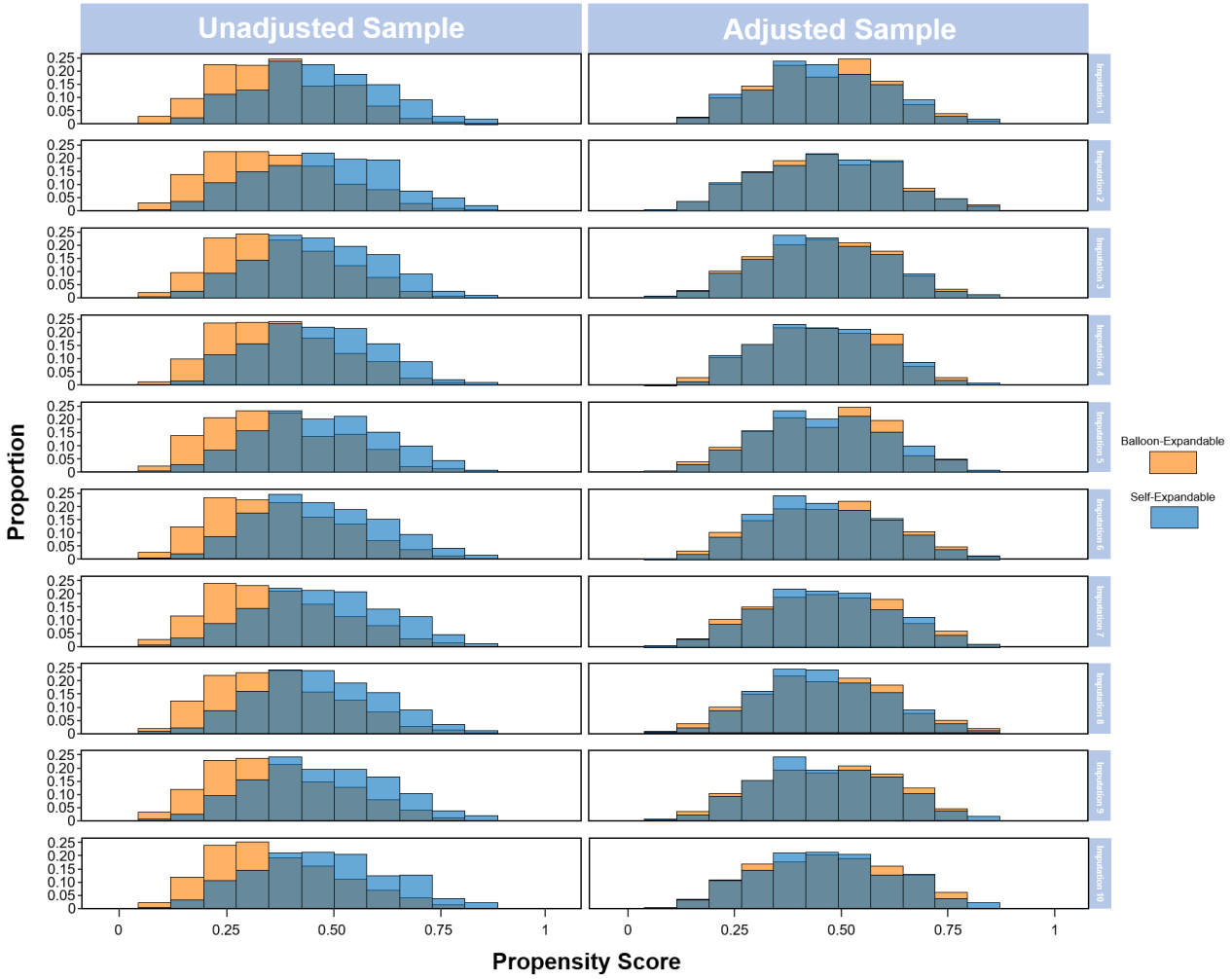
