Clinical Research in Cardiology (2019) 108:39–47
https://doi.org/10.1007/s00392-018-1309-0

ORIGINAL PAPER

Gender-dependent association of diabetes mellitus with mortality in patients undergoing transcatheter aortic valve replacement

Axel Linke[1] · Florian Schlotter[2] · Stephan Haussig[1] · Felix J. Woitek[1] · Georg Stachel[2] · Jennifer Adam[2] · Robert Höllriegel[1] · Anna Lindner[2] · Friedrich W. Mohr[3] · Gerhard Schuler[2] · Philipp Kiefer[4] · Sergey Leontyev[4] · Holger Thiele[2] · Michael A. Borger[4] · David Holzhey[4] · Norman Mangner[1]

Received: 23 April 2018 / Accepted: 18 June 2018 / Published online: 25 June 2018

Abstract

Background Diabetes mellitus (DM) is a risk factor for cardiovascular disease. However, its effect on procedural and follow-up performance after transcatheter aortic valve replacement (TAVR) remains controversial.

Methods and results We performed an observational study of all consecutive patients treated with a transfemoral TAVR in a single-center cohort ($n=1818$). All patients were stratified by diabetes status and gender. All-cause 3-year mortality was the primary endpoint. Male patients with DM were identified to have substantially increased 3-year mortality [125/314 (39.8%)] compared to males without DM [142/478 (29.7%), $p<0.01$]. Male patients with DM had significantly higher 3-year mortality in comparison to female patients with ($p<0.01$) or without DM ($p<0.01$). There was no difference in 3-year mortality for female patients with [135/465 (29.0%)] and without DM [151/554 (27.3%); $p=0.70$]. This increase in mortality in male DM patients was triggered by both cardiovascular and non-cardiovascular mortality. Furthermore, DM served as an independent predictor of 3-year mortality after TAVR selectively only in men. The interaction between male gender and diabetes mellitus was identified as an independent predictor of 3-year mortality [HR 1.88 (1.25; 2.82); $p<0.01$]. DM did not affect 30-day mortality for the overall cohort and for males.

Conclusion Males with DM are a high-risk subgroup of patients after TAVR and require close medical attention including aggressive therapy of modifiable risk factors. Intensified diabetes management may improve long-term survival after TAVR.

Keywords Aortic stenosis · Diabetes mellitus · Gender · TAVR · Outcome

Abbreviations

DM	Diabetes mellitus
TAVR	Transcatheter aortic valve replacement
BMI	Body mass index
CAD	Coronary artery disease
NYHA	New York Heart Association
STS	Society of Thoracic Surgeons
PAD	Peripheral artery disease
MI	Myocardial infarction
CABD	Coronary artery bypass grafting
PCI	Percutaneous coronary intervention
CKD	Chronic kidney disease
VARC	Valve Academic Research Consortium
AR	Aortic valve regurgitation
MR	Mitral valve regurgitation
PPM	Permanent pacemaker
ICD	Implantable cardioverter/defibrillator

Introduction

Diabetes mellitus (DM) is a risk factor for cardiovascular disease [1], including aortic valve stenosis [2–4], and the prevalence of DM is projected to increase in the future [5, 6]. Transcatheter aortic valve replacement (TAVR) is a rapidly evolving treatment option for patients at increased operative risk and carries the potential to expand the current indication to low-risk patients [7–9], while it has been

Axel Linke and Florian Schlotter contributed equally to this work and should be regarded as shared first authors.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00392-018-1309-0) contains supplementary material, which is available to authorized users.

✉ Norman Mangner
norman.mangner@mailbox.tu-dresden.de

Extended author information available on the last page of the article

approved for intermediate-risk patients by the FDA. Numerous risk factors have been identified but only limited mid- and long-term performance data exist [10]. In the light of expanding indications, there is a shifting focus to identify factors influencing durability of the procedural success and to determine long-term contributors of morbidity and mortality. DM and gender were identified as such predictors of procedural follow-up mortality. In two recent meta-analyses, DM was associated with increased mid-term mortality [11, 12], while another meta-analysis showed no difference in 1-year survival between patients with and without DM [13]. This inconsistent finding warrants further investigation. In addition, a meta-analysis on the role of gender on mortality after TAVR recognized that males were at increased risk of mortality at mid-term follow-up [14].

The current study sought to elicit the role of DM on short- and mid-term outcomes after TAVR in an observational cohort study and to assess the potential differential effect and interactions of gender and DM to identify subgroups of increased risk.

Methods

Patient cohort

In total, 1818 consecutive patients with aortic valve stenosis or bio-prosthetic aortic valve stenosis received a transfemoral TAVR after heart team review. DM was defined by reference in the patient's medical history and medication review for pharmacological DM treatment. DM was sub-categorized in insulin-dependent DM and non-insulin-dependent DM. The study was approved by the Ethics Committee of the University of Leipzig (Registration Number: 167-10-12072010), conforms to the ethical guidelines of the 1975 Declaration of Helsinki, and informed consent for the procedure and inclusion into the registry was obtained from all patients. No exclusion criteria were applied. Baseline characteristics, procedural data and outcome data were prospectively collected. Follow-up was performed after 30 days, 3, 6 and 12 months and annually up to 5 years.

Endpoints

All-cause mortality at 3 years was the primary endpoint of the analysis and was sub-divided into cardiovascular and non-cardiovascular mortality. Furthermore, 30-day and 1-year survival was also analyzed. One-year survival was additionally evaluated in a landmark analysis after 30 days. Three-year mortality was sub-divided into cardiovascular and non-cardiovascular mortality according to the definition of Valve Academic Research Consortium 2 (VARC-2). Cause of death was verified by two authors (NM, FJW) reviewing medical records and death certificates to receive consensus. According to VARC-2, patients with unknown cause of death were categorized as cardiovascular mortality. All other endpoint including mortality, efficacy and complications were also subject to the VARC-2 definitions [15].

