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Bleeding and thrombotic risk of different anti-platelet regimens post transcatheter edge-to-edge mitral valve repair in patients with an indication for oral anticoagulation: Results from an all-comers national registry.

Running title: Anti-thrombotic therapy post-TEER and outcome

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Abstract

Background

Evidence-based recommendations for antithrombotic treatment in patients who have an indication for oral anticoagulation (OAC) after transcatheter edge-to-edge mitral valve repair (TEER) are lacking.

Aims

To compare bleeding and thrombotic risk for different antithrombotic regimens post-TEER with MitraClip in an unselected population with the need for OACs.

Methods

Bleeding and thrombotic complications (stroke and myocardial infarction) up to three months after TEER with mitraclip were evaluated in 322 consecutive pts with an indication for OACs. These endpoints were defined by the Mitral Valve Academic Research Consortium criteria and were compared between two antithrombotic regimens: single antithrombotic therapy with OAC (single ATT) and double/triple ATT with a combination of OAC and aspirin and/or clopidogrel (combined ATT).

Results

Collectively, 108 (34%) patients received single ATT, 203 (63%) received double ATT and 11 (3%) received triple ATT. Bleeding events occurred in 67 patients (20.9%), with access site related events being the most frequent cause (37%). Bleeding complications were observed more frequently in the combined ATT group than in the single ATT group: 24% versus 14% (p=0.03, adjusted RR; 0.55 (0.3-0.98)). Within the combined group, the bleeding risk was 23% in the double ATT and 45% in the triple ATT group. Thrombotic complications occurred in only 3 patients (0.9%), and all belonged to the combined ATT group.

Conclusions

In patients with an indication for OACs, withholding of antiplatelet therapy post-TEER with Mitraclip was associated with a 45% reduction in bleeding and without a signal of increased thrombotic risk.

Keywords: mitral valve repair, MitraClip, antithrombotic therapy, bleeding, thrombosis

Abbreviations

AF:	Atrial fibrillation
ATT:	antithrombotic treatment
MR:	Mitral regurgitation
OAC:	Oral anticoagulation
MVARC:	Mitral Valve Academic Research Consortium criteria
TAVI:	Transcatheter aortic valve implantation
TEER:	Transcatheter edge-to-edge mitral valve repair

Summary Table

1. Antithrombotic treatment (ATT) in patients who have an indication for oral anticoagulation (OAC) after transcatheter edge-to-edge mitral valve repair (TEER) is not well defined
2. In the present national TEER registry, 34% patients received single ATT (=OAC), 63% received double ATT and 3% received triple ATT
3. Single antithrombotic regimen was associated with a 45% risk reduction in bleeding complications and without a signal towards an increased thrombotic risk.
4. In the absence of recent coronary stenting, anticoagulation without antiplatelet drug might become the preferred anti-thrombotic regimen post TEER.

Background

Transcatheter edge-to-edge mitral valve repair (TEER) by means of MitraClip (Abbott Vascular) has emerged as a valuable treatment for symptomatic severe mitral regurgitation (MR) despite optimal HF treatment in patients at high risk for surgical intervention. [1, 2] Similar to other valve interventions, the procedure involves the implantation of potentially thrombogenic materials and alteration of pressure and flow conditions, which both may lead to embolic complications, such as stroke and myocardial infarction. [3] For this reason, antithrombotic therapy represents the cornerstone of adjunctive pharmacologic therapy, although the type and doses of antithrombotic agents remain mostly empiric for these indications.

Atrial fibrillation (AF) is present in more than 60% of patients undergoing TEER and constitutes an indication for long-term oral anticoagulation (OAC) therapy with a vitamin K antagonist or direct-acting oral anticoagulant.[4] Current practice guidelines on antithrombotic treatment (ATT) in patients who have an indication for OAC after TEER are based on expert opinion and suggest a OAC either alone or in combination with aspirin and/or clopidogrel. [5] The difficult trade-off between thrombosis and bleeding has been clearly shown in observational studies from patients with atrial fibrillation undergoing transcatheter aortic valve implantation (TAVI). The addition of antiplatelet agents (aspirin or clopidogrel) conferred no clinical benefit to OACs in terms of thrombotic events but was harmful in terms of a higher incidence of major or life-threatening bleeding events[6, 7] A recent randomized clinical trial in patients with AF undergoing TAVI showed a higher incidence of bleeding with OAC plus a single antiplatelet therapy than with OAC monotherapy, with a similar incidence of thromboembolic events in the two groups. [8]

Data about antithrombotic treatment post TEER in AF patients are scarce, and no studies have systematically evaluated the thrombotic/bleeding risk according to antithrombotic regimen in this population.

