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Impact of baseline left ventricular ejection fraction on thirty-day and one-year mortality after transfemoral aortic valve implantation

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Karim El Chilali

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Dekan:	Herr Univ.-Prof. Dr. med. J. Buer
1. Gutachter:	Herr Univ.-Prof. Dr. med. P. Kahlert
2. Gutachter:	Herr Priv.-Doz. Dr. med. D. Dirkmann

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Table of contents

1. Introduction

1.1. Overview

Transcatheter aortic valve implantation (TAVI) has become the standard therapy for symptomatic severe aortic stenosis (AS) in elderly patients (> 75 years), especially if transfemoral access is possible (TF-TAVI). These patients commonly present with comorbidities and a substantial proportion of them has an impaired left ventricular ejection fraction (LVEF).

It is controversial whether an impaired LVEF per se increases the risk of mortality after TAVI. The results of observational studies are conflicting and the cutoff points for LVEF that are associated with an increased risk vary markedly between different studies.

Moreover, impaired LVEF may result in a low flow state producing a low pressure gradient across the stenotic aortic valve despite the presence of a severe AS (aortic valve area < 1.0 cm^2 and mean transvalvular aortic gradient < 40 mmHg). This condition is known as low gradient aortic stenosis (LGAS) and was classically described in patients with an impaired LVEF, but is also paradoxically seen in elderly patients with a normal LVEF. Patients with LGAS are deemed at increased risk of adverse outcome after TAVI.

The American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI) recommended new cutoff values for a normal, mildly abnormal, moderately abnormal and severely abnormal LVEF. The impact of this categorization on the outcome after TAVI has not been previously tested.

We aimed to assess the impact of the ASE/EACVI classification of LVEF on 30-day and 1-year mortality after TF-TAVI and to evaluate if the presence of LGAS in patients with an impaired LVEF is associated with a worse outcome.

1.2. Degenerative aortic valve stenosis

1.2.1. Epidemiology and pathogenesis

Degenerative AS is the most common valvular heart disease in developed countries. With increasing life expectancy of the general population, more patients with degenerative AS are expected to be seen in the Western world (Freeman and Otto 2005, Otto 2006). In a previous report from Norway, AS can affect up to 9.8% of people ≥ 80 years with an overall prevalence of 2.8% in patients > 75 years of age (Eveborn et al. 2013).

AS is an active disease characterized by lipid accumulation, inflammation, and calcification. Many believe that AS is not a disease of the aortic valve only but rather of the entire vascular system including the left ventricle and systemic vasculature (Otto 2006). Additionally, AS is a progressive disease that carries a high mortality within a few years, if left untreated once symptoms occur. When severe AS is present, the rate of progression to symptoms is high, with an event-free survival of only 30% to 50% at two-years. Progression of AS can be more rapid in older patients and in those with more severe leaflet calcification (Nishimura et al. 2014).

1.2.2. Assessment and grading of severity

The classical symptoms of a severe AS are angina pectoris, dyspnea and syncope. A loud systolic ejection murmur over the right upper sternal border detected by auscultation with late peaking and radiation to the carotids is usually the first clinical clue for diagnosis of severe AS (Vahanian et al. 2012).

Historically, diagnosis of severe AS was made invasively through cardiac catheterization and determination of the aortic valve area using the Gorlin formula. At present, this has been replaced by transthoracic echocardiography (TTE) which plays a crucial role not only in

diagnosis, but also in the proper patient selection prior to valve replacement (Popovic et al. 1997, Carabello 2013, Rashedi and Otto 2015).

Two-dimensional TTE allows the proper assessment of valve morphology, leaflets' excursion, calcification (presence and extent), and determines the degree of left ventricular hypertophy, left ventricular systolic function and left atrial enlargement. TTE allows additionally the grading of the severity of AS based on the Doppler assessment of the peak velocity across the aortic valve, on the mean transvalvular aortic gradient and on the calculation of the aortic valve area. The peak jet velocity is measured from multiple views (apical, right parasternal, suprasternal) to detect the highest velocity. The mean transvalvular pressure gradient is estimated from the jet flow profile by applying the simplified Bernoulli equation. It estimates the average gradient across the valve throughout the entire systole. The aortic valve area is calculated using the continuity equation and has the advantage of being more accurate, unlike the above mentioned two parameters, in patients with a very low or a very high flow rate (Holmes et al. 2012). Both the left ventricular outflow diameter and velocity must be measured for calculation of the aortic valve area (Baumgartner et al. 2009, Vahanian et al. 2012). Indexing of the aortic valve area to the body surface area may be helpful to diagnose severe AS in patients with a very small body size. Grading of the severity of AS based on these parameters is shown in **table 1** [modified from (Lindman et al. 2016)].

Table 1: Assessment of the severity of aortic stenosis

	Mild	**Moderate**	**Severe**
Peak jet velocity (m/s)	2 - 3	3 - 4	≥ 4
Mean transvalvular aortic gradient (mmHg)	10 - 19	20 - 39	≥ 40
Aortic valve area (cm^2)	1.6 – 2.0	> 1 – 1.5	≤ 1.0
Indexed aortic valve area (cm^2/m^2)	> 0.9	> 0.6 – 0.9	≤ 0.6

Transoesophageal echocardiography may be used if the quality of the TTE image is poor or inadequate. Planimetry of the aortic valve orifice, measurement of the aortic annulus and detection of a bicuspid aortic valve can be performed by transoesophageal echocardiograpy.

Cardiac catheterization is still indicated for the assessment of the severity of AS in a subset of patients, in whom the findings of nonivasive tests are inconclusive or if there is a discrepancy between the results of noninvasive investigations and clinical findings. Assessment of coronary anatomy is indicated before aortic valve replacement (Baumgartner et al. 2017, Hildebrandt et al. 2017).

1.2.3. Low gradient aortic stenosis

In a subset of patients with severe AS, however, the above mentioned hemodynamic parameters are discordant, and this poses a diagnostic dilemma. These patients may have an aortic valve area < 1.0 cm^2 (consistent with severe AS) with a peak flow velocity < 4 m/s and a mean transvalvular aortic gradient < 40 mmHg (consistent with nonsevere AS). After careful revision of all TTE data to exclude measurement errors, the diagnosis of a LGAS is made (Baumgartner et al. 2009, Clavel et al. 2016, Margulescu 2017). A LGAS can be detected in patients with an impaired LVEF (classical low-flow LGAS) as well as in those with a normal LVEF (paradoxical low-flow LGAS). The classical LGAS is due to impairment of LVEF with the decrease of blood flow across the aortic valve secondary to a decrease in stroke volume. Patients with paradoxical LGAS usually have small ventricles with concentric hypertrophy and increased vascular impedance (Barboza et al. 2011, Lindman et al. 2016).

Further diagnostic evaluation may be performed in patients with LGAS. Assessment of aortic valve calcification with multidetector computer tomography is recommended in patients with LGAS and a normal LVEF, and dobutamine stress echocardiography is

recommended in patients with LGAS and an abnormal LVEF for both diagnostic and prognostic purposes (Baumgartner et al. 2017).

1.2.4. Treatment

Management of AS depends on its severity, the presence of symptoms and the left ventricular systolic function. Once symptomatic, aortic valve replacement should be performed without delay. If symptom status is unclear, further tests such as exercise testing and assessment of B-natriuretic peptide levels may be performed for better selection of patients who are candidates for valve replacement (Capoulade et al. 2014, Lindman 2014). Hypertension, heart failure and associated coronary artery disease should be treated appropriately as in patients without AS.

Medical treatment does not improve the prognosis of patients with severe symptomatic AS, and aortic valve replacement is the only treatment that relieves symptoms and prolongs survival (Otto 2006, Nishimura et al. 2014). Despite this fact, many of these patients do not undergo surgical valve replacement due to comorbidities that render them at high risk for adverse events after surgery. A substantial proportion of these patients have an impaired LVEF (Powell et al. 2000, Sharony et al. 2003).

In the eighties of the last century, percutaneous balloon aortic valvuloplasty was introduced as a minimally invasive alternative to surgical aortic valve replacement in patients at prohibitive surgical risk. The enthusiasm for that novel procedure faded quickly after realizing that the symptomatic benefit was not durable and that balloon aortic valvuloplasty added no prognostic benefit compared to medical therapy alone (Sherman et al. 1989, Otto et al. 1994). It was not until the first-in-human percutaneous implantation of a balloon expandable aortic bioprosthesis in 2002 (Cribier et al. 2002) that a new era in management of severe AS started with an effective alternative to surgical aortic valve replacement.

1.3. Transcatheter aortic valve implantation

1.3.1. Historical overview

The percutaneous insertion of a bioprosthesis and its implantation within a severely stenotic aortic valve was a great achievement of modern medicine (Cribier 2012). The 57-year-old patient who underwent the first-in-human TAVI in the year 2002 had severe inoperable AS on top of a calcified bicuspid aortic valve (Cribier et al. 2002). Surgical aortic valve replacement was declined because of hemodynamic instability and significant comorbidities. Interestingly, the LVEF was 14%, the mean transvalvular aortic gradient was 30 mmHg and the patient showed no myocardial contractile reserve on dobutamine stress echocardiography. The procedure was performed using a complex antegrade transvenous, transseptal approach. Despite the initial rapid improvement of his cardiac symptoms and valve hemodynamics, the patient died 17 weeks post intervention due to non-cardiac causes (Cribier et al. 2002).

The use of femoral venous access, transseptal puncture and antegrade passage of the stenotic aortic valve made the procedure very complicated, especially in the absence of adequate operators' experience limiting its widespread application (Sakata et al. 2005). Subsequently, a retrograde transarterial (i.e. transfemoral) approach was introduced and simplified the procedure (Hanzel et al. 2005, Webb et al. 2006). This approach was used for both the balloon and the self-expandable prostheses that were initially available (Grube et al. 2005, Grube et al. 2006, Webb et al. 2006). TF-TAVI replaced rapidly the more complex antegrade transvenous approach. TF-TAVI, however, was not suitable for patients with small femoral arteries and those with advanced peripheral vascular disease. This led to the development of alternative access routes such as the transapical, the transsubclavian and the transaortic approaches. Both the balloon expandable Edwards Sapien prosthesis and the self-expandable CoreValve prosthesis received the Conformité Européenne (CE) mark in 2007 and became

commercially available in Europe. By that time, TF-TAVI and transapical TAVI were the most commonly used vascular access approaches. Continuous development and refinement of valve technology led to downsizing of the access sheaths and delivery system profiles. Hence, the rate of vascular access complications related to the procedure could be significantly reduced (Wendler et al. 2017). Thus, more patients became suitable for TF-TAVI. Meanwhile, observational studies and randomized trials showed consistently that the outcomes of TF-TAVI are superior to transapical TAVI (Thomas et al. 2011, Di Mario et al. 2013, Blackman et al. 2014, van der Boon et al. 2014, Leon et al. 2016). Consequently, TF-TAVI became the standard procedure today with alternative vascular access routes used only in exceptional cases (Baumgartner et al. 2017).

1.3.2. Indications for transcatheter aortic valve implantation

After the first-in-human TAVI, two feasibility trials were conducted in France to study the safety and feasibility of percutaneous valve implantation in patients with inoperable severe symptomatic AS. The French Administration approved them in 2003. These trials were restricted to compassionate use only and recruited 36 patients. The results were promising with a 75% procedural success rate (Cribier et al. 2004, Cribier et al. 2006). Thereafter, many tertiary care centers in Europe and USA started the procedure for treatment of prohibitive surgical risk patients with severe symptomatic AS. A randomized Food and Drug Administration driven pivotal study, the Placement of Aortic Transcatheter Valves (PARTNER) trial, was initiated. The trial showed that TAVI was superior to standard medical therapy in inoperable patients (Leon et al. 2010) and not inferior to surgical aortic valve replacement in terms of all-cause mortality at 1-year follow-up in high risk patients (Smith et al. 2011). Based on these results, TAVI was approved by the Food and Drug Administration in 2011 for non-surgical high risk candidates. Long-term follow-up of the

PARTNER trial showed that the outcome of TAVI was similar to surgery at 5-year with no detected prosthetic valve deterioration requiring aortic valve replacement (Mack et al. 2015).

In the 2012 European and the 2014 American guidelines for the management of valvular heart disease, TAVI was indicated for the treatment of symptomatic severe AS in patients with prohibitive surgical risk and as an alternative for surgery in patients at high risk for surgical aortic valve replacement (Vahanian et al. 2012, Nishimura et al. 2014).

Further prospective randomized controlled trials consolidated the evidence for TAVI. In the U.S. CoreValve High Risk Study, TAVI was superior to surgical aortic valve replacement in terms of 1-year survival in patients at high-surgical risk (Adams et al. 2014, Mack et al. 2015). In the 2-year follow-up of the PARTNER-2 trial which included 2032 patients, TAVI was non-inferior to surgical aortic valve replacement in patients at an intermediate surgical risk. The outcome of TF-TAVI was even superior to surgery (Leon et al. 2016). Similar findings have also been shown in the Surgical Replacement and Transcatheter Aortic Valve Implantation (SURTAVI) trial, where 1660 patients at intermediate risk for surgery were randomly assigned to undergo either TAVI or surgical aortic valve replacement. At 2-year follow-up, all-cause mortality was similar in both groups (Reardon et al. 2017).

Currently and according to the 2017 European guidelines for the management of valvular heart disease, TAVI is favored over surgery in elderly patients with severe symptomatic AS who are at increased surgical risk. Both TAVI and surgical aortic valve replacement can be used for patients with severe symptomatic AS who have an intermediate surgical risk. The decision to perform either procedure should be taken by a multidisciplinary heart team. **Table 2** summarizes the conditions favoring TAVI [modified from (Baumgartner et al. 2017)].

Table 2: Factors that favor transcatheter aortic valve implantation over surgery in patients with symptomatic severe aortic stenosis

Clinical characteristics
Society of Thoracic Surgeons Score or EuroSCORE II ≥ 4% (logistic EuroSCORE ≥10%)
Presence of severe comorbidities (not adequately reflected by scores)
Age ≥ 75 years
Previous cardiac surgery
Frailty
Restricted mobility and conditions that may affect the rehabilitation process after the procedure
Anatomical and technical aspects
Favorable access for TF-TAVI
Sequalae of chest radiation
Porcelain aorta
Presence of intact coronary bypass graft at risk when sternotomy is performed
Expected patient-prosthesis mismatch
Severe chest deformation or scoliosis

1.4. Impact of left ventricular ejection fraction on outcome in severe aortic stenosis

Patients with severe AS and an impaired LVEF have a dismal prognosis if left to medical treatment only, and life expectancy is less than two years if symptoms of congestive heart failure develop (Ross and Braunwald 1968). The only effective treatment for such patients is to relieve the mechanical obstruction, either surgically or percutaneously (Baumgartner et al. 2017). Although surgical aortic valve replacement improves both the symptoms and the survival in this group of patients, an impaired LVEF increases both the surgical risk as well as the perioperative mortality, especially among those patients with a low mean transvalvular aortic gradient (Connolly et al. 2000, Levy et al. 2008).

