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Impact of bleeding complications after transcatheter mitral valve repair

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ABSTRACT

Background: Bleeding in the context of cardiac catheterization is frequent and negatively impacts on short- and long-term patient outcome. We evaluated the clinical impact of in-hospital bleeding events after transcatheter mitral valve repair (TMVr) in the long-term follow- up.

Methods: 586 consecutive patients treated with first-time TMVr were enrolled in this registry. In-hospital MVARC (Mitral Valve Academic Research Council) bleedings were assessed and patients were grouped according to the incidence of a bleeding event. Multivariate logistic regression was used to identify significant independent predictors of MVARC bleeding. This study received approval by local ethics committee.

Results: 78 patients (13.3%) suffered from an MVARC bleeding event (Access site-related bleedings: 46.2%; GI tract bleeding: 35.9%; Other bleedings: 17.9%). Among these bleeding subgroups, neither relevant differences in baseline characteristics nor in severity of bleeding events were observed. Despite not being an independent predictor for overall death in the multivariate Cox regression analysis, MVARC bleeding was associated with prolonged hospital stay. The ORBIT bleeding score was the best match to predictors of any MVARC bleeding found in our cohort (c-score overall cohort: 0.68; c-score GI bleeding cohort: 0.72).

Conclusion: MVARC bleedings after TMVr are frequent findings but were only in half of the cases related to the access site. The ORBIT score could be useful for identification of patients at high risk for non-access site bleeding and especially GI bleeding.

1. Introduction

Bleeding events following cardiac interventions are known to negatively impact short and long- term patient outcome [1,2]. Transcatheter mitral valve repair (TMVr) with the MitraClip (MC) system has been increasingly used as treatment for moderate-to-severe or severe symptomatic, degenerative (DMR) as well as functional (FMR) mitral regurgitation over the last two decades [3]. It is mostly used in patients considered poorly suited for surgical intervention due to comorbidities and burdening risk factors [3]. Low rates of both in-hospital and 30-day adverse events make TMVr a low-risk procedure. Among reported adverse events, however, bleeding is among the most frequent [4]. In order to universally report bleeding complications associated with TMVr the Mitral Valve Academic Research Council (MVARC) adopted a bleeding classification for TMVr [5]. A recent analysis in a patient cohort treated with the MC system showed bleeding events to be associated with longer fluoroscopy time and coronary artery disease (CAD). However, especially obscure bleeding with a decrease in hemoglobin levels of ≥ 4 g/dl not defined by MVARC were reported to increase mortality [6]. Other risk factors for bleeding, such as age and gender were identified among patients treated with Trans Catheter Aortic Valve (TAVI) repair [7]. Common bleeding scores, designed to quantify bleeding risk in patients with atrial fibrillation (AF), comprise composites of several other known bleeding

Abbreviations: TMVr, Transcatheter Mitral Valve Repair; MC, MitraClip; MVARC, Mitral Valve Academic Research Council; CKD, Chronic Kidney Disease; AKI, Acute Kidney Injury; NOAC, Novel oral anticoagulant; HAS-BLED, Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (>65 years), Drugs/Alcohol ATRIA, Anticoagulation and Risk factors In Atrial fibrillation; ORBIT, Outcomes Registry for Better Informed Treatment of Atrial Fibrillation.

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risk factors [8,9]. However, it still remains a challenge to properly identify TMVr patients at increased risk of bleeding. In an attempt to understand and sensitize patients at risk, we identified independent predictors associated with in-hospital bleeding after TMVr. Furthermore, we matched our findings to existing composite bleeding risk scores. Risk scores were assessed regarding their ability to predict bleeding in patients treated with TMVr.

2. Methods

2.1. Study population

For this single-center study we retrospectively analyzed all 586 consecutive patients receiving first-time TMVr treatment for either FMR or DMR using the MC system at our institution between January 1st 2010 and December 31st 2018. Patients eligible for TMVr suffered from chronic, symptomatic MR (grade III or IV) confirmed by transesophageal echocardiography (TEE) despite guideline directed medical therapy (GDMT). Patients were evaluated by interdisciplinary heart team and directed towards TMVr by joint decision based on current guidelines [10].

This study was approved by local ethics committee (Ethics Committee of Ulm University) and complied with the standards outlined in the declaration of Helsinki.

2.2. Procedural details and characteristics

TMVr was performed under general anesthesia, using echocardiographic guidance (TEE) and fluoroscopy. Precise details of TMVr using the MC system have been described elsewhere [11]. Most notably, in order to perform TMVr a 24 French (F) introducer sheath via patients' right femoral vein has to be established. This vascular access site in patients' groin was closed with a Z-suture technique after completion of procedure. No specific closure devices were applied. Administration of anticoagulation and platelet inhibitory agents was discontinued prior to procedure according to current guidelines. During the intervention, activated clotting time (ACT) was targeted at 250–300 s. Procedural success was defined as reduction of MR < 2. In general, patients were started on oral anticoagulation on the first postprocedural day for a period of 30 days. Patients with indication for antiplatelet therapy, oral anticoagulation or a combination thereof received an individual treatment strategy (see results).

