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ALTERNATIVE VERSUS PERCUTANEOUS TRANSFEMORAL ACCESS IN TAVI: PERIPROCEDURAL COMPLICATIONS AND FIVE-YEAR SURVIVAL IN A MULTICENTRE REGISTRY

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ABSTRACT

Introduction

Percutaneous transfemoral access is the reference route for transcatheter aortic valve implantation (TAVI), and the guidelines reserve the alternative routes for patients who are not suitable for it. The comparison between the two strategies is nevertheless burdened by confounding by indication, since patients who receive an alternative access are selected for an unfavourable vascular anatomy, and by the evolution of the technique over time. The present work assesses the periprocedural complications associated with the access route in an unselected regional cohort, the factors associated with the use of an alternative access and long-term survival.

Methods

We conducted a multicentre retrospective-prospective observational study including patients treated with TAVI for severe aortic stenosis between 2010 and 2022 in six centres in the Emilia-Romagna region, Italy. Patients were classified according to percutaneous transfemoral access or alternative access. The primary endpoint was a composite of periprocedural complications defined by the Valve Academic Research Consortium-2 criteria, comprising acute kidney injury, major bleeding, major vascular complication, cerebrovascular event within 30 days and the need for transfusion. Secondary endpoints were the individual components, the length of stay and periprocedural, 30-day and one-year mortality. Associations were explored with multivariable logistic regression adjusted for clinical characteristics, valve type and procedural era, and survival was estimated with the Kaplan-Meier method.

Results

A total of 1308 patients were included, 1051 treated through percutaneous transfemoral access and 257 through an alternative access. The primary composite endpoint occurred in 29.6% of patients with alternative access against 21.7% of those treated transfemorally, and the association remained significant after adjustment (odds ratio 2.10; $p = 0.003$). The excess was driven mainly by acute kidney injury, which occurred in 23.7% against 8.9% (adjusted odds ratio 3.28; $p < 0.001$) and for which alternative access was the strongest independent predictor, despite comparable baseline renal function.

The length of stay was also longer (median 8 against 7 days; $p < 0.001$) and periprocedural mortality higher (2.7% against 0.9%; $p = 0.025$), whereas the difference did not reach significance when in-hospital and 30-day deaths were considered together. Breaking the group down by individual route showed substantial heterogeneity, since the excess was concentrated in the thoracic routes, transapical and transaortic, whereas femoral access with surgical exposure did not differ from the percutaneous one. All-cause survival did not differ up to five years. The use of an alternative access was associated with peripheral artery disease, with previous coronary artery bypass grafting and, to a far greater extent, with the procedural era.

Conclusions

In this unselected multicentre cohort, alternative access was associated with an excess of periprocedural complications, driven mainly by acute kidney injury and persisting after adjustment, together with a longer stay and higher periprocedural mortality. The excess was not uniform within the group but concentrated in the approaches that require opening the chest. The observed cost was confined to the periprocedural window, with no detectable association with mortality up to five years.

SOMMARIO

Introduzione

L'accesso transfemorale percutaneo è la via di riferimento per l'impianto valvolare aortico transcatetere (TAVI), e le linee guida riservano le vie alternative ai pazienti che non vi risultano idonei. Il confronto fra le due strategie è tuttavia gravato dal confondimento per indicazione, poiché chi riceve un accesso alternativo è selezionato per un'anatomia vascolare sfavorevole, e dall'evoluzione della metodica nel tempo. Il presente lavoro valuta le complicanze peri-procedurali associate alla via di accesso in una coorte regionale non selezionata, i fattori associati alla scelta di un accesso alternativo e la sopravvivenza a distanza.

Metodi

È stato condotto uno studio osservazionale multicentrico, a raccolta retrospettiva e prospettica, che ha incluso i pazienti sottoposti a TAVI per stenosi aortica severa fra il 2010 e il 2022 presso sei centri della regione Emilia-Romagna. I pazienti sono stati classificati secondo l'accesso transfemorale percutaneo o alternativo. L'endpoint primario era un composito di complicanze peri-procedurali definite secondo i criteri del Valve Academic Research Consortium-2, comprendente danno renale acuto, sanguinamento maggiore, complicanza vascolare maggiore, evento cerebrovascolare entro 30 giorni e necessità trasfusionale. Erano endpoint secondari le singole componenti, la durata della degenza e la mortalità peri-procedurale, a 30 giorni e a un anno. Le associazioni sono state esplorate con regressione logistica multivariata aggiustata per caratteristiche cliniche, tipo di protesi ed epoca procedurale, e la sopravvivenza è stata stimata con il metodo di Kaplan-Meier.

Risultati

Sono stati inclusi 1308 pazienti, 1051 trattati per via transfemorale percutanea e 257 per via alternativa. L'endpoint composito primario si è verificato nel 29,6% dei pazienti ad accesso alternativo contro il 21,7% di quelli trattati per via transfemorale, e l'associazione è rimasta significativa dopo aggiustamento (odds ratio 2,10; p = 0,003).

L'eccesso è sostenuto prevalentemente dal danno renale acuto, presente nel 23,7% contro l'8,9% (odds ratio aggiustato 3,28; $p < 0,001$), del quale l'accesso alternativo è il predittore indipendente più forte, a fronte di una funzione renale basale sovrapponibile. Anche la degenza è risultata più lunga (mediana 8 contro 7 giorni; $p < 0,001$) e la mortalità peri-procedurale più elevata (2,7% contro 0,9%; $p = 0,025$), mentre la differenza non raggiunge la significatività considerando cumulativamente i decessi intraospedalieri o entro 30 giorni. La scomposizione per singola via documenta un'eterogeneità sostanziale, poiché l'eccesso si concentra nelle vie toraciche, transapicale e transaortica, mentre l'accesso femorale con esposizione chirurgica non differisce da quello percutaneo. La sopravvivenza per tutte le cause non differisce fino a cinque anni. Il ricorso a un accesso alternativo è risultato associato all'arteriopatia periferica, al pregresso bypass aortocoronarico e, in misura nettamente maggiore, all'epoca procedurale.

Conclusioni

In questa coorte multicentrica non selezionata l'accesso alternativo si è associato a un eccesso di complicanze peri-procedurali, sostenuto prevalentemente dal danno renale acuto e persistente dopo aggiustamento, cui si accompagnano una degenza più lunga e una mortalità peri-procedurale più elevata. L'eccesso non è uniforme all'interno del gruppo, ma si concentra negli approcci che comportano l'apertura del torace. Il costo osservato si esaurisce nella finestra peri-procedurale, senza che emerga un'associazione rilevabile con la mortalità fino a cinque anni.

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LIST OF ABBREVIATIONS

ACEF	Age, Creatinine and Ejection Fraction (score)
AKI	Acute Kidney Injury
AS	Aortic Stenosis
AVA	Aortic Valve Area
AVEN	Area Vasta Emilia Nord
BNP	B-type Natriuretic Peptide
BSA	Body Surface Area
CABG	Coronary Artery Bypass Grafting
CAVD	Calcific Aortic Valve Disease
CI	Confidence Interval
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CMR	Cardiac Magnetic Resonance
COPD	Chronic Obstructive Pulmonary Disease
CSA	Cross-Sectional Area
ECM	Extracellular Matrix
ECV	Extracellular Volume
eGFR	estimated Glomerular Filtration Rate
eNOS	endothelial Nitric Oxide Synthase
GLS	Global Longitudinal Strain
HR	Hazard Ratio
IQR	Interquartile Range
LDL	Low-Density Lipoprotein

LGE	Late Gadolinium Enhancement
LV	Left Ventricle
LVEF	Left Ventricular Ejection Fraction
LVOT	Left Ventricular Outflow Tract
MV	Mitral Valve
NYHA	New York Heart Association
OR	Odds Ratio
oxLDL	Oxidised Low-Density Lipoprotein
PAD	Peripheral Artery Disease
PCI	Percutaneous Coronary Intervention
SAVR	Surgical Aortic Valve Replacement
SFAR	Sheath to Femoral Artery Ratio
STJ	Sinutubular Junction
STS	Society of Thoracic Surgeons (risk score)
TAVI	Transcatheter Aortic Valve Implantation
TF	Transfemoral
TIA	Transient Ischaemic Attack
VARC	Valve Academic Research Consortium
VEC	Valvular Endothelial Cell
VIC	Valvular Interstitial Cell
VTI	Velocity-Time Integral

1. INTRODUCTION

1.1 Definition of Aortic Stenosis

Aortic stenosis (AS) is a disease of the aortic valve cusps that obstructs the outflow of the left ventricle (LV) (1). It results from a progressive fibrocalcific remodelling that thickens the cusps and restricts the systolic opening of the valve orifice (2).

The clinical relevance of the disease follows from a dissociation between the site of the lesion, which is confined to the valve cusps, and the site of the haemodynamic burden, which falls on the left ventricle as a pressure overload (3). No pharmacological treatment has been shown to prevent or stop valve calcification, and valve replacement, either surgical or transcatheter, remains the only treatment able to alter the natural history of the disease (2,4,5).

1.2 Epidemiology and Aetiology

1.2.1 Epidemiology

Aortic stenosis is the most common acquired valvular disease in Western countries (2) and the leading valve disorder requiring replacement (4). In its calcific form it affects approximately 12.6 million people worldwide and accounts for more than 100,000 deaths every year, and its prevalence is higher in high-income than in low- and middle-income countries (1). Age is the main determinant, since prevalence rises from 0.2% in the sixth decade to 9.8% among octogenarians (4), and in the elderly population the severe form affects about 3% of individuals, three quarters of whom are symptomatic (6). As the population ages, prevalence is expected to triple over the next forty years (7). Candidates for transcatheter aortic valve implantation (TAVI) in Europe and North America are estimated at around 290,000, with approximately 27,000 new cases every year (6).

1.2.2 Aetiology and Risk Factors

Three aetiological categories are recognised (1):

1. degenerative calcific aortic stenosis, which develops on a normal tricuspid valve or on a congenitally bicuspid valve and accounts for the large majority of cases in high-income countries (1);
2. congenital forms, comprising the unicuspid, bicuspid and quadricuspid variants (8);
3. rheumatic aortic stenosis, which retains epidemiological relevance where rheumatic disease is still endemic and is the predominant cause in low- and middle-income countries (1,3).

A congenitally bicuspid aortic valve is present in 1-2% of the world population (1) and accounts for 60% of the cases requiring valve replacement below the age of 70 years and for 40% of those above it (4).

Calcific disease of the aortic valve forms a continuum whose first stage is aortic sclerosis, a focal thickening of the cusps with mild calcification of an otherwise normal tricuspid valve, in the absence of significant valvular dysfunction. It affects about 25% of individuals older than 65 years and progresses to aortic stenosis at a rate of approximately 2% per year, and it is also recognised as a marker of increased atherosclerotic risk (1). Further factors that raise the risk of disease are older age, male sex, arterial hypertension, cigarette smoking, diabetes mellitus, ischaemic heart disease, high serum lipoprotein(a) concentrations and reduced renal function (1). The risk profile therefore overlaps substantially with that of atherosclerotic disease (1,9). Genetic determinants have also been described, among them mutations affecting NOTCH1 and members of the GATA transcription factor family (2).

1.3 Anatomy of the Aortic Root

1.3.1 The Aortic Valve Complex

The aortic root continues directly from the left ventricular outflow tract (LVOT) and extends from the basal attachment of the cusps to their peripheral attachment at the sinotubular junction. It is made up of the sinuses of Valsalva, the fibrous interleaflet triangles and the cusps. About two thirds of the circumference of its lower portion rest

on the muscular interventricular septum, while the remaining third is in fibrous continuity with the anterior leaflet of the mitral valve (10).

Within the root no single ring can be identified, but rather three circular rings and one crown-shaped ring. The cusps insert along the whole height of the root, and in three dimensions they take the configuration of a three-pointed crown. The base of the crown is the basal virtual ring, obtained by joining the basal attachment points of the cusps, while its apex corresponds to the sinotubular junction. The undifferentiated use of the term annulus has therefore been identified as a source of ambiguity, since its meaning changes according to which ring is being indicated (8,10) (Figure 1).

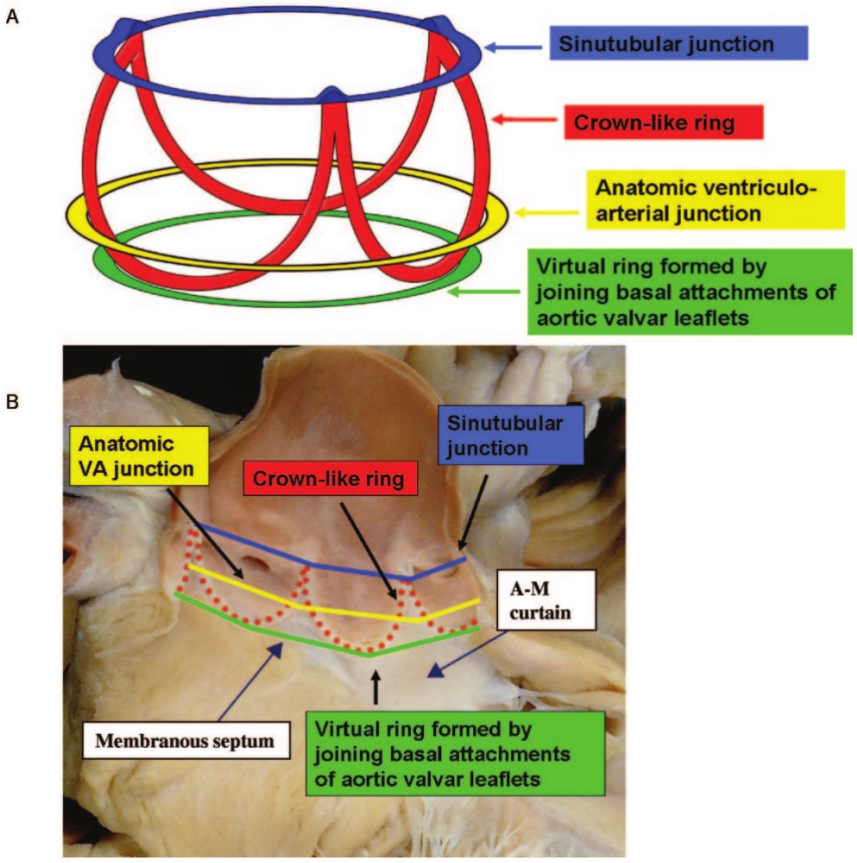


Figure 1. Three-dimensional arrangement of the aortic root.
(A) The root contains three circular rings, the sinotubular junction (blue), the anatomical ventriculo-arterial junction (yellow) and the virtual ring obtained by joining the basal attachments of the leaflets (green), while the leaflets are suspended within it as a semilunar crown (red). (B) The same arrangement in an anatomical specimen after removal of the leaflets. A-M = aortic-mitral; VA = ventriculo-arterial. Source: Piazza et al., 2008 – Circulation: Cardiovascular Interventions, p. 76 (10).

1.3.2 Geometry and Dimensions

The overall configuration of the root is that of a truncated cone, whose diameter at the sinotubular junction exceeds that of the basal virtual ring. It is a dynamic structure that changes between diastole and systole (10).

The basal virtual ring is oval rather than circular, so that the distance between the basal attachments of adjacent cusps averages about 26 mm on coronal reconstructions against about 23 mm on sagittal ones. Two-dimensional measurements obtained by echocardiography or aortography therefore do not intercept the true diameter of the outflow tract, but a tangential section of the root. To this variability is added that of the individual cusps, which are only exceptionally of equal size (10) (Figure 2).

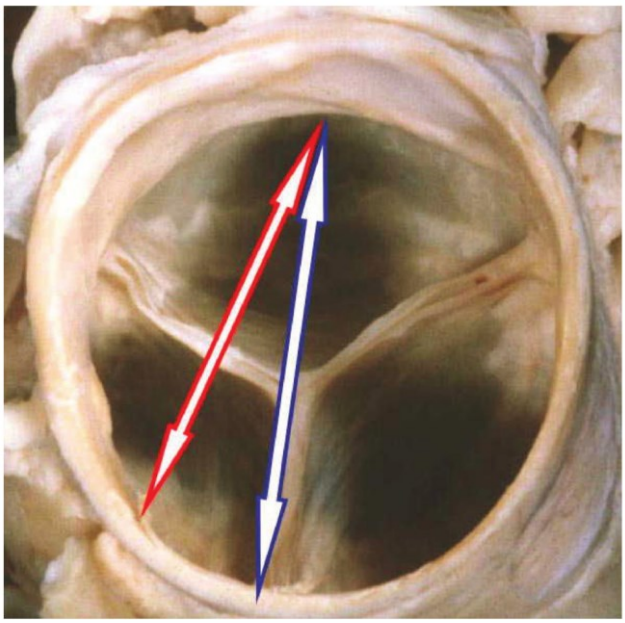


Figure 2. Basal short-axis view of the closed aortic valve.
The arrows illustrate the risk inherent in the two-dimensional measurement of the annulus: a measurement taken on the basal attachments of the leaflets does not cross the true diameter of the outflow tract, but cuts an oblique chord across it. Source: Piazza et al., 2008 – Circulation: Cardiovascular Interventions, p. 76 (10).

1.3.3 Relations with Adjacent Structures

The coronary ostia arise in most cases from the two anterior sinuses of Valsalva, immediately below the sinotubular junction. With respect to the plane of the basal attachments they lie on average 14 mm above it for the left ostium and 17 mm for the right one (10).

The interleaflet triangles, formed by the thinned fibrous walls of the aorta interposed between the sinuses, are extensions of the outflow tract that reach the sinotubular junction. The triangle between the right coronary and the non-coronary cusp is confluent with the membranous septum, and together with the right fibrous trigone forms the central fibrous body of the heart (10).

From these relations follows the proximity to the conduction system. The conduction axis pierces the membranous septum and emerges on the left side immediately below it. It then runs along the crest of the interventricular septum in close relation with the base of the interleaflet triangle that separates the non-coronary cusp from the right coronary cusp (8,10).

1.3.4 Anatomical Variants

Congenital malformations of the root are described by counting the sinuses present, distinguishing trisinuate, bisinuate and, more rarely, quadrisinuate forms (8). The functionally bileaflet valve, present in 1-2% of the general population (1), accounts for almost nine tenths of all congenitally malformed roots. Its defining element is the fusion of two cusps, with formation of a raphe and hypoplasia of the corresponding interleaflet triangle, most commonly between the right and left coronary cusps (8).

A particular geometry follows from this arrangement, since the asymmetry between the fused cusps and the third cusp, together with hypoplasia of the interleaflet triangle, tilts the plane of the valve orifice relative to the axis of the ascending aorta more than is seen in the normal root (8) (Figure 3).