Moreover, patients with severe AS and an impaired LVEF are usually elderly, comorbid patients with higher surgical risk scores compared to patients with a normal LVEF and are usually denied aortic valve replacement surgery. Accordingly, a substantial proportion of patients with severe symptomatic AS and an impaired LVEF are referred for TAVI. The prevalence of an impaired LVEF in patients undergoing TAVI is highly variable in the

literature and depends on the cutoff values used, varying from 6% to 11% if a cutoff value < 30% was used, and from 27% to 46% if LVEF is considered impaired when between 30% and 50% (Bax et al. 2014).

The association of an impaired LVEF with an increased mortality after TAVI is still debatable, and the cutoff value below which LVEF has a significant impact on mortality is not consistent throughout the available studies. Moreover, a proportion of patients with an impaired LVEF has LGAS, a combination that may further increase the risk of an adverse outcome in these patients.

1.5. Cutoff values for left ventricular ejection fraction

LVEF is considered a powerful predictor of clinical outcome in patients with cardiovascular diseases including AS (Quere et al. 2006). LVEF is usually measured by means of two-dimensional TTE using the modified Simpson's method to estimate the left ventricular end diastolic and end systolic volumes.

Recently, new cutoff values were recommended for the assessment of LVEF by the ASE and the EACVI. This classification provides gender-specific cutoff values for a normal LVEF (**table 3**). These normal reference values for LVEF derived from 2-dimensional TTE have been updated using population based studies, and the cutoff value for normal represents two standard deviations around the mean in healthy adults (Lang et al. 2015). Furthermore, impairment of LVEF in these recommendations is subdivided into 3 categories of severity. Such a detailed sub-classification of an impaired LVEF was not used in previous studies assessing the impact of LVEF on outcome after TAVI. Likewise, the different cutoff values for a normal LVEF in males and females are not yet adopted in practice clinical guidelines, which consider LVEF to be normal when ≥ 50% in both genders (Nishimura et al. 2014,

Baumgartner et al. 2017). The significance of this difference in patients with severe AS is unknown.

Nevertheless, the importance of a detailed categorization of the impairment of LVEF was recently addressed by the latest European guidelines for the management of patients with acute and chronic heart failure, which has introduced the new category of heart failure with mid-range LVEF, underlining the need of more clinical data on outcomes of patients with a mildly abnormal LVEF (Ponikowski et al. 2016).

Table 3: Classification of the impairment of left ventricular ejection fraction

Left ventricular ejection fraction (%)				
	Normal range	Mildly abnormal	Moderately abnormal	Severely abnormal
Female	54-74	41-53	30-40	<30
Male	52-72	41-51	30-40	<30

Adopted from (Lang et al. 2015)

1.6. Aim of the study

The aim of this retrospective analysis was to evaluate the impact of baseline LVEF, classified according to the 2015 ASE/EACVI recommendations, on 30-day and 1-year all-cause mortality after TF-TAVI and to assess the impact of the possible interaction between baseline LVEF and mean transvalvular aortic gradient on outcome in these patients.

2. Materials and Methods

2.1. Patient population

We retrospectively analyzed the clinical data of all patients with severe AS who underwent TF-TAVI at the West German Heart and Vascular Center Essen between January 2006 and July 2015. All patients had severe symptomatic AS and were considered to be at a prohibitive or high risk for surgical aortic valve replacement based on a logistic EuroSCORE > 15% (Smith et al. 2011) or the presence of comorbidities that increase the operative surgical risk such as porcelain aorta, liver cirrhosis, previous chest radiation, previous coronary artery bypass surgery with a patent left internal mammary artery graft. All patients had an angiogram of their aorta and pelvic arteries, and the femoral access site was considered suitable for the delivery of the TAVI-system. Patient selection for TF-TAVI was done by the institutional heart team consisting of an interventional cardiologist, cardiothoracic surgeon and cardiac anesthesiologist.

Patients were excluded from the study if the baseline TTE was not performed in our center, if the indication for TAVI was other than severe native AS or if TF-TAVI could not be performed. This analysis was approved by the local ethics committee (17-7610-BO), and patient consent was waived due to the retrospective nature of the analysis.

Demographic and procedural data were obtained from the hospital's medical records. The following patient characteristics were collected:

- Demographics: age, gender, body mass index defined as body weight/(body height)^2 (kg/m^2)
- Comorbidities: chronic obstructive pulmonary disease; pulmonary hypertension defined as pulmonary artery systolic pressure > 60 mmHg; recent myocardial infarction defined as myocardial infarction within 90 days before TAVI; extracardiac

arteriopathy defined as the presence of claudication, carotid occlusion or > 50% stenosis and/or previous or planned intervention on the abdominal aorta, limb arteries or carotids (Roques et al. 2003); diabetes mellitus; chronic kidney disease (CKD) categorized into mild/absent if the glomerular filtration rate was > 60 ml/min/1.73m^2, moderate if between 30 and 60 ml/min/1.73m^2 and severe if < 30 ml/min/1.73m^2 (Piepoli et al. 2016); permanent atrial fibrillation; the presence of permanent pacemaker/implantable cardioverter defibrillator before TF-TAVI; and presence of coronary artery disease defined as a stenosis > 50% in diameter of a major epicardial coronary artery, a history of coronary artery bypass graft surgery, a history of percutaneous coronary intervention or performance of a percutaneous coronary intervention during patient preparation for TF-TAVI.

- Laboratory values: serum creatinine (the latest in-hospital serum value on the day before TF-TAVI), glomerular filtration rate in ml/min/1.73m^2 as calculated from serum creatinine level according to the Modification of Diet in Renal Disease equation (Levey et al. 2006).
- Assessment of the operative risk using the logistic EuroSCORE (Roques et al. 2003).

2.2. Determination of left ventricular ejection fraction

The following data were extracted from TTE reports or offline analysis of the saved corresponding TTE studies, as needed: baseline LVEF, mean transvalvular aortic gradient, aortic valve area, grade of concomitant aortic regurgitation and grade of concomitant mitral regurgitation. If baseline LVEF was not precisely documented in the TTE report, the exact LVEF value was obtained by offline analysis of the original TTE study loops stored in our DICOM archive (McKesson Workstation, McKesson, Tel Aviv) from standard 2-dimensional apical views according to the 2015 ASE/EACVI recommendations for cardiac chamber quantification by echocardiography (Lang et al. 2015). In this case, the left

ventricular endocardial border was traced manually from end-diastolic and end-systolic apical frames. The workstations' software provided automatically the corresponding left ventricular end-diastolic and left ventricular end-systolic volumes (LVEDV and LVESV, respectively) calculated by modified Simpson's method. LVEF was then calculated as:

$$\text{LVEF (\%)} = (\text{LVEDV} - \text{LVESV}) / \text{LVEDV}$$

All LVEF data were collected by two independent reviewers. In case of disagreement, the LVEF was determined by consensus. LVEF data were then entered and locked in the local TF-TAVI database before the start of data analysis.

Patients were divided into four groups according to their baseline LVEF following the 2015 recommendations of the ASE/EACVI for cardiac chamber quantification by echocardiography: a normal LVEF, defined as a baseline LVEF > 51% in males or > 53% in females, a mildly abnormal LVEF, defined as a baseline LVEF > 40% and ≤ 51% in males or > 40% and ≤ 53% in females, a moderately abnormal LVEF, defined as a baseline LVEF ≥ 30% and ≤ 40% and a severely abnormal LVEF, defined as a baseline LVEF <30% (Lang et al. 2015).

The value of the mean transvalvular aortic gradient was obtained from TTE reports. Patients were considered to have LGAS if the mean transvalvular aortic gradient at baseline was < 40 mmHg (Clavel et al. 2016) as determined from the continuous wave Doppler spectrum analysis across the aortic valve from multiple echocardiographic windows during TTE examination, taking the continuous wave Doppler spectrum with the highest recorded Doppler velocity. The commercially available echocardiography machine software (iE33; Philips Medical Systems, Andover, MA and Vivid E9 Ultrasound system; GE Healthcare, Waukesha, WI) provided automatically the velocity time integral and the mean transvalvular aortic gradient upon manual tracing of the continuous wave Doppler spectrum.

Aortic valve area was obtained from TTE reports, where it was calculated from the left ventricular outflow tract diameter measured in the parasternal long axis view (LVOTd), the velocity time integral of the pulsed wave Doppler signal recorded from apical views with the sample volume placed in the left ventricular outflow tract ($LVOT_{VTI}$) and the velocity time integral of the highest continuous wave velocity signal across the aortic valve (AV_{VTI}) according to the continuity equation:

$$\text{Aortic valve area} = \pi * (LVOTd/2)^2 * LVOT_{VTI} / AV_{VTI}$$

Mitral regurgitation severity and aortic regurgitation severity were obtained from TTE reports and graded according to the guidelines for management of valvular heart diseases (Vahanian et al. 2012). For this analysis, mitral or aortic regurgitation was considered significant if it was moderate or severe.

2.3. Transfemoral aortic valve implantation procedure

TF-TAVI procedures were performed in a hybrid operating room (Bonatti et al. 2007) using either the successive generations of the balloon expandable Edwards bioprosthesis (Cribier Edwards, Edwards Sapien, Edwards Sapien XT and Sapien 3, Edwards Lifesciences, Irvine, CA, USA) or the self-expandable Medtronic CoreValve device (CoreValve, CoreValve Evolut, Medtronic, Minneapolis, MN, USA) in a standardized fashion. The procedure was predominantly performed under conscious sedation monitored by a cardiac anesthesiologist. Invasive hemodynamics and electrocardiographic data of the patient were monitored continuously during the procedure from an arterial catheter and a central venous catheter as well as a 12-lead electrocardiogram. Premedications included acetyl salicylic acid (100mg daily) and clopidogrel (300mg loading dose, then 75mg daily) and a single intravenous dose of ceftriaxone 2g before the procedure. The procedure was performed under anticoagulation with intravenous heparin aiming at an activated clotting time between 250 and 300 seconds during the procedure. The arterial access of the common femoral artery on one side was

gained using Seldinger's technique to introduce a 6 French arterial sheath and a pigtail catheter in the descending thoracic aorta above the level of the aortic bifurcation. Then fluoroscopically guided arterial access of the other common femoral artery was gained in a similar fashion, and a suture-mediated closure device was pre-deployed with the sutures secured with a mosquito forceps till the end of the procedure. The sheath was then exchanged over a stiff wire for the required device sheath (14 French to 24 French according to device type, size and generation). The contralateral pigtail was then pushed to the aortic root to perform contrast injections as needed during the procedure. The aortic valve was crossed with a straight-tip wire guided by an Amplatz left catheter and simultaneous left ventricular and aortic pressure curves were recorded. Afterwards, the wire was exchanged for a stiff pre-shaped wire. Valvuloplasty of the aortic valve was then performed under rapid right ventricular pacing (180 to 200 beats per minute), followed by implantation of either the balloon expandable prosthesis under a similar pacing rate or the self-expandable prosthesis under a slower pacing rate between 110 and 130 beats per minute. After prosthesis implantation, position and grade of aortic regurgitation were assessed angiographically. Invasive simultaneous left ventricular and aortic pressure curves were registered again followed by withdrawal of the device sheath and tying the sutures of the preloaded closure device. Angiography of the aorto-iliac bifurcation was performed to ascertain the successful closure of the arterial access and the other puncture side was then closed in a standard manner. A pressure bandage was then fixed for 24 hours with regular check-up of limb perfusion and signs of bleeding (Kahlert et al. 2008, Patsalis et al. 2013, Kahlert et al. 2017). Procedural outcomes were defined according to the Valve Academic Research Consortium-2 (VARC-2) criteria (Kappetein et al. 2012).

2.4. Follow-up

Mortality data were obtained from hospital records and from telephone contact with the patients, their relatives or their primary care physicians. Patients were censored at the day of death or at completion of 1-year follow-up, whichever came first. Patient inclusion ended in July 2015, hence, 1-year mortality status was available for all patients.

Baseline clinical, procedural and mortality data were compared between the categories of LVEF. We also compared the outcome of patients with LGAS and those without LGAS in the whole study population, as well as within each category of LVEF.

2.5. Statistical analysis

Categorical variables were presented as count (percentage). The normality of distribution of continuous variables was tested with the Kolmogorov-Smirnov test. Normally distributed variables were presented as mean ± standard deviation, whereas skewed data were presented as median (lower quartile, upper quartile). The patients were divided into four groups according to their baseline LVEF and into two groups according to the presence of LGAS. The comparisons between the study groups were performed with the Chi-square or Fischer's exact test for categorical variables or Kruskal-Wallis test for continuous variables. The correlation between baseline LVEF and mean aortic transvalvular gradient was tested with Spearman's rho method.

The impact of baseline LVEF and LGAS on all-cause mortality was tested using the Kaplan-Meier method. Patients were censored at the time of death or at completion of 1-year follow-up, whichever came first and the Kaplan-Meier curves were compared visually and with log-rank test (Bewick et al. 2004, Zwiener et al. 2011).

To identify the predictors of 30-day and 1-year mortality, survival analysis was performed using the Cox regression method. Variables entered in the univariate analysis included age,

gender, CKD, diabetes mellitus, extracardiac arteriopathy, coronary artery disease, previous coronary artery bypass graft surgery, previous percutaneous coronary intervention, recent myocardial infarction, atrial fibrillation, previous permanent pacemaker or implantable cardioverter defibrillator implantation, pulmonary hypertension, significant mitral regurgitation, LVEF, LGAS, aortic valve area, logistic EuroSCORE and type of implanted prosthesis. Based on the results of Kaplan-Meier analysis, baseline LVEF was entered in the univariate Cox regression model as well as in the subsequent multivariate regression models as a dichotomous variable with a cutoff point of 40% (> 40% versus ≤ 40%) (Zwiener et al. 2011). This cutoff point represents the cutoff point between mildly abnormal and moderately abnormal LVEF (Lang et al. 2015).

