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Transcatheter aortic valve replacement in patients with concomitant mitral stenosis

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Aims Multivalvular disease is of increasing concern in elderly patients undergoing transcatheter aortic valve replacement (TAVR). The objective of the present analysis was to investigate the impact of concomitant mitral stenosis (MS) on clinical outcomes in patients undergoing TAVR for severe, symptomatic aortic stenosis (AS).

Methods and results Among 1339 patients undergoing TAVR between August 2007 and December 2015, adequate echocardiographic data for the assessment of severity and aetiology of MS was available in 971 (72.5%) patients. Patients were stratified according to degree and aetiology of concomitant MS. Mitral stenosis was documented in 176 (18.1%) TAVR patients (mean mitral valve area 1.9 ± 0.4 cm^2) and considered degenerative in 110 (62.5%) and rheumatic in 66 (37.5%) patients, respectively. Mitral stenosis was categorized as moderate/severe in 28 patients (2.9%). Baseline characteristics were comparable between patients with vs. without MS. At 1 year, patients with MS were at increased risk of cardiovascular death [36 (21.4%) vs. 66 (8.7%); adjusted hazard ratio (HR_{adj}) 3.64, 95% confidence interval (CI) 2.38–5.56] and disabling stroke [12 (7.1%) vs. 23 (3.0%); HR_{adj} 2.98, 95% CI 1.46–6.09] as compared to patients without MS. Differences in cardiovascular death and disabling stroke emerged within 30 days of the index procedure and were largely driven by a difference in patients with rheumatic MS [cardiovascular death: 7 (10.6%) vs. 24 (3.2%), HR_{adj} 4.80, 95% CI 1.98–11.6; disabling stroke: 4 (6.1%) vs. 16 (2.0%), HR_{adj} 4.18, 95% CI 1.34–13.0].

Conclusion Concomitant MS was documented in approximately one-fifth of patients undergoing TAVR for severe, symptomatic AS and associated with a three-fold increased risk of cardiovascular adverse events at 1 year. The difference emerged early and was largely driven by patients with rheumatic MS.

Keywords Aortic stenosis • Mitral stenosis • Transcatheter aortic valve replacement • Echocardiography • Clinical outcomes

Introduction

Multivalvular disease has been documented in more than one-third of patients with a diagnosis of valvular heart disease and imposes unique challenges with respect to diagnosis and treatment.[1] Concomitant valvular disease is of increasing concern in elderly patients with severe, symptomatic aortic stenosis (AS) undergoing transcatheter aortic valve replacement (TAVR).

The impact of mitral valve disease among patients undergoing TAVR has been investigated in various contexts. A multicentre analysis showed comparable mortality in patients undergoing TAVR irrespective of the presence of a prosthetic mitral surgical valve.[2] Conversely, the presence of mitral annular calcification (MAC) has been associated with adverse outcomes among patients undergoing TAVR.[3] Recently, an analysis from the Society of Thoracic Surgeons (STS)/American College of Cardiology (ACC) Transcatheter Valve

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Therapies (TVT) Registry reported a prevalence of mitral stenosis (MS) in 11.6% of patients undergoing TAVR, and found an association of severe MS with increased mortality rates.[4] In the absence of echocardiographic details on MS the analysis did not address the impact of disease aetiology on clinical outcome. Therefore, the objective of the present analysis was two-fold: first, to investigate the impact of concomitant MS on clinical outcomes in patients undergoing TAVR for AS; and second, to analyse whether the aetiology of MS has a differential impact on clinical outcomes.

Methods

Study design

The present analysis is a retrospective analysis of prospectively acquired echocardiographic data, and forms part of the Swiss transcatheter aortic valve implantation (TAVI) registry, a prospective registry of consecutively enrolled patients undergoing TAVR in Switzerland (ClinicalTrials.gov NCT01368250).

Patient population

All patients with severe AS undergoing TAVR between August 2007 and December 2015 at Bern University Hospital, Switzerland, were eligible for inclusion into the present study. Patients were excluded for the purpose of the present analysis in case TAVR was performed for an indication other than AS, if non-Confédération Européenne-marked devices were used, and in the absence of echocardiographic raw data within a time window of 3 months prior to TAVR. Furthermore, patients with a prosthetic mitral valve and patients with a poor acoustic window that did not allow for a reliable assessment of the mitral valve were excluded. The Bern TAVI registry has been approved by the local ethics committee. All patients provided written informed consent for participation in the registry.

Assessment of mitral stenosis

All subjects underwent transthoracic and/or transoesophageal echocardiography by a board-certified cardiologist with a Philips iE33 machine (Philips Healthcare, Andover, MA, USA). Acquired images were transferred to a workstation for offline analysis (Syngo Dynamics Workplace, version 9.5, Siemens Medical Solutions, Inc., PA, USA) in the Corelab and re-evaluated by an independent second reader. At least three consecutive heartbeats were averaged for the accurate measurement of echocardiographic parameters. All echocardiographic assessments were performed in accordance with the current guidelines of the European Society of Cardiology/European Association for Cardio-Thoracic Surgery.[5] Degree and aetiology of MS were assessed in all patients by the use of 2- or 3-dimensional echocardiography. First, valve anatomy was evaluated by visual assessment using parasternal short- and long-axis view, and apical two-chamber view. In line with the American Society of Echocardiography/European Association of Echocardiography guidelines, mean gradient (mild <5 mmHg, moderate 5–10 mmHg, and severe >10 mmHg) and valve area (normal >2.5 cm^2, mild 1.5–2.5 cm^2, moderate 1.0–1.5 cm^2, and severe <1.0 cm^2) by the use of pressure half-time or planimetry were used for the classification of the severity of MS.[6] In patients suspected to have MS based on visual assessment of the mitral apparatus and/or increased transmitral gradients (MGs), mitral valve area (MVA) by planimetry was prioritized over MVA calculated by pressure half-time. Conversely, in patients with no signs of MS, MVA was estimated using pressure half-time. In patients with MS, the aetiology was categorized as rheumatic, degenerative, or congenital MS, respectively.[6] Rheumatic MS was recorded in the presence of commissural fusion, chordal shortening and fusion, and leaflet thickening, or restricted leaflet motion due to extensive calcification. Degenerative MS was recorded in case of annular calcification in combination with leaflet thickening and/or calcification, and restriction of leaflet motion without commissural fusion (*Figure 1*). Congenital MS was documented in case of MS in combination with abnormalities of the sub-valvular apparatus.

