



UNIVERSITA' DEGLI STUDI "G. D'Annunzio"

Chieti-Pescara

SCUOLA SUPERIORE "G. D'Annunzio"

Dottorato di Ricerca in

INNOVATIVE TECHNOLOGIES IN CLINICAL MEDICINE AND DENTISTRY

CICLO XXXVIII

**ZERO-CONTRAST TRANSCATHETER AORTIC VALVE
IMPLANTATION (TAVI): SAFETY AND FEASIBILITY IN PATIENTS
WITH AORTIC STENOSIS AND RENAL IMPAIRMENT.**

Dipartimento di Tecnologie Innovative in Medicina e Odontoiatria

Settore Scientifico Disciplinare MEDS-26/D

Dottoranda

Dott.ssa Melissa Foglietta

Coordinatore

Prof. Sergio Caputi

Tutor

Prof. Jacopo Pizzicannella

Anni Accademici 2023/2025

SUMMERY

1. BACKGROUND

1.1 AORTIC VALVE STENOSIS

1.1.1 DIAGNOSIS

1.1.2 TREATMENTS

1.2 TAVI

1.3 CHRONIC KIDNEY DISEASE

1.4 ACUTE KIDNEY INJURY

1.5 TAVI ZERO CONTRAST

2. ZERO CONTRAST TAVI STUDY

2.1 OBJECTIVES

2.2 MATERIALS AND METHODS

2.3 STATISTICAL ANALYSIS

2.4 RESULTS

2.5 DISCUSSION

2.6 LIMITATIONS

2.7 CONCLUSION

REFERENCES

ABBREVIATIONS AND ACRONYMS

AKI acute kidney injury

AS aortic stenosis

AV aortic valve

AVA aortic valve area

BAV bicuspid aortic valve

BHV bioprosthetic heart valve

CT computed tomography

CV contrast volume

CV/CrCl contrast volume-to-creatinine clearance ratio

CIN contrast-induced nephropathy

CMR cardiac magnetic resonance

CKD chronic kidney disease

eGFR estimated glomerular filtration rate

HT heart team

LVEF left ventricle ejection function

LVOT left ventricle obstruction tract

MHV mechanical heart valve

NSVD non-structural valve dysfunction

PPM permanent pacemaker

PVL paravalvular leaks

SIRS systemic inflammatory response syndrome

SVD structural valve deterioration

TIA transient ischemic attack

TAVI transcatheter aortic valve implantation

TOE transesophageal echocardiography

TTE Transthoracic echocardiography

VTI velocity time integral

ZC zero-contrast

1. BACKGROUND

1.1. AORTIC VALVE STENOSIS

Aortic stenosis (AS) is the most common primary and clinically significant valvular heart disease and referred for intervention in developed countries. Degenerative pathogenesis with cusps calcification is now the predominant aetiology in industrialized countries, whereas rheumatic heart disease - usually presented combined with rheumatic mitral valve disease - remains more common in low-and middle-income countries.^{1 2}

Risk factors for calcific aortic stenosis overlap with those of atherosclerosis and include advanced age, male sex, arterial hypertension, hyperlipidaemia, diabetes mellitus, and smoking. Genetic predispositions, such as bicuspid aortic valve - present in 1–2% of the population - or rarely unicuspid aortic valve, also play an important role, with earlier degeneration and faster progression and frequently are associated with dilatation of the aortic root or ascending aorta.³

4 5

The prevalence of aortic stenosis increases significantly with age, making it a major public health concern in aging populations.

Population-based studies estimate that moderate-to-severe AS affects approximately 2–4% of adults over the age of 65, and up to 10% of individuals older than 80 years.

AS is a disease slowly evolving from mild to severe valve obstruction because of increasing valve fibrosis and calcification, although progression accelerates as haemodynamic severity increases.

It is characterized by a progressive narrowing of the aortic valve orifice, leading to obstruction of left ventricular outflow, increased afterload, compensatory left ventricular hypertrophy, and ultimately heart failure if untreated.

The natural history of the disease involves a long latent phase during which the valve area progressively decreases due to active calcification and fibrosis. Once symptoms such as angina, syncope, or dyspnoea on exertion appear, the prognosis worsens dramatically without intervention.⁶

In fact, symptomatic severe aortic stenosis carries a poor prognosis, with average survival rates of two to three years without valve replacement.

Advances in imaging, surgical techniques, and percutaneous interventions have dramatically changed the landscape of diagnosis and management in recent decades.

1.1.1 DIAGNOSIS

Diagnosis of aortic stenosis is based on a combination of clinical evaluation, non-invasive imaging, and, in selected cases, invasive hemodynamic assessment.

Clinical findings may include a harsh, crescendo–decrescendo systolic murmur best heard at the right upper sternal border, radiating to the carotid arteries, often accompanied by a diminished and delayed carotid upstroke (pulsus parvus et tardus). In advanced stages, chest pain, fatigue, exertional dyspnoea, syncope and symptoms of heart failure can be found.

The 2025 European guidelines for the management of valvular heart disease⁷ and international guidelines⁸ promotes an integrative imaging assessment of all the valvular heart diseases.

Echocardiography is the cornerstone of diagnosis and severity assessment of aortic stenosis. Transthoracic echocardiography (TTE) provides information on cardiac chamber anatomy, geometry and function, cardiac damage and remodelling, concomitant valve diseases and on valve morphology, valve calcifications, peak (PG) and mean (MG) transvalvular gradients, and aortic valve area (AVA).

Current European recommendations⁷ for the echocardiographic grading of AS rely on measurement of the mean pressure gradient (most robust parameter), peak transvalvular velocity (Vmax), and effective AVA. Although AVA is theoretically the ideal parameter for assessing severity, there are numerous technical limitations associated with its calculation.^{9 10}
2025

AS may be further categorized according to flow state based on stroke volume index (SVi) when there is discordance between echocardiographic parameters. A threshold of 35 ml/m² is conventionally accepted to discern low from normal flow, although sex-specific thresholds have been proposed.¹¹

Concordant criteria:

- High gradient severe AS ($MG \geq 40$ mmHg, $V_{max} \geq 4$ m/s, $AVA \leq 1.0$ cm², $AVA_i \leq 0.6$ cm²) is considered severe irrespective of left ventricle ejection function (LVEF) and flow conditions.

Discordant criteria:

- Low flow-low gradient AS with reduced LVEF ($MG < 40$ mmHg, $V_{max} < 4$ m/s, $AVA \leq 1.0$ cm², $AVA_i \leq 0.6$ cm², $EF < 50\%$, $SV_i \leq 35$ ml/m²)
- Low flow-low gradient AS with preserved LVEF ($MG < 40$ mmHg, $V_{max} < 4$ m/s, $AVA \leq 1.0$ cm², $AVA_i \leq 0.6$ cm², $EF \geq 50\%$, $SV_i \leq 35$ ml/m²).
- Normal flow-low gradient AS with preserved LVEF ($MG < 40$ mmHg, $V_{max} < 4$ m/s, $AVA \leq 1.0$ cm², $AVA_i \leq 0.6$ cm², $EF \geq 50\%$, $SV_i > 35$ ml/m²).
- Discordant high-gradient AS ($MG \geq 40$ mmHg, $AVA > 1.0$ cm²).

Patients with discordant normal-flow, low-gradient AS usually have moderate stenosis.^{12 13 14}

Discordant high-gradient AS is considered severe if not caused by a reversible high-flow status.^{15 16 17}

In cases with low-flow, low-gradient with reduced or preserved LVEF AS, additional tests such as dobutamine stress echocardiography – in the presence of flow reserve such as increase in stroke volume $\geq 20\%$ - or CT calcium scoring respectively may help differentiate true severe stenosis from pseudo-severe disease.^{18 19}

In fact, cardiac CT aortic valve calcium scoring and dobutamine stress echocardiography provide complementary information; if findings are equivocal, an integrated assessment considering all available clinical, morphological, and haemodynamic factors is required.

Values of >2000 Agatston units (AU) in men and 1200 AU in women indicate severe AS with high sensitivity and specificity ($\sim 85\%$).^{20 21} While higher thresholds (men >3000 AU, women >1600 AU) are very specific, severe AS becomes unlikely in patients with calcium AV scoring of <1600 AU in men and <800 AU in women.²²(Figure 1).

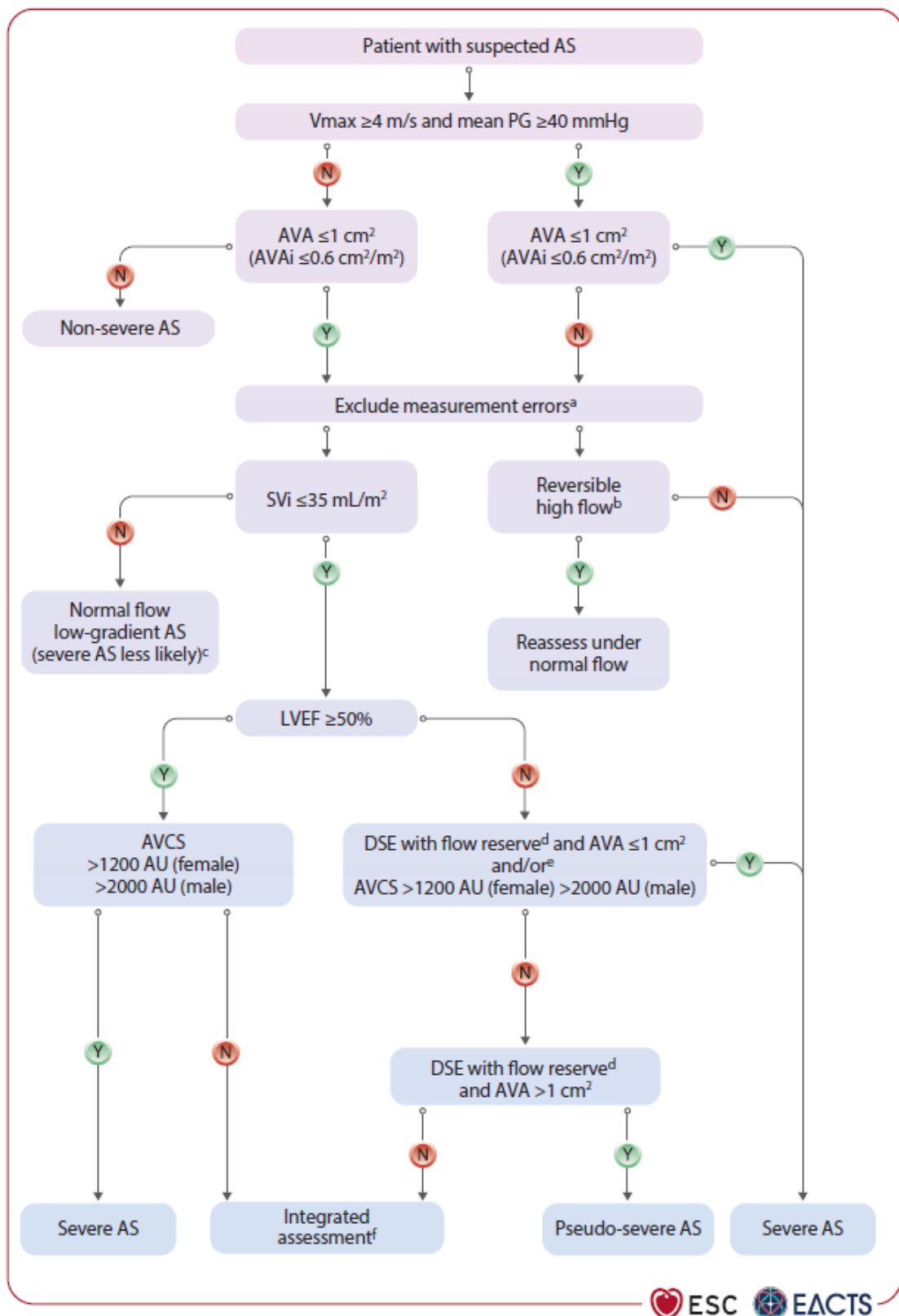


Figure 1. Integrative imaging assessment of patients with aortic stenosis. 2025 ESC/EACTS Guidelines for the management of valvular heart disease.⁷

Cautious interpretation is required in patients who can develop severe AS without pronounced aortic valve (AV) calcification such as in bicuspid aortic valve (BAV), concomitant amyloidosis, and predominantly fibrotic stenosis associated with post-rheumatic, radiation-induced and inflammatory disease.^{23 24 25 26 27}

The ratio of the LVOT to the AV doppler jet velocity time integral (VTI) does not require the calculation of LVOT diameter and area and may assist evaluation when other parameters are equivocal (DVI <0.25 suggests that severe AS is highly likely). Assessment of global longitudinal strain (GLS) can be useful for the risk stratification and evaluation of extravalvular cardiac damage.

Transoesophageal echocardiography (TOE) with a higher resolution allows morphological evaluation of the valve planimetry of AVA, mechanisms of valvular heart disease, assessment of potential subvalvular obstruction, 3D valve visualization and can be a guide of interventions.

Natriuretic peptides can be used to arbitrate the sources of symptoms in patients with multiple potential causes and help to identify those with high-risk asymptomatic AS who may benefit from early intervention.^{28 29}

Exercise testing can unmask symptoms and haemodynamic intolerance and is recommended for risk stratification in asymptomatic patients with severe AS.^{30 31}

Cardiac magnetic resonance is used to identify altered global LV geometry due to remodelling, as well as to quantify myocardial scarring and diffuse fibrosis, which are associated with the occurrence of adverse events.^{32 33}

Cardiac catheterization is rarely needed for diagnosis but is often performed preoperatively to assess for concomitant coronary artery disease.

1.1.2 TREATMENTS

No medical therapies have been shown to influence the natural history of AS to date.

Symptomatic severe AS has an unfavourable prognosis if left untreated, and early intervention is strongly recommended in all patients with an estimated life expectancy exceeding 1 year.³⁴

Intervention is recommended in all eligible symptomatic patients with high-gradient severe AS. However, management of patients with low-gradient AS is more challenging.

