IJC Heart & Vasculature 21 (2018) 16–21

Contents lists available at ScienceDirect

IJC Heart & Vasculature

journal homepage: http://www.journals.elsevier.com/ijc-heart-and-vasculature

Incidence and prognostic implications of late bleeding events after percutaneous mitral valve repair

Tomás Benito-González [a], Rodrigo Estévez-Loureiro [a,d,*], Armando Pérez de Prado [a], Carlos Minguito-Carazo [a], Samuel del Castillo García [a], Carmen Garrote-Coloma [a], Ignacio Iglesias-Gárriz [a], David Alonso-Rodríguez [a], Javier Gualis Cardona [b], Carlos Cuellas Ramón [a], María López Benito [a], Julia Vidán Estévez [c], Felipe Fernández-Vázquez [a]

[a] Department of Cardiology, University Hospital of León, León, Spain
[b] Department of Cardiovascular Surgery, University Hospital of León, León, Spain
[c] Department of Hematology, University Hospital of León, León, Spain
[d] Department of Cardiology, University Hospital Puerta de Hierro-Majadahonda, Madrid, Spain

ARTICLE INFO

Article history:
Received 19 July 2018
Received in revised form 4 September 2018
Accepted 11 September 2018
Available online 19 September 2018

Keywords:
MitraClip
Atrial fibrillation
Bleeding events

ABSTRACT

Objectives: MitraClip is an established therapy for patients with mitral regurgitation (MR) that are considered of high-risk or inoperable. However, late bleeding events (BE) after hospital discharge and their impact on prognosis in this cohort of patients have been poorly investigated. Our purpose is to address the incidence, related factors and clinical implications of BE after hospital discharge in patients treated with MitraClip.

Methods: Prospective registry of all consecutive patients (n = 80) who underwent MitraClip implantation in our Institution between June 2014 and December 2017. BE were defined according to MVARC definitions. A combined clinical end-point including admission for heart failure (HF) and all-cause mortality was established to analyze prognostic implications of BE.

Results: During a median follow up of 523.5 days, 41 BE were reported in 21 patients. Atrial fibrillation (AF, HR 4.54, CI95% 1.20–17.10) and combined antithrombotic therapy at discharge (HR 3.52, CI95% 1.03–11.34) were independently associated with BE. In the study period, 15 (18.8%) patients died, 20 (25%) were admitted for HF and 29 (36.3%) presented the combined end-point. After multivariable adjustment BE remained independently associated with an adverse outcome (HR 3.80, CI 95% 1.66–8.72). In the subgroup of patients with AF, HAS-BLED score was higher among subjects with BE (3.1 ± 1.3 vs 2.1 ± 0.9, p = 0.003). HAS-BLED score had a significant discrimination power for the occurrence BE (AUC: 0.677 [0.507–0.848]) in this subgroup.

Conclusions: BE are common after MitraClip and are associated with an impaired outcome. Strategies to reduce bleeding events are paramount in this cohort of patients.

1. Introduction

Percutaneous mitral valve repair (PMVR) with MitraClip© (Abbot Vascular, Santa Clara, USA) has emerged in the last decade as an alternative treatment for patients with symptomatic mitral regurgitation (MR) deemed at high risk or inoperable for conventional mitral valve surgery [1,2]. This population is therefore characterized by increased comorbidities, advanced age and frailty, which might lead to high risk for bleeding events [3–5]. Prevalence of atrial fibrillation (AF), previous valvular surgery, prior coronary revascularization or peripheral artery disease (PAD) is high in this scenario [6–8]. Therefore, most of these patients have indication for long-term antithrombotic therapy, thus increasing hemorrhagic risk. The risk of bleeding events (BE) might further increase due to frequent indication for combined antiplatelet and chronic oral anticoagulation (OAC) treatment in this population [9,10].

Periprocedural bleeding events following other transcatheter valvular therapies are related to poor outcomes [11,12]. In contrast to other cardiovascular interventions, the majority of BE after PMVR are not access site related and postprocedural obscure bleeding is particularly associated with worse outcomes [13]. However, no data are available regarding the incidence and prognosis implications of BE during follow up after discharge for PMVR. Therefore, the aim of our study is to analyze the incidence and prognostic implications of late BE in a population of patients undergoing PMVR.

* Corresponding author at: Department of Cardiology, University Hospital of León, Altos de Nava SN, 24071 León, Spain.
E-mail addresses: roiestevez@hotmail.com, rodrigo.estevez@salud.madrid.org (R. Estévez-Loureiro).

https://doi.org/10.1016/j.ijcha.2018.09.004

2. Methods

2.1. Study population

Prospective registry of all consecutive patients (n = 80) who underwent PMVR in the University Hospital of León between June 2014 and December 2017 was performed. A sensitivity analysis segregating patients with AF was also conducted. The subgroup of patients with AF were also analyzed separately.