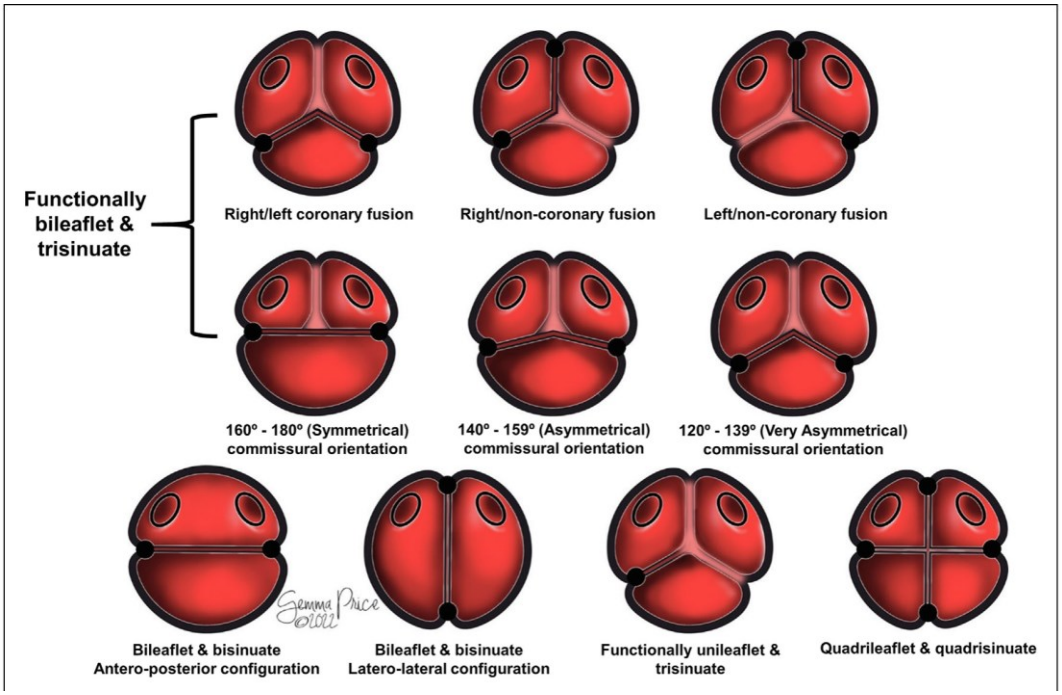


Figure 3. Classification of the congenitally malformed aortic root.
The description becomes simpler when the root is defined in terms of the number of leaflets, sinuses and interleaflet triangles: the figure shows the functionally bileaflet and trisinuate variants according to the pair of fused leaflets and to commissural orientation, the bileaflet and bisinuate variants, the functionally unileaflet variant and the quadrileaflet, quadrisinuate root. Source: Tretter et al., 2023 – The Annals of Thoracic Surgery, p. 9 (8).

1.4 Pathophysiology of Calcific Aortic Stenosis

1.4.1 The Initiation Phase

Calcific aortic stenosis was historically interpreted as the passive consequence of the mechanical trauma produced by repeated valve closure, that is as a purely degenerative process (1). Current evidence has changed that reading, since it is a biologically active process that shares many mechanisms with atherosclerosis. Among these are endothelial dysfunction, infiltration by immune cells, myofibroblastic and osteoblastic differentiation and, finally, calcification (1,2,9).

The aortic cusp is covered on both sides by valvular endothelial cells (VECs), while the interstitium is populated mainly by valvular interstitial cells (VICs) (2). The process is conventionally divided into an initiation phase, marked by injury and inflammation, and a propagation phase, dominated by calcification (2,5).

Mechanical stress and oscillatory shear stress cause dysfunction of the endothelial layer, with consequent deposition of lipoproteins and infiltration by immune cells. The result

is a chronic inflammation that can be documented long before calcification appears (2). Oxidative stress promotes the formation of oxidised low-density lipoproteins, which induce apoptosis of the VICs and amplify the recruitment of immune cells. Localised cell death leads to the release of extracellular vesicles containing calcium-phosphate complexes, which form hydroxyapatite crystals acting as nucleation sites for macrocalcification. This in turn triggers a more pronounced immune response, and a vicious circle is established (2) (Figure 4).

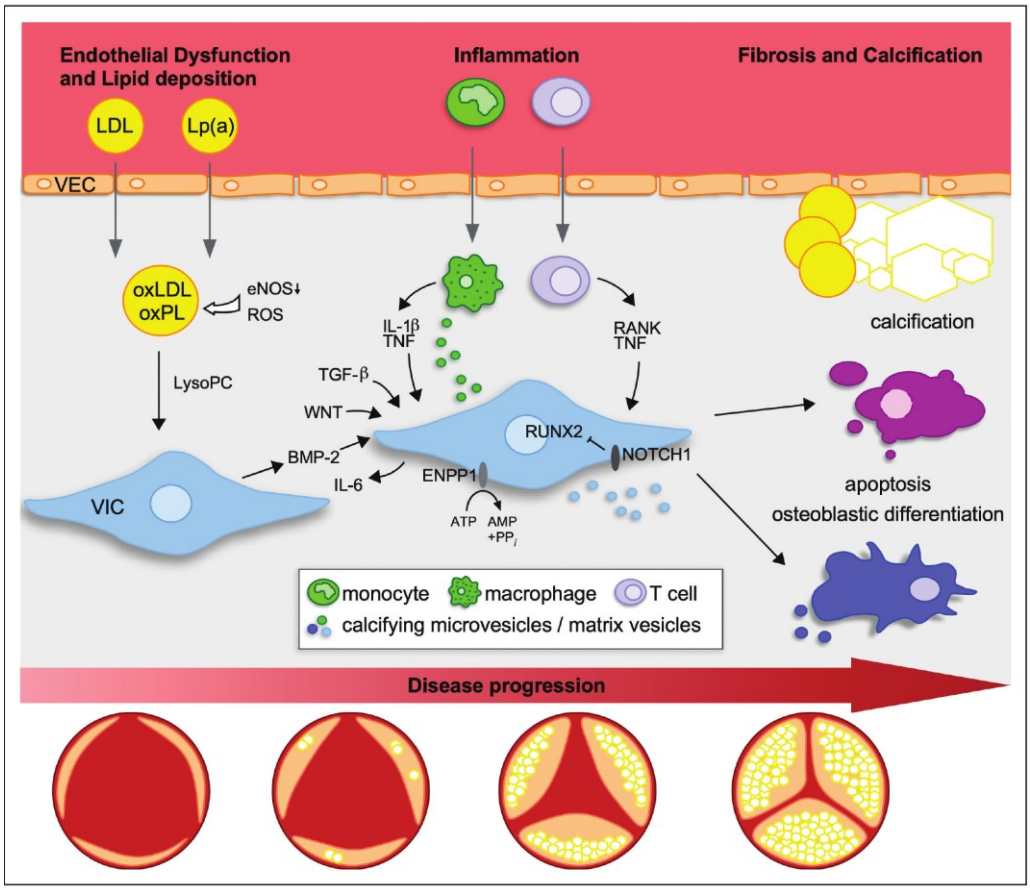


Figure 4. Stages of calcific aortic valve disease.
The process unfolds through endothelial dysfunction with lipid deposition, then inflammation, fibrosis and calcification, with progressive reduction of valve opening (lower panels). Lp(a) = lipoprotein(a); lysoPC = lysophosphatidylcholine; oxPL = oxidised phospholipids; ROS = reactive oxygen species. Source: Goody et al., 2020 – Arteriosclerosis, Thrombosis, and Vascular Biology, p. 887 (2).

1.4.2 The Propagation Phase and Molecular Pathways

In the propagation phase calcification becomes the dominant process and progressively independent of immune cells. The key step is the differentiation of the VICs towards myofibroblastic and osteoblastic phenotypes, initially regulated by cytokines of immune origin. The main molecular pathways involved are the RANK/RANKL/osteoprotegerin

axis, the Wnt/β-catenin pathway and the factors BMP-2 and Runx2, whereas the Notch1 pathway has a protective effect (2).

Despite the identification of these targets, no treatment able to prevent valve calcification is available today (2,5). The distinction between the two phases nevertheless defines a window of time, because it is in the early phase, potentially still modifiable, that a pharmacological treatment would have some chance of affecting progression. Traditional markers, such as rising gradients and a falling valve area, do not capture that phase well, hence the interest in more sensitive indicators such as the quantification of valve calcification (2,5,9).

1.4.3 Haemodynamic Consequences and Ventricular Remodelling

Progressive fibrocalcific remodelling reduces the systolic opening and obstructs ventricular outflow, with a progressive rise in transvalvular velocity from the normal value of about 1.0 m/s (1,2).

Pressure overload grows with the severity of the obstruction, and the changes in the ventricle do not all appear at the same time. Left atrial dilatation and impaired relaxation are already seen in moderate stenosis, whereas concentric hypertrophy develops only after the stenosis has become severe (11). The adaptive mechanisms, which serve to reduce wall stress and to maintain cardiac output, consist precisely of hypertrophy and dilatation of the chamber. These compensatory phenomena are followed by maladaptive changes made of reactive fibrosis, microvascular ischaemia and cell loss followed by replacement fibrosis, and these substantially impair ventricular function. Reactive interstitial fibrosis is probably reversible, whereas focal replacement fibrosis is not and is preceded by the appearance of diffuse fibrosis (11). The fall in left ventricular ejection fraction (LVEF) is the late consequence of this process.

Although it is a powerful prognostic indicator, it reflects the complete exhaustion of the compensatory mechanisms and lacks sensitivity in documenting myocardial damage that has already occurred (3). Adverse cardiac remodelling is in fact the main determinant of prognosis in degenerative valve disease (3).

From this limitation comes the interest in markers able to document maladaptive changes early, before global systolic function declines (3).

1.5 Clinical Presentation

1.5.1 Symptoms

Aortic stenosis runs an asymptomatic course until the obstruction limits the physiological rise in cardiac output during exercise. The presenting symptoms are reduced exercise tolerance, exertional dyspnoea and dizziness or syncope, while the classical triad of heart failure, syncope and angina is uncommon outside end-stage disease (1).

Clinical recognition is made difficult by the poor specificity of symptoms in the elderly and by the limited accuracy of physical examination, which allows neither the diagnosis to be excluded nor its severity to be graded (1).

1.5.2 Physical Examination

The findings typical of aortic stenosis on physical examination are a high-pitched midsystolic ejection murmur at the cardiac base radiating to the vessels of the neck and a single and soft second heart sound. To these is added a carotid pulse of reduced amplitude and slow upstroke, described as parvus et tardus (1,4). The murmur is usually heard at the upper right sternal border and in most cases has an intensity of 3/6 or more. In patients with a low cardiac output it may instead be softer, extending into late systole with a late peak (1,12).

A slow and reduced carotid upstroke has a specificity of 100% for severe aortic stenosis, but a sensitivity of 12% (1). Taken as a whole, the examination is reliable neither for identifying the disease nor for estimating its severity (1), and about half of the patients who might benefit from intervention are estimated not to be identified on clinical examination alone (12). Clinical suspicion must therefore be confirmed systematically by echocardiography (12).

1.5.3 Electrocardiogram

The electrocardiogram allows neither the diagnosis nor the quantification of aortic stenosis. It is nevertheless a low-cost and widely available examination, which makes it possible to recognise the signs of left ventricular overload even where advanced imaging is not available or not applicable (13,14). The first of the three findings looked

for is left ventricular hypertrophy, which can be assessed by the Sokolow-Lyon voltage criteria, the Cornell voltage-duration product and the Romhilt-Estes criteria. The second is the pattern of left ventricular strain, defined by T-wave inversion in the lateral leads from V4 to V6. The third is made of intraventricular conduction disturbances, in particular bundle branch block (13–15).

Their detection carries prognostic meaning, since in asymptomatic aortic stenosis electrocardiographic strain is associated with an increased risk of myocardial infarction and left ventricular hypertrophy with an increased risk of heart failure and of valve replacement (14). Among patients referred for valve replacement, strain and bundle branch block identify subjects who are older, in a more advanced NYHA functional class and with more advanced myocardial disease on echocardiography, and they are associated with a higher incidence of major cardiac events during follow-up (13).

In the candidate for transcatheter implantation the prognostic meaning of electrocardiographic hypertrophy is less clear-cut and varies with the criterion used, and the finding should therefore be interpreted within the clinical context and not on its own (15).

1.6 Diagnostic Assessment

1.6.1 Transthoracic Echocardiography

Transthoracic echocardiography is the first-line method for the diagnosis and the quantification of aortic stenosis (16,17). The principle of the examination is that the velocity of blood across the valve rises as the stenosis becomes more severe, which makes it the parameter most directly linked to the disease and the strongest predictor of clinical events (17). The haemodynamic assessment rests on three parameters: peak transvalvular velocity, mean transvalvular pressure gradient and aortic valve area (AVA) (17).

From the velocity the simplified Bernoulli equation gives the pressure difference that the ventricle must generate to drive the blood past the obstruction. The gradient grows with the square of the velocity, and the coefficient 4 summarises the density of blood and the conversion of the units of measurement (17):

$$\Delta P = 4v^2$$

The peak gradient corresponds to the single instant of maximum velocity, whereas the mean gradient is the average of the instantaneous gradients across the whole ejection and is obtained by tracing the contour of the velocity curve. This is the value that must always be reported, and it cannot be derived from the mean velocity (17).

Velocity and gradient depend on flow, so that a ventricle which ejects little blood may show low values even with a very narrow valve, while a high cardiac output raises them independently of the valve. Reversible causes of increased flow, among them fever, anaemia, hyperthyroidism and arteriovenous shunts for dialysis, must therefore be excluded before a high gradient is attributed to the stenosis (17). A measure of the area, which does not depend on flow, is therefore also needed. The continuity equation applies to the valve the principle that all the blood crossing the left ventricular outflow tract then crosses the stenotic orifice. The valve area is obtained from the cross-sectional area (CSA) of the outflow tract, calculated from its diameter on the assumption of a circular shape, and from the velocity-time integrals (VTI) measured at the two points (17):

$$AVA = (CSA_{LVOT} \times VTI_{LVOT}) / VTI_{AV}$$

Transvalvular velocity is recorded with continuous-wave Doppler from several acoustic windows, apical, right parasternal and suprasternal, taking as peak velocity the highest value obtained. Misalignment between the ultrasound beam and the stenotic jet leads to underestimation, which the quadratic relation amplifies in the gradient. The diameter of the outflow tract is measured in mid-systole on the parasternal long-axis view, from inner edge to inner edge. Velocity in the same tract is recorded instead from an apical approach with pulsed-wave Doppler, with the sample volume placed immediately upstream of the flow acceleration region (17) (Figure 5).

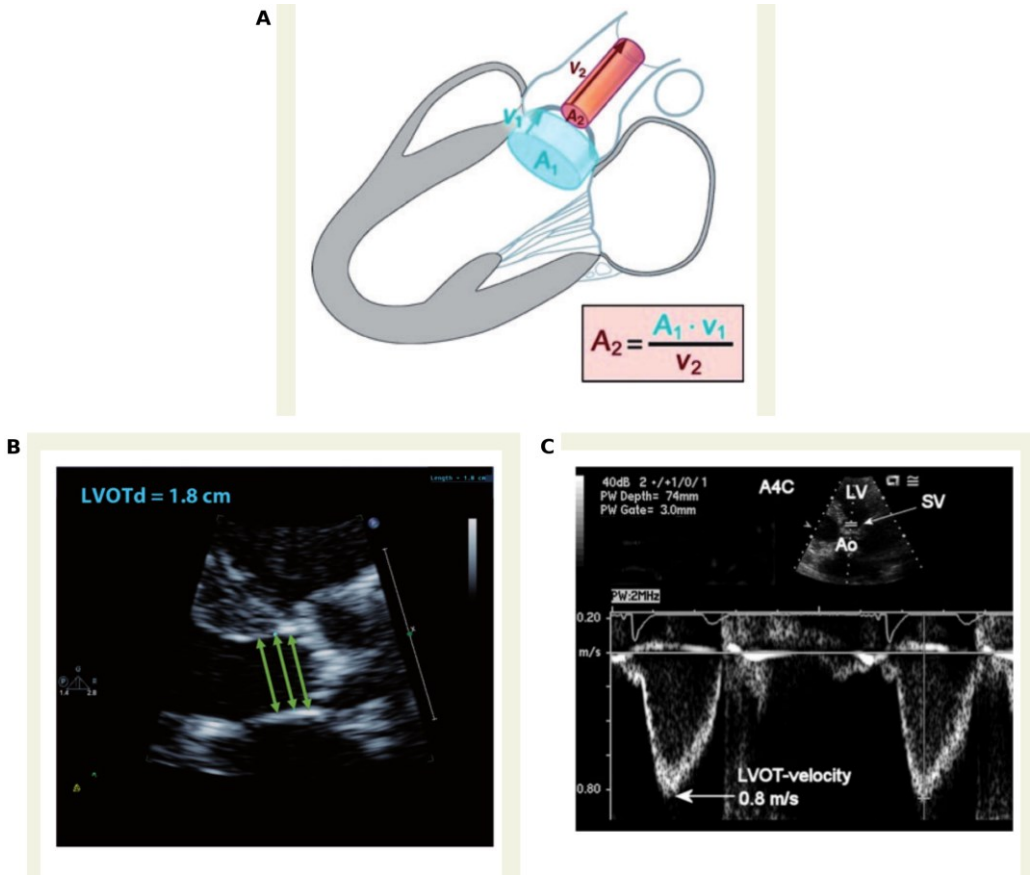


Figure 5. Principles of the echocardiographic quantification of aortic stenosis.
(A) Scheme of the continuity equation: the stroke volume crossing the outflow tract (area A1, velocity v1) equals the one crossing the stenotic orifice (area A2, velocity v2), from which A2 = A1 · v1 / v2. (B) Measurement of the diameter of the outflow tract in a zoomed parasternal long-axis view, from black-white interface to black-white interface. (C) Recording of the velocity in the outflow tract with pulsed-wave Doppler in the apical view. A4C = apical four-chamber; Ao = aorta; LVOTd = diameter of the outflow tract; SV = sample volume. Source: Baumgartner et al., 2017 – European Heart Journal Cardiovascular Imaging, pp. 262-263 (17), modified.

Measurement of the diameter is the weak point of the whole calculation, since it is squared to obtain the area and its variability, which is 5-8%, becomes the largest source of potential error in the continuity equation (17). When that measurement is unreliable, the ratio between the velocity-time integral of the outflow tract and that of the transvalvular jet is used, in which the diameter does not appear and in which a value of 0.25 or less indicates severe stenosis (17).

1.6.2 Severity Criteria and Haemodynamic Classification

The main criteria for severe stenosis are a valve area below 1.0 cm², a peak velocity of 4.0 m/s or more and a mean gradient of 40 mmHg or more. The presence of any one of them points to severe stenosis, and agreement between all of them is desirable (1,16,17) (Table 1).