Accordingly, the present observational multicentre study aims to assess short-term bleeding and thrombotic risk of different antithrombotic regimens in an unselected population with an indication for anticoagulation OAC and who underwent percutaneous TEER with Mitraclip in Belgium.

Methods

Study population

The study compromised 322 consecutive patients with symptomatic severe MR referred for TEER with MitraClip at 6 Belgian centres from 2011 to 2021. All patients were selected for the procedure by the heart team after thorough assessment of the patient's medical history. The clinical characteristics were extracted from the MITRABEL database, which prospectively gathers information on all TEER procedures with MitraClip in Belgium, including bleeding and thrombotic complications. At the time of the evaluation, 515 patients were included in the database, of which 322 patients (63%) were treated with OAC mainly because of AF (74%). The majority (71%) received direct-acting oral anticoagulation (DOAC). The ethical committee of the Antwerp University Hospital approved the study protocol, and all patients provided written informed consent. The database is registered with clinicaltrials.gov (NCT02506387).

TEER procedure

All procedures were performed under general anaesthesia using transesophageal echocardiography (TEE) and fluoroscopic guidance. A comprehensive description of the procedure has been previously described. [9, 10] Procedural success was defined as a noncomplicated implantation of ≥ 1 clip together with a postprocedural (predischarge) MR reduction to ≤ grade 2. Peri-procedural and post discharge pharmacologic management, including antithrombotic therapy, was left at the discretion of the local investigators. The study population was divided into two groups based upon the antithrombotic regimen during hospitalization: single anti-thrombotic therapy with OAC (single ATT) versus double/triple anti-thrombotic therapy with a combination of OAC plus an antiplatelet agent (aspirin and/or clopidogrel) (combined double/triple ATT).

Clinical follow-up

Clinical assessment was performed before and up to 3 months after the intervention with a focus on bleeding and thrombotic complications. The follow-up period was limited to 3 months, as antiplatelet therapy is targeting to prevent thromboembolic complications in the first 6-8 weeks before completion of endothelialization of the implanted clips . After that period, most of the antiplatelet therapy are usually stopped or de-escalated.

Bleeding complications were defined according to the Mitral Valve Academic Research Consortium criteria MVARC with subdivision into minor, major/extensive and life-threatening/fatal bleeding.[11]

Minor bleeding indicates bleeding requiring medical intervention and/or transfusion of 1 to 2 units of whole blood or packed cells (UPC) .

Major/extensive bleeding indicates bleeding associated with a drop in haemoglobin of ≥3.0 g/dl/≥4.0 g/dl or requiring transfusion of ≥3 /≥4 UPC, respectively.

Thrombotic complications consisted of clinically relevant myocardial infarctions and cerebrovascular ischaemic events subdivided into stroke or transient ischaemic attack (TIA) according to MVARC definitions.

All records were reviewed on the drop in haemoglobin during hospitalization and on the need for blood transfusion. In addition, all bleeding complications were reviewed to classify bleeding complications according to the MVARC scale and to identify the bleeding source. Additionally, all thrombotic events were reviewed and classified according to the MVARC definition.

Statistical analysis

Continuous variables are presented as the mean (SD), and categorical variables are presented as percentages. Characteristics and endpoints were compared between single ATT and combined double/triple ATT therapy with chi-square tests for categorical variables and T tests or Mann–Whitney U tests for continuous variables. Cumulative event-free survival estimates were plotted using the Kaplan–Meier technique. The Cox proportional hazards model was applied to identify independent predictors of bleeding complications. The following baseline factors were included in the model: age, sex, arterial hypertension, diabetes, renal failure (defined as glomerular filtration rate <60 ml/min/1.73 m2), body mass index (BMI), haemoglobin concentration at baseline, coronary artery disease and antithrombotic regimen (single versus combination). A two-tailed p value <0.05 was considered statistically significant. Statistical analyses were performed using MedCalc for Windows, version 15.0 (MedCalc Software, Ostend, Belgium).

Results

Baseline characteristics

The study population consisted of 322 patients with an mean age of 77 ± 11 years and an increased risk of bleeding, as shown by a high proportion of patients over 65 years (92%), with renal failure (78%), with arterial hypertension (65%) and anaemia (hb<12 g/dl, 38%). In addition, all patients received ATT: 108 patients (34%) received single (OAC only), 203 (63%) double therapy, and 11 (3%) received triple ATT. Clopidogrel was the antiplatelet agent in 69% of the double ATT group. The clinical and procedural characteristics of 108 patients with single ATT and 214 patients (66%) with combined ATT are presented in Table 1. There were no significant differences between the groups except for a higher prevalence of AF in the single ATT group (81% s 71%, p= 0.04). There was a trend towards more coronary artery disease in the combined ATT group (66% vs. 55%, p=0.05).