2.2. Study procedures

Indication for PMVR was discussed in an interdisciplinary heart team including interventional and clinical cardiologists, cardiac surgeons and specialists in cardiovascular imaging. The procedure was performed according to standard practices under general anesthesia with transesophageal echocardiographic and fluoroscopic guidance. In patients with AF or another indication for OAC therapy (such as mechanical prosthetic valve), antithrombotic therapy (ATT) at discharge was individualized in each case according to comorbidities and hemorrhagic and thromboembolic risks. In patients with no indication for chronic OAC, dual antiplatelet therapy (DAPT) with Aspirin 100 mg and Clopidogrel 75 mg once a day was maintained for one month after PMVR. Unless there was another indication for longer single or DAPT, both antiplatelet drugs were stopped at 30 days of follow up. In case of indication for antiplatelet therapy in association with anticoagulation, Aspirin 100 mg and/or Clopidogrel 75 mg once a day were used alongside with physician's criteria. According to recent ECS guidelines [14], modifiable and potentially modifiable factors associated with higher risk for bleeding in patients with AF (such as uncontrolled hypertension, anemia or impaired renal function) were addressed and treated during follow up at our local HF unit. None of the included patients was on nonsteroid anti-inflammatory drugs or active alcohol abuse.

Baseline, echocardiographic and procedural characteristics were collected. Blood tests including serum free hemoglobin (Hb) and hematocrit (Ht) were performed the day of the procedure and within routine first out of hospital clinical follow up at 2 months. Preprocedural platelet count and serum albumin was also retrieved. Clinical follow up was carried out including BE (up to 5 events were recorded in each patient), admission for heart failure (HF) and all-cause mortality. Regional blood transfusion database and electronic medical records were checked. Patients were contacted by phone if necessary. Data collection was approved by the local ethics committee of the University Hospital of León.

2.3. Study end-points

Bleeding and clinical events were defined according to Mitral Valve Academic Research Consortium (MVARC) definitions [15]. Only BE after hospital discharge was reported in the present analysis. Significant drop in Hb over 3 g/dL and/or requiring transfusion of blood products without apparent source of bleeding was defined as obscure bleeding [13]. Anemia was defined by the WHO definitions as Hb < 12 g/dL in woman and Hb < 13 g/dL in men [16]. CHA_2DS_2VASc [17] and HAS-BLED [18] scores were used to assess thromboembolic and hemorrhagic risks in the subgroup of patients with AF. High risks were defined by $CHA_2DS_2VASc \geq 3$ and HAS-BLED ≥ 3, respectively. For comparative analysis, ongoing treatment at the time of bleeding and at 30 days follow up were considered as the ATT in patients with and without BE. In patients with follow up shorter than 30 days, ATT at discharge was selected. Combined antithrombotic therapy was defined as the concomitant administration of anticoagulants and antiplatelet drugs, either single or DAPT. A combined clinical end-point including admission for HF and all-cause mortality was established to analyze prognostic implications of late BE.

2.4. Statistical analysis

Continuous variables were summarized as mean ± standard deviation (SD) or as medians and interquartile range (IQR), and were compared using Student *t*-test or Mann-Whitney rank sum tests depending on normality. Categorical variables were described as percentages and compared using Chi-square or Fisher exact tests accordingly. Survival curves for time-to-event variables were constructed on the basis of all available follow-up data using Kaplan-Meier estimates and comparisons were performed using the log-rank test.

Cox regression multivariate analysis was performed to identify independent predictors of BE and adjustment of prognostic impact of BE regarding the combined primary end-point. Parameters for which a statistically significant difference was found between patients with and without BE were entered in the analyses. Other covariates with clinical interest were also included. Proportionality assumption for the COX regression model was checked by using the Schoenfeld and scaled Schoenfeld residuals. A p-value < 0.05 was regarded as statistically significant. Statistical analyses were performed using STATA software version 14.2.

3. Results

Patients undergoing MitraClip implantation were severely symptomatic at the time of the procedure so that 96.3% of them had been admitted for HF within the prior year and/or were in advanced functional class NYHA III-IV. PMVR was successfully performed (residual MR ≤ 2+) in all but 3 cases (96.3%) and more than one clip was implanted in 33 (41.3%) cases.