Up to 40% of patients with severe AS do not report symptoms at the time of diagnosis.^{35 36}

In roughly one-third of these, exercise testing can uncover symptoms or reduced exercise capacity attributable to AS and such patients should be treated as symptomatic.^{37 38}

However, exercise testing is not always feasible because of frailty or impaired mobility.

Intervention is recommended in asymptomatic patients with severe AS and an LVEF of <50% without another cause.

For patients with severe high-gradient AS and no adverse prognostic features, close active clinical surveillance, so-called ‘watchful waiting’, has previously been the default management strategy.

The mode of AV intervention depends on the estimated life expectancy, expected prosthesis durability, patient preference, and specific trade-offs associated with different treatment options.

Surgical aortic valve replacement (SAVR) has long been the gold standard therapy. The procedure involves open-heart surgery with cardiopulmonary bypass, excision of the stenotic valve, and implantation of a prosthetic valve - either mechanical or bioprosthetic.³⁹

Advances in surgical techniques, including minimally invasive approaches such as right anterior thoracotomy or upper hemisternotomy and improved perioperative care, have reduced morbidity and mortality, making SAVR a safe and effective option for patients with acceptable surgical risk profiles.

Concomitant SAVR at the time of coronary artery bypass grafting or ascending aorta surgery is recommended in symptomatic and asymptomatic patients with severe AS undergoing CABG or surgical intervention on the ascending aorta (Class I, level C) and should be considered in symptomatic and asymptomatic patients with moderate AS undergoing CABG or surgical intervention on the ascending aorta (class IIa, level C).⁷

In general, a mechanical heart valve (MHV) should be preferred in patients aged <60 years. Mechanical valves offer excellent durability but require lifelong anticoagulation with warfarin due to the risk of thromboembolism.

Replacement of the AV using an autograft - Ross procedure - is an alternative to an MHV in young patients that should be performed at experienced centres by operators with dedicated expertise.

Most patients aged >65 years with AS undergoing valve intervention in Europe and North America receive a bioprosthetic heart valve (BHV), by either SAVR or transcatheter aortic valve implantation (TAVI).

Bioprosthetic valves, typically derived from bovine or porcine tissue, avoid long-term anticoagulation but have limited durability (10–20 years), especially in younger patients.

Balloon aortic valvuloplasty may be rarely considered as a bridge to TAVI or SAVR in carefully selected patients with decompensated AS, and in those with severe AS who require urgent high-risk non-cardiac surgery (Figure 2, 3).

Risk stratification, evaluation of age, life expectancy, anatomical features, lifetime management and concomitant conditions permit to choose the SAVR or TAVI approach.

Risk stratification of patients with severe AS has been mainly developed based on surgical populations. The European System for Cardiac Operative Risk Evaluation II (Euroscore II)^{40 41} and the Society of Thoracic Surgeon predicted risk of mortality (STS-PROM) score are the most used scoring systems to estimate surgical risk. Both risk scores have been calibrated to predict post-operative outcomes; in patients candidates for TAVI, surgical risk have lower accuracy and tend to overestimate the risk of events.^{42 43 44}

There are discrepancies between observed and predicted peri-procedural mortality after TAVI using surgical risk scores point towards a need for TAVI-specific scores. Models predicting

short- and medium-term survival specifically designed for TAVI are rarely used in daily clinical practice due to limitations of their predictive performance.

The advantages of TAVI demonstrated in RCTs are largely confined to patients treated via the transfemoral approach.⁴⁵

Anatomical factors that favour SAVR or led to exclusion of patients from randomized controlled trials (RCT) comparing TAVI with SAVR are the aortic annular dimensions that lie outside sizing recommendations for currently available transcatheter devices, the excessive or bulky calcifications of the annulus or LVOT, which increase the risk of paravalvular leaks, annular rupture and the increased risk of coronary obstruction with TAVI - cusp height greater than coronary height in combination with shallow sinuses of Valsalva, or high calcium burden of corresponding cusp -. ⁴⁶

For all other candidates for a bioprosthesis, the most appropriate mode of intervention should be carefully selected by the Heart Team, considering procedural risk based on anatomical characteristics and comorbidities, expected outcomes, lifetime management considerations, and patient preference.

Considering life-time management aspects and the scarcity of randomized data in patients younger than 70 years, SAVR remains the preferred treatment in patients <70 years of age if surgical risk is low.

TAVI is recommended as the primary treatment modality in elderly patients ≥ 70 years of age with a tricuspid AV, if anatomy is suitable and transfemoral access is feasible, to reduce the risk of early adverse outcomes and accelerate recovery.

Anatomical findings such as transfemoral access suitable for TAVI, porcelain aorta, intact coronary artery bypass graft, severe chest deformity or scoliosis, comorbidities or cardiac conditions increasing surgical risk, frailty and sequelae of chest radiation are factors to consider selecting TAVI.

For stenotic bicuspid aortic valve, SAVR is the primary mode of treatment particularly if patients are young or have coexistent aortopathy or unfavourable valve morphology.

Hostile annulus or LVOT calcification, bicuspid aortic valve, annulus dimensions unsuitable for TAVI, risk of coronary obstruction, other relevant primary valvular heart disease, complex

coronary artery obstruction, aortic root or ascending aortic aneurysm and septal hypertrophy requiring myectomy are the major factors to consider preferring SAVR.

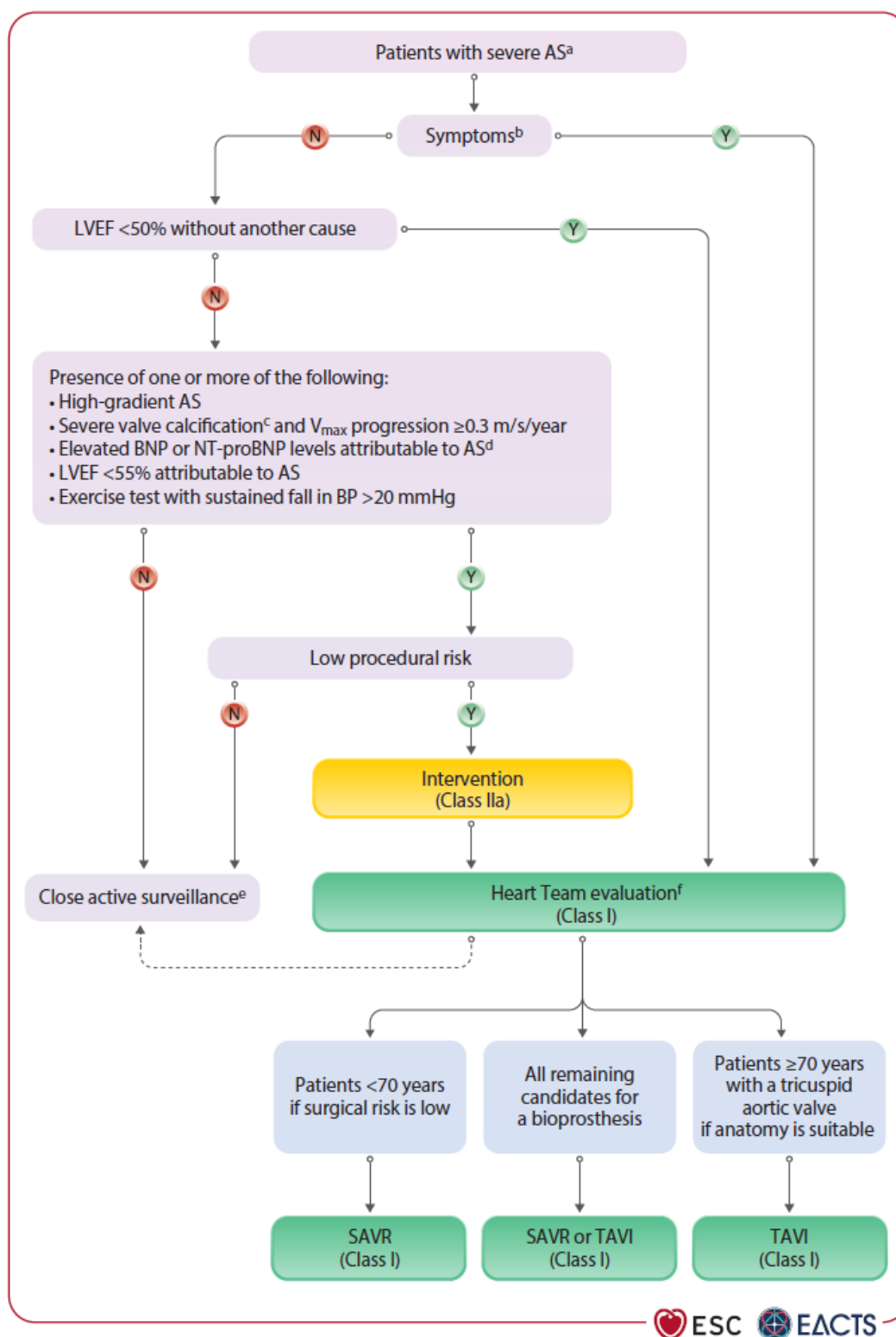


Figure 2. Management of patients with severe aortic stenosis. 2025 ESC/EACTS Guidelines for the management of valvular heart disease.⁷

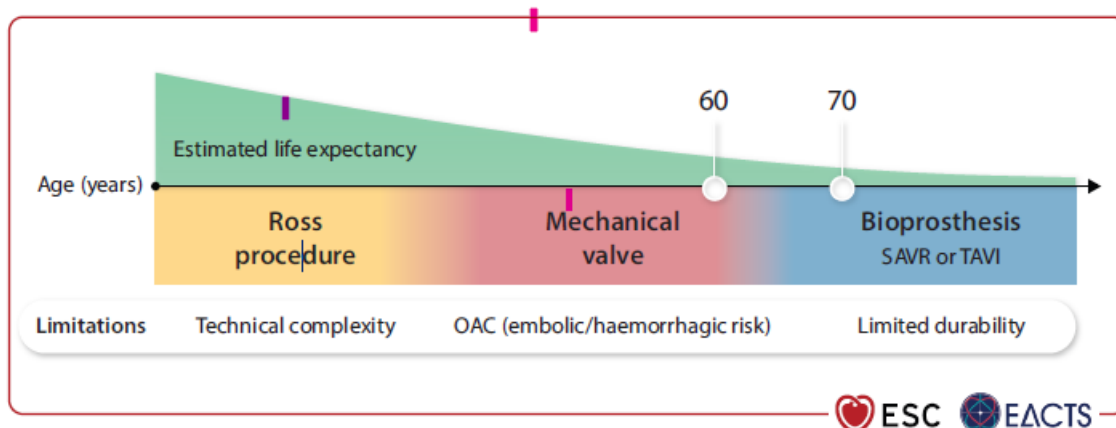


Figure 3. Aortic valve treatment options. 2025 ESC/EACTS Guidelines for the management of valvular heart disease.⁷

1.2 TRANSCATHETER AORTIC VALVE IMPLANTATION (TAVI)

Transcatheter Aortic Valve Implantation (TAVI) is a minimally invasive procedure performed through a catheter-based approach, most commonly via the femoral artery.

TAVI offers the advantages of reduced hospital stay, faster recovery, and lower immediate perioperative risk, but potential complications and uncertain long-term valve durability compared to surgical prostheses.

The effectiveness and safety of the procedure depend significantly on careful pre-procedural planning, in which multidetector computed tomography (CT) is an essential to standard in TAVI planning.

Pre-procedural CT allows for a detailed - and especially three-dimensional - assessment of cardiovascular anatomy, providing essential data for optimal selection of the prosthesis to be implanted and of the procedural strategy. In detail, CT imaging permits to evaluate the dimensions and morphology of the aortic annulus – an accurate measurement of the annulus diameter is essential to select the correct size and type of prosthesis, minimizing the risk of complications such as paravalvular regurgitation and annular rupture -, analyse the geometry of the left ventricular outflow tract (LVOT) to reduce the risk of annular rupture and atrioventricular block in presence of significant calcifications in the LVOT.

In addition, CT permits to determine the distance between the annulus and the coronary arteries - the minimum distance between the annulus and the coronary ostia is a critical parameter to prevent coronary occlusion, a rare but potentially fatal complication - and to identify valvular and annular calcifications, both influencing the valve positioning and the risk of paravalvular regurgitation. (Figure 4).