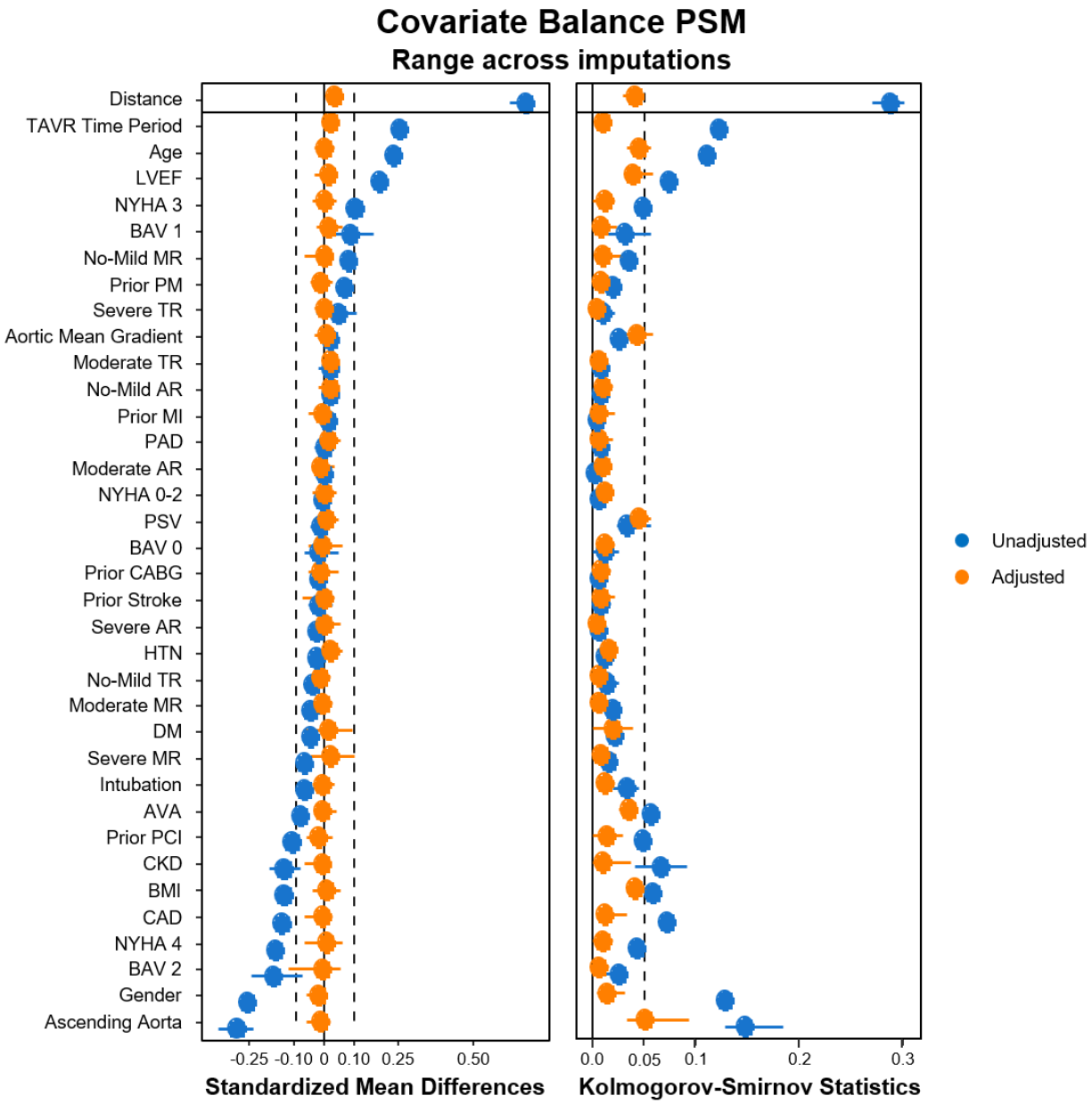


