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Antiplatelet effects of aspirin and clopidogrel after left atrial appendage (LAA) occluder implantation

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ABSTRACT

Background: The optimal antithrombotic strategy after interventional left atrial appendage closure (LAAC) is controversial. Dual antiplatelet therapy with aspirin and clopidogrel is the most frequently used regiment. However, pharmacodynamic response to antiplatelet medication differs significantly between individuals. Therefore, we aimed to analyse pharmacodynamic response to aspirin and clopidogrel after LAAC.
Methods: In this study, we included 129 patients undergoing interventional LAAC. Primary end point was pharmacodynamic response to antiplatelet medication. Platelet reactivity was measured by light transmittance aggregometry and vasodilator stimulated protein phosphorylation assay. Secondary endpoints were TIMI bleeding events and MACCE during hospital course and one-year follow-up.
Results: Insufficient pharmacodynamic response (high on-treatment platelet reactivity — HTPR) to clopidogrel occurred in 67 patients (52%); HTPR to aspirin in 15 patients (12%); low on-treatment platelet reactivity — LTPR — to clopidogrel in 13 patients (10%). No occluder thrombosis or stroke occurred during one year follow-up. Pharmacodynamic response to antiplatelet medication was not associated with MACCE. However, the incidence of TIMI minor bleeding was increased in patients with LTPR to clopidogrel.
Conclusions: Impaired clopidogrel antiplatelet effects were very frequent in patients after LAAC. No stroke or occluder thrombosis occurred. Patients with LTPR to clopidogrel showed more minor bleeding events. Therefore, this hypothesis generating pilot study raises the question if clopidogrel early after LAAC is needed. This question should be addressed in large scale trials.

1. Introduction

Atrial fibrillation (AF) is a common cardiac arrhythmia associated with ischemic complications [1]. Therefore, oral anticoagulation is used to prevent ischemic events in AF patients [2]. However, oral anticoagulation can cause bleeding [3]. Furthermore, different registers have shown that >10% of patients are considered unsuitable for oral anticoagulation by physicians due to a high bleeding risk. These patients are only on antiplatelet therapy or without antithrombotic medication at all [4]. Interventional occlusion of the left atrial appendage (LAA) is a safe and effective alternative to oral anticoagulation. Five-year follow-up analysis of the LAAC landmark trials revealed superiority of interventional LAAC in comparison to VKA [5].

Optimal antithrombotic regime after LAAC is still a matter of discussion. The Watchman landmark trial PROTECT-AF continued oral anticoagulation for 45 days after LAAC followed by dual antiplatelet therapy (DAPT) for 135 days and subsequent aspirin monotherapy, if sufficient LAAC was approved in transesophageal echocardiography [6–8]. This reflects current manufacture's recommendations. For Amplatzer-device, DAPT for three to six months or warfarin and aspirin followed by aspirin indefinite is recommended [9]. In clinical practice, DAPT with aspirin and clopidogrel early after LAAC followed by indefinite aspirin monotherapy is predominantly used [10]. However, different

Abbreviations: DAPT, dual antiplatelet therapy; HTPR, high on-treatment platelet reactivity; LAA, left atrial appendage; LAAC, left atrial appendage closure; LTPR, low on-treatment platelet reactivity; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; OT, occluder thrombosis; PRI, platelet reactivity index; TAVI, transcatheter aortic valve implantation; TIA, transient ischemic attack.

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studies and registries described that single antiplatelet therapy with aspirin was not associated with higher risk of devise related thrombus formation or stroke [11,12].

Additionally, pharmacodynamic response to aspirin and clopidogrel shows substantial inter-individual differences [13]. Insufficient antiplatelet effects are called high on-treatment platelet reactivity (HTPR). HTPR is associated with an increased rate of ischemic events [14,15]. It has been shown that HTPR is common in patients undergoing percutaneous coronary interventions [16], transcatheter aortic valve implantation (TAVI) [17], patent foramen ovale/atrium septum defect closure [18] and MitraClip [19]. A plethora of causes for HTPR have been described including genetic polymorphisms [20], comorbidities [21], drug-drug-interactions [22] and patient incompliance. Enhanced pharmacodynamic response to clopidogrel is called low on-treatment platelet reactivity (LTPR) and has been shown to be associated with bleeding complications [23].

