*Catheterization and Cardiovascular Interventions*

WILEY

ORIGINAL ARTICLE - CLINICAL SCIENCE OPEN ACCESS

# Less Symptom Improvement in Patients Undergoing TAVI With Concomitant COPD, Atrial Fibrillation and Heart Failure

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**Received:** 14 April 2025 | **Revised:** 20 June 2025 | **Accepted:** 2 July 2025

**Funding:** This work was supported by an unrestricted research grant from Medtronic and Us2.ai to the University Medical Center Groningen (UMCG).

**Keywords:** atrial fibrillation | COPD | heart failure | symptoms | TAVI

## ABSTRACT

**Background:** Comorbidities like a history of chronic obstructive pulmonary disease (COPD), atrial fibrillation (AF) and heart failure (HF) can cause similar symptoms as aortic stenosis (AS). However, how they influence symptom improvement and long-term outcomes after transcatheter aortic valve implantation (TAVI) is unclear.

**Aims:** To study the impact of COPD, AF and HF on outcomes after TAVI.

**Methods:** A history of COPD, AF and HF were collected in three TAVI cohorts (Groningen, Netherlands, Brescia, Italy and Bern, Switzerland). Symptom improvement was defined as $\geq 1$ improvement of New York Heart Association (NYHA) functional class at 12 months, compared with baseline. Adverse events were defined as cardiovascular mortality, stroke or HF-hospitalisation at 5-year follow-up (VARC-3).

**Results:** The pooled analysis included 5173 patients (mean age: 81.5 years, 49.7% women). Patients with COPD, AF or HF underwent TAVI at significantly lower mean aortic valve gradients, higher cardiac damage stage and higher NYHA-class. After adjusting for sex, NYHA-class, age, other comorbidities, flow-type and cardiac damage stage pre-TAVI, a history of COPD (Odds Ratio (OR): 1.75 (95% Confidence interval (CI): 1.10–2.75), $p = 0.017$) and a history of HF (1.65 (1.03–2.58), $p = 0.038$) were associated with no symptom improvement, while AF was not (1.12 (0.71–1.74, $p = 0.629$). Patients with COPD, AF or HF had higher risks of adverse events and lower survival at long-term follow-up.

**Conclusions:** Patients with symptomatic AS and concomitant comorbidities of COPD, AF and HF, undergo TAVI at a lower severity of AS, have a higher symptomatic burden and higher cardiac damage stage before TAVI. They have a greater risk of residual symptoms, and a higher risk of long-term adverse events.

## 1 | Introduction

Severe aortic stenosis (AS) often leads to dyspnea, caused by impaired filling of the left ventricle, which leads to increased pulmonary pressures, causing pulmonary and systemic fluid overload and congestion [1]. However, other comorbidities like chronic obstructive pulmonary disease (COPD), atrial fibrillation (AF) and heart failure (HF) frequently coexist with AS and might also present with dyspnea [2, 3].

Transcatheter aortic valve implantation (TAVI) has become the preferred procedure to treat AS in elderly and high-risk patients [4, 5]. From a patient's perspective, especially that of an elderly patient, symptom improvement and quality of life after TAVI might be the most important outcome [6]. Comorbidities such as COPD, AF and HF could also present with dyspnea. When dyspnea in patients undergoing TAVI is primarily driven by comorbidities, a valve replacement will likely not lead to an improvement in symptoms. Accurate identification of these patients is necessary to avoid futile TAVI procedures and manage patient expectations. A simple risk stratification regarding symptom improvement and long-term adverse events in patients with one of these comorbidities is lacking. Defining the stage of extra-valvular cardiac damage and flow status of the AS can accurately indicate the true severity of AS. It could potentially better phenotype patients with one of the comorbidities [7–9]. Ultimately, this may help to differentiate between symptoms associated with AS or any comorbidity, and thus could aid in clinical decision-making.

Therefore, we aimed to determine baseline characteristics including flow-status and cardiac damage staging and the impact of COPD, AF and HF on symptom improvement 1 year after TAVI, as well as 5-year adverse events, in three tertiary TAVI centres in the Netherlands, Italy and Switzerland.

## 2 | Methods

All patients who received a TAVI procedure in a tertiary centre in the Netherlands (University Medical Centre Groningen (*UMCG*), Groningen, between 2009 and 2020), Italy (*Spedali Civili di Bresci*, Brescia, between 2007 and 2023) and Switzerland (*Inselspital*, Bern, between 2009 and 2023) were eligible for this retrospective analysis. Patients with an indication for TAVI other than severe native AS and with previous aortic valve replacement (AVR) were excluded from this analysis. The approval for this study was obtained from the local research ethical committee (local number: 202100641) following the 1964 Declaration of Helsinki guidelines.

Baseline clinical characteristics were prospectively collected at the treating centres and aggregated retrospectively. The baseline visit was conducted (within) 1 month before the initial TAVI procedure and performed by a medical professional. Follow-up visits took place according to the local protocol at the treating centre after 30 days and at the referring hospitals 6 months and 12 months after TAVI procedure. Follow-up data was collected retrospectively from electronic patient records at both treating and referring hospitals. Five-year follow-up data for the present analysis was only available in the UMCG Cohort (Supporting Information: Figure S1).