Variables with a p-value < 0.2 in the univariate analysis were introduced into a Cox multivariate regression analysis using a stepwise forward selection method. A predefined multivariate Cox regression model with the same variables and, in addition, the interaction term abnormal LVEF*LGAS, was also constructed.

All p-values were two-sided and considered statistically significant when < 0.05.

3. Results

3.1. Patient characteristics

Five-hundred-eighty-five TF-TAVI procedures were performed in 581 patients between January 2006 and July 2015. Four patients had two TF-TAVI procedures during the study period. In two patients, the index TF-TAVI was aborted (and excluded from this analysis) due to a large native aortic annulus not permitting the implantation of the largest aortic valve prosthesis available at time. In each case, another TF-TAVI procedure was performed few months later after commercial availability of the larger aortic valve prosthesis. The latter procedure was included in this analysis. In the other two patients, the grade of paravalvular leak was considered clinically significant during follow-up and a second TF-TAVI procedure was later performed to seal the leak as a so-called valve-in-valve procedure. In both cases, only the index TF-TAVI was included in this analysis. According to the predefined exclusion criteria for this study, 76 patients were also excluded for the following reasons:

1. Baseline TTE was performed only in the referring hospital (55 patients).
2. TF-TAVI was performed for a degenerated surgical bioprosthesis as a valve-in-valve procedure (18 patients).
3. TF-TAVI was performed for native aortic regurgitation (1 patient).
4. TF-TAVI was performed for the treatment of a stenotic bicuspid aortic valve (1 patient).
5. TF-TAVI was aborted due to a too large native aortic annulus without a subsequent procedure (1 patient).

After exclusion of these patients, 505 patients were included in this analysis (**figure 1**)

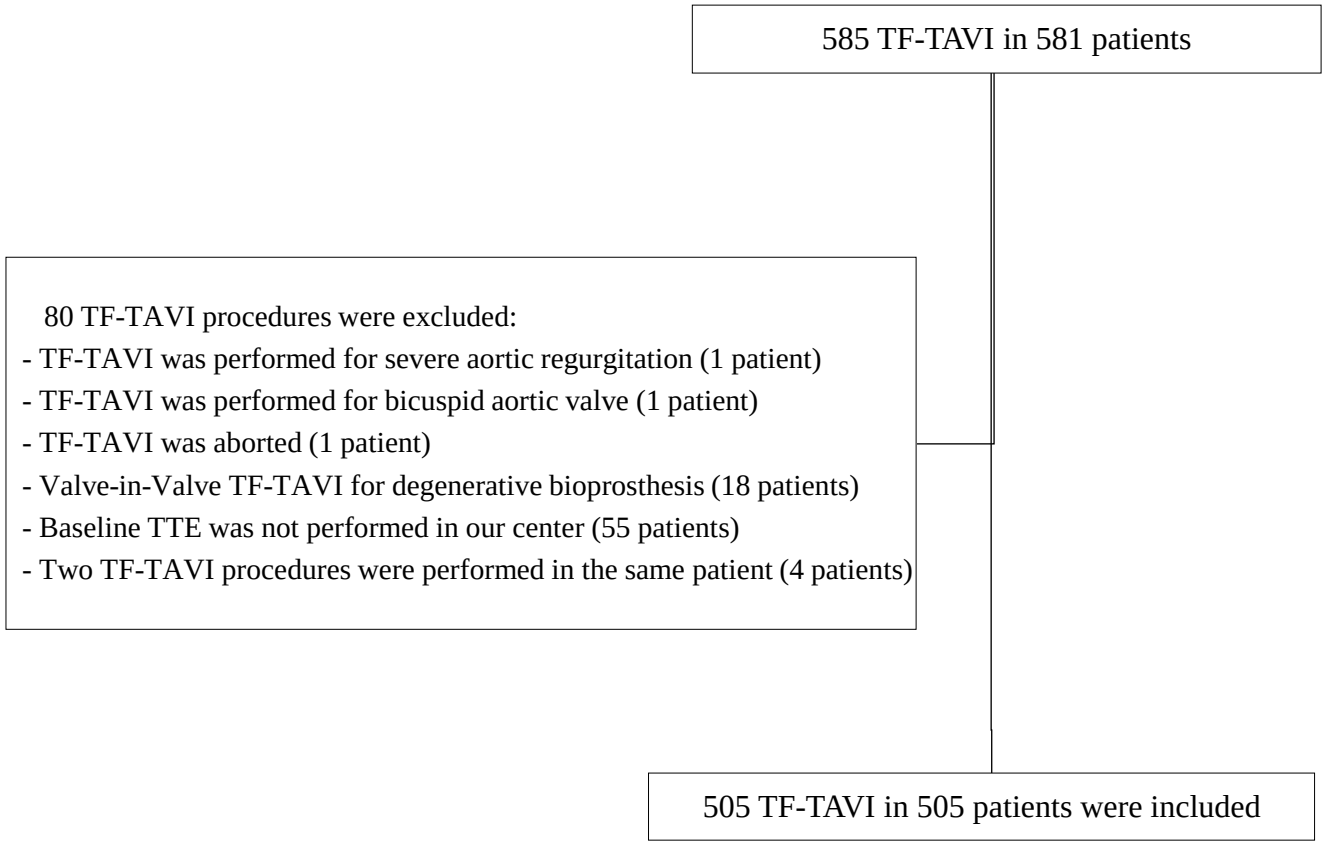


Figure 1: Flow chart of the patient selection

The median age of these patients was 82 (78, 85) years, 277 (55%) were female and the logistic EuroSCORE was 14.4% (9%, 22.7%). Coronary artery disease was present in 278 (55%) patients. Sixty-two (12%) patients had prior coronary artery bypass graft surgery and 203 (40%) patients had prior percutaneous coronary intervention. Diabetes mellitus was present in 198 (39%) patients. Three-hundred-seventy-six (74%) patients had at least moderate CKD.

3.2. Procedural data

The balloon expandable (Cribier Edwards, Edwards Sapien, Edwards Sapien XT and Sapien 3, Edwards Lifesciences, Irvine, CA, USA) bioprosthesis was implanted in 408 (81%) patients, while the self-expandable (CoreValve and Evolut, Medtronic, Minnepolis, MN, USA) bioprosthesis was implanted in 97 (19%) patients. TF-TAVI was performed without preparatory balloon aortic valvuloplasty in 16 (3%) patients, mostly during the implantation of the self-expandable prosthesis (13 patients, $p < 0.001$). Post dilatation was performed in 41 (8%) patients and was more common with the self-expandable prosthesis [21 (20%) patients versus 20 (5%) patients, $p < 0.001$] than with the balloon expandable prosthesis. The median volume of contrast medium used during the procedure was 210 (169, 270) ml and was not significantly different between the self-expandable [200 (150, 251) ml] and the balloon expandable prosthesis [210 (173, 273) ml], $p = 0.073$. VARC-2 procedural outcomes were comparable between both prostheses types and are summarized in **table 4**.

Table 4: Procedural outcomes of transfemoral aortic valve implantation

	All patients (n = 505)	Balloon expandable prosthesis (n = 408)	Self-expandable prosthesis (n = 97)	p
Coronary artery obstruction	4 (< 1)	4 (< 1)	0	1
Conversion to open heart surgery	3 (< 1)	3 (< 1)	0	1
Ventricular perforation	6 (1)	6 (1.5)	0	0.601
Myocardial infarction after TF-TAVI	10 (2)	10 (2.5)	0	0.221
- Periprocedural	6 (1)	6 (1.5)	0	0.601
- Spontaneous	4 (< 1)	4 (< 1)	0	1
Pericardial tamponade	6 (1)	6 (1.5)	0	0.601
Post procedural stroke	20 (4)	18 (4)	2 (2)	0.392
- Major	10 (2)	8 (2)	2 (2)	1
- Minor	10 (2)	10 (2.5)	0	0.221
Post procedural bleeding	69 (14)	57 (14)	12 (12)	0.68
- Life threatening	17 (3)	16 (4)	1 (1)	0.216
- Major	31 (6)	26 (6)	5 (5)	0.653
- Minor	21 (4)	15 (4)	6 (6)	0.262
Vascular complications	89 (18)	71 (17)	18 (19)	0.788
- Major	59 (12)	47 (12)	12 (12)	0.814
- Minor	30 (6)	24 (6)	6 (6)	0.91
Acute kidney injury	111 (22)	90 (22)	21 (22)	0.93
- Grade 1	64 (13)	49 (12)	15 (16)	0.358
- Grade 2	26 (5)	21 (5)	5 (5)	1
- Grade 3	21 (4)	20 (5)	1 (1)	0.096

Data are presented as count (percentage). TF-TAVI = transfemoral aortic valve implantation.

3.3. Echocardiographic data

Baseline LVEF was 54% (44%, 59%), mean transvalvular aortic gradient was 45 (43, 57) mmHg and aortic valve area was 0.7 (0.52, 0.84) cm^2 in the entire patient population. Significant mitral and aortic regurgitation at baseline were present in 221 (44%) and 87 (17%) patients, respectively.

Baseline LVEF was normal in 280 (55%), mildly abnormal in 121 (24%), moderately abnormal in 74 (15%) and severely abnormal in 30 (6%) patients, respectively.

Mean transvalvular aortic gradients correlated significantly with the degree of LVEF impairment (Spearman's rho = 0.25, $p < 0.001$), and LGAS was present in 192 (38%) patients. The prevalence of LGAS was higher in patients with a severely (23 patients, 77%) and a moderately abnormal LVEF (44 patients, 60%) compared to patients with a mildly abnormal (36 patients, 30%) and a normal LVEF (89 patients, 32%).

The calculated aortic valve area was smaller in patients with a moderately abnormal LVEF compared to patients with a normal LVEF ($p < 0.05$), and patients with a moderately abnormal LVEF had a higher incidence of concomitant significant mitral regurgitation compared to the other groups. The findings of the baseline TTE study are presented in **table 5**.

Table 5: Baseline echocardiographic findings

LVEF	All patients (n = 505)	Normal (n=280)	Mildly abnormal (n=121)	Moderately abnormal (n=74)	Severely abnormal (n=30)	p
Time interval from TTE to TF-TAVI (days)	12 (6, 25)	11 (5,25)	12 (6,24)	13 (7,28)	15 (5,31)	0.373
LVEF (%)	54 (44, 59)	58 (55, 63)	49 (45,51)	36 (32,38)	25 (20,27)	_
Mean transvalvular aortic gradient (mmHg)	45 (33, 57)	48 (36, 61)	47 (36,61)	36 (27,50)#	26 (20,39)#	< 0.001
Aortic valve area (cm^2)	0.7 (0.5, 0.8)	0.7 (0.59,0.9)	0.67(0.5,0.8)	0.68 (0.5,0.8)*	0.6 (0.42,0.92)	0.013
LGAS	192 (38)	89 (32)	36 (30)	44 (60)#	23 (77)#	< 0.001
Significant mitral regurgitation	221 (44)	109 (39)	51 (42)	48 (65)#	13 (43)	0.001
Significant aortic regurgitation	87 (17)	53 (19)	20 (17)	10 (14)	4 (13)	0.649

Data are presented as count (percentage) or median (25th percentile, 75th percentile)

** p < 0.05 compared to patients with a normal LVEF*

 # p < 0.01 compared to patients with a normal LVEF

LGAS = low gradient aortic stenosis, LVEF = left ventricular ejection fraction, TTE = transthoracic echocardiography, TF-TAVI = transfemoral aortic valve implantation.

3.4. Patient characteristics and procedural data stratified by baseline ejection fraction

3.4.1. Differences in patient characteristics

Age of the patients was similar across the study groups. Males represented the majority of patients in the groups with a moderately and a severely abnormal LVEF (65% and 60%, respectively), whereas the groups with a normal and a mildly abnormal LVEF showed female predominance (59% and 61%, respectively, $p < 0.001$). The prevalence of coronary artery disease was more common in patients with a moderately abnormal LVEF (69%, $p < 0.01$) and in patients with a severely abnormal LVEF (73%, $p < 0.05$) than in patients with a normal LVEF (49%). Extracardiac arterial disease was more common in patients with a moderately abnormal LVEF (34%, $p < 0.001$) compared to patients with a normal LVEF (20%). Patients with a normal LVEF had significantly less frequent permanent pacemakers and implantable cardiac defibrillators than those with a mildly, a moderately and a severely abnormal LVEF (10%, 17%, 27%, 37% respectively, $p < 0.001$). Severe CKD was more common in patients with a severely abnormal LVEF (27%, $p < 0.01$) compared to patients with a normal LVEF (9%). The logistic EuroSCORE in patients with a moderately abnormal LVEF (22.5%) and in patients with a severely abnormal LVEF (30.8%) was significantly higher compared to patients with a normal LVEF (11.1%, $p < 0.01$). Apart from more frequent implantable pacemaker or cardioverter defibrillator devices in patients with a mildly abnormal LVEF compared to patients with a normal LVEF, there were no significant differences in baseline characteristics between both patient groups. These results are summarized in **table 6**.

Table 6: Patient characteristics stratified by baseline ejection fraction

LVEF	All patients (n = 505)	Normal (n = 280)	Mildly abnormal (n = 121)	Moderately abnormal (n = 74)	Severely abnormal (n = 30)	p
Age (years)	82 (78, 85)	82 (78, 85)	83 (78, 86)	82 (77, 87)	80 (74, 83)	0.57
Female	277 (55)	165 (59)	74 (61)	26 (35)#	12 (40)*	< 0.001
BMI (kg/m^2)	26.4 (23.9,29.8)	26.6 (24.1,29.7)	25.9 (23.5, 8.9)	26.8 (23, 30.4)	26 (22.2, 31.6)	0.678
Logistic EuroSCORE (%)	14.4 (9, 22.7)	11.1 (7.8, 18)	15.5 (10.5,21.5)	22.5 (12.8,30.5)#	30.8 (22.4,35.1)#	< 0.001
COPD	111 (22)	71 (25)	20 (24)	14 (19)	6 (20)	0.218
Extracardiac arteriopathy	124 (25)	57 (20)	31 (26)	25 (34)#	11 (37)	0.036
Recent MI	17 (3)	5 (2)	5 (4)	3 (4)	4 (13)#	0.015
Pulmonary hypertension	99 (20)	46 (16)	27 (22)	17 (23)	9 (30)	0.176
Coronary artery disease	278 (55)	138 (49)	67 (55)	51 (69)#	22 (73)*	0.004
Previous PCI	203 (40)	103 (37)	50 (41)	37 (50)	13 (43)	0.212
Previous CABG	62 (12)	27 (10)	15 (12)	15 (20)	5 (17)	0.076
Diabetes mellitus	198 (39)	105 (38)	46 (38)	35 (47)	12 (40)	0.484
Atrial fibrillation	156 (31)	78 (28)	39 (32)	29 (39)	10 (33)	0.286
Previous PPM/ ICD	81 (16)	29 (10)	21 (17)*	20 (27)#	11 (37)#	< 0.001
Serum creatinine (mg/dl)	1.3 (1.1, 1.6)	1.23 (1.03,1.56)	1.25 (1.07,1.58)	1.37 (1.19, 1.82)#	1.53 (1.2, 2.11)#	< 0.001
GFR(ml/min/1.73m^2)	49 (39, 60)	50 (39, 60)	49 (38, 61)	46 (36, 56)	44 (26, 55)	0.052
CKD						0.037
- No/ Mild	129 (26)	78 (28)	33 (27)	14 (19)	4 (13)	
- Moderate	313 (62)	177 (63)	69 (57)	49 (66)	18 (60)	
- Severe	63 (12)	25 (9)	19 (16)	11 (15)	8 (27)#	

Data are presented as count (percentage) or median (25th percentile, 75th percentile)

** p < 0.05 compared to patients with a normal LVEF, # p < 0.01 compared to patients with a normal LVEF*

BMI = body mass index, CABG = coronary artery bypass surgery, CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, ICD = implantable cardioverter defibrillator, GFR = glomerular filtration rate, LVEF = left ventricular ejection fraction, MI = myocardial infarction, PCI = percutaneous coronary intervention, PPM = permanent pacemaker.