Statistical analysis

Categorical variables are presented as numbers and percentages and were compared using Chi-square testing. Continuous data were expressed as median with the 25th and 75th quartile and were compared using *t* test or Mann–Whitney *U* test for two group comparisons. For multi-group comparisons, analysis of variance or Kruskal–Wallis test was performed. The underlying assumptions of these statistical tests were evaluated. A two-sided p value < 0.05 was considered statistically significant. Thirty-day-, 1-year- and 3-year-mortality was analyzed with the Kaplan–Meier method and the log rank test was used for group comparisons.

Cox proportional hazards regression was performed for the multivariate analyses and the proportionality of hazards assumption was confirmed for all Cox models. Variables with a value of $p < 0.1$ in univariate analysis were included in this model and a p value < 0.05 was considered statistically significant in the multivariate analysis. The Cox proportional hazards model evaluating the effect of an interaction between diabetes mellitus and male gender on 3-year survival further included the covariates: age per 1 year increase, male gender, BMI > 30 kg/m², NYHA III/IV, STS score mortality > 15, ejection fraction < 45%, diabetes mellitus, insulin-treated diabetes mellitus, peripheral artery disease, previous myocardial infarction, previous coronary artery bypass grafting, previous PCI, previous stroke, CKD stage ≥ 3b, dialysis at baseline, mitral regurgitation ≥ grade 2, coronary artery disease, atrial fibrillation, residual aortic valve regurgitation ≥ grade 2, new postprocedural pacemaker/ICD, VARC success, VARC life-threatening bleeding and VARC renal failure. The gender-specific Cox proportional hazards models on 3-year survival included these covariates: age per 1 year increase, male gender, BMI > 30 kg/m², NYHA III/IV, STS score mortality > 15, ejection fraction < 45%, diabetes mellitus, insulin-treated diabetes mellitus, peripheral artery disease, previous myocardial infarction, previous coronary artery bypass grafting, previous PCI, previous stroke, CKD stage ≥ 3b, dialysis at baseline, mitral regurgitation ≥ grade 2, coronary artery disease, atrial fibrillation, residual aortic valve regurgitation ≥ grade 2, new postprocedural pacemaker/ICD, VARC success, VARC life-threatening bleeding and VARC renal failure.

All statistical analyses were performed with SPSS version 22 (IBM Corporation, Armonk, New York).

Results

Patient characteristics

In total, 1818 patients were enrolled from 02/2006 to 09/2014 and retrospectively analyzed. Of these, 1035 (56.9%) were non-diabetic and 783 (43.1%) had DM and 1026 (56.4%) were females and 792 (43.5%) were males. Baseline clinical and echocardiographic characteristics are listed in Table 1. Male patients with DM were younger, had more co-morbidities reflected by the highest

Table 1 Pre-procedural clinical and echocardiographic characteristics stratified by diabetes status and gender

	No diabetes mellitus [$n=1035$ (56.9%)]		Diabetes mellitus [$n=783$ (43.1%)]		p value for four-group comparison	p value for two-group within females comparison	p value for two-group within males comparison
Gender, n (%)	Female [557 (30.6)]	Male [478 (26.3)]	Female [469 (25.8)]	Male [314 (17.3)]	0.10		
Age (years), median (IQR)	81.7 (78; 85)	79.6 (76; 84)	80.5 (77; 84)	78.5 (75; 83)	< 0.01	< 0.01	0.01
BMI (kg/m²), median (IQR)	27.0 (23.4; 30.1)	26.7 (24.0; 29.4)	30.3 (25.9; 33.5)	28.7 (25.1; 31.6)	< 0.01	< 0.01	< 0.01
BMI > 30 kg/m², n (%)	146/552 (26.4)	93/475 (19.6)	216/465 (46.5)	111/312 (35.6)	< 0.01	< 0.01	< 0.01
Arterial hypertension, n (%)	510/551 (92.6)	429/474 (90.5)	448/465 (96.3)	300/313 (95.8)	< 0.01	0.01	< 0.01
NYHA III/IV, n (%)	425/557 (76.3)	339/478 (70.9)	391/469 (83.4)	250/313 (79.9)	< 0.01	< 0.01	< 0.01
STS score mortality (%)	7.5 (4.1; 9.6)	6.3 (3.1; 8.0)	10.8 (5.9; 13.4)	9.1 (4.4; 11.9)	< 0.01	< 0.01	< 0.01
Ejection fraction (%)	58 (52; 67)	51 (41; 63)	57 (49; 67)	50 (39; 60)	< 0.01	0.09	0.13
Ejection fraction < 45%, n (%)	77/493 (15.6)	123/423 (29.1)	77/422 (18.2)	90/280 (32.1)	< 0.01	0.29	0.39
CAD, n (%)	167/496 (33.7)	260/444 (58.6)	187/432 (43.3)	192/291 (66.0)	< 0.01	< 0.01	0.04
PAD, n (%)	41/551 (7.4)	65/474 (13.7)	30/465 (6.5)	71/313 (22.7)	< 0.01	0.54	< 0.01
Previous MI, n (%)	24/550 (4.4)	80/473 (16.9)	48/465 (10.3)	66/313 (21.1)	< 0.01	< 0.01	0.14
Previous CABG, n (%)	19/551 (3.4)	99/475 (20.8)	34/465 (7.3)	73/313 (23.3)	< 0.01	< 0.01	0.41
Previous PCI, n (%)	81/551 (14.7)	131/474 (27.6)	96/464 (20.7)	103/313 (32.9)	< 0.01	0.01	0.11
Previous stroke, n (%)	36/551 (6.5)	53/474 (11.2)	51/465 (11.0)	40/313 (12.8)	< 0.01	0.01	0.50
CKD stage ≥ 3b, n (%)	150/557 (26.9)	104/478 (21.8)	205/469 (43.7)	102/313 (32.6)	< 0.01	< 0.01	< 0.01
Dialysis baseline (%)	7/553 (1.3)	11/475 (2.3)	13/468 (2.8)	11/311 (3.5)	0.16	0.08	0.31
Aortic valve area (cm²)	0.6 (0.5; 0.7)	0.7 (0.6; 0.8)	0.7 (0.5; 0.8)	0.8 (0.6; 0.9)	< 0.01	0.02	0.75
Mean gradient (mmHg)	47 (35; 57)	43 (33; 51)	45 (35; 54)	39 (29; 46)	< 0.01	0.03	< 0.01
Mitral regurgitation ≥ 2, n (%)	61/505 (12.1)	50/432 (11.6)	57/431 (13.2)	30/284 (10.6)	0.74	0.60	0.68
Atrial fibrillation, n (%)	219/557 (39.3)	208/478 (43.5)	216/469 (46.1)	158/314 (50.3)	0.01	0.05	0.02
Insulin-dependent diabetes, n (%)	–	–	203/469 (43.3)	126/314 (40.1)	0.38	–	–