Baseline, echocardiographic and periprocedural characteristics of the cohort are displayed in Tables 1 and 2 grouped according to the occurrence of BE during follow up.

During a median follow up of 523.5 [IQR 283–788.5] days, 41 BE were reported in 21 (26.3%) patients, 31(78%) of them requiring transfusion of at least 1 unit of whole blood or packed red blood cells. Nine (42.9%) patients presented repeated BE during follow up and 15 (71.4%) subjects presented BE requiring transfusion or major or extensive BE. First BE occurred mostly in patients under OAC or combined ATT (Table 3), and gastrointestinal (39%) and obscure bleeding (29.3%) were the most frequent sources of BE reported. Neither intracranial hemorrhage nor pericardial effusion was documented. No life-threatening nor fatal hemorrhages were either reported.

3.1. Predictors of bleeding events after percutaneous mitral valve repair

After multivariate COX regression analysis, preprocedural serum hemoglobin, platelet count, serum creatinine, prior coronary revascularization, AF and combined ATT during follow up were identified as independent predictors of BE in our cohort (Table 4).

3.2. Prognostic impact of bleeding events

During follow-up, 15 (18.8%) patients died, 20 (25%) were admitted for HF and 29 (36.3%) presented the combined end-point. In survival Kaplan-Meier analysis (Fig. 1), the occurrence of BE was associated with a higher incidence of the combined end-endpoint (p long rank < 0.001).

After multivariate COX regression analysis, the occurrence of BE during follow up remained significantly related to the combined clinical end-point, with a HR of 3.80 (CI 95% 1.66–8.72, p = 0002) (Table 5).

3.3. Atrial fibrillation and incidence of bleeding events

Paroxysmal (26) or permanent (21) AF was document in 47 patients (58.8%). Most of them (87.2%) were at high risk for thromboembolic events (mean CHA_2DS_2VASC score 4.4 ± 1.6). Mean HASBLED score

Table 1
Baseline characteristics according to occurrence of bleeding events during follow up.

	All (n = 80)	No BE (n = 59)	BE (n = 21)	p value
Age (years)	74.6 ± 10.1	73.6 ± 10.4	77.4 ± 9.1	0.067
Men (%)	65.0	61.0	76.2	0.211
Body mass index (kg/m^2)	26.7 ± 5.1	26.6 ± 5.5	27.0 ± 3.9	0.632
Hypertension (%)	65	59.3	81.0	0.074
Diabetes (%)	28.8	25.4	38.1	0.271
History of smoking (%)	42.5	42.4	42.9	0.969
Ischemic heart disease (%)	51.3	44.1	71.4	0.031
Prior myocardial infarction (%)	36.3	33.9	42.9	0.463
Prior percutaneous coronary intervention (%)	40	33.9	57.1	0.062
Prior coronary artery bypass graft (%)	13.8	6.8	33.3	0.006
Prior coronary revascularization (%)	45	35.6	71.4	0.005
Prior cardiac valvular surgery (%)	13.8	10.2	23.8	0.146
Peripheral artery disease (%)	10	10.2	9.5	0.999
Prior stroke (%)	3.6	4.7	0	0.999
Atrial fibrillation (%)	58.8	52.5	76.2	0.059
Serum creatinine (g/dL)	1.4 ± 0.9	1.2 ± 0.5	1.8 ± 1.4	0.007
Serum creatinine > 1.5 g/dL(%)	32.5	27.1	47.6	0.085
Serum hemoglobin (g/dL)	12.4 ± 2.0	12.6 ± 1.9	11.5 ± 2.0	0.014
Anemia (%)	47.5	35.6	81.0	0.001
Serum albumin (g/dL)	4.0 ± 0.5	4.0 ± 0.5	3.9 ± 0.4	0.086
Serum albumin < 3.5 g/dL	12.5	10.2	19.1	0.243
Platelet count (∗10^3/mL)	189.3 ± 69.8	190.3 ± 67.1	186.5 ± 78.6	0.416
NT-proBNP (pg/mL)	2862 [1474–4176]	2959 [1441–5022]	2091 [1525.5–3352]	0.391
Heart Failure Seattle Score 1 year survival (%)	79.5 ± 13.2	80.1 ± 13.1	77.7 ± 13.5	0.477
EuroScore Logistic (%)	21.6 ± 15.0	20.9 ± 14.8	23.6 ± 15.6	0.475
Combined antithrombotic therapy	11.3	5.1	28.6	0.009

was 2.4 ± 1.2 and 40.4% of the cohort were at high risk for bleeding events according to this scale (all of them with CHA_2DS_2VASC score ≥ 3). Eight (15.7%) patients had history of prior major BE.