Parameter	Sclerosis	Mild	Moderate	Severe
Peak velocity (m/s)	≤ 2.5	2.6–2.9	3.0–4.0	≥ 4.0
Mean gradient (mmHg)	–	< 20	20–40	≥ 40
AVA (cm²)	–	> 1.5	1.0–1.5	< 1.0
Indexed AVA (cm²/m²)	–	> 0.85	0.60–0.85	< 0.6
Dimensionless index	–	> 0.50	0.25–0.50	< 0.25

Table 1. Echocardiographic criteria for grading the severity of aortic stenosis.
AVA = aortic valve area. Source: Baumgartner et al., 2017 – European Heart Journal Cardiovascular Imaging (17), adapted.

In patients with an unusually small or large body surface area, indexing of the valve area has been proposed, with a threshold of 0.6 cm²/m² for severe stenosis, although its role remains debated and retains relevance mainly in short adults. Arterial hypertension can alter peak velocity and mean gradient and should be recorded at every examination, since the assessment should ideally be made under controlled blood pressure (17).

1.6.3 Discordant Low-Flow, Low-Gradient Phenotypes

Classification is straightforward when velocity, gradient and valve area agree, and becomes problematic when they diverge. A patient with a reduced transvalvular flow volume, defined by a stroke volume index (SVi) below 35 mL/m², may in fact have a severe stenosis with a reduced valve area alone, without a high velocity or gradient. Before the discordance is attributed to a specific phenotype, spurious causes must be excluded, in particular underestimation of the area of the outflow tract (17).

Of the two conditions distinguished, the first is the low-flow, low-gradient form with reduced ejection fraction, in which low-dose dobutamine stress echocardiography separates truly severe stenosis from pseudo-severe stenosis, where the reduced area reflects the inability of the ventricle to open the valve completely. The examination also documents contractile reserve, whose absence predicts an unfavourable prognosis. The second is the form with preserved ejection fraction, which is harder to interpret and in

which severity must be established by combining several methods, among them the computed tomography quantification of the valvular calcium burden (17).

1.6.4 Transoesophageal and Three-Dimensional Echocardiography

Transoesophageal echocardiography allows direct planimetry of the valve orifice as an alternative to the Doppler estimate, which is useful when Doppler measurements cannot be obtained or are unreliable. The three-dimensional approach gives a more accurate definition of the geometry of the outflow tract, overcoming the assumption of circularity implicit in the two-dimensional calculation of the cross-sectional area (17,18).

Besides the parameters of severity, echocardiography allows longitudinal systolic function to be assessed at an early stage. Global longitudinal strain (GLS) of the left ventricle, measured with speckle-tracking as the average longitudinal deformation of the ventricular segments, has proved a sensitive marker of systolic dysfunction. In patients with severe stenosis and an ejection fraction above 50% a value below 14.7% is associated with a 2.5-fold higher risk of death (3).

1.6.5 Computed Tomography

Computed tomography has two distinct purposes in aortic stenosis, to settle severity when the echocardiographic findings are discordant and to plan transcatheter implantation (1,19,20). In the first case the valvular calcium burden is quantified, a measure that is independent of the flow state and therefore not subject to the limitations of the Doppler parameters in low-flow forms (1,19). Quantification can be performed in two ways, of which the first is the calcium score, obtained on a scan without contrast medium and expressed in Agatston units, which is zero in a normal valve and indicates severe stenosis above 2000 in men and above 1300 in women. It is not useful, however, for following the progression of the disease over time (1).

The calcium volume indexed to the annular area is obtained on contrast-enhanced computed tomography angiography and indicates severe stenosis above 122 mm^3/cm^2 in men and above 61 mm^3/cm^2 in women (19). The two measures correlate closely with each other and with peak transaortic velocity (19).

1.6.6 Cardiac Magnetic Resonance

The strength of cardiac magnetic resonance is the tissue characterisation of the myocardium, which covers fibrosis and inflammation as well as perfusion and energetics, so that it works as a virtual histology in vivo. Quantification of the extracellular volume by T1 mapping and identification of replacement fibrosis by late gadolinium enhancement are its main tools (3).

1.6.7 Biomarkers

Their clinical interest comes from the ability to predict the onset of symptoms and clinical events before and after valve replacement, with incremental value over the classical echocardiographic criteria in risk stratification (21). Their use belongs to the same perspective as the imaging markers of myocardial damage, that is to identify damage before a fall in ejection fraction makes it manifest and irreversible (3,22).

The main classes investigated are the natriuretic peptides (BNP and NT-proBNP), the cardiac troponins, the markers of tissue and systemic inflammation and further molecules such as ST2, GDF-15 and galectin-3. Troponins I and T are cardiac-specific components of the contractile apparatus of the cardiomyocyte, and their rise in serum has traditionally been referred to cell necrosis with degradation of the contractile filaments. It has been shown, however, that they are also present in cytosolic pools and that smaller amounts may be released whenever the cell membrane loses its integrity (21).

1.7 Natural History and Timing of Intervention

1.7.1 Disease Progression

Aortic stenosis is a slowly progressive chronic disease, and once a transvalvular velocity of 2 m/s has been passed progression to the severe form usually takes place within ten years. The recommended surveillance intervals are 3-5 years for the mild form, 1-2 years for the moderate form and 6-12 months for the severe form (1).

Among patients with moderate stenosis followed over time with repeated echocardiograms, almost half progress to the severe form within little more than four

years. The speed of valvular progression nevertheless predicts only weakly the speed of the myocardial changes (11).

1.7.2 Staging of Extravalvular Cardiac Damage

Pressure overload does not stop at the left ventricle, since as the disease progresses its consequences extend to the left atrium, to the pulmonary circulation and to the right heart. The quantification of myocardial damage has been formalised in a classification by stages based on the extent of the extravalvular cardiac damage detectable on echocardiography. Five stages are identified, from the absence of extravalvular damage (stage 0) to left ventricular damage (stage 1), damage to the left atrium or the mitral valve (stage 2), damage to the pulmonary circulation or the tricuspid valve (stage 3) and right ventricular damage (stage 4) (22).

The staging was validated in the population of the PARTNER 2 trials, in which most patients already had damage extending beyond the left ventricle at the time of valve replacement. One-year mortality after the procedure rose progressively across the stages, from 4.4% in stage 0 to 24.5% in stage 4, and the extent of cardiac damage proved an independent predictor of mortality (22) (Figure 6).

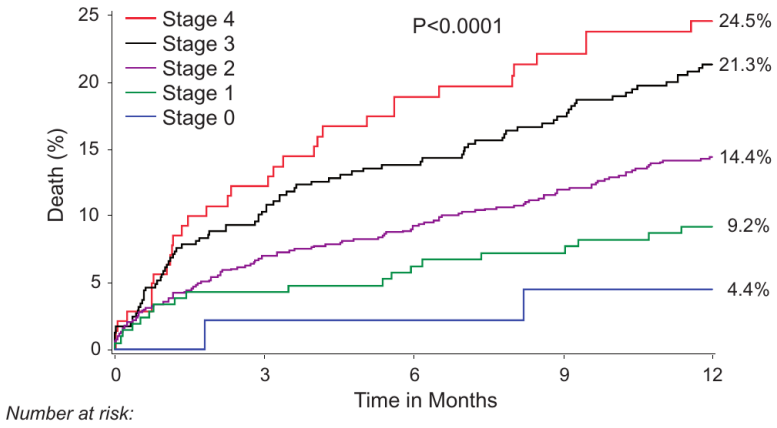


Figure 6. All-cause mortality at one year after aortic valve replacement according to the extent of extravalvular cardiac damage.
Mortality rises progressively from stage 0 (4.4%) to stage 4 (24.5%). The numbers of patients at risk in each stage are given below. Source: Généreux et al., 2017 – European Heart Journal, p. 3354 (22), modified.

1.7.3 Prognosis of Symptomatic Severe Stenosis

The passage to the symptomatic phase marks a prognostic discontinuity, since without valve replacement symptomatic severe aortic stenosis carries an annual mortality that may reach 50% (1), with a two-year mortality of similar size (2). Valve replacement, whether surgical or transcatheter, restores life expectancy to values that are substantially comparable with those of age-matched controls (1).

1.7.4 Moderate Stenosis

The boundary between moderate and severe stenosis is being redefined, because long-term mortality is far from negligible in the moderate form as well. It is associated with NYHA functional class and with ejection fraction even after the analysis has accounted for the other clinical variables, that is in a way that comorbidities alone do not explain. Taking an ejection fraction of 60% or more as the reference, patients with values between 50% and 59% already show a higher mortality, although they fall within what the conventional threshold of 50% defines as preserved function. Subjects with systolic function at the lower limits of normal and mild symptoms therefore carry a risk of adverse events higher than the haemodynamic classification alone would suggest (23).

This does not mean, however, that moderate stenosis should be treated. The randomised TAVR UNLOAD trial compared transcatheter implantation with clinical surveillance in patients with heart failure with reduced ejection fraction and moderate aortic stenosis, without showing a significant benefit of treatment (24). The move towards earlier intervention concerns rather severe stenosis, in which valve replacement has been proposed in many patients who are still asymptomatic (25).

1.7.5 The Problem of Undertreatment

On the natural history of the disease is superimposed a problem of the care pathway, because a substantial proportion of the patients who might benefit from valve replacement never reach it. The first filter is clinical, since about half of the treatable patients are estimated not to be identified on physical examination alone (12). The second filter is diagnostic, since among the patients in whom echocardiography raises the suspicion of a low-gradient severe stenosis, fewer than one in five undergo within a year the investigations needed to confirm the diagnosis. The figure is all the more

relevant because mortality and hospitalisations for heart failure are highest precisely in the low-gradient forms and in the advanced stages of cardiac damage, that is in the patients who are most likely to escape diagnostic confirmation. Valve replacement, by contrast, is associated with a halving of one-year mortality (26).

1.8 From Surgical Replacement to Transcatheter Therapy

1.8.1 Surgical Aortic Valve Replacement

Aortic valve replacement therapies have evolved progressively since the 1960s, and surgical aortic valve replacement (SAVR) was for decades the only treatment able to alter the natural history of aortic stenosis (4).

The operation is performed on cardiopulmonary bypass and with cardiac arrest induced by cardioplegia. The aorta is opened a few centimetres above the valve, the native cusps are excised and the annulus is cleared of calcification. The prosthesis is then anchored with sutures in an intra-annular or supra-annular position. Access is through a median sternotomy, although techniques with a smaller incision have been introduced (4). The need to open the chest, to arrest the heart and to replace its function temporarily with an extracorporeal circuit determines the operative risk of the procedure.

The population with severe aortic stenosis is, however, made up largely of elderly patients carrying multiple comorbidities, in whom the operative risk may be prohibitive, to the point that the surgeon judges the patient unsuitable for operation (27). A substantial proportion of patients with an indication for valve replacement were therefore never referred for surgery, which created a gap between diagnosed and treated disease (12,26).

1.8.2 The First Human Implantation and the Spread of the Technique

Transcatheter therapy was born from this clinical need, and the design of a valve prosthesis that could be implanted percutaneously was a research goal for years. The device that was developed consisted of three leaflets of bovine pericardium mounted inside a balloon-expandable stent. After ex vivo testing and implantation studies in animals, the first implantation in a human being was performed in 2002 in a patient with calcific aortic stenosis (28).

Within little more than a decade TAVI moved from a treatment reserved for inoperable patients to the preferred therapeutic option in suitable patients with symptomatic severe aortic stenosis, and it substantially transformed the management of the disease (4,29). In the United States, in 2021 alone, more than 40,000 surgical valve replacements and about 80,000 transcatheter procedures were performed (1). Dedicated national registries document its spread and its outcomes in real-world practice in several European countries and in the United States, and the comparison between successive surveys shows a progressive shift towards the transfemoral route, which in the most recent French registry exceeds 80% of procedures (30–33).

1.8.3 Comparison with Surgical Replacement

The extension of the indication was achieved through a succession of randomised controlled trials, conducted in bands of progressively decreasing surgical risk. Patients judged inoperable (27) were followed by those at high risk (34,35), those at intermediate risk (36,37) and finally those at low risk (38,39). In every band transcatheter implantation showed outcomes on the primary endpoints of mortality and stroke that were non-inferior or superior to those of SAVR, so that the comparison between the two strategies concerns the profile of complications rather than survival.

The meta-analysis of the randomised trials conducted in the low- and intermediate-risk bands shows that the two procedures exchange their respective risks. After transcatheter implantation bleeding, new-onset atrial fibrillation and acute kidney injury are less frequent, whereas permanent pacemaker implantation, paravalvular leak and major vascular complications are more frequent (40). Among the latter, the vascular complication is the one that arises from the route travelled to reach the valve (41), so that its risk changes as the route changes.

On these grounds the European guidelines distinguish first by age and life expectancy. In the patient below seventy years of age with a low operative risk, life expectancy exceeds the presumed durability of the bioprosthesis, so that the choice made at the first operation conditions all subsequent reinterventions, and SAVR remains the preferred treatment. In the elderly patient the reference modality is instead transcatheter implantation, provided that transfemoral access is feasible (42) (Figure 7).

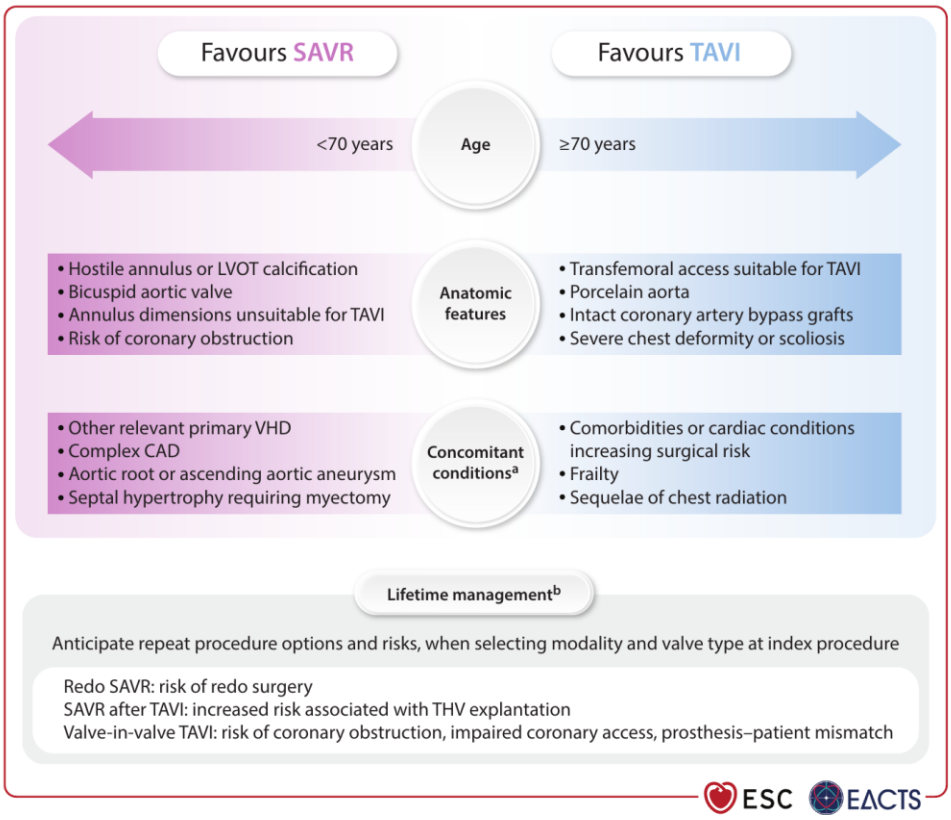


Figure 7. Factors to be considered in the choice of the intervention modality in aortic stenosis.
The comparison is organised by age, anatomical features and concomitant conditions, and the lower panel summarises the long-term management perspective. Among the elements that favour transcatheter implantation is the suitability of the transfemoral access. CAD = coronary artery disease; THV = transcatheter heart valve; VHD = valvular heart disease. Source: Praz et al., 2025 – European Heart Journal, p. 4669 (42).

1.9 Indications and Decision-Making

1.9.1 Assessment of the Candidate

The availability of two techniques of valve replacement moves the clinical problem from the choice of whether to intervene to the choice of how and when to do so. The decision calls for an assessment that goes beyond the valve and covers symptoms, the coronary arteries, comorbidities and the general condition of the patient (42).

The first element is the presence of symptoms, which in severe stenosis is the main determinant of the indication. Up to 40% of patients with severe stenosis report none at the time of diagnosis. In about one third of these the exercise test brings out their appearance or a reduced exercise capacity attributable to the stenosis, and such patients must be considered symptomatic. The test cannot always be performed, however, because of frailty or reduced mobility (42).

Among the elements that feed the multidisciplinary discussion is the assessment of the coronary arteries, since the presence of coronary disease conditions the mode and the timing of treatment. In patients with a low or intermediate pre-test probability of obstructive coronary disease, that is 50% or less, coronary computed tomography angiography is recommended, whereas in patients with a higher probability invasive coronary angiography is recommended. In candidates for transcatheter implantation the tomography performed for procedural planning can serve this purpose as well, and when its quality is sufficient to rule out relevant coronary disease, invasive angiography may be omitted (42).

Finally, the biomarkers of wall stress and myocardial damage contribute to the decision, since their trend helps to establish the most appropriate moment for intervention. The assessment of the general condition also contributes, and it covers comorbidities, nutritional status and a systematic estimate of frailty with validated tools (42).

1.9.2 Operative Risk and Frailty

Stratification of operative risk conventionally uses the STS-PROM and EuroSCORE II scores, which the European recommendations employ as decision thresholds (42). These tools do not incorporate frailty, however, whose prognostic weight is independent and whose prevalence among candidates for valve replacement ranges from 26% to 68% depending on the scale used. In a comparison of seven scales the Essential Frailty Toolset proved the strongest predictor of death at one year (43). Frailty and procedural futility are therefore complementary elements of the Heart Team assessment, which the risk scores alone cannot replace (42,43).

1.9.3 The Heart Team and the Care Network

Multidisciplinary assessment is the organizational element on which the therapeutic decision rests (42).

The Heart Team brings together the cardiologist in charge of the patient, cardiovascular imaging specialists, cardiac surgeons and interventional cardiologists experienced in valve procedures, supported by specialised nursing staff. In the most complex cases experts in heart failure and electrophysiology, geriatricians and anaesthetists are added. The meeting serves to present all the options, medical, interventional and surgical, in a

balanced way. The recommendation that follows rests on the balance between the risks and the benefits of each procedure and is discussed with the patient, who makes an informed choice (42).

The value of the collegial approach is greatest where there is uncertainty or where solid evidence is lacking, since many patients in everyday practice have features that do not correspond to those of the participants in the randomised trials (42). This is the condition in which decisions on the access route belong, entrusted to the anatomy of the individual patient and to the experience of the centre (44).

On the organizational side the European recommendations describe a network made of dedicated clinics for diagnosis and surveillance and of valve centres for advanced imaging and for interventions, with interventional cardiology and cardiac surgery on site. An annual volume of about 50 procedures per operator is associated with better outcomes, a finding confirmed by the United States registry, which documents an inverse relation between hospital volume and adverse outcomes (42,45).