3.4.2. Baseline parameters in patients with low and high mean transvalvular aortic gradient

Patients with LGAS tended to be younger (81 years versus 82 years, p = 0.069), had a higher logistic EuroSCORE (17.2% versus 12.8%, p < 0.001) and a higher prevalence of coronary artery disease (66% versus 48%, p < 0.001), extracardiac arterial disease (30% versus 22%, p = 0.021), diabetes mellitus (45% versus 36%, p = 0.044) as well as atrial fibrillation (39% versus 26%, p = 0.004) than those without LGAS. Females constituted 48% of patients with LGAS compared to 59% of patients without LGAS (p =0.023). Serum creatinine was higher in patients with LGAS than those without LGAS but the prevalence of CKD was similar in both groups (p = 0.231). LVEF (51% versus 55%, p < 0.001) and aortic valve area (0.62 cm^2 versus 0.8 cm^2, p < 0.001) were lower in patients with LGAS than in patients without LGAS. These data are presented in **table 7**.

3.4.3. Procedural data stratified by baseline ejection fraction and mean transvalvular aortic gradient

The self-expandable prosthesis was implanted in 37% of the patients with a severely abnormal LVEF, in 28% of patients with a moderately abnormal LVEF, in 21% of patients with a mildly abnormal LVEF and in 14% of patients with a normal LVEF (p = 0.002). TF-TAVI was performed without preparatory balloon valvuloplasty in 16 (3%) patients, more commonly in patients with a severely (7%) and a moderately abnormal LVEF (12%) than in patients with a mildly abnormal (2.5%) and a normal LVEF (3%, p < 0.001). Post dilatation of the implanted prosthesis was least frequent in patients with a normal LVEF (4%) and most frequent in patients with a severely abnormal LVEF (23%, p < 0.001). Procedural outcomes were comparable between the groups of LVEF and in patients with and without LGAS. The procedural data for the different groups of baseline LVEF are presented in **table 8** and for patients with LGAS compared to patients without LGAS in **table 9**.

Table 7: Baseline characteristics and echocardiographic findings in patients with and without low gradient aortic stenosis

	not LGAS (n = 313)	LGAS (n = 192)	p
Age (years)	82 (78, 86)	81 (77, 84.5)	0.069
Female	184 (59)	93 (48)	0.023
BMI (kg/m^2)	26.4 (24, 29.8)	26.4 (23.4, 29.9)	0.944
Logistic EuroSCORE (%)	12.8 (8.4, 19.5)	17.2 (10.8, 27.1)	< 0.001
COPD	67 (21)	44 (23)	0.691
Extracardiac arteriopathy	66 (21)	58 (30)	0.021
Recent MI	6 (2)	11(6)	0.021
Pulmonary hypertension	62 (20)	37 (19)	0.883
Coronary artery disease	151 (48)	127 (66)	< 0.001
Previous PCI	111 (36)	92 (48)	0.006
Previous CABG	24 (8)	38 (20)	< 0.001
Diabetes mellitus	112 (36)	86 (45)	0.044
Atrial fibrillation	82 (26)	118 (39)	0.004
Previous PPM/ ICD	39 (13)	42 (22)	0.005
Serum creatinine (mg/dl)	1.24 (1.07, 1.52)	1.33 (1.1, 1.67)	0.025
GFR (ml/min/1.73m^2)	50 (39, 61)	47 (37, 57)	0.066
CKD			0.235
- No/ Mild	88 (28)	41 (21)	
- Moderate	188 (60)	125 (65)	
- Severe	37 (12)	26 (14)	
Time interval from TTE to TF-TAVI (days)	11 (6, 21)	13 (6, 29)	0.108
LVEF (%)	55 (49, 60)	51 (36, 58)	< 0.001
Mean transvalvular aortic gradient (mmHg)	53 (46, 64)	30 (22, 25)	_
Aortic valve area (cm^2)	0.8 (0.61, 0.93)	0.62 (0.5, 0.78)	< 0.001
Significant mitral regurgitation	136 (44)	85 (44)	0.857
Significant aortic regurgitation	61 (20)	26 (14)	0.086

Data are presented as count (percentage) or median (25th percentile, 75th percentile). BMI = body mass index, CABG = coronary artery bypass surgery, CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, ICD = implantable cardioverter defibrillator, GFR = glomerular filtration rate, LGAS = low gradient aortic stenosis, LVEF = left ventricular ejection fraction, MI = myocardial infarction, PCI = percutaneous coronary intervention, PPM = permanent pacemaker, TF-TAVI = transfemoral aortic valve implantation, TTE = transthoracic echocardiography.

Table 8: Procedural data stratified by baseline left ventricular ejection fraction

LVEF	All patients (n = 505)	Normal (n = 280)	Mildly abnormal (n =121)	Moderately abnormal (n = 74)	Severely abnormal (n = 30)	p
Self-expandable prosthesis	97 (19)	40 (14)	25 (21)	21 (28)[#]	11 (37)[#]	0.002
Post-dilatation	41 (8)	11 (4)	13 (11)[*]	10 (13.5)[#]	7 (23)[#]	< 0.001
TF-TAVI without BAV	16 (3)	2 (1)	3 (2.5)	9 (12)[#]	2 (7)[#]	< 0.001
Contrast medium (ml)	210(169,270)	210 (173,279)	200 (160,254)	220 (181,288)	197 (155,247)	0.326
Coronary artery obstruction	4 (< 1)	4 (1)	0	0	0	0.356
Conversion to open heart surgery	3 (< 1)	1 (< 1)	2 (2)	0	0	0.364
Ventricular perforation	6 (1)	5 (2)	1 (< 1)	0	0	0.525
MI after TF-TAVI	10 (2)	8 (3)	1 (< 1)	1 (1)	0	0.441
- Periprocedural	6 (1)	6 (2)	0	0	0	0.181
- Spontaneous	4 (< 1)	2 (< 1)	1 (< 1)	1 (1)	0	0.906
Pericardial tamponade	6 (1)	6 (2)	0	0	0	0.181
Post procedural stroke	20 (4)	11 (4)	3 (2.5)	5 (7)	1 (3)	0.522
- Major	10 (2)	4 (< 1)	3 (2.5)	3 (4)	0	0.417
- Minor	10 (2)	7 (2.5)	1 (< 1)	2 (1)	1 (3)	0.686
Post procedural bleeding	69 (14)	31 (11)	18 (15)	12 (16)	5 (17)	0.509
- Life threatening	17 (3)	13 (5)	3 (2.5)	1 (1)	0	0.3
- Major	31 (6)	11 (4)	9 (7)	8 (11)	3 (10)	0.098
- Minor	21 (4)	8 (3)	6 (5)	5 (7)	2 (7)	0.375
Vascular complications	89 (18)	48 (17)	23 (19)	12 (16)	6 (20)	0.936
- Major	59 (12)	33 (12)	12 (10)	9 (12)	5 (17)	0.775
- Minor	30 (6)	15 (5)	11 (9)	3 (4)	1 (3)	0.368
Acute kidney injury	111 (22)	65 (23)	20 (17)	17 (23)	9 (30)	0.319
- Grade 1	64 (13)	37 (13)	14 (12)	7 (9.5)	6 (20)	0.502
- Grade 2	26 (5)	16 (6)	2 (2)	7 (9.5)	1 (3)	0.101
- Grade 3	21 (4)	12 (4)	4 (3)	3 (4)	2 (7)	0.871

Data are presented as count (percentage) or median (25th percentile, 75th percentile)
** p < 0.05 compared to patients with a normal LVEF*
 # p < 0.01 compared to patients with a normal LVEF
BAV = balloon aortic valvuloplasty, TF-TAVI = transfemoral aortic valve implantation.

Table 9: Procedural data in patients with and without low gradient severe aortic stenosis

	Not LGAS (n = 313)	LGAS (n = 192)	p
Self-expandable prosthesis	53 (17)	44 (23)	0.098
Post-dilatation	21 (7)	20 (10)	0.139
TF-TAVI without BAV	6 (2)	10 (5)	0.04
Contrast medium (ml)	206 (160, 272)	210 (180, 271)	0.309
Coronary artery obstruction	4 (1)	0	0.303
Conversion to open heart surgery	2 (0.6)	1 (0.5)	1
Ventricular perforation	5 (1.6)	1 (0.5)	0.415
Myocardial infarction after TF-TAVI	7 (2.2)	3 (1.6)	0.749
- Periprocedural	5 (1.6)	1 (0.5)	0.415
- Spontaneous	2 (0.6)	2 (1)	0.637
Pericardial tamponade	4 (1.3)	2 (1)	1
Post procedural stroke	11 (3.5)	9 (4.7)	0.512
- Major	5 (1.6)	5 (2.6)	0.516
- Minor	6 (1.9)	4 (2.1)	1
Post procedural bleeding	40 (13)	29 (15)	0.46
- Life threatening	12 (3.8)	5 (2.6)	0.457
- Major	17 (5.4)	14 (7.3)	0.398
- Minor	11 (3.5)	10 (5.2)	0.355
Vascular complications	53 (17)	36 (19)	0.603
- Major	34 (11)	25 (13)	0.464
- Minor	19 (6)	11 (6)	0.875
Acute kidney injury	71 (23)	40 (21)	0.626
- Grade 1	42 (13)	22 (12)	0.52
- Grade 2	16 (5)	10 (5)	0.962
- Grade 3	13 (4)	8 (4)	0.994

Data are presented as count (percentage) or median (25th percentile, 75th percentile)
BAV = balloon aortic valvuloplasty, TF-TAVI = transfemoral aortic valve implantation.

3.5. All-cause mortality after transfemoral aortic valve implantation

3.5.1. Thirty-day and one-year mortality

At the end of 1-year follow-up, 113 patients died (22.4%). Of these, 43 patients (8.5%) died within 30 days after TF-TAVI. Patients who died at 30 days had a significantly higher logistic EuroSCORE [19.2% (10.7%, 28.9%) versus 13.9% (9%, 22.2%), p = 0.24], and lower mean transvalvular aortic gradients [37 (20, 52) mmHg versus 45 (34, 54) mmHg, p = 0.004] than 30-day survivors. The comparison of baseline and echocardiographic data between both groups is summarized in **table 10**.

At 1-year follow-up, patients who died had both a lower LVEF [52% (37%, 58%) versus 55% (45%, 59%), p = 0.045] and a lower mean transvalvular aortic gradient [40 (26, 51) mmHg versus 47 (35, 59) mmHg, p < 0.001] than survivors. Male patients had a higher 1-year mortality compared to females (29% versus 17%, p = 0.01). Baseline serum creatinine was higher in patients who died than in survivors, but the glomerular filtration rate and grades of CKD were similar in both groups. These data are summarized in **table 11**.

There was no significant difference in the 30-day mortality between patients receiving the self-expandable prosthesis and those receiving the balloon expandable prosthesis (10% versus 8%, p = 0.505). One-year mortality was numerically higher in patients who received the self-expandable prosthesis, yet statistically non-significant (27% versus 21%, p = 0.231).

Table 10: Baseline characteristics and echocardiographic data of patients who died and patients who survived at thirty-day follow-up

	Patients who survived (n = 462)	Patients who died (n = 43)	p
Age (years)	82 (77, 85)	83 (80, 86)	0.222
Female	257 (56)	20 (47)	0.251
BMI (kg/m^2)	26.4 (23.9, 29.8)	26.5 (23.7, 29.8)	0.915
Logistic EuroSCORE (%)	13.9 (9, 22.2)	19.2 (10.7, 28.9)	0.024
COPD	100 (22)	11 (26)	0.551
Extracardiac arteriopathy	115 (25)	9 (21)	0.564
Recent MI	15 (3)	2 (5)	0.648
Pulmonary hypertension	91 (20)	8 (19)	0.863
Coronary artery disease	253 (55)	25 (58)	0.67
Previous PCI	186 (40)	17 (40)	0.926
Previous CABG	57 (12)	5 (12)	0.892
Diabetes mellitus	186 (40)	12 (28)	0.113
Atrial fibrillation	141 (31)	15 (35)	0.554
Previous PPM/ ICD	74 (16)	7 (16)	0.964
Serum creatinine (mg/dl)	1.26 (1.08, 1.59)	1.33 (1.1, 1.71)	0.4
GFR (ml/min/1.73m^2)	49 (39, 60)	47 (34, 59)	0.688
CKD			0.719
- No/ Mild CKD	119 (26)	10 (23)	
- Moderate CKD	287 (62)	26 (61)	
- Severe CKD	56 (12)	7 (16)	
Time interval from TTE to TF-TAVI (days)	11 (6, 25)	13 (7, 24)	0.356
LVEF (%)	55 (45, 59)	52 (34, 60)	0.182
Mean transvalvular aortic gradient (mmHg)	45 (34, 58)	37 (20, 52)	0.004
Aortic valve area (cm^2)	0.7 (0.52, 0.83)	0.74 (0.5, 0.9)	0.362
Significant mitral regurgitation	204 (44)	17 (40)	0.559
Significant aortic regurgitation	81 (18)	6 (14)	0.552

Data are presented as count (percentage) or median (25th percentile, 75th percentile)
BMI = body mass index, CABG = coronary artery bypass surgery, CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, ICD = implantable cardioverter defibrillator, GFR = glomerular filtration rate, LGAS = low gradient aortic stenosis, LVEF = left ventricular ejection fraction, MI = myocardial infarction, PCI = percutaneous coronary intervention, PPM = permanent pacemaker, TF-TAVI = transfemoral aortic valve implantation, TTE = transthoracic echocardiography.