Figure 13. Balance between treatment groups before and after nearest neighbour propensity score matching.



Balance statistics between treatment groups across 10 datasets generated by multiple imputation with chained equations before and after inverse probability of treatment weighting based on the propensity score. With respect to standardized mean difference the most commonly used conventional threshold to declare the achievement of a good balance between groups is 0.10. With respect to Kolmogorov-Smirnov statistics there is no strong consensus about the threshold to declare the achievement of a good balance. A very conservative 0.05 threshold was considered.

Figure 14. Distributional balance between treatment groups before and after nearest neighbour propensity score matching.

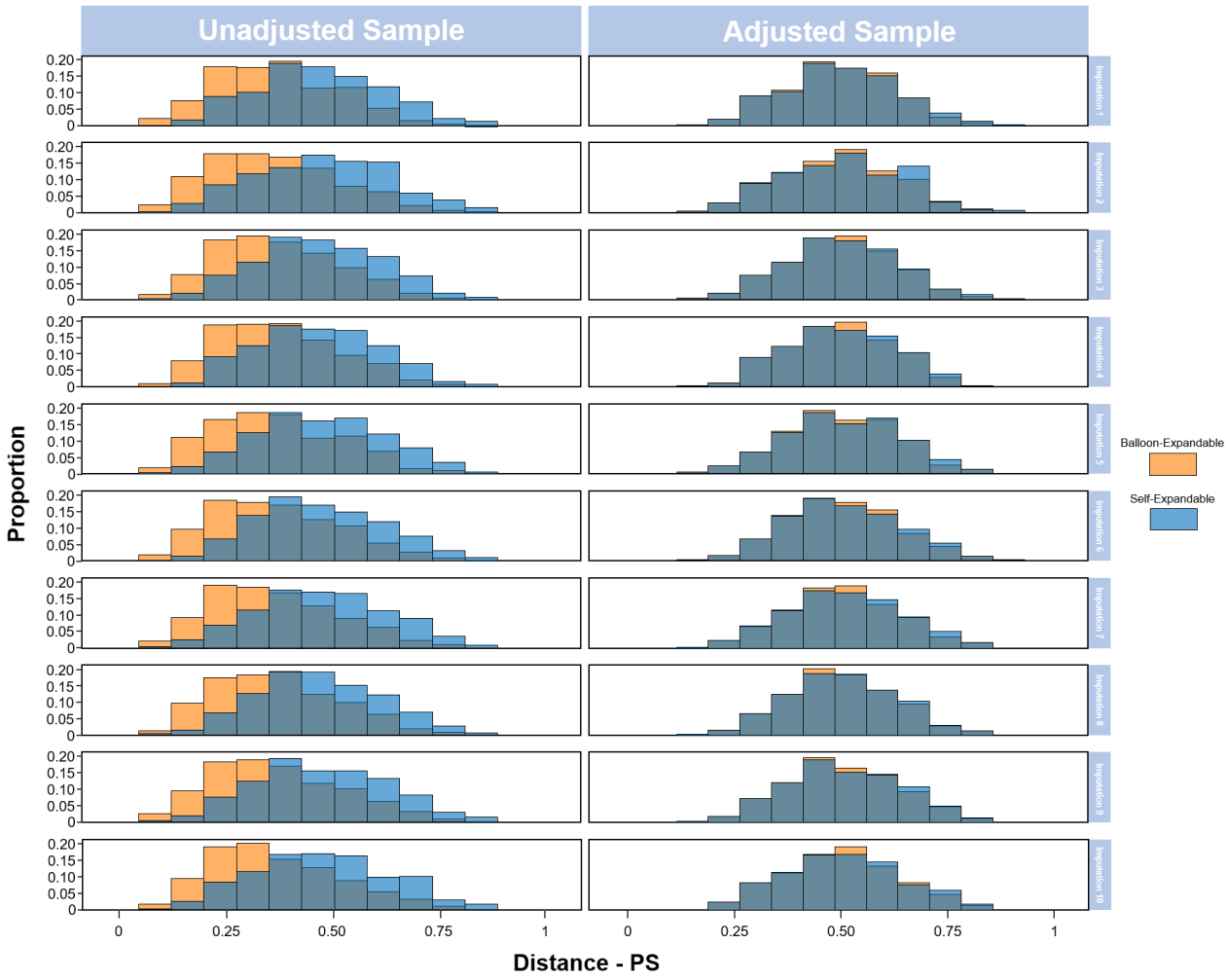
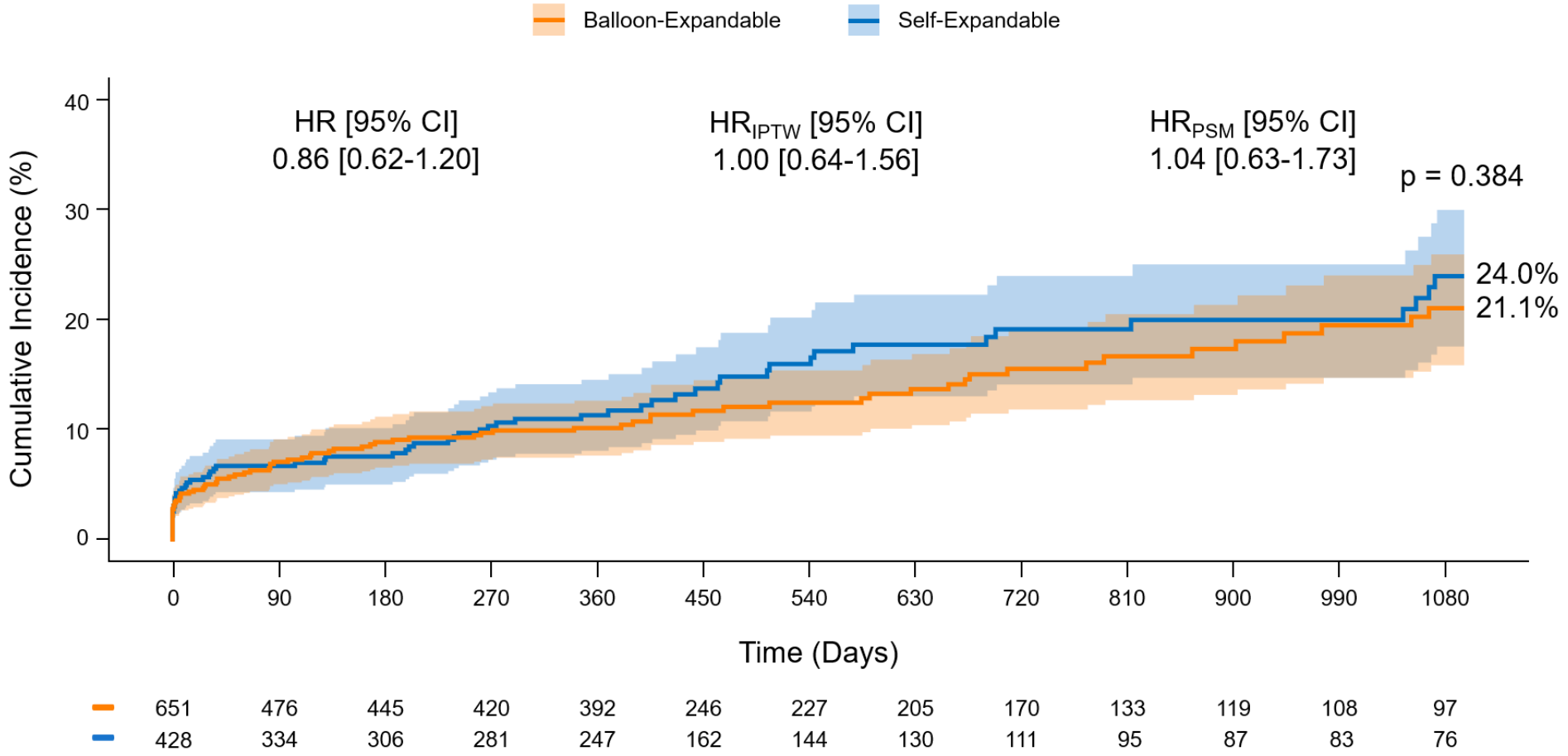


