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

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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, CI95% 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.

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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.

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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 along with physician’s criteria. According to recent ESC guidelines [14], modifiable and potentially modifiable factors associated with increased 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 non-steroid 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 Mitrail 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]. CHA2DS2-VASC [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 CHA2DS2-VASC ≥ 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-point (p log 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 documented in 47 patients (58.8%). Most of them (87.2%) were at high risk for thromboembolic events (mean CHA2DS2-VASC score 4.4 ± 1.6). Mean HASBLED score
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 CHA2DS2VASc 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 CHA2DS2VASc 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 (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 Köhrer 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 might 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 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/m²) | 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     | 10.6          | 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 (>10³/µL) | 189.3 ± 69.8 | 190.3 ± 67.1  | 186.5 ± 78.6 | 0.416 |
| NT-proBNP (pg/mL)       | 2862 [1474–4176] | 2595 [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   |

### 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   |
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 ALT. 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 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           | 27/80 (33.3%)        | 15/79 (19.0%)                | 7/21 (33.3%)        | 7/29 (24.1%)                                |
| DAPT                   | 10/80 (12.5%)        | 2/10                          | 2/6                 | 2/2                                         |
| VKA                    | 13/80 (16.3%)        | 2/10                          | 6/21 (28.6%)        | 6/10 (60%)                                  |
| DOAC                   | 27/80 (33.3%)        | 10/79 (12.7%)                | 4/10                | 4/10                                        |
| Combined therapy       | 54/80 (67.5%)        | 54/79 (68.3%)                | 20/21 (95.2%)       | 20/21 (95.2%)                               |

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

And Table 4:

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

| Predictor                                      | HR      | 95% CI  | 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.
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.

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