1.9.4 Current Recommendations

The 2025 ESC/EACTS guidelines state that the choice of the intervention modality must rest on the Heart Team assessment of the clinical, anatomical and procedural features of the individual patient. The recommendation that follows is then discussed with the patient, who makes an informed choice (Class I, Level C) (42).

The indications concerning the intervention modality in symptomatic severe aortic stenosis are the following (42):

1. transcatheter implantation is recommended in patients aged 70 years or older with stenosis on a tricuspid valve, if the anatomy is suitable (Class I, Level A);
2. surgical replacement is recommended in patients younger than 70 years, if the surgical risk is low (Class I, Level B);
3. for all the remaining candidates for an aortic bioprosthesis, both procedures are recommended on the basis of the Heart Team assessment (Class I, Level B).

A specific recommendation is devoted to the access routes: non-transfemoral transcatheter implantation should be considered in patients who are suitable neither for SAVR nor for transfemoral access (Class IIa, Level B) (42) (Figure 8).

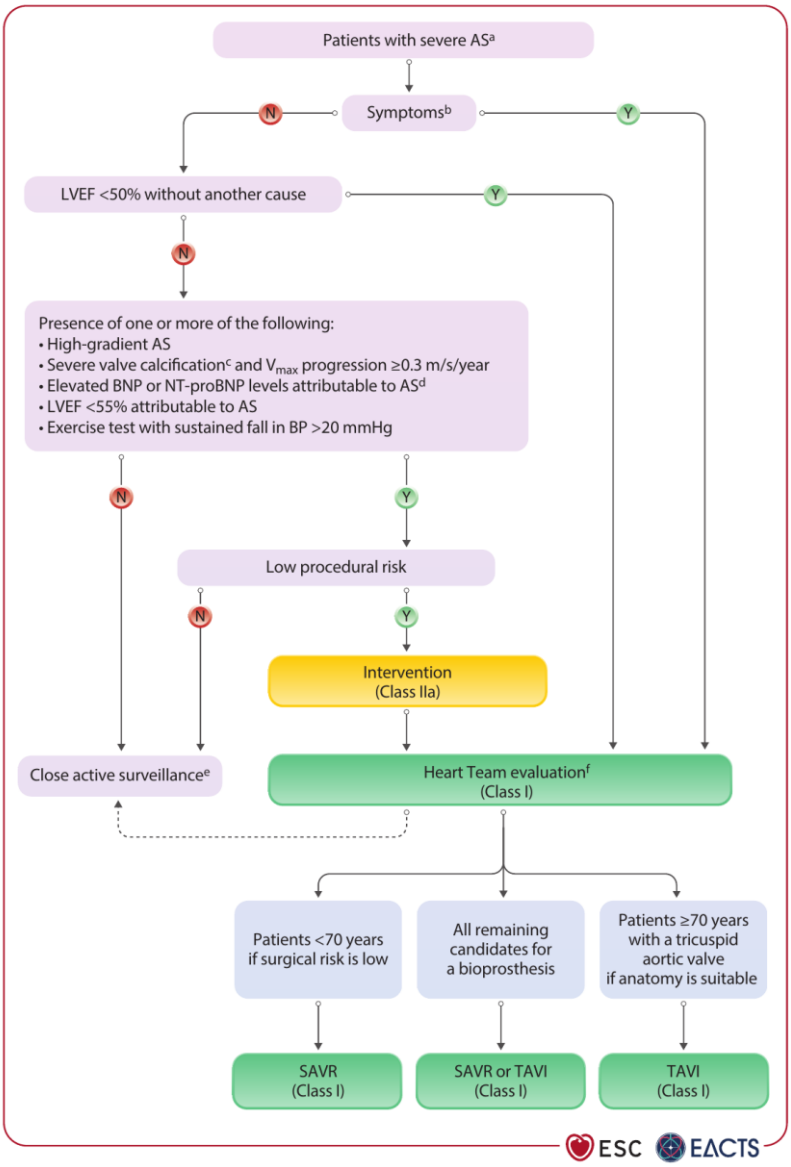


Figure 8. Management of the patient with severe aortic stenosis.
The algorithm distinguishes the symptomatic patient, in whom intervention is indicated, from the asymptomatic patient, in whom the indication follows from ventricular function or, at low procedural risk, from criteria of progression risk, while in the other cases active clinical surveillance is indicated. The choice of the intervention modality is entrusted to the Heart Team. Source: Praz et al., 2025 – European Heart Journal, p. 4666 (42).

The United States guidelines adopt a similar criterion based on age and estimated surgical risk, with slightly different thresholds (1,46).

1.9.5 Treatment of Asymptomatic Severe Aortic Stenosis

The same recommendations have also changed the paradigm of symptom-guided watchful waiting, and support an earlier intervention in many asymptomatic patients with severe aortic stenosis (42). On that basis an international consensus document has proposed an operational model founded on early referral to the Heart Valve Team, on simplification of the diagnostic pathway and on timely valve replacement in many asymptomatic patients (25). The approach is justified by the evidence that extravalvular myocardial damage, once established, independently conditions prognosis even after valve replacement (22).

1.10 The Procedure and Access Planning

1.10.1 The Percutaneous Transfemoral Procedure

Transcatheter aortic valve implantation consists in placing a biological prosthesis inside the native valve without removing it. The percutaneous transfemoral route is its reference access, on which the current recommendations and almost all the available data rest (42,47). The common femoral artery is punctured under ultrasound and fluoroscopic guidance above the bifurcation, where the vessel is compressible against the femoral head, and one or two suture-based closure devices are pre-positioned before the calibre is raised to that of the definitive sheath (48–50).

The prosthesis is crimped onto a delivery catheter and carried up to the aortic root through the sheath. The system ascends the aorta in a retrograde direction and reaches the stenotic valve, which is crossed with a metal guidewire advanced into the left ventricle. In the procedures that require it, the native valve is first dilated with a balloon, a manoeuvre that eases the passage of the delivery system (10,44). The prosthesis is deployed during a period of rapid ventricular pacing, which transiently reduces cardiac output and keeps the device stable in position while it expands. The prosthesis displaces the native cusps against the aortic wall and anchors itself there, taking over their function (10,44).

At the end the delivery system is withdrawn and the arteriotomy is closed by tightening the pre-positioned sutures under angiographic control, completed where necessary by a plug device (48–50). Besides the main access the procedure uses a secondary vascular

access, femoral or radial, for control aortography and for temporary ventricular pacing (44,51). The procedure requires neither cardiopulmonary bypass nor cardiac arrest, and it can be performed under local anaesthesia with conscious sedation and without a skin incision, so that the patient can be mobilised early (4,44). Complications occur in the arterial segment crossed by the sheath, which may dissect, tear while the system is advanced or remain occluded by the closure device, and their main determinant is the ratio between the calibre of the sheath and that of the vessel (41,52).

1.10.2 Computed Tomography Planning and Annular Measurement

Multislice computed tomography with electrocardiographic gating is the standard for planning transcatheter valve implantation. The consensus document issued by the Society of Cardiovascular Computed Tomography defines the acquisition protocol, the parameters to be measured and the way findings are reported (20).

In implantation practice the term annulus conventionally designates the basal virtual ring, and this is the structure measured for prosthesis sizing (20). Since that ring is oval, two-dimensional measurements intercept only a tangential section of it, and for this reason multislice computed tomography, which allows the ring to be reconstructed on a dedicated plane, has become the reference method (20).

On the root the annular plane is identified and its area and perimeter are measured, both preferred to two-dimensional diameters alone for the choice of prosthesis. The height of the coronary ostia, on which the estimate of the risk of coronary obstruction depends, and the dimensions of the sinuses of Valsalva and of the sinotubular junction are also measured. Finally the number of cusps, any raphe and the morphology of annular and subannular calcification are described, since the last conditions the risk of annular rupture and of paravalvular regurgitation (20). The valvular calcium burden, which can be quantified on the same scan, is in addition a measure independent of the flow state, used to settle severity when the echocardiographic findings are discordant (19) (Figure 9).

In the bileaflet root, finally, the prosthesis finds a housing of elliptical and oblique geometry rather than circular and orthogonal, because of the tilt of the valve plane that characterises this variant (8).

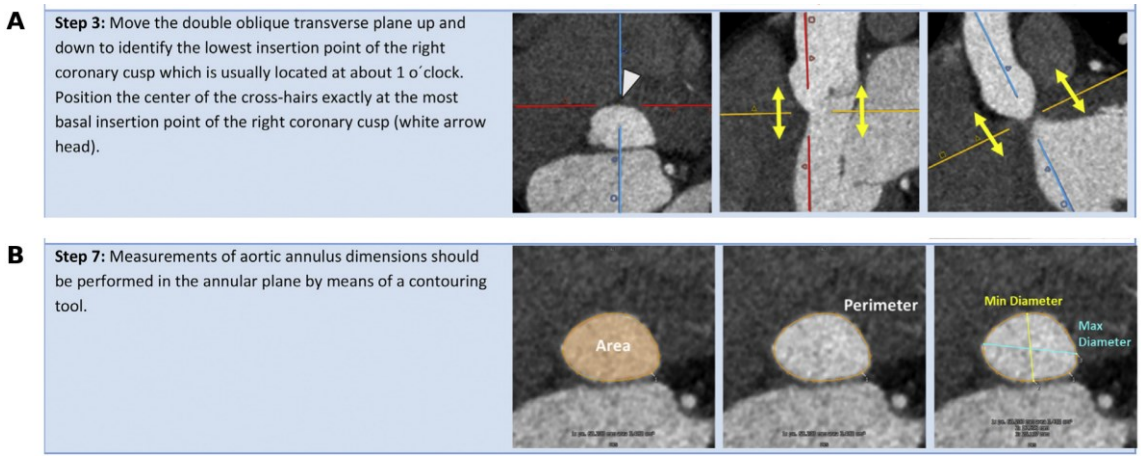


Figure 9. Identification of the annular plane and measurement of the annulus on computed tomography.

(A) The double-oblique transverse plane is moved in the cranio-caudal direction until the lowest insertion point of the right coronary leaflet is identified (white arrowhead). (B) In the annular plane so defined, area, perimeter and minimum and maximum diameters are measured with a contouring tool. Source: Blanke et al., 2019 – JACC: Cardiovascular Imaging, p. 6 (20), modified.

Transoesophageal echocardiography, including the three-dimensional mode, contributes to the definition of the geometry of the outflow tract and to intraprocedural monitoring, and it is used in the pre-procedural assessment of transcatheter procedures on the aortic valve apparatus (18).

1.10.3 Prostheses and the Profile of Delivery Systems

From the measurements follows the choice of device, which consists of a metal frame on which leaflets of biological tissue are mounted, together with a dedicated delivery system (10,44). Two types are distinguished, which differ in the mechanism by which the frame expands and in the relation they establish with the annulus (10) (Figure 10):

- balloon-expandable prostheses, in which the cylindrical frame carries pericardial leaflets and a fabric skirt intended to prevent paravalvular regurgitation, with intra-annular anchoring and intra-annular valve function;
- self-expanding prostheses, in which the nitinol frame extends from the ventricular outflow tract up to the ascending aorta, with annular anchoring and supra-annular valve function.

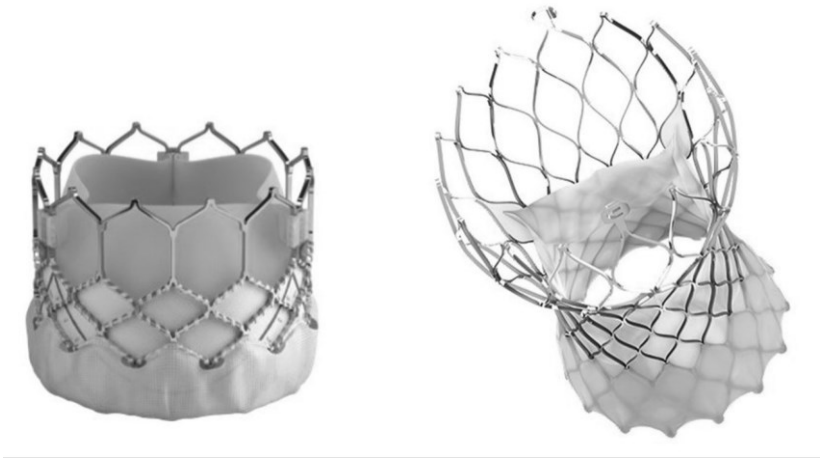


Figure 10. Transcatheter prostheses distinguished by the expansion mechanism of the frame.
From left: Sapien S3 (Edwards Lifesciences), balloon-expandable; Evolut Pro+ (Medtronic), self-expanding. Source: Boskovski and Gleason, 2021 – Circulation Research, p. 1406 (4), modified.

The randomised trials comparing the different types of prosthesis have not documented substantial differences in composite clinical outcomes, while the differences observed concern mainly the haemodynamic profile, in favour of the supra-annular self-expanding device in patients with a small annulus (53–55).

Technological development has brought a progressive reduction in the calibre of delivery systems (44). In the earliest series sheaths of 18 to 24 French were used (52). The reduction in profile has widened the proportion of patients anatomically suitable for transfemoral access and has lowered the incidence of vascular complications, and it has been one of the main drivers of the evolution of the access routes (44,47).

1.10.4 The Iliofemoral Axis and Suitability for the Femoral Route

Assessment of the iliofemoral system is carried out on the same tomographic scan used for the aortic root, and it establishes whether the femoral route is practicable (20,56). The consensus document makes strong recommendations on the reporting of vascular access and requires the calibre, the calcium burden and the tortuosity of the iliofemoral vessels to be reported, with the anatomical site of the abnormalities indicated (20).

The relation between the calibre of the sheath and the diameter of the vessel has been formalised in the sheath to femoral artery ratio (SFAR), defined as the ratio between the external diameter of the sheath and the minimum diameter of the femoral artery, both expressed in millimetres (52).

In the prospective series in which the ratio was proposed, conducted with sheaths of 18 to 24 French, the independent predictors of major vascular complication were the SFAR, the experience of the centre and femoral calcification (52). The finding was confirmed in a contemporary prospective series, in which, for major complications alone, the sheath to artery ratio remained the only risk factor identified (57). A SFAR threshold of 1.05 separates two populations with clearly different risk, since above it both major vascular complications and 30-day mortality rise more than fourfold. It has therefore been proposed as a criterion for selecting candidates for transfemoral access (52).

Calibre does not exhaust the assessment, however, since the main obstacle to the femoral route is severe iliofemoral calcification and stenosis, all the more when they are combined with tortuosity of the vessel, because in such conditions advancing the delivery system becomes difficult. The presence of dissections, aneurysms and soft plaque also makes the standard approach inadvisable, because of the risk of damaging the wall while the sheath passes (44). The prevailing clinical substrate of these abnormalities is peripheral artery disease (56).

The threshold beyond which the femoral route becomes less safe than an alternative remains a matter of expert consensus, since no randomised comparisons exist. The international Hostile registry has proposed for this purpose a score built on seven anatomical variables assessed on tomography along six arterial segments, which describes the extent and the complexity of the arterial disease. Below the threshold of 8.5 points the femoral route was associated with lower mortality than the transthoracic approach and with a lower incidence of cerebrovascular events than the alternative transvascular routes, while above it the available data are conflicting (44,56).

The margin of feasibility of the femoral route has also widened progressively. Preparation of the vessel by angioplasty and, more recently, by intravascular lithotripsy makes it possible to treat by the femoral route even patients with severe circumferential calcification, so that the threshold of unsuitability shifts and the number of procedures requiring an alternative route falls further (44).

1.11 Alternative Access Routes

When the femoral route is not practicable, the recommendation is to prefer a non-thoracic transvascular access, axillary, carotid or transcaval, to a transthoracic, transaortic or transapical access (44). The alternative endovascular routes were developed precisely in order to mitigate the unfavourable outcomes associated with transthoracic approaches (58). It is by the same distinction between extrathoracic and intrathoracic routes that pooled comparisons group the alternative accesses (59). The extrathoracic routes share with the femoral one their endovascular nature, can be performed under local anaesthesia or conscious sedation and do not involve opening the chest. The intrathoracic routes are instead surgical operations in every respect, since they require general anaesthesia with intubation, an incision of the chest wall and the placement of a pleural drain (44). Among the extrathoracic routes the femoral access with surgical exposure of the vessel must also be considered, which the literature treats as a variant of the femoral route and not as a true alternative access (60), and among the transvascular routes the rarer transinnominate access is also found (42).

1.11.1 Extrathoracic Routes

Femoral access with surgical exposure. It uses the same vessel and the same path as the percutaneous route, and differs from it only in the way the artery is opened and closed. The common femoral artery is isolated through a groin incision, and the arteriotomy is made and repaired under direct vision, so that control of the vessel is immediate but the operation more often requires general anaesthesia. Complications accordingly move from the puncture site to the surgical wound, in the form of infection and of seromas or lymphatic collections. In the meta-analysis of the comparative studies the two techniques do not differ in short-term mortality, bleeding, length of stay or major vascular complications, while minor vascular complications are more frequent with the percutaneous route, a difference that weakens in matched studies. The two approaches are therefore considered equally effective (60).

Axillary and subclavian access. It is the most widely used alternative route in Europe (44). The arteriotomy is made in the third segment of the axillary artery, lateral to the pectoralis minor muscle and upstream of the subscapular and circumflex humeral branches. The left side is usually preferred, since it allows a more coaxial alignment

with the aortic root and reduces the risk of compromising the carotid artery. The artery can be exposed surgically through a small incision in the deltopectoral groove, and in that case the arteriotomy is closed with a purse-string suture or with continuous Prolene stitches. Alternatively it is punctured percutaneously under ultrasound guidance at a shallow angle, with a pre-positioned closure device (44). The complications of this route follow from the anatomical features of the artery used. Its calibre is smaller than that of the femoral artery, so that a minimum diameter of about 6 mm is recommended, and the vessel runs in close relation with the brachial plexus. The sheath also crosses an artery that arises from the aortic arch close to the trunks directed to the brain, and to this circumstance is attributed the excess of cerebrovascular events reported in some series (44,61,62). Occlusion of the subclavian artery or of the brachiocephalic trunk and a calibre insufficient for the planned sheath are contraindications. The presence of a patent mammary graft is not in itself a contraindication, but it requires the diameter to be measured at that level and the sheath to be placed downstream of the origin of the graft (44) (Figure 11).