Therefore, in this study, we examined pharmacodynamic response to aspirin and clopidogrel and clinical outcome in patients undergoing interventional LAAC.

2. Methods

2.1. Patients and study design

132 patients with percutaneous LAAC between 2013 and 2017 were screened for this study. Patients with unsuccessful implantation were excluded (supplemental 5). Pharmacodynamic response to antiplatelet medication was the primary endpoint. It was measured by light transmittance aggregometry (LTA) and vasodilator-stimulated phosphoprotein (VASP) phosphorylation assay respectively. Secondary endpoints were major adverse cardiac and cerebrovascular events (MACCE) and bleeding complications during hospitalization and one-year follow-up. The study was approved by the ethics committee of the Heinrich-Heine University Duesseldorf.

2.2. Procedural details

Pre-procedural transesophageal echocardiography was conducted in all patients for morphological assessment and for definition of the appropriate device. Pre-existing platelet inhibition by aspirin and clopidogrel was continued. In case of platelet-inhibitor native patients, DAPT with aspirin (100 mg o.d.) and clopidogrel (600 mg loading dose followed by 75 mg o.d.) was initiated. Clopidogrel loading was conducted the day before LAAO. As post-procedural antiplatelet medication, patients received DAPT with clopidogrel 75 mg and aspirin 100 mg for three month, followed by aspirin monotherapy indefinitely. Oral anticoagulation was stopped at least 48 h prior to LAAO. Occluder thrombosis and sufficient LAA closure was evaluated by echocardiography three and six months after LAAC.

2.3. Primary endpoint (platelet function testing)

Pharmacodynamic response to aspirin and clopidogrel was measured in all 129 patients. Measurements were conducted during hospital course, approximately 48 h after LAAO. Blood withdrawal was conducted using a 21 G needle in citrate vacutainers (1:10). Pharmacodynamic response to aspirin was measured by LTA. For this purpose, platelet rich plasma was generated by centrifugation (270 ×g, 10 min) after 15 min storage by room temperature. 1 mM arachidonic acid as specific agonist was used to induce platelet aggregation. Aggregation was measured with the APACT 4004 (LABiTec; Arensburg, Germany). HTPR to aspirin was defined as maximum of aggregation >20% [24].

Pharmacodynamic response to clopidogrel was measured by VASP assay as this is the pharmacologically most specific assay in determination of P2Y12 inhibition. This was performed by dual flow cytometry which was conducted with the PLT VASP/P2Y12 Test Kit® (Diagnostica Stago, Biocytex, Asnières sur Seine, France). Prostaglandin E1 or ADP and prostaglandin E1 was incubated with whole blood and phosphorylation of VASP was measured afterwards. Ratio of the mean fluorescence intensity of the probe incubated with prostanglandin E1 or with prostanglandin E1 and ADP was calculated as Platelet reactivity index (PRI). HTPR was defined as PRI ≥ 50, therapeutic window as PRI as 16–49 and LTPR as PRI < 16 [23].

2.4. Secondary endpoint (MACCE and bleeding)

Death, major/minor stroke, transient ischemic attack (TIA), myocardial infarction (MI), occluder thrombosis (OT) and major/minor bleeding represented the secondary endpoint. MACCE was defined as death, stroke and MI and OT [25]. Bleeding was defined according to TIMI classification [26]. Data were collected during hospitalization and during one-year follow-up. Follow-up was conducted in our outpatient unit or standardized questionnaire by telephone interview.

2.5. Statistics

GraphPad-Prism© software (GraphPad software Inc., San Diego) and IBM SPSS©-Software (New York, USA) were used for statistical analyses. Chi^2 was used for in hospital and log-rank test for follow-up data. Unpaired *t*-test and ANOVA analysis were used for patients' characteristics. Multivariate cox-regression (with forward selection) of twelve potential confounders (gender, age, body mass index, diabetes mellitus, chronic kidney disease, CHA2DS2VASC, CHA2DS2, HASBLED, prior coronary artery bypass grafting, haemoglobin, use of angiotensin converting enzyme -inhibitors and oral anticoagulation) were performed for association between LTPR to clopidogrel and bleeding. *p*-Values < 0.05 were considered significant. This hypothesis generating pilot study was descriptive. Therefore, no power analysis was conducted.