In-hospital bleeding and vascular access site complications were documented according to standards laid out by the Mitral Valve Academic Research Council (MVARC). Concisely, MVARC criteria differentiate minor and major bleeding. Whereas minor MVARC bleeding essentially is any overt bleeding resulting in intensified patient care or requiring up to two units of blood, major bleeding is an overt bleeding resulting in drop of total Hb of $\geq$ 3 g/dl or requiring the equivalent of $\geq$ 3 units of blood. The MVARC criteria further discern extensive (Hb drop of $\geq$ 4 g/dl), life threatening (bleeding in critical organ or hypovolemic shock or hypotension) and fatal bleedings [5]. For diagnosis of acute kidney injury maximum peak and nadir in serum creatinine levels during hospital stay was used.

2.3. Patient follow-up

Standardized patient follow-up was completed by routine clinical visit or telephone interview at 1, 3, 6 and 12 months, and yearly thereafter. Telephone interviews were carried out by trained study nurses.

2.4. Statistical analysis

For statistical analysis patients were first grouped according to the incidence of MVARC bleeding events. Continuous variables were expressed using mean and standard deviation. Categorical variables were shown as frequencies and percentages. Continuous variables were compared using Mann-Whitney Test or Student's T-test depending on distribution of variables. Categorical variables were compared using Chi-square test or Fisher's exact test as appropriate. For variables significantly differing between groups, which were considered clinically relevant, univariate binary logistic regression was performed. A multivariate logistic regression model was created by forward likelihood inclusion with significant predictors from univariate logistic regression. Variance inflation factor (VIF > 3), Pearson's and Spearman's correlation coefficients (r > 0,4) were used to detect multicollinearity or autocorrelation among variables. Analysis of survival was conducted by Kaplan-Maier curves and Log-Rank test was used to compare MVARC bleeding and non-bleeding groups. Multivariate cox proportional hazards regression was used to quantify the combined impact of any MVARC bleeding on survival. Bleeding scores were compared using c-statistics. A p-value < 0.05 was considered significant for all statistical testing. Statistical analysis was carried out using SPSS, Version 25 (SPSS Statistics, IBM).

3. Results

A total of 586 patients were analyzed for this study. Baseline and procedural characteristics grouped according to in-hospital MVARC bleeding events are shown in Tables 1–3. There were no significant differences in terms of age (p = 0.1), gender (p = 0.57) and body mass index (p = 0.7) in both groups. FMR was the dominating etiology in our patient cohort (overall 62.9%). Technical procedural success was substantial in both patient groups resulting in a total success rate of 98.6% with overall low postprocedural grades of MR (see Table 3). 78 (13.3%) MVARC bleedings occurred during patients' stay at our institution (see Fig. 1). These events were further categorized as 57 (9.7%) minor, 10 (1.7%) major, 8 (1.4%) extensive and 3 (0.5%) life-threatening MVARC bleedings. No fatal bleeding occurred. Thirty six (46.2%) bleeding events were associated with vascular access site complications, whereas about half of bleeding events were non-access site-related. More than one-third (35.9%) of bleeding events were related to the (upper and lower) gastrointestinal tract (GIT). In patients suffering from bleeding events combined stage 3 and 4 chronic kidney disease (CKD) (90.9% vs. 73.6%; p = 0.01) as well as combined NYHA class 3 and 4 (93.6% vs. 84.6%; p = 0.04) were more frequent. 19 (3.7%) patients suffered from acute kidney injury of any stage during their hospital stay. The occurrence of acute kidney injury (AKI) was significantly more frequent in the MVARC bleeding group (8.1% vs. 2.9%; p = 0.04). Regarding baseline medication before MC procedure, NOACs were used to a lesser extent in the MVARC bleeding group (25.6% vs. 42.1%; p = 0.01). Conversely, there was a tendency towards more frequent use of acetylic salicylic acid (56.4% vs. 45.1%), however, this finding narrowly missed the prespecified level of significance (p = 0.06) (see Table 4).

3.1. Follow-up and subgroup analysis according to bleeding sites

Median follow-up time after discharge was 577 days (IQR: 295–1059). Follow-up time was defined as time period until most recent follow-up or death. 17 (2.9%) patients were lost to follow-up, all of which were in the non-bleeding group. Hence, a total of 569 (97.1%) patients were included in the Kaplan-Maier analysis. Moreover, median follow-up time was similar for bleeding and

Table 1
Baseline Characteristics.