Transcatheter aortic valve replacement procedure

Transcatheter aortic valve replacement was performed by transfemoral access unless prohibited by peripheral vascular disease. Transapical and transsubclavian TAVR were performed as the preferred alternative access routes. Device selection was based on careful anatomical assessment of the aortic valvular complex using computed tomography (CT) angiography and peri-procedural management was left to the discretion of the operator. Post-procedural care included rhythm monitoring for at least 48 h after the intervention, laboratory testing, and 12-lead electrocardiograms directly after the procedure as well as daily thereafter. Transthoracic echocardiography was performed prior to discharge.

Clinical follow-up and endpoint assessment

Clinical follow-up data at 30 days and 1 year were obtained by standardized interviews, documentation from referring physicians, and hospital discharge summaries. All adverse events were systematically collected and adjudicated by an independent clinical event adjudication committee according to the Valve Academic Research Consortium (VARC)-2 criteria.[7] The primary endpoint of the present analysis was cardiovascular death within 1 year after TAVR. Secondary endpoints included the combined endpoint major adverse cardiac and cerebrovascular events, as well as its individual components all-cause mortality, disabling stroke, and myocardial infarction at 30 days and at 1 year. Life-threatening and major bleeding, kidney injury (Stage 3), and major access site complications were assessed at 30-day follow-up.

Statistical analysis

Patients with concomitant MS were compared with patients with isolated AS. All continuous measures are presented as mean ± standard deviation or median (interquartile range), and categorical variables were presented as frequency and percentages. Differences between groups were assessed using Student's *t*-test or Wilcoxon rank-sum test in case of continuous variables and the χ^2 or Fisher's exact test in case of categorical variables.

We used Cox proportional hazards model to calculate crude and adjusted hazard ratios (HRs_{adj}) and 95% confidence intervals (CIs) for the between-group comparisons of clinical outcomes. In all time-to-event analyses for each type of event, data for a patient were censored at the time of the first event that occurred in that patient. We performed univariate and multivariable analysis to assess predictive factors for cardiovascular death within 1 year. All variables with a *P*-value <0.1 in the univariate model were included in the multivariable prediction model. In a bootstrap analysis with 1000 replications, we validated our results with normal approximation, percentile-based and bias-corrected CIs. These variables were also used for the adjusted analysis of all time-to-event data and include baseline and echocardiographic variables such as age, diabetes mellitus, New York Heart Association classification III or IV, coronary artery disease, peripheral artery disease, atrial fibrillation, left ventricular ejection fraction (%), and STS score. All statistical tests were two-sided and *P*-values <0.05 were considered statistically significant. All analyses were performed using Stata 14.2 (StataCorp, College Station, TX, USA) and R version 3.4.3.

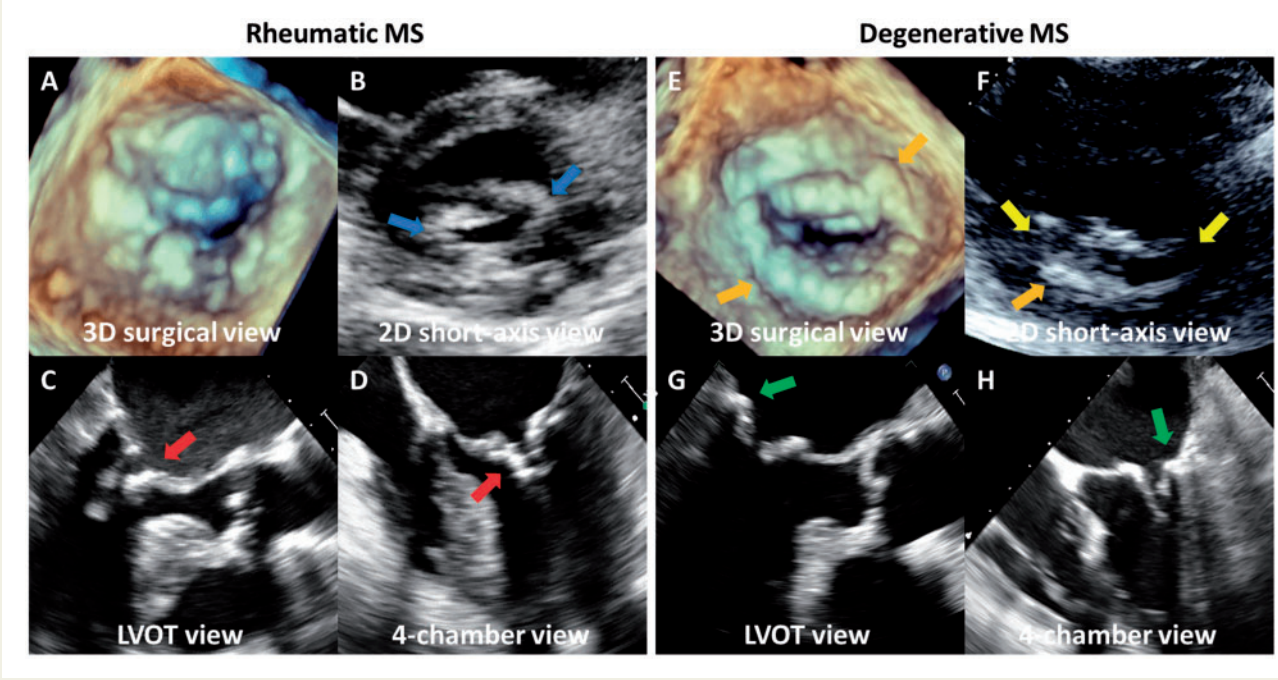


Figure 1 Echocardiographic still frames of patients with degenerative and rheumatic mitral stenosis. Rheumatic mitral stenosis is characterized by commissural fusion, chordal shortening and fusion, and leaflet thickening or restricted leaflet motion due to extensive calcification (*A–D*). Degenerative mitral stenosis is characterized by annular calcification in combination with leaflet thickening and/or calcification, and restriction of leaflet motion without commissural fusion (*E–H*). Blue arrows indicate commissural fusion. Red arrows indicate leaflet thickening due to extensive calcification. Orange arrows indicate mitral annular calcification. Yellow arrows indicate absence of commissural fusion. Green arrows indicate annular calcification in combination with leaflet calcification.