3. Results

3.1. Study patients — baseline characteristics

The mean age of the study participants was 76.5 ± 7.4 years at the date of the intervention. 76 (59%) were male, 45 (34.9%) suffered from diabetes mellitus, 38 (29.5%) were obese and 115 (89.1%) had arterial hypertension. Patients' characteristics are presented in Table 1. In dependence of pharmacodynamic response to aspirin, there were significant differences regarding CHA2DS2VASC (no$HTPR_{ASA}$ − 4.3 ± 1.4 vs. $HTPR_{ASA}$ − 4.1 ± 0.96, $p = 0.02$) and comedication with angiotensin converting enzyme inhibitors (no$HTPR_{ASA}$ − 57% vs. $HTPR_{ASA}$ − 33.3%, $p = 0.04$) (supplemental 7–10). Concerning pharmacodynamic response to clopidogrel, there were significant differences regarding male gender ($LTPR_{P2Y12}$ − 61.5%, TW_{P2Y12} − 47%, $HTPR_{P2Y12}$ − 67.2%, $p = 0.09$), prior coronary artery bypass graft ($LTPR_{P2Y12}$ − 0%, TW_{P2Y12} − 16.3%, $HTPR_{P2Y12}$ − 26.9%, $p = 0.06$), dose of unfractionated heparing during procedure ($LTPR_{P2Y12}$ − 5090.91 ± 2022.6, TW_{P2Y12} − 6743.59 ± 2684.93, $HTPR_{P2Y12}$ − 7421.05 ± 2951.68, $p = 0.04$), comedication with oral anticoagulation ($LTPR_{P2Y12}$ − 46.2%, TW_{P2Y12} − 30.6%, $HTPR_{P2Y12}$ − 50.7%, $p = 0.09$) and initial haemoglobin ($LTPR_{P2Y12}$ − 10.1 ± 1.89, TW_{P2Y12} − 12.46 ± 1.79, $HTPR_{P2Y12}$ − 12.11 ± 1.93, $p = 0.0001$) (supplemental 8–14). 87 (67.4%) patients received Amplatzer Cardiac Plug occluder, 32 (24.8%) Amulet occluder, 6 (4.7%) Watchman occluder and 2 (1%) Occlutech occluder. Mean device size was 23.5 ± 3.5 mm. Time of intervention was 86 ± 25.6 min, fluoroscopy time 17.6 ± 9.5 min. Patients received 115.4 ± 88.2 ml contrast medium and 6935 ± 2840 IU of unfractionated heparin. Mean dose area product was 5654 ± 4192 Gy cm^2. No patient died during procedure (supplemental 1).

Table 1
Baseline characteristics, cardiovascular risk factors, comorbidities and medical history.

Characteristics	Total $n = 129$
Age — years (mean ± SD)	76.5 ± 7.4
Male gender — no. (%)	76 (59%)
Body mass index (mean ± SD)	27.6 ± 4.5
Cardiovascular risk factors — no. (%)	
Hypertension	115 (89.1%)
Diabetes mellitus	45 (34.9%)
COPD	23 (17.8%)
Obesity (BMI > 30)	38 (29.5%)
Comorbidities and medical history — no. (%)	
Prior MI	46 (35.7%)
Prior PCI	70 (54.3%)
Prior CABG	26 (20.2%)
Prior valvular procedure	31 (23.5%)
Prior stroke	24 (18.6%)
Prior cerebrovascular intervention	5 (3.8%)
CKD stages 3–5	71 (55%)

SD = standard deviation, COPD = chronic obstructive pulmonary disease, BMI = body mass index, MI = myocardial infarction, PCI = percutaneous coronary intervention, CABG = coronary artery bypass graft.

Table 2
Secondary endpoint in-hospital.