Thrombotic complications

Ischaemic cerebrovascular events occurred in 2 patients (0.6%), one stroke and one TIA, both in the combined ATT group. (see central illustration)

Clinically relevant myocardial infarction occurred in 1 patient (0.3%) in the combined ATT group.

Bleeding complications

Bleeding events occurred in 67 patients (20.9%), predominantly during hospitalization (only 10% post discharge). There were 30 (9%) minor bleeding events, 33 (10%) major/extensive bleeding events and 3 (1%) life-threatening/fatal bleeding events. A total of 17 patients from the 67 patients with bleeding complications received blood transfusion: 7 of 30 patients with minor bleeding and 11 of 37 patients with major/extensive/LT bleeding. Access site was the most frequent cause of bleeding (37%), followed by urogenital bleeding (10%), gastrointestinal bleeding (7.5%), skin bleeding (3.0%), respiratory tract bleeding (3.0%), pericardial bleeding (3.0%), cerebrovascular bleeding (1.5%) and other or non-specified bleeding (34%). Bleeding complications occurred more frequently in the combined ATT group than in the single ATT group: 24% versus 14% (p=0.03). Cumulative event-free survival reveals that Kaplan–Meier Meier curves diverge mainly during the first days after intervention

(see Fig. 1). Within the combined group, the incidence of bleeding events was 23% in the double ATT group and 45% in the triple ATT group (p=0.009 for trend, see central illustration). Within the double ATT group, the incidence of bleeding events was 25.7% for patients treated with clopidogrel and 17.5% for those treated with aspirin (p=0.2). The difference in bleeding between the study groups was mainly observed for minor and LF/fatal bleeding, whereas the reduction in bleeding related to single ATT was seen across all sources of bleeding. (see Table 2)

Cox regression analysis revealed that single ATT was independently associated with a 45% risk reduction in bleeding complications (adjusted RR; 0.55 (0.3-0.98). The only other independent risk factor was arterial hypertension (adjusted RR: 1.8 (1.01-1.18).

Discussion

The current analysis relates antithrombotic regimens after TEER to bleeding/thrombotic complications in patients with an indication for chronic OAC. We demonstrated that withholding of antiplatelet therapy was associated with less bleeding and without a signal of increased thrombotic risk.

The use of antiplatelet drugs post MitraClip was inspired by the experience in coronary stenting, where a combination of aspirin and clopidogrel is being used to prevent stent thrombosis before endothelialization of the stent struts is completed. For patients with a need for anticoagulation (e.g., patients with atrial fibrillation), the addition of dual antiplatelet therapy (DAPT) poses these patients to a high bleeding risk. In recent decades, de-escalation strategies in patients with AF and a recent coronary stent have been thoroughly tested. It became evident that withdrawal of one antiplatelet drug (after a short period of DAPT) resulted in fewer bleeding complications without an increase in the risk of stent thrombosis.[12] In addition, recent guidelines recommend stopping all antiplatelet drugs one year after stent implantation in patients under long-term OAC therapy.[13] This process of de-escalation has also been tested in TAVI. The POPULAR TAVI EU trial demonstrated that OAC alone compared to OAC plus clopidogrel was associated with a 37% reduction in bleeding (3-month bleeding risk of 18% vs. 32%) and no increase in thrombotic risk. [8] In TEER, no randomized clinical trials about de-escalation are available. However, the findings of the present study concur well with the POPULAR TAVI data with an observed 45% risk reduction in bleeding events for patients treated with a single antithrombotic drug (3-month bleeding rate of 14% vs. 24%). Likewise, in POPULAR, the majority of the bleeding occurred during hospitalization, and the most common source of bleeding was vascular access. Vascular access complications during TEER procedures have been related to a large catheter size (24 French), accidental puncture of the femoral artery , and other known bleeding risk factors (such as advanced age, frailty, and anticoagulant use). [14]

Subgroup analysis revealed that the highest bleeding risk was observed in patients receiving triple ATT (bleeding rate of 45%!). In our study population, triple therapy was applied in only 3% of the patients. The proportion of single therapy increased over time from 18% before 2017 to 38% from 2017 on. Double therapy remained the largest group, probably related to the high prevalence of concomitant coronary artery disease.