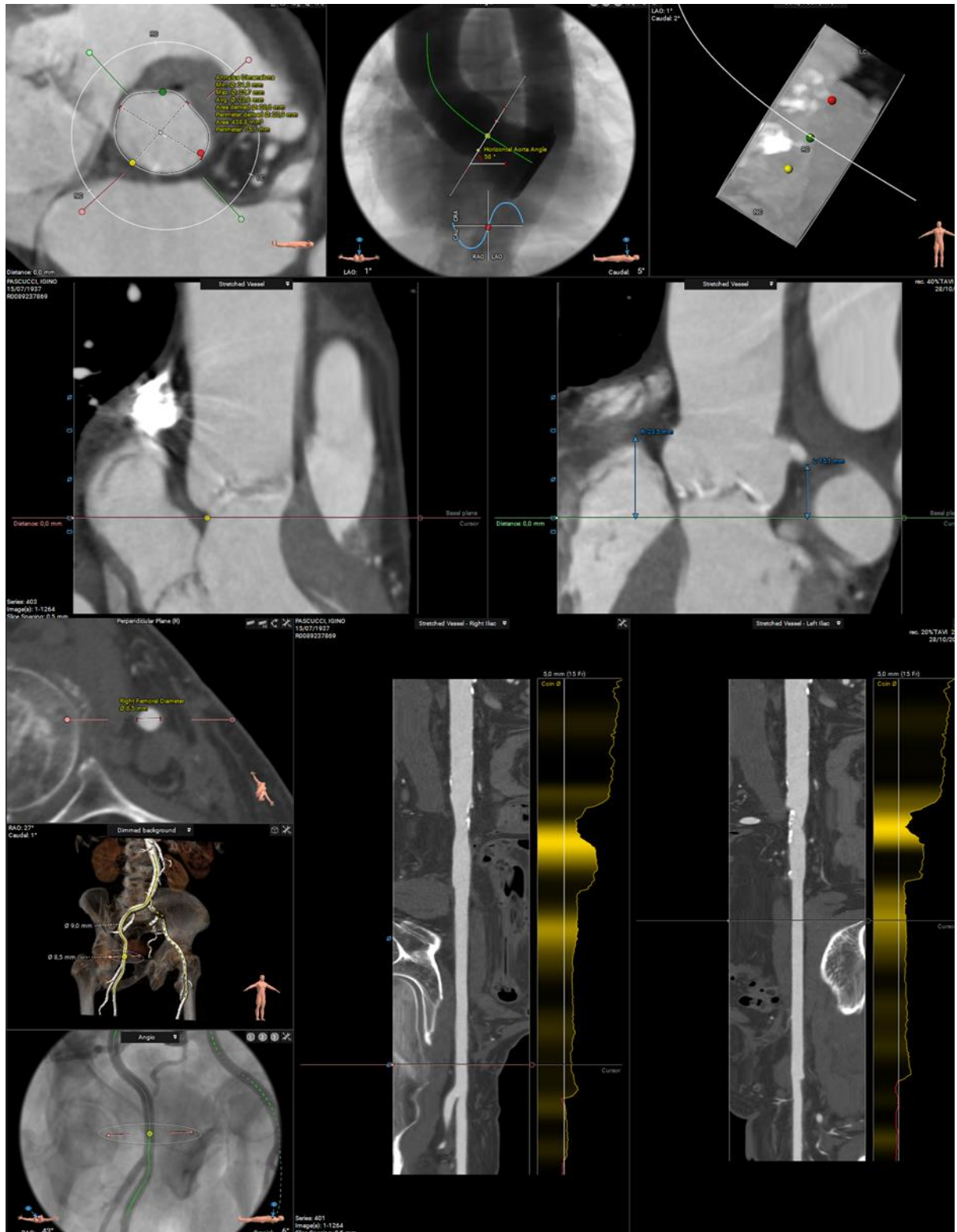


Figure 4. Analysis and reconstruction of contrast-enhanced CT for TAVI planning.

The assessment of vascular access with the evaluation of diameter, tortuosity, and calcifications of the femoral, iliac, and aortic arteries, helping determine the safest access route - femoral, transapical, transaortic, or transcarotid - and the simulation of valve implantation with three-dimensional rendering techniques, are possible with CT to anticipate technical challenges and approximate the optimal approach to be used during the procedure.

The procedure usually begins with obtaining arterial access through the common femoral artery.

The most used approach in TAVI is the transfemoral route. Access is typically obtained through the common femoral artery, a vessel with an adequate calibre that allows safe insertion of a 14–16F introducer. The puncture is performed under ultrasound or fluoroscopic guidance with angiography and the vascular closure devices are employed.

In patients with unsuitable femoral arteries - due to severe calcifications or small vessel diameter - alternative routes such as subclavian, transcarotid, or transapical approaches are used. Although more invasive, these options bypass anatomical limitations of the peripheral arteries.

A secondary arterial access and a venous access are also obtained, the latter for temporary right ventricular pacing during valve deployment.

Catheters are positioned in the aorta and left ventricle to measure baseline pressures and to guide imaging during the procedure. The aortic valve is crossed with a catheter and guidewire to facilitate positioning of the delivery system.

In many cases, a balloon valvuloplasty is performed - briefly inflating a balloon across the native valve to open the stenotic leaflets - typically during rapid ventricular pacing to stabilize the cardiac cycle.

The transcatheter heart valve, mounted on a delivery catheter, is advanced across the aortic valve. Under continuous fluoroscopic guidance, the prosthesis is carefully aligned with the aortic annulus. (Figure 5).

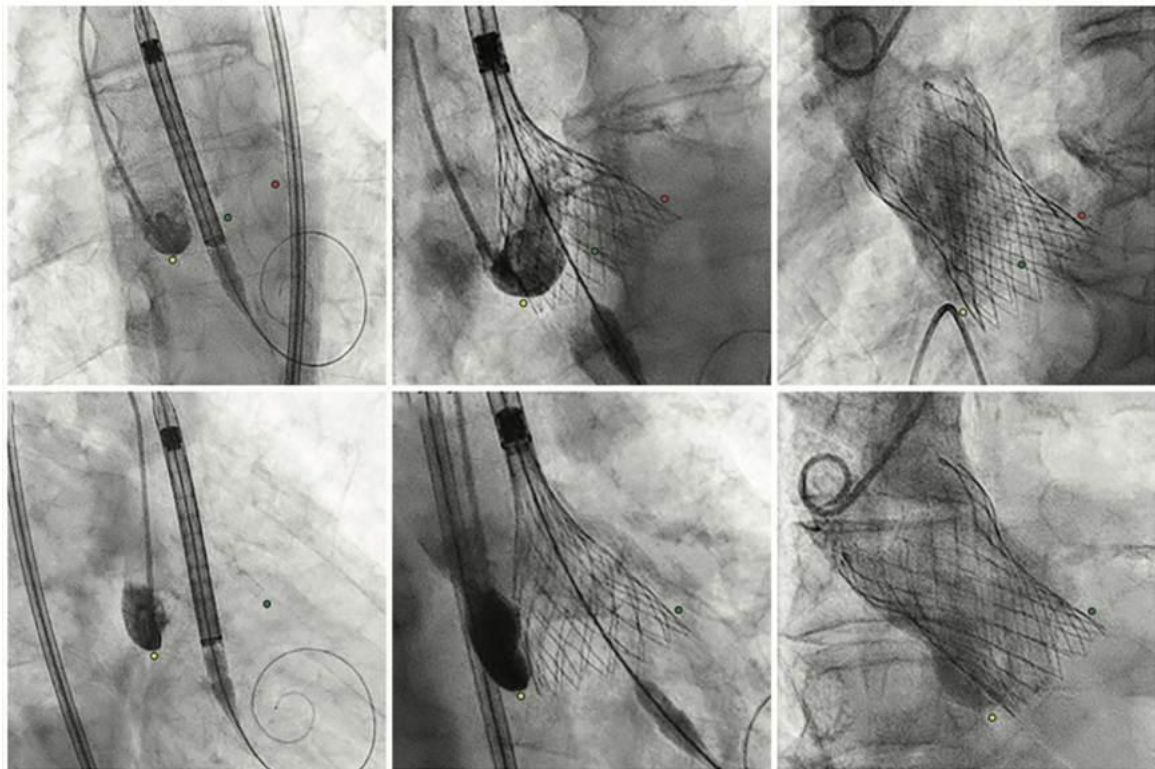


Figure 5. Fluoroscopic images showing the stages of deployment of a self-expanding aortic valve prosthesis.

Depending on the valve type, deployment may occur by balloon expansion or by gradual release of a self-expanding frame; correct positioning is crucial to avoid complications such as conduction disturbances, coronary obstruction, or paravalvular leak and after prosthesis release angiography is repeated to confirm the correct positioning, the function, the absence of presence of significant paravalvular regurgitation and the stability of conduction parameters.

The most frequent procedure complications are represented by vascular access complications and conduction abnormalities following TAVI.

Vascular complications at the access site, including dissection, stenosis, rupture, pseudoaneurysm or hematoma formation, nerve injury, and failure of closure devices are the major issues; these are more frequent in patients with vascular calcifications or peripheral atherosclerotic disease. To reduce these risks, accurate evaluation of peripheral vessels with CT and the use of ultrasound - or fluoroscopy - guided access techniques are essential. (Figure 6).

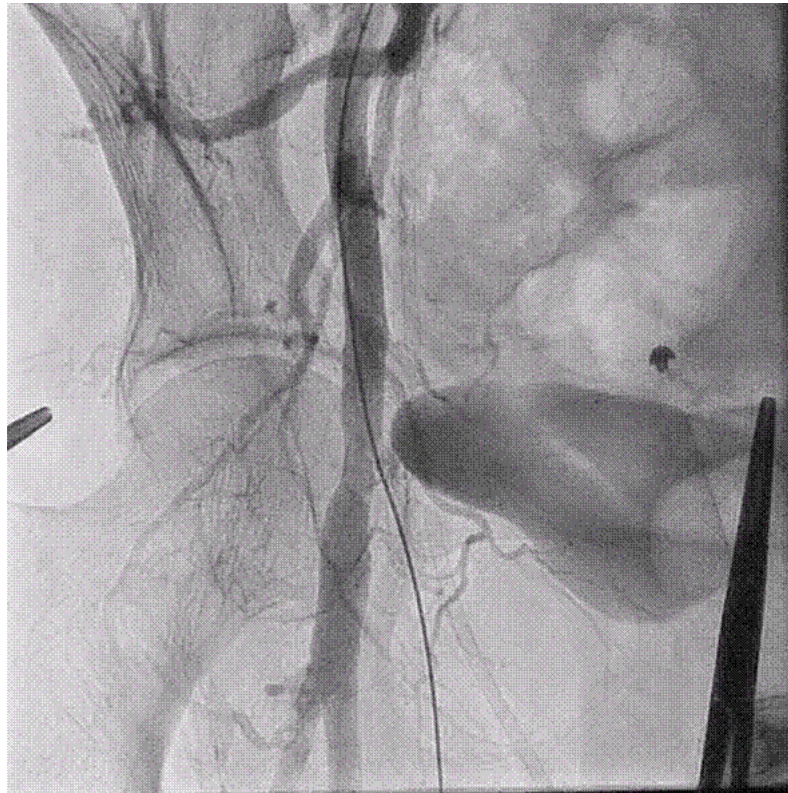


Figure 6. Angiographic image for assessment of hemostasis at the main femoral access site.

Conduction abnormalities are among the most common procedural complications and may require permanent pacemaker (PPM) implantation.

Risk factors include pre-existing right bundle branch block, first-degree AV block, extensive LVOT calcifications, and deeper valve implantation depth; PPM implantation is more frequent with self-expanding valves. Post-procedural telemetry monitoring is essential to detect progression toward conduction disturbances requiring PPM - such as alternating bundle branch block, third-degree AV block -.

Among rare and uncommon but severe complications there are the rupture of valve landing zone, the device embolization, the coronary artery occlusion and stroke.

The rupture of the valve landing zone may occur at the aortic annulus, LVOT, sinus of Valsalva, or sino-tubular junction. Significant LVOT calcium, cusp asymmetry, and a high annular coverage index are key risk factors. Oversizing by more than 20% relative to CT-measured

annulus diameter and post-dilation increase the risk further. In the event of rupture, emergency surgery is the only solution.

Device embolization derives by a dislocation of the prosthesis, migrating into the aorta or left ventricle. Factors include excessively high or low positioning, inadequate alignment during implantation, asymmetric calcifications, or undersizing relative to the true annulus. Management may require snaring the embolized valve, implanting a second valve, or resorting to cardiac surgery.

Coronary artery occlusion occurs when calcified cusps obstruct the coronary arteries during prosthesis expansion. Patients with low coronary height (<10 mm) and small sinus of Valsalva diameter (<30 mm) are at higher risk. This complication is more common in valve-in-valve procedures with supra-annular valves. Management requires immediate angioplasty with stent placement, but prevention relies on careful CT planning and, when necessary, protective techniques such as the "chimney" stenting technique.

Stroke may occur early - within 10 days - or late - after 10 days -. Associated factors include peripheral atherosclerotic disease, prior transient ischemic attacks, low BMI, and prolonged procedural time. Subclinical ischemic cerebral lesions are more frequent.

Acute kidney injury (AKI) in patients undergoing TAVI - particularly in those affected by chronic kidney disease (CKD) - is a common complication that ranges from 4 to more than 57% among different registries.^{47 48}

Contrast-induced nephropathy (CIN) is the major cause of peri-procedural AKI. Zero- contrast TAVI procedure has been studied as a viable option in TAVI patients with CKD or at high-risk of CIN.

1.3 CHRONIC KIDNEY DISEASE

Chronic Kidney Disease (CKD) is defined as a persistent - for more than 3 months- abnormality of kidney structure or function with health implications. CKD constitutes a major global health burden, with an estimated prevalence of 9.1% in 2017 - about 697.5 million cases -, and more recent estimates exceeding 850 million affected individuals. Its rising incidence - driven by

population aging and increased prevalence of diabetes mellitus and arterial hypertension - has made CKD the 11th leading cause of global mortality in 2019.

Because early stages are frequently asymptomatic, timely clinical assessment is essential to enable early detection, attenuate disease progression, and manage complications.

The diagnostic process begins with risk-based screening, primarily in patients with arterial hypertension, diabetes mellitus, cardiovascular disease - including heart failure -, prior acute kidney injury (AKI) or acute kidney disease, family history of kidney disorders, exposure to nephrotoxic agents or environmental toxins, and pregnancy-related conditions such as pre-eclampsia.

KDIGO 2024⁴⁹ recommends simultaneous assessment of glomerular filtration rate (GFR) and albuminuria, as both independently inform diagnosis, staging, and prognostic stratification for CKD progression, cardiovascular morbidity, and mortality.

CKD is formally diagnosed when one or more markers of kidney damage is present for at least 3 months, or when $\text{GFR} < 60 \text{ ml/min/1.73 m}^2$ persists over the same period. Markers of kidney damage include albuminuria - urine albumin-to-creatinine ratio [ACR] $\geq 30 \text{ mg/g}$ -, urinary sediment abnormalities, tubular electrolyte handling defects, structural or histopathological abnormalities on imaging or biopsy or history of kidney transplantation.

Notably, CKD may exist with preserved GFR ($> 90 \text{ ml/min/1.73 m}^2$) if kidney damage markers are persistently present.

GFR assessment is the cornerstone of CKD evaluation.

Although direct GFR measurement (mGFR) using exogenous filtration markers - such as iothexol, iothalamate - remains the analytic gold standard it is limited by high costs.

Thus, estimated GFR (eGFR) derived from endogenous markers is the standard practice. Serum creatinine is widely used but is influenced by non-GFR determinants such as muscle mass, diet, medications.

KDIGO 2024⁴⁹ guidelines recommend the use of validated estimating equations, notably CKD-EPI, which exclude race coefficients to avoid diagnostic disparities.