	ASS			Clopidogrel			
	No HTPR ($n = 114$)	HTPR ($n = 15$)	p value*	LTPR ($n = 13$)	TW ($n = 49$)	HTPR ($n = 67$)	p value*
MACCE	2 (2%)	1 (6%)	0.24	0 (0%)	1 (2%)	2 (3%)	0.8
Death	2 (2%)	1 (6%)	0.24	0 (0%)	1 (2%)	2 (3%)	0.8
MI	0 (0%)	0 (0%)	–	0 (0%)	0 (0%)	0 (0%)	–
OT	0 (0%)	0 (0%)	–	0 (0%)	0 (0%)	0 (0%)	–
TIA/stroke	0 (0%)	0 (0%)	–	0 (0%)	0 (0%)	0 (0%)	–
Bleeding							
Major	2 (2%)	0 (0%)	0.61	0 (0%)	2 (4%)	0 (0%)	0.19
Minor	8 (7%)	1 (6.3%)	0.96	4 (31%)	1 (2%)	4 (6%)	**0.0013**

* p-value calculated using the chi^2 test.

3.2. Primary endpoint (platelet function testing)

Mean maximum of aggregation was 15.28% ± 19.17%. In 15 (12%) patients HTPR to aspirin was detected. Mean PRI was 50.79 ± 25.43. 67 (52%) of the patients showed HTPR to clopidogrel, 13 (10%) showed LTPR (PRI < 16) (supplemental 6).

3.3. Secondary endpoint in-hospital (MACCE and bleeding)

In-hospital-MACCE did not differ between patients without (noHTPR$_{ASA}$) or with HTPR (HTPR$_{ASA}$) to aspirin (noHTPR$_{ASA}$ − 2% vs. HTPR$_{ASA}$ − 6%, $p = 0.24$). Two patients without HTPR and one patient with HTPR died during hospitalization (noHTPR$_{ASA}$ − 2% vs. HTPR$_{ASA}$ − 6%, $p = 0.24$). One patient died as a result of a therapy-refractory septic shock 25 days after the LAAC. One death occurred due to a cardiogenic shock as a result of ventricular fibrillation two days after LAAC. Two days after the intervention, one patient died because of a cardiogenic shock due to acute myocardial infarction. OT and stroke/TIA did not occur. The occurrence of major and minor bleeding did not differ between groups (major bleeding: noHTPR$_{ASA}$ − 2% vs. HTPR$_{ASA}$ − 0%, $p = 0.61$, minor bleeding: noHTPR$_{ASA}$ − 7% vs. HTPR$_{ASA}$ − 6.3%, $p = 0.96$).

Regarding pharmacodynamic response to clopidogrel, in-hospital-MACCE did not differ between patients with LTPR (LTPR$_{P2Y12}$), optimal antiplatelet activity (TW$_{P2Y12}$) or HTPR (HTPR$_{P2Y12}$), (LTPR$_{P2Y12}$ − 0%, TW$_{P2Y12}$ − 2%, HTPR$_{P2Y12}$ − 3%, $p = 0.8$). As substitutes of MACCE, there was no difference in death, (death: LTPR$_{P2Y12}$ − 0%, TW$_{P2Y12}$ − 2%, HTPR$_{P2Y12}$ − 3%, $p = 0.8$) MI and Stroke/TIA did not occur. Patients in the therapeutic window of clopidogrel suffered numerically more often from major bleeding (LTPR$_{P2Y12}$ − 0%, TW$_{P2Y12}$ − 4%, HTPR$_{P2Y12}$ − 0%, $p = 0.19$). Minor bleeding occurred more frequently in patients with LTPR to clopidogrel (LTPR$_{P2Y12}$ − 31%, TW$_{P2Y12}$ − 2%, HTPR$_{P2Y12}$ − 6%, $p = 0.0013$) (Table 2).

3.4. Secondary endpoint in one-year follow-up (MACCE and bleeding)

During one-year follow-up, rate of MACCE and MI did not differ between patients with or without HTPR to aspirin (MACCE: noHTPR$_{ASA}$ − 13.2% vs. HTPR$_{ASA}$ − 20%, HR 0.41, 95% CI 0.12–2.37, $p = 0.41$; MI: noHTPR$_{ASA}$ − 6.1% vs. HTPR$_{ASA}$ − 7.1%, HR 0.82, 95% CI 0.08–7.75, $p = 0.85$). There was a trend towards increased mortality in patients with HTPR to aspirin (noHTPR$_{ASA}$ − 7% vs. HTPR$_{ASA}$ − 20%, HR 0.32, 95% CI 0.03–1.2, $p = 0.08$). Stroke/TIA and OT did not occur in both groups. There were no differences regarding major and minor bleeding for patients without HTPR to aspirin (major bleeding: noHTPR$_{ASA}$ − 1.8% vs. HTPR$_{ASA}$ − 6.3%, HR 0.26, 95% CI 0.004–4.13, $p = 0.22$, minor bleeding: noHTPR$_{ASA}$ − 7.9% vs. HTPR$_{ASA}$ − 6.7%, HR 1.2, 95% CI 0.18–8.16, $p = 0.85$) (Fig. 1 and supplemental 4).