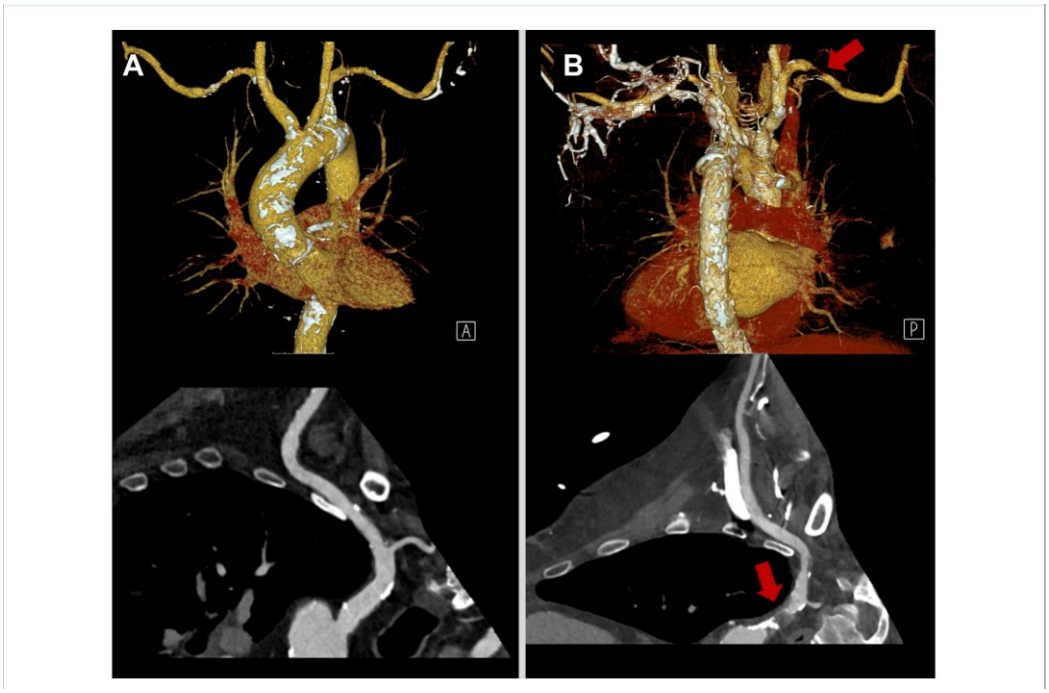


Figure 11. Assessment of the transaxillary access by computed tomography angiography.
(A) Suitable patient: left axillary artery with a minimum diameter of 7 mm, free of relevant stenosis, with minimal calcification and mild to moderate tortuosity. (B) Unsuitable patient: the left subclavian artery is completely occluded (red arrow) and the right brachiocephalic trunk partly occluded. Source: Feistritzer et al., 2025 – JACC: Cardiovascular Interventions, p. 2314 (44).

Carotid access. It uses the common carotid artery, in the great majority of cases the left one, and has become in recent years the most widely used alternative in the United States (44). An incision of two or three centimetres above the clavicle, between the sternal head and the clavicular head of the sternocleidomastoid, gives access to the vessel, with care taken to move the vagus nerve away from the operative field. Vascular clamps secure proximal and distal control before the artery is punctured under direct vision, and at the end of the procedure the arteriotomy is closed with a monofilament suture and the patency of the vessel is verified by ultrasound or aortography (44). The path to the aortic root is short and straight, and allows accurate control of the positioning of the prosthesis. The route involves, however, the temporary occlusion of one carotid artery, which is why it now tends to be performed under local anaesthesia, allowing continuous neurological monitoring during clamping (44).

Before the delivery system is introduced, a clamping test of a few minutes may be performed, in order to verify neurological tolerance of the temporary occlusion of the vessel (63). The contraindications follow from this, and they are a stenosis of 50% or more or occlusion of the contralateral carotid artery, absent patency of the ipsilateral vertebral artery, significant calcification or mobile atheroma of the target vessel, a calibre below 5 mm and previous operations on the vessel (44,64,65).

Transcaval access. It is the only alternative route that is entirely percutaneous and does not use an artery. After puncture of the femoral vein the abdominal aorta is reached by crossing electrosurgically the wall that separates it from the inferior vena cava, in a segment lying below the renal arteries and above the aortic bifurcation, and from that point the procedure runs as for the femoral route. At the end the aortic breach is closed with a nitinol occluder, which is not immediately haemostatic but seals by thrombosis, while the residual aorto-caval tract closes spontaneously in most cases (44,66). The procedure is usually performed under conscious sedation, and the feared complication is retroperitoneal bleeding from extravasation, for which the bail-out strategy with a tamponading balloon and a covered stent is planned on tomography before the operation (44,67–69). There are only two absolute contraindications, uninterrupted calcification of the infrarenal aortic wall at the crossing point and the presence of structures interposed between the cava and the aorta, such as a bowel loop or an arterial vessel. Neither the distance between the two vessels nor the calibre of the sheath is an obstacle (44).

1.11.2 Intrathoracic Routes

Since the two transthoracic routes are surgical operations, the postoperative course usually takes place in intensive care, and to this is added exposure to the complications proper to surgery, such as nosocomial infection, delirium and impaired wound healing, in patients whose operative risk is already high (44).

Transapical access. The apex of the left ventricle is identified on tomography and reached through a small thoracotomy. Purse-string stitches are placed on the myocardium, the apex is punctured directly and the valve is crossed in an antegrade direction, which makes the crossing technically simpler and in theory less liable to dislodge calcific debris. Only balloon-expandable prostheses can be used, since they are the only ones that can be loaded in the reverse direction onto the delivery system, and at the end of the procedure the apex is closed with the pre-positioned stitches (44). Complications arise from two distinct sites, the chest wall and the ventricular wound, whose feared complication is intraprocedural tearing of the myocardium. The absolute contraindications are few and comprise an apex in a position that cannot be reached and the presence of apical thrombus (44).

Transaortic access. The ascending aorta is reached through a skin incision of four or five centimetres with a partial sternotomy, shaped as a T or a J, in the second intercostal space, or through a right mini-thoracotomy. Purse-string stitches secured by tourniquets delimit the entry point, the aorta is punctured under direct vision and the sheath is brought progressively to the definitive calibre. The prosthesis is then deployed in a retrograde direction as in the vascular routes, and at the end the aortotomy is closed with the pre-positioned stitches (44). Feasibility depends on a precise anatomical condition, since the ascending aorta must be long enough, roughly six centimetres from the valve, and must have a calcification-free zone in which the puncture can be made (44). The complications reflect the surgical nature of the access, with a higher frequency of bleeding and of recourse to transfusion (44,59).

1.11.3 The Selection Algorithm

The choice of the access route belongs to the Heart Team and rests on the integration of the tomographic data, the clinical profile and the experience of the centre, for which structured decision algorithms have been proposed (42,44)(Figure 12).

The review devoted to the alternative routes and the NORTHOSTAVI registry agree in noting that no randomised comparison has set the different alternative routes against one another and that observational comparisons remain scarce, so that the choice between them depends largely on the experience gained by the individual centre and on the resources locally available (44,58).

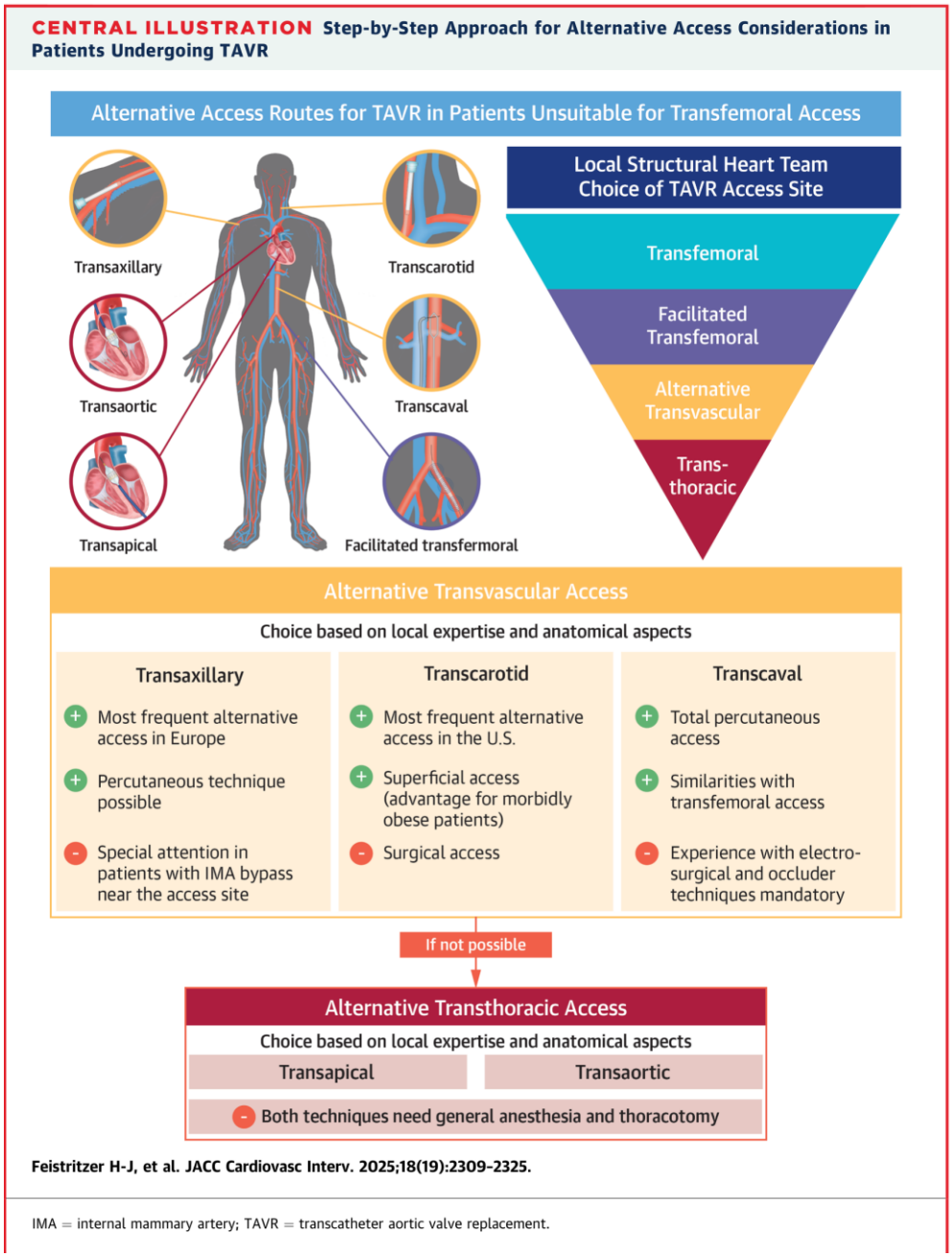


Figure 12. Stepwise approach to the choice of the access route.
At the top are shown the alternative routes available and the decision hierarchy of the local Heart Team: transfemoral, facilitated transfemoral, alternative transvascular accesses and, as a last resort, transthoracic accesses. The lower panels summarise the advantages and the disadvantages of each option. Source: Feistritzer et al., 2025 – JACC: Cardiovascular Interventions, p. 2312 (44).

1.12 Complications of TAVI

1.12.1 The VARC Definitions

The outcomes of the procedure are reported according to event categories defined in a uniform way, which cover mortality, stroke, myocardial infarction, acute kidney injury, bleeding complications, vascular complications and conduction disturbances (70).

The heterogeneity of the definitions used in the early studies had made their elaboration necessary, and in 2012 the consensus document of the Valve Academic Research Consortium (VARC-2) standardised those definitions for transcatheter aortic valve implantation (70), which were later revised in 2021 by the VARC-3 document (71). It follows that comparison between series is possible only where the same definition has been used, and that the reference system adopted must be stated.

The revision substantially changed some definitions, with relevant quantitative consequences. Applied to the same population, the VARC-3 criteria identify two and a half times as many bleeding events as the VARC-2 criteria. Both systems nevertheless retain prognostic relevance, since the bleeding events classified as severe are associated in both with an increase in 30-day mortality (72).

1.12.2 Vascular Complications and Bleeding

Vascular complications are by definition linked to the access, and their mechanism is mechanical. The sheath is a rigid tube that must travel along a vessel that is often calcified, sometimes tortuous and of a calibre not much larger than its own, and damage may occur at three moments of the procedure. During advancement the wall may dissect or tear, on withdrawal of the sheath the puncture site may avulse, and at closure the device may fail to hold or may occlude the lumen. To this is added distal embolisation of atheromatous material detached from the wall as the system passes. The main determinant remains the ratio between the calibre of the sheath and that of the artery, and the reduction in the profile of delivery systems has therefore lowered the incidence of these complications more than any other measure (41).

In the series conducted with first-generation systems and large-calibre sheaths, major vascular complications affected a substantial proportion of patients and were associated with higher rates of bleeding, transfusion, renal failure and mortality (41). In

contemporary cohorts the overall incidence has remained similar, while the distribution is deeply different. Almost all events are minor complications, two thirds of them referable to the primary puncture site and one third to the secondary one. They resolve with medical treatment alone in three cases out of four (57).

Bleeding arises mostly from the same site as the vascular complications. Bleeding events defined according to VARC-3 affect about one third of patients, and the primary vascular access site is the most frequent source among the early ones, while gastrointestinal sites prevail among the late ones (73). The determinants of early risk are consistent with this mechanism, since they all act either on the ratio between the calibre of the sheath and that of the vessel or on the extent of the wound. Female sex acts through the smaller average calibre of the femoral artery for a given sheath, and indeed in national registries in-hospital vascular complications are more frequent in women (74), while thoracotomy access adds to the vascular puncture a wound of the chest wall and of the heart or the aorta. A larger sheath calibre and dual antiplatelet therapy contribute in the same direction, while use of the radial artery as the secondary access lowers the risk, because it replaces a second femoral puncture with a compressible one. Complications of the secondary site are indeed significantly more frequent when it is femoral rather than radial, even after matching (51,73).

The transfusion that follows is not a neutral event. In the multicentre TRITAVI registry it was given to about one patient in six among those treated by the transfemoral route. In the propensity-score matched population it was associated with a doubling of 30-day mortality and with a more than fourfold increase in acute kidney injury. It also proved an independent predictor of early mortality irrespective of the bleeding that had made it necessary (35).

1.12.3 Acute Kidney Injury

The kidney is directly affected by changes in perfusion, and the procedure produces several of them in rapid succession. The rapid ventricular pacing needed for deployment of the prosthesis, the valvuloplasty and the deployment itself entail periods of hypotension during which renal flow falls. It is to this sequence that the largest share of renal damage after transcatheter implantation is attributed today, given the high sensitivity of renal tissue to haemodynamic disturbance (75,76). Contrast medium,

which would be the intuitive explanation, has not proved consistently associated with renal damage in this setting, and the association emerges only when the amount given exceeds a threshold related to creatinine and body weight (75,76). Embolisation of atheromatous material from the aortic wall during catheter manipulation, the systemic inflammatory response, which is more marked the more invasive the access, and bleeding with the transfusion that follows from it also contribute (75,76).

The meta-analysis of the predictors of acute kidney injury after transcatheter implantation reflects this double origin. Alongside factors belonging to the patient, such as arterial hypertension, diabetes mellitus, peripheral artery disease and a reduced ejection fraction, it identifies factors belonging to the procedure, such as transapical access, major bleeding and transfusion (76).

The risk of all-cause death rises progressively with the severity of the renal damage, and the association with short- and long-term mortality persists after adjustment for confounders (76). The gradation is seen for lesser degrees of damage as well, since in the Danish registry, which collects the entire national series, modest rises in creatinine are accompanied by a progressively higher risk of dialysis and of death at one year (77).

The damage is not always permanent, however, since among the surviving patients about three quarters had fully recovered renal function within six months, while the remaining quarter retained persistent damage, in a small proportion in the form of chronic dialysis (77).

The access route also contributes to the risk, and indeed in the Danish national series recourse to a non-transfemoral access was clearly more frequent among the patients who developed acute kidney injury than among those who remained free of it (77). In the comparison between intrathoracic and extrathoracic accesses the former are in addition more often associated with acute kidney injury at 30 days requiring renal replacement therapy (59).

The definition of acute kidney injury itself requires a qualification. It rests on the rise in serum creatinine, whose production depends largely on muscle mass and is therefore reduced in elderly or undernourished subjects and in those with little muscle mass (78). In the population that is a candidate for transcatheter implantation, elderly and often

frail, a low creatinine may therefore not mirror true renal function and may delay or mask recognition of the damage (77).

1.12.4 Cerebrovascular Events

Crossing the valve with the guidewire, the valvuloplasty and deployment of the prosthesis may detach calcific debris from the cusps and from the aortic wall, which reaches the cerebral circulation as emboli. Alongside this embolic component there is a haemodynamic one, since the fall in pressure during rapid pacing and balloon inflation produces a transient hypoperfusion, which in a brain with an already compromised collateral circulation may translate into watershed infarcts (79). That the embolic mechanism is not the only one is suggested by the randomised PROTECTED TAVR trial, in which the use of a cerebral embolic protection device did not significantly reduce the incidence of periprocedural stroke (80).

The access route acts on the embolic component, since the routes that use vessels directed to the brain are those for which an excess of cerebrovascular events compared with the transfemoral route has been reported, and it persists after adjustment for baseline characteristics (81). The carotid route involves the temporary occlusion of a common carotid artery, while in the axillary and subclavian route the sheath crosses a vessel that arises from the arch close to the supra-aortic trunks. In the Hostile registry transfemoral access was associated with a lower risk of stroke or transient ischaemic attack at one year than the alternative accesses (56,79). The risk is not uniform among the routes that use the supra-aortic trunks, however, since in the direct comparison between alternative endovascular accesses the carotid route showed the lowest stroke frequency, lower than that of the percutaneous axillary route (58).

1.12.5 Conduction Disturbances and Pacemaker Implantation

The bundle of His and the left bundle branch run within the membranous septum, immediately below the commissure between the non-coronary and the right cusp, and the prosthetic frame anchors itself in precisely that part of the outflow tract, compressing them (4,10). The risk therefore depends less on the characteristics of the patient than on the site and the mode of deployment. A deep implantation in the outflow tract and a radial force that goes on being exerted over time, such as that of self-

expanding systems, increase the probability of block, while a pre-existing right bundle branch block multiplies it, since residual conduction already depends on the branch that the implantation puts at risk (82). On this premise standardised deployment techniques have been developed, based on the fluoroscopic overlap of the cusps in order to obtain a less deep implantation and combined with structured pathways for the management of conduction disturbances (83). Consistently, in the randomised comparisons with SAVR permanent pacemaker implantation proved about three times more frequent after a transcatheter procedure with a self-expanding device, both at intermediate risk (36) and at low risk (39). With balloon-expandable prostheses no significant differences from surgery emerged (38).

1.12.6 Mortality and Causes of Death

Among the patients who die within one year of implantation, non-cardiac causes account for more than two thirds of the deaths (33). The figure reflects the nature of the population treated, elderly and with multiple diseases, in which the valve is one among several competing problems and long-term survival is determined largely by conditions unrelated to the procedure. It follows that a difference in risk produced within the periprocedural window tends to be diluted, as time passes, by causes of death that bear no relation to the access route.