	No MVARC Bleeding (n = 508)	MVARC Bleeding (n = 78)	Total (n = 586)	p-value
Female	206 (40.6%)	29 (37.2%)	235 (40.1%)	0.57
Age	76.8 ± 8.7	78.6 ± 6.8	77.1 ± 8.5	0.1
BMI (kg/m^2)	25.7 ± 4.5	25.7 ± 5.0	25.7 ± 4.6	0.7
NYHA Class	3.1 ± 0.7	3.3 ± 0.7	3.1 ± 0.7	**0.01**
NYHA Class III/IV	430 (84.6)	73 (93.6)	503 (85.8)	**0.04**
Euro Score II	7.9 ± 7.4	9.7 ± 7.8	8.1 ± 7.4	**0.01**
STS Risk of mortality score	4.5 ± 5.4	5.4 ± 7.7	4.5 ± 5.74	0.37
CCS Score	1.2 ± 0.6	1.0 ± 0.2	1.2 ± 0.6	**<0.01**
FMR	268 (64.3%)	37 (54.4%)	301 (62.9%)	0.12
LVEF (%)	44.2 ± 17.6	43.8 ± 17.7	47.0 ± 16.6	0.18
eGFR (ml/min)	48.2 ± 19.5	43.2 ± 15.5	47.5 ± 19.1	0.08
Stage of CKD	2.9 ± 0.7	3.2 ± 0.6	2.9 ± 0.7	**<0.01**
CKD Stage III/IV	366 (73.6%)	70 (90.9%)	436 (76.0)	**<0.01**
Atrial fibrillation	339 (66.7%)	55(70.5%)	394 (67.2%)	0.508
Diabetes	145 (28.5%)	20 (25.6%)	165 (28.2%)	0.6
Pulmonary Hypertension	168 (33.1%)	31 (39.7%)	199 (34.0%)	0.25
Stroke in history	59 (11.6%)	5 (6.4%)	64 (10.9%)	0.17
COPD	66 (13.0%)	9 (11.5%)	75 (12.8%)	0.72
Bleeding in history	24 (4.8%)	14 (18.2%)	38 (6.6%)	**<0.01**
HAS-BLED score sum	2.5 ± 0.9	2.7 ± 1.0	2.5 ± 1.0	**0.04**
ATRIA score sum	4.4 ± 2.5	5.3 ± 2.7	4.5 ± 2.6	**<0.01**
ORBIT score sum	3.0 ± 1.5	4.1 ± 1.5	3.1 ± 1.5	**<0.01**

Abbreviations: BMI = Body Mass Index (kg/m^2); NYHA = New York Heart Association; STS = Society of Thoracic Surgeons; CCS = Canadian Cardiovascular Society; FMR = functional mitral regurgitation; LVEF = left ventricular ejection fraction; eGFR = estimated glomerular filtration rate; CKD = chronic kidney disease; COPD = Chronic Obstructive Pulmonary Disease.

Table 2
Preprocedural Laboratory Parameters and Patient Medication.

	No MVARC Bleeding (n = 508)	MVARC Bleeding (n = 78)	Total (n = 586)	p-value
Troponin T, ng/l	38.7 ± 40.4	47.22 ± 39.9	39.7 ± 40.4	0.14
NT-pro BNP, pg/ml	6040.8 ± 6710.4	8856.5 ± 7009.9	5984.6 ± 7319.1	**0.01**
INR	1.4 ± 2.0	1.4 ± 0.5	1.4 ± 1.8	0.05
PTT (s)	38.2 ± 18.8	38.9 ± 16.1	38.3 ± 18.5	0.57
Hemoglobin level (g/dl)	12.6 ± 5.6	11.6 ± 1.9	12.5 ± 5.2	**<0.01**
Platelet count (per nl)	198.8 ± 79.8	190 ± 87.0	197.6 ± 80.8	0.35
VKA	76 (15.0%)	16 (20.5%)	92 (15.7%)	0.21
ASS	229 (45.1%)	44 (56.4%)	273 (46.6%)	0.06
NOAC	214 (42.1%)	20 (25.6%)	234 (39.9%)	**0.01**
Rivaroxaban	87 (17.1%)	4 (5.1%)	91 (15.5%)	**0.01**
Apixaban	102 (20.1%)	11 (14.1%)	113 (19.3%)	0.21
Edoxaban	18 (3.5%)	4 (5.1%)	22 (3.8%)	0.49
Dabigatran	7 (1.4%)	1 (1.3%)	8 (1.4%)	0.95
$P2Y_{12}$ Inhibitor	113 (22.2%)	20 (25.6%)	133 (22.7%)	0.51
Ticagrelor	7 (1.4%)	0 (0.0%)	7 (1.2%)	0.3
Clopidogrel	100 (19.7%)	19 (24.4%)	119 (20.3%)	0.34
Prasugrel	6 (1.2%)	1 (1.3%)	7 (1.2%)	0.94
Triple Therapy	17 (3.3%)	3 (3.8%)	20 (3.4%)	0.821
DAPT	79 (15.6%)	16 (20.5%)	95 (16.2%)	0.268
$P2Y_{12}$ Inhibitor and NOAC	43 (8.5%)	6 (7.7%)	49 (8.4%)	0.819

Abbreviations: NT-proBNP = N-terminal pro hormone brain natriuretic peptide; INR = international normalized ratio; PTT = partial thromboplastin time; VKA = vitamin K antagonists; ASS = acetylic salicylic acid; NOAC = novel oral anticoagulant; $P2Y_{12}$ Inhibitor = adenosine diphosphate receptor antagonists.
DAPT = dual antiplatelet therapy.

Table 3
Procedural Characteristics.