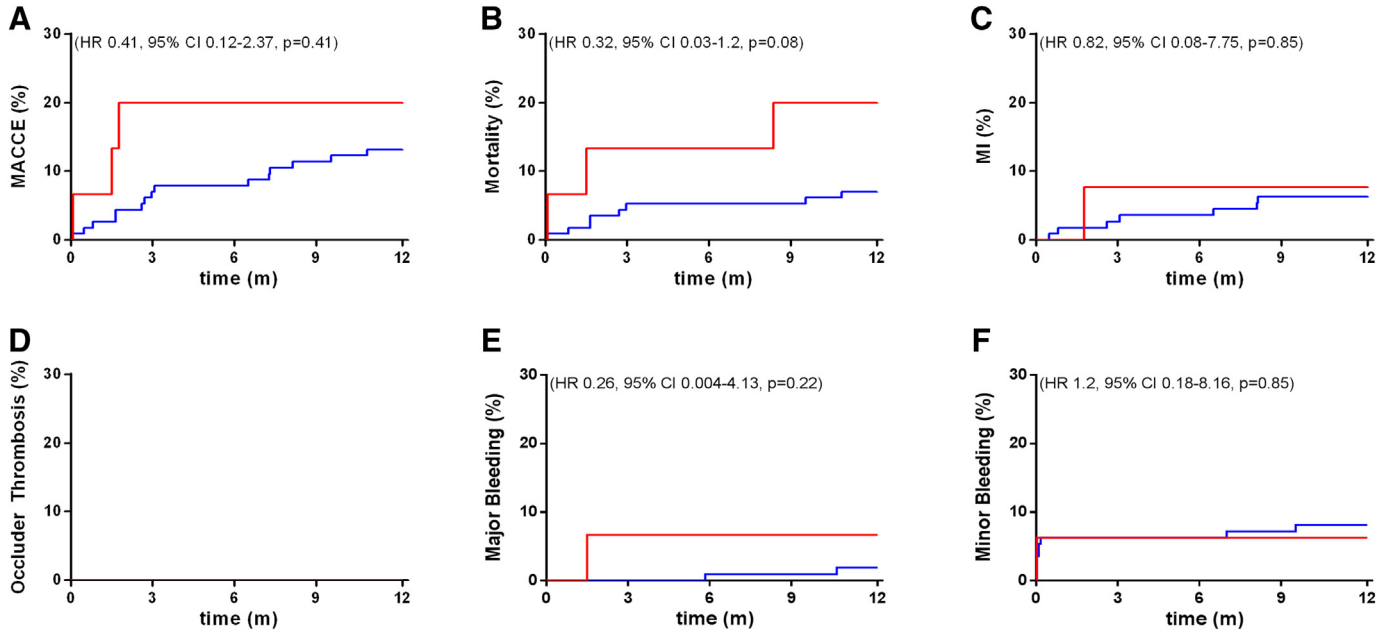

Fig. 1. Kaplan–Meier plots for occurrence of secondary endpoints in dependence of pharmacodynamic response to aspirin in one-year follow-up (red line: high on-treatment platelet reactivity (HTPR) to aspirin, blue line: no HTPR to aspirin). (A) MACCE (HR 0.41, 95% CI 0.12–2.37, $p = 0.41$), (B) death (HR 0.32, 95% CI 0.03–1.2, $p = 0.08$), (C) MI (HR 0.82, 95% CI 0.08–7.75, $p = 0.85$), (D) occluder thrombosis, (E) major bleeding (HR 0.26, 95% CI 0.004–4.13, $p = 0.22$) and (F) minor bleeding (HR 1.2, 95% CI 0.18–8.16, $p = 0.85$).