proportion of coronary artery disease (CAD), peripheral artery disease (PAD), and atrial fibrillation in comparison to females and males without DM and females with DM (Table 1). Male and female diabetics did not differ significantly in the proportions of insulin-dependent diabetes (males: $n = 126/314$ (40.1%); females: $n = 203/469$ (43.3%); $p = 0.38$).

Procedural data and complications

Procedural parameters and outcomes are summarized in Table 2. Males were more likely to receive a self-expandable valve and larger devices than females, with the latter leading to a higher prosthetic valve orifice area. A valve-in-valve procedure was more frequently performed in males. The procedure time was lower in diabetics than in non-diabetics. Procedural bleeding rates were higher in females than in males and non-diabetic females had the highest rate of life-threatening bleeding and access site complications. Female and male diabetics and non-diabetics did not differ significantly with respect to VARC defined myocardial infarction, stroke or new permanent pacemaker/implantable cardioverter defibrillator (PPM/ICD) implantation.

Mortality analysis

Mortality data are summarized in Table 2. Thirty-day all-cause mortality was similar between female and male diabetics and non-diabetics ($p = 0.58$, Suppl. Figure 1a). One-year all-cause mortality (27.1%, $p = 0.02$, Suppl. Figure 1b) and 1-year mortality in a landmark analysis after 30 days ($p < 0.01$, Suppl. Figure 1c). was highest in diabetic males. Three-year mortality was still highest among diabetic males (39.8%, $p < 0.01$, Fig. 1a) and was triggered by both cardiovascular (28.7%, $p < 0.05$, Suppl. Figure 1d) and non-cardiovascular causes (11.1%, $p < 0.01$, Suppl. Figure 1e). Three-year all-cause mortality was higher in diabetics than in non-diabetics (33.4 vs. 28.4%, $p = 0.03$, Fig. 1b) and higher in males compared to females (33.7 vs 28.1%, $p < 0.01$, Fig. 1c). The separation between the mortality curves occurred earlier in males vs. females than in diabetics vs. non-diabetics.

Predictors of 3-year mortality

Cox proportional hazard modeling including the interaction between diabetes mellitus and male gender identified this interaction as an independent risk factor for 3-year mortality [HR 1.88, 95% confidence interval (CI): 1.25–2.82, $p < 0.01$, Table 3].

A gender-specific Cox multivariate analysis revealed DM (HR 1.44, 95% CI 1.07–1.93, $p = 0.02$), pre-procedural NYHA III or IV functional status (HR 1.68, 95% CI: 1.15–2.44, $p = 0.007$), and dialysis at baseline (HR 2.57, 95% CI 1.31–5.02, $p = 0.006$) as independent predictors of 3-year mortality in males (Suppl. Table 1, 2). VARC success (HR 0.52, 95% CI: 0.35–0.76, $p = 0.001$) served as an independent predictor of 3-year mortality after TAVR in female patients (Suppl. Table 1, 3). In both genders, three additional independent predictors of 3-year mortality were identified: atrial fibrillation (females: HR 1.36, 95% CI 1.05–1.77, $p = 0.02$) and males: HR 1.51 (95% CI 1.12–2.03, $p = 0.006$), VARC life-threatening bleeding (females: HR 1.90, 95% CI 1.34–2.70, $p < 0.001$); males: HR: 2.71 (95% CI 1.69–4.32, < 0.001) and VARC renal failure (females: HR: 2.16, 95% CI 1.59–2.93, $p < 0.001$); (males: HR: 2.04, 95% CI 1.42–2.92, $p < 0.001$) (Suppl. Tables 1, 2, 3).