Data from “real-world” registries and meta-analyses show bleeding rates within the first 30 days from 2.0 to 13.4% .[15-18] The higher bleeding rate of 21% observed in our study may be related to the use of

OAC in all patients, differences in bleeding definitions but also to the review of the patient files to check a drop in haemoglobin and need for transfusion, minimizing the risk of underreporting.

With regard to thrombotic complications, the incidence of clinically overt stroke after TEER is reported to be very low, ranging from 0.2% to 0.4% at discharge and from 0.7% to 0.9% at 30 days, which is in line with our findings.[15, 16, 19, 20] However, it should be acknowledged that not all cardiac thrombi will become clinically apparent, and the available evidence on this topic is inconsistent and limited.

Concomitant antiplatelet therapy use does not appear to reduce the incidence of stroke in our study population, but the present study was underpowered to prove it. However, the validity of this observation is strengthened by data from AF studies or surgical valve replacements showing no beneficial effect for ischaemic stroke prevention using a combination treatment of OAC and antiplatelet therapy. [5, 21]

Limitations:

The results of this study should be considered in the context of the following limitation.

While the MITRABEL database is a prospective registry, the present analysis was performed in a retrospective manner, with addition of specific parameters related to bleeding and thrombotic events.

Although there was no monitoring of endpoints, the dedicated review of these endpoints represents equally a strength of the study.

Due to the nonrandomized study design, matching of the study groups might not be perfect. We tried to overcome this by careful risk adjustment, but the possibility of residual selection bias remains and can only be overcome by a prospective randomized clinical trial.

Conclusion and Impact on daily practice

In a significant proportion of TEER patients with a need for anticoagulation, the addition of an antiplatelet agent, predominantly clopidogrel, has become empirically established and was also specified in pivotal randomized trials in the field. The present study highlights that a single antithrombotic regimen with AOC was associated with a 45% risk reduction in bleeding complications and no signal towards an increased thrombotic risk. In the absence of recent coronary stenting, anticoagulation without antiplatelet drug might become the preferred anti-thrombotic regimen.

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Table 1: Baseline characteristics

Characteristics	combination ATT (N= 214)	Single ATT (N= 108)	P value
Clinical features			
Age (years)	77.5 ± 10.2	78.0 ±11.6	0.7
Female, %	35.5	43.5	0.16
BMI (kg/m²) >30, %	15	11	0.4
Medical history			
Atrial fibrillation, %	71.1	81.6	0.04
eGFR <60 ml/min/1,73 m^2, %	76.6	79.6	0.5
Arterial hypertension, %	68.,3	59.8	0.13
Diabetes mellitus, %	22.9	22.2	0.9
Previous CAD, %	66	55	0.05
Euroscore 2	10.1 ± 10.7	10.3 ± 7.7	0.8
Functional capacity			
NYHA class 2/3/4, %	12.9/71.0/15.7	7.5/68.,2/24.3	0.15
Medication			
Beta-blockers, %	80.7	83	0.6
RAS inhibition, %	59	53	0.3
Diuretics, %	85	82	0.5
Echocardiography and laboratory			
LVEF (%)	42.0 ± 15.0	42.,4 ± 17.1	0.8
MR grade 3/4, %	35.5/63.5	50/50	0.05
Etiology: FMR ,%	55	57	0.6
SPAP, mmHg	49.6 ± 17.2	53.0 ± 14.8	0.13
Baseline Hb, mg%	12.6 ± 1.7	12.5 ± 1.8	0.8
Procedure			
Nr of clips used	1.6 ± 0.6	1.6 ± 0.6	0.5
Post MR grade ≤ 2, %	97.1	95.2	0.2

Continuous data are presented as the means ± standard deviation. Categorical data are presented as percentages.

ATT, anti-thrombotic therapy; BMI, body mass index; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; FMR, functional mitral regurgitation, Hb, haemoglobin; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MR, mitral regurgitation; NYHA, New York Heart Association; RAS, renin-angiotensin system; SPAP, systolic pulmonary artery pressure;