Hazard for MACCE, mortality and MI did not differ between patients with LTPR, optimal antiplatelet effect of clopidogrel and HTPR (MACCE: $LTPR_{P2Y12}$ – 23.1%, TW_{P2Y12} – 16.3%, $HTPR_{P2Y12}$ – 10.4%, Log rank: $p = 0.45$; mortality: $LTPR_{P2Y12}$ – 7.7%, TW_{P2Y12} – 10.2%, $HTPR_{P2Y12}$ – 7.5%, Log rank: $p = 0.88$; MI: $LTPR_{P2Y12}$ – 15.4%, TW_{P2Y12} – 6.1%, $HTPR_{P2Y12}$ – 4.5%, Log rank: $p = 0.33$). Major bleeding was numerically higher in patients in the therapeutic window of clopidogrel compared to patients with HTPR and LTPR ($LTPR_{P2Y12}$ – 0%, TW_{P2Y12} – 6.1%, $HTPR_{P2Y12}$ – 0%, Log rank: $p = 0.64$). Minor bleeding was non-significantly increased in patients with LTPR to clopidogrel ($LTPR_{P2Y12}$ – 23.1%, TW_{P2Y12} – 6.1%, $HTPR_{P2Y12}$ – 6%, Log rank: $p = 0.056$) (Fig. 2 and supplemental 4).

After multivariate cox-regression, clopidogrel medication is the only independent variable for bleeding. All other significant differences in patients' characteristics are not associated with bleeding during one-year follow-up (supplemental 15).

3.5. Bleeding in three months follow-up

Rate of major and minor bleeding did not differ between patients with and without HTPR to aspirin (major bleeding: $noHTPR_{ASA}$ – 2% vs. $HTPR_{ASA}$ – 0%, HR 3.16, 95% CI 0.05–21.55, $p = 0.59$; minor bleeding: $noHTPR_{ASA}$ – 8.7% vs. $HTPR_{ASA}$ – 6.3%, HR 1.11, 95% CI 0.15–8.41, $p = 0.92$). In patients with LTPR, sufficient pharmacodynamic response to clopidogrel and HTPR to clopidogrel, the occurrence of minor bleeding differed between groups whereas the rate of major bleeding did not (major bleeding: $LTPR_{P2Y12}$ – 0%, TW_{P2Y12} – 4%, $HTPR_{P2Y12}$ – 0%, Log rank: $p = 0.19$; minor bleeding: $LTPR_{P2Y12}$ – 31%, TW_{P2Y12} – 2%, $HTPR_{P2Y12}$ – 6%, Log rank: $p = 0.001$) (supplementals 16 and 17).

Multivariate cox-regression analysis revealed CHA2DS2VASC and CHADS2 as relevant factors to be associated with the occurrence of minor bleeding next to LTPR to clopidogrel (supplemental 18).

3.6. Aetiology of bleeding events

Type of bleeding was assessed. 18.2% of bleedings were gastrointestinal, 0% intracranial, 72.7% access site related or other peri-procedural bleeding and 18.2% were other bleedings (supplemental 19).

4. Discussion

The major findings of this study were that (i) HTPR to clopidogrel is frequent after interventional LAAC, (ii) no occluder thrombosis or stroke occurred and (iii) bleeding events were more frequent in patients with LTPR to clopidogrel.

The demonstrated rate of HTPR to aspirin and clopidogrel in patients of our cohort is comparable to other interventional cardiac procedures [17,19]. Especially pharmacodynamic response to clopidogrel varies widely between individuals. Patients undergoing LAAC are usually elderly and have many co-morbidities like arterial hypertension and diabetes mellitus [27]. This was additionally reflected in the present study. These co-morbidities might be possible reasons for the demonstrated rate of HTPR and LTPR in the present cohort [28–30]. Our study involves significantly more males in the groups of LTPR and HTPR to clopidogrel. The literature regarding pharmacodynamic response to clopidogrel in dependence of gender is inconsistence as there are studies that revealed no influence or a higher risk for female [30]. In addition, patients with LTPR to clopidogrel had significant lower initial haemoglobin concentration. These results contrast a study from 2012 that revealed anaemia as a risk factor for HTPR to clopidogrel. The comparability may be limited, because in this study LTA and VerifyNow P2Y12 assay were used for platelet function testing [31].