COPD was defined according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) report and included all 4 GOLD-stages (Inselspital and UMCG), or according to the definition of the EuroSCORE: long-term use of bronchodilators or steroids for lung disease (Spedali Civili di Bresci) [10, 11]. For AF, all entities - paroxysmal, persistent and permanent—documented in the medical history or most recent ECG before the procedure, were considered as a history of AF. HF was defined according to the ESC guidelines as history of HF, as mentioned in medical history and included both acute and chronic HF [12]. History of HF was only available in the UMCG and Spedali Civili di Bresci cohorts ($N = 1772$).

Transthoracic echocardiography was performed according to local guidelines before the TAVI procedure. Echocardiographic images at the UMCG were analysed with a fully automated, validated and clinical available deep learning-based echocardiography software (Us2. ai, version 2.0.0). This software has shown effective performance previously [13].

Cardiac damage stage was determined to further characterize patients with comorbidities (only available in the UMCG and Inselspital ($N = 3171$)). Cardiac damage staging was classified based on previously proposed classification and patients were classified into the five stages based on the presence and severity of extra-aortic valve cardiac damage [9]. Stage 0: absence of any extra-aortic valve cardiac damage. Stage 1: left ventricular (LV) damage, defined as a left ventricular ejection fraction (LVEF) of less than 50%, left ventricular mass index greater than 95 g/m$^2$ (women) or 115 g/m$^2$ (men), or an E/e' ratio of 14 or higher. Stage 2: left atrial or mitral valve damage, indicated by a left atrial volume index greater than 34 mL/m$^2$, moderate or severe mitral regurgitation, or the presence of AF. Stage 3: either pulmonary vasculature or tricuspid valve damage, evidenced by a pulmonary systolic artery pressure of $\geq 60$ mm, or moderate to severe tricuspid regurgitation. Stage 4: right ventricular (RV) damage, defined by RV dysfunction, which was determined by at least one of the following parameters: tricuspid annular plane systolic excursion (TAPSE) less than 1.7 cm, S' less than 9.5 cm/s, or fractional area change less than 35%. Patients were classified according to the most advanced stage of cardiac damage present.

Different flow types of AS were defined according to previously published classification [7, 14]. High-gradient AS (HG-AS) was defined as an aortic valve area (AVA) $\leq 1.0$ cm$^2$ and a mean aortic gradient (AV MG) $\geq 40$ mmHg. Classical low-flow, low-gradient AS (cLF LG-AS) was defined as an AVA $< 1.0$ cm$^2$, left ventricular ejection fraction (LVEF) $< 50\%$, AV MG $< 40$ mmHg, and stroke volume index (SVI) $< 35$ mL/m$^2$. Low-flow, low-gradient AS with preserved ejection fraction (LF-LG pEF) (LVEF $\geq 50\%$) was defined as an AVA $< 1.0$ cm$^2$, AV MG $< 40$ mmHg, and SVI $< 35$ mL/m$^2$. Normal-flow, low-gradient AS (NF LG-AS) was defined as an AVA $< 1.0$ cm$^2$, LVEF $\geq 50\%$, MG $< 40$ mmHg, and SVI $> 35$ mL/m$^2$.

The endpoint of interest was symptom improvement, defined as New York Heart Association (NYHA) class I at 12 months or $\geq 1$ improvement in NYHA at 12 months compared to baseline. In the absence of 12 months (symptomatic) follow-up information, either 6 months or 30-day symptomatic information

was taken. Patients with NYHA class I at baseline were excluded due to their inability to improve in symptoms (Supporting Information: Figure S2). The secondary endpoints were: (1) Adverse event 1-year post-TAVI, defined as a composite of cardiovascular mortality, stroke, or heart failure (HF) hospitalisation, according to the VARC-3 criteria, (2) Combination of adverse events and lack of symptom improvement, (3) All-cause mortality during long-term (with a maximum of 5 years) follow-up [15].

Categorical variables were presented as n (%) and continuous variables were reported as mean ± (SD) for normally distributed variables or median [IQR] in case of non-normally distributed variables. *t*-tests performed comparisons, Mann–Whitney *U* tests or Chi-square test, depending on the distribution. Logistic regression was performed to examine associations between comorbidities and outcomes, and corrected for sex, age, NYHA class, other comorbidities and cohorts. Due to missing parameters, these associations were also corrected for flow-status and cardiac damage staging in a subset of patients in different models. Time to HF hospitalisations and to mortality were evaluated using Kaplan-Meier analysis with log-rank tests and cox proportional hazards modelling. The proportional hazards assumption was checked by Schoenfeld residuals and *cox. zph* test in R/. *p*-value of $< 0.05$ was considered statistically significant. All statistical analyses were performed using R/software (version 4.3.1).

## 3 | Results

We included 5173 patients in this analysis: 741 from the UMCG, 637 from Spedali Civili di Bresci and 3795 from Inselspital (Supporting Information: Figure S1). The patients' mean age was 81.5 (±6.6) years, and 49.7% were women (Table 1). Most patients had NYHA class III or IV at baseline (3599 (69.6%)), with a mean NYHA class of 2.8. (0.6). More than half of the patients (57.2%) had a high gradient AS (HG-AS), and most patients had cardiac damage stage 2 (37.6%). At baseline, 12.7% (656/5173 patients) had COPD, 32.8% (1698/5173) had a history of AF and 26.8% (369/1772) had HF. Baseline characteristics for each cohort can be found in Supporting Information: Table S1.