The independent predictors of mortality include age above 80 years, comorbidities, poor functional status, a non-elective procedure, in-hospital complications and non-femoral access (33). The finding is consistent with the mortality gradient documented in the meta-analyses comparing access routes (59,84).

1.13 Comparison Between Access Routes

The evidence on the comparison between access routes is entirely observational (44), and the comparisons identified all point in the same direction. Mortality at 30 days is about twice as high after non-transfemoral access as after transfemoral access, and the difference persists at one year, although attenuated (84). Within the alternative group the distinction follows the anatomical one, since the intrathoracic routes are associated with an early mortality about twice that of the extrathoracic ones, as well as with a

higher frequency of potentially fatal bleeding, new-onset atrial fibrillation and acute kidney injury requiring renal replacement therapy (59).

Two independent observations point in the same direction, beginning with the randomised PARTNER 2 trial, which stratified patients according to the access route planned before assignment to treatment. At five years the incidence of death or disabling stroke did not differ between transcatheter implantation and SAVR in the cohort destined for transfemoral access. It was instead higher after transcatheter implantation in the cohort destined for transthoracic access, although the access route was not itself randomised (85). The international Hostile registry enrolled patients with a hostile femoral access. In it both the femoral route after treatment of the vessel and the non-thoracic alternative route were associated with fewer major adverse events at 30 days than the transthoracic route. The difference was driven by complications of the access site (56).

2. AIM OF THE STUDY

2.1 Rationale

Percutaneous transfemoral access is the reference route for transcatheter aortic valve implantation, and the guidelines reserve the alternative routes for patients who are not suitable for it (42). However, the comparison between the two strategies is hindered by an inherent interpretive bias. Patients referred to an alternative access are selected on the basis of an unfavourable vascular anatomy, itself an expression of systemic atherosclerotic disease, and for this reason they carry a higher baseline risk irrespective of the route used (44,86). A temporal dimension further compounds this confounding by indication. The reduction in the calibre of delivery systems and the spread of the minimally invasive approach have progressively narrowed the use of alternative routes, so that the access route is also associated with the era in which the procedure was performed (44,47).

Existing studies consistently document an excess of early events after non-transfemoral access (59,84), but they are entirely observational. A 2025 review notes that no randomised data comparing the alternative routes are available and that no studies are ongoing or planned (44). The comparisons cited here also group the alternative routes into a single category (84) and report outcomes at thirty days and one year (59,84), while the methods used do not correct for confounding due to unmeasured variables (86).

The present work analyses a regional multicentre cohort that covers the whole span over which the technique spread. This study aims to evaluate which clinical and procedural features are associated with the use of an alternative access and which periprocedural complications are associated with the route used. It further examines whether those differences persist after adjustment for clinical features and for procedural era, whether they are distributed uniformly across the individual alternative routes and whether they translate into a difference in long-term survival.

2.2 Primary Endpoint

The primary endpoint is a composite of in-hospital periprocedural complications, defined according to the VARC-2 criteria, comprising acute kidney injury of any stage, major bleeding, major vascular complication, cerebrovascular event (stroke or transient ischaemic attack) within 30 days and the need for transfusion of at least one unit of packed red cells. The main comparison is made between percutaneous transfemoral access and alternative accesses taken as a whole.

2.3 Secondary Endpoints

The secondary endpoints are the individual components of the composite endpoint, the length of stay, periprocedural, 30-day and one-year mortality, and the clinical and procedural determinants of the choice of access route. All-cause survival up to five years is also assessed, overall and according to the route used.

3. MATERIALS AND METHODS

3.1 Study Design and Population

This work is a multicentre observational cohort study with retrospective and prospective data collection, based on the Emilia-Romagna North TAVI registry. The registry gathers the patients who underwent transcatheter aortic valve implantation at six centres of the Emilia-Romagna region, namely Ospedale Civile di Piacenza, Ospedale Civile Sant'Agostino-Estense, Policlinico di Modena, Hesperia Hospital di Modena, Ospedale Maggiore di Parma and Arcispedale Santa Maria Nuova di Reggio Emilia.

Patients were identified retrospectively from the registry. Follow-up information was then gathered prospectively, by outpatient review or by telephone contact, and vital status was in addition checked against the municipal civil registers.

The present analysis covers the patients who underwent transcatheter aortic valve implantation between 2010 and 2022. Of the 1317 procedures held in the registry, one was excluded because the access code could not be attributed and eight because the access route was not recorded, which leaves a final population of 1308 patients (Figure 13).

Eligible patients were those in whom symptomatic severe aortic stenosis had been confirmed on echocardiography and in whom the Heart Team of the treating centre had judged the procedure indicated, following the international guidelines.

Excluded were patients whose aortic stenosis was not severe, patients in whom the implantation was carried out as a bail-out during a cardiac surgical operation, and patients treated for a failing bioprosthesis already in place, that is valve-in-valve procedures.

Informed consent to the collection of the data was given by every patient. The protocol received the approval of the Ethics Committee of the Area Vasta Emilia Nord (AVEN) on 4 January 2019 under study code 726/2018, and the institutional authorisation followed on 8 January 2019.

3.2 The Procedure and the Classification of Access Routes

Each participating centre carried out the procedures according to its own standard practice.

The access route is coded in the registry, and for the purposes of the comparison the patients were divided into two groups on a restrictive criterion, so that the transfemoral group contains only the patients treated by the percutaneous femoral route, while the alternative access group contains the other coded routes, including femoral access with surgical exposure of the vessel.

Since the literature does not agree on where femoral access with surgical exposure belongs, the more restrictive criterion was preferred, which assigns it to the alternative access group.

The main comparison therefore sets a percutaneous transfemoral group against an alternative access group that brings together the transapical, transaortic, axillary and surgical femoral routes.

3.3 Endpoints and Definitions

The definitions of the Valve Academic Research Consortium-2 (VARC-2) were used for the procedural endpoints and for the periprocedural complications (70).

The composite endpoint counts as positive when at least one of its components is present. Because transfusion is recorded in only a minority of the patients treated by an alternative route, an analysis of the composite endpoint without that component was pre-specified. The single components are also considered separately as secondary endpoints, together with the length of stay and with periprocedural, 30-day and one-year mortality. Conduction disturbances and permanent pacemaker implantation were not included among the endpoints, since they depend on the type of prosthesis and on the depth of implantation rather than on the site of vascular access.

3.4 Data Collection and Follow-Up

The baseline clinical profile of every patient was recorded and comprised the demographic data, that is age and sex, the body mass index and the surgical risk scores,

EuroSCORE II and STS score. The major comorbidities were registered as well, namely arterial hypertension, dyslipidaemia, diabetes mellitus, chronic obstructive pulmonary disease, peripheral artery disease, chronic kidney disease of stage 3 or above, atrial fibrillation and previous ischaemic heart disease.

The echocardiographic study performed before the procedure supplied the aortic valve area, the mean transaortic gradient, the left ventricular ejection fraction and the presence of associated valve disease. The severity of mitral regurgitation was graded following the echocardiographic guidelines, and concomitant aortic regurgitation was looked for. Frailty scores were left out, since they had not been collected systematically in every patient.

Clinical follow-up was scheduled at one month, at six months, at one year and once a year from then on, and took the form of an outpatient cardiology review or of a telephone contact. Vital status was verified in every patient by consulting the municipal civil registers. Mortality is treated throughout as death from any cause.

Periprocedural death is taken from the dedicated variable of the registry, while in-hospital or 30-day mortality and one-year mortality were classified from the vital status recorded in the series, whose last documented contact dates to 23 November 2025. Patients alive at that date were counted as survivors for any interval that had already elapsed, and the one-year analysis is confined to the procedures performed up to 2021. Seventy-two deaths carry no documented date: one is coded as periprocedural and was counted as such, while the remaining 71, fifty-five transfemoral and sixteen with alternative access, cannot be placed in time. They are therefore excluded from the one-year analysis while remaining in the denominator of the earlier windows, with a possible slight underestimate of early mortality in both groups.

The long-term survival analysis was carried out in the patients for whom both the date of the procedure and the vital status were known. Since two centres hold no date of last contact for their living patients, these were censored at the date of the most recent registry check made by their own centre. Follow-up was truncated at five years.

3.5 Statistical Analysis

Continuous variables are given as mean ± standard deviation or as median with interquartile range and were compared with the Mann-Whitney U test. Categorical variables are given as absolute frequencies with percentages and were compared with the chi-square test or, where appropriate, with Fisher's exact test. Odds ratios and their 95% confidence intervals refer to alternative access compared with percutaneous transfemoral access, taken as the reference.

Multivariable logistic regression models were built for the primary composite endpoint, for its version without the transfusion component, for acute kidney injury and for one-year mortality. These models estimate the effect of the access route while the other characteristics of the patient are held fixed, and they therefore serve to separate the contribution of the route used from that of the clinical profile that determined its choice. The covariates were pre-specified, namely age, sex, estimated glomerular filtration rate by the CKD-EPI equation, haemoglobin, left ventricular ejection fraction, pre-procedural atrial fibrillation, prosthesis type and procedural era. Centre was not entered among the covariates because it almost entirely coincides with the access route, and for this reason the main analysis was repeated in the single site where both strategies were practised.

The determinants of the choice of access route were examined with a similar model whose outcome was the use of an alternative access. It was also checked whether the association between access route and primary endpoint changed within pre-specified subgroups, that is eGFR below 60 ml/min/1.73 m², age of 85 years or more, valve type and procedural era.

Outcomes were in addition compared between the individual access routes, with percutaneous transfemoral access as the reference, and the length of stay was compared across all groups with the Kruskal-Wallis test. These comparisons are unadjusted and, given the overlap between access route, centre and procedural era, they are regarded as exploratory.

All-cause survival was estimated with the Kaplan-Meier method and compared between the two access routes with the log-rank test. The effect of the access route on long-term mortality is also expressed as an adjusted hazard ratio, derived from a multivariable model for time to event.

Missing data were not imputed in the main analysis, and the unadjusted comparisons were made on the available cases, with the number of patients holding a documented value reported for each variable, while the variables documented in fewer than one quarter of the patients of either group are reported without comparison. The composite endpoint was taken as positive when at least one component was present and as negative when all the documented components were absent and at least three of the five had been recorded. The models were run on complete cases, and their stability was checked by repeating them after imputation of the missing covariates.

The loss of numbers in the models comes mainly from the ejection fraction, undocumented in about one quarter of the transfemoral patients, and from the date of the procedure, missing in 216 patients and with it the procedural era, to which is added, for the model on the determinants of the choice alone, peripheral artery disease, recorded only in the two centres of the Modena area. The analyses that use the procedural era are therefore confined to the 1092 procedures whose date is documented.

All tests are two-sided, with a significance threshold of 0.05 and without correction for multiple comparisons, and the subgroup analyses and those by individual access route are regarded as exploratory. The analyses were performed in Python 3.12 and the figures produced with matplotlib.

4. RESULTS

4.1 Study Population

Of the 1308 patients with a documented access route, 1051 (80.4%) underwent implantation by the percutaneous transfemoral route and 257 (19.6%) through an alternative access. Among the latter the transapical route is the most represented (118 patients, 9.0% of the cohort), followed by surgical femoral access (65, 5.0%), transaortic access (64, 4.9%) and axillary access (10, 0.8%).

The composition of the access routes changed deeply over the observation period. Among the 1092 procedures with an available date, alternative access accounted for more than 80% of the procedures in 2010 and 2011 and fell progressively over the decade. It went from 37.6% of the procedures performed up to 2017 to 5.6% of those performed from 2018 onwards, and to about 1% from 2019 (Figure 13).

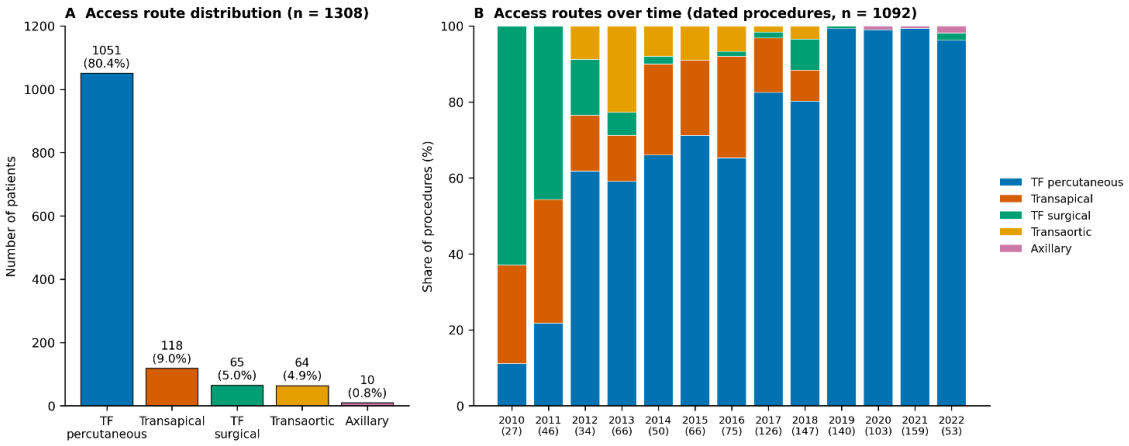


Figure 13. Access routes for transcatheter aortic valve implantation in the study cohort.
(A) Overall distribution of the access routes in the study population (n = 1308). Percutaneous transfemoral access was used in 1051 patients (80.4%), followed by transapical access (118, 9.0%), surgical femoral access (65, 5.0%), transaortic access (64, 4.9%) and axillary access (10, 0.8%). (B) Yearly composition of the access routes among the procedures with an available date (n = 1092; the total for each year is given in brackets).

Alternative accesses are in addition clustered by centre, since 248 of the 257 procedures performed by an alternative route (96.5%) were carried out at a single site, while at the other centres alternative access accounts for 3.5% of the procedures of one site and was not used at the remaining ones (Figure 14). This clustering shaped the analytical

strategy, since it made adjustment for centre impracticable and prompted the sensitivity analysis carried out within the single site where both strategies were practised.

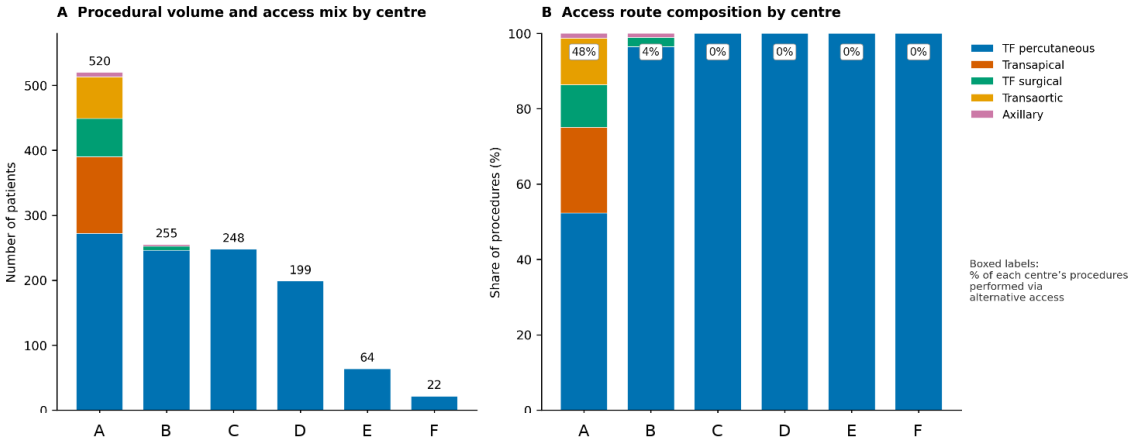


Figure 14. Access routes by treating centre.
(A) Procedural volume and composition of the access routes at each centre, with the totals above the bars. (B) Percentage composition of the access routes by centre; the boxed labels give the share of procedures performed by an alternative route at each site. The sites are identified by letters.

4.2 Baseline Characteristics by Access Route

The two groups are comparable for age (83.0 ± 4.4 against 83.0 ± 5.9 years), body mass index, renal function (eGFR 55.0 ± 20.9 against 55.4 ± 21.1 ml/min/1.73 m²) and haemoglobin. The differences are concentrated in the vascular and surgical profile, since the patients treated by an alternative route more often have peripheral artery disease (33.9% against 13.9%) and a previous coronary artery bypass operation (19.1% against 9.6%), and are less often female (43.6% against 54.6%).

The clinical picture is also more advanced in the alternative access group, which more often presents NYHA functional class III-IV (91.1% against 78.6%), a higher mean transvalvular gradient (48 against 45 mmHg) and a slightly lower ejection fraction. Several variables are, however, documented in a small share of patients, and for some of them the difference between the two groups is particularly marked. Peripheral artery disease is recorded in 504 of the 1051 transfemoral patients against all of those with alternative access, while smoking habit, previous stroke and previous myocardial infarction are documented in only 48 patients of the alternative group. The STS score, available in seven patients of that group, allows no interpretable comparison. Diabetes mellitus and pre-procedural atrial fibrillation are, finally, less frequent in the alternative

access group (Table 2). Serum creatinine, documented in 583 transfemoral patients against all of those with alternative access, is slightly higher in the latter (1.1 against 1.0 mg/dl), and the comparison of renal function was therefore made on eGFR, available in almost the whole population and used as a covariate in the models.

Two further differences concern procedural rather than clinical features, since the alternative accesses were performed almost exclusively with balloon-expandable prostheses (97.3% against 58.8%). The era also differs, since only 15.6% of the procedures by an alternative route were performed from 2018 onwards, against 65.0% of the transfemoral ones.

Variable	Percutaneous TF (n = 1051)	Alternative access (n = 257)	Documented data (TF / alt.)	p
Age, years	83.0 ± 4.4	83.0 ± 5.9	1051 / 257	0.125
Female sex	574 (54.6%)	112 (43.6%)	1051 / 257	0.002
Body mass index, kg/m²	26.4 ± 4.7	26.1 ± 4.1	1038 / 257	0.569
Arterial hypertension	941 (89.6%)	222 (86.4%)	1050 / 257	0.156
Diabetes mellitus	257 (24.5%)	43 (16.7%)	1049 / 257	0.035
Dyslipidaemia	730 (69.7%)	180 (70.0%)	1047 / 257	0.998
Smoking	285 (30.7%)	31 (64.6%)	927 / 48	< 0.001
Peripheral artery disease	70 (13.9%)	87 (33.9%)	504 / 257	< 0.001
COPD or asthma	164 (15.6%)	42 (16.3%)	1048 / 257	0.859
Previous stroke or TIA	104 (11.1%)	6 (12.5%)	933 / 48	0.956
Previous myocardial infarction	140 (15.0%)	10 (20.8%)	933 / 48	0.374
Previous PCI	242 (23.0%)	54 (21.0%)	1050 / 257	0.533
Previous CABG	101 (9.6%)	49 (19.1%)	1050 / 257	< 0.001
Pre-procedural atrial fibrillation	303 (28.9%)	53 (20.6%)	1050 / 257	0.010
Pre-procedural pacemaker	94 (9.0%)	20 (7.8%)	1049 / 256	0.646
NYHA III-IV	791 (78.6%)	234 (91.1%)	1006 / 257	< 0.001
LVEF, %	55.0 [50.0-60.0]	55.0 [48.0-60.0]	783 / 257	0.012
Mean gradient, mmHg	45.0 [40.0-55.0]	48.0 [40.0-57.0]	963 / 256	0.008
AVA, cm²	0.7 [0.6-0.8]	0.7 [0.6-0.9]	618 / 44	0.818
eGFR CKD-EPI, ml/min/1.73 m²	55.0 ± 20.9	55.4 ± 21.1	1026 / 257	0.477
Creatinine, mg/dl	1.0 ± 0.37	1.1 ± 0.38	583 / 257	< 0.001
Haemoglobin, g/dl	12.1 ± 1.7	12.1 ± 1.6	979 / 257	0.860
STS score, %	3.2 [2.2-4.7]	6.9 [4.9-8.8]	426 / 7	0.009
ACEF II	1.7 [1.5-2.2]	1.8 [1.5-2.6]	504 / 257	0.007
Balloon-expandable prosthesis	599 (58.8%)	249 (97.3%)	1018 / 256	< 0.001
Recent era (≥ 2018)	568 (65.0%)	34 (15.6%)	874 / 218	< 0.001

Table 2. Baseline characteristics of the study population according to the access route.