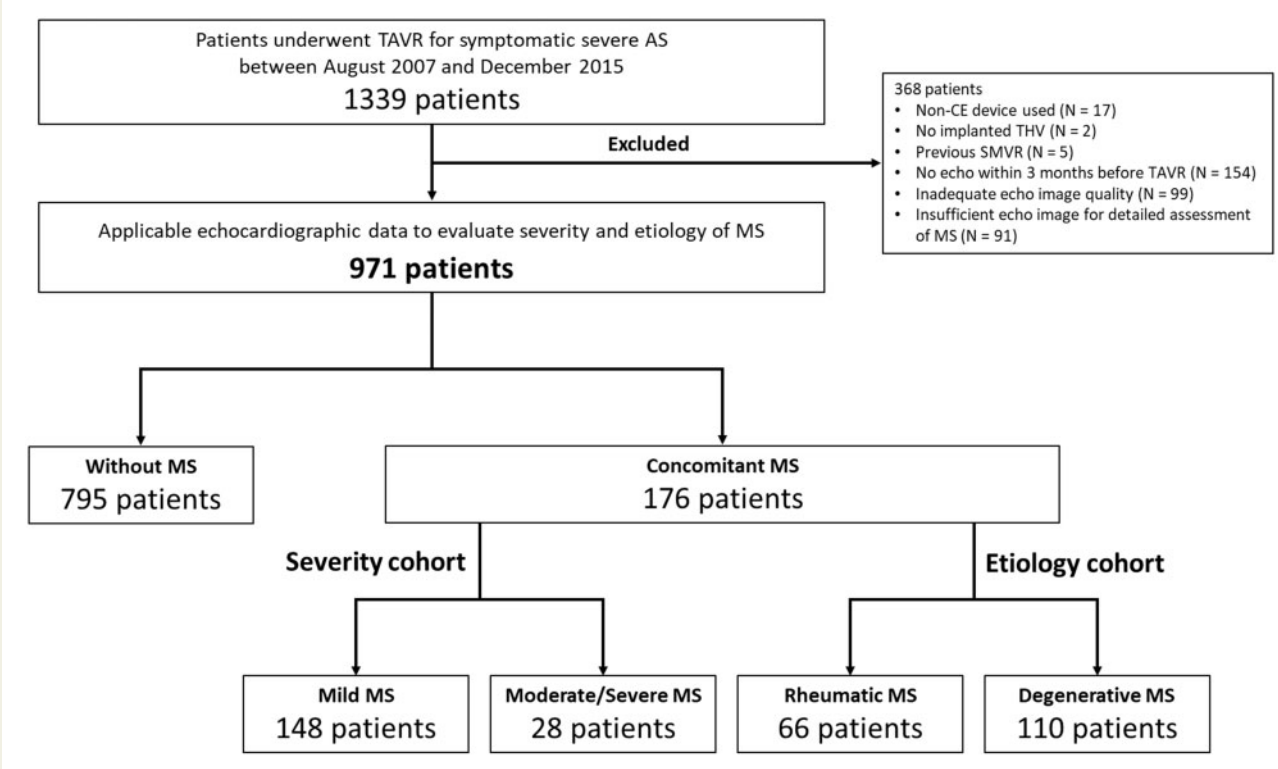


Figure 2 A flowchart of patients included in the present analysis.

Table 1 Baseline characteristics

	Overall (*N* = 971)	Without mitral stenosis (*N* = 795)	Concomitant mitral stenosis (*N* = 176)	*P*-value
Age (years)	82.2 ± 6.1	82.2 ± 6.1	82.5 ± 5.8	0.46
Female gender, *n* (%)	479 (49.3)	397 (49.9)	82 (46.6)	0.42
Body mass index (kg/m^2)	26.2 ± 5.1	26.2 ± 5.0	26.4 ± 5.6	0.66
Cardiac risk factors, *n* (%)				
Diabetes mellitus	246 (25.3)	197 (24.8)	49 (27.8)	0.40
Hypercholesterolaemia	612 (63.0)	517 (65.0)	95 (54.0)	0.006
Hypertension	817 (84.1)	674 (84.8)	143 (81.2)	0.25
Past medical history, *n* (%)				
Previous myocardial infarction	149 (15.3)	128 (16.1)	21 (11.9)	0.17
Previous PCI	252 (26.0)	208 (26.3)	43 (24.4)	0.61
Previous CABG	115 (11.8)	95 (11.9)	20 (11.4)	0.83
Previous stroke or TIA	90 (9.5)	74 (9.5)	16 (9.3)	0.93
Peripheral vascular disease	149 (15.3)	128 (16.1)	21 (11.9)	0.17
Chronic obstructive pulmonary disease	124 (12.8)	104 (13.1)	20 (11.4)	0.53
Renal failure (eGFR <60 mL/min/1.73 m^2)	696 (71.7)	574 (72.2)	122 (69.3)	0.44
Baseline cardiac rhythm, *n* (%)				
Atrial fibrillation	319 (32.9)	268 (33.7)	51 (29.0)	0.23
Permanent pacemaker	91 (9.4)	71 (8.9)	20 (11.4)	0.32
Symptoms, *n* (%)				
NYHA classification III or IV	648 (66.8)	532 (66.9)	116 (66.3)	0.87
CCS III or IV	92 (9.5)	79 (9.9)	13 (7.4)	0.30
Syncope	124 (12.8)	105 (13.2)	19 (10.8)	0.40
Risk assessment				
Logistic EuroSCORE (%)	20.5 ± 13.3	21.0 ± 13.6	18.2 ± 11.5	0.01
STS score (%)	6.0 ± 4.1	6.1 ± 4.1	5.9 ± 4.5	0.63
Laboratory values				
Brain natriuretic peptide (pg/mL)	327 (136–842)	343 (138–863)	285 (130–720)	0.35
Medications, *n* (%)				
Aspirin	616 (63.6)	507 (63.9)	109 (61.9)	0.62
Clopidogrel	176 (18.2)	146 (18.4)	30 (17.0)	0.67
Oral anticoagulation	230 (23.7)	188 (23.7)	42 (23.9)	0.96

Values are expressed as mean ± standard deviation where appropriate.
CABG, coronary artery bypass grafting; CCS, Canadian Cardiovascular Society; eGFR, estimate glomerular filtration rate; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; STS, Society of Thoracic Surgeons; TIA, transient ischaemic attack.