	No MVARC Bleeding (n = 508)	MVARC Bleeding (n = 78)	Total (n = 586)	p-value
Technical Success	501 (98.6)	77 (98.7)	587 (98.7)	1.0
Grade of MR post (I-IV)	1.51 ± 0.6	1.6 ± 0.7	1.52 ± 0.7	0.28
MR Grade IV post	2 (0.4)	0 (0)	2 (0.3)	1.0
No. of MCs implanted	1.3 ± 0.5	1.4 ± 0.5	1.3 ± 0.5	0.1
Fluoroscopy time (s)	1772.96 ± 937.6	1840.7 ± 863.9	1781.6 ± 927.0	0.23
ACT peak	270.3 ± 63.9	277.4 ± 57.8	271.3 ± 63.1	0.07

Abbreviations: MR = mitral regurgitation; No. = number; MC = MitraClip; ACT = activated clotting time.

non-bleeding groups (Non-bleeding group: 541 days, IQR: 303–1043; Bleeding group: 662 days, IQR: 209–1203; p = 0.45). Kaplan-Maier survival analysis showed a significant difference in survival between these groups (48% vs. 22% for the non-bleeding and bleeding group, respectively; log rank test p = 0.01; see also figure 2A in supplements). In univariate Cox regression analysis

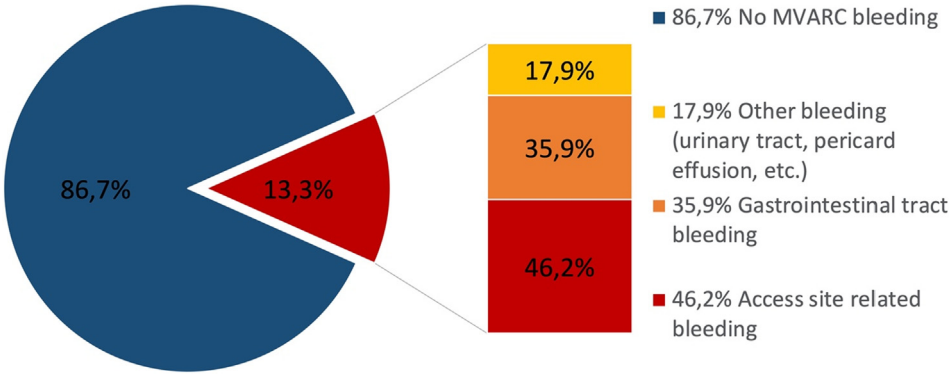

Fig. 1. Incidence of MVARC bleeding and bleeding sites after TMVr.

Table 4
Postprocedural Characteristics and Patient Medication.

	No MVARC Bleeding (n = 508)	MVARC Bleeding (n = 78)	Total (n = 586)	p-value
(AKIN I, II, III)	13 (2.9%)	6 (8.1%)	19 (3.7%)	**0.04**
Hospital stay (days)	6.3 ± 4.8	9.6 ± 5.5	6.7 ± 5.0	**<0.01**
Troponin T, ng/ml	66.4 ± 56.3	46.9 ± 20.2	71.9 ± 64.3	0.11
NT-pro BNP, pg/ml	6040.8 ± 6710.4	8856.5 ± 7009.9	6311.5 ± 6756.3	0.13
INR	1.5 ± 2.1	1.4 ± 0.5	1.5 ± 1.9	0.26
PTT	48.0 ± 31.8	43.4 ± 16.1	47.2 ± 29.7	0.61
Hemoglobin level (g/dl)	11.3 ± 1.8	10.3 ± 1.7	11.1 ± 1.8	**<0.01**
Platelet count	184.7 ± 86.0	175.0 ± 74.7	183.4 ± 84.6	0.39
VKA	29 (5.8%)	11 (14.3%)	40 (7.0%)	**<0.01**
NOAC	405 (81.2%)	47 (61.0%)	452 (78.5%)	**<0.01**
ASS and Clopidogrel	72 (14.4%)	17 (22.1%)	89 (15.5%)	0.08
Triple Therapy	43 (8.6%)	10 (13.0%)	53 (9.2%)	0.22
DAPT	79 (15.8%)	17 (22.1%)	96 (16.7%)	0.17
$P2Y_{12}$ Inhibitor and NOAC	73 (14.6%)	14 (18.2%)	87 (15.1%)	0.42

Abbreviations: AKIN = acute kidney injury stadium; NT-proBNP = N-terminal pro hormone brain natriuretic peptide; INR = international normalized ratio; PTT = partial thromboplastin time; ; VKA = vitamin K antagonists; NOAC = novel oral anticoagulant; DAPT = dual antiplatelet therapy; $P2Y_{12}$ Inhibitor = adenosine diphosphate receptor antagonists.