Discussion

In this study of outcomes of patients undergoing TAVR stratified by gender and diabetes status, male gender and DM significantly increased 3-year mortality. Moreover, the interaction of DM and male gender contributed significantly to substantially increased 3-year mortality and DM was identified as an independent risk factor for reduced 3-year survival only in males. Furthermore, this finding was accounted for by both cardiovascular and non-cardiovascular mortality. Of note, survival was reduced in diabetic males; 1-year post TAVR and survival curves started to diverge 90 days after TAVR. Diabetes status- and gender-dependent survival followed different temporal trends as the survival curves for gender separated earlier after TAVR than survival for diabetes status. One may speculate that the lower ejection fraction, a numerically higher rate of residual AR and endocarditis in males led to this earlier separation of the survival curves when comparing gender-dependent survival separately. Our findings are consistent in their temporal trend with prior observations of an early effect of gender on survival after TAVR [16, 17].

The increase in mortality among male diabetics occurred despite their lowest baseline age. On the contrary, the high prevalence of pre-existing cardiovascular disease (PAD and CAD) might have triggered subsequent events that increased cardiovascular mortality after TAVR in diabetic males. Overall 3-year mortality was not independently predicted by these preexisting cardiovascular conditions in the multivariate analysis. Of note, although males without DM had almost twice the rate of residual AR ≥ 2 (8.1 vs. 4.8%; $p = 0.09$), yet they have better survival outcomes than males with DM.

Short-term mortality after TAVR has substantially decreased in recent years, mainly driven by improvements in vascular access device and valve design. This development shifted the focus towards lasting long-term

Table 2 Survival, procedural parameters and outcomes after TAVR per diabetes status and gender

	No diabetes mellitus [$n=1035$ (56.9%)]		Diabetes mellitus [$n=783$ (43.1%)]		p value for four group comparison	p value for two group within females comparison	p value for two group within males comparison
Gender, n (%)	Female [557 (30.6)]	Male [478 (26.3)]	Female [469 (25.8)]	Male [314 (17.3)]			
30-day mortality n, (%)	45/554 (8.1)	32/478 (6.7)	28/465 (6.0)	20/314 (6.4)	0.58	0.20	0.84
1-year mortality n, (%)	109/554 (19.7)	103/478 (21.5)	83/465 (17.8)	85/314 (27.1)	0.02	0.44	0.09
1-year mortality—landmark analysis after 30 days n, (%)	64/509 (12.6)	71/446 (15.9)	55/437 (12.6)	65/294 (22.1)	<0.01	0.99	0.03
3-year mortality (%)	151/554 (27.3)	142/478 (29.7)	135/465 (29.0)	125/314 (39.8)	<0.01	0.70	<0.01
3-year mortality—cardiovascular mortality n, (%)	124/554 (22.4)	106/478 (22.2)	105/465 (22.6)	90/314 (28.7)	0.04	0.96	0.02
3-year mortality—non-cardiovascular mortality n, (%)	27/554 (4.9)	36/478 (7.5)	30/465 (6.5)	35/314 (11.1)	<0.01	0.35	0.03
Indication							
Native valve	542/557 (97.3)	453/478 (94.8)	460/469 (98.1)	301/313 (96.2)	0.03	0.80	0.58
Valve-in-valve	15 (2.7)	25 (5.2)	9 (1.9)	12 (3.8)			
Type of valve							
Self-expandable, n (%)	400/557 (71.8)	379/478 (79.3)	328/469 (69.9)	249/313 (79.6)	<0.01	0.51	0.92
Balloon-expandable, n (%)	157 (28.2)	99 (20.7)	141 (30.1)	64 (20.4)			
Valve size (mm)	25.9 (26; 29)	28.5 (26; 29)	26.1 (26; 29)	28.5 (26; 29)	<0.01	0.82	0.14
Procedure time (min)	52 (37; 60)	52 (37; 60)	49 (35; 56)	49 (36;57)	0.02	<0.01	0.63
Contrast dye (ml)	135 (100; 150)	135 (100; 160)	127 (100; 142)	131 (104; 155)	0.31	0.89	0.75
VARC success, n (%)	467/528 (88.4)	428/472 (90.7)	424/454 (93.4)	277/306 (90.5)	0.07	<0.01	0.94
Residual AR ≥ grade 2, n (%)	22/494 (4.5)	35/432 (8.1)	16/424 (3.8)	14/289 (4.8)	0.02	0.61	0.09
Residual mean gradient (mmHg)	9 (4;11)	10 (6; 12)	9 (6;11)	9 (6; 11)	0.44	0.31	0.22
Aortic valve area (cm²)	1.81 (1.50; 2.1)	2.01 (1.70; 2.30)	1.81 (1.50; 2.10)	2.02 (1.70; 2.30)	<0.01	0.62	0.69
VARC myocardial infarction, n (%)	8/529 (1.5)	6/473 (1.3)	3/454 (0.7)	1/307 (0.3)	0.31	0.21	0.17
VARC stroke, n (%)	30/529 (5.7)	17/473 (3.6)	28/454 (6.2)	8/307 (2.6)	0.06	0.74	0.44
VARC renal failure, n (%)	78/532 (14.7)	73/471 (15.5)	90/461 (19.5)	59/308 (19.2)	0.12	0.58	0.04

Table 2 (continued)

	No diabetes mellitus [$n=1035$ (56.9%)]		Diabetes mellitus [$n=783$ (43.1%)]		p value for four group comparison	p value for two group within females comparison	p value for two group within males comparison
VARC bleeding, n (%)	245/528 (46.4)	172/473 (36.4)	171/454 (37.7)	94/307 (30.6)	<0.01	<0.01	0.10
VARC major bleeding, n (%)	126/528 (23.9)	90/473 (19.0)	102/454 (22.5)	47/307 (15.3)	0.02	0.65	0.18
VARC life-threatening bleeding	69/527 (13.1)	30/473 (6.3)	32/454 (7.0)	16/307 (5.2)	<0.01	<0.01	0.51
VARC access site complication, n (%)	190/529 (35.9)	100/473 (21.1)	119/454 (26.2)	59/307 (19.2)	<0.01	<0.01	0.52
New PPM/ICD, n (%)	138/557 (24.8)	139/478 (29.1)	148/469 (31.6)	96/313 (30.7)	0.08	0.02	0.63
NYHA class improvement by at least 1 after 12 months	253/316 (80.1)	216/270 (80.0)	230/273 (84.2)	135/168 (80.4)	0.52	0.19	0.93
Endocarditis, n (%)	15/557 (2.7)	16/478 (3.3)	10/469 (2.1)	14/314 (4.5)	0.28	0.56	0.42