At 1 year follow-up, 1295 patients (27.6%) had no symptom improvement, while 814 (15.7%) had one or more adverse events. After 5-year follow-up, mortality rates increased to 305 (41.2%) and 195 (26.3%) patients had a hospitalisation for HF. Outcomes for each cohort can be found in Supporting Table 2.

Patients with COPD more frequently had NYHA class III or IV, (77.3% vs. 68.4%, $p < 0.001$), similarly in patients with AF (74.3% vs. 65.1%, $p < 0.001$) and in patients with HF (92.3% (504/546) vs. 78.6% (963/1226), $p < 0.001$) (Table 2). Patients with COPD had a lower AV MG ($37.3 \pm 14.9$ mmHg vs. $40.3 \pm 16.5$, $p < 0.001$) than those without COPD, also seen in patients with AF ($36.8 \pm 16.1$ mmHg vs. $41.5 \pm 16.3$), $p < 0.001$) and in patients with HF ($38.8 \pm 15.9$ vs. $43.2 \pm 14.5$ mmHg, $p < 0.001$). Further phenotyping of patients by flow and gradient status showed that patients with AF and COPD more frequently had a LF-LG pEF phenotype. On the other hand, patients with HF had more cLF-LG AS phenotype. Cardiac damage staging was available in 3171 patients and showed that there was no difference in staging for patients with and without COPD. In contrast, patients with AF or HF more frequently had higher

**TABLE 1** | Baseline characteristics and outcomes.

| | N | |
|---|---|---|
| Baseline characteristics | | |
| Age *(years)* | 5173 | 81.5 (6.6) |
| Sex *(women)* | 5173 | 2572 (49.7) |
| NYHA III or IV | 5173 | 3599 (69.6) |
| AV Mean Gradient *(mmHg)* | 4966 | 40.0 (16.4) |
| Flow Type‡ | 3595 | |
| HG-AS | | 2056 (57.2) |
| cLF-LG | | 343 (9.5) |
| LF-LG pEF | | 820 (22.8) |
| NF-LG | | 375 (10.4) |
| Cardiac damage stage | 3171 | |
| Stage 0 | | 103 (3.2) |
| Stage 1 | | 338 (10.7) |
| Stage 2 | | 1192 (37.6) |
| Stage 3 | | 629 (19.8) |
| Stage 4 | | 908 (28.6) |
| COPD | 5168 | 656 (12.7) |
| Atrial fibrillation | 5173 | 1698 (32.8) |
| Heart failure | 1376 | 369 (26.8) |
| Outcomes | | |
| 1-year outcomes | | |
| Lack of symptom improvement | 4687 | 1295 (27.6) |
| NYHA | 4221 | |
| I | | 2173 (51.5) |
| II | | 1617 (38.3) |
| III | | 386 (9.1) |
| IV | | 43 (1.0) |
| Adverse events | 5173 | 814 (15.7) |
| Mortality *(CV)* | 5173 | 500 (9.7) |
| Stroke | 5173 | 287 (5.5) |
| HF hospitalisation | 1376 | 111 (8.1) |
| Combined outcome | 3730 | 563 (15.1) |
| 5-year outcomes§ | | |
| Mortality *(all-cause)* | 740 | 305 (41.2) |
| HF hospitalisation | 740 | 195 (26.3) |

*Note:* Values are shown as n (%) for categorical variables and mean ± (SD) or median [IQR] for continuous variables.
Abbreviations: AV, Aortic Valve; CV, cardiovascular death; COPD, chronic obstructive pulmonary disease; HF, heart failure; NYHA, New York Heart Association.
*A *p* value of $< 0.05$ was considered as statistically significant. ‡Flow type: high gradient (HG): aortic valve mean gradient > 40 mmHg, classical low-flow low-gradient (cLF-LG): LVEF < 50 and stroke volume index (Svi)< 35. LF-LG with preserved ejection fraction (pEF): LVEF > 50, SVI < 35, normal flow low-gradient, NF-LG: SVI > 35. §Long term outcomes only available in UMCG Cohort.