MVARC bleeding was associated with 1.55-fold increased odds for overall death (95% CI: 1.093–2.201; p = 0.01). Moreover, we compared survival of patients with access site-related bleeding events and GI tract related bleeding events with non-bleeding patients (see figure 2). Survival in patients with access site-related bleeding or other bleeding did not differ from non-bleeding patients (see figure 2C and D in supplements). However, survival in patients with GI tract bleeding was significantly different from non-bleeding patients in Kaplan Maier analysis (see figure 2B in supplements). GI tract bleeding was associated with 1.87-fold increased odds for overall death (95% CI: 1.131–3.093; p = 0.02) in univariate Cox regression analysis. GI tract bleeding patients were compared to non GI tract bleeding sites (see Table 9). Severity of bleeding events (rate of major, extensive, life threatening or fatal MVARC bleeding) was similar in the access site and non-access site bleeding group (10 (27.8%) vs. 11 (26.2%); p = 0.88), as well as in the GI tract bleeding group compared to all other bleeding groups (5 (17.9%) vs. 16 (32.0%); p = 0.18) (see Table 9). Preprocedural hemoglobin level was significantly lower in GI tract bleeding patients compared to non GI tract bleeding patients (11.1 ± 1.9 vs. 12.0 ± 1.8; p = 0.04). 30 day mortality rate did not vary between any of the subgroups and non-bleeding patients (see Table 9). Most importantly, in multivariate cox regression analysis strongest predictors for death were NYHA class (OR: 2.658; 95% CI 1.072–6.59;

Table 5
Univariate Logistic Regression for Predictors of MVARC Bleeding.

	No MVARC (n = 508)	MVARC (n = 78)	Total (n = 586)	
	b	**OR**	**95% CI**	**p-value**
NYHA Class III/IV	0.974	2.6	1.037–6.764	**0.04**
EURO Score II	0.014	1.028	1.0–1.057	**0.049**
CCS Score	−1.53	0.214	0.058–0.787	0.02
NT-pro BNP	0.763	2.145	1.193–3.854	**0.01**
Hemoglobin level (g/dl) (preprocedural)	−0.216	0.806	0.711–0.914	**<0.01**
NOAC (preprocedural)	−0.221	0.802	0.613–1.048	0.11
Rivaroxaban (preprocedural)	−1.34	0.262	0.093–0.734	**0.01**
CKD Stage III/IV	1.275	3.58	1.605–7.983	**<0.01**
ACT peak (s)	0.002	1.002	0.998–1.005	0.37
Bleeding history	1.49	4.44	2.18–9.0	**<0.01**

Abbreviations: NYHA = New York Heart Association; CCS = Canadian Cardiovascular Society; NT-proBNP = N-terminal pro hormone brain natriuretic peptide; NOAC = novel oral anticoagulant; CKD = chronic kidney disease; ACT = activated clotting time.

p = 0.04), atrial fibrillation (OR: 1.839; 95% CI 1.096–3.087, p = 0.02) and NT-proBNP (OR: 2.025, 95% CI 1.309–3.133, p = 0.02) (see supplements), whereas the combined incidence of any MVARC bleeding did not remain an independent predictor of death in our cohort.

Results of univariate and multivariate logistic regression for independent predictors of MVARC bleeding events are presented in Tables 5 and 6. In multivariate logistic regression combined stage III and IV CKD and history of bleeding remained as significant independent predictors of MVARC bleeding.

3.2. Assessment of bleeding risk

We compared common bleeding scores (HAS-BLED, ATRIA, ORBIT Scores) widely used in clinical practice regarding their ability to predict bleeding (see figure 2). Table 7 shows c-statistics applied on our patient cohort for these scores. Among these, the ORBIT score performed best in accurately predicting MVARC bleeding (c-score: 0.68) compared to the HAS-BLED (c-score:0.59) and the ATRIA score (c-score: 0.6). In the subgroup of GI tract bleeding the ORBIT score performs even better with a c-score of 0.72 (95% CI: 0.62–0.81; p < 0.01). The ORBIT Score calculates bleeding risk based on hemoglobin level (gender specific), impaired renal function (stage III and IV CKD), history of bleeding, treatment with antiplatelet agents and older age (≥74) [8] (see Table 8).

Table 6
Multivariate Logistic Regression for Predictors of MVARC bleeding.

	B	OR	95% CI	p-value
CKD Stage III/IV	1.545	4.686	1.62–13.56	**<0.01**
Bleeding history	1.465	4.329	1.789–10.473	**<0.01**

Abbreviations: CKD = chronic kidney disease.

Table 7
C-Statistics for Composite Bleeding Scores.

Bleeding scores - All MVARC bleeding	c-score	95% CI for c-score	p-value
ORBIT score	0.68	0.62–0.74	**<0.01**
ATRIA score	0.60	0.53–0.67	**<0.01**
HAS BLED score	0.59	0.52–0.66	**0.02**
Non-access site bleeding			
ORBIT score	0.68	0.6–0.76	**<0.01**
ATRIA score	0.59	0.5–0.68	0.07
HAS BLED score	0.61	0.52–0.69	**0.03**
Access site-related bleeding			
ORBIT score	0.65	0.56–0.75	**<0.01**
ATRIA score	0.6	0.5–0.71	**0.04**
HAS BLED score	0.55	0.45–0.65	0.29
GI Tract bleeding			
ORBIT score	0.72	0.63–0.81	**<0.01**
ATRIA score	0.64	0.53–0.75	**0.02**
HAS BLED score	0.64	0.53–0.74	**0.02**
Other bleeding			
ORBIT score	0.64	0.49–0.78	0.09
ATRIA score	0.52	0.38–0.66	0.81
HAS BLED score	0.56	0.42–0.7	0.43

Table 8
Subgroup comparison of 30 day mortality rates compared to non-bleeding patients.

