

SUPPLEMENTARY DATA

Appendix 1.

Subgroup analysis for objective functional improvement

Population

During the study period all patients scheduled for TAVR who met the following criteria were included in the study: *a)* diagnosis of significant and symptomatic AS; *b)* absence of moderate or severe disease of any valve other than the aortic valve, since significant concomitant valve disease would confound both the hemodynamic measurements and the functional recovery assessment; *c)* indication for TAVR established by the institutional Heart Team; *d)* undergoing a TAVR procedure through femoral artery access. Patients who did not consent or who exhibited cognitive impairment that prevented them from properly understanding the investigational procedures were excluded.

All procedures were performed in a catheterization laboratory dedicated to structural heart interventions. The study was approved by the Institutional Review Board and all participating patients signed the informed consent form after receiving proper explanation of the investigational procedures. The database was completely anonymized.

Preprocedural and postprocedural clinical and functional evaluation

Once TAVR had been indicated by the Heart Team, patients were evaluated at the structural heart disease outpatient clinic. At this visit, all clinical information was collected, and functional status, including quality of life and frailty, was assessed using established questionnaires and scales (SF-36, EQ-5D, Barthel Index, Essential Frailty Toolset, NYHA functional class, and Kansas City Cardiomyopathy Questionnaire [KCCQ]), the 6-minute walk test, and baseline N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels.

On the day of the procedure, immediately before entering the catheterization laboratory, all patients underwent simultaneous hemodynamic and cardiac imaging assessment. Hemodynamic parameters

were assessed noninvasively using the SphygmoCor XCEL device (AtCor Medical, Naperville, IL, USA), which derives central blood pressure from peripheral measurements. Three consecutive measurements were obtained and averaged to calculate central blood pressure, pressure amplification (defined as the difference between systolic blood pressure measured at the brachial artery and that measured in the ascending aorta), and augmentation index standardized to a heart rate of 75 bpm (AIx75), defined as the percentage increase in pulse pressure resulting from augmentation of the forward pressure wave by the reflected wave. All measurements were obtained by trained personnel experienced in performing these assessments in a hypertension clinic. Protocol-specific transthoracic echocardiography was also performed to obtain a complete dataset on morphological and functional characteristics of the aortic valve, left ventricle, and ascending aorta.

All clinical and functional assessments were repeated 30 days, 6 months and 12 months after the TAVR procedure by the same team and in the same setting.

Definition of objective and subjective functional improvement

Objective functional improvement was defined as an increase of at least 10% in the distance covered on the 6-minute walk test or, in the absence of such an increase, a reduction of at least 50% in NT-proBNP levels compared with pre-TAVR values. The use of both criteria allowed consideration of potential factors unrelated to cardiovascular capacity that could limit walking speed. In the few cases in which the patient's functional status was so severely impaired that they were unable to perform the 6-minute walk test, improvement was considered to have occurred if the patient survived the procedure and was able to perform the test at follow-up, with a corresponding reduction in NT-proBNP levels compared with pre-TAVR values.

For patients who died after the 30-day assessment but before the 6-month time point, improvement was assessed on the basis of the earlier evaluation but was considered absent if the patient subsequently developed or died of heart failure.

Among patients who died before the 30-day follow-up, those who died of heart failure were considered not to have improved, whereas those who died of other causes were excluded from the analysis because no functional assessment was available. Subjective improvement was defined as an improvement of at least 1 NYHA functional class and/or an increase of at least 10 points in the KCCQ score.

Figure S1. Survival analysis was also performed using additional subgroups defined according to mean gradient. A graded association between mean gradient and survival was observed, which was more pronounced at very low gradients and was no longer evident above 40 mmHg. HG, high-gradient; LG, low-gradient; VLG, very low-gradient; LF, low-flow.