Table 11: Baseline characteristics and echocardiographic data of patients who died and patients who survived at 1-year follow-up

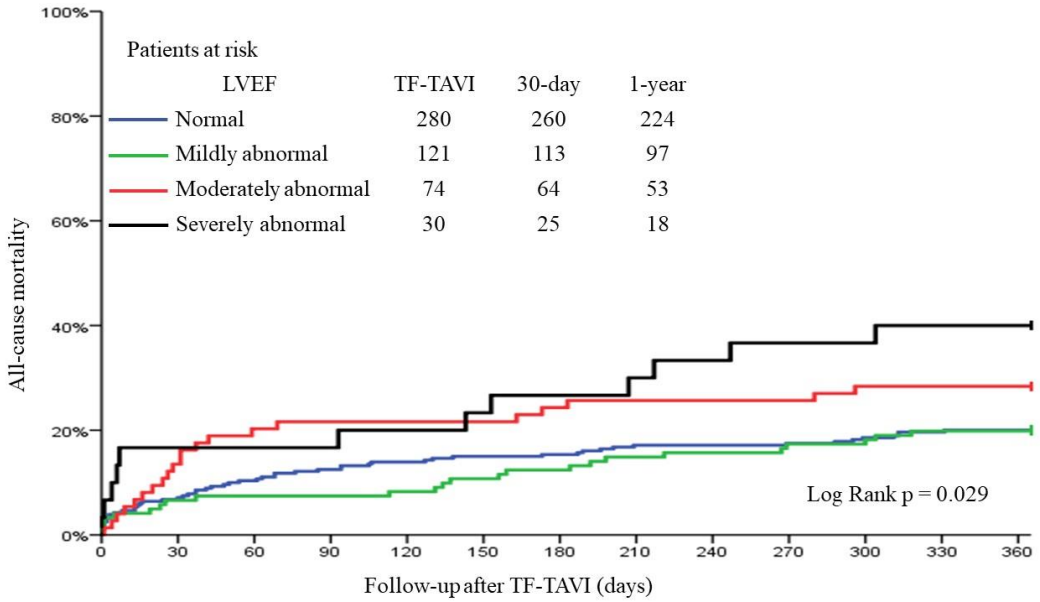
	Patients who survived (n = 392)	**Patients who died (n = 113)**	**p**
Age (years)	82 (78, 85)	82 (77, 85)	0.821
Female	227 (58)	50 (44)	0.01
BMI (kg/m^2)	26.5 (24, 29.8)	26.2 (23.4, 29.7)	0.385
Logistic EuroSCORE (%)	13.8 (9, 22.5)	16.2 (10, 25)	0.126
COPD	88 (22)	23 (20)	0.636
Extracardiac arteriopathy	97 (25)	27 (24)	0.853
Recent MI	9 (2)	8 (7)	0.032
Pulmonary hypertension	73 (19)	26 (23)	0.301
Coronary artery disease	211 (54)	67 (59)	0.303
Previous PCI	152 (39)	51 (45)	0.225
Previous CABG	50 (13)	12 (11)	0.542
Diabetes mellitus	153 (39)	45 (40)	0.879
Atrial fibrillation	116 (30)	40 (35)	0.239
Previous PPM/ ICD	65 (17)	16 (14)	0.536
Serum creatinine (mg/dl)	1.25 (1.06, 1.57)	1.37 (1.11, 1.7)	0.052
GFR ($ml/min/1.73m^2$)	50 (39, 60)	47 (34, 61)	0.445
CKD			0.322
- No/ Mild	98 (25)	31 (27)	
- Moderate	249 (63.5)	64 (57)	
- Severe	45 (11.5)	18 (16)	
Time interval from TTE to TF-TAVI (days)	12 (5, 26)	12 (6, 23)	0.823
LVEF (%)	55 (45, 59)	52 (37, 58)	0.045
Mean transvalvular aortic gradient (mmHg)	47 (35, 59)	40 (26, 51)	< 0.001
Aortic valve area (cm^2)	0.7 (0.52, 0.82)	0.7 (0.56, 0.9)	0.385
Significant mitral regurgitation	173 (44)	48 (43)	0.755
Significant aortic regurgitation	71 (18)	16 (14)	0.327

Data are presented as count (percentage) or median (25th percentile, 75th percentile)
BMI = body mass index, CABG = coronary artery bypass surgery, CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, ICD = implantable cardioverter defibrillator, GFR = glomerular filtration rate, LGAS = low gradient aortic stenosis, LVEF = left ventricular ejection fraction, MI = myocardial infarction, PCI = percutaneous coronary intervention, PPM = permanent pacemaker, TF-TAVI = transfemoral aortic valve implantation, TTE = transthoracic echocardiography.

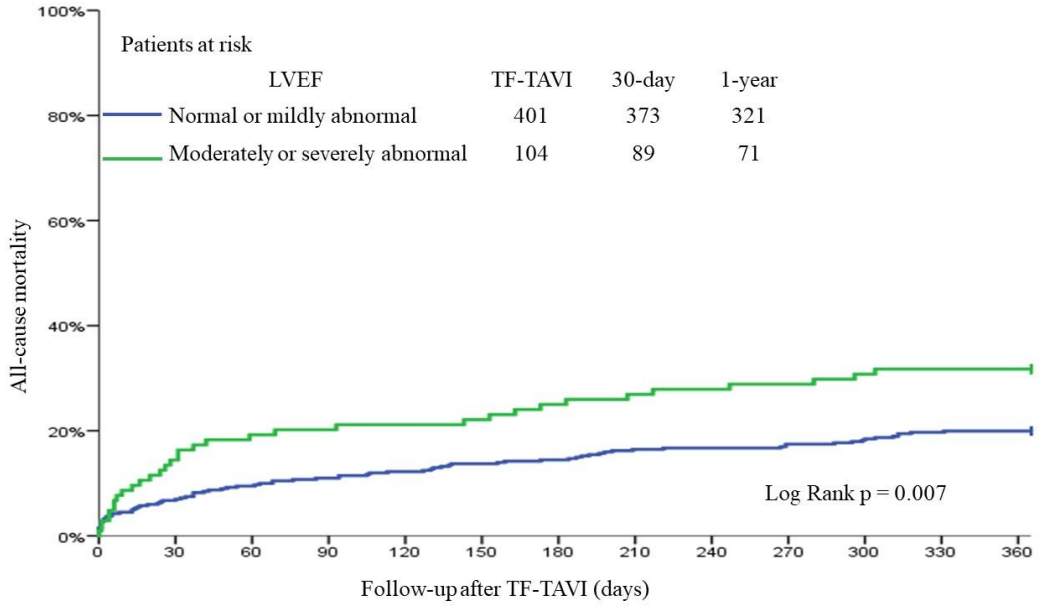
3.5.2. Mortality in the different categories of baseline left ventricular ejection fraction

All-cause mortality at 30 days after TF-TAVI was 7.1% in patients with a normal LVEF (20 of 280 patients), 6.6% in patients with a mildly abnormal LVEF (8 of 121 patients), 13.5% in patients with a moderately abnormal LVEF and 16.7% in patients with a severely abnormal LVEF (5 of 30 patients). One-year mortality was 20% in patients with a normal LVEF (56 of 280 patients), 19.8% in patients with a mildly abnormal LVEF (24 of 121 patients), 28.4% in patients with a moderately abnormal LVEF (20 of 74 patients) and 40% in patients with a severely abnormal LVEF (12 of 30 patients).

There was, however, no difference in all-cause mortality between patients with a normal and a mildly abnormal LVEF at 30-day and 1-year follow-up. Likewise, there was no significant difference in all-cause mortality between patients with a moderately and a severely abnormal LVEF (**figure 2, panel a**). When combining the patients with a normal and a mildly abnormal LVEF in one group and the patients with a moderately and a severely abnormal LVEF in another group, both, 30-day (14.4% versus 7%, p = 0.017) and 1-year mortality (31.7% versus 20%, p=0.007) were significantly higher in the latter group (**figure 2, panel b**). Further baseline and echocardiographic characteristics of these two patient groups are summarized in **table 12**.



(a) All-cause mortality in all four categories of LVEF



(b) All-cause mortality in patients with a normal or mildly abnormal LVEF and patients with a moderately or severely abnormal LVEF

Figure 2: Mortality in different categories of baseline ejection fraction

Table 12: Comparison of patients with normal or mildly abnormal ejection fraction and patients with moderately or severely abnormal ejection fraction

LVEF	Normal or mildly abnormal (n = 401)	Moderately or severely abnormal (n = 104)	p
Age (years)	82 (78, 85)	81 (76.5, 84)	0.113
Female	239 (60)	38 (36.5)	< 0.001
BMI (kg/m^2)	26.4 (24, 29.7)	26.4 (23.9, 30.9)	0.912
Logistic EuroSCORE (%)	12.8 (8.4, 19.1)	25.3 (14.6, 32)	< 0.001
COPD	91 (23)	20 (19)	0.447
Extracardiac arteriopathy	88 (22)	36 (35)	0.007
Recent MI	10 (2.5)	7 (7)	0.059
Pulmonary hypertension	73 (18)	26 (25)	0.12
Coronary artery disease	205 (51)	73 (70)	< 0.001
Previous PCI	153 (38)	50 (48)	0.066
Previous CABG	42 (10.5)	20 (19)	0.015
Diabetes mellitus	151 (38)	47 (45)	0.161
Atrial fibrillation	117 (29)	39 (37.5)	0.102
Previous PPM/ ICD	50 (12.5)	31 (30)	< 0.001
Serum creatinine (mg/dl)	1.24 (1.04, 1.57)	1.39 (1.19, 1.89)	< 0.001
GFR (ml/min/1.73m^2)	50 (39. 60)	46 (34, 56)	0.014
CKD			0.028
- No/ Mild	111 (28)	18 (17)	0.031
- Moderate	246 (61)	67 (65)	0.565
- Severe	44 (11)	19 (18)	0.045
Time interval from TTE to TF-TAVI (days)	11 (6, 25)	14 (6, 29)	0.154
LVEF (%)	56 (51, 61)	33 (28, 37)	_
Mean transvalvular aortic gradient (mmHg)	48 (36, 61)	34 (21, 46)	< 0.001
Aortic valve area (cm^2)	0.7 (0.57, 0.85)	0.65 (0.5, 0.8)	0.037
LGAS	125 (31)	67 (64)	< 0.001
Significant mitral regurgitation	160 (40)	61 (59)	0.001
Significant aortic regurgitation	73 (18)	14 (13.5)	0.254

Data are presented as count (percentage) or median (25th percentile, 75th percentile)
BMI = body mass index, CABG = coronary artery bypass surgery, CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, ICD = implantable cardioverter defibrillator, GFR = glomerular filtration rate, LGAS = low gradient aortic stenosis, LVEF = left ventricular ejection fraction, MI = myocardial infarction, PCI = percutaneous coronary intervention, PPM = permanent pacemaker, TF-TAVI = transfemoral aortic valve implantation, TTE = transthoracic echocardiography.

3.5.3. Mortality in patients with and without low gradient aortic stenosis

The presence of LGAS was associated with both an increased 30-day (12.5% in patients with LGAS versus 6.1% in patients without LGAS, p = 0.011) and an increased 1-year mortality (27.6% in patients with LGAS versus 19.2% in patients without LGAS, p = 0.017) (**figure 3**).

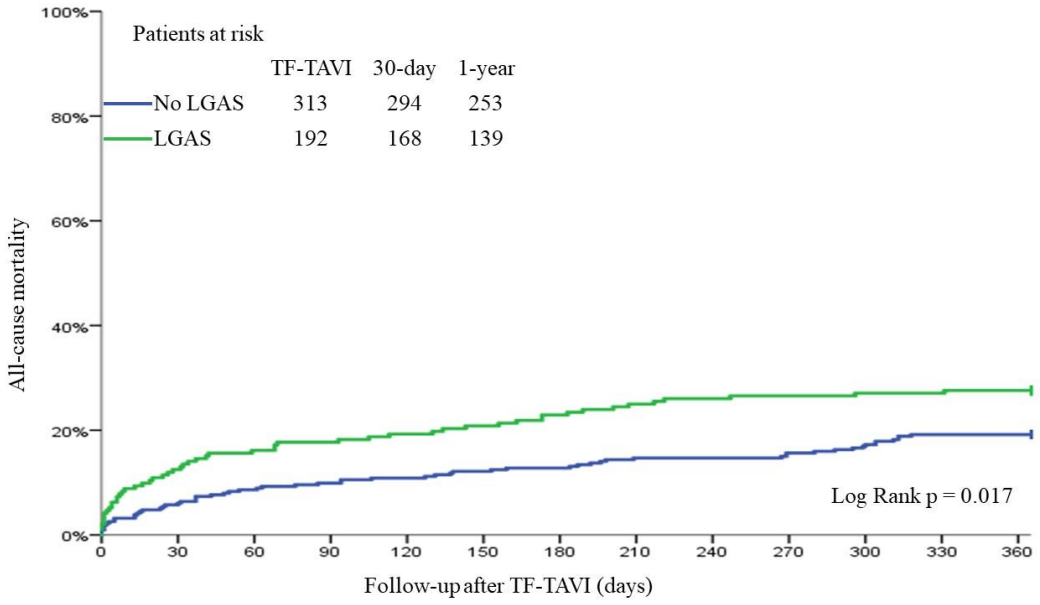
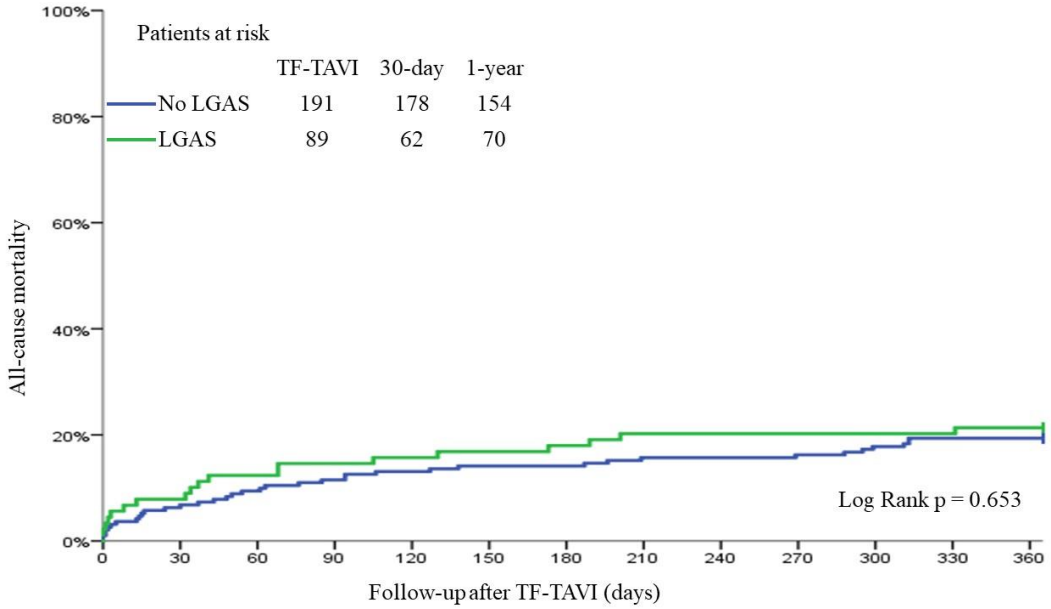