	30 day mortality	p-value
No MVARC bleeding	20 (4.1%)	
Access site-related bleeding	1 (2.8%)	0.7
GI tract bleeding	3 (10.7%)	0.1
Other bleeding	1 (7.1%)	0.57

Abbreviations: GI = gastrointestinal tract.

4. Discussion

4.1. Main findings

We present the results of our single-center retrospective analysis focused on in-hospital MVARC bleeding complications and its influence on outcome after TMVr with the MC system. To the best of our knowledge, this is the largest analysis specifically addressing such bleeding complications so far. The main findings of this study are as follows:

(1) Half of the in-hospital MVARC bleedings after TMVr and 24F sheath insertion were related to the vascular access site.
(2) Severe chronic kidney disease and bleeding in patients' history are independent predictors for all subgroups of MVARC bleedings.
(3) Bleeding led to prolonged hospital stays, however, MVARC bleeding was not an independent predictor of death.
(4) The ORBIT scores composites most accurately matched predictors of bleeding found in our cohort. Thus, the ORBIT score performed best in predicting bleeding events in the overall cohort and especially in bleeding subgroups.

4.2. Incidence of MVARC bleeding events and impact in mortality - site matters?

In our cohort, 13.3% of patients suffered from any type of MVARC bleeding event. 9.7% were considered only minor bleedings. 3.6% were major, extensive or life threatening according to MVARC definitions. Similar to our findings, in the ACCESS-EU registry a rate of 3.9% severe bleeding (safety outcomes at 30 days) was observed [12]. The TRAMI and EVEREST II investigators reported rates of 7.5% and 13.4% of severe bleeding or transfusion [3,13]. Therefore, this investigation confirms bleeding to be a frequent finding among patients treated with TMVr. Körber et al. previously reported 33.3% in 347 patients treated with the MC procedure [6]. In our cohort, almost half of bleedings (46.2%) were attributable to access site complications. Access site bleeding requires additional special care (compression treatment, ultrasound exams) leading to prolonged hospital stay. For this reason, more effort should be directed towards reduction of access site-related bleedings. Ultrasound guided puncture has shown to reduce rate of access site-related bleedings in cardiac interventions requiring venous femoral access [14]. Steppich et al. investigated possible advantages of closure devices (ProGlide, Abott Vascular) for venous femoral access closure in MitraClip patients. 150 patients treated with a Z-suture were compared to 127 patients in which vascular access closure was performed using a closure device. Since the rate of vascular complications and mortality were similar in both groups, utilization of a closure device did not seem to be beneficial. First, slightly more than half of bleeding events in this study were not access site-related, similar to our results. Second, vascular access site-related complications did not increase mortality [15]. However, Körber et al. found an increase in mortality when combining patients suffering from either MVARC or obscure extensive bleeding. Obscure extensive bleeding was defined as decreased hemoglobin levels ≥ 4 g/dl without obvious bleeding source. In accordance to Steppich et al. and our results, Körber et al. did not report increased mortality in their MVARC access site bleeding population [6].

At first glance, it seemed GI bleeding might be associated with increased mortality in the long-term follow-up. However, multi-

Table 9
Comparison of GI tract bleeding and non GI tract bleeding sites.