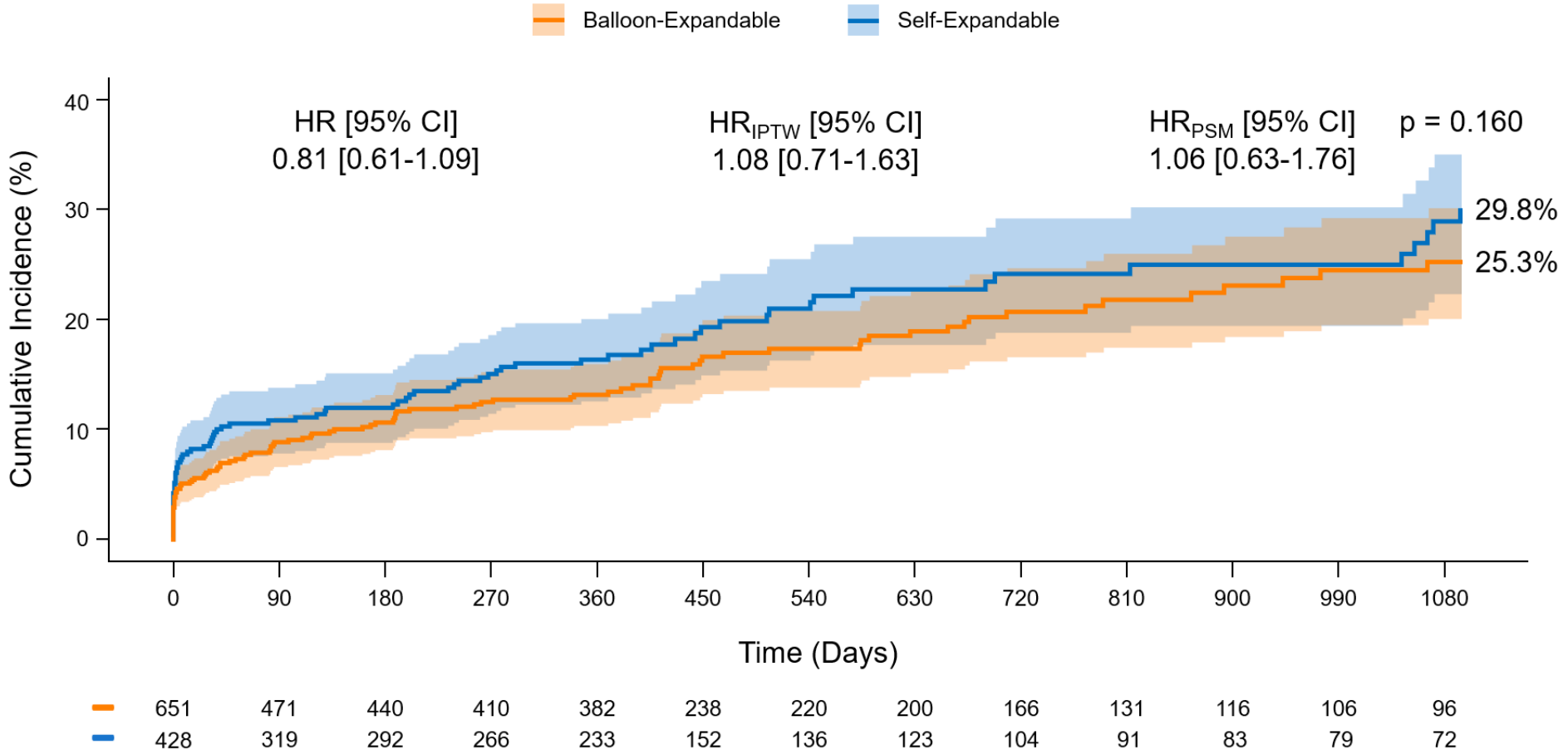
Figure 15. Death or stroke.