In the subgroup of patients with AF, HAS-BLED score was higher among subjects with BE (3.1 ± 1.3 vs 2.1 ± 0.9, p = 0.003), while CHA_2DS_2VASc score was similar in both groups (4.4 ± 1.6 vs 4.3 ± 1.6, p = 0.407). High risk for bleeding according to HAS-BLED score was related to a lower serum Hb and Ht and a higher prevalence of anemia before the procedure and at first follow up. In this series, HAS-BLED score had a significant discrimination power for the occurrence BE (AUC: 0.677 [0.507–0.848]) and, especially, for major or extensive BE according to MVARC classification (AUC: 0.750 [0.600–0.890]) with a good calibration (Hosmer-Lemeshow test: p = 0.640 and p = 0.183, respectively).

4. Discussion

This is the first study to specifically address the incidence and implications of post-discharge bleeding complications in a contemporary cohort of MitraClip patients. The main findings of our study are: 1) BE are not uncommon, occurring approximately in one of four patients in our sample; 2) the main factors associated with these events were prior coronary revascularization, AF and the use of combination anticoagulants and antiplatelets; 3) the occurrence of BE during follow up is linked to a worse outcome with increasing number of admissions due to HF and death; 4) HAS-BLED score has a moderate discrimination power to detect those patients at high risk for BE among the subgroup of patients with AF.

Patients suffering from a BE have an almost 4-fold increase in the risk of readmission due to HF or mortality in our cohort. It has been recognized recently that late bleeding events after TAVR are associated with an impaired outcome [19]. However, very little information is available regarding the association between BE and outcomes after PMVR. Prognostic impact of BE after MitraClip has only been studied in a previous report by Körber et al. [13].The authors reported that peri-procedural BE (using MVARC classification) was not associated with adverse outcomes up to 1 year of follow-up. However, obscure bleeding with a loss >4 g/dL of hemoglobin has a strong impact in patients' survival. Nonetheless, this study accounted only for early bleeding events after MitraClip and not for those appearing after the hospitalization. This fact may explain the differences with our findings.

Several reasons may account for the results of our investigation. First, the population included in the study were old, frail and with several comorbidities, similar to other contemporary series of PMVR [3–8]. These factors increase patients' bleeding susceptibility, which is boosted by the antithrombotic therapy. Second, the vast majority of patients suffered from FMR that is usually associated to previous episodes of HF, poor functional class and depressed left ventricular function. In this subgroup of patients BE can easily trigger an adverse event.

In our series, preprocedural anemia was much more frequent among patients who presented BE during follow up. This finding is probably related to patients' general condition, being a marker of a general predisposition to bleed under several circumstances. The effect of anemia in

Table 2
Echocardiographic and procedural features according to occurrence of bleeding events.

	All (n = 80)	No BE (n = 59)	BE (n = 21)	p value
Functional mitral regurgitation (%)	75	76.3	71.4	0.660
Left ventricular ejection fraction < 40% (%)	55	57.6	47.6	0.429
Left ventricular end diastolic diameter (mm)	60.3 ± 8.9	61.2 ± 9.5	57.9 ± 6.4	0.148
Left atrial volume (mL)	116.8 ± 41.3	119.1 ± 41.5	110.2 ± 41.1	0.406
Pulmonary artery pressure (mm Hg)	46.9 ± 16.2	46.8 ± 15.6	47.2 ± 18.3	0.943
Tricuspid regurgitation grade 3+ or 4+ (%)	28.8	25.4	38.1	0.271
Procedural success (%)	96.3	96.6	95.2	0.999
Multiple clips implanted (%)	41.3	42.4	38.1	0.732

Table 3
Antithrombotic therapy after percutaneous mitral valve repair.

Antithrombotic therapy	At discharge (n = 80)	At one month follow up (n = 79)	At first BE (n = 21)	Incidence of BE according to type of therapy
None or SAPT	–	13/79 (16.5%)	2/21 (9.5%)	2/13 (15.4%)
DAPT	30/80 (37.5%)	15/79 (19.0%)	3/21 (14.3%)	3/15 (20%)
VKA	27/80 (33.8%)	28/79 (35.4%)	7/21 (33.3%)	7/29 (24.1%)
DOAC	13/80 (16.3%)	13/79 (16.5%)	3/21 (14.3%)	3/13 (23.1%)
Combined therapy	10/80 (12.5%)	10/79 (12.7%)	6/21 (28.6%)	6/10 (60%)
VKA + DAPT	2/10	2/10	2/6	2/2
VKA + SAPT	4/10	4/10	2/6	2/4
DOAC + SAPT	4/10	4/10	2/6	2/4