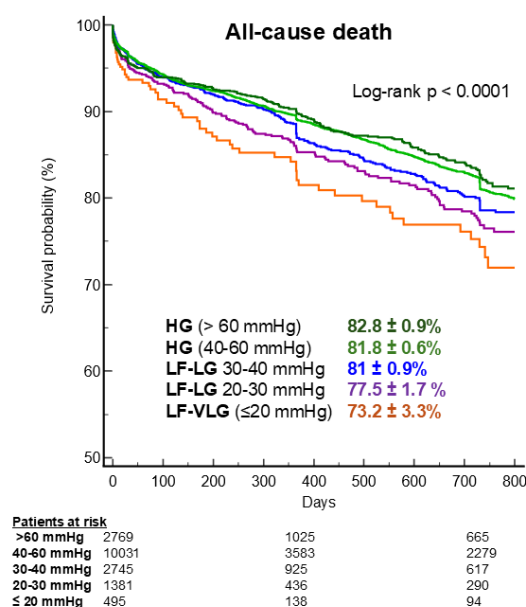


Figure S2. Survival analysis was performed in patients treated during 2 consecutive periods (2010-2019 and 2020-2024). Overall, survival improved among all gradient subgroups. However, the adverse prognostic impact of LF-VLG was observed in both periods and was even more pronounced in the more recent period, owing to the greater improvement in outcomes among patients with higher gradients. HG, high-gradient; LG, low-gradient; VLG, very low-gradient; LF, low-flow.

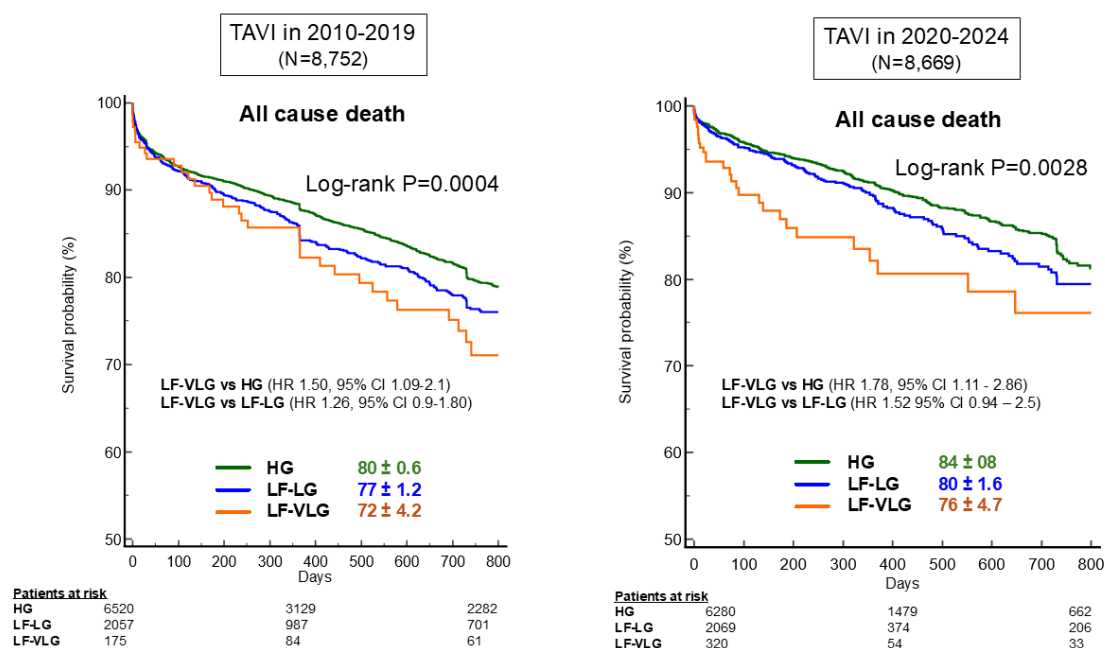


Figure S3. Survival analysis was performed in patients in the LF-VLG group according to preserved or reduced LVEF (<50%), with no significant differences observed between the groups. VLG, very low-gradient; LF, low-flow; LVEF, left ventricular ejection fraction.