Values are expressed as n (%), mean ± standard deviation or median [interquartile range]. The column of documented data gives the number of patients with a recorded value in each group, to which the percentages refer. The EuroSCORE is not reported because it is documented in versions that are not comparable between centres, while the STS score, available in seven patients of the alternative access group, is reported for descriptive purposes. Continuous variables were compared with the Mann-Whitney U test and categorical variables with the chi-square test or Fisher's exact test. ACEF = age-creatinine-ejection fraction; AVA = aortic valve area; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; STS = Society of Thoracic Surgeons; TF = transfemoral.

4.3 Primary Endpoint

The primary composite endpoint occurred more frequently in the alternative access group than in the percutaneous transfemoral one, in 76 patients out of 257 (29.6%) against 228 out of 1050 (21.7%), with an odds ratio of 1.51 ($p = 0.010$). When the transfusion component is excluded from the composite, since it is recorded in only a minority of the patients treated by an alternative route, the difference widens to 27.2% against 15.6%, with an odds ratio of 2.02 ($p < 0.001$).

The excess is attributable mainly to acute kidney injury, which affected 23.7% of the patients treated by an alternative route against 8.9% of those treated transfemorally (OR 3.18; $p < 0.001$). Among the other components, transfusion of at least one unit of red cells was numerically more frequent after alternative access (25.5% against 14.4%; $p = 0.059$), while the cerebrovascular event within 30 days does not differ between the groups (3.5% against 2.2%). Major vascular complications show a numerically lower frequency, not significant, in the alternative access group (2.7% against 4.7%). Major bleeding according to the VARC-2 criteria was less frequent after alternative access (0.8% against 6.1%; $p < 0.001$), a finding that rests on two events only and that is explained by the single-centre sensitivity analysis. The length of stay was one day longer in the alternative access group (median 8 against 7 days; $p < 0.001$) (Table 3).

Outcome	Percutaneous TF	Alternative access	OR (95% CI)	p
Primary composite endpoint	228/1050 (21.7%)	76/257 (29.6%)	1.51 (1.12-2.05)	0.010
Composite without transfusion	164/1049 (15.6%)	70/257 (27.2%)	2.02 (1.47-2.79)	< 0.001
Acute kidney injury (any stage)	93/1042 (8.9%)	61/257 (23.7%)	3.18 (2.22-4.54)	< 0.001
Major bleeding (VARC-2)	63/1038 (6.1%)	2/241 (0.8%)	0.13 (0.03-0.53)	< 0.001
Major vascular complication	49/1047 (4.7%)	7/256 (2.7%)	0.57 (0.26-1.28)	0.229
Stroke or TIA within 30 days	23/1050 (2.2%)	9/257 (3.5%)	1.62 (0.74-3.55)	0.320
Transfusion of ≥ 1 unit of red cells	133/926 (14.4%)	12/47 (25.5%)	2.04 (1.03-4.04)	0.059
Length of stay, days (median [IQR])	7 [5-10]	8 [7-11]	—	< 0.001

Table 3. Unadjusted periprocedural complications according to the access route.
The odds ratio expresses the risk associated with alternative access relative to percutaneous transfemoral access, taken as the reference. The denominators give the patients with a documented value for each outcome. IQR = interquartile range; OR = odds ratio; TF = transfemoral; TIA = transient ischaemic attack; VARC = Valve Academic Research Consortium.

In the multivariable logistic regression analysis, carried out on 788 patients and 178 events, alternative access remained independently associated with the primary endpoint

relative to percutaneous transfemoral access, with an adjusted odds ratio of 2.10 (p = 0.003). The association strengthened in the model without the transfusion component (aOR 2.58; p < 0.001) and was greatest for acute kidney injury, of which alternative access is the strongest independent predictor (aOR 3.28; p < 0.001).

Among the other covariates, a lower baseline renal function was independently associated both with the composite endpoint and with acute kidney injury, while age, sex, atrial fibrillation and ejection fraction showed no independent association. The use of a balloon-expandable prosthesis was associated with a lower probability of the composite endpoint (OR 0.60), an effect that is attenuated and no longer significant once the transfusion component is excluded (Table 4).

Since the alternative accesses are concentrated at a single site, which practised both strategies, the main analysis was repeated in the 520 patients treated at that centre. The excess is confirmed, with the primary composite endpoint in 29.0% of the patients treated by an alternative route against 15.8% (OR 2.18; p < 0.001) and acute kidney injury in 23.8% against 8.5%, while major bleeding and major vascular complications do not differ between the two routes. The lower frequency of bleeding seen with alternative access in the whole population is therefore not confirmed within the single centre.

Model (outcome)	Variable	OR (95% CI)	p
Primary composite endpoint	Alternative access	2.10 (1.28-3.45)	0.003
(n = 788; 178 events)	eGFR CKD-EPI	0.98 (0.97-0.99)	< 0.001
	Balloon-expandable prosthesis	0.60 (0.39-0.92)	0.018
	Haemoglobin	0.90 (0.81-1.01)	0.066
Composite without transfusion	Alternative access	2.58 (1.54-4.32)	< 0.001
(n = 788; 143 events)	eGFR CKD-EPI	0.98 (0.97-0.99)	0.002
Acute kidney injury	Alternative access	3.28 (1.83-5.89)	< 0.001
(n = 782; 100 events)	eGFR CKD-EPI	0.98 (0.97-1.00)	0.014
One-year mortality	Alternative access	1.47 (0.66-3.24)	0.347
(n = 744; 54 events)	Haemoglobin	0.78 (0.66-0.93)	0.006
	Pre-procedural atrial fibrillation	1.90 (1.06-3.42)	0.032

Table 4. Multivariable analysis of the association between access route and outcomes.

The variables with a significant association and those of clinical interest are reported, and all models are adjusted for age, sex, eGFR, haemoglobin, pre-procedural atrial fibrillation, ejection fraction, prosthesis type and procedural era. Percutaneous transfemoral access is the reference category. eGFR = estimated glomerular filtration rate; OR = odds ratio.

4.4 Secondary Endpoints

Periprocedural mortality was higher in the alternative access group, with 7 deaths out of 257 (2.7%) against 9 out of 1041 (0.9%), an odds ratio of 3.21 (p = 0.025). When in-hospital deaths and those within 30 days are considered together, including the periprocedural ones, the difference weakens and does not reach statistical significance (3.9% against 2.0%; OR 1.99; p = 0.105). At one year mortality is comparable between the two groups (9.8% against 9.4%; OR 1.05; p = 0.896) (Table 5).

The absence of an association at one year is confirmed by the multivariable model, in which the access route is not independently associated with mortality (adjusted OR 1.47; p = 0.347; 744 patients, 54 events). The only independent predictors of death at one year were a lower haemoglobin concentration (OR 0.78 per g/dl) and pre-procedural atrial fibrillation (OR 1.90), and given the small number of events relative to the covariates included the model should be regarded as exploratory. Taken as a whole, the cost associated with alternative access is concentrated in the periprocedural window and weakens thereafter, and no detectable association with mortality at a distance emerges.

Endpoint	Percutaneous TF	Alternative access	OR (95% CI)	p
Periprocedural mortality	9/1041 (0.9%)	7/257 (2.7%)	3.21 (1.18-8.70)	0.025
In-hospital or 30-day mortality	21/1051 (2.0%)	10/257 (3.9%)	1.99 (0.92-4.27)	0.105
One-year mortality	76/808 (9.4%)	21/214 (9.8%)	1.05 (0.63-1.74)	0.896

Table 5. Periprocedural, 30-day and one-year mortality according to the access route.

Periprocedural death is taken from the dedicated variable of the registry. In-hospital or 30-day mortality includes, cumulatively, the periprocedural deaths and those documented within 30 days of the procedure and is computed on the whole population, so that the 71 deaths without a documented date and not coded as periprocedural do not appear among the events. The one-year analysis is confined to the procedures performed up to 2021, counts the periprocedural deaths as events and does not include the same 71 deaths, which cannot be placed in time, so that a slight underestimate of early mortality in both groups may follow. Comparisons were made with Fisher's exact test. OR = odds ratio; TF = transfemoral.

4.5 Long-Term Survival

The Kaplan-Meier analysis was carried out in the 1053 patients with a known date of procedure and vital status, of whom 838 were treated by the percutaneous transfemoral route and 215 by an alternative route, with 420 deaths in all. Over five years all-cause survival does not differ between the two groups (p = 0.22). The survival estimates at one, three and five years were 90.9%, 75.7% and 59.7% with percutaneous transfemoral access and 91.6%, 79.5% and 67.3% with alternative access (Figure 15).

The numerically higher survival seen in the alternative access group does not express an advantage of the route used, but reflects the concentration of that group in the early procedural era, to which a longer completed follow-up corresponds. After multivariable adjustment the access route is not associated with long-term mortality (HR 1.13; p = 0.37). Taken together with the estimates by time interval, these analyses indicate that the excess risk associated with alternative access is confined to the periprocedural phase, and that no detectable association between access route and long-term mortality emerges.

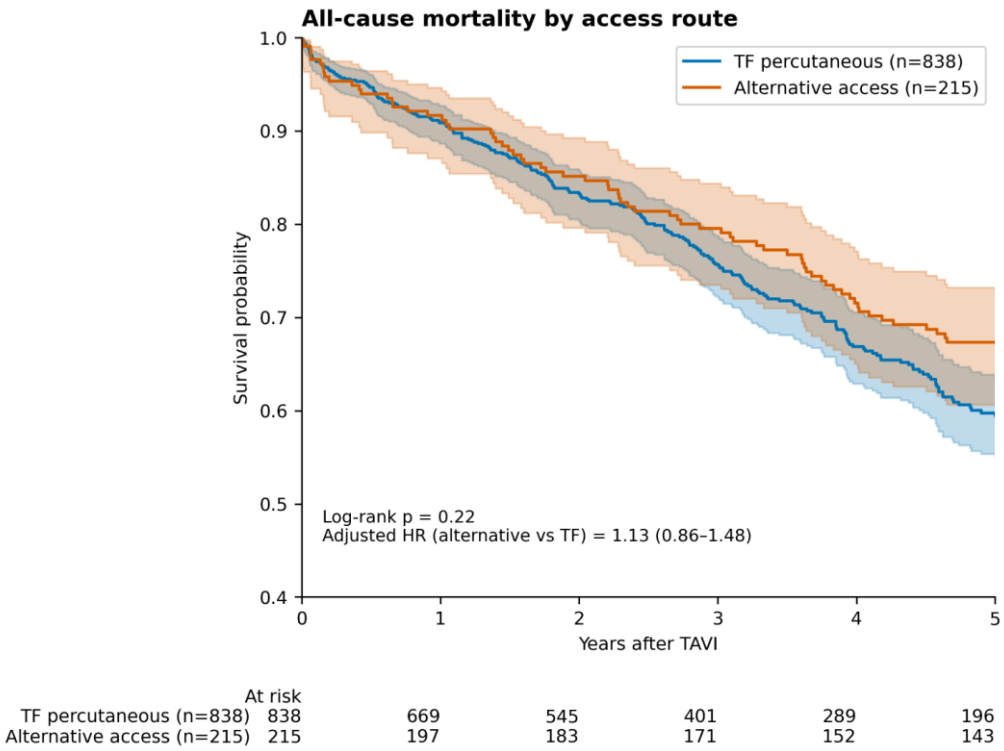


Figure 15. All-cause survival according to the access route.
Kaplan-Meier estimates with the number of patients at risk. Patients without an individual date of last contact were censored at the date of the most recent registry check of their own centre. The shaded areas represent the 95% confidence intervals and the y-axis is truncated at 0.4.

4.6 Outcomes According to the Individual Access Route

Breaking the alternative access group down into the individual routes documents a substantial heterogeneity. The periprocedural excess is concentrated in the thoracic approaches, since acute kidney injury affected 27.1% of the patients treated by the transapical route and 28.1% of those treated by the transaortic route, against 8.9% for percutaneous transfemoral access, with odds ratios of 3.80 and 3.99 respectively (both p

< 0.001). Transaortic access is in addition associated with an excess of the primary composite endpoint (37.5% against 21.7%; OR 2.16; p = 0.005) and of periprocedural mortality (4.7% against 0.9%; OR 5.64; p = 0.028). Transapical access instead shows a higher in-hospital or 30-day mortality (5.1% against 2.0%; OR 2.63; p = 0.047). In the composite without the transfusion component both thoracic routes remain significantly associated with the endpoint (Figure 16).

Femoral access with surgical exposure of the vessel behaves instead like the percutaneous one, with no significant excess for any early outcome, since the primary composite endpoint affected 23.1% of patients against 21.7% (OR 1.08). The axillary group, made of ten patients, allows no interpretable comparison. The length of stay was one day longer with both thoracic routes (median 8 days against 7; p < 0.001 in the comparison across all groups).

The early differences are not maintained over time, and mortality at one, three and five years does not differ significantly between any of the individual routes and percutaneous transfemoral access, with a five-year mortality of 34.9% for the transapical route, 42.5% for the transaortic one and 25.4% for the surgical femoral one, against 35.0% for the percutaneous route. Given the overlap between access route, centre and procedural era, these unadjusted comparisons should be regarded as exploratory (Table 6).

Outcome	Percutaneous TF	Surgical TF	Transapical	Transaortic	Axillary
Primary composite endpoint	228/1050 (21.7%) (reference)	15/65 (23.1%) 1.08 (0.60-1.96) p = 0.759	33/118 (28.0%) 1.40 (0.91-2.15) p = 0.130	24/64 (37.5%) 2.16 (1.28-3.66) p = 0.005	4/10 (40.0%) 2.40 (0.67-8.59) p = 0.239
Composite without transfusion	164/1049 (15.6%) (reference)	14/65 (21.5%) 1.48 (0.80-2.74) p = 0.221	33/118 (28.0%) 2.10 (1.36-3.24) p = 0.002	20/64 (31.2%) 2.45 (1.41-4.27) p = 0.003	3/10 (30.0%) 2.31 (0.59-9.04) p = 0.199
Acute kidney injury (any stage)	93/1042 (8.9%) (reference)	10/65 (15.4%) 1.86 (0.92-3.76) p = 0.118	32/118 (27.1%) 3.80 (2.40-6.00) p < 0.001	18/64 (28.1%) 3.99 (2.22-7.17) p < 0.001	1/10 (10.0%) 1.13 (0.14-9.05) p = 0.609
Periprocedural mortality	9/1041 (0.9%) (reference)	1/65 (1.5%) 1.79 (0.22-14.36) p = 0.456	3/118 (2.5%) 2.99 (0.80-11.21) p = 0.115	3/64 (4.7%) 5.64 (1.49-21.36) p = 0.028	0/10 (0.0%) —
In-hospital or 30-day mortality	21/1051 (2.0%) (reference)	1/65 (1.5%) 0.77 (0.10-5.79) p = 1.000	6/118 (5.1%) 2.63 (1.04-6.65) p = 0.047	3/64 (4.7%) 2.41 (0.70-8.31) p = 0.155	0/10 (0.0%) —
One-year mortality	76/839 (9.1%) (reference)	2/64 (3.1%) 0.32 (0.08-1.35) p = 0.161	12/109 (11.0%) 1.24 (0.65-2.37) p = 0.485	6/40 (15.0%) 1.77 (0.72-4.35) p = 0.257	1/3 (33.3%) —
Three-year mortality	171/839 (20.4%) (reference)	7/64 (10.9%) 0.48 (0.21-1.07) p = 0.073	28/109 (25.7%) 1.35 (0.85-2.14) p = 0.212	10/40 (25.0%) 1.30 (0.62-2.72) p = 0.547	2/3 (66.7%) —

Outcome	Percutaneous TF	Surgical TF	Transapical	Transaortic	Axillary
Five-year mortality	240/686 (35.0%) (reference)	16/63 (25.4%) 0.63 (0.35-1.14) p = 0.130	38/109 (34.9%) 0.99 (0.65-1.52) p = 1.000	17/40 (42.5%) 1.37 (0.72-2.62) p = 0.395	2/2 (100%) —
Length of stay, days, median [IQR]	7 [5-10]	7 [7-10]	8 [7-11]	8 [7-11]	7 [6-8]

Table 6. Early and late outcomes according to the individual access route.

The odds ratios with their 95% confidence intervals are expressed relative to percutaneous transfemoral access, taken as the reference category. Comparisons were made with the chi-square test or Fisher's exact test, and the length of stay was compared across all groups with the Kruskal-Wallis test ($p < 0.001$). The mortality estimates at one, three and five years derive from the vital status at data lock and do not include the deaths without a documented date. In the axillary group, made of ten patients, the estimates are not interpretable, and the odds ratios are not reported where they would rest on empty cells. IQR = interquartile range; TF = transfemoral.