CI = Confidence Interval; HR = Hazard Ratio from standard proportional hazard regression models; HR_{IPTW} = Hazard ratios from multivariable mixed-effects models accounting for effect variations across participating centres, valve generation, and differences in procedural characteristics after inverse probability of treatment weighting on datasets produced by multiple imputation; HR_{PSM} = Hazard ratios from multivariable mixed-

effects models accounting for effect variations across participating centres, valve generation, and differences in procedural characteristics after propensity score matching on datasets produced by multiple imputation.

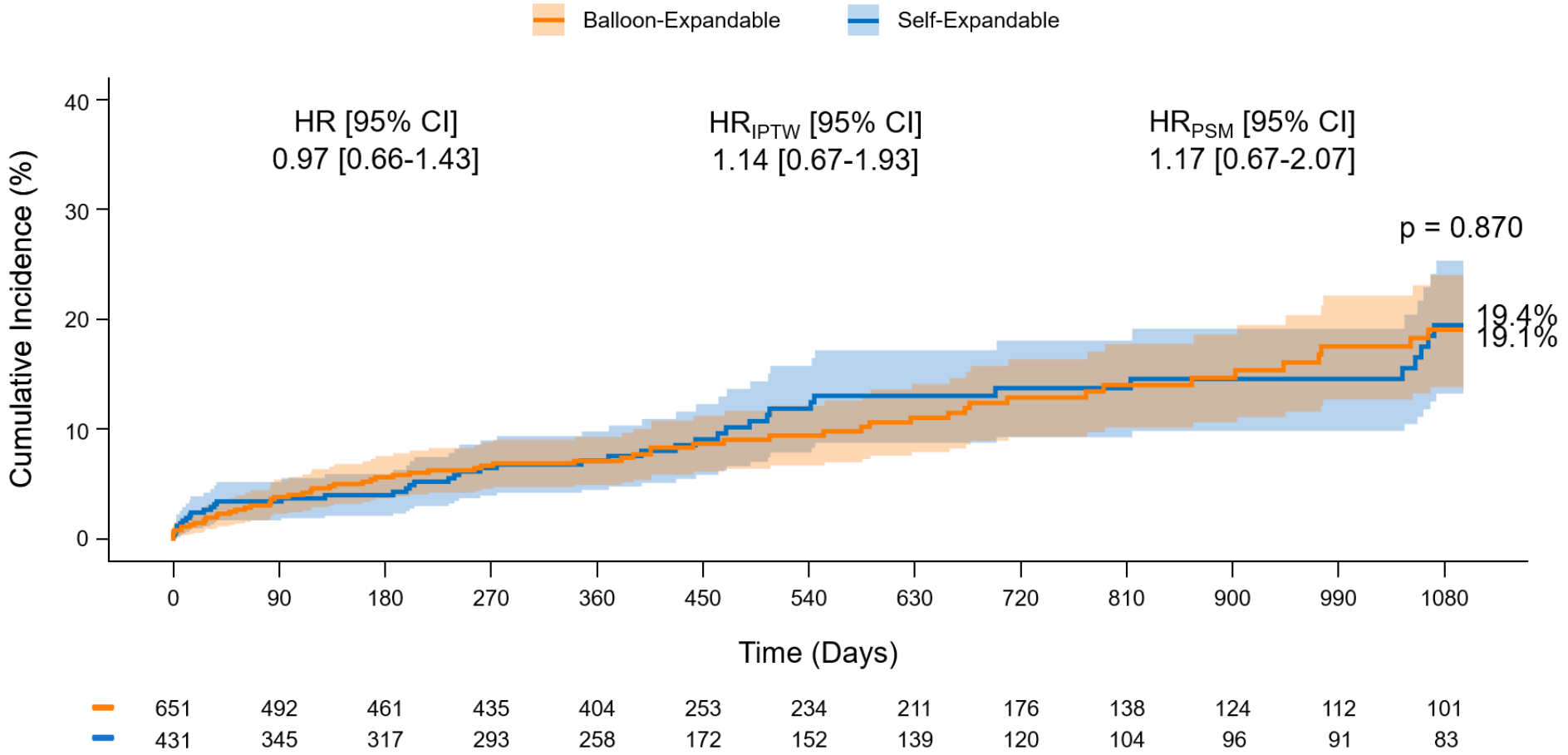
Figure 16. Death, stroke, repeat aortic valve replacement, or valve dysfunction.



CI = Confidence Interval; HR = Hazard Ratio from standard proportional hazard regression models; HR_{IPTW} = Hazard ratios from multivariable mixed-effects models accounting for effect variations across participating centres, valve generation, and differences in procedural characteristics after inverse probability of treatment weighting on datasets produced by multiple imputation; HR_{PSM} = Hazard ratios from multivariable mixed-effects models

accounting for effect variations across participating centres, valve generation, and differences in procedural characteristics after propensity score matching on datasets produced by multiple imputation.