In previous studies, a loading dose of 600 mg clopidogrel is described to prevent HTPR more effectively than a 300 mg loading dose [32]. Although we used the higher loading dose in this study, it was not possible to prevent a high rate of HTPR to clopidogrel. Despite the high rate of HTPR, no occluder thrombosis or stroke occurred. Furthermore, the novel P2Y12-antagonists ticagrelor and prasugrel are shown to reduce the rate of HTPR [33]. On the other hand, rate of LTPR is higher as compared to clopidogrel [34]. Both are currently used in patients with coronary artery disease. They might also be an interesting option after LAAC. However, bleeding risk of LAAC patients is very high (reflecting, that they are not suitable for oral anticoagulation). In our study, no OT occurred during hospitalization and one-year follow-up. This differs from previously reported rates of OT [12] as rates up to 17.6% were described [35]. A potential reason may be that only patients

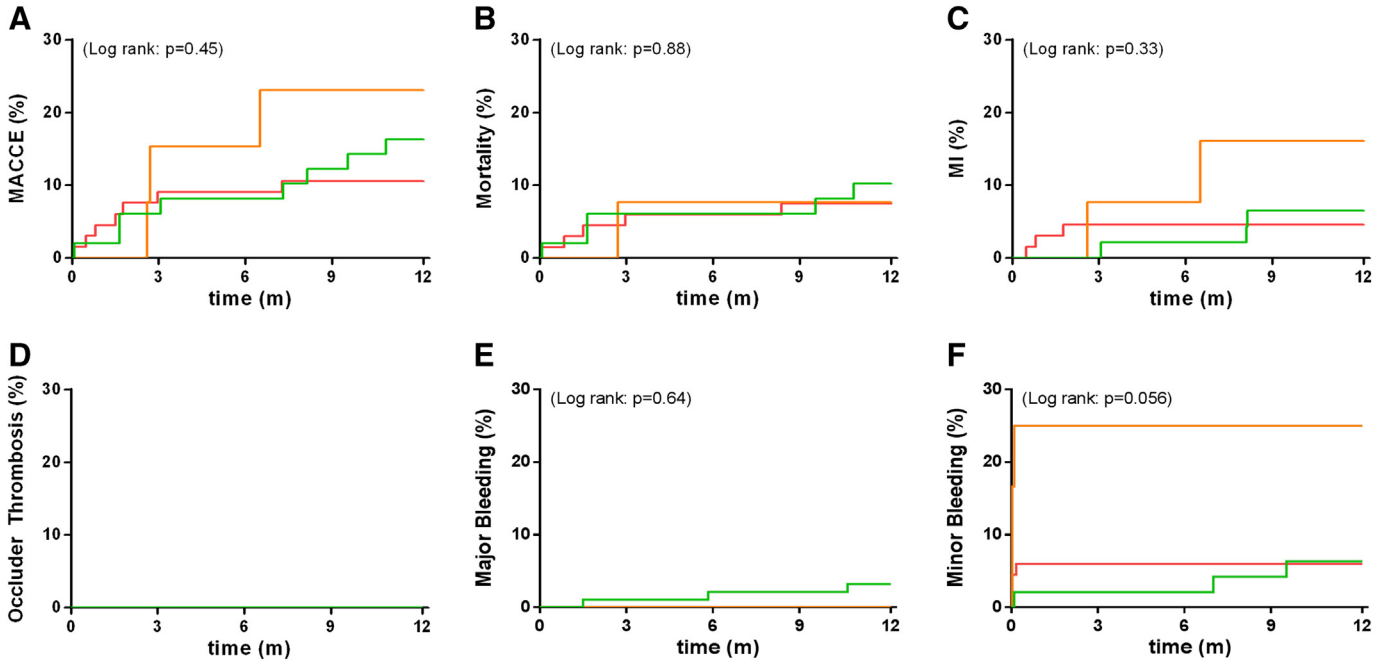

Fig. 2. Kaplan–Meier plots for occurrence of secondary endpoints in dependence of pharmacodynamic response to clopidogrel in one-year follow-up (orange line: low on-treatment platelet reactivity to clopidogrel, green line: therapeutic window, red line: high on-treatment platelet reactivity to clopidogrel). (A) MACCE ($p = 0.45$), (B) death ($p = 0.88$), (C) MI ($p = 0.33$), (D) occluder thrombosis, (E) major bleeding ($p = 0.64$) and (F) minor bleeding ($p = 0.056$).

with sufficient procedural occlusion of the LAA were included in our study. Other factors might be used device and peri- and post-interventional antithrombotic regimen.