Results

Study population

Among 1339 consecutive patients undergoing TAVR, 971 patients (72.5%) had adequate echocardiographic data to assess the mitral valvular apparatus (*Figure 2*). Concomitant MS was documented in 176 (18.1%) patients of which 110 (62.1%) had degenerative and 67 (37.9%) rheumatic MS. Moderate or severe MS was present in 28 patients (2.9%) while 148 patients (15.2%) had mild MS. Demographic characteristics were comparable between patients with vs. without MS with the exception of a lower logistic EuroSCORE (18.2 ± 11.5% vs. 21.0 ± 13.6%, $P = 0.01$) and a lower rate of hypercholesterolaemia (54% vs. 65%, $P < 0.006$) in patients with concomitant MS (*Table 1*).

No significant differences were observed with respect to antithrombotic regimen at discharge between the two groups (Supplementary material online, *Table S1*).

Echocardiographic and computed tomographic assessment

Echocardiographic measurements are summarized in *Table 2*. Among patients with MS, the mean MVA and MG amounted to 1.93 ± 0.42 cm^2 and 3.6 ± 2.4 mmHg, respectively. Among the 28 patients with at least moderate MS (MVA 1.22 ± 0.25 cm^2, MG 6.1 ± 3.2 mmHg) 18 patients (64.3%) had a rheumatic, and 10 patients (35.7%) a degenerative aetiology. Patients with concomitant MS had a higher left ventricular ejection fraction (56.3 ± 14.7% vs.

Table 2 Echocardiographic characteristics

	Overall (*N* = 971)	Without mitral stenosis (*N* = 795)	Concomitant mitral stenosis (*N* = 176)	*P*-value
Aortic stenosis severity				
Aortic valve area (cm^2)	0.71 ± 0.24	0.72 ± 0.25	0.66 ± 0.21	0.044
Mean gradient (mmHg)	42.3 ± 18.0	41.5 ± 17.2	45.6 ± 21.1	0.01
Mitral valve apparatus				
Anatomical presentation, *n* (%)				
Normal	795 (81.9)	795 (100.0)	0 (0.0)	<0.001
Rheumatic	66 (6.8)	0 (0.0)	66 (37.5)	<0.001
Degenerative	110 (11.3)	0 (0.0)	110 (62.5)	<0.001
Congenital	0 (0.0)	0 (0.0)	0 (0.0)	
Mitral valve area by planimetry (cm^2)	—	NA	1.93 ± 0.42	
Mitral valve area by pressure half-time (cm^2)	—	4.37 ± 1.60	2.23 ± 1.14	
Mitral valve VTI (cm/s)	0.26 ± 0.11	0.24 ± 0.09	0.36 ± 0.16	<0.001
Mean gradient (mmHg)	2.0 ± 1.7	1.7 ± 1.3	3.6 ± 2.4	<0.001
Pressure half-time (ms)	67.6 ± 30.5	58.1 ± 20.2	110.6 ± 31.9	<0.001
LA volume index ($mL \cdot m^2$)	44.0 ± 21.3	43.0 ± 16.1	48.6 ± 36.1	0.002
LA spontaneous echo contrast, *n* (%)	156 (25.7)	104 (20.0)	52 (59.1)	<0.001
LV systolic function				
LV ejection fraction (%)	54.1 ± 14.9	53.7 ± 14.9	56.3 ± 14.7	0.04
Evaluation of valvular abnormality, *n* (%)				
Aortic regurgitation ≥moderate	105 (11.3)	93 (12.2)	12 (7.1)	0.06
Mitral regurgitation ≥moderate	187 (20.3)	165 (22.0)	22 (12.9)	0.008
Tricuspid regurgitation ≥moderate	144 (15.2)	122 (15.7)	22 (12.8)	0.33
Right-sided haemodynamics				
Pulmonary artery systolic pressure (mmHg)	45.9 ± 14.6	46.4 ± 15.0	44.0 ± 12.3	0.11
Mean pulmonary artery pressure (mmHg)	32.5 ± 12.1	32.9 ± 12.2	30.8 ± 11.6	0.10
Pulmonary hypertension, *n* (%)	510 (76.7)	421 (78.0)	89 (71.2)	0.11

Values are expressed as mean ± standard deviation where appropriate.
LA, left atrial; LV, left ventricle; NA, not applicable; VTI, velocity time integral.

53.7 ± 14.9%, $P = 0.04$) and a higher mean gradient across the aortic valve (45.6 ± 21.1 mmHg vs. 41.5 ± 17.2 mmHg, $P = 0.01$). Although patients with concomitant MS had significantly larger left atrium volume index (LAVi) as compared to patient with no MS (*Table 2*), there were no significant differences between patients with or without concomitant MS with regards to pulmonary hypertension and atrial fibrillation.

Computed tomographic measurements were available in 133 patients with MS (75.6%) and are summarized in the Supplementary material online, *Table S2*. Mitral annular calcification was documented in 73.3% of patients with mild and 86.7% of patients with moderate or severe MS and tended to be more severe in patients with advanced MS. At the same time, aortic valvular complex calcium volume was greater in patients with advanced stages of MS.

Treatment strategy and procedural characteristics

Procedural characteristics are displayed in *Table 3* and showed no significant differences between the two groups. Anatomical and clinical reasons for a heart team decision against surgical mitral valve replacement, and against percutaneous mitral commissurotomy or transcatheter mitral valve replacement, are summarized in the Supplementary material online, *Tables S3 and S4*, respectively. Four patients underwent mitral balloon valvuloplasty during the index procedure for TAVR; transapical transcatheter mitral valve replacement was attempted in one patient but aborted due to impending left ventricular outflow tract obstruction.[8] Three patients were still alive at more than 2 years of follow-up, while two patients died 23 months after the intervention.