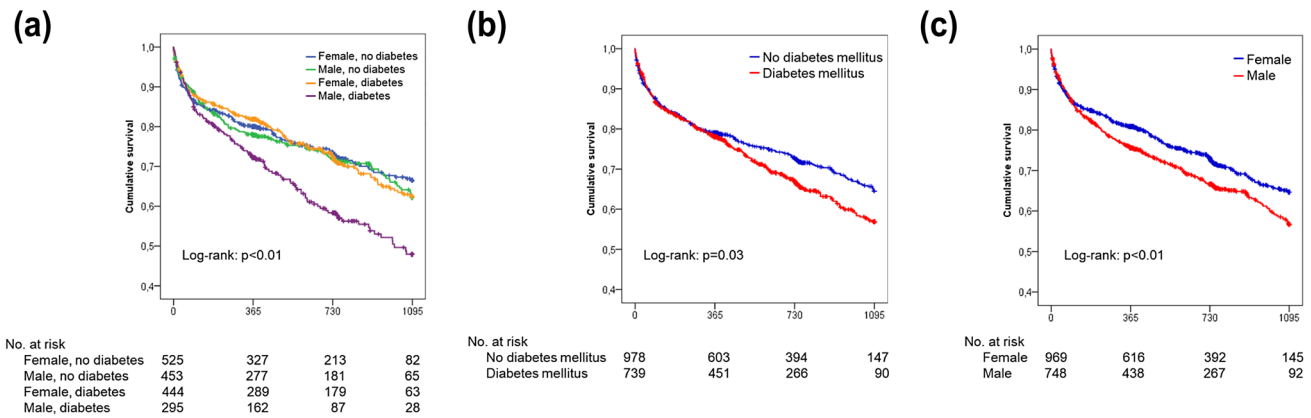

Fig. 1 **a** Kaplan–Meier analysis for 3-year survival stratified by diabetes status and gender; Kaplan–Meier 3-year survival analysis for **b** diabetes status and **c** gender after TAVR

durability of the procedural success. Durability is governed by valve- and patient-specific factors. Among these risks, one of the modifiable risk factors is DM. DM was highly prevalent in the current study, consistent with the epidemiology in the general aged population. Prior studies unadjusted for gender returned mixed results on the impact of DM on outcome parameters after TAVR. Two meta-analyses on the effect of DM on short- and mid-term mortality after TAVR showed conflicting results: a meta-analysis by Sun et al. comprising 16 studies reported no difference in 30-day and 1-year mortality after TAVR [13], while two additional meta-analyses revealed a significant increase in 1-year mortality in patients with DM [11, 12]. We here demonstrate that DM has a detrimental effect on survival after TAVR selectively in males, which may help to clarify why prior studies unadjusted for this gender-specific effect may have failed to reveal consistent results for the impact of DM on mortality after TAVR. Of note, these findings after TAVR are converse to findings after PCI, where DM women have worse outcomes than non-DM men [18]. Despite the fact that women with DM had a higher prevalence of CKD stage ≥ 3b at baseline,

Table 3 Diabetes gender interaction Cox proportional hazard analysis of predictors of 3-year mortality