**TABLE 2** | Baseline characteristics and outcomes per comorbidity.

| | COPD | | | Atrial fibrillation | | | Heart failure | | |
|---|---|---|---|---|---|---|---|---|---|
| **n** | **No 4513** | **Yes 656** | ***p* value** | **No 3475** | **Yes 1698** | ***p* value** | **No 1009** | **Yes 369** | ***p* value** |
| Baseline | | | | | | | | | |
| NYHA class III/IV | 3088 (68.4) | 507 (77.3) | **< 0.001*** | 2329 (67.0) | 1270 (74.8) | **< 0.001*** | 825 (81.8) | 334 (90.5) | **< 0.001*** |
| AV mean gradient | 40.3 (16.5) | 37.3 (14.9) | **< 0.001*** | 41.5 (16.3) | 36.8 (16.1) | **< 0.001*** | 43.2 (14.5) | 38.8 (15.9) | **< 0.001*** |
| Flow type[a] | | | **< 0.001*** | | | **< 0.001*** | | | **< 0.001*** |
| HG-AS | 1828 (58.9) | 226 (46.5) | | 1497 (61.5) | 559 (48.2) | | 202 (46.4) | 82 (40.6) | |
| cLF-LG | 288 (9.3) | 55 (11.3) | | 205 (8.4) | 138 (11.9) | | 48 (11.0) | 57 (28.2) | |
| LF-LG pEF | 669 (21.5) | 151 (31.1) | | 498 (20.5) | 322 (27.8) | | 159 (36.6) | 45 (22.3) | |
| NF-LG | 321 (10.3) | 54 (11.1) | | 235 (9.7) | 140 (12.1) | | 26 (6.0) | 18 (8.9) | |
| Cardiac damage | | | 0.142 | | | **< 0.001*** | | | **< 0.001*** |
| Stage 0 | 90 (3.4) | 13 (2.7) | | 103 (5.2) | 0 (0.0) | | 20 (4.7) | 1 (0.4) | |
| Stage 1 | 290 (10.8) | 47 (9.8) | | 338 (17.1) | 0 (0.0) | | 35 (8.3) | 13 (5.6) | |
| Stage 2 | 1023 (38.1) | 168 (35.0) | | 729 (36.8) | 463 (38.9) | | 154 (36.5) | 74 (31.6) | |
| Stage 3 | 537 (20.0) | 91 (19.0) | | 363 (18.3) | 266 (22.4) | | 49 (11.6) | 18 (7.7) | |
| Stage 4 | 746 (27.8) | 161 (33.5) | | 448 (22.6) | 460 (38.7) | | 164 (38.9) | 128 (54.7) | |
| 1-year outcomes | | | | | | | | | |
| Lack of symptom improvement[b] | 1087 (26.6) | 208 (35.4) | **< 0.001*** | 798 (25.1) | 497 (33.0) | **< 0.001*** | 244 (24.3) | 123 (33.4) | **< 0.001*** |

*Note:* Values are shown as n (%) for categorical variables and mean ± (SD) for continuous variables.
Abbreviations: AV, Aortic valve; COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association.
*A $p$ value of $< 0.05$ was considered as statistically significant.
[a]Flow type: high gradient (HG): aortic valve mean gradient > 40 mmHg, classical low-flow low-gradient (cLF-LG): LVEF < 50 and stroke volume index (Svi)< 35. LF-LG with preserved ejection fraction (pEF): LVEF > 50, SVI < 35, normal flow low-gradient, NF-LG: SVI > 35.
[b]Crude outcome rates.

stages of cardiac damage. Stage 4 cardiac damage was seen in 460/1698 (38.7%) patients with AF, versus 448/3475 (22.6%) in patients without AF. This difference was even more pronounced in patients with HF, as 128/369 (54%) patients had stage 4 cardiac damage, versus 164/1009 (38.9%) in patients without HF.

After 1 year follow-up, 35.4% (208/656) of patients with COPD did not improve in symptoms, versus 26.6% (1087/4513) without COPD, $p < 0.001$, and a similar trend was seen in patients with AF (33.0% (497/1698) vs. 25.1% (798/3475), $p < 0.001$), and in patients with HF, (33.4% (123/369) vs. 24.3% (244/1009), $p < 0.001$) (Table 2).

Patients with lack of symptom improvement had higher comorbidity rates compared to those with symptom improvement (Table 3). Patients with lack of symptom improvement were older (81.3 years old (6.6) in patients with symptom improvement vs. 81.8 years (6.66) with lack of symptom improvement, $p = 0.024$), had a lower mean gradient (41.2 (16.5) vs. 37.7 (15.7), $p < 0.001$), and more often a LF-LG pEF status (505 (21.2%) vs. 236 (27.9%), higher cardiac damage stage ($p < 0.001$), more often stage 4 (564 (26.4%) vs. 272 (33.3%)), and higher rates of COPD (379 (11.2%) vs. 208 (16.1%), $p < 0.001$), AF (1007 (29.7%) vs. 497 (38.4%), $p < 0.001$) and HF (245 (24.3%) vs. 123 (33.5%), $p < 0.001$). Interestingly, patients with lack of symptom improvement less often had a NYHA III or IV (2593 (76.5%) vs. 702 (54.2%), $p < 0.001$).

Without adjustment, a history of COPD (Odds Ratio (OR) 1.52 (95% Confidence interval (CI): 1.26–1.82), $p < 0.001$), a history of AF (OR: 1.47 (1.29–1.68, $p < 0.001$), and a history of HF (OR: 1.57 (95%: 1.21–2.03), $p < 0.001$) were associated with lack of symptom improvement (Figure 1, Table 4). While after adjusting for sex, age, NYHA class, other comorbidities, cardiac damage and flow-type, a history of COPD and HF were still associated with lack of symptom improvement (COPD: 1.75 (1.10–2.75), $p = 0.017$ and HF: 1.63 (1.03–2.58), $p = 0.038$), a history of AF was not (1.12 (0.71–1.74), $p = 0.629$).

During long-term follow-up, patients with COPD had a higher risk of mortality after 5-year (HR: 1.53 (95% CI: [1.20–1.94], $p < 0.001$), which was also seen in patients with AF (HR: 1.59 [1.26–1.99], $p < 0.001$), and HF (HR: 1.36 [1.08–1.72], $p = 0.093$) (all unadjusted) (Supporting Information: Table S3 and Figure 2). The same trend was seen for HF hospitalisations after 5-year follow-up in patients with AF (HR: 1.63 [1.23–2.17], $p < 0.001$) and HF (HR: 1.83 [1.38–2.42], $p < 0.001$), but this was not seen in patients with COPD (HR: 1.24 [0.91–1.69], $p = 0.180$) (all unadjusted) (Supporting Information: Table S4).