Clinical outcomes

Clinical outcomes according to the presence or absence of concomitant MS are shown in *Table 4*. After adjustment for comorbidities, patients with MS had an increased risk of cardiovascular death [16 (9.2%) vs. 24 (3.2%); HR_{adj} 4.05, 95% CI 2.10–7.82], disabling stroke [11 (6.4%) vs. 16 (2.0%); HR_{adj} 3.74, 95% CI 1.69–8.25], and the VARC-2 early composite safety endpoint [50 (28.4%) vs. 158 (19.9%); HR_{adj} 1.52, 95% CI 1.09–2.12] at 30 days. At 1 year, patients with MS had an increased risk of cardiovascular death [36 (21.4%) vs. 66 (8.7%); HR_{adj} 3.64, 95% CI 2.38–5.56] and disabling stroke [12

Table 3 Procedural characteristics

	Overall (*N* = 971)	Without mitral stenosis (*N* = 795)	Concomitant mitral stenosis (*N* = 176)	*P*-value
Procedural characteristics				
Procedure time (min)	67.4 ± 32.7	67.1 ± 30.9	69.0 ± 40.0	0.48
Length of hospital stay (days)	8 (6–10)	8 (6–10)	8 (6–11)	0.94
General anaesthesia, *n* (%)	279 (28.7)	218 (27.4)	61 (34.7)	0.055
Access route				
Femoral, *n* (%)	836 (86.1)	681 (85.7)	155 (88.1)	0.40
Type of valve, *n* (%)				0.68
Self-expandable	436 (45.0)	362 (45.6)	74 (42.0)	
Balloon-expandable	474 (48.9)	383 (48.3)	91 (51.7)	
Mechanically expandable	59 (6.1)	48 (6.1)	11 (6.2)	
Revascularization				
Concomitant PCI, *n* (%)	140 (14.4)	123 (15.5)	17 (9.7)	0.047
Procedural specifications, *n* (%)				
Post-TAVR AR ≥2	668 (68.9)	543 (68.4)	125 (71.4)	0.43
Post-TAVR need for PPM within 30 days	208 (21.4)	168 (21.1)	40 (22.7)	0.64
Valve in series	16 (1.6)	13 (1.6)	3 (1.7)	1.00

Values are expressed as mean ± standard deviation where appropriate. Self-expandable valve: CoreValve and CoreValve Evolut R (Medtronic Inc., Minneapolis, MN, USA), ACURATE-TA and -TF (Symetis/Boston scientific, Natick, MA, USA), Portico (St. Jude Medical/Abbott, Plymouth, MN), and Direct Flow Medical (Direct Flow Medical, Santa Rosa, CA, USA). Balloon-expandable valve: SAPIEN XT and 3 (Edwards Lifesciences Inc., Irvine, CA, USA). Mechanically expandable valve: Lotus (Boston Scientific, Natick, MA, USA).
AR, aortic regurgitation; PCI, percutaneous coronary intervention; PPM, permanent pacemaker implantation; TAVR, transcatheter aortic valve replacement.

(7.1%) vs. 23 (3.0%); HR_{adj} 2.98, 95% CI 1.46–6.09] as compared to patients without MS (*Figures 3* and 4). Among 12 patients with concomitant MS experiencing stroke, five were found to have spontaneous echo contrast in the left atrium. Detailed characteristics of all MS patients that experienced a disabling stroke are summarized in Supplementary material online, *Table S5*. In a landmark analysis with the landmark set at 1 month, the increased risk of death in patients with concomitant MS as compared with patients without MS was documented both within and beyond 30 days of TAVR. Conversely, the increased risk of stroke seemed to be confined to the peri-procedural period. Furthermore, the effect of TAVR in patients with vs. without MS is consistent across time (see Supplementary material online, *Table S6*). Cardiovascular death or disabling stroke as a function of severity of MS is shown in the Supplementary material online, *Table S7* and *Figure S1*. Conversely, compared to patients with no MS patients with rheumatic MS were found to have a significantly increased risk of cardiovascular death [7 (10.6%) vs. 24 (3.2%); HR_{adj} 4.80, 95% CI 1.98–11.6] and disabling stroke [4 (6.1%) vs. 16 (2.0%); HR_{adj} 4.18, 95% CI 1.34–13.0] within 30 days of the index procedure, whereas differences between patients with degenerative MS and no MS were borderline significant (*Figure 4B* and Supplementary material online, *Table S8*). Mixed mitral valve disease with concomitant MS and mitral regurgitation (MR) was documented in 156 (16.1%) patients. We found an additive effect of MS and MR on the risk of cardiovascular death. The effect of mixed mitral valve disease on cardiovascular death stratified by severity of MR is shown in the Supplementary material online, *Table S9*. In a multivariable analysis, MS emerged as a predictor of cardiovascular death at 1 year (HR_{adj} 3.64, 95% CI 2.38–5.56) (*Table 5*). The CIs estimated using bootstrap analysis (Supplementary material online, *Table S10*) were similar for all predictive factors in the multivariable model, suggesting that the bootstrap distribution is approximately normal.

Discussion

The salient findings of our analysis can be summarized as follows: (i) MS was documented in 18.1% of TAVR patients and assessed as moderate or severe MS in 2.9%; (ii) the aetiology of MS was degenerative in 62.5% and rheumatic in 37.5% of patients; (iii) patients with MS had a three-fold increased risk of cardiovascular death and disabling stroke at 1 year; (iv) differences between patients with vs. without MS emerged within the first 30 days and were largely driven by patients with rheumatic MS; and (v) MS was identified as an independent predictor of cardiovascular mortality at 1 year.

Multivalvular disease is of increasing concern in elderly patients undergoing TAVR. Previous studies showed an important effect of concomitant MR[9] and tricuspid regurgitation[10] on clinical outcomes among patients undergoing TAVR. Although considerably lower than the prevalence of MR,[9] almost one in five patients was affected by some degree of MS. Even though MS was mild in the majority of cases and did not result in secondary pulmonary hypertension or manifest valvular atrial fibrillation, it was associated with a significantly increased risk of cardiovascular death and disabling stroke at 30 days and 1 year.