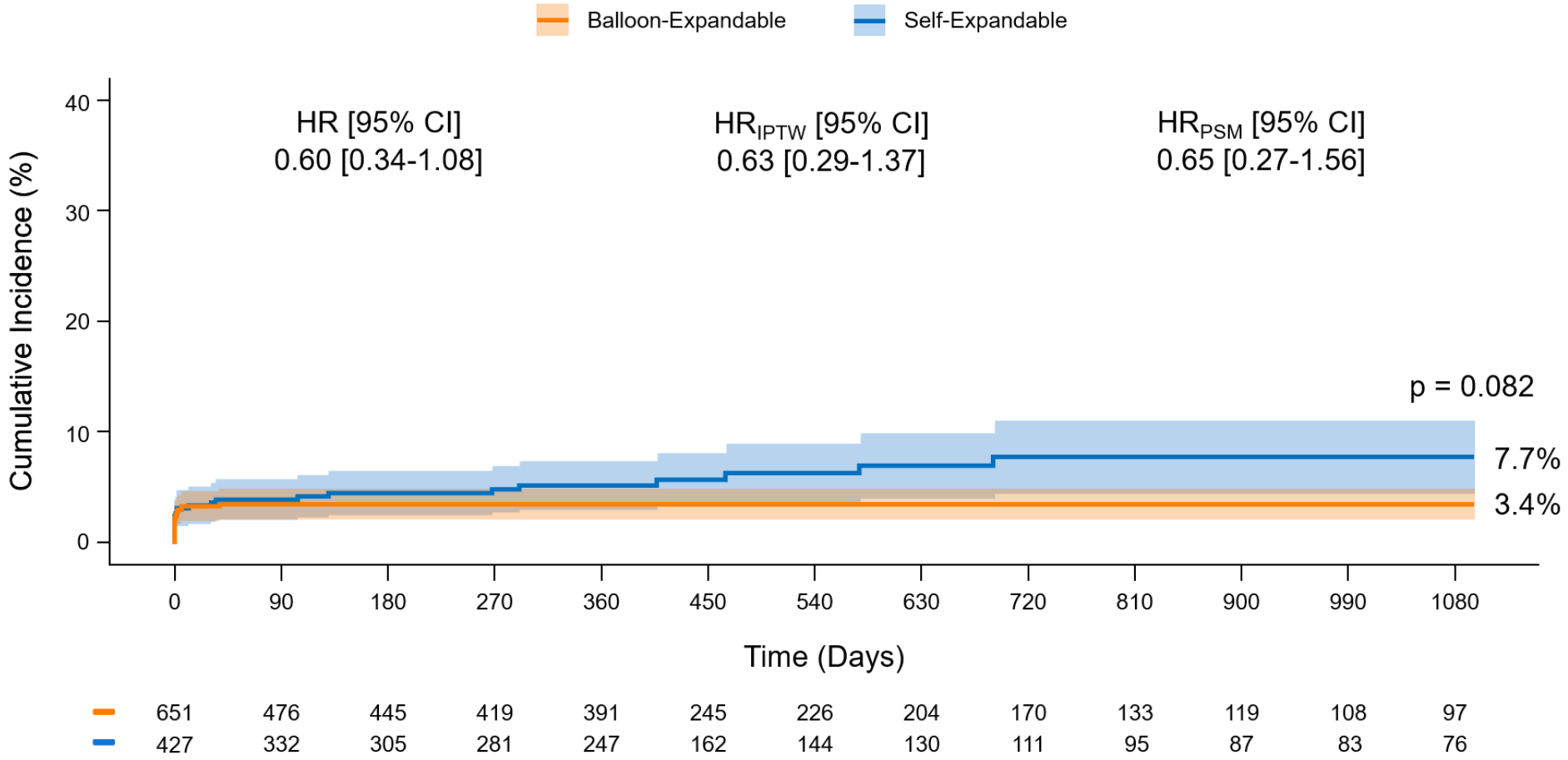
Figure 17. Death.



CI = Confidence Interval; HR = Hazard Ratio from standard proportional hazard regression models; HR_{IPTW} = Hazard ratios from multivariable mixed-effects models accounting for effect variations across participating centres, valve generation, and differences in procedural characteristics after inverse probability of treatment weighting on datasets produced by multiple imputation; HR_{PSM} = Hazard ratios from multivariable mixed-effects models

accounting for effect variations across participating centres, valve generation, and differences in procedural characteristics after propensity score matching on datasets produced by multiple imputation.

Figure 18. Stroke.



CI = Confidence Interval; HR = Hazard Ratio from standard proportional hazard regression models; HR_{IPTW} = Hazard ratios from multivariable mixed-effects models accounting for effect variations across participating centres, valve generation, and differences in procedural characteristics after inverse probability of treatment weighting on datasets produced by multiple imputation; HR_{PSM} = Hazard ratios from multivariable mixed-effects models

accounting for effect variations across participating centres, valve generation, and differences in procedural characteristics after propensity score matching on datasets produced by multiple imputation.