## 4 | Discussion

The most important findings of this retrospective, multicentre, European, observational cohort of patients undergoing TAVI for symptomatic AS were that patients with a concomitant symptom-associated comorbidity: (1) have higher NYHA class,

**TABLE 3** | Baseline characteristics by symptomatic improvement outcome.

| | Lack of symptom improvement | | |
|---|---|---|---|
| | No $N = 3390$ | Yes $N = 1295$ | *p*-value |
| Age *(years)* | 81.3 (6.6) | 81.8 (6.6) | **0.024*** |
| Sex *(women)* | 1728 (51.0%) | 635 (49.0%) | 0.248 |
| NYHA III or IV | 2593 (76.5%) | 702 (54.2%) | **< 0.001*** |
| AV Mean Gradient *(mmHg)* | 41.2 (16.5) | 37.7 (15.7) | **< 0.001*** |
| Flow Type | | | **< 0.001*** |
| HG-AS | 1439 (60.5%) | 411 (48.5%) | |
| cLF-LG | 221 (9.29%) | 86 (10.2%) | |
| LF-LG pEF | 505 (21.2%) | 236 (27.9%) | |
| NF-LG | 215 (9.03%) | 114 (13.5%) | |
| Cardiac damage stage | | | **< 0.001*** |
| Stage 0 | 67 (3.14%) | 31 (3.80%) | |
| Stage 1 | 255 (11.9%) | 66 (8.09%) | |
| Stage 2 | 839 (39.3%) | 289 (35.4%) | |
| Stage 3 | 409 (19.2%) | 158 (19.4%) | |
| Stage 4 | 564 (26.4%) | 272 (33.3%) | |
| COPD | 379 (11.2%) | 208 (16.1%) | **< 0.001*** |
| Atrial fibrillation | 1007 (29.7%) | 497 (38.4%) | **< 0.001*** |
| Heart failure | 245 (24.3%) | 123 (33.5%) | **0.001*** |

*Note:* Values are shown as n (%) for categorical variables and mean ± (SD) or median [IQR] for continuous variables.
Abbreviations: AV, Aortic valve; CV, cardiovascular death; COPD, chronic obstructive pulmonary disease; HF, heart failure; NYHA, New York Heart Association.
*A $p$ value of $< 0.05$ was considered as statistically significant. ‡ Flow type: high gradient (HG): aortic valve mean gradient > 40 mmHg, classical low-flow low-gradient (cLF-LG): LVEF < 50 and stroke volume index (Svi)< 35. LF-LG with preserved ejection fraction (pEF): LVEF > 50, SVI < 35, normal flow low-gradient, NF-LG: SVI > 35. § Long term outcomes only available in UMCG Cohort.

(2) have lower mean gradient and more low-flow low gradient status, (3) have higher cardiac damage stage, (4) are less likely to improve in NYHA class 1-year after TAVI and (5) have higher rates of mortality and HF hospitalisations during 5-year follow-up.

A substantial percentage of patients undergoing TAVI have concomitant comorbidities that could also cause symptoms. Previous literature shows widely varying rates of these comorbidities, depending on country and indication of TAVI, and this variation is reflected in the different cohorts of this study [5, 16, 17]. At the time of the procedure, most patients have NYHA class III or IV, a direct result of current guidelines, in which symptoms are essential for the TAVI indication [4].

Patients with at least one of the comorbidities had a higher NYHA class at baseline than those without. In AS, an increased afterload results in left ventricular hypertrophy and stiffening of the left ventricular walls, causing left ventricular diastolic dysfunction, ultimately causing left atrial dilation. So, the higher NYHA class can be a direct reflection of advanced (symptomatic) HF or decompensated AS. On the other hand, it is known that AF itself causes dyspnea in combination with severe AS and the pathophysiological process of AS leading to left atrial dilation is associated with higher rates of AF itself [18]. In patient with COPD, poorer exercise tolerance could overestimate the NYHA class, especially in combination with HF [19, 20].

Interestingly, patients with a comorbidity tend to have a lower mean aortic valve gradient at baseline, with a higher NYHA class. One explanation is that these patients get symptoms at a lower mean gradient, because symptoms are not caused by AS but the comorbidity instead. Alternatively, one could hypothesize that symptoms do come from AS but are manifest earlier due to the presence of comorbidities. In addition, it is known that patients with a low-flow type of AS often have comorbidities such as AF or COPD, and a significant group has HF [21]. In the current study, patients with COPD more often had LF-LG pEF compared to those without COPD, and the same held true for patients with AF. Patients with HF on the other hand, had more classical LF-LG than those without HF. It could be postulated that this low-flow status resulted from the comorbidity and thus indicated indeed a lower severity of AS. Alternatively, the low flow status could reflect an underestimated AS and a more advanced stage of the disease, due to lower cardiac output, lower flow and thus a lower gradient [7]. Having AF results in a low-flow status on its own, and the arrhythmic conditions lead to further lowering of the stroke volume [22]. The combination of cLF-LG, with AF and COPD has shown to predict for lack of symptom improvement before, and this combination of comorbidities and low-flow AS can represent patients with a difficult-to-treat overlap syndrome of HFpEF, AF and AS [21, 23, 24]. In addition, COPD exacerbations or treatment could even trigger AF, further underscoring the complex interplay between these comorbidities [25].