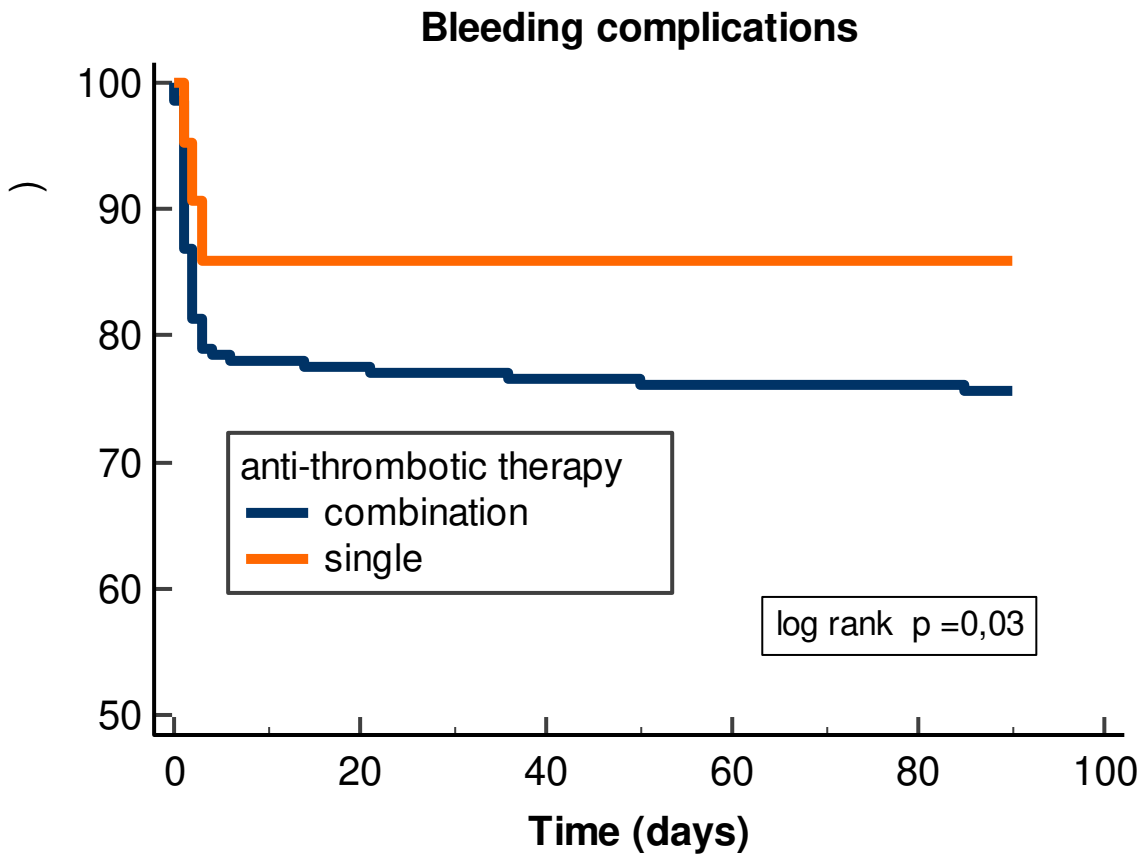
Table 2: Bleeding complications

Characteristics	Combination ATT (N= 214)	Single ATT (N= 108)	P value
Severity			
Minor, %	11.7	4.7	0.04
Major/extensive, %	10.8	9.3	0.7
LT/fatal, %	1.4	0	0.2
Source			
Vascular access, %	9.8	2.8	0.02
Urogenital, %	3.3	0.9	0.2
Gastro-intestinal, %	2.8	0	0.08
Cardiac, %	0.5	0	0.5
Cerebrovascular, %	0.5	0	0.5
Respiratory, %	0.9	0	0,4
Skin, %	0.9	0	0.4
Other/unspecified,%	6.5	8.3	0.5

Categorical data are presented as percentages.

ATT, anti-thrombotic therapy ; LT, life threatening

Figure 1



Kaplan-Meier curves representing cumulative event-free plot for bleeding

for the two study groups (single versus combined anti-thrombotic therapy)

LEGENDS

Figure 1

Kaplan-Meier curves representing cumulative event-free plot for bleeding

for the two study groups (single versus combined anti-thrombotic therapy)

Central illustration

From 322 TEER patients with an indication of oral anticoagulation, 11 (3%) received triple ATT therapy, 203 (63%) double ATT and 108 (34%) single ATT. Bar graphs showing bleeding and thrombotic risk for the different ATT. Withholding of antiplatelet drugs was associated with decreased bleeding risk (p value for trend=0.009) without a signal of increased thrombotic risk.

ATT, anti-thrombotic treatment; MI, myocardial infarction; OAC, oral anticoagulation TEER, transcatheter edge-to-edge mitral valve repair

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National TEER registry

N=322 pts with indication for OAC

Anti-thrombotic treatment	Bleeding at 3 months	Stroke/MI at 3 months
	N=67 (21%)	*N=3 (0,9%)*
OAC + Clopidogrel + Aspirin N= 11 (3%)	45	0
OAC + Clopidogrel or aspirin N= 203 (63%)	23	1,5
OAC N= 108 (34%)	14	0

Single ATT was independently associated with a 45% risk reduction in bleeding complications (adjusted RR; 0.55 (0.3-0.98))