Table 4 Short- and long-term clinical outcomes according to presence or absence of mitral stenosis

	Without mitral stenosis (*N* = 795)	Concomitant mitral stenosis (*N* = 176)	Crude hazard ratio		Adjusted hazard ratio	
			HR (95% CI)	*P*-value	Adjusted HR (95% CI)	Adjusted *P*-value
30-day follow-up						
All-cause death	27 (3.5)	17 (9.7)	2.92 (1.59–5.36)	0.001	3.84 (2.05–7.22)	<0.001
Cardiovascular death	24 (3.2)	16 (9.2)	3.09 (1.64–5.82)	0.001	4.05 (2.10–7.82)	<0.001
Myocardial infarction	10 (1.3)	2 (1.2)	0.91 (0.20–4.14)	0.90	1.19 (0.25–5.59)	0.83
Cerebrovascular events						
Disabling stroke	16 (2.0)	11 (6.4)	3.17 (1.47–6.84)	0.003	3.74 (1.69–8.25)	0.001
Composite outcomes						
Cardiovascular death and disabling stroke	34 (4.4)	20 (11.4)	2.74 (1.57–4.75)	<0.001	3.41 (1.93–6.03)	<0.001
MACCE	41 (5.3)	22 (12.5)	2.49 (1.48–4.18)	0.001	3.16 (1.85–5.39)	<0.001
Bleeding						
Life-threatening	60 (7.6)	20 (11.4)	1.52 (0.92–2.52)	0.10	1.55 (0.90–2.65)	0.11
Major	113 (14.3)	34 (19.6)	1.38 (0.94–2.03)	0.10	1.32 (0.89–1.98)	0.17
Kidney injury						
Stage 3	28 (3.6)	7 (4.0)	1.13 (0.50–2.60)	0.76	1.27 (0.54–2.98)	0.59
Access site complications						
Major	167 (21.1)	36 (20.6)	0.97 (0.68–1.39)	0.88	0.88 (0.61–1.29)	0.52
VARC-2 early safety endpoints	158 (19.9)	50 (28.4)	1.46 (1.07–2.01)	0.02	1.52 (1.09–2.12)	0.01
1-year follow-up						
All-cause death	96 (12.3)	50 (28.8)	2.60 (1.85–3.66)	<0.001	3.27 (2.28–4.68)	<0.001
Cardiovascular death	66 (8.7)	36 (21.4)	2.70 (1.80–4.05)	<0.001	3.64 (2.38–5.56)	<0.001
Myocardial infarction	18 (2.4)	4 (2.6)	1.07 (0.36–3.18)	0.90	1.29 (0.43–3.89)	0.65
Cerebrovascular events						
Disabling stroke	23 (3.0)	12 (7.1)	2.49 (1.24–5.00)	0.01	2.98 (1.46–6.09)	0.003
Composite outcomes						
Cardiovascular death and disabling stroke	84 (11.0)	40 (23.7)	2.37 (1.63–3.45)	<0.001	3.05 (2.06–4.51)	<0.001
MACCE	123 (15.8)	55 (31.6)	2.24 (1.63–3.08)	<0.001	2.76 (1.98–3.84)	<0.001

Values are given as *n* (%). Hazard ratios (HRs) [95% confidence intervals (CIs)] from Cox regression. Adjusted for baseline and echocardiographic variables age, diabetes mellitus, NYHA classification III or IV, coronary artery disease, peripheral artery disease, atrial fibrillation, left ventricular ejection fraction (%), and STS score.
MACCE, major adverse cardiovascular and cerebrovascular events (composite of all-cause death, major stroke, and myocardial infarction); STS, Society of Thoracic Surgeons; VARC, valvular academic research consortium.

Our findings are consistent with recently published data from the STS/ACC TVT registry, reporting a prevalence of any degree of MS in 11.6% and severe MS in 2.7% of patients undergoing TAVR.[4] Comparable to our analysis, the report from the STS/ACC TVT registry showed a higher left ventricular ejection fraction in patients with as compared to patients without MS, and similar rates of atrial fibrillation in patients with vs. without MS. The latter may relate both to the mild degree of MS in the majority of patients and absence of dedicated screening for atrial fibrillation, for example by means of implantable loop recorders.

Data from the STS/ACC TVT registry indicated a 1.2 times increased risk of mortality at 1 year in patients with severe as compared to patients without MS, but did not show an increased risk of stroke. We found an even stronger effect of MS on mortality despite a comparable proportion of advanced MS, and observed an important impact of MS on the occurrence of stroke. The present analysis differs in several aspects from the recent analysis from the STS/ACC TVT registry.[4] In our study, the identification of patients with evidence of MS was based on Corelab assessment of echocardiographic raw data applying the echocardiographic criteria recommended by the European Association of Echocardiography and the American Society of Echocardiography.[6] The echocardiographic clips of all patients included into our analysis were re-evaluated by an independent second reader for the purpose of this study. Planimetry was used for the classification of severity of MS in all patients, since calculations from pressure half-time or the Gorlin formula are dependent on flow status, heart rate, heart rhythm, and concomitant MR. Detailed evaluation of echocardiographic clips allowed for a differentiation of MS according to aetiology. Furthermore, characterization of the mitral apparatus is complemented by detailed CT assessment of MAC. All events have been independently adjudicated and completeness of follow-up at 1 year amounted to 99%.

Concomitant AS involves a particular challenge in the assessment of MS and vice versa. The rather low MGs recorded in our analysis may be explained by haemodynamics. Severe AS can result in low-flow low-gradient MS with prolonged pressure half-time which is