SAPT: single antiplatelet therapy.
DAPT: double antiplatelet therapy.
VKA: vitamin k antagonists.
DOAC: direct oral anticoagulants.

patients undergoing PMVR has been previously addressed, and might be related to reduced survival [6,20]. Anemia in HF patients is multifactorial and is present in almost one third of such subgroup [21]. The frequent presence of chronic kidney disease, increased systemic inflammation, iron deficiency, insufficient levels of erythropoietin, bone marrow unresponsiveness and the effect of chronic medical therapy may lead to this fact [22–25]. Anemia could lead to decreased oxygen delivery and, subsequently, aggravation of symptoms such as dyspnea and fatigue, and thus further impair exercise tolerance and quality of life, prompting hospital admission [16,26]. In a large meta-analysis with 153,180 patients with HF, the crude mortality risk of anemia had an odds ratio of 1.96 (95% confidence interval: 1.74 to 2.21), and the adjusted hazard ratio was 1.46 (95% confidence interval: 1.26 to 1.69), with no difference between patients with a reduced or preserved LVEF [27]. Ischemic heart disease requiring revascularization was also a predictor of BE in our cohort. This condition is usually associated with several comorbidities, significant vascular disease in other territories and high proportion of ATT. Likewise, risk factors for thrombotic events are often shared by bleeding risk scores, such as CKD [28]. CKD appeared as well in our series as a risk factor for bleeding. The increased risk of bleeding may be due to platelet dysfunction, prolonged bleeding time, and small vessel disease associated with CKD [29]. Furthermore, the association of CKD with HF episodes confers an extra risk for BE [30].

Antithrombotic therapy is recommended after MitraClip implantation, but there is no clear consensus of which is the best regimen. Based on expert agreement, we used DAPT for one month in patients with no other indication for antithrombotic therapies. In the presence of comorbidities such as AF, mechanical prosthesis and/or vascular disease requiring OAC and/or APT, treatment was individualized taking into account the baseline characteristics of patients. At this regard, there was a very high proportion of patients with AF in our study. This feature is associated with a high percentage of anticoagulation and even combination therapy that is a well-recognized main risk factor for BE [10,31–34]. AF has been reported to be present in 27% of patients in EVEREST trial [35], and this feature was not associated with worse outcomes. In the recently published randomized trial MitraFR no formal report of the percentage of atrial fibrillation is presented, neither the bleeding events during follow-up [36]. Compared to this trial our population was older and with greater estimated risk. However, our procedural success was higher (77/80 in our series vs 113/152 in MitraFR) and the combined death or hospital admission was lower (36.3% vs. 54.6%). Likewise, in publication from TRAMI registry [6], AF rates were much higher (and closer to our figures), reflecting the different population that is treated with MitraClip in real world. Patients in TRAMI were older and with more comorbidities. In this series patients with AF experienced higher mortality rates at one-year follow-up compared to sinus rhythm patients. Although it was not an adjusted analysis this finding deserves attention since BE may be a link between AF and the outcome. Therefore, special caution must be taken in this population and a better evaluation of patient thrombotic and bleeding risk is mandatory, especially in the subgroup of patients with indication for combined therapy.

In the past years the development of left atrial appendage occlusion (LAAC) has become a major breakthrough in the decrease of bleeding events in patients with AF. Recent publications have demonstrated that, compared to warfarin, LAAC with Watchman device is associated with a significant reduction of major bleeding events, hemorrhagic stroke and mortality [37,38] In this sense, LAAC in patients during or after PMVR might be a reasonable strategy to reduce bleeding complications and therefore to improve patients' outcome. Although the timing of the procedures is still debatable, two publications have demonstrated the safety and efficacy of combining both interventions at the same time [39,40]. Kuwata and co-workers [39] reported 25 patients with combined procedures (with Amulet device) compared to 25 isolated MitraClip cases. Combination resulted in longer procedural times and higher radiation exposure, but the addition of LAAC to MitraClip did not result in different clinical event rates. Freixa et al. [40] reported 6 cases with the use of Watchman and Amulet devices. Likewise, no significant events were reported in these cases, thus reassuring the safety of combining. Of interest, in our study the presence of a HAS-BLED score ≥ 3 in patients with AF predicted the development of bleeding complications. Alongside with this finding, Guo et al. have recently

Table 4
Predictors of bleeding events after percutaneous mitral valve repair.