While patients with COPD showed no difference compared to patients without COPD in cardiac damage stage, patients with HF and AF had higher rates of cardiac damage stage 3 or 4. The latter might not be surprising, as a history of AF is part of the classification system and results in at least stage 2 cardiac damage. The difference in staging in patients with AF (and also HF patients) was most predominant in stage 4, indicating right sided HF and thus possibly a higher severity of AS where a TAVI procedure cannot resolve all of the extensive cardiac damage. In addition, it is known that patients with higher cardiac damage stage persist in this higher stage of damage [26]. However, the higher cardiac damage stage does not correlate with symptoms, as the latter can be attributable to a comorbidity [7, 8, 27]. Patients with COPD or AF were less likely to show improvement in symptoms 1 year after the procedure, in line with previous reports [2, 19]. In addition, patients that did not improve in symptoms had higher rates of all comorbidities, together with a higher cardiac damage stage and more often a LF-LG pEF status. Interestingly, they had a lower NYHA III/IV class compared to those with improvement in symptoms, possibly because patients with a higher NYHA class at baseline are more prone to improve in symptoms, known as regression to the mean. The higher rate of lack of symptom improvement in

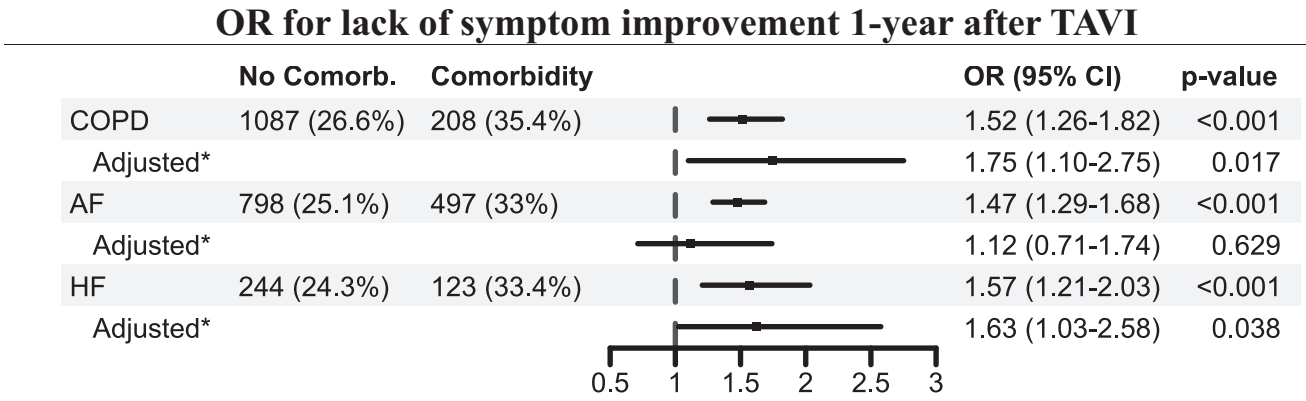


**FIGURE 1** | Forest plot for lack of symptom improvement. Odds Ratios (OR) for lack of symptom improvement, 1-year after TAVI. *Adjusted for sex, age, NYHA class pre-TAVI, AF and/or COPD and cardiac damage and flow-type. A $p$ value of $< 0.05$ was considered as statistically significant. AF, Atrial fibrillation; COPD, chronic obstructive pulmonary disease; HF, heart failure; NYHA, New York Heart Association.

**TABLE 4** | Association of comorbidities and lack of symptom improvement.

| | | | | | |
|---|---|---|---|---|---|
| A | **COPD** | | | | |
| | | | **N** | **OR** (95% CI) | ***p* value** |
| | Crude OR | | 4681 | 1.52 (1.26–1.82) | **< 0.001*** |
| | **Adjusted** | Sex, age, NYHA, AF, cohort | 4681 | 1.87 (1.53–2.27) | **< 0.001*** |
| | | Sex, age, NYHA, AF, cohort, HF | 1374 | 1.56 (1.11–2.17) | **0.009*** |
| | | Sex, age, NYHA, AF, cohort, cardiac damage, flow-type | 2456 | 2.00 (1.54–2.58) | **< 0.001*** |
| | | Sex, age, NYHA, AF, cardiac damage, flow-type, HF | 569 | 1.75 (1.10–2.75) | **0.017*** |
| B | **Atrial fibrillation** | | | | |
| | | | **N** | **OR** (95% CI) | ***p* value** |
| | Crude OR | | 4681 | 1.47 (1.29–1.68) | **< 0.001*** |
| | **Adjusted** | Sex, age, NYHA, COPD, cohort | 4681 | 1.62 (1.41–1.86) | **< 0.001*** |
| | | Sex, age, NYHA, COPD, cohort, HF | 1374 | 1.40 (1.07–1.83) | **0.013*** |
| | | Sex, age, NYHA, COPD, cohort, cardiac damage, flow-type | 2456 | 1.29 (1.05–1.58) | **0.015*** |
| | | Sex, age, NYHA, COPD, cardiac damage, flow-type, HF | 569 | 1.12 (0.71–1.74) | 0.629 |
| C | **Heart failure** | | | | |
| | | | **N** | **OR** (95% CI) | ***p* value** |
| | Crude OR | | 1374 | 1.57 (1.21–2.03) | **0.001*** |
| | **Adj.** | Sex, age, NYHA, COPD, AF, cohort | 1374 | 1.94 (1.47–2.58) | **< 0.001*** |
| | | Sex, age, NYHA, COPD, AF, cardiac damage, flow-type | 569 | 1.63 (1.03–2.58) | **0.038*** |