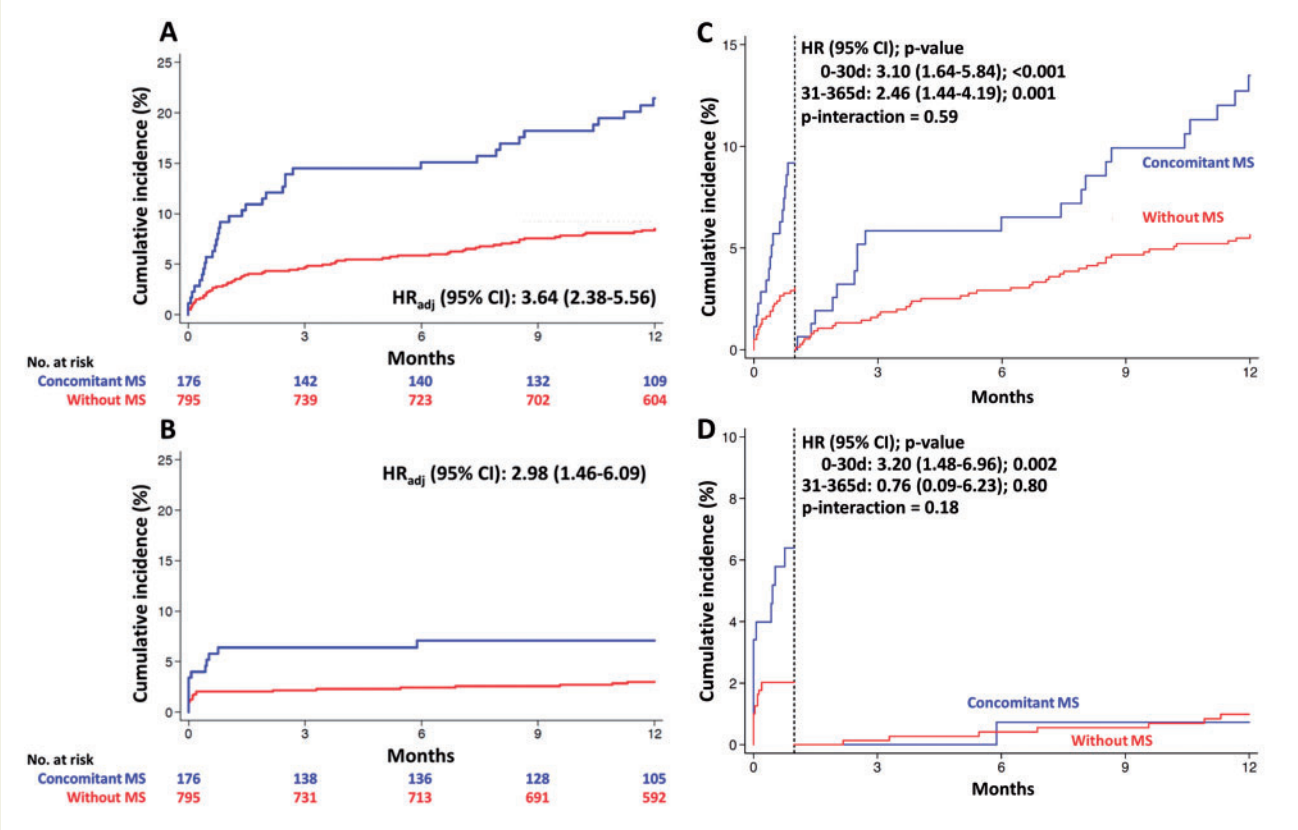


Figure 3 The Kaplan–Meier curve of (*A*) cardiovascular death and (*B*) disabling stroke for patients with concomitant mitral stenosis (blue) and without mitral stenosis (red). Landmark analysis at 30 days of (C) cardiovascular death and (D) disabling stroke for patients with concomitant mitral stenosis (blue) and without mitral stenosis (red).

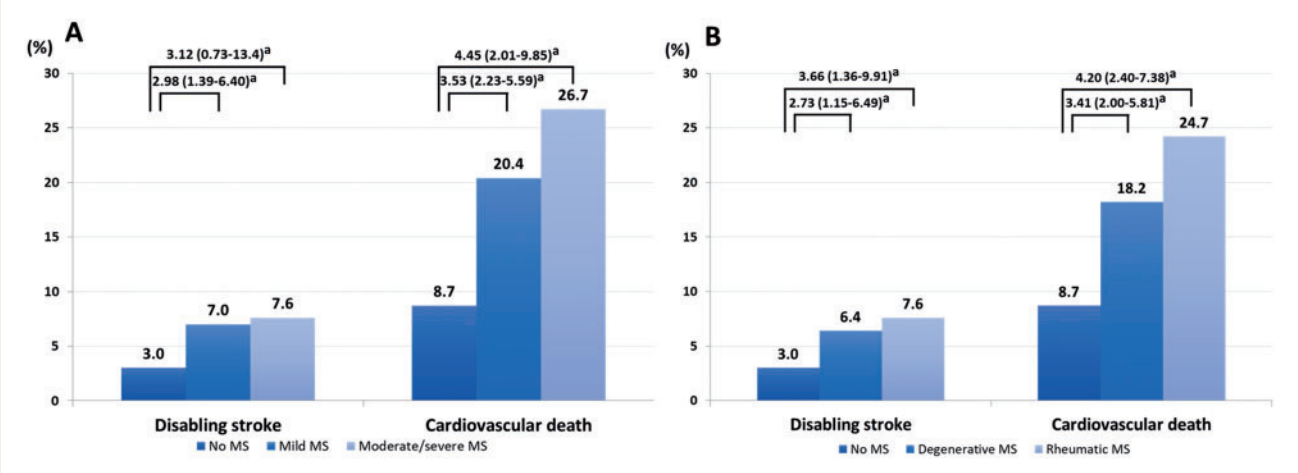


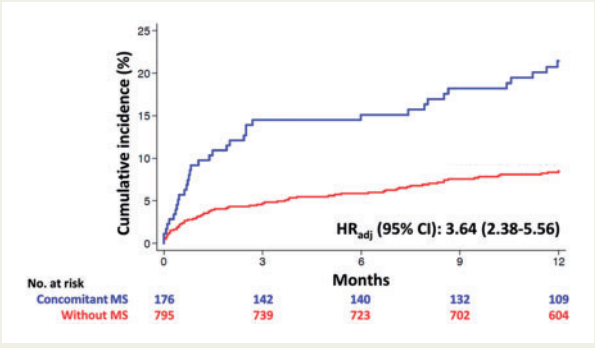
Figure 4 Bar graph illustrating disabling stroke and cardiovascular death in (*A*) patients with no, mild, and moderate/severe mitral stenosis and (*B*) patients with no, degenerative, and rheumatic mitral stenosis at 1 year. [a]Adjusted hazard ratios (95% confidence intervals).

related to impaired left ventricular relaxation. For this reason, assessment of MVA is considered more reliable for diagnosis in this setting.[11] Conversely, AS may be underestimated as a result of decreased left ventricular filling and a reduced stroke volume.

We documented an additive effect of MS and MR on the rates of cardiovascular death. However, quantitative assessment of mixed mitral valve disease is challenging because of the interdependence of echocardiographic assessment of transmitral flow, while qualitative

evaluation resorts to the visual assessment of orifice areas and flow patterns.