	GI Bleeding (n = 28)	Non GI bleeding sites (n = 50)	Total (n = 78)	p-value
MVARC bleeding (major, extensive, life-threatening, fatal)	5 (17.9%)	16 (32.0%)	21 (26.9%)	0.18
MVARC bleeding (minor)	23 (82.1)	34 (68.0%)	57 (73.1%)	0.18
Female	12 (42.9%)	17 (34.0%)	29 (37.2%)	0.44
Age	80.4 ± 6.3	77.6 ± 6.9	78.6 ± 6.8	0.08
BMI (kg/m^2)	24.5 ± 4.9	26.4 ± 4.9	25.7 ± 5.0	0.09
NYHA Class	3.4 ± 0.7	3.3 ± 0.7	3.3 ± 0.7	0.2
NYHA Class III/IV	27 (96.4%)	46 (92.0%)	73 (93.6%)	0.44
Euro Score II	11.3 ± 8.2	8.77 ± 7.5	9.7 ± 7.8	0.17
STS Risk of mortality score	4.7 ± 4.1	5.8 ± 9.1	5.4 ± 7.8	0.56
CCS Score	1.0 ± 0.2	1.0 ± 0.1	1.0 ± 0.2	0.68
FMR	14 (53.8%)	23 (54.8%)	37 (54.4%)	0.94
eGFR (ml/min)	41.0 ± 13.3	44.4 ± 16.6	43.2 ± 15.5	0.36
Stage of CKD	3.2 ± 0.6	3.1 ± 0.6	3.2 ± 0.6	0.4
CKD Stage III/IV	25 (92.6%)	45 (90.0%)	70 (90.9)	0.71
Atrial fibrillation	22 (78.6%)	33 (66.0%)	55 (70.5%)	0.24
Diabetes	4 (14.3%)	16 (32.0%)	20 (25.6%)	0.09
Bleeding in history	9 (18.0%)	5 (18.5%)	14 (18.2%)	0.96
HAS-BLED score sum	2.9 ± 1.0	2.7 ± 1.0	2.7 ± 1.0	0.46
ATRIA score sum	5.7 ± 2.7	5.1 ± 2.7	5.3 ± 2.7	0.36
ORBIT score sum	4.2 ± 1.4	4.0 ± 1.6	4.1 ± 1.5	0.47
Procedural Details				
Technical Success	28 (100%)	49 (100.0%)	77 (98.7)	0.45
Grade of MR post (I-IV)	1.7 ± 0.7	1.5 ± 0.7	1.6 ± 0.7	0.32
No. of MCs implanted	1.3 ± 0.4	1.5 ± 0.5	1.4 ± 0.5	0.06
Fluoroscopy time (s)	1822.6 ± 656.1	1850.5 ± 965.3	1840.7 ± 863.9	0.91
ACT peak	274.0 ± 82.1	279.3 ± 38.1	277.4 ± 57.8	0.7
Preprocedural Laboratory Parameters and Patient Medication				
Troponin T (ng/l)	47.1 ± 40.0	47.3 ± 40.5	47.2 ± 39.9	0.99
NT-pro BNP (pg/ml)	7413.5 ± 7544.9	9104.8 ± 9133.4	8498.5 ± 8562.4	0.5
INR	1.4 ± 0.4	1.3 ± 0.5	1.4 ± 0.4	0.69
PTT (s)	38.7 ± 8.9	39.1 ± 19.1	38.9 ± 16.1	0.92
Hemoglobin level (g/dl)	11.1 ± 1.9	12.0 ± 1.8	11.6 ± 1.9	**0.04**
Platelet count (per nl)	173.2 ± 69.2	199.7 ± 94.8	190.2 ± 87.0	0.2
VKA	8 (28.6%)	8 (16.0%)	16 (20.5%)	0.19
NOAC	4 (14.3%)	16 (32.0%)	20 (25.6%)	0.09
Rivaroxaban	0 (0.0%)	4 (8.0%)	4 (5.1%)	0.12
Apixaban	8 (16.0%)	3 (10.7%)	11 (14.1%)	0.52
Edoxaban	0 (0.0%)	4 (8.0%)	4 (5.1%)	0.12
Dabigatran	1 (3.6%)	0 (0.0%)	1 (1.3%)	0.18
$P2Y_{12}$ Inhibitor	6 (21.4%)	14 (28.0%)	20 (25.6%)	0.52
Ticagrelor	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Clopidogrel	6 (21.4%)	13 (26.0%)	19 (24.4%)	0.65
Prasugrel	0 (0.0%)	1 (2.0%)	1 (1.3%)	0.45
Triple Therapy	1 (3.6%)	2 (4.0%)	3 (3.8%)	0.93
DAPT	5 (17.9%)	11 (22.0%)	16 (20.5%)	0.66
$P2Y_{12}$ Inhibitor and NOAC	2 (7.1%)	4 (8.0%)	6 (7.7%)	0.89

Abbreviations: BMI = Body Mass Index (kg/m^2); NYHA = New York Heart Association; CCS = Canadian Cardiovascular Society; STS = Society of Thoracic Surgeons; FMR = functional mitral regurgitation; eGFR = estimated glomerular filtration rate; CKD = chronic kidney disease; MR = mitral regurgitation; No. = number; MC = MitraClip; ACT = activated clotting time; NT-proBNP = N-terminal pro hormone brain natriuretic peptide ; INR = international normalized ratio; PTT = partial thromboplastin time; VKA = vitamin K antagonists; NOAC = novel oral anticoagulant; $P2Y_{12}$ Inhibitor = adenosine diphosphate receptor antagonists; DAPT = dual antiplatelet therapy.

variate Cox regression determined other factors such as NYHA class, AF and NT-proBNP outweigh the impact of bleeding on survival.

We found that preprocedural NOAC use was significantly lower in bleeding patients (42.1% vs. 25.6%; p = 0.01). It is retrospectively paradoxical that those patients not receiving NOAC appear to have higher bleeding risk. A possible explanation could be that patients with high bleeding risk were denied any form of OAC to avoid bleedings in the first place. Thus, periprocedural anticoagulation might be especially harmful for these patients.