	Alive ($n=1258$, 69.2%)	Dead ($n=553$, 30.4%)	Univariate model	p	Multivariate model	p
Interaction diabetes and male gender			1.54 (1.27; 1.89)	<0.01	1.88 (1.25; 2.82)	<0.01
Pre-procedural						
Age per 1 year increase			1.01 (1.00; 1.03)	0.14	–	–
Male	525/1258 (41.7%)	267/553 (48.3%)	1.27 (1.07; 1.50)	<0.01	0.84 (0.63; 1.12)	0.24
BMI > 30 kg/m², *n* (%)	411/1254 (32.8%)	154/549 (28.1)	0.84 (0.70; 1.02)	0.07	0.79 (0.63; 1.00)	0.05
Arterial hypertension, *n* (%)	1182/732 (94.0%)	504/545 (92.5)	0.90 (0.65; 1.23)	0.49	–	–
NYHA III/IV, *n* (%)	931/1257 (74.1%)	470/553 (85.0%)	1.81 (1.43; 2.29)	<0.01	1.66 (1.26; 2.18)	<0.01
STS score mortality > 15, *n* (%)	98/1207 (8.1%)	101/514 (19.6%)	2.01 (1.62; 2.50)	<0.01	1.24 (0.93; 1.66)	0.14
Ejection fraction < 45%, *n* (%)	234/1125 (20.8%)	133/492 (27.0%)	1.31 (1.08;1.60)	<0.01	1.04 (0.81; 1.33)	0.79
Diabetes mellitus, *n* (%)	518/1257 (41.2%)	260/553 (47.0%)	1.20 (1.02;1.42)	0.03	0.79 (0.58; 1.07)	0.13
Insulin-treated diabetes mellitus, *n* (%)	217/1258 (17.2%)	112/553 (20.3%)	1.19 (0.97; 1.47)	0.09	1.03 (0.76; 1.40)	0.84
PAD, *n* (%)	125/1257 (9.9%)	82/545 (15.0%)	1.48 (1.17; 1.87)	<0.01	1.30 (0.98; 1.72)	0.07
Previous MI, *n* (%)	136/1255 (10.8%)	82/545 (15.0%)	1.38 (1.09; 1.75)	<0.01	1.08 (0.79; 1.49)	0.63
Previous CABG, *n* (%)	139/1257 (11.1%)	86/546 (15.8%)	1.30 (1.03; 1.64)	0.03	1.22 (0.89; 1.67)	0.22
Previous PCI, *n* (%)	273/1256 (21.7%)	138/545 (25.3%)	1.18 (0.97; 1.43)	0.09	0.97 (0.73; 1.29)	0.84
Previous Stroke, *n* (%)	136/1257 (10.8%)	44/545 (8.1%)	0.81 (0.60; 1.10)	0.18	–	–
CKD stage ≥ 3b, *n* (%)	323/1257 (25.7%)	237/553 (42.9%)	1.80 (1.52; 2.13)	<0.01	1.20 (0.95; 1.52)	0.12
Dialysis baseline, *n* (%)	15/1257 (1.2%)	27/548 (4.9%)	2.41 (1.64; 3.54)	<0.01	1.69 (0.99; 2.90)	0.05
MR ≥ grade 2, *n* (%)	117/1146 (10.2%)	81/505 (16.0%)	1.52 (1.20; 1.93)	<0.01	1.14 (0.85; 1.52)	0.40
Coronary artery disease, *n* (%)	547/1169 (46.8%)	259/493 (52.5%)	1.20 (1.01; 1.44)	0.04	1.06 (0.82; 1.36)	0.67
Atrial fibrillation, *n* (%)	449/1230 (36.5%)	250/519 (48.2%)	1.54 (1.30; 1.83)	<0.01	1.44 (1.17; 1.77)	<0.01
Procedural						
Residual aortic valve regurgitation ≥ grade 2, *n* (%)	54/1204 (4.5%)	33/435 (7.7%)	1.16 (0.97; 1.38)	0.10	–	–
New PPM/ICD TAVR, *n* (%)	344/1257 (27.4%)	176/553 (31.8%)	1.15 (0.97; 1.38)	0.12	–	–
VARC success, *n* (%)	1132/1229 (92.1%)	464/530 (87.5%)	0.60 (0.47; 0.78)	<0.01	0.72 (0.52; 0.99)	0.04
VARC life-threatening bleeding, *n* (%)	66/1230 (5.4%)	81/530 (15.3%)	2.67 (2.11; 3.39)	<0.01	2.33 (1.74; 3.12)	<0.01
VARC renal failure, *n* (%)	133/1232 (10.8%)	164/536 (30.6%)	2.95 (2.45; 3.45)	<0.01	1.88 (1.25; 2.82)	<0.01

and experienced higher stroke rates than DM men (6.2 vs. 2.6%), they continued to show better survival based on less CAD and higher LVEF.

In our study, insulin-dependent DM did not increase mid-term mortality in univariate analysis while any type of DM had predictive value in males, which invokes the hypothesis that non-pharmacologically treated DM or DM under oral antidiabetic treatment could trigger the increase in mortality and may subsequently suggest that these patients may be undertreated and may, therefore, profit from earlier implementation of more aggressive diabetes treatment to achieve more stringent glycemic control to prevent secondary DM effects.

In the gender-specific Cox proportional hazard model, VARC success served as an independent predictor of 3-year mortality in females, while besides DM, New York Heart Association classes III and IV were independent predictors of mortality in males. Atrial fibrillation, VARC life-threatening bleeding and VARC renal failure were independently predictive of 3-year mortality regardless of gender, consistent with previous studies [19–21].

The present single-center observational study has several limitations that need to be noted. Data on glycemic control (HBA1c), type of oral antidiabetic treatment, duration and severity of DM were not included in the definition of DM, encompassing patients treated with dietary and lifestyle modification (non-pharmacological treatment strategies). Baseline clinical parameters varied between the study groups, representing the expected higher cardiovascular disease burden in patients with DM. Unaccounted for confounders may not have been included in the current analysis.

The detection of the interaction effect of gender and DM, including DM as one modifiable risk factor will help to address the pending question of which subgroups are at increased risk of adverse outcomes after TAVR. Furthermore, more stringent DM therapy with the aim to reduce cardiovascular mortality in patients with DM may improve long-term survival in patients after TAVR.

Conclusions

The current results indicate that DM is an independent risk factor for substantially decreased mid-term survival in males and identified males with DM as a subgroup in need of heightened medical attention after TAVR to increase durability of the procedural success. Intensified diabetes management may improve long-term survival after TAVR.

Compliance with ethical standards

Conflict of interest Axel Linke: reports grants and personal fees from Medtronic, personal fees from St. Jude Medical, grants from Claret Medical, personal fees and other from Claret Medical, personal fees from Boston Scientific, personal fees from Bard, personal fees from Edwards, outside the submitted work. Florian Schlotter: No conflict of Interest. Stephan Haussig: No conflict of Interest. Felix J. Woitek: No conflict of Interest. Georg Stachel: No conflict of Interest. Jennifer Adam: No conflict of Interest. Robert Höllriegel: No conflict of Interest. Anna Lindner: No conflict of Interest. Friedrich W. Mohr: No conflict of Interest. Gerhard Schuler: No conflict of Interest. Philipp Kiefer: No conflict of Interest. Sergey Leontyev reports other from St. Jude Medical, other from Medtronic, outside the submitted work. Holger Thiele: No conflict of interest. Michael M. Borger: Speakers' honoraria and consulting fees from Edwards Lifesciences, Medtronic, and CryoLife, outside the submitted work. David Holzhey reports other from Symetis, other from Medtronic, outside the submitted work. Norman Mangner: No conflict of Interest.