*Note:* Odds Ratios (OR) for lack of symptom improvement, 1-year after TAVI. (A) OR for history of COPD and lack of symptom improvement, (B) OR for history of AF and lack of symptom improvement, (C) OR for history of COPD and lack of symptom improvement.
Abbreviations: AF, Atrial fibrillation; COPD, chronic obstructive pulmonary disease; HF, heart failure; NYHA, New York Heart Association.
*A $p$ value of $< 0.05$ was considered as statistically significant.

patients with one of the comorbidities persisted even after adjusting for flow-type and cardiac damage staging, COPD and HF, corroborating the idea that the initial symptoms were caused by the comorbidity. Another explanation for the lack of symptom improvement might be worsening (or persistence) of symptoms due to COPD exacerbation, AF progression, AF-related stroke, or HF hospitalisation, again not necessarily related to AS.

Patients with one of the comorbidities had higher rates of mortality and HF hospitalisations during a longer-term follow-up of up to 5-years. COPD has shown to predict for long-term mortality in patients undergoing TAVI before [28]. In AF, the higher rates of long-term adverse events might be contributable to the reduced ventricular filling by the loss of systolic atrial contraction, or tachycardia induced cardiomyopathy or complications associated by AF, such as CVA [29]. For patients with

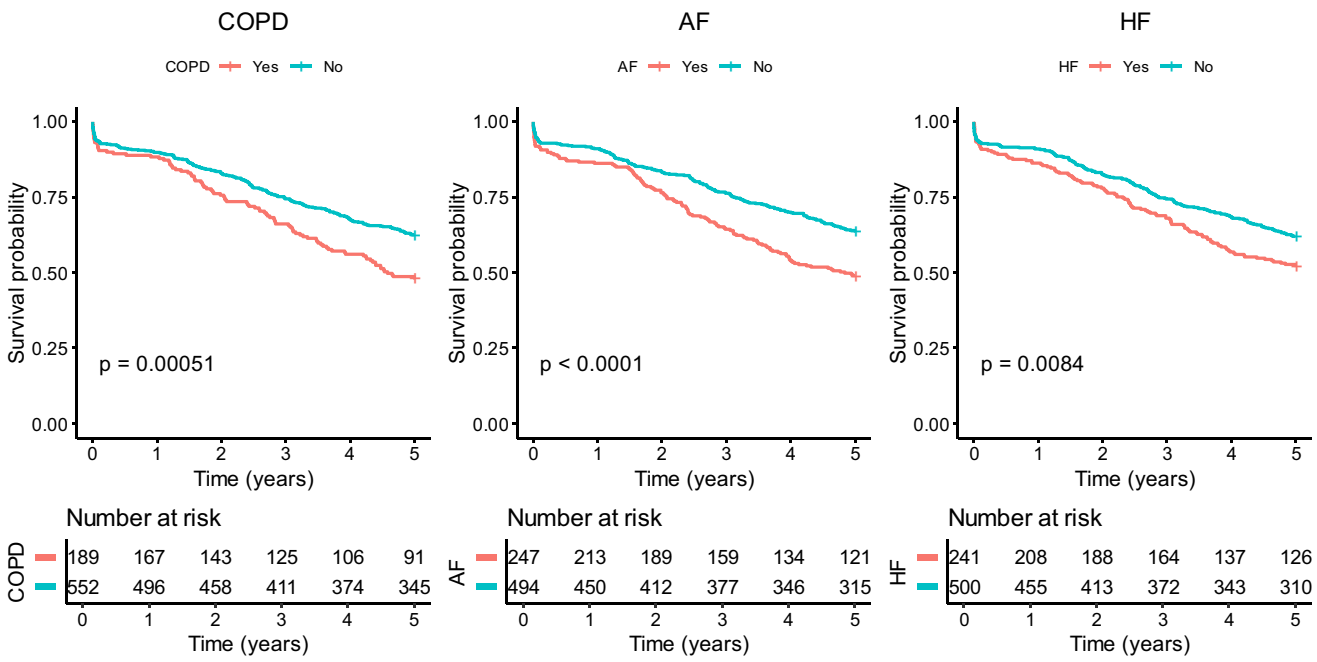


**FIGURE 2** | Kaplan Meier curves for comorbidities and long-term mortality. Kaplan Meier (KM) Curves for cardiovascular mortality 5-year after TAVI, in the Groningen cohort only. A $p$ value of $< 0.05$ was considered as statistically significant. AF, Atrial fibrillation; COPD, chronic obstructive pulmonary disease; HF, heart failure; NYHA, New York Heart Association. [Color figure can be viewed at wileyonlinelibrary.com]

HF undergoing TAVI, it is known that they have higher mortality rates, in line with higher (re-)hospitalisation rates in a general HF population [30]. The findings of higher rates of long-term adverse events in patients with COPD, AF or HF supports the hypothesis that the complaints of these patients are not only contributable to the AS, but the comorbidity, and careful assessment of these patients is thus needed.