Figure 3: Mortality in patients with and without low gradient aortic stenosis

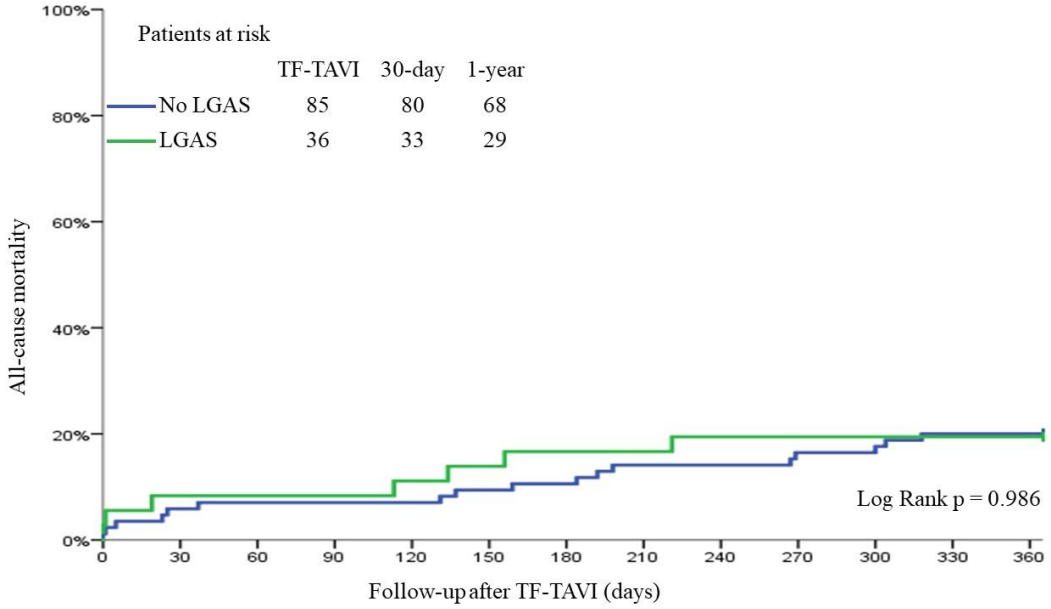
3.5.4. Mortality in patients with low gradient aortic stenosis according to baseline ejection fraction

Both 30-day and 1-year mortality in patients with LGAS were similar compared to those without LGAS in the groups with a normal baseline LVEF (7.9% versus 6.8% at 30 days, p = 0.728 and 21.3% versus 19.4% at one year, p = 0.653) and a mildly abnormal LVEF (8.3% versus 5.9% at 30 days, p = 0.609 and 19.4% versus 20% at one year, p = 0.986). They were higher compared to those without LGAS in the groups with a moderately abnormal LVEF (20.5% versus 3.3% at 30 days, p = 0.038 and 38.6% versus 13.3% at one year, p = 0.019) and a severely abnormal LVEF (21.7% versus 0 at 30 days, p = 0.196 and 43.4% versus

28.6% at one year, p = 0.399), albeit the difference was not statistically significant in the latter group, most likely due to the low number of patients (**figure 4**).

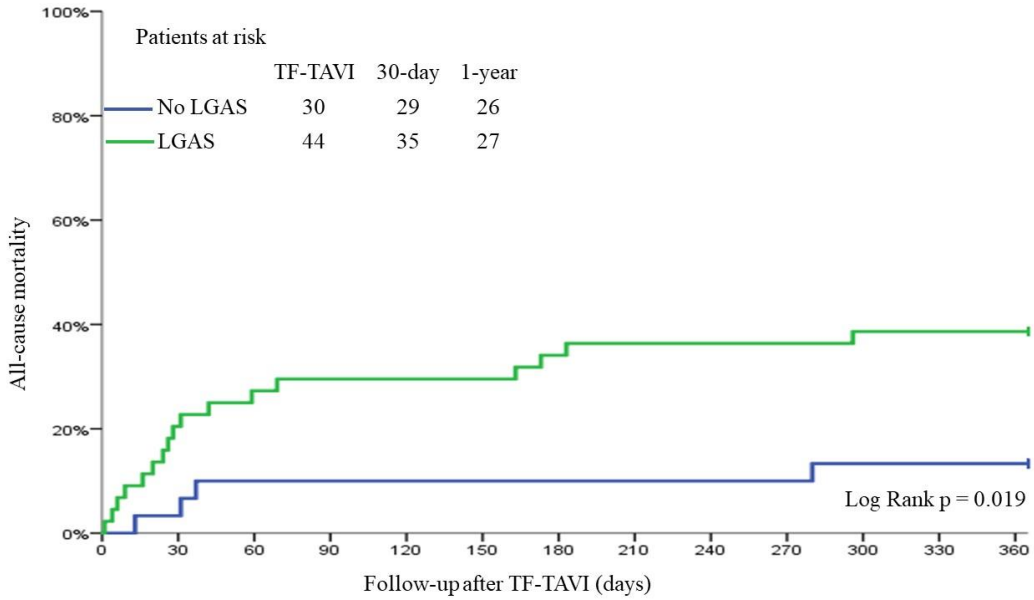


(a) All-cause mortality in patients with and without LGAS and a normal LVEF

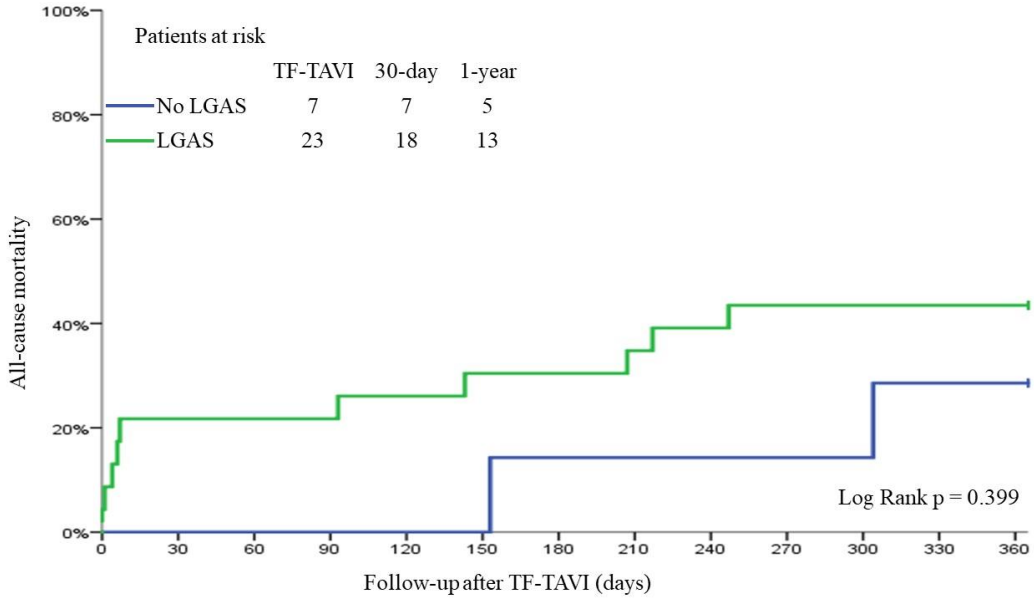


(b) All-cause mortality in patients with and without LGAS and a mildly abnormal LVEF

Figure 4: Mortality in patients with low gradient aortic stenosis according to baseline left ventricular ejection fraction



(c) All-cause mortality in patients with and without LGAS and a moderately abnormal LVEF



(d) All-cause mortality in patients with and without LGAS and a severely abnormal LVEF

Figure 4 (continued): Mortality in patients with low gradient aortic stenosis according to baseline left ventricular ejection fraction

For further assessment of the impact of LGAS on mortality, patients with a normal and a mildly abnormal LVEF were again combined in one group and patients with a moderately and severely abnormal LVEF were combined in another group (see 3.5.2). Consequently,

the following four groups were analyzed regarding 30-day and 1-year all-cause mortality: patients with a moderately or severely abnormal LVEF and LGAS (n = 67), patients with a moderately or severely abnormal LVEF without LGAS (n = 37), patients with a normal or mildly abnormal LVEF and LGAS (n = 125) and patients with a normal or mildly abnormal LVEF without LGAS (n = 276). Patients with a moderately or severely abnormal LVEF and LGAS showed an increased mortality at 30 days (20.9% versus 2.7% / 8% / 6.5%, p = 0.001) and at one year after TF-TAVI (40.3% versus 16.2% / 20.8% / 19.6%, p = 0.001) compared to the other groups (**figure 5**).

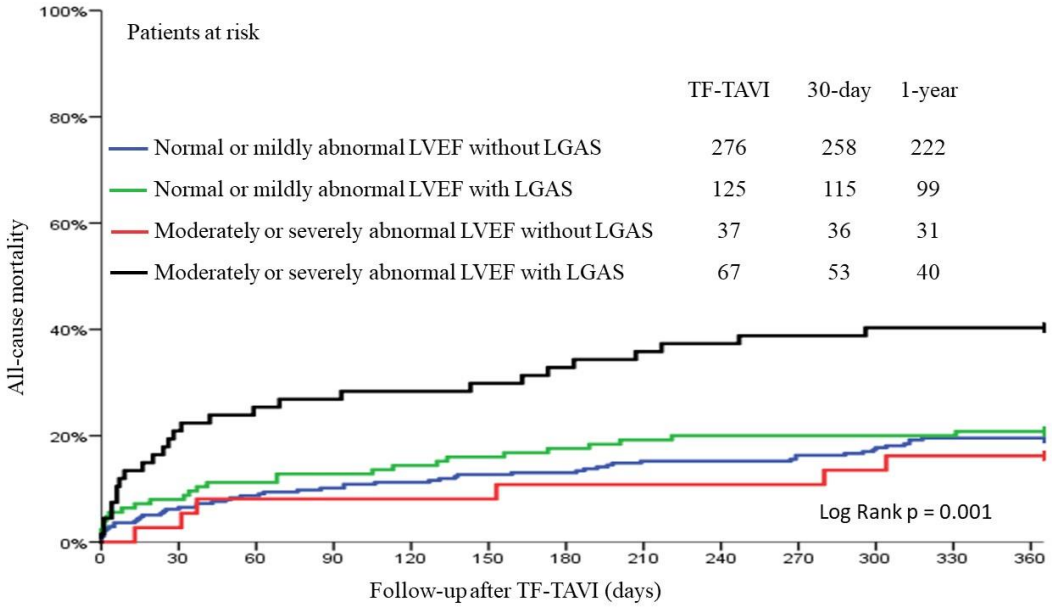


Figure 5: All-cause mortality in patients with normal or mildly abnormal left ventricular ejection fraction and patients with moderately or severely abnormal left ventricular ejection fraction in the presence and absence of low gradient aortic stenosis

3.5.5. Predictors of thirty-day and one-year mortality

A moderately or severely abnormal LVEF (hazard ratio 2.112, 95% confidence interval 1.128 to 3.955, p = 0.019) and a LGAS (hazard ratio 2.132, 95% confidence interval 1.168 to 3.893, p = 0.014) were identified as predictors of 30-day mortality in the univariate Cox regression analysis (**table 13**).

Table 13: Univariate Cox regression analysis of thirty-day mortality

	B	SE	HR	95% Confidence interval	p
Age	0.018	0.027	1.019	0.967 to 1.073	0.492
Female	-0.34	0.306	0.712	0.391 to 1.296	0.266
Logistic EuroSCORE	0.019	0.01	1.019	0.999 to 1.039	0.06
Extracardiac arteriopathy	-0.205	0.375	0.814	0.391 to 1.698	0.814
Recent myocardial infarction	0.343	0.724	1.41	0.341 to 5.827	0.635
Pulmonary hypertension	-0.065	0.392	0.937	0.435 to 2.021	0.869
Coronary artery disease	0.132	0.309	1.141	0.623 to 2.092	0.669
Previous CABG	-0.066	0.472	0.936	0.369 to 2.379	0.89
Previous PPM/ ICD	0.008	0.413	1.008	0.448 to 2.265	0.985
Atrial fibrillation	0.19	0.32	1.21	0.646 to 2.265	0.552
CKD					
- No/ mild	_	_	_	_	_
- Moderate	0.073	0.372	1.076	0.519 to 2.231	0.884
- Severe	0.38	0.493	1.462	0.557 to 3.842	0.441
COPD	0.192	0.35	1.211	0.61 to 2.403	0.584
Diabetes mellitus	-0.521	0.34	0.594	0.305 to 1.157	0.126
Moderately/ severely abnormal LVEF	0.748	0.32	2.112	1.128 to 3.955	0.019
LGAS	0.757	0.307	2.132	1.168 to 3.893	0.014
Aortic valve area	0.824	0.591	2.28	0.715 to 7.268	0.163
Significant mitral regurgitation	0.172	0.312	1.188	0.645 to 2.189	0.581
TF-TAVI with a self-expandable prosthesis	0.24	0.361	1.271	0.626 to 2.578	0.507

B = B coefficient, SE = Standard error, HR = Hazard ratio

CABG = coronary artery bypass surgery, CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, ICD = implantable cardioverter defibrillator, LGAS = low gradient aortic stenosis, LVEF = left ventricular ejection fraction, PPM = permanent pacemaker, TF-TAVI = transfemoral aortic valve implantation.