References

1. Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, Di Angelantonio E, Ingelsson E, Lawlor DA, Selvin E, Stampfer M, Stehouwer CD, Lewington S, Pennells L, Thompson A, Sattar N, White IR, Ray KK, Danesh J (2010) Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet 375(9733):2215–2222. https://doi.org/10.1016/s0140-6736(10)60484-9
2. Katz R, Wong ND, Kronmal R, Takasu J, Shavelle DM, Probstfield JL, Bertoni AG, Budoff MJ, O'Brien KD (2006) Features of the metabolic syndrome and diabetes mellitus as predictors of aortic valve calcification in the Multi-Ethnic Study of Atherosclerosis. Circulation 113(17):2113–2119. https://doi.org/10.1161/CIRCULATIONAHA.105.598086
3. Owens DS, Katz R, Takasu J, Kronmal R, Budoff MJ, O'Brien KD (2010) Incidence and progression of aortic valve calcium in the Multi-ethnic Study of Atherosclerosis (MESA). Am J Cardiol 105(5):701–708. https://doi.org/10.1016/j.amjcard.2009.10.071
4. Otto CM, Prendergast B (2014) Aortic-valve stenosis–from patients at risk to severe valve obstruction. N Engl J Med 371(8):744–756. https://doi.org/10.1056/NEJMra1313875
5. Boyle JP, Thompson TJ, Gregg EW, Barker LE, Williamson DF (2010) Projection of the year 2050 burden of diabetes in the US adult population: dynamic modeling of incidence, mortality, and prediabetes prevalence. Popul Health Metr 8:29. https://doi.org/10.1186/1478-7954-8-29
6. Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration (2014) Cardiovascular disease, chronic kidney disease, and diabetes mortality burden of cardiometabolic risk factors from 1980 to 2010: a comparative risk assessment. Lancet Diabetes Endocrinol 2 (8):634–647. https://doi.org/10.1016/s2213-8587(14)70102-0
7. Reardon MJ, Van Mieghem NM, Popma JJ, Kleiman NS, Sondergaard L, Mumtaz M, Adams DH, Deeb GM, Maini B, Gada H, Chetcuti S, Gleason T, Heiser J, Lange R, Merhi W, Oh JK, Olsen PS, Piazza N, Williams M, Windecker S, Yakubov SJ, Grube E, Makkar R, Lee JS, Conte J, Vang E, Nguyen H, Chang Y, Mugglin AS, Serruys PW, Kappetein AP (2017) Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. N Engl J Med 376(14):1321–1331. https://doi.org/10.1056/NEJMoa1700456
8. Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, Thourani VH, Tuzcu EM, Miller DC, Herrmann HC, Doshi D, Cohen DJ, Pichard AD, Kapadia S, Dewey T, Babaliaros V, Szeto WY, Williams MR, Kereiakes D, Zajarias A, Greason KL, Whisenant BK, Hodson RW, Moses JW, Trento A, Brown DL, Fearon WF, Pibarot P, Hahn RT, Jaber WA, Anderson WN, Alu MC, Webb JG (2016) Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. N Engl J Med 374(17):1609–1620. https://doi.org/10.1056/NEJMoa1514616
9. Holmes DR Jr, Nishimura RA, Grover FL, Brindis RG, Carroll JD, Edwards FH, Peterson ED, Rumsfeld JS, Shahian DM, Thourani VH, Tuzcu EM, Vemulapalli S, Hewitt K, Michaels J, Fitzgerald S, Mack MJ (2015) Annual outcomes with transcatheter valve therapy: from the STS/ACC TVT registry. J Am Coll Cardiol 66(25):2813–2823. https://doi.org/10.1016/j.jacc.2015.10.021
10. Gerckens U, Tamburino C, Bleiziffer S, Bosmans J, Wenaweser P, Brecker S, Guo J, Linke A (2017) Final 5-year clinical and echocardiographic results for treatment of severe aortic stenosis with a self-expanding bioprosthesis from the ADVANCE Study. Eur Heart J. https://doi.org/10.1093/eurheartj/ehx295
11. Ando T, Takagi H, Briasoulis A, Umemoto T (2017) Does diabetes mellitus impact prognosis after transcatheter aortic valve implantation? Insights from a meta-analysis. J Cardiol. https://doi.org/10.1016/j.jjcc.2017.01.005
12. Mina GS, Gill P, Soliman D, Reddy P, Dominic P (2017) Diabetes mellitus is associated with increased acute kidney injury and 1-year mortality after transcatheter aortic valve replacement: a meta-analysis. Clin Cardiol 40(9):726–731. https://doi.org/10.1002/clc.22723
13. Sun Y, Liu X, He Y, Tang M, Zhu Q, Xu X, Guo D, Shi K, Hu P, Wang L, Kong H, Jiang J, Lin X, Xu Q, Gao F, Wang J (2017) Meta-analysis of impact of diabetes mellitus on outcomes after transcatheter aortic valve implantation. Am J Cardiol 119(4):623–629. https://doi.org/10.1016/j.amjcard.2016.10.048
14. Saad M, Nairooz R, Pothineni NVK, Almomani A, Kovelamudi S, Sardar P, Katz M, Abdel-Wahab M, Bangalore S, Kleiman NS, Block PC, Abbott JD (2017) Long-term outcomes with transcatheter aortic valve replacement in women compared with men: evidence from a meta-analysis. JACC Cardiovasc Interv. https://doi.org/10.1016/j.jcin.2017.08.015
15. Kappetein AP, Head SJ, Genereux P, Piazza N, van Mieghem NM, Blackstone EH, Brott TG, Cohen DJ, Cutlip DE, van Es GA, Hahn RT, Kirtane AJ, Krucoff MW, Kodali S, Mack MJ, Mehran R, Rodes-Cabau J, Vranckx P, Webb JG, Windecker S, Serruys PW, Leon MB (2012) Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. J Am Coll Cardiol 60(15):1438–1454. https://doi.org/10.1016/j.jacc.2012.09.001
16. Sherif MA, Zahn R, Gerckens U, Sievert H, Eggebrecht H, Hambrecht R, Sack S, Richardt G, Schneider S, Senges J, Brachmann J (2014) Effect of gender differences on 1-year mortality after transcatheter aortic valve implantation for severe aortic stenosis: results from a multicenter real-world registry. Clin Res Cardiol 103(8):613–620. https://doi.org/10.1007/s00392-014-0690-6