Predictor	HR	CI 95%	p value
Preprocedural serum creatinine	1.52	1.02–2.28	0.041
Preprocedural serum hemoglobin	0.57	0.40–0.81	0.002
Preprocedural platelet count	0.99	0.98–0.99	0.033
Prior coronary revascularization	5.70	1.64–19.88	0.006
Combined antithrombotic therapy	3.42	1.03–11.34	0.044
Atrial fibrillation	4.54	1.20–17.10	0.025

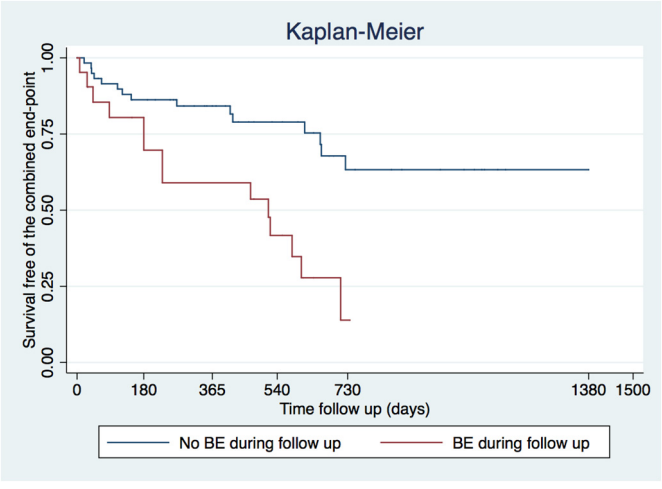

Fig. 1. Kaplan Meier graphics showing survival free of heart failure and all-cause mortality.

Table 5
Cox regression analysis of re-admission for heart failure and all-cause mortality.

Covariates	Unadjusted HR	95% CI	p value	Adjusted HR	95% CI	p value
Bleeding events	3.15	1.48–6.68	0.003	3.80	1.66–8.72	0.002
Atrial fibrillation	2.11	0.96–4.68	0.064	3.45	1.35–8.80	0.010
Chronic kidney disease (GFR < 60)	2.46	1.14–5.29	0.022	3.00	1.27–7.11	0.012
Residual MR ≤ 2+ at discharge	0.43	0.16–1.14	0.089	0.30	0.09–0.97	0.044
Prior multiple admission for HF	1.90	0.91–3.96	0.086	2.38	1.07–5.31	0.034
NT proBNP > 1000 pg/mL	4.84	0.66–35.64	0.131	3.67	0.46–29.03	0.218
LFEF ≤ 40%	1.52	0.69–3.36	0.301	2.55	1.02–6.41	0.046

reported the superiority of HAS-BLED score compared to other bleeding risk assessment strategies in the general population with AF [41]. If this score cut-off might be useful for selecting patients for the combination with LAAC in order to reduce BE should be assessed in further studies.

5. Limitations

This study presents several limitations. First, its non-randomized design might have precluded the introduction of some variables related to bleeding and prognosis. However, the multivariate adjustment for all possible confounders may have overcome this limitation. Second, ATT in patients with or without AF was heterogeneous. In this sense, further research is warranted to confirm the association between AF, treatment and BE. And finally, the sample size is limited. This should prompt further research with larger sample size in order to confirm our findings.

6. Conclusions

Late BE are common after PMVR with MitraClip and are associated with an impaired outcome. Strategies to reduce bleeding events are of importance in this cohort of patients.

Conflict of interest

Dr. Estévez-Loureiro is consultant for Abbott vascular and proctor for MitraClip. The rest of authors have nothing to disclose.

Acknowledgments

Funding: this study was supported by a research grant (PdH) in Interventional Cardiology of the Spanish Society of Cardiology.