4.3. Negative effects of MVARC bleeding events on patient survival and the role of chronic kidney disease

Körber et al. reported the procedural ACT peak and intervention duration, reflecting prolonged exposure to heparin, to be associated with increased risk of bleeding [6]. In our patients a tendency towards higher ACT peaks was observed in bleeding patients (277.4 ± 57,8 vs. 270.3 ± 63,9; p = 0.06). The use of unfractionated heparin (UFH) and ACT monitoring for cardiovascular disease patients is recommended in European guidelines [16]. It is considered safe and widely used when treating cardiovascular disease patients [17]. Nevertheless, chronic kidney and cardiovascular disease share an odd relationship when it comes to bleeding risk and anticoagulants. While CKD seems to result in a hypercoagulable state due to the various metabolic disturbances it entails (e.g. systemic inflammation, oxidative stress, RAAS activation, hyperhomocysteinemia) the hemorrhagic risk also increases with declining kidney function [18]. Physicians have to consider this special relationship when treating patients with high prevalence of renal and cardiovascular disease. In a *meta*-analysis conducted by Shah et al. of 5213 patients who had undergone TMVr in North American centers only 1203 (23%) were found to have near normal renal function (GFR > 60 ml/min). The majority of patients (N = 2872; 74%) were found either in CKD class III (GFR < 60 ml/min) or CKD class IV (GFR < 30 ml/min). Although not significant, in this investigation

major in-hospital bleeding occurred more frequently in patients with GFR < 60 ml/min compared to patients with near normal renal function (3.1% vs. 1.8%, respectively; p = 0.10). Renal disease (CKD stage III) was associated with a higher risk of all-cause mortality (OR = 1.57; 95% CI = 1.14–2.16; p < 0.006) as well as any bleeding event (OR = 1.38; 95% CI = 1.04–1.84; p = 0.03) at 1-year follow-up [19]. The results of the national cardiovascular data registry of the society of thoracic surgeons/American college of cardiology conform to our findings. In our cohort 73.6% of patients had stage III or IV CKD and this stage of CKD was strongly associated with in-hospital MVARC bleeding events (OR = 4.686; 95% CI: 1.62–13.56; p < 0.01).

4.4. How can bleeding risk be properly assessed before TMVr?

Comparison of c-statistics showed that the ORBIT score's ability to predict bleeding in MC patients seems to exceed that of other commonly used bleeding scores (HASBLED and ATRIA). This finding also applies to our subgroups (see Table 7). The simple, five-item ORBIT score was initially developed to predict bleeding in patients with atrial fibrillation [8]. In our cohort we identified advanced CKD (GFR < 60 ml/min) and history of bleeding as independent predictors of bleeding. Thus, the ORBIT score best matches predictors of bleeding found in our cohort. It must be pointed out that it still remains difficult to determine at risk patients with very high precision. C-scores do neither exceed 0.7 in the original ORBIT score study, nor in the HAS-BLED study when patients with OAC were analyzed [8,9].

Both the ATRIA as well as the HAS-BLED score account differently for renal damage: ATRIA uses a lower GFR cut-off than ORBIT (<30 ml/min vs. 60 ml/min) and in HAS-BLED renal disease is based on serum creatinine level as opposed to GFR [8,20]. All of these scores emphasize the fact that age increases the risk of bleeding, however, cut-off levels are different (65, 75 and 74 for HAS-BLED, ATRIA and ORBIT score, respectively) [8,9,20]. The HAS-BLED score further accounts for the presence of other diseases such as alcohol abuse and liver injury [9]. In our cohort, the more comprehensive character of HAS-BLED seems to diminish its discriminatory power to accurately predict bleeding.

We did not include acute kidney injury in regression analysis as it represents a condition developing during or in the aftermath of the MC procedure and can therefore not be used to predict bleeding in advance. However, we note that AKI is more frequent in the bleeding group (8.1% vs. 2.9%, p = 0.04). Patients suffering from CKD are at risk to develop acute on chronic AKI in the context of cardiac catheterization [21]. Whether AKI is the cause or complication of bleeding in these patients cannot be determined with utmost certainty.

We like to point out that MVARC bleeding led to prolonged hospital stays incurring higher costs on health care providers.

4.5. Strengths and limitations

We present the results of a single-center retrospective analysis of patients with MVARC bleeding complications. During a median follow-up period of 579 days (IQR: 295–1059) 2.9% of patients were lost to follow-up. Our study provides risk factors associated with bleeding rather than precise causes of bleeding since those events often are multifactorial, especially in a multimorbid patient group. Due to this study's retrospective and single-center character design, systematic bias among baseline risk factors for death and bleeding cannot be ruled out. MVARC bleeding was associated with increased risk for overall death in univariate cox regression, however, did not remain an independent predictor in multivariate cox regression.

5. Conclusion

MVARC bleedings are a frequent finding after TMVr. Severe chronic kidney disease and bleeding history are independent predictors of MVARC bleeding events. This is reflected in the instance that bleeding in TMVr treated cohorts is a systemic, rather than simply a vascular access site problem in about half of the cases. We suggest the use of the ORBIT score to assess bleeding risk in TMVr treated cohorts to identify patients at risk for bleeding. Patients with high ORBIT score (≥4 and higher) should receive special attention when TMVr is performed. Efforts to shorten procedure time and minimize periprocedural heparin exposure, and postprocedural close monitoring in particular could be key in reduction of bleeding events.

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Appendix A. Supplementary material

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