17. Holmes DR Jr, Brennan J, Rumsfeld JS et al (2015) Clinical outcomes at 1 year following transcatheter aortic valve replacement. JAMA 313(10):1019–1028. https://doi.org/10.1001/jama.2015.1474
18. Farhan S, Baber U, Vogel B, Aquino M, Chandrasekhar J, Faggioni M, Giustino G, Kautzky-Willer A, Sweeny J, Shah S, Vijay P, Barman N, Moreno P, Kovacic J, Dangas G, Kini A, Mehran R, Sharma S (2017) Impact of diabetes mellitus on ischemic events in men and women after percutaneous coronary intervention. Am J Cardiol 119(8):1166–1172. https://doi.org/10.1016/j.amjcard.2016.12.035
19. Rodes-Cabau J, Webb JG, Cheung A, Ye J, Dumont E, Osten M, Feindel CM, Natarajan MK, Velianou JL, Martucci G, DeVarennes B, Chisholm R, Peterson M, Thompson CR, Wood D, Toggweiler S, Gurvitch R, Lichtenstein SV, Doyle D, DeLarochelliere R, Teoh K, Chu V, Bainey K, Lachapelle K, Cheema A, Latter D, Dumesnil JG, Pibarot P, Horlick E (2012) Long-term outcomes after transcatheter aortic valve implantation: insights on prognostic factors and valve durability from the Canadian multicenter experience. J Am Coll Cardiol 60(19):1864–1875. https://doi.org/10.1016/j.jacc.2012.08.960
20. Bleiziffer S, Bosmans J, Brecker S, Gerckens U, Wenaweser P, Tamburino C, Linke A (2017) Insights on mid-term TAVR performance: 3-year clinical and echocardiographic results from the CoreValve ADVANCE study. Clin Res Cardiol 106(10):784–795. https://doi.org/10.1007/s00392-017-1120-3
21. Barbanti M, Latib A, Sgroi C, Fiorina C, De Carlo M, Bedogni F, De Marco F, Ettori F, Petronio AS, Colombo A, Testa L, Klugmann S, Poli A, Maffeo D, Maisano F, Aruta P, Gulino S, Giarratana A, Patane M, Cannata S, Imme S, Mangoni L, Rossi A, Tamburino C (2014) Acute kidney injury after transcatheter aortic valve implantation with self-expanding CoreValve prosthesis: results from a large multicentre Italian research project. EuroIntervention 10(1):133–140. https://doi.org/10.4244/eijv10i1a20

Affiliations

Axel Linke[1] · Florian Schlotter[2] · Stephan Haussig[1] · Felix J. Woitek[1] · Georg Stachel[2] · Jennifer Adam[2] · Robert Höllriegel[1] · Anna Lindner[2] · Friedrich W. Mohr[3] · Gerhard Schuler[2] · Philipp Kiefer[4] · Sergey Leontyev[4] · Holger Thiele[2] · Michael A. Borger[4] · David Holzhey[4] · Norman Mangner[1]

Axel Linke
axel.linke@tu-dresden.de

Florian Schlotter
florian.schlotter@medizin.uni-leipzig.de

Stephan Haussig
stephan.haussig@herzzentrum-dresden.com

Felix J. Woitek
felix.woitek@herzzentrum-dresden.com

Georg Stachel
georg.stachel@medizin.uni-leipzig.de

Jennifer Adam
jennifer.adam@helios-kliniken.de

Robert Höllriegel
robert.hoellriegel@herzzentrum-dresden.com

Anna Lindner
anna_lindner@gmx.net

Friedrich W. Mohr
friedrich.mohr@medizin.uni-leipzig.de

Gerhard Schuler
gerhard.schuler@medizin.uni-leipzig.de

Philipp Kiefer
philipp.kiefer@medizin.uni-leipzig.de

Sergey Leontyev
sergey.leontyev@medizin.uni-leipzig.de

Holger Thiele
holger.thiele@medizin.uni-leipzig.de

Michael A. Borger
michael.borger@helios-kliniken.de

David Holzhey
dholzhey@web.de

[1] Department of Internal Medicine and Cardiology, Heart Center Dresden, Technical University of Dresden, Fetscherstr. 76, 01307 Dresden, Germany

[2] Department of Internal Medicine/Cardiology, Heart Center Leipzig, University Hospital, Leipzig, Germany

[3] Leipzig Heart Institute, Leipzig, Germany

[4] Department of Cardiac Surgery, Heart Center Leipzig, University Hospital, Leipzig, Germany