References

[1] Ted Feldman, Elyse Foster, Donald D. Glower, Saibal Kar, Michael J. Rinaldi, Peter S. Fail, Richard W. Smalling, Robert Siegel, Geoffrey A. Rose, Eric Engeron, Catalin Loghin, Alfredo Trento, Eric R. Skipper, Tommy Fudge, George V. Letsou, Percutaneous repair or surgery for mitral regurgitation, N. Engl. J. Med. 364 (2011) 1395–1406.
[2] R. Estevez-Loureiro, O. Franzen, Current state of percutaneous transcatheter mitral valve therapies, Panminerva Med. 55 (2013) 327–337.
[3] M. Mirabel, B. Iung, G. Baron, et al., What are the characteristics of patients with severe, symptomatic, mitral regurgitation who are denied surgery? Eur. Heart J. 28 (2007) 1358–1365.
[4] S.S. Goel, N. Bajaj, B. Aggarwal, et al., Prevalence and outcomes of unoperated patients with severe symptomatic mitral regurgitation and heart failure: comprehensive analysis to determine the potential role of mitraclip for this unmet need, J. Am. Coll. Cardiol. 63 (2014) 185–186.
[5] G. Nickenig, R. Estevez-Loureiro, O. Franzen, et al., Percutaneous mitral valve edge-to-edge repair: in-hospital results and 1-year follow-up of 628 patients of the 2011–2012 pilot European Sentinel Registry, J. Am. Coll. Cardiol. 64 (2014) 875–884.
[6] M. Puls, E. Lubos, P. Boekstegers, et al., One-year outcomes and predictors of mortality after MitraClip therapy in contemporary clinical practice: results from the German transcatheter mitral valve interventions registry, Eur. Heart J. 37 (2016) 703–712.
[7] A. Jabs, R. von Bardeleben, P. Boekstegers, et al., Effects of atrial fibrillation and heart rate on percutaneous mitral valve repair with MitraClip: results from the TRAnscatheter Mitral valve Interventions (TRAMI) registry, EuroIntervention 12 (2017) 1697–1705.
[8] H.C. Herrmann, Z.M. Gertz, F.E. Silvestry, et al., Effects of atrial fibrillation on treatment of mitral regurgitation in the EVEREST II (Endovascular valve edge-to-edge repair study) randomized trial, J. Am. Coll. Cardiol. 59 (2012) 1312–1319.
[9] F. Maisano, O. Franzen, S. Baldus, et al., Percutaneous mitral valve interventions in the real world: early and 1-year results from the ACCESS-EU, a prospective, multicenter, nonrandomized post-approval study of the Mitraclip therapy in Europe, J. Am. Coll. Cardiol. 62 (2013) 1052–1061.
[10] T.I. Shireman, P.A. Howard, T.F. Kresowik, et al., Combined anticoagulant-antiplatelet use and major bleeding events in elderly atrial fibrillation patients, Stroke 35 (2004) 2362–2367.
[11] T. Pilgrim, S. Stortecky, F. Luterbacher, et al., Transcatheter aortic valve implantation and bleeding: incidence, predictors and prognosis, J. Thromb. Thrombolysis 35 (2013) 456–462.
[12] J. Rodés-Cabau, H.L. Dauerman, M.G. Cohen, et al., Antithrombotic treatment in transcatheter aortic valve implantation: insights for cerebrovascular and bleeding events, J. Am. Coll. Cardiol. 62 (2013) 2349–2359.
[13] M.I. Körber, J. Silwedel, K. Friedrichs, et al., Bleeding complications after percutaneous mitral valve repair with the MitraClip, Am. J. Cardiol. 121 (2018) 94–99.
[14] P. Kirchhof, S. Benussi, D. Kotecha, et al., ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS, Eur. Heart J. 37 (2016) 2893–2962.
[15] G.W. Stone, D.H. Adams, W.T. Abraham, et al., Clinical trial design principles and endpoint definitions for transcatheter mitral valve repair and replacement: part 2: endpoint definitions a consensus document from the Mitral Valve Academic Research Consortium, J. Am. Coll. Cardiol. 66 (2015) 308–321.
[16] C.-C. Wei, S.-T. Zhang, G. Tan, et al., Impact of anemia on in-hospital complications after ischemic stroke, Eur. J. Neurol. (February 12 2018)https://doi.org/10.1111/ene.13595 (Epub ahead of print).
[17] G.Y.H. Lip, R. Nieuwlaat, R. Pisters, et al., Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on atrial fibrillation, Chest 137 (2010) 263–272.
[18] R. Pisters, D.A. Lane, R. Nieuwlaat, et al., A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey, Chest 138 (2010) 1093–1100.
[19] P. Généreux, D.J. Cohen, M. Mack, et al., Incidence, predictors, and prognostic impact of late bleeding complications after transcatheter aortic valve replacement, J. Am. Coll. Cardiol. 64 (2014) 2605–2615.
[20] K. Hellhammer, J. Balzer, T. Zeus, et al., Percutaneous mitral valve repair using the MitraClip® systemin patients with anemia, Int. J. Cardiol. 184 (2015) 399–404.
[21] D.J. Van Veldhuisen, S.D. Anker, P. Ponikowski, et al., Anemia and iron deficiency in heart failure: mechanisms and therapeutic approaches, Nat. Rev. Cardiol. 8 (2011) 485–493.
[22] W.H.W. Tang, W. Tong, A. Jain, et al., Evaluation and long-term prognosis of new-onset, transient, and persistent anemia in ambulatory patients with chronic heart failure, J. Am. Coll. Cardiol. 51 (2008) 569–576.
[23] I.T. Klip, J. Comin-Colet, A.A. Voors, et al., Iron deficiency in chronic heart failure: an international pooled analysis, Am. Heart J. 165 (2013) 575–582 (e3).
[24] B.D. Westenbrink, A.A. Voors, R.A. De Boer, et al., Bone marrow dysfunction in chronic heart failure patients, Eur. J. Heart Fail. 12 (2010) 676–684.
[25] A. Ishani, E. Weinhandl, Z. Zhao, et al., Angiotensin-converting enzyme inhibitor as a risk factor for the development of anemia, and the impact of incident anemia on mortality in patients with left ventricular dysfunction, J. Am. Coll. Cardiol. 45 (2005) 391–399.
[26] N. Grote Beverborg, D.J. van Veldhuisen, P. van der Meer, Anemia in heart failure. Still relevant? JACC Heart Fail. 6 (2017) 201–208.
[27] H.F. Groenveld, J.L. Januzzi, K. Damman, et al., Anemia and mortality in heart failure patients. A systematic review and meta-analysis, J. Am. Coll. Cardiol. 52 (2008) 818–827.
[28] U. Baber, R. Mehran, G. Giustino, et al., Coronary thrombosis and major bleeding after PCI with drug-eluting stents risk scores from Paris, J. Am. Coll. Cardiol. 67 (2016) 2224–2234.
[29] A.N. Bonde, G.Y.H. Lip, A.L. Kamper, et al., Net clinical benefit of antithrombotic therapy in patients with atrial fibrillation and chronic kidney disease: a nationwide observational cohort study, J. Am. Coll. Cardiol. 64 (2014) 2471–2482.
[30] L. Melgaard, T.F. Overvad, F. Skjøth, et al., Risk of stroke and bleeding in patients with heart failure and chronic kidney disease: a nationwide cohort study, ESC Heart Fail. 5 (2018) 319–326.
[31] J. Eikelboom, J. Hirsh, Combined antiplatelet and anticoagulant therapy: clinical benefits and risks, J. Thromb. Haemost. 5 (2007) 255–263.
[32] D.R. Holmes, D.J. Kereiakes, N.S. Kleiman, et al., Combining antiplatelet and anticoagulant therapies, J. Am. Coll. Cardiol. 54 (2009) 95–109.