In clinical contexts where creatinine-based eGFR (eGFR_{cr}) is unreliable - such as sarcopenia, severe obesity, cachexia, or interference with tubular creatinine secretion - measurement of serum cystatin C is advised. Combined-marker equations (eGFR_{cr-cys}) provide superior accuracy and improve risk discrimination across all CKD-related outcomes.

Assessment of albuminuria is equally essential. Albumin is the predominant urinary protein in most renal pathologies, and albumin quantification is more sensitive than total proteinuria for detecting early glomerular injury. The preferred test is the spot urine albumin-to-creatinine ratio (ACR), ideally from the first morning void, which correlates strongly with 24-hour albumin excretion and avoids the inaccuracies of timed collections.

Once CKD is confirmed, staging follows the Cause–GFR–Albuminuria (CGA) classification introduced by KDIGO 2012 recommendations⁵⁰, integrating disease cause (C), GFR category (G1–G5), and albuminuria category (A1–A3). CGA classification provides a comprehensive overview of disease severity and individual prognostic risk.

CGA classification helps the staging and prognostication, and etiologic determination of CKD guiding individualized management.

There are 6 GFR categories (G1–G5), based on eGFR: G1 (eGFR ≥ 90 ml/min/1.73 m²), G2 (eGFR 60–89 ml/min/1.73 m²), G3a (eGFR 45–59 ml/min/1.73 m²), G3b (eGFR 30–44 ml/min/1.73 m²), G4 (eGFR 15–29 ml/min/1.73 m²), G5 (eGFR < 15 ml/min/1.73 m²).

Otherwise, there are 3 albuminuria categories (A1–A3): A1 (< 30 mg/g), A2 (30–300 mg/g), A3 (> 300 mg/g).

Combining G and A categories enables precise risk stratification for kidney failure, major adverse cardiovascular events, AKI, and all-cause mortality. Risk escalates progressively with declining GFR and increasing albuminuria.

Determining the aetiology of CKD (the “C” in CGA) is critical, as it directs disease-specific interventions and informs genetic counselling when applicable. Etiologic evaluation integrates clinical history, physical examination, urinalysis, serological testing, renal imaging, and - when indicated - renal biopsy, a safe and diagnostically high - yield procedure that informs on activity, chronicity, and underlying pathology.

Advances in genomic testing have expanded identification of monogenic kidney diseases, which are more prevalent than previously recognized and may occur even without overt family history.

1.4 ACUTE KIDNEY INJURY

CKD is a powerful predictor of peri-procedural acute kidney injury (AKI) in fact patients with pre-existing impaired renal function are associated with an increased mortality and risk of development of Contrast-Induced Nephropathy (CIN) after intravascular administration of iodinated contrast media.

CIN accounts for approximately 10–15% of cases of hospital-acquired acute renal failure.

Now CIN is more commonly referred to as post-contrast Acute Kidney Injury.

To standardize diagnosis, several definitions have been proposed. Contrast-Induced Nephropathy (CIN) is classically defined as a relative increase in serum creatinine (SCr) $\geq 25\%$ or an absolute increase ≥ 0.5 mg/dL ($44 \mu\text{mol/L}$) from baseline, in the absence of other evident causes of renal injury. The typical course involves an increase in SCr within 24–48 hours after contrast exposure, peaking at 3–5 days, with a return to baseline values within 1–3 weeks.⁵¹

A broader and more recently adopted definition is based on the KDIGO (Kidney Disease: Improving Global Outcomes) and Acute Kidney Injury Network criteria, defining AKI as an absolute increase in SCr ≥ 0.3 mg/dL ($\geq 26.5 \mu\text{mol/L}$) or a relative increase $\geq 50\%$ from baseline within 48 hours of the procedure. Serum creatinine typically rises within 24–48 hours, peaks at 3–5 days and returns to baseline within 1–3 weeks.

The incidence of AKI following transcatheter aortic valve implantation (TAVI) varies widely across studies and registries, ranging from less than 4% to over 57%.^{52 53 54}

This discrepancy is largely attributable to heterogeneity in AKI definitions, differences in patient populations, and procedural variations such as the volume of contrast media administered. In a study of 150 consecutive patients by Gebauer et al.⁵², AKI occurred in 20% of cases (28 of 140 patients analysed). Another study reported an incidence of 26% in a cohort of 77 patients.⁵⁵ These data highlight AKI as a common complication in this population.

The development of AKI is a strong independent predictor of adverse clinical outcomes, regardless of baseline renal function; short and long-term mortality, long-term renal function and length of hospital stay are the main adverse events influenced by AKI.

Gebauer et al.⁵² demonstrated that patients who develop AKI exhibit markedly higher 30-day mortality rates - mortality of 29% in the AKI group versus 7% in the non-AKI group ($p < 0.0001$) -. Similarly, Sinning et al.⁵⁵ identified AKI as a strong predictor of 30-day mortality (HR: 4.9). In addition, Venturi et al.⁵⁶ demonstrated that a contrast volume-to-creatinine clearance ratio (CV/CrCl) ≥ 2.2 was independently associated with increased 90-day mortality (HR: 1.90).

The adverse impact of AKI extends to long-term follow-up and long-term mortality; in fact, the same studies showed how patients with AKI had significantly higher 1-year mortality (43% vs. 18%, $p < 0.0001$).⁵³ Multivariate analysis in the study by Sinning et al.⁵⁵ confirmed AKI as an independent predictor of 1-year mortality (HR: 5.9), even after adjustment for other risk factors. Notably, while AKI remained predictive of 1-year mortality, the CV/CrCl ratio did not, suggesting that acute renal injury itself - rather than contrast dose alone - drives long-term prognosis.⁵⁶

In addition, all patients with AKI have significantly longer hospital stays (20 ± 12 days vs. 15 ± 10 days, $p = 0.03$)⁵² and long-term renal function worse in patients who experience AKI compared with those without AKI, indicating potential irreversible renal damage.⁵⁶

The pathophysiology of CIN is multifactorial and not fully elucidated, but direct tubular toxicity, renal hemodynamic alterations, oxidative stress and reperfusion injury, inflammation and tubular obstruction are the main mechanisms involved in CIN.

Direct tubular toxicity is related to contrast agent filtration but not reabsorption, increasing tubular fluid osmolarity; tubular epithelial cells exposed to this osmotic load undergo alterations in intracellular transport and energy metabolism, which may lead to vacuolization (so-called “osmotic nephrosis”) and, in severe cases, necrosis.

Renal hemodynamic alterations are related to contrast administration induces a biphasic vascular response, consisting of an initial transient increase in renal blood flow followed by sustained vasoconstriction. This reduction disproportionately affects the outer medulla, a region

with high metabolic demand and particular susceptibility to ischemia. Vasoconstriction is mediated by endogenous vasoconstrictors such as adenosine and endothelin.

Oxidative stress and reperfusion injury consist in the ischemic phase followed by reperfusion, which generates reactive oxygen species (ROS), further contributing to cellular injury. Elderly patients and those with CKD or diabetes mellitus are particularly vulnerable due to reduced antioxidant reserves and increased baseline oxidative stress.⁵¹

In addition, contrast media may activate the complement cascade of inflammation and stimulate the release of inflammatory cytokines, amplifying renal parenchymal damage. In some TAVI patients, the development of systemic inflammatory response syndrome (SIRS) has been associated with an increased risk of AKI.⁵⁶

Tubular Obstruction although previously hypothesized to result from intratubular protein precipitation - such as Tamm–Horsfall protein or Bence Jones light chains - now less supported particularly with modern contrast agents and adequate hydration.⁵¹

Risk factors for post-TAVI AKI can be classified as intrinsic - patient-related - and extrinsic - procedure-related -.

Patient-related - or intrinsic risk factors are pre-existing CKD, comorbidities and age.

CKD is universally recognized as the most important risk factor. Mortality increases progressively with worsening baseline CKD stage. Patients with CKD stage 4 (eGFR 15–29 mL/min/1.73 m²) exhibit extremely high 30-day and 1-year mortality rates (26.2% and 47.8%, respectively), making TAVI in this population a major clinical challenge.⁵⁷

Diabetes mellitus, anaemia, congestive heart failure, arterial hypertension, and peripheral artery disease (PAD) are well-established the major comorbidities considered as risk factors. PAD has been associated with an increased incidence of AKI (65% in patients with AKI vs. 39% without AKI, $p = 0.04$).⁵⁵

Controversial results emerged about age; if advanced age has been always indicated as a risk factor for AKI, paradoxically, Gebauer et al⁵² identified younger age as an independent predictor of post-TAVI AKI (OR: 0.93). However, this result may reflect confounding, as younger patients undergoing TAVI are often more severely ill and deemed at high surgical risk.

Procedure-related - or extrinsic - risk factors are represented by contrast volume (CV), contrast volume-to creatinine clearance ratio (CV/CrCl), procedural approach, periprocedural complications and SIRS.

The amount of contrast media used is a crucial modifiable risk factor and represents the only procedural risk factor directly controllable by the operator.

Contrast volume-to-creatinine clearance ratio (CV/CrCl) has proven to be as a more robust predictor than contrast volume alone. In a large multicentre retrospective study, Venturi et al⁵⁶. including 1,381 patients, a CV/CrCl threshold ≥ 2.2 was identified as the optimal predictor of AKI and 90-day mortality. Exceeding this threshold was associated with nearly doubled 90-day mortality risk (HR: 1.90, 95% CI: 1.01–3.59, $p = 0.047$) and remained an independent predictor of adverse outcomes even in patients without baseline CKD (p for interaction = 0.22).

About the procedural approaches, the transapical approach has been associated with a significantly higher incidence of AKI compared with the transfemoral approach (31% vs. 11%, $p = 0.001$); this may reflect both the higher-risk patient profile and the more invasive nature of the procedure.⁵²

Periprocedural complications such as atheroembolic events, hypotension - due to rapid pacing or bleeding -, post-procedural SIRS, the need for red blood cell transfusions, and significant - moderate-to-severe- paravalvular regurgitation contribute to increased AKI risk. Paravalvular regurgitation ≥ 2 and development of post-procedural SIRS were strongly correlated with AKI (35% in AKI patients vs. 9% without AKI, $p = 0.02$ and 60% in patients with AKI vs. 21% without AKI, $p = 0.002$ respectively).⁵⁵

In the absence of a specific therapy once CIN has developed, prevention remains the cornerstone of management.

Hydration-based nephroprotection is the only strategy with proven efficacy.

Standard practice involves infusion of isotonic saline (0.9% NaCl) at 1 mL/kg/h for 12 hours before and after the procedure. In patients with severe left ventricular dysfunction (LVEF <35%), the infusion rate is reduced to 0.5 mL/kg/h to avoid volume overload. Some studies and meta-analyses suggest a potential benefit of sodium bicarbonate infusion, as alkalinization of tubular fluid reduces reactive oxygen species formation.⁵¹

Among nephroprotective medications, a prophylactic use of N-acetylcysteine (NAC) has long been debated. Despite early positive studies, the large, randomized trial involving over 2,300 patients demonstrated no benefit of high-dose NAC in reducing CIN incidence, even in high-risk subgroups. Current evidence does not support its routine use. Other vasoactive agents – such as dopamine, fenoldopam, theophylline - have likewise failed to demonstrate consistent benefit.

When clinically feasible discontinuation of nephrotoxic drugs - such as nonsteroidal anti-inflammatory drugs and metformin (discontinued 24 hours before and resumed 48 hours after the procedure in the absence of AKI) - should be avoided during the periprocedural period.

The choice of contrast is also important with the exclusive use of iso-osmolar - such as iodixanol - or low-osmolar -such as iohexol - contrast agents recommended, as these have been shown to reduce the incidence of CIN compared with high-osmolar agents, particularly in patients with CKD. In addition, contrast volume should be minimized, maintaining the CV/CrCl ratio below risk thresholds (ideally <2.2).^{51 56}

1.5 ZERO-CONTRAST TRANSCATHETER AORTIC VALVE IMPLANTATION

Patients affected by severe AS candidates to TAVI are usually at high-risk of acute kidney injury (AKI); AKI is considered as a frequent complication with an unfavourable prognostic impact, particularly in patients with chronic kidney disease which represents one of the strongest independent predictors of post-procedural mortality.

The prevalence of CKD among patients with severe aortic stenosis undergoing TAVI is high, ranging from 60% to 65% in the main published cohorts^{55 56} and in patients with stage 4 CKD (eGFR 15–29 ml/min/1.73 m²), 30-day mortality may reach 26%, with a progressive increase at one year.⁵⁷

Among the mechanisms of acute renal injury, contrast-induced nephropathy (CIN) following intravascular administration of iodinated contrast media, plays a central role. It results from the use of iodinated contrast media employed for TAVI planning and fluoroscopic guidance.

In this context, the zero-contrast TAVI (ZC-TAVI) strategy has emerged, aiming to eliminate exposure to iodinated contrast media, thereby reducing a primary, modifiable procedural risk factor directly related to renal morbidity.^{58 59}

Zero-contrast TAVI is a procedure of transcatheter aortic valve implantation without the use of iodinated contrast agents primarily to protect patients with severe chronic kidney disease who are at high risk for contrast-induced nephropathy or who require renal preservation due to multiple comorbidities or rarely in case of iodine contrast allergies.

From a pathophysiological perspective, reducing contrast exposure mitigates osmotic and vasoconstrictive injury to the renal microcirculation, thereby decreasing the risk of contrast-induced nephropathy. However, post-TAVI renal injury is a multifactorial phenomenon, with ischemia, systemic inflammation, intraoperative hypotension, and microvascular embolization all contributing to the risk of AKI. Consequently, while the zero-contrast approach does not totally eliminate the risk of renal injury, it represents a rational renal-protective strategy in appropriately selected patients.

The goal is to maintain procedural safety and accuracy while completely avoiding nephrotoxic contrast media by combining different imaging modalities to obtain comprehensive anatomical and functional data without the use of iodine or gadolinium. It maintains high procedural success while protecting renal function.