The only predictor of 30-day mortality in the multivariate analysis, which included LVEF, LGAS, aortic valve area, logistic EuroSCORE and diabetes mellitus, was LGAS (hazard ratio 2.132, 95% confidence interval 1.168 to 3.893, p = 0.014). After introduction of the predefined interaction term (LVEF*LGAS), the only predictor of an increased 30-day mortality was the co-existence of a moderately or severely abnormal LVEF and a LGAS (hazard ratio 3.33, 95% confidence interval 1.759 to 6.303, p < 0.001).

At 1-year follow-up, a moderately or severely abnormal LVEF (hazard ratio 1.732, 95% confidence interval 1.154 to 2.598, p = 0.008), a LGAS (hazard ratio 1.559, 95% confidence interval 1.077 to 2.256, p = 0.019), recent myocardial infarction (hazard ratio 2.378, 95% confidence interval 1.159 to 4.881, p = 0.018) and female gender (hazard ratio 0.621, 95% confidence interval 0.428 to 0.9, p = 0.012) were predictors of mortality in the univariate analysis (**table 14**). In the multivariate analysis that included LVEF, LGAS, recent myocardial infarction and gender, only a moderately or severely abnormal LVEF (hazard ratio 1.664, 95% confidence interval 1.105 to 2.504, p=0.015) and recent myocardial infarction (hazard ratio 2.137, 95% confidence interval 1.035 to 4.143, p=0.04) predicted 1-year mortality after TF-TAVI. When the prespecified interaction term of moderately/severely abnormal LVEF and LGAS was introduced to this model, the interaction between a moderately/severely abnormal LVEF and LGAS was the only independent predictor of increased 1-year mortality after TF-TAVI (hazard ratio 2.415, 95% confidence interval 1.566 to 3.722, p < 0.001).

Table 14: Univariate Cox regression analysis of one-year mortality

	B	SE	HR	95% Confidence interval	p
Age	-0.009	0.016	0.991	0.961 to 1.022	0.573
Female	-0.476	0.189	0.621	0.428 to 0.9	0.012
Logistic Euroscore	0.009	0.007	1.009	0.995 to 1.023	0.216
Extracardiac arteriopathy	-0.032	0.221	0.969	0.629 to 1.493	0.886
Recent myocardial infarction	0.866	0.367	2.378	1.159 to 4.881	0.018
Pulmonary hypertension	0.218	0.224	1.243	0.802 to 1.927	0.33
Coronary artery disease	0.19	0.191	1.21	0.831 to 1.761	0.32
Previous CABG	-0.173	0.305	0.841	0.462 to 1.53	0.57
Previous PPM/ ICD implantation	-0.166	0.27	0.847	0.499 to 1.438	0.539
Atrial fibrillation	0.226	0.197	1.253	0.852 to 1.842	0.257
CKD					
- No/ mild	_	_	_	_	_
- Moderate	0.148	0.219	1.16	0.755 to 1.781	0.498
- Severe	0.215	0.296	1.24	0.694 to 2.216	0.468
COPD	-0.101	0.234	0.904	0.572 to 1.429	0.665
Diabetes mellitus	0.008	0.192	1.008	0.692 to 1.469	0.966
Moderately/ severely abnormal LVEF	0.549	0.207	1.732	1.154 to 2.598	0.008
LGAS	0.444	0.189	1.559	1.077 to 2.256	0.019
Aortic valve area	0.42	0.388	1.522	0.712 to 3.255	0.279
Significant mitral regurgitation	-0.069	0.19	0.933	0.643 to 1.355	0.717
TF-TAVI with a self-expandable prosthesis	0.267	0.224	1.306	0.842 to 2.023	0.233

B = B coefficient, SE = Standard error, HR = Hazard ratio

CABG = coronary artery bypass surgery, CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, ICD = implantable cardioverter defibrillator, LGAS = low gradient aortic stenosis, LVEF = left ventricular ejection fraction, MI = myocardial infarction, PPM = permanent pacemaker, TF-TAVI = transfemoral aortic valve implantation.

4. Discussion

4.1. Findings of the study

This study aimed to assess the impact of LVEF on the outcome of patients with severe AS undergoing TF-TAVI. We found that LVEF was normal in 55%, mildly abnormal in 24%, moderately abnormal in 15% and severely abnormal in 6% of the patients, and that moderately or severely abnormal LVEF (21% of all patients) was an independent predictor of 1-year mortality after TF-TAVI. Patients with a mildly abnormal LVEF had a similar outcome compared to patients with a normal LVEF.

We also aimed to assess the impact of LGAS, a common condition in patients with impaired LVEF, on outcome and its possible interaction with LVEF. We found that a LGAS was present in 38% of patients and its prevalence varied according to the baseline LVEF. A LGAS was detected in nearly one-third of the patients with a normal or mildly abnormal LVEF and in two-thirds of the patients with a moderately or severely abnormal LVEF. LGAS was an independent predictor of 30-day mortality after TF-TAVI (hazard ratio 2.132).

The co-existence of a moderately or severely abnormal LVEF and a LGAS (13% of all patients) was the strongest predictor of 30-day (hazard ratio 3.33) and 1-year mortality (hazard ratio 2.415).

4.2. Prevalence of abnormal ejection fraction and low gradient aortic stenosis

Baseline LVEF was mildly abnormal in 24%, moderately abnormal in 15% and severely abnormal in 6% of patients in this study. Age was similar between all study groups. The baseline characteristics of the patients with a mildly abnormal LVEF were similar to those with a normal LVEF except for more frequent implanted permanent pacemaker or cardioverter defibrillator devices. Whereas patients with a moderately or severely abnormal LVEF (21% of all patients) had more comorbidities than those with a normal or mildly

abnormal LVEF, they exhibited a higher prevalence of coronary artery disease, extracardiac atherosclerotic vascular disease, CKD, implanted pacemakers or cardioverter defibrillator devices and showed male predominance. Their logistic EuroSCORE was higher than that of patients with a normal LVEF. These patients had a smaller aortic valve area than patients with a normal or mildly abnormal LVEF, which may be related to an increased aortic valve calcification due to more advanced vascular and kidney disease.

A LGAS was present in 38% of all patients and was more common in patients with a moderately or severely abnormal LVEF (64%) compared to those with a normal or mildly abnormal LVEF (31%).

Our findings are similar to previously reported data from other studies, although direct comparisons are difficult due to different cutoff points used to describe an impairment of LVEF. In the German Aortic Valve Registry, severe impairment of LVEF (≤ 30%) was present in 12% of 1,432 patients undergoing TAVI. These patients had a higher logistic EuroSCORE, increased comorbidities, a higher prevalence of significant mitral regurgitation and LGAS compared to patients with a LVEF > 30%. Patients with a severely impaired LVEF were also more likely to be males and were younger compared to patients with a LVEF > 30% (Schaefer et al. 2015). In the United Kingdom-TAVI registry, the prevalence of a severely abnormal LVEF in patients undergoing TAVI was 10% (Ludman et al. 2015) and in a multicenter Italian registry patients with a LVEF < 40% represented 20% of the whole TAVI population (Tamburino et al. 2011). Clinical data from the Transcatheter Valve Therapy Registry, which included 11,292 patients undergoing TAVI, showed that about two-thirds of patients had a normal LVEF (> 50%), 26% had a LVEF between 30% and 50%, and only 8% had a LVEF < 30%. Similar to our patients, those with a severely impaired LVEF had more comorbidities, higher risk scores (assessed by the Society of Thoracic

Surgeons risk score), significant mitral valve regurgitation and a smaller aortic valve area. One-third of these patients had a LGAS (Baron et al. 2016). These examples demonstrate that our study population, though coming from a single center, mirrors real world multicenter and registry data. In brief, approximately one-fifth of TAVI patients has at least a moderate impairment of LVEF and about one-third of all patients has LGAS.

4.3. Impact of left ventricular ejection fraction on all-cause mortality

In the univariate analysis, we found that a moderately or severely abnormal baseline LVEF is associated with an increased 30-day and 1-year mortality after TF-TAVI. In the multivariate analysis, however, a moderately or severely abnormal LVEF was only associated with an increased 1-year mortality. The outcome of patients with a mildly abnormal LVEF was similar to that of patients with a normal LVEF both at 30 days and one year.

We used the current ASE/EACVI recommendations to assess the grade of the impairment of LVEF (Lang et al. 2015), which represent a more detailed approach than the commonly used cutoffs to define a normal LVEF as > 50% or a severely impaired LVEF as < 30% (Roques et al. 2003, Duncan et al. 2015, Baron et al. 2016). The ASE/EACVI also offered different cutoff values for females and males. These appear to be of no prognostic relevance in patients undergoing TF-TAVI compared to the 50% cutoff value for a normal LVEF for both genders as endorsed by the current guidelines for the management of valvular heart disease (Baumgartner et al. 2017). However, patients with a mildly abnormal LVEF could be identified as a subgroup of patients with an impaired LVEF that showed similar baseline characteristics and outcomes both at 30 days and at one year compared to patients with a normal LVEF.

The association between the baseline LVEF and the outcome after TAVI was previously reported in observational studies, in national TAVI registries as well as in meta-analyses. The results of these different studies are conflicting. Many investigators found a predictive value for an impaired LVEF on outcome after TAVI. Analysis of the clinical data from the German Aortic Valve Registry revealed that a baseline LVEF ≤ 30% is a predictor of an increased 30-day and 1-year mortality. In this registry, patients were classified into two groups based on their baseline LVEF with a cutoff value of 30%. TF-TAVI was the most frequently used access in both groups (88.8% vs 87.6%, p = 0.46) with the Medtronic CoreValve being the most commonly implanted prosthesis. Both groups of patients showed comparable improvement of their functional status, while both 30-day and 1-year mortality were significantly higher in patients with a LVEF ≤ 30% (Schaefer et al. 2015). Similar findings were detected in the United Kingdom-TAVI Registry that enrolled 870 patients. In that registry, a LVEF < 30% was a predictor of increased 1-year mortality (hazard ratio 1.65, p= 0.06) (Moat et al. 2011), whereas LVEF values between 30% to 49% and LVEF values < 30% were both independent predictors of mortality at longer term follow-up (Duncan et al. 2015). Likewise, in a retrospective two-center study from Italy with 384 patients, investigators found a three-fold higher 30-day and a two-fold higher 1-year mortality in patients with a LVEF ≤ 35% compared to patients with a LVEF > 35%. The majority of patients (75%) were treated using the transfemoral approach. Patients with a LVEF ≤ 35% were younger, had more comorbidities, and a higher logistic EuroSCORE compared to those with a LVEF > 35% (Fraccaro et al. 2012). Similarly, Elhmidi et al. showed that patients with a LVEF < 35% had a two-fold higher mortality at six months compared to patients with a normal LVEF (> 50%) (Elhmidi et al. 2014). In another study, a baseline LVEF ≤ 40% predicted death from heart failure in patients undergoing TAVI and was associated with higher risk of sudden cardiac death (Urena et al. 2015). In the France-2 Registry that enrolled

3,933 consecutive TAVI patients, an impaired LVEF (< 50%) was an independent predictor of 1-year mortality after TAVI (Amabile et al. 2014).

In addition to these studies, two recent meta-analyses showed that any degree of impairment of LVEF is associated with an increased 1-year mortality after TAVI. Eleid et al. included 16 observational studies published between 2010 and 2014 in a meta-analysis on the impact of a reduced stroke volume index, a low mean transvalvular aortic gradient and a reduced LVEF on 1-year all-cause mortality after TAVI. The meta-analysis comprised 7,673 patients. Data of all patients were included in the LVEF analysis, while data of 3,790 patients were available for the low mean transvalvular aortic gradient analysis and only data of 2,032 patients for the stroke volume index analysis. They found that these three parameters are all associated with an increased 1-year mortality after TAVI (Eleid et al. 2015). Luo et al. analyzed data from 28 studies comprising 14,099 patients to determine the association between an impaired LVEF and the prognosis of patients after TAVI. While an impaired LVEF was not related to 30-day mortality, it was related to midterm mortality at one and two years (Luo et al. 2015).

In contrast to these findings, other investigators did not find that an impaired LVEF had an impact on mortality in patients with severe AS undergoing TAVI. In a single center registry, clinical outcomes of high risk patients with severe AS undergoing medical treatment (n= 71) or TAVI (n= 256) stratified by LVEF with a cutoff point of 30% were compared. Twenty-five patients (35%) among the medical cohort and 37 patients (14%) among the TAVI cohort had a LVEF ≤ 30%. During follow-up of 2.5 years, patients undergoing TAVI had similar mortality rates irrespective of their baseline LVEF, whereas mortality was markedly increased in patients with a LVEF ≤ 30% who were treated medically (Pilgrim et al. 2011). Likewise, a multicenter retrospective Italian study included 649 patients to assess the impact

of a reduced baseline LVEF on both short and mid-term mortality after TAVI. A cutoff value of 30% was used to indicate severe impairment of the LVEF. Although patients with a LVEF of ≤ 30% had a higher EuroSCORE and a higher New York Heart Association functional class compared to those with a LVEF > 30%, all cause and cardiac mortality were similar in both patient groups (Ferrante et al. 2016). In a multicenter registry including 663 patients undergoing TAVI using the self-expandable CoreValve prosthesis, LVEF < 40% was a predictor of 30-day mortality but not 1-year mortality (Tamburino et al. 2011). Likewise, patients with a LVEF ≤ 45% had similar in-hospital and 1-year outcomes after TAVI compared to patients with a LVEF > 45% in a single center study comprising 371 consecutive patients. One-year mortality was 22% in both groups (Barbash et al. 2014). A recent analysis of the data of all TAVI procedures performed in the United Kingdom (3,980 patients from 2007 to 2012) concluded that comorbidities such as atrial fibrillation, chronic obstructive pulmonary disease, creatinine > 200 micromol/l, diabetes mellitus and coronary artery disease were predictors of long-term mortality. A moderately impaired LVEF (defined as LVEF values between 30% and 49%) was a predictor of 30-day mortality in the univariate but not the multivariate analysis (Ludman et al. 2015). Baron et al. analyzed data of the Transcatheter Valve Therapy Registry to assess the impact of an impaired LVEF and a low mean transvalvular aortic gradient on clinical outcomes after TAVI. Patients were divided into three groups based on their LVEF with the cutoff points < 30% and > 50%. Severe impairment of LVEF was associated with higher rates of mortality (29.3% versus 25.5% versus 21.9%, $p < 0.001$) at 1-year follow-up. Nevertheless, LVEF was not an independent predictor of mortality in the multivariate analysis, where it was analyzed as a continuous rather than a categorical variable (Baron et al. 2016).