Mitral annular calcification as assessed by CT has been shown to be associated with MS.[3] Our findings corroborate the results of a previous report, showing that volumetric quantification of MAC significantly correlated with the severity of MS.[12] Mitral annular calcification and degenerative MS may in fact be different expressions of the same disease process. While MAC occurs in up to half of all patients evaluated for TAVR, moderate or severe MS has been reported in one-third of patients with MAC,[3,12] suggesting a considerably higher prevalence of relevant MS as corroborated in the present echocardiographic analysis. Conversely, we documented MAC in three out of four patients with evidence of MS on echocardiographic evaluation. Severe MAC has been identified as an independent predictor of cardiovascular mortality after TAVR and has been associated with a 2.4-fold (95% CI 1.2–4.7) increased risk of death after TAVR in a retrospective analysis of 761 patients.[3] Along the same line, in the present analysis of 971 patients, echocardiographic evidence of MS independently correlated with a 3.6-fold increased risk of cardiovascular death at 1 year. Mitral annular calcification may be a marker for underlying functional valvular disease, rather than a causal factor for adverse outcome.



Take home figure The Kaplan–Meier curve of cardiovascular death.

Our analysis suggests that the aetiology of MS importantly affects clinical outcomes. Differences in event rates between patients with vs. without MS were apparent within 30 days of the index procedures and were largely driven by patients with rheumatic MS. Patients with rheumatic MS conferred a 4.8-times increased risk of cardiovascular death and a 4.2-times increased risk of disabling stroke at 30 days. Conversely, patients with degenerative MS had a 4.0- and 3.9-fold increased risk of cardiovascular death or disabling stroke within the same time frame. The reason for the early difference in risk and the strong impact of rheumatic as opposed to degenerative MS remains unclear, but may be related to a higher proportion of advanced stages of MS in patients with rheumatic MS. However, a comparison of the event rates according to aetiology and according to severity of MS show a considerably stronger impact of aetiology on rates of death and stroke in adjusted analyses (Supplementary material online, *Tables S7* and *S8*). Presence of MS was associated with increased LAVi. Previous analyses indicated an association between left atrial enlargement and the incidence of cardiovascular death, ischaemic stroke, and heart failure,[13–16] thus providing a potential pathophysiological mechanism of our observed findings. We documented no difference in complications of longstanding MS, such as atrial fibrillation or pulmonary hypertension. However, residual confounding cannot be ruled out.

Our findings may have important implications on peri-procedural management of patients with combined AS and MS undergoing TAVR. A striking difference in the occurrence of early stroke (Supplementary material online, *Table S11*) may advocate the use of systematic transoesophageal echocardiography in this particular subset of patients.

Table 5 Predictive factors for cardiovascular death within 1 year

	Univariate analysis		Multivariable analysis	
Variables	**HR (95% CI)**	***P*-value**	**Adjusted HR (95% CI)**	***P*-value**
Mitral stenosis	2.70 (1.80–4.05)	<0.001	3.64 (2.38–5.56)	<0.001
Atrial fibrillation	1.79 (1.21–2.64)	0.004	1.89 (1.26–2.84)	0.002
Peripheral vascular disease	1.63 (1.02–2.59)	0.04	1.71 (1.05–2.81)	0.03
Diabetes mellitus	1.52 (1.01–2.30)	0.046	1.58 (1.01–2.48)	0.047
Age (years)	1.04 (1.00–1.08)	0.03	1.06 (1.02–1.10)	0.006
LV ejection fraction	0.97 (0.96–0.98)	<0.001	0.97 (0.96–0.99)	<0.001
STS score	1.07 (1.04–1.11)	<0.001	1.04 (1.00–1.08)	0.07
Coronary artery disease	1.54 (1.00–2.37)	0.048	1.38 (0.88–2.15)	0.16
NYHA classification III or IV	1.65 (1.04–2.60)	0.03	0.97 (0.60–1.58)	0.91
Periprocedural stroke	0.97 (0.49–1.93)	0.93		
Post-AR ≥moderate	1.31 (0.84–2.05)	0.24		
Female gender	1.17 (0.79–1.72)	0.43		
Creatinine >200 µmol/L	1.63 (0.72–3.72)	0.24		
COPD	0.78 (0.46–1.33)	0.36		

AR, aortic regurgitation; COPD, chronic obstructive pulmonary disease; LV, left ventricular; NYHA, New York Heart Association; STS, Society of Thoracic Surgeons.

Limitations

The present analysis needs to be interpreted in view of several limitations. Functional assessment of MS is challenging in the presence of concomitant AS. We, therefore, relied on planimetric assessment of MVA in the assessment of MS, while measured and calculated MGs, as well as echocardiographic appearance completed the comprehensive assessment. Furthermore, not all patients deemed to have rheumatic MS had a corresponding clinical history of manifest rheumatic heart disease; categorization based on echocardiographic criteria may have been subject to measurement bias. We, therefore, included only patients into the present analysis that had adequate echocardiographic raw data for a comprehensive assessment of the mitral valve apparatus. As a consequence, 27.5% of patients were excluded from the analysis, which conversely may have introduced a certain degree of selection bias. Additionally, operable candidates with a combination of relevant MS and severe AS were primarily referred for bivalvular replacement rather than transcatheter treatment. Moreover, we do not have echocardiographic long-term follow-up of patients with MS. And finally, numbers of patients are limited and the findings need to be corroborated in larger patient populations using multicentre designs. However, the robustness of our findings is underscored by a rigorous analysis of echocardiographic raw data according to validated criteria, detailed characterization of the mitral valvular apparatus using echocardiography and CT data, independent event adjudication, and high rates of clinical follow-up.

Conclusions

Concomitant MS was documented in one in five TAVR candidates. Although mild in the majority of patients, concomitant MS was associated with an approximately three-fold increased risk of cardiovascular death and disabling stroke at 1 year, respectively. The difference emerged within the first 30 days and was largely driven by patients with rheumatic MS. Concomitant mitral valve disease, particularly the presence of MS needs to be considered in the workup of potential TAVR candidates and the decision upon the best treatment strategy.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Conflict of interest: S.W. has received research grants to his institution from Abbott, Amgen, Boston Scientific, Biotronik, and St. Jude Medical. S.W.: Edwards Lifesciences, Medtronic, Terumo, and Bayer. L.R. has received research grants to his institution from Biotronik, Sanofi, and Regeneron. T.P. has received research grants to the institution from Edwards Lifesciences, Symetis/Boston Scientific, and Biotronik, and speaker fees from Boston Scientific and Biotronik. All other authors have no relationships relevant to the contents of this article to disclose.

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