If the meticulous pre-procedural planning of a TAVI procedure is essential for optimal outcomes and it is traditionally performed using contrast-enhanced CT to provide excellent spatial imaging of the heart and the thoraco-abdominal vascular system, in zero-contrast TAVI contrast-CT can be replaced by multimodality imaging including non-contrast CT or low-contrast CT - used to assess aortic annulus dimensions, LVOT geometry, valve calcifications and aortic root anatomy -, cardiac magnetic resonance (CMR) - to assess annulus and root measurements, LVOT visualization, functional assessments and coronary ostia height estimation -, echocardiography - TTE and three-dimensional transoesophageal echocardiography -, carbon dioxide (CO₂) angiography, and peripheral vascular ultrasound. (Figure 7)

Echocardiography permits to value hemodynamics, aortic valve severity, annular dimensions (complementary) and rarely coronary ostia visualization; otherwise, vascular ultrasound

evaluates the diameter of femoral and iliac arteries, calcifications, plaque burden and feasibility of transfemoral access.

The use of iodinate contrast plays a central role also during the performance of the procedure but fluoroscopy, CO₂ angiography - if disponible, to visualize access vessels without iodinated contrast -, and intraprocedural echocardiography - used to confirm valve position and to detect complications such as paravalvular leak, effusion and to optimize the placement - can replace the use of contrast.

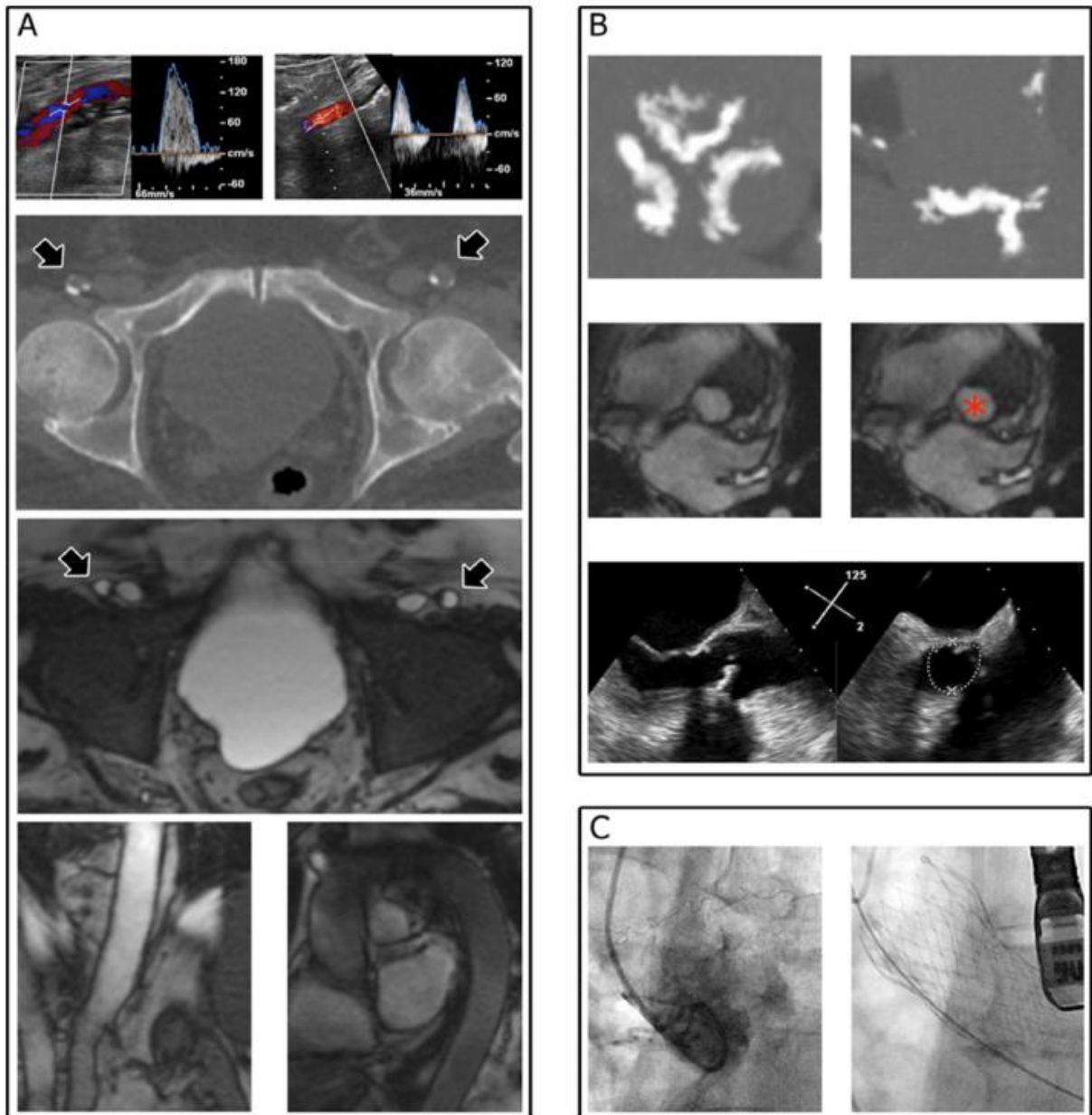


Figure7. Image taken from “Zero-contrast imaging for assessment of transcatheter aortic valve implantation in candidates with renal dysfunction,” Prado et al., 2023.⁶⁰ Multimodal imaging for the evaluation of TAVI candidates with renal dysfunction. Femoro–ilio–aortic endovascular access (A) assessed by duplex ultrasound (upper panel showing the left and right femoral arteries), computed tomography (arrows indicate the left and right femoral arteries), and magnetic resonance imaging (arrows in the panel indicate the left and right femoral arteries). The aortic root and aortic annulus (B) assessed by non-contrast computed tomography (upper panel), magnetic resonance imaging (the red asterisk in the central panel indicates the region of the aortic annulus), and echocardiography (lower panel), and subsequently reassessed for confirmation during the procedure (C, left panel). The final shape of the prosthetic metal frame is shown in panel C.

To enable continuous monitoring and precise valve positioning, zero-contrast TAVI is often performed under general anaesthesia, allowing continuous monitoring with transoesophageal echocardiography (TEE). Alternatively, mild sedation may be used, which still allows the performance of transoesophageal echocardiography (TEE). Moreover, zero-contrast TAVI - like standard TAVI - is typically performed via femoral arterial approach, based on the characteristics of the femoro-iliac axis assessed with the selected pre-procedural imaging modality. In addition to the main femoral access, other required accesses include a femoral venous access through which pacing is performed, and at least two additional arterial accesses, preferably radial, for hemodynamic monitoring as in standard TAVI, as well as for identification of the coronary sinuses using catheters or guidewires. Femoral artery puncture is achieved - as in the standard procedure - under ultrasound or fluoroscopic guidance with angiography to optimize access-site management and prevent complications. A temporary 6F introducer is placed, allowing subsequent deployment of vascular closure devices and insertion of a 10F introducer, which is then replaced by the introducer through which the delivery system will pass (typically a 14F or 16F introducer). In some centres, femoral access may be obtained via surgical cutdown to optimize access-site management and address potential vascular complications.

During valve deployment or during balloon valvuloplasty, rapid ventricular pacing is required to reduce blood pressure for stability. This can be achieved using temporary pacing catheters or by using a 4F JR4 (Judkins Right 4F) catheter with a J-tipped guidewire advanced into the right ventricle via the femoral venous approach. The main difference from the standard TAVI approach is that the absence of conventional aortography requires integration of non-contrast imaging techniques and strategic placement of guidewires and catheters under fluoroscopic guidance, both for selecting implantation projections and for assessing the implantation plane and prosthesis positioning. The optimal implantation projection - often the cusp-overlap projection - is defined using non-contrast CT or CMR. To determine the implantation plane and valve alignment, radiopaque markers are used; a pigtail catheter is positioned in the non-coronary sinus to serve as a fixed reference point in the absence of contrast, a second catheter in the left coronary sinus; it is an Amplatz Left catheter with a protruding guidewire positioned at the bottom of the left coronary sinus. Some techniques involve the use of three different guidewires to identify the three cusps

and the valvular plane. Moreover, calcifications of the native cusps are used as landmarks to guide positioning of the TAVI prosthesis. (Figure 8)



Figure 8. Fluoroscopic images showing the placement of radiopaque markers in the sinuses of Valsalva to identify the height of the valvular plane.

New-generation prosthesis - such as the Medtronic Evolut FX -, have feature gold markers on the basal frame. These markers facilitate commissural alignment in both standard procedures and zero-contrast TAVI; however, in the latter they are also useful for better understanding implantation height. The operator can visualize a “2:1 pattern” - two markers on one side and one on the other - in the cusp-overlap projection to confirm correct alignment of the prosthesis with the native valve commissures.

Transoesophageal echocardiography (TEE) is the primary imaging modality used for guidance during implantation and for immediate confirmation of post-implant valve function. The long-axis view is useful for selecting the implantation depth of the prosthetic valve. TEE is not strictly required; indeed, some centres do not use it for planning and implantation, relying exclusively on radiopaque landmarks to identify the valvular plane.

After placing reference markers to identify the valvular plane, implantation proceeds with crossing, left heart catheterization, and valve expansion. The stenotic aortic valve is crossed using an Amplatz Left catheter and a J-tipped or straight guidewire introduced through the main access, which are then exchanged for a pigtail catheter to assess the simultaneous transvalvular gradient. The pigtail catheter is subsequently replaced with a stiff guidewire. Balloon expansion during rapid pacing is performed at the operator's discretion, based on the degree of calcification observed on non-contrast CT.

Then, the delivery system with the prosthetic valve is advanced from the main femoral access along the stiff guidewire until crossing the stenotic aortic valve. In some cases, this process requires specific rotational and flexion manoeuvres of the delivery system to achieve optimal commissural alignment.

In zero-contrast TAVI procedures, the use of self-expanding, repositionable, and recapturable prosthesis is preferable, though not strictly necessary, to mitigate the risk of sizing or positioning errors resulting from the absence of contrast angiographic control during deployment. Once TEE and fluoroscopy confirm optimal positioning - depth, symmetry, and alignment -, the valve is fully released. (Figure 9)

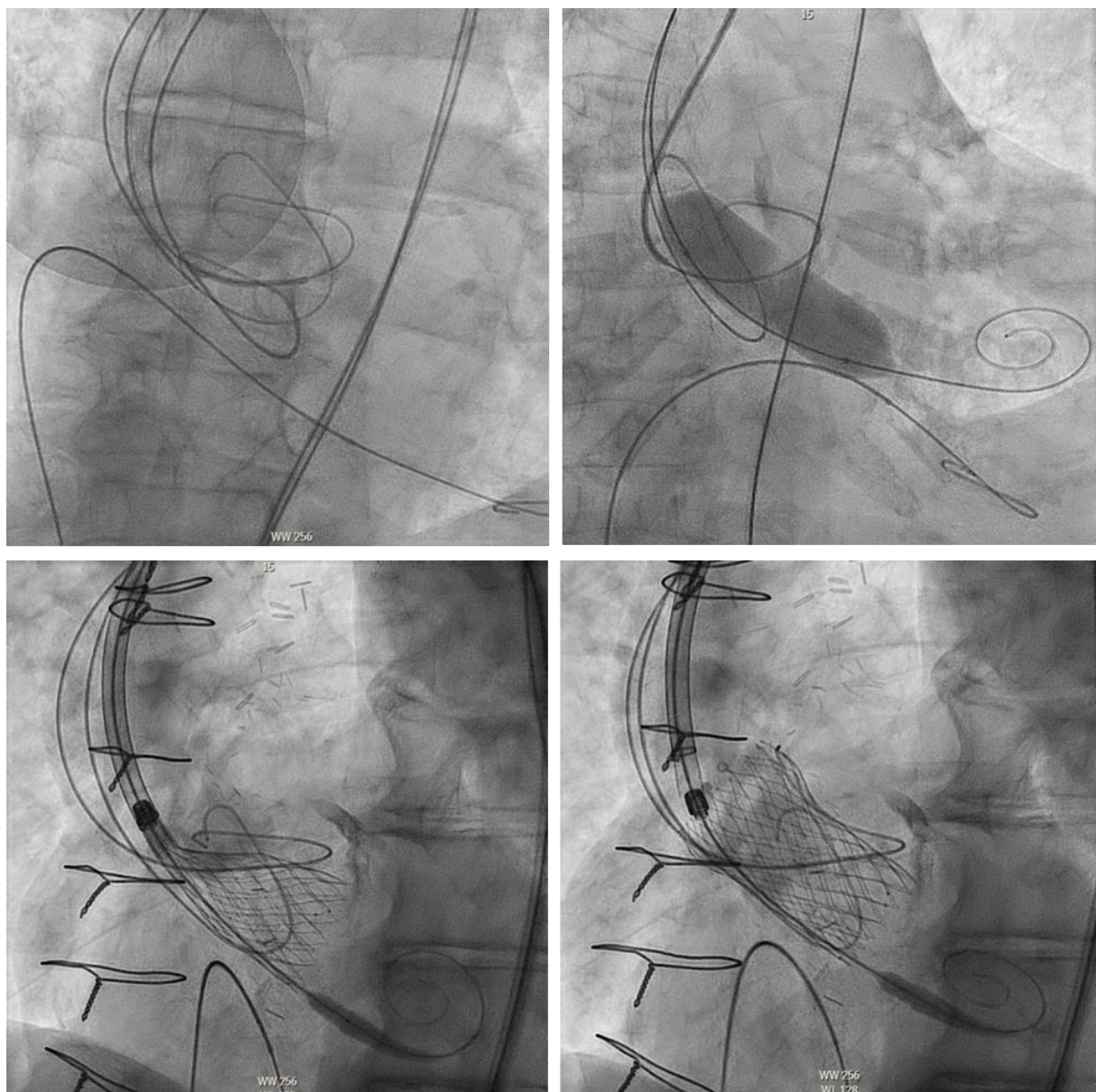


Figure 9: Fluoroscopic images illustrating the different phases of the zero-contrast TAVI procedure.