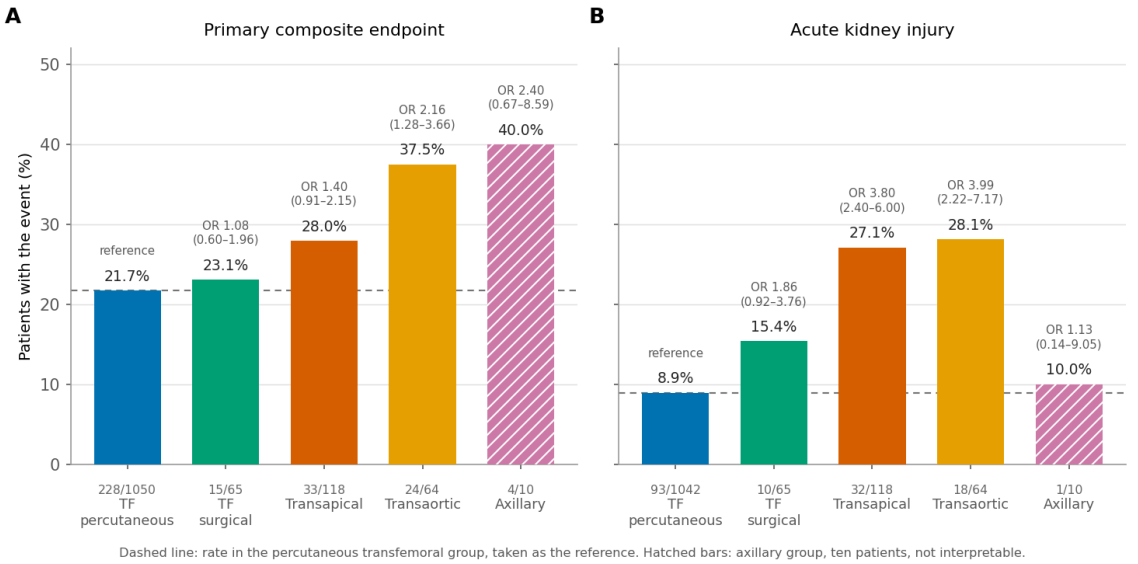


Figure 16. Periprocedural outcomes according to the individual access route.

(A) Primary composite endpoint. (B) Acute kidney injury. The dashed line marks the rate observed in the percutaneous transfemoral group, taken as the reference. Above each bar are the unadjusted odds ratio with its 95% confidence interval, and below the axis the number of events over the number of patients with a documented outcome. The hatched bars are the axillary group, made of ten patients, whose estimates are not interpretable.

4.7 Determinants of Access Route Selection

The determinants of the choice of access route were analysed in the 550 patients treated at the centres where both strategies were practised and for whom the peripheral vascular status was documented, of whom 218 underwent an alternative access. Since peripheral artery disease is recorded only at the two centres of the Modena area, the model is in practice limited to those sites. The strongest clinical determinant was peripheral artery disease (OR 2.74; $p < 0.001$), followed by previous coronary artery bypass grafting (OR 2.13; $p = 0.021$).

By far the largest effect is nevertheless exerted by the procedural era, since the procedures performed from 2018 onwards show a reduction of about 91% in the probability of recourse to an alternative access (OR 0.089; $p < 0.001$), independently of all clinical characteristics. Advanced age and female sex are associated with a lower probability of alternative access, while body mass index, diabetes, renal function and ejection fraction show no independent association (Table 7).

Variable	OR (95% CI)	p
Peripheral artery disease	2.74 (1.59-4.74)	< 0.001
Previous CABG	2.13 (1.12-4.05)	0.021
Recent era (≥ 2018)	0.089 (0.056-0.142)	< 0.001
Age (per year)	0.96 (0.92-1.00)	0.033
Female sex	0.59 (0.37-0.93)	0.022
Body mass index	0.97 (0.92-1.01)	0.153
Diabetes mellitus	0.75 (0.52-1.10)	0.141
eGFR CKD-EPI	0.99 (0.98-1.00)	0.160
Ejection fraction	1.00 (0.98-1.02)	0.898

Table 7. Independent determinants of recourse to an alternative access.
Multivariable logistic regression model carried out on 550 patients, of whom 218 underwent an alternative access; the dependent variable is recourse to an alternative access. CABG = coronary artery bypass grafting; eGFR = estimated glomerular filtration rate; OR = odds ratio.

4.8 Subgroup Analysis

The association between alternative access and the primary endpoint was directionally consistent in all the pre-specified subgroups, with no significant modification of the effect (all values of p for interaction ≥ 0.106). In the adequately populated strata the odds ratios lie between 1.30 and 1.81, and the excess is present in the patients with eGFR below 60 ml/min/1.73 m² and in those with preserved renal function, as well as below and above 85 years of age, although it reaches significance only in the strata with preserved renal function and with age below 85 years (Table 8).

Two strata allow no interpretation, since the one of the patients treated with a self-expanding prosthesis contains only 7 patients who underwent an alternative access, so that the corresponding estimate has no clinical meaning.

In the recent era, in which alternative access has become infrequent (34 patients), the point estimate weakens towards the absence of an effect compared with the earlier era, but the interaction does not reach significance and the finding should be regarded as hypothesis-generating.

Subgroup	Percutaneous TF	Alternative access	OR (95% CI)	p for interaction
eGFR < 60 ml/min/1.73 m²	160/602 (26.6%)	50/147 (34.0%)	1.42 (0.97-2.10)	0.468
eGFR ≥ 60 ml/min/1.73 m²	62/424 (14.6%)	26/110 (23.6%)	1.81 (1.08-3.03)	0.468
Age ≥ 85 years	104/402 (25.9%)	30/96 (31.2%)	1.30 (0.80-2.12)	0.414
Age < 85 years	124/648 (19.1%)	46/161 (28.6%)	1.69 (1.14-2.51)	0.414
Balloon-expandable prosthesis	113/599 (18.9%)	71/249 (28.5%)	1.72 (1.22-2.42)	0.106
Self-expanding prosthesis	111/418 (26.6%)	5/7 (71.4%)	6.91 (1.32-36.15)	0.106
Earlier era (≤ 2017)	60/305 (19.7%)	50/184 (27.2%)	1.52 (0.99-2.34)	0.413
Recent era (≥ 2018)	130/568 (22.9%)	8/34 (23.5%)	1.04 (0.46-2.35)	0.413

Table 8. Consistency of the association between alternative access and the primary endpoint in the pre-specified subgroups.

The odds ratios are unadjusted and are computed within each stratum, and values are expressed as events/patients (%). The estimate for the self-expanding stratum rests on seven patients and is not interpretable. eGFR = estimated glomerular filtration rate; OR = odds ratio; TF = transfemoral.

5. DISCUSSION

5.1 Periprocedural Risk and Acute Kidney Injury

In a regional multicentre cohort that spans the whole period over which transcatheter aortic valve implantation has spread, alternative access was associated with an excess of periprocedural complications compared with percutaneous transfemoral access. The association remained significant after adjustment for the clinical characteristics, the prosthesis type and the procedural era.

The excess is primarily driven by acute kidney injury, of which alternative access proved the strongest independent predictor. Alongside renal damage, the length of stay and periprocedural mortality are also higher, while no solid association emerges for the other components of the composite. The lower frequency of major bleeding seen in the whole cohort is not confirmed within the single centre and is therefore likely to reflect differences in the recording of events between sites rather than an effect of the route used.

The finding is consistent with the literature, as the meta-analysis by Liao et al. on the predictors of acute kidney injury after transcatheter implantation identifies transapical access, major bleeding and transfusion among the independent determinants, alongside the comorbidities of the patient (76). The frequencies observed here, 8.9% after percutaneous transfemoral access and 23.7% after an alternative access, fall within the range reported in that meta-analysis, whose width reflects the different definitions adopted. In the Danish national registry the use of a non-transfemoral access proved markedly more frequent among the patients who developed acute kidney injury than among those who remained free of it (77).

The prevailing mechanism indicated by the literature is not the contrast load, which in the same meta-analysis did not prove an independent predictor of acute kidney injury, but the fall in cardiac output and the resulting multi-organ damage. The authors therefore recommend limiting the duration of the hypotension linked to rapid pacing, to valvuloplasty and to deployment of the prosthesis, and they point to periprocedural hydration as a protective measure, alongside the prevention of bleeding and transfusion (76). The thoracic approaches, which add to that mechanism general anaesthesia, the

opening of the chest and a greater blood loss, sit consistently at the least favourable end of this gradient.

That the damage is attributable to the procedure rather than to the pre-existing renal condition is supported by the baseline profile of the two groups, comparable for estimated glomerular filtration, and by the association observed also in the patients with preserved renal function. It should be remembered, however, that the population treated has impaired renal function from the outset, with a mean glomerular function corresponding to stage 3 and with about six patients in ten below the threshold of 60 ml/min/1.73 m². This does not weaken the comparison, since the two groups start from the same renal function, but it explains why in this population the procedural insult produces damage so frequently, given that chronic kidney disease is itself a risk factor for acute kidney injury (76) and the insult falls on an organ whose reserve is already reduced.

5.2 Heterogeneity Between Access Routes

The comparisons made so far group the alternative routes into two blocks, whereas the present cohort makes it possible to observe them separately. The excess is not distributed uniformly among them, but is concentrated in the thoracic approaches. Acute kidney injury affects about one quarter of the patients treated by the transapical or transaortic route, against fewer than one in ten of those treated percutaneously, and these two approaches are also associated with the longest stay and the highest early mortality. Femoral access with surgical exposure of the vessel shows instead no significant excess for the early outcomes and behaves like percutaneous access, while the axillary group is too small to allow a comparison. The comparisons between the individual routes are unadjusted and are therefore to be taken as exploratory.

The distribution finds a plausible explanation in the nature of the procedures themselves, because transapical and transaortic access require the opening of the chest, general anaesthesia and direct handling of the heart or of the ascending aorta. This results in greater expected blood loss and longer periods of haemodynamic instability follow. Femoral access, whether percutaneous or with surgical exposure of the vessel, involves instead the puncture of a peripheral artery and does not substantially alter the

haemodynamic course of the procedure. This is most likely the reason why the two femoral modalities behave in the same way (60).

The gradient observed in the present cohort is consistent with the literature. The meta-analysis by Chandrasekhar et al., which compares femoral access with alternative accesses, documents a higher periprocedural mortality with the non-femoral routes (84), while the one by Abellan et al., devoted to the comparison between intrathoracic and extrathoracic routes, attributes to the former a greater risk of early mortality and of acute kidney injury requiring renal replacement therapy (59). In the Hostile registry, which compared the routes used in patients with peripheral artery disease, both the transfemoral route and the non-thoracic alternative route showed a lower rate of major adverse events than the transthoracic route (56).

Furthermore, direct comparisons in the literature between a single extrathoracic route and the femoral route indicate that the renal cost is confined to the thoracic approaches. A propensity-score matched analysis of the carotid route against the femoral route was conducted in a population in which, before matching, peripheral artery disease was far more widespread and the operative risk higher in the carotid group. In this study acute kidney injury proved comparable between the two groups both in hospital and at thirty days, as did mortality up to two years (63). A comparison between the percutaneous axillary route and the femoral route likewise documented no significant differences in the early outcomes (87). The non-thoracic routes are not, however, equivalent to one another, nor free of costs of their own. In the NORTHOSTAVI registry, which compares the alternative endovascular accesses with each other, the frequency of acute kidney injury varies appreciably according to the route used (58), and the British registry devoted to the percutaneous axillary route documents a far from negligible share of cerebrovascular events and of major vascular complications (88). Therefore, the risk profile of this routes differs from that of thoracic approaches, rather than being entirely absent.

The comparison between the two femoral modalities highlights the limitation of considering the alternative group as homogeneous, a finding consistent with the literature. In the meta-analysis by Riaz et al. percutaneous femoral access and femoral access with surgical exposure do not differ in clinically relevant outcomes, except for a

higher frequency of minor vascular complications in the percutaneous group (60). It follows that, for the purposes of the periprocedural outcomes, the relevant distinction does not concern the way in which the vessel is exposed, but the site through which the valve is reached.

5.3 The Course over Time

Over five years no detectable association emerges between access route and all-cause mortality, either in the overall comparison or when the individual routes are considered. This should not be interpreted as evidence that the routes are prognostically equivalent, given that the absence of a statistically detectable difference is not proof that no difference exists. It does indicate, however, that the excess risk documented in the periprocedural window does not extend into an evident disadvantage later on.

The course of the renal damage helps to explain this pattern, as in the Danish national registry the patients who developed acute kidney injury showed at one year a markedly higher risk of dialysis and a markedly higher mortality than the patients who remained free of it. The association proved graded with respect to the size of the rise in creatinine. About three quarters of the survivors had, however, fully recovered renal function within six months, while the remaining quarter retained persistent damage (77). The recovery of most patients helps to understand why an excess concentrated in the periprocedural phase may not translate into a prognostic gap detectable later on.

The comparisons recalled here stop at thirty days or at one year (59,84). Extending the observation to five years, and breaking it down by individual route, makes it possible to place the periprocedural excess in a longer perspective, in which it is not followed by a detectable gap in survival.

5.4 Determinants of the Choice of Access Route

The use of an alternative access is associated with peripheral artery disease and with previous coronary artery bypass grafting, but by far the largest effect is exerted by the procedural era, independently of all the clinical characteristics considered. The procedures performed from 2018 onwards show a reduction of about 91% in the probability of undergoing an alternative approach. Advanced age and female sex are

associated instead with a lower probability of alternative access. The direction is the opposite of the one that the smaller femoral calibre of women would suggest, and it is most plausibly explained by the clinical profile that leads to an alternative route, in which peripheral artery disease and previous bypass surgery weigh most.

The finding reflects the progressive reduction in the calibre of delivery systems, which has widened the proportion of patients anatomically suitable for the femoral route and has narrowed recourse to the alternative routes to the cases that remain excluded from it (44,52). It follows that a comparison between access routes conducted over an extended span of time also incorporates the difference between two eras of the technique, and it is for this reason that the procedural era was included among the covariates of the models. The association remains significant after that adjustment, while in the recent era alone the estimate weakens without the interaction reaching significance, on a number of alternative procedures too small for a comparison.

5.5 Clinical Implications

A first implication concerns patient selection, considering that the absence of a detectable association between access route and long-term mortality provides no evidence that the impossibility of using the femoral route constitutes in itself a prognostically unfavourable condition in the medium term. It is therefore not an argument for leaving the patient untreated. The question moves to the management of the periprocedural phase, which is the window in which the risk is concentrated.

As to the choice between the alternatives, the data presented here indicate that the clinically relevant distinction runs between the routes that involve opening the chest and those that do not, rather than between femoral and non-femoral access. The European recommendations already place the alternative transvascular routes before the transthoracic ones in the decision-making hierarchy of the Heart Team (42,44). The present observations are consistent with that ordering, although they cannot test it directly, since in the cohort the non-thoracic routes other than the femoral one are represented by a small number of patients. That ordering finds, moreover, an explicit foundation in the literature, since the alternative endovascular routes were developed in order to mitigate the unfavourable outcomes of the transthoracic approaches (58).

As to the protection of the patient referred to a thoracic route, since the excess of renal damage is observed also in the patients with preserved renal function, a pre-procedural assessment resting on glomerular filtration alone does not capture this risk. It follows that the patient who is a candidate for a thoracic access should be regarded as being at renal risk irrespective of the baseline filtration. Attention should be directed to the elements that the literature indicates as modifiable, namely the duration of intraprocedural hypotension, periprocedural hydration and the prevention of bleeding and transfusion (76). A check of renal function after discharge is also justified, given the prognostic weight that acute kidney injury retains later on (77).

These indications must finally be placed in their temporal context, since the use of thoracic access has fallen sharply over the observation period. The phenomenon described concerns in large part a season of the technique now superseded by the reduction in the calibre of delivery systems (44). What remains, however, is the risk profile of the patients who are still today referred to a thoracic route, who are by definition those without alternatives and therefore the most fragile.

5.6 Study Limitations

The main limitation is inherent in the observational design. The access route is not assigned at random, but follows from a clinical assessment that combines vascular anatomy, risk profile and comorbidities, so that confounding by indication cannot be eliminated and no adjustment can guarantee control of the unmeasured variables (86). How far adjustment may change the estimates is documented by the meta-analysis by Faroux et al. on carotid and subclavian access, in which the excess of 30-day mortality and of bleeding seen in the unadjusted data disappears after adjustment, while the excess of stroke persists in both analyses (81).

An additional limitation is specific to the present cohort. Access route, centre and procedural era are almost completely overlapping, beacause nearly all the alternative accesses come from a single site and are concentrated in the first years of the observation period.

Centre could not therefore be included among the covariates, and the comparisons between the individual routes, made without adjustment, should be regarded as exploratory. The analysis confined to the site that practised both strategies weakens but does not remove this limitation.

Some groups are, in addition, too small to allow conclusions. Axillary access comprises ten patients and the carotid and transcaval routes are not represented, so that the considerations concerning the non-thoracic alternatives rest on the literature and not on a direct comparison made within the study.

Regarding data completeness, some variables are incompletely documented. The surgical risk scores cannot be used for the comparison, the ejection fraction is missing in a substantial proportion of the patients treated by the femoral route and the date of the procedure is not available for everyone. A loss of numbers in the models follows, although the sensitivity analysis carried out after imputation of the missing covariates returned estimates in the same direction. A far from negligible number of deaths is also without a documented date, with a possible slight underestimate of early mortality in both groups. It should finally be recalled that surgical femoral access was kept in the alternative access group, although in the outcomes it behaves like the percutaneous one, a choice that weakens the difference between the two groups rather than amplifying it.

5.7 Future Perspectives

Several of the limitations described point to as many directions for further work, the first of which concerns the individual access routes. Adjusted estimates for the thoracic approaches, and the extension of the comparison by route to complications other than acute kidney injury, would make it possible to check whether the gradient observed withstands control for the clinical characteristics. A series that included an adequate number of non-femoral transvascular accesses would also make it possible to check directly whether those routes avoid the renal cost attributed to the thoracic approaches.

The second direction concerns renal damage as an outcome in its own right. The systematic documentation of creatinine in the days following the procedure and during follow-up, alongside indicators less dependent on muscle mass, would make it possible to estimate the true incidence of the damage and the share of patients who do not

recover their baseline function. Looking further ahead, the prospective evaluation of a structured pathway of renal protection in patients referred to a thoracic route would mark the step from observation to intervention.

The third direction is descriptive in kind, since the composition of the access routes has changed deeply over time. An update of the registry limited to the most recent years would therefore make it possible to establish what the profile is today of the few patients who still receive a thoracic access and whether the risk associated with it has changed as the techniques have evolved.

6. CONCLUSIONS

The results of this cohort indicate that the use of an alternative route carries a measurable periprocedural cost, of which acute kidney injury is the main component, accompanied by a longer stay and a higher periprocedural mortality. Given that the baseline renal function is comparable in the two groups, that cost appears attributable to the procedure rather than to the condition of the patient.

The cost does not, however, fall equally on all the alternative routes, but on the approaches that involve opening the chest, while femoral access with surgical exposure of the vessel showed no excess, in agreement with the published comparison between the two femoral modalities. The clinically useful distinction therefore appears to concern the site through which the valve is reached, rather than the technique by which the vessel is exposed.

Up to five years no association was detected between the route used and all-cause mortality, although prognostic equivalence between the routes cannot be inferred from this. The risk documented therefore appears confined to the periprocedural phase.

It follows that the impossibility of using the femoral route is not in itself an argument against treatment, and that attention should be directed to the conduct of the procedure in the patient referred to a thoracic route. In these patients the excess of renal damage is observed also when the baseline glomerular filtration is preserved, so that surveillance of renal function should be planned irrespective of the baseline value.

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