These different results between studies are multifactorial. First, the cutoff point for an abnormal LVEF differs considerably between the various studies. Second, different

statistical models were used in various studies: while two recently reported registries analyzed LVEF as a continuous variable and found that LVEF had no effect on outcome after TAVI (Baron et al. 2016, Kataoka et al. 2017), other registries categorized patients into normal and impaired LVEF and found an independent prognostic impact of the LVEF on all-cause mortality (Amabile et al. 2014, Schaefer et al. 2015). Third, most of the studies included transfemoral and non-transfemoral procedures in the same analysis. This may constitute a confounder that masked the impact of baseline LVEF on mortality. On the one hand patients with a severely abnormal LVEF undergo transapical TAVI less frequently than those with a preserved LVEF (Baron et al. 2016), but on the other hand the outcomes of TF-TAVI are consistently better than those of transapical TAVI (Thomas et al. 2011, Di Mario et al. 2013, Blackman et al. 2014, van der Boon et al. 2014).

4.4. Impact of low gradient aortic stenosis on all-cause mortality

In our study, presence of a LGAS was associated with an increased 30-day mortality in the multivariate analysis. At 1-year follow-up, LGAS predicted an increased mortality in the univariate analysis but not in the multivariate analysis. In the multivariate analysis, only baseline LVEF and recent myocardial infarction were independent predictors of increased 1-year mortality.

Previous studies showed that a LGAS is associated with poorer long-term outcome after TAVI (Zahn et al. 2013, Amabile et al. 2014, Baron et al. 2016). The 1-year follow-up of the German Aortic Valve Registry, in which the clinical data of 1,318 consecutive patients were reviewed, showed that a LGAS was an independent predictor of 1-year mortality (hazard ratio 1.83, 95% confidence interval 1.29 to 2.61) as well as previous myocardial infarction (hazard ratio 1.48, 95% confidence interval 1.08 to 2.03). However, baseline LVEF was not included in the analysis (Zahn et al. 2013). In the France-2 Registry, LGAS

was present in 23.5% of patients and was associated with an increased 1-year mortality after TAVI (hazard ratio 1.53, 95% confidence interval 1.15 to 2.04). Impaired LVEF (< 50%) was also an independent predictor of mortality (hazard ratio 1.66, 95% confidence interval 1.23 to 2.27) (Amabile et al. 2014). Likewise, LGAS was an independent predictor of 1-year mortality (hazard ratio 1.21, 95% confidence interval 1.11 to 1.32) in the Transcatheter Valve Therapy Registry (Baron et al. 2016).

Our results should not be interpreted as being contradictory with these findings. We found that LGAS and a moderate or severe impairment of LVEF for themselves were predictors of 1-year mortality in the univariate analysis. Indeed, the unadjusted hazard ratio for LGAS in our univariate analysis (1.559) was similar to the unadjusted hazard ratio in the France-2 Registry (1.6) (Amabile et al. 2014). The different results of the multivariate analysis in our study compared to others may be explained by a larger number of patients in the nationwide registries (Zahn et al. 2013, Amabile et al. 2014, Baron et al. 2016) and methodological differences in study design (Zahn et al. 2013, Baron et al. 2016). Yet, the combination of LGAS and a moderately or severely abnormal LVEF was an independent predictor of both 30-day and 1-year mortality (see below).

4.5. Impact of ejection fraction and low gradient aortic stenosis on all-cause mortality

We found that patients with a moderately or severely abnormal LVEF were at increased risk of 30-day and 1-year mortality in the presence of a LGAS. Patients with a moderately or severely abnormal LVEF who did not have a LGAS had a comparable outcome to patients with a normal or mildly abnormal LVEF.

Several recent studies investigated the additive prognostic value of LGAS and LVEF in patients undergoing TAVI. In a single center study, 202 consecutive patients undergoing TAVI with the self-expandable CoreValve prosthesis were divided into four groups

according to LVEF (> 50% versus ≤ 50%) and mean transvalvular aortic gradient (> 40 mmHg versus ≤ 40 mmHg) and followed up for one year. Overall, 1-year mortality was 23% and was highest in the group of patients with an impaired LVEF and a low gradient (39%) (Gotzmann et al. 2012). Researchers from a multicenter observational study in Italy investigated the effect of LVEF and mean transvalvular aortic gradients on the outcome after TAVI analyzing data of 764 consecutive patients. They assigned the cutoff point of 40% for a preserved versus an impaired LVEF and found that the combination of LGAS with a LVEF < 40% was a predictor of increased mortality (hazard ratio 2.4) at a median follow-up of 396 days (Conrotto et al. 2017). Two single center studies from Germany demonstrated similar findings. Schewel et al. found that patients with a severely impaired LVEF (≤ 30%) and a LGAS had an increased 30-day and 1-year mortality. One-year mortality in these patients was 38.2% compared to 11.4% in patients with a normal LVEF (> 50%) and a high mean transvalvular aortic gradient (Schewel et al. 2016). Puls et al. analyzed the data of 400 consecutive TAVI patients. They classified the enrolled patients according to baseline LVEF and mean transvalvular aortic gradient to study their impact on long-term outcome. One-hundred-and-forty-seven patients had a normal LVEF (≥ 50%) and a high mean transvalvular aortic gradient (≥ 40 mmHg), 63 patients had an impaired LVEF and high mean transvalvular aortic gradient, 77 patients had a normal LVEF and a low mean transvalvular aortic gradient, and 81 patients had an impaired LVEF and a low mean transvalvular artic gradient. The overall 1-year mortality was 26% with the highest rate of death in the group of patients with an impaired LVEF and a low mean transvalvular aortic gradient (43% versus 14% in the group with a normal LVEF and a high mean transvalvular aortic gradient). Multivariate analysis showed that the combined status of an impaired LVEF and a low mean transvalvular aortic gradient predicted both all-cause and cardiovascular mortality after TAVI (Puls et al. 2017). Likewise, analysis of data from national TAVI registries showed similar findings.

Patients with a LGAS and an impaired LVEF (< 40%) in the German Aortic Valve Registry had a higher in-hospital and 1-year mortality than those with LGAS and a normal LVEF (> 50%). In contrast, the outcome of patients with LGAS and a normal LVEF was comparable to those with a high mean transvalvular aortic gradient (Lauten et al. 2014). In the United Kingdom-TAVI registry, an abnormal LVEF (< 50%) was associated with an increased mortality at 2-year follow-up only in patients with a low transvalvular aortic gradient (defined as a peak gradient < 64 mmHg). In the group of patients with a normal LVEF, there was no difference in mortality between patients with low transvalvular aortic gradients and those with high gradients (Malkin et al. 2016).

The prognostic impact of the co-existence of an impaired LVEF with LGAS seems to be consistent between studies. All-cause mortality of the patients with a LVEF < 40% and LGAS in two previous studies was 40.6% at median follow-up of 396 days (Conrotto et al. 2017) and 43% at 1-year follow-up (Puls et al. 2017). This is similar to the 1-year all-cause mortality rate (40.3%) in patients with a moderately or severely abnormal LVEF and coexisting LGAS in our study.

In contrast to these findings O'Sullivan et al. found no differences in 30-day or 1-year all-cause mortality between patients with combined LGAS and an impaired LVEF (< 50%) and those with a normal LVEF after TAVI in a retrospective single center study (O'Sullivan et al. 2013). Baron et al. found that LGAS, but not an impaired LVEF, was predictive of 1-year mortality. They found no interaction between LVEF (as a continuous variable) and LGAS on outcome. Nevertheless, the highest 1-year mortality in their study was found in the group of patients with a severely abnormal LVEF and LGAS (33%) and the lowest 1-year mortality was found in patients with a normal LVEF and a high mean transvalvular aortic gradient (21%) (Baron et al. 2016).

Overall, the coexistence of a moderately or severely abnormal LVEF and LGAS increases 30-day and 1-year mortality after TF-TAVI. When either LVEF is preserved or the mean transvalvular aortic gradient is high in the setting of severe AS, the outcome appears to be favorable due to the presence of a contractile reserve of the left ventricular myocardium or the absence of significant myocardial fibrosis (Herrmann et al. 2011). The proportion of patients with at least a moderately abnormal LVEF and a LGAS undergoing TAVI is considerably low and accounts for 13% of all patients in our study and for 8.4% to 22.5% of all patients in previous reports (Debry et al. 2016, Malkin et al. 2016, Schewel et al. 2016, Conrotto et al. 2017). This patient cohort is at high risk for an adverse outcome after TAVI and may, thus, deserve further testing in the decision making process in order to better stratify the individual risk of a TAVI procedure (Hayek et al. 2015). After careful revision of all available clinical data and confirmation of the presence of severe AS, TF-TAVI in these patients still should be strongly considered given the dismal prognosis if treated conservatively (Baumgartner et al. 2017).

4.6. Clinical implications

This study shows that the co-existence of a moderately or severely abnormal LVEF and a LGAS identifies a group of patients with an increased mortality after TF-TAVI. Yet, the procedural outcome remains favorable when either the LVEF is preserved or the mean transvalvular aortic gradient is high, as already proposed in the current guidelines for the management of valvular heart disease (Baumgartner et al. 2017). Furthermore, we showed that a mildly abnormal LVEF is not associated with an increased mortality after TF-TAVI, irrespective of the mean transvalvular aortic gradient. Accordingly, risk stratification of patients with mildly abnormal LVEF, especially if accompanied with LGAS, should follow the pathway of patients with a normal LVEF, since these patients still have a favorable prognosis after TF-TAVI. Though the co-existence of a moderately or severely abnormal

LVEF and a LGAS identifies patients with an increased mortality after TF-TAVI, their outcome is still better than medical therapy alone. TF-TAVI may improve the prognosis in this very high risk group but further studies are needed to define outcome predictors after TF-TAVI in these patients.

4.7. Limitations

Our study has certain limitations including the inherent limitations of observational reports. In addition, we did not include flow state across the stenotic aortic valve in our analysis, since the required data were not routinely documented in the TTE reports. Only all-cause mortality was reported in this study and not cardiovascular mortality, as the exact cause of death was not known to us for every patient. Stress echocardiography was not performed in patients who had both an abnormal LVEF and LGAS for further risk stratification. Follow-up TTE data that might detect an improvement of LVEF after TAVI were not collected. Thus, recovery of the LVEF was not evaluated as part of our study. Nevertheless, no loss of patients at follow-up, direct access to baseline TTE data, adherence to ASE/EACVI recommendations for the classification of LVEF impairment and including only TF-TAVI patients in this analysis are remarkable strengths of this study.

5. Conclusion

A moderately or severely abnormal LVEF at baseline is associated with increased mortality after TF-TAVI when the mean transaortic gradient is less than 40 mmHg, while outcomes in patients with a normal and mildly abnormal LVEF are comparable regardless the pressure gradient across the aortic valve.

6. Summary

Data on the impact of baseline left ventricular ejection fraction (LVEF) on outcome after transcatheter aortic valve implantation (TAVI) are inconsistent, and there is a potential confounding effect of a low transvalvular aortic gradient (< 40 mmHg = LGAS). Moreover, the cutoff points to define an impaired LVEF in previous TAVI studies are rather arbitrary. We, therefore, studied the impact of the recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging for classification of an impaired LVEF on the 30-day and 1-year mortality in patients with severe symptomatic aortic stenosis who underwent transfemoral (TF-) TAVI. The impact of a LGAS was also evaluated.

Baseline LVEF was normal in 280 (55%), mildly abnormal in 121 (24%), moderately abnormal in 74 (15%) and severely abnormal in 30 (6%) patients, respectively. Thirty-day and 1-year mortality were 8.5% and 22.4%, respectively, and patients with a normal or mildly abnormal LVEF (> 40%) had similar outcomes. However, mortality was increased in patients with a moderately or severely abnormal LVEF (≤ 40%), especially in the presence of LGAS. Patients with a moderately or severely abnormal LVEF and a LGAS exhibited nearly a 2-fold higher 1-year mortality (40.3%) compared to any other patient subgroup. In the multivariate analysis, the combination of a moderately or severely abnormal LVEF and a LGAS predicted an increased 30-day (hazard ratio 3.33, 95% CI 1.76 to 6.3) and 1-year mortality (hazard ratio 2.42, 95% CI 1.57 to 3.72).

We concluded that a moderately or severely abnormal LVEF at baseline is associated with an increased mortality after TF-TAVI when the mean transvalvular aortic gradient is less than 40 mmHg, while outcomes in patients with a normal and mildly abnormal LVEF are comparable regardless the transvalvular aortic gradient.

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8. Appendix

8.1. List of tables

8.2. List of figures

8.3. List of abbreviations

AS	aortic stenosis
ASE	American Society of Echocardiography
AV_{VTI}	aortic valve time velocity integral
BAV	balloon aortic valvuloplasty
BMI	body mass index
CABG	coronary artery bypass graft surgery
CE	Conformité Européenne
CKD	chronic kidney disease
COPD	chronic obstructive pulmonary disease
EACVI	European Association of Cardiovascular Imaging
EuroSCORE	European System for Cardiac Operative Risk Evaluation
GFR	glomerular filtration rate
ICD	implantable cardioverter defibrillator
LGAS	low gradient aortic stenosis
LVEDV	left ventricular end diastolic volume
LVEF	left ventricular ejection fraction
LVESV	left ventricular end systolic volume
LVOTd	left ventricular outflow tract diameter
$LVOT_{VTI}$	left ventricular outflow tract time velocity integral
MI	myocardial infarction
PARTNER	Placement of AoRTic TraNscathetER valve trial
PCI	percutaneous coronary intervention
PPM	permanent pacemaker
SURTAVI	Surgical Replacement and Transcatheter Aortic Valve Implantation
TAVI	transcatheter aortic valve implantation
TF-TAVI	transfemoral transcatheter aortic valve implantation
TTE	transthoracic echocardiography
VARC-2	The second edition of the Valve Academic Research Consortium document.

8.4. Acknowledgements

Scientific research is a collaborative work that starts with problem identification, data collection to find possible solutions, hypothesis generation and rigorous testing of the hypothesis to reach new insights. The collaboration with peers, guidance and advice from mentors and meticulous work are keys for success.

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8.5. Curriculum Vitae

Der Lebenslauf ist in der Online-Version aus Gründen des Datenschutzes nicht enthalten.