Immediately after release, prosthesis function and the presence of paravalvular leaks (PVL) are assessed using TEE or transthoracic echocardiography. Echocardiography provides immediate confirmation of the residual transvalvular gradient and of any moderate or severe PVL. Post-expansion is performed only in the presence of significant PVL identified on echocardiography or in cases of a residual transvalvular gradient on post-implant left heart catheterization. Although the goal is a zero-contrast procedure, many pilot studies included the use of minimal amounts of contrast for safety reasons (safety checkpoints). Some centres use contrast for final

aortography, performed immediately before final valve release to ensure that an acceptable position had been achieved while true “zero-contrast” use no contrast at all.

The mean volume of contrast used for safety checkpoints and final aortography in these studies varied, for example, 45 ± 35 mL or a median of 42.5 mL, volumes that are significantly lower than those used in standard TAVI.⁶¹ In zero-contrast TAVI, unlike the standard procedure, angiography of the femoro-iliac axis cannot be performed after removal of the delivery system and closure of the vascular access devices. Haemostasis of the access site is therefore followed by final verification using ultrasound to exclude vascular complications. In some centres, haemostasis assessment is performed using CO₂ angiography.⁶²

All these techniques allow accurate planning and safe procedural guidance even in the absence of iodinated contrast.

The feasibility and clinical safety of zero-contrast TAVI technique are confirmed by multiple recent studies.

In a recent study, Freire et al.⁶² demonstrated that a completely zero-contrast TAVI strategy is feasible and safe in patients with chronic kidney disease, suggesting that it may become the preferred approach in this patient population. These results confirmed the proposal a zero-contrast TAVI protocol in patients with severe renal insufficiency, demonstrating the technical feasibility of this approach showed by Castriota et al.⁶³ Additional evidence derived from the study by Koga et al.⁶⁴ who further confirms the feasibility of zero-contrast TAVI in patients with stage 4 CKD, without an increase in major complications. Moreover, the recent review by Kassis⁶⁵ highlights the growing relevance of low- or zero-contrast strategies in contemporary clinical practice.

A meta-analysis including 1,505 patients conducted by Badran et al.⁵⁸ demonstrated a procedural success rate of 97%, comparable to that of standard TAVI (RR = 1.02; $p = 0.34$), with no significant differences in mortality, stroke, or vascular complications. A “leave-one-out” sensitivity analysis further showed a significant reduction in the incidence of AKI in favour of the zero-contrast approach (RR = 0.47; $p = 0.03$). Consistently, Nerla et al.⁶⁶ reported a lower incidence of AKI (1.2% vs 25.9%, $p = 0.01$) and greater long-term stability of renal function in

patients with severe CKD (eGFR ≤ 35 mL/min) treated with zero-contrast TAVI, with a median follow-up of 3.3 years. Other pilot studies and single-centre series have confirmed stability or improvement of eGFR after zero-contrast TAVI, avoiding the need for dialysis.^{67 59}

However, some studies, including that by Badran et al.⁵⁸, have reported an increased risk of permanent pacemaker (PPM) implantation in the zero-contrast TAVI group (RR = 2.06; 95% CI 1.04–4.09; $p = 0.037$), likely related to lower valve prosthesis implantation required to optimize alignment in the absence of contrast angiography.

Overall, the literature suggests that zero-contrast TAVI represents a safe and potentially nephroprotective strategy in patients with advanced CKD, with procedural success rates comparable to those of standard TAVI and a lower risk of AKI.

However, most of the available evidence derives from small, single-centre observational studies with limited follow-up, highlighting the need for further large-scale, multicentre randomized trials to confirm safety, efficacy, and long-term renal outcomes.

2. ZERO-CONTRAST TAVI STUDY

2.1 OBJECTIVES

The prevalence of CKD among patients with severe aortic stenosis candidates to TAVI is high and they are usually at high-risk of acute kidney injury. Among the mechanisms of acute renal injury, contrast-induced nephropathy (CIN) following intravascular administration of iodinated contrast media, plays a central role.

The development of AKI in patients undergoing TAVI is a strong independent predictor of adverse clinical outcomes in fact short and long-term mortality, long-term renal function and length of hospital stay are all severe adverse events influenced by the development of AKI.

In this contest, zero-contrast TAVI strategy has emerged, aiming to eliminate exposure to iodinated contrast media, thereby reducing a primary, modifiable procedural risk factor directly related to renal morbidity.

The aim of the study is to evaluate the clinical safety and non-inferiority of zero-contrast TAVI (ZC-TAVI) compared with standard TAVI (S-TAVI) in patients with severe aortic stenosis and chronic kidney disease.

The safety and the non-inferiority of zero-contrast TAVI were considered through the evaluation of primary and secondary endpoints.

The primary endpoint was a composite endpoint evaluating the different complications expressed as absence of complications (0) or presence of at least one complication (1) among the following:

- All-cause mortality
- Vascular complications
Failure of vascular closure devices, dissection, rupture, or peri-procedural vascular injury requiring surgical or percutaneous vascular treatment.
- Major bleeding
Significant reduction in haemoglobin levels requiring red blood cell transfusion.
- Conduction abnormalities requiring peri- and/or post-procedural pacemaker implantation

Second-degree atrioventricular block type II or third-degree atrioventricular block, new-onset left bundle branch block associated with marked first-degree AV block (PR >240 ms) or QRS prolongation (>150–160 ms), alternating left and right bundle branch block.

- Neurological events
Stroke - ischemic or haemorrhagic - or transient ischemic attack (TIA).
- Prosthetic valve dysfunction
Any abnormality, including structural valve deterioration, non-structural valve dysfunction, thrombosis, endocarditis, or valve embolization, assessed by echocardiography or CT.
- Significant paravalvular leak
Assessed by transthoracic echocardiography in the post-procedural setting at 30-60 days follow-up, resulting in at least moderate regurgitation.
- Acute kidney injury
Assessed during hospitalization and defined as at least a 150–200% increase in serum creatinine from baseline or an increase >0.3 mg/dl within 48 hours and subsequently staged according to the KDIGO (Kidney Disease: Improving Global Outcomes) classification.
- Structural cardiac complications
Perforation, injury, or cardiac damage resulting in death, bleeding, hemodynamic compromise, or tamponade, or requiring unplanned surgical or percutaneous intervention.
- Other procedural and technical complications
Conversion to cardiac surgery, unplanned use of mechanical circulatory support.
- Periprocedural myocardial infarction (<48 h from the procedure)
Defined according to the Fourth Universal Definition of Myocardial Infarction.
- Rehospitalization
Admission for new complications or hospitalizations not directly related to the valve replacement procedure.

The main procedural and clinical outcomes were defined according to VARC-3 (Valve Academic Research Consortium) criteria.

The Secondary endpoints included comparison between the groups of ZC-TAVI and S-TAVI about:

- Singular complications already included in the composite primary endpoint
- Evaluation of changes in renal function after the procedure

In-hospital eGFR variation and eGFR variation at 30-60-days post-TAVI follow-up.

2.2 MATERIALS AND METHODS

The study is a prospective single-centre study in which 27 consecutive patients were enrolled from July 2022 to May 2025 at the Cardiology and Hemodynamics Unit of “G. Mazzini” Hospital of Teramo.

All patients provided written informed consent.

All patients were affected by chronic kidney disease and severe aortic stenosis with indication for TAVI; 13 patients underwent to zero-contrast TAVI procedure, while 14 patients underwent to standard TAVI. Patient evaluation included the collection of clinical, echocardiographic, laboratory, and radiological data. The first assessment was performed in the pre-procedural setting, followed by two additional evaluations: within 3 days after the index procedure and at 30-60 days follow-up after the index procedure.

The inclusion criteria of the study were:

- Male or female patients with severe aortic stenosis, aged >18 years, evaluated by the Heart Team as candidates for TAVI according to the most recent cardiology guidelines.
- Estimated glomerular filtration rate (eGFR) calculated using the Cockcroft–Gault formula <40 ml/min.

The exclusion criteria of the study were:

- End-stage renal disease requiring renal replacement therapy.
- Any contraindication to TAVI procedure.
- TAVI performed via non-transfemoral access.

Some patient selection and first evaluation were carried out at spoke centres and then referred to our centre.

Pre-procedural planning contrast-enhanced CT was performed in all patients due to the unavailability of additional non-iodinated-contrast radiological imaging modalities; CT was performed during the index hospitalization, or it was carried out in the preceding months according to the pre-admission protocol.

Coronary angiography was not routinely performed as part of standard care and when it was deemed necessary, it was performed during the same TAVI procedure or in the days immediately before.

The reported contrast volume represented the total amount of contrast administered during all interventional and diagnostic procedures performed during the hospitalization.

Standard measures for the prevention of contrast-induced nephropathy were adopted according to the patient's risk profile; standard care included hydration with 0.9% saline initiated 24 hours before the procedure in patients with impaired renal function at a rate of 1 ml/kg/h - reduced to 0.5 ml/kg/h in the presence of left ventricular dysfunction -. Intravenous hydration was continued for 24 hours after the procedure, and creatinine clearance was monitored using the Cockcroft–Gault formula.

In diabetic patients, metformin therapy was discontinued at least 24 hours before contrast procedures and resumed 48 hours afterward, except in cases of acute kidney injury.

Assignment to the zero-contrast TAVI group was determined based on operator experience and the feasibility of performing the procedure without contrast, as assessed by pre-procedural imaging and patient anatomical characteristics.

The choice of bioprosthesis type was based on pre-procedural computed tomography analysis; implanted prostheses included Edwards SAPIEN 3 Ultra, Medtronic Evolut PRO, Evolut PRO+, and Evolut FX.

Zero-contrast TAVI procedures were performed without transoesophageal echocardiographic guidance but using fluoroscopy alone with radiopaque landmarks.

At the end of the procedure, prosthetic valve function was assessed by transthoracic echocardiography, and potential vascular complications were evaluated by vascular ultrasound of the femoral axis at the main access site.

When contrast use was necessary, iso-osmolar contrast agents were administered intra-arterially, including Iomeron 400, Visipaque 320, or Xenetix 350.

2.3 STATISTICAL ANALYSIS

All statistical analyses were conducted using IBM SPSS Statistics software.

To compare baseline characteristics between the two study groups, continuous variables were first assessed for normality using the Shapiro–Wilk test. Since some distributions did not meet the assumptions of normality, continuous variables were described as median $\pm$ standard error of the mean (SEM) and compared using the Mann–Whitney U test for independent samples.

Categorical variables were expressed as absolute number (n) and percentage (%).

Between-group comparisons were performed using Pearson's χ^2 test or Fisher's exact test (two-tailed), as appropriate.

Comparison of the incidence of complications between the two groups (standard TAVI vs zero-contrast TAVI) was carried out using the same statistical methods (Pearson's χ^2 test or two-tailed Fisher's exact test), depending on cell size.

For intra-group evaluation of renal function, expressed as estimated glomerular filtration rate (eGFR) measured at the pre-procedural phase, at post-procedural peak, and at 30-60 days follow-up, the Wilcoxon signed-rank test for paired samples was applied.

Subsequently, for inter-group comparison of the magnitude of renal function change, individual differences were calculated (Δ eGFR = post value – pre value) for both the pre–peak and pre–30-60-days follow-up intervals, and these changes were compared between groups using the Mann–Whitney U test for independent samples.

All statistical tests were two-tailed, with the level of statistical significance set at $p < 0.05$.

2.4 RESULTS

Baseline characteristics were analysed to assess the homogeneity of the two patient groups undergoing TAVI using either the standard approach (S-TAVI) or the zero-contrast technique (ZC-TAVI).

For continuous variables - age, body surface area (BSA), and pre-procedural estimated glomerular filtration rate (eGFR) - the Shapiro–Wilk test demonstrated a non-normal distribution of age in the standard TAVI group ($p = 0,047$), whereas age was normally distributed in the zero-contrast group ($p = 0,059$).

Body surface area (BSA) showed a normal distribution in both groups ($p = 0,101$ for S-TAVI; $p = 1,000$ for ZC-TAVI).

Pre-procedural renal function was also normally distributed in both groups ($p = 0,164$ and $p = 0,196$, respectively).

Comparisons between the two groups - performed using the Mann–Whitney U test - revealed no significant differences in age ($U = 519,000$; $p > 0,05$) or BSA ($p > 0,05$), indicating good demographic and anthropometric homogeneity; in contrast, pre-procedural eGFR differed significantly between groups ($U = 22,000$; $p < 0,05$), with lower values observed in the zero-contrast TAVI group. This finding is consistent with the clinical selection of patients with more impaired renal function for the zero-contrast approach, aimed at minimizing exposure to iodinated contrast media.

Categorical variables - sex, diabetes mellitus, arterial hypertension, atrial fibrillation, ischemic heart disease, prior TIA/stroke, renal transplantation, and type of implanted prosthesis - were analysed using the Chi-square test (or Fisher's exact test when appropriate).

No statistically significant differences were observed between the two groups regarding sex ($p = 0,586$), diabetes mellitus ($p = 0,173$), arterial hypertension ($p = 0,303$), atrial fibrillation ($p = 0,580$), ischemic heart disease ($p = 0,333$), or type of implanted prosthesis (self-expandable vs. balloon-expandable; $p = 0,345$).

The variable “prior stroke/TIA” was constant in both groups and therefore not amenable to statistical analysis.

A non-significant trend toward a higher prevalence of renal transplantation was observed in the zero-contrast TAVI group ($p = 0,057$), consistent with the preferential selection of patients with chronic kidney disease for the zero-contrast procedure.

Overall, the two populations were homogeneous in terms of age, anthropometric characteristics, and major cardiovascular risk factors, differing only in pre-procedural renal function, which was significantly more impaired in the zero-contrast group (Table 1); this clinically expected difference confirms appropriate patient selection for the zero-contrast TAVI approach and supports the reliability of post-procedural outcome comparisons between the two groups.