## 5 | Implications

Symptom improvement is one of the most important outcomes for the predominantly older TAVI population. While it is known that symptoms before the procedure can be caused by other (concomitant) comorbidities, once a patient develops symptoms together with a severe AS on echocardiography, a TAVI procedure is indicated [4]. AS and other symptom-associated comorbidities are closely related and share similar pathophysiological mechanisms and symptoms, making differentiation difficult. Based on current analysis in three large single-centre cohorts, patients with concomitant AS and COPD, AF or HF, have worse outcomes after TAVI. These patients may need closer monitoring and evaluation of symptoms. They should be treated with optimal, (medical) treatment before and after the procedure, to avoid adverse events [3].

## 6 | Limitations

Due to its retrospective observational nature, the symptomatic outcomes were non-standardised and assessed by different clinicians in different hospitals. Patient-reported outcomes should be included in future research. Moreover, while we corrected for sex, age, and NYHA class, at baseline, together with cardiac damage stage and AS type, we did not correct for other factors that might interact with the outcomes, like patient prosthesis mismatch or paravalvular regurgitation and there is a risk of residual confounding. Lastly, due to different indications in national guidelines, results may not apply to other, (non-) European cohorts. However, the association between co-morbidities and outcomes was also found within different cohorts, demonstrating the generalisability of the findings.

## 7 | Conclusion

Patients with symptomatic AS undergoing TAVI might have an alternative explanation for their symptoms, such as COPD, AF or HF. These patients undergo TAVI at a lower severity of AS and a higher cardiac damage stage and have higher symptomatic burden before the procedure. However, they show less symptom improvement 1 year after TAVI and higher mortality and HF hospitalisation rates during 5-year follow-up. The contribution of these comorbidities to symptoms of a patient referred for TAVI should be carefully assessed to select those patients with the greatest likelihood of symptom improvement after TAVI.


### Acknowledgments

The authors would like to especially thank Ineke Cruining-Krijnen, Franz Hanenburg and Otto Bosma for their help in collecting data on symptom status. This work was supported by an unrestricted research grant from Medtronic and Us2.ai to the University Medical Center Groningen (UMCG).

## Conflicts of Interest

Jasper Tromp is supported by the National University of Singapore Start-up grant, the tier 1 grant from the Ministry of Education and the CS-IRG New Investigator Grant from the National Medical Research Council; has received research support from AstraZeneca and consulting or speaker fees from Us2.ai, and owns patent US-10702247-B2 unrelated to the present work. Yoran M. Hummel received contracts from US2.ai as employee. Wouter Ouwerkerk received consulting fees from US2.ai as medical advisor. Thomas Pilgrim reports research grants from the Swiss National Science Foundation, the Swiss Heart Foundation, the Swiss Polar Institute, and the Bangerter-Rhyner Foundation. Research, travel or educational grants to the institution without personal remuneration from Biotronik, Boston Scientific, Edwards Lifesciences, and ATSens; speaker fees and consultancy fees to the institution from Biotronik, Boston Scientific, Edwards Lifesciences, Abbott, Medtronic, Biosensors, and Highlife. Stephan Windecker reports Research, travel or educational grants to the institution from Abbott, Abiomed, Amgen, Astra Zeneca, Bayer, Bbraun, Biotronik, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, Cardinal Health, CardioValve, Cleerly Inc., Cordis Medical, Corflow Therapeutics, CSL Behring, Daiichi Sankyo, Edwards Lifesciences, Farapulse Inc. Fumedica, GE Medical Systems, Gebro Pharma, Guerbet, Idorsia, Inari Medical, InfraRedx, Janssen-Cilag, Johnson & Johnson, Medalliance, Medicure, Medtronic, Merck Sharp & Dohm, Miracor Medical, Neucomed, Novartis, Novo Nordisk, Organon, OrPha Suisse, Pharming Tech, Pfizer, Philips AG, Polares, Regeneron, Sanofi-Aventis, Servier, Siemens Healthcare, Sinomed, SMT Sahajanand Medical Technologies, Terumo, Vifor, V-Wave, Zoll Medical. He is Advisory board member and/or member of the steering/executive group of trials funded by Abbott, Abiomed, Amgen, Astra Zeneca, Bayer, Boston Scientific, Biotronik, Bristol Myers Squibb, Edwards Lifesciences, MedAlliance, Medtronic, Novartis, Polares, Recardio, Sinomed, Terumo, and V-Wave with payments to the institution but no personal payments. Matteo Pagnesireportspersonal fees from AstraZeneca, Abbott Vascular, Boehringer Ingelheim, Novartis, Roche Diagnostics and Vifor Pharma. Mariana Adamo reports consulting fees from Abbott Vascular and Edwards Lifesciences. Dr. Voors received research grants from AnaCardio, Bayer, BMS, Boehringer Ingelheim, Corteria, Cytokinetics, Eli Lilly, Merck, Novartis, Novo Nordisk, Roche Diagnostics, Pfizer and Moderna and consulting fees from AnaCardio, Bayer, BMS, Boehringer Ingelheim, Corteria, Cytokinetics, Eli Lilly, Merck, Novartis, Novo Nordisk and Roche Diagnostics. Dr. Wykrzykowska received research grants from Medtronic and US2.ai and consulting fees from BSC, Abbot, Meril, Medtronic, Novo Nordisk, SMT, Sinomed and Medis. The other authors declare no conflicts of interest.

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## Supporting Information

Additional supporting information can be found online in the Supporting Information section.