[33] Y. Uchida, F. Mori, H. Ogawa, et al., Impact of anticoagulant therapy with dual antiplatelet therapy on prognosis after treatment with drug-eluting coronary stents, J. Cardiol. 55 (2010) 362–369.
[34] C.H. So, M.H. Eckman, Combined aspirin and anticoagulant therapy in patients with atrial fibrillation, J. Thromb. Thrombolysis 43 (2017) 7–17.
[35] T. Feldman, S. Kar, S. Elmariah, et al., Randomized comparison of percutaneous repair and surgery for mitral regurgitation 5-year results of EVEREST II, J. Am. Coll. Cardiol. 66 (2015) 2844–2854.
[36] J.-F. Obadia, D. Messika-Zeitoun, G. Leurent, et al., Percutaneous repair or medical treatment for secondary mitral regurgitation, N. Engl. J. Med. (2018) (Epub Ahead of print).
[37] D.R. Holmes, S.K. Doshi, S. Kar, et al., Left atrial appendage closure as an alternative to warfarin for stroke prevention in atrial fibrillation: a patient-level meta-analysis, J. Am. Coll. Cardiol. 65 (2015) 2614–2623.
[38] V.Y. Reddy, S.K. Doshi, S. Kar, et al., 5-Year outcomes after left atrial appendage closure: from the PREVAIL and PROTECT AF trials, J. Am. Coll. Cardiol. 70 (2017) 2964–2975.
[39] S. Kuwata, M. Taramasso, M. Zuber, et al., Feasibility of concomitant MitraClip and left atrial appendage occlusion, EuroIntervention 12 (January 3 2017)https://doi.org/10.4244/EIJ-D-16-00784 (Epub ahead of print).
[40] X. Freixa, R. Estevez-Loureiro, F. Carrasco-Chinchilla, et al., Initial results of combined MitraClipA(R) implantation and left atrial appendage occlusion, J. Heart Valve Dis. 26 (2017) 169–174.
[41] Y. Guo, H. Zhu, Y. Chen, et al., Comparing bleeding risk assessment focused on modifiable risk factors only versus validated bleeding risk scores in atrial fibrillation, Am. J. Med. 131 (2017) 185–192.