	S-TAVI	ZC-TAVI	p Value
	n=14	n=13	
Age (years)	83,4 ± 1,2	79,5 ± 2,6	>0,05
BSA (m²)	1,81 ± 0,11	1,82 ± 0,05	>0,05
eGFR pre (ml/min/1,73 m²)	35,3 ± 1,1	26,7 ± 2,7	<0,05 *
Male sex (%)	64%	68%	0,586
Diabetes Mellitus (%)	45%	33%	0,173
Arterial hypertension (%)	88%	82%	0,303
Atrial Fibrillation (%)	37%	33%	0,580
Prior stroke/TIA (%)	8%	8%	—
Ischemic heart disease (%)	42%	50%	0,333
Kidney transplant (%)	0%	18%	0,057
Self-expandable bioprosthetic (%)	58%	64%	0,345

Table 1. The values are expressed as n (%) or mean ± standard error. A p value < 0.05 indicates a statistically significant difference. S-TAVI= standard TAVI, ZC-TAVI=zero-contrast TAVI.

The incidence of procedural and post-procedural complications was compared between groups using Pearson's Chi-square test or Fisher's exact test when expected cell counts were <5.

No statistically significant differences were observed between the two groups in the occurrence of at least one post-procedural complication (composite primary endpoint; $p = 0,420$), nor in individual major complications, including acute kidney injury ($p = 0,863$), major bleeding ($p = 1,000$), conduction disturbances requiring permanent pacemaker implantation ($p = 0,678$), vascular complications ($p = 0,596$), paravalvular leak ($p = 0,576$), or rehospitalization within 60 days after TAVI ($p = 0,385$); similarly, no differences were observed in the incidence of acute kidney injury at 30-60 days follow-up ($p = 1,000$) (Table 2).

For outcomes such as all-cause mortality, prosthetic valve dysfunction, structural cardiac complications, myocardial infarction, and other procedural complications, statistical analysis was not performed due to the absence of events in both groups.

Complications	S-TAVI n (%)	ZC-TAVI n (%)	Test	p Value
Composite endpoint	11 (78,6%)	8 (61,5%)	Fisher test	0,420
AKI	6 (42,9%)	6 (46,2%)	Pearson's Chi-square	0,863
Pacemaker implantation	5 (35,7%)	3 (23,1%)	Fisher	0,678
Significant paravalvular leak	1 (7,1%)	2 (15,4%)	Fisher	0,576
Vascular complications	3 (21,4%)	1 (7,7%)	Fisher	0,596
Major bleeding	2 (14,3%)	2 (15,4%)	Fisher	1
Rehospitalization	2 (14,3%)	4 (30,8 %)	Fisher	0,385
AKI at 30-60 days follow-up	4 (28,6%)	3 (23,1%)	Fisher	1

Table 2. Incidence of procedural and post-procedural complications. AKI = acute kidney injury; S-TAVI= standard TAVI, ZC-TAVI=zero-contrast TAVI Values are presented as n (%) or mean $\pm$ standard error. Percentages were calculated based on the total number of patients within each group. A p-value < 0.05 was considered statistically significant.

Intra-group analysis using the Wilcoxon signed-rank test did not reveal statistically significant changes in eGFR in either the standard TAVI group or the zero-contrast TAVI group. In both groups, a modest reduction in eGFR was observed at the post-procedural peak ($p = 0,311$ and $p = 0,477$, respectively), which did not reach statistical significance, followed by complete recovery at 30-60 days follow-up ($p = 0,767$ and $p = 1,000$, respectively) (Table 3).

Group	e GFR comparison	p Value	Interpretation
S-TAVI	Pre vs Peak	0,311	Modest reduction (10↓ / 3↑)
S-TAVI	Pre vs 30-60 days follow-up	0,767	Recovery
ZC-TAVI	Pre vs Peak	0,477	Modest reduction (8↓ / 3↑)
ZC-TAVI	Pre vs 30-60 days follow-up	1,000	No variations

Table 3. Intragroup analysis in eGFR comparison in standard TAVI and Zero-contrast TAVI groups; e GFR = estimated glomerular filtration rate. S-TAVI= standard TAVI. ZC-TAVI=zero-contrast TAVI.

Comparison of eGFR changes between the two groups (standard TAVI vs. zero-contrast TAVI) using the Mann–Whitney U test did not reveal statistically significant differences either in the acute phase (pre–peak: $p = 0,382$) or at 30-60 days follow-up (pre–30-60 days follow-up: $p = 0,624$). Analysis of eGFR variation demonstrated an acute decline in renal function in both groups, which was more pronounced in patients undergoing standard TAVI (median Δ pre–peak = $-4,42$ mL/min/ $1,73$ m²) compared with the zero-contrast group ($-3,69$ mL/min/ $1,73$ m²; $p = 0,382$). At 30-60 days follow-up (Δ pre–post), recovery of renal function was observed in the standard TAVI group (median $+4,11$ mL/min/ $1,73$ m²), whereas renal function remained stable in the zero-contrast group ($0,00$ mL/min/ $1,73$ m²; $p = 0,624$).

Although these differences did not reach statistical significance, the overall renal profile suggests that the zero-contrast approach is associated with a smaller acute change in eGFR and substantial mid-term stability, without evidence of chronic deterioration of renal function (Table 4).

	median Δ eGFR S-TAVI	median Δ eGFR ZC- TAVI	Test	p Value
Δ eGFR pre– peak	-4,42	-3,69	Mann–Whitney	0,382
Δ eGFR pre–30- 60 days follow-up	+ 4,11	0,00	Mann–Whitney	0,624

Table 4. Intergroup analysis in eGFR variations in standard TAVI and Zero-contrast TAVI groups; eGFR = estimated glomerular filtration rate.

2.5 DISCUSSION

The introduction of transcatheter aortic valve implantation (TAVI) has revolutionized the management of severe aortic stenosis, enabling effective treatment of patients at high surgical risk or with significant comorbidities. However, the use of iodinated contrast media during the procedure represents a potential risk factor for acute kidney injury (AKI), particularly in patients with pre-existing renal impairment.

In recent years, increasing attention has therefore been directed toward the development of contrast-sparing strategies, culminating in the implementation of fully zero-contrast approaches, performed without any administration of contrast media.

In the present study, a small cohort of patients undergoing standard TAVI and zero-contrast TAVI was analysed, comparing baseline characteristics, complication rates, and the trajectory of renal function during hospitalization and follow-up. The two groups were largely homogeneous with respect to age, sex, body surface area, and major comorbidities, with significant differences observed only in baseline eGFR values, which were lower in the standard TAVI group.

The results indicate that the zero-contrast procedure does not confer an increased risk of major complications compared with standard TAVI in the analysed cohort, supporting the non-inferiority of the zero-contrast approach relative to the conventional procedure. Given the significant difference in pre-procedural eGFR between groups, baseline renal function represents a potential confounding factor in the analysis of post-procedural complications. Nevertheless, univariate analyses did not reveal significant differences between groups in the overall incidence of complications or in individual endpoints, suggesting that the zero-contrast approach does not entail an independent additional risk, despite its application in patients with more severely impaired renal function.

Analysis of renal function demonstrated that TAVI, in both procedural variants, does not result in clinically meaningful deterioration of eGFR. Specifically, an acute post-procedural decline in eGFR was observed, which was more pronounced in the standard TAVI group (median $-4,42$ mL/min/1,73 m²) compared with the zero-contrast group ($-3,69$ mL/min/1,73 m²), although this difference did not reach statistical significance ($p = 0,382$); at 30-60 days follow-up,

functional recovery was observed in the standard group (median +4,11 mL/min/1,73 m²), whereas renal function remained stable in the zero-contrast group (0,00 mL/min/1,73 m²; p = 0,624).

These findings suggest that the zero-contrast approach may limit acute renal function fluctuations, ensuring a stable and safe clinical course even in patients with more advanced renal impairment.

The present results are consistent with previously published evidence.

2.6 LIMITATIONS

The study is a single-center study with a relatively small sample size.

Additional limitations include heterogeneity in baseline eGFR values and the lack of long-term follow-up. Moreover, the selection of patients in the zero-contrast group with more severely impaired renal function, compared with the standard TAVI group, may represent a selection bias.

Pre-procedural imaging in our study involved the use of contrast-enhanced CT in both groups due to the unavailability of alternative non-contrast imaging methods.

2.7 CONCLUSION

In conclusion, the study results indicate that TAVI performed without contrast media is safe and non-inferior to the standard procedure in terms of post-procedural complications, both for singular complications and the composite endpoint.

No statistically significant deterioration in renal function was observed either between groups or within groups (pre- vs. post-procedure).

The greater stability of eGFR levels in the zero-contrast TAVI group, although not statistically significant, may suggest a more stable post-operative course for patients undergoing the procedure without contrast. The zero-contrast approach should be considered a preferred strategy for patients with advanced renal insufficiency or at high risk of AKI.

Prospective randomized studies on larger populations are warranted to more precisely determine the impact of this technique on long-term renal and clinical outcomes.

REFERENCES⁶⁸

-
- ¹ Joanna L. d'Arcy et al., «Large-Scale Community Echocardiographic Screening Reveals a Major Burden of Undiagnosed Valvular Heart Disease in Older People: The OxVALVE Population Cohort Study», *European Heart Journal* 37, fasc. 47 (2016): 3515–22, <https://doi.org/10.1093/eurheartj/ehw229>.
- ² Bernard Jung et al., «Contemporary Presentation and Management of Valvular Heart Disease: The EURObservational Research Programme Valvular Heart Disease II Survey», *Circulation* 140, fasc. 14 (2019): 1156–69, <https://doi.org/10.1161/CIRCULATIONAHA.119.041080>.
- ³ William C. Roberts e Jong M. Ko, «Frequency by Decades of Unicuspid, Bicuspid, and Tricuspid Aortic Valves in Adults Having Isolated Aortic Valve Replacement for Aortic Stenosis, With or Without Associated Aortic Regurgitation», *Circulation* 111, fasc. 7 (2005): 920–25, <https://doi.org/10.1161/01.CIR.0000155623.48408.C5>.
- ⁴ Subodh Verma e Samuel C. Siu, «Aortic Dilatation in Patients with Bicuspid Aortic Valve», *New England Journal of Medicine* 370, fasc. 20 (2014): 1920–29, <https://doi.org/10.1056/NEJMra1207059>.
- ⁵ Liesl Zühlke et al., «Characteristics, Complications, and Gaps in Evidence-Based Interventions in Rheumatic Heart Disease: The Global Rheumatic Heart Disease Registry (the REMEDY Study)», *European Heart Journal* 36, fasc. 18 (2015): 1115–22, <https://doi.org/10.1093/eurheartj/ehu449>.
- ⁶ Philippe G  n  reux et al., «The Mortality Burden of Untreated Aortic Stenosis», *Journal of the American College of Cardiology* 82, fasc. 22 (2023): 2101–9, <https://doi.org/10.1016/j.jacc.2023.09.796>.
- ⁷ Fabien Praz et al., «2025 ESC/EACTS Guidelines for the Management of Valvular Heart Disease», *European Heart Journal* 46, fasc. 44 (2025): 4635–736, <https://doi.org/10.1093/eurheartj/ehaf194>.
- ⁸ Catherine M. Otto et al., «2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease», *Journal of the American College of Cardiology* 77, fasc. 4 (2021): e25–197, <https://doi.org/10.1016/j.jacc.2020.11.018>.
- ⁹ Marc R Dweck et al., «Multi-Modality Imaging in Aortic Stenosis: An EACVI Clinical Consensus Document», *European Heart Journal - Cardiovascular Imaging* 24, fasc. 11 (2023): 1430–43, <https://doi.org/10.1093/ehjci/jead153>.

-
- ¹⁰ Helmut Baumgartner et al., «Recommendations on the Echocardiographic Assessment of Aortic Valve Stenosis: A Focused Update from the European Association of Cardiovascular Imaging and the American Society of Echocardiography», *Journal of the American Society of Echocardiography* 30, fasc. 4 (2017): 372–92, <https://doi.org/10.1016/j.echo.2017.02.009>; Jaffar M. Khan et al., «Coronary Obstruction From TAVR in Native Aortic Stenosis», *JACC: Cardiovascular Interventions* 16, fasc. 4 (2023): 415–25, <https://doi.org/10.1016/j.jcin.2022.11.018>.
- ¹¹ Ezequiel Guzzetti et al., «Transvalvular Flow, Sex, and Survival After Valve Replacement Surgery in Patients With Severe Aortic Stenosis», *Journal of the American College of Cardiology* 75, fasc. 16 (2020): 1897–909, <https://doi.org/10.1016/j.jacc.2020.02.065>.
- ¹² P. Mehrotra et al., «Differential Left Ventricular Remodelling and Longitudinal Function Distinguishes Low Flow from Normal-Flow Preserved Ejection Fraction Low-Gradient Severe Aortic Stenosis», *European Heart Journal* 34, fasc. 25 (2013): 1906–14, <https://doi.org/10.1093/eurheartj/ehf094>.
- ¹³ Christophe Tribouilloy et al., «Low-Gradient, Low-Flow Severe Aortic Stenosis With Preserved Left Ventricular Ejection Fraction», *Journal of the American College of Cardiology* 65, fasc. 1 (2015): 55–66, <https://doi.org/10.1016/j.jacc.2014.09.080>.
- ¹⁴ Nikolaus Jander et al., «Outcome of Patients With Low-Gradient “Severe” Aortic Stenosis and Preserved Ejection Fraction», *Circulation* 123, fasc. 8 (2011): 887–95, <https://doi.org/10.1161/CIRCULATIONAHA.110.983510>.
- ¹⁵ Yohann Bohbot et al., «Survival and Management of Patients With Discordant High-Gradient Aortic Stenosis», *JACC: Cardiovascular Imaging* 14, fasc. 8 (2021): 1672–74, <https://doi.org/10.1016/j.jcmg.2021.02.010>.
- ¹⁶ Philippe Unger et al., «Prevalence and Outcomes of Patients With Discordant High-Gradient Aortic Stenosis», *Journal of the American College of Cardiology* 83, fasc. 12 (2024): 1109–19, <https://doi.org/10.1016/j.jacc.2024.01.025>.
- ¹⁷ Saki Ito et al., «High-Gradient Aortic Stenosis With Valve Area >1.0 Cm²», *JACC: Cardiovascular Imaging* 18, fasc. 2 (2025): 166–76, <https://doi.org/10.1016/j.jcmg.2024.07.025>.
- ¹⁸ Mohamed-Salah Annabi et al., «Dobutamine Stress Echocardiography for Management of Low-Flow, Low-Gradient Aortic Stenosis», *Journal of the American College of Cardiology* 71, fasc. 5 (2018): 475–85, <https://doi.org/10.1016/j.jacc.2017.11.052>.

-
- ¹⁹ Henrique Barbosa Ribeiro et al., «Transcatheter Aortic Valve Replacement in Patients With Low-Flow, Low-Gradient Aortic Stenosis», *Journal of the American College of Cardiology* 71, fasc. 12 (2018): 1297–308, <https://doi.org/10.1016/j.jacc.2018.01.054>.
- ²⁰ Marie-Annick Clavel et al., «The Complex Nature of Discordant Severe Calcified Aortic Valve Disease Grading», *Journal of the American College of Cardiology* 62, fasc. 24 (2013): 2329–38, <https://doi.org/10.1016/j.jacc.2013.08.1621>.
- ²¹ Tania Pawade et al., «Computed Tomography Aortic Valve Calcium Scoring in Patients With Aortic Stenosis», *Circulation: Cardiovascular Imaging* 11, fasc. 3 (2018): e007146, <https://doi.org/10.1161/CIRCIMAGING.117.007146>.
- ²² Dweck et al., «Multi-Modality Imaging in Aortic Stenosis».
- ²³ Mylène Shen et al., «Computed Tomography Aortic Valve Calcium Scoring in Patients With Bicuspid Aortic Valve Stenosis», *Structural Heart* 6, fasc. 1 (2022): 100027, <https://doi.org/10.1016/j.shj.2022.100027>.
- ²⁴ Mylène Shen et al., «Effect of Age and Aortic Valve Anatomy on Calcification and Haemodynamic Severity of Aortic Stenosis», *Heart* 103, fasc. 1 (2017): 32–39, <https://doi.org/10.1136/heartjnl-2016-309665>.
- ²⁵ Wisarut Wanchaitanawong et al., «Diagnostic Role of Aortic Valve Calcium Scoring in Various Etiologies of Aortic Stenosis», *Scientific Reports* 13, fasc. 1 (2023): 8019, <https://doi.org/10.1038/s41598-023-34118-7>.
- ²⁶ Zi Ye et al., «Computed Tomography Calcium Scoring in Aortic Stenosis: Bicuspid versus Tricuspid Morphology», *Heart* 110, fasc. 8 (2024): 594–602, <https://doi.org/10.1136/heartjnl-2023-323281>.
- ²⁷ Annette Maznyczka et al., «Fibrotic vs Calcific Aortic Stenosis», *JACC: Cardiovascular Interventions* 17, fasc. 24 (2024): 2969–71, <https://doi.org/10.1016/j.jcin.2024.09.041>.
- ²⁸ Jutta Bergler-Klein et al., «Natriuretic Peptides Predict Symptom-Free Survival and Postoperative Outcome in Severe Aortic Stenosis», *Circulation* 109, fasc. 19 (2004): 2302–8, <https://doi.org/10.1161/01.CIR.0000126825.50903.18>.
- ²⁹ Marie-Annick Clavel et al., «B-Type Natriuretic Peptide Clinical Activation in Aortic Stenosis», *Journal of the American College of Cardiology* 63, fasc. 19 (2014): 2016–25, <https://doi.org/10.1016/j.jacc.2014.02.581>.
- ³⁰ Paul Das et al., «Exercise Testing to Stratify Risk in Aortic Stenosis», *European Heart Journal* 26, fasc. 13 (2005): 1309–13, <https://doi.org/10.1093/eurheartj/ehi250>.

-
- ³¹ Asim M. Rafique et al., «Meta-Analysis of Prognostic Value of Stress Testing in Patients With Asymptomatic Severe Aortic Stenosis», *The American Journal of Cardiology* 104, fasc. 7 (2009): 972–77, <https://doi.org/10.1016/j.amjcard.2009.05.044>.
- ³² Rong Bing et al., «Imaging and Impact of Myocardial Fibrosis in Aortic Stenosis», *JACC: Cardiovascular Imaging* 12, fasc. 2 (2019): 283–96, <https://doi.org/10.1016/j.jcmg.2018.11.026>.
- ³³ George D Thornton et al., «Myocardial Scar and Remodelling Predict Long-Term Mortality in Severe Aortic Stenosis beyond 10 Years», *European Heart Journal* 45, fasc. 22 (2024): 2019–22, <https://doi.org/10.1093/eurheartj/ehae067>.
- ³⁴ Génèreux et al., «The Mortality Burden of Untreated Aortic Stenosis».
- ³⁵ Patricia A. Pellikka et al., «Outcome of 622 Adults With Asymptomatic, Hemodynamically Significant Aortic Stenosis During Prolonged Follow-Up», *Circulation* 111, fasc. 24 (2005): 3290–95, <https://doi.org/10.1161/CIRCULATIONAHA.104.495903>.
- ³⁶ H. J. Heuvelman et al., «Clinical Course of Patients Diagnosed with Severe Aortic Stenosis in the Rotterdam Area: Insights from the AVARIJN Study», *Netherlands Heart Journal* 20, fasc. 12 (2012): 487–93, <https://doi.org/10.1007/s12471-012-0309-3>.
- ³⁷ Das et al., «Exercise Testing to Stratify Risk in Aortic Stenosis».
- ³⁸ Rafique et al., «Meta-Analysis of Prognostic Value of Stress Testing in Patients With Asymptomatic Severe Aortic Stenosis».
- ³⁹ Philippe Pibarot et al., «Association of Paravalvular Regurgitation With 1-Year Outcomes After Transcatheter Aortic Valve Replacement With the SAPIEN 3 Valve», *JAMA Cardiology* 2, fasc. 11 (2017): 1208, <https://doi.org/10.1001/jamacardio.2017.3425>.
- ⁴⁰ S. A. M. Nashef et al., «EuroSCORE II», *European Journal of Cardio-Thoracic Surgery* 41, fasc. 4 (2012): 734–45, <https://doi.org/10.1093/ejcts/ezs043>.
- ⁴¹ Niv Ad et al., «Comparison of EuroSCORE II, Original EuroSCORE, and The Society of Thoracic Surgeons Risk Score in Cardiac Surgery Patients», *The Annals of Thoracic Surgery* 102, fasc. 2 (2016): 573–79, <https://doi.org/10.1016/j.athoracsur.2016.01.105>.
- ⁴² Miriam Compagnone et al., «Surgical Risk Scores Applied to Transcatheter Aortic Valve Implantation: Friends or Foes? Short-Term and Long-Term Outcomes From a Single-Center Registry», *The Journal of Invasive Cardiology* 31, fasc. 10 (2019): E282–88.
- ⁴³ Karim Al-Azizi et al., «Assessment of TVT and STS Risk Score Performances in Patients Undergoing Transcatheter Aortic Valve Replacement», *Journal of the Society for*

Cardiovascular Angiography & Interventions 2, fasc. 3 (2023): 100600, <https://doi.org/10.1016/j.jscai.2023.100600>.

⁴⁴ Giuseppe Tarantini et al., «One-Year Outcomes of a European Transcatheter Aortic Valve Implantation Cohort According to Surgical Risk: Subanalysis of the SOURCE 3 Registry», *Circulation: Cardiovascular Interventions* 12, fasc. 1 (2019): e006724, <https://doi.org/10.1161/CIRCINTERVENTIONS.118.006724>.

⁴⁵ George C M Siontis et al., «Transcatheter Aortic Valve Implantation vs. Surgical Aortic Valve Replacement for Treatment of Symptomatic Severe Aortic Stenosis: An Updated Meta-Analysis», *European Heart Journal* 40, fasc. 38 (2019): 3143–53, <https://doi.org/10.1093/eurheartj/ehz275>.

⁴⁶ Khan et al., «Coronary Obstruction From TAVR in Native Aortic Stenosis».

⁴⁷ Craig R. Smith et al., «Transcatheter versus Surgical Aortic-Valve Replacement in High-Risk Patients», *The New England Journal of Medicine* 364, fasc. 23 (2011): 2187–98, <https://doi.org/10.1056/NEJMoa1103510>.

⁴⁸ Azeem Latib et al., «Transcatheter vs Surgical Aortic Valve Replacement in Intermediate-Surgical-Risk Patients with Aortic Stenosis: A Propensity Score-Matched Case-Control Study», *American Heart Journal* 164, fasc. 6 (2012): 910–17, <https://doi.org/10.1016/j.ahj.2012.09.005>.

⁴⁹ Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group, «KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease», *Kidney International* 105, fasc. 4S (2024): S117–314, <https://doi.org/10.1016/j.kint.2023.10.018>.

⁵⁰ Arif Khwaja, «KDIGO Clinical Practice Guidelines for Acute Kidney Injury», *Nephron. Clinical Practice* 120, fasc. 4 (2012): c179-184, <https://doi.org/10.1159/000339789>.

⁵¹ Tilman Perrin et al., «Contrast-Induced Nephropathy in Invasive Cardiology», *Swiss Medical Weekly* 142 (2012): w13608, <https://doi.org/10.4414/smw.2012.13608>.

⁵² Katrin Gebauer et al., «The Risk of Acute Kidney Injury and Its Impact on 30-Day and Long-Term Mortality after Transcatheter Aortic Valve Implantation», *International Journal of Nephrology* 2012 (2012): 483748, <https://doi.org/10.1155/2012/483748>.

⁵³ Kenichi Chatani et al., «Acute Kidney Injury after Transcatheter Aortic Valve Implantation: Impact of Contrast Agents, Predictive Factors, and Prognostic Importance in 203 Patients with

Long-Term Follow-Up», *Journal of Cardiology* 66, fasc. 6 (2015): 514–19, <https://doi.org/10.1016/j.jjcc.2015.02.007>.

⁵⁴ Rutger-Jan M. Nuis et al., «Frequency, Determinants, and Prognostic Effects of Acute Kidney Injury and Red Blood Cell Transfusion in Patients Undergoing Transcatheter Aortic Valve Implantation», *Catheterization and Cardiovascular Interventions: Official Journal of the Society for Cardiac Angiography & Interventions* 77, fasc. 6 (2011): 881–89, <https://doi.org/10.1002/ccd.22874>.

⁵⁵ Jan-Malte Sinning et al., «Renal Function as Predictor of Mortality in Patients after Percutaneous Transcatheter Aortic Valve Implantation», *JACC. Cardiovascular Interventions* 3, fasc. 11 (2010): 1141–49, <https://doi.org/10.1016/j.jcin.2010.09.009>.

⁵⁶ Gabriele Venturi et al., «Volume of Contrast to Creatinine Clearance Ratio Predicts Early Mortality and AKI after TAVI», *Catheterization and Cardiovascular Interventions: Official Journal of the Society for Cardiac Angiography & Interventions* 99, fasc. 6 (2022): 1925–34, <https://doi.org/10.1002/ccd.30156>.

⁵⁷ Masanori Yamamoto et al., «Prognostic Value of Chronic Kidney Disease after Transcatheter Aortic Valve Implantation», *Journal of the American College of Cardiology* 62, fasc. 10 (2013): 869–77, <https://doi.org/10.1016/j.jacc.2013.04.057>.

⁵⁸ Ahmed Samy Badran et al., «Evaluating Zero-Contrast Transcatheter Aortic Valve Implantation (TAVI) for Patients With Renal Impairment: A Pooled Meta-Analysis of 1505 Patients», *Catheterization and Cardiovascular Interventions: Official Journal of the Society for Cardiac Angiography & Interventions* 106, fasc. 4 (2025): 2147–59, <https://doi.org/10.1002/ccd.70050>.

⁵⁹ Noman Ali et al., «Trans-Catheter Aortic Valve Implantation without Contrast Using the Lotus Mechanically-Expanded Heart Valve», *Journal of Cardiology Cases* 18, fasc. 4 (2018): 141–44, <https://doi.org/10.1016/j.jccase.2018.06.007>.

⁶⁰ Guy F. A. Prado et al., «Zero-Contrast Imaging for the Assessment of Transcatheter Aortic Valve Implantation in Candidates with Renal Dysfunction», *Renal Failure* 45, fasc. 1 (2023): 2224888, <https://doi.org/10.1080/0886022X.2023.2224888>.

⁶¹ Prado et al., «Zero-Contrast Imaging for the Assessment of Transcatheter Aortic Valve Implantation in Candidates with Renal Dysfunction».

-
- ⁶² Antônio Fernando Diniz Freire et al., «Non-Contrast Transcatheter Aortic Valve Implantation for Patients with Aortic Stenosis and Chronic Kidney Disease: A Pilot Study», *Frontiers in Cardiovascular Medicine* 10 (2023): 1175600, <https://doi.org/10.3389/fcvm.2023.1175600>.
- ⁶³ Fausto Castriota et al., «Contrast-Zero Transcatheter Aortic Valve Replacement for Patients With Severe Renal Dysfunction: A Single-Center Experience», *JACC. Cardiovascular Interventions* 11, fasc. 8 (2018): 820–22, <https://doi.org/10.1016/j.jcin.2018.01.280>.
- ⁶⁴ Masashi Koga et al., «Safety and Feasibility of Zero-Contrast Transcatheter Aortic Valve Implantation Using Balloon-Expandable Valves in Patients with Aortic Stenosis and Severe Renal Impairment: A Single-Center Study», *Cardiovascular Revascularization Medicine: Including Molecular Interventions* 58 (gennaio 2024): 68–76, <https://doi.org/10.1016/j.carrev.2023.07.014>.
- ⁶⁵ {Citation}
- ⁶⁶ Roberto Nerla et al., «Zero-Contrast Transcatheter Aortic Valve Implantation vs. Standard Practice: Periprocedural and Long-Term Clinical Outcomes», *Journal of Clinical Medicine* 13, fasc. 18 (2024): 5405, <https://doi.org/10.3390/jcm13185405>.
- ⁶⁷ Łukasz Pyka et al., «Zero-Contrast TAVI: Novel Alternative for Challenging Patient Population», *Kardiologia Polska* 82, fasc. 7–8 (2024): 814–15, <https://doi.org/10.33963/v.phj.101283>.