The mortality in our study was relatively high in comparison to the mortality described in other studies. Possible reasons for this are the older age and the higher CHA2DS2-VASc-score of patients in our cohort [5,36,37].

In our study, patients with LTPR to clopidogrel suffered more often from minor bleeding. This observation is in alignment with other studies that revealed a higher risk for bleeding in patients with LTPR to clopidogrel [23]. After multivariate analysis for bleeding events during one-year follow-up, clopidogrel remains the only significant variable for bleeding in our study. This is consistent with various studies showing LTPR to clopidogrel as risk factor for bleeding [38,39]. However, major bleedings only occurred in patients with clopidogrel response within the therapeutic window and not in patients with LTPR to clopidogrel. Moreover, additional three months follow-up was conducted. Also after three months, patients with LTPR to clopidogrel showed significantly more minor bleeding events. This finding remained robust after adjustment for gender, age, BMI, existing diabetes mellitus or chronic kidney disease, HASBLED score, prior CABG, haemoglobin and intake of ACE-inhibitors or oral anticoagulation. However, multivariate regression analysis revealed that also CHA2DS2VASC and CHADS2 were associated with the occurrence of bleeding in this time period. Though these scores are well established for stroke risk prediction in AF patients, several other studies also showed a correlation with the occurrence of bleeding [40–42]. Nevertheless, both scores did not differ between patients with LTPR, sufficient response and HTPR to clopidogrel in our study.

With regard to this finding the question rises, if single antiplatelet medication with aspirin might be enough after LAAC. In patients undergoing transcatheter aortic valve replacement (TAVR), this question has now been evaluated by three randomized controlled trials. A recent patient level meta-analysis revealed less bleeding events with similar rates of ischemic events in aspirin alone treated patients as compared to DAPT treated patients. Especially life-threatening bleedings were more frequent in DAPT treated patients [43]. For patients undergoing interventional LAAC, the safety and efficiency of single antiplatelet therapy with aspirin has additionally been described [11,12]. This supports our finding, that clopidogrel may be unnecessary after interventional LAAC.

Another option might be continuation of oral anticoagulation early after LAAC as conduced in the LAAC landmark trials. In TAVI patients, it has been shown that oral anticoagulation is superior to prevent subclinical leaflet thrombosis. However, in comparison to LAAC, subclinical leaflet thrombosis is more frequent (12% of patients) [44]. Furthermore, detecting subclinical leaflet thrombosis on the prosthesis is challenging [45]. In comparison, rate of OT after interventional LAAC is low [27,46,47] and well detectable by echocardiography. Therefore, anticoagulation does not seem reasonable, especially as bleeding risk is very high in LAAC patients. However, anticoagulation with non-vitamin K anticoagulants are already first choice as compared to vitamin K antagonists. Due to the first results of the EWOLUTION-registry, the use of novel oral anticoagulation may be a safety and efficient alternative for antithrombotic medication after LAAC, as the incidence of occluder thrombosis was low [48]. Despite the lack of evidence, in clinical practice various regimes (DAPT, oral anticoagulation followed by DAPT, oral anticoagulation and DAPT simultaneously or single antiplatelet therapy) are performed [10]. Clinical trials are needed to address the optimal antithrombotic regiment.

4.1. Study limitations

We conducted a hypothesis generating pilot study to measure pharmacodynamic response to aspirin and clopidogrel after interventional LAA-occluder-implantation. The study was not powered to correlate pharmacodynamic response to DAPT with clinical endpoints. In addition, due to the mono-center character of the study, we had a limited sample size.

Regarding type of bleeding, the majority was access site related. However, clopidogrel medication was continued or — in case of P2Y12 naïve patients — loading was conducted the day before LAAC. Hence, pharmacodynamic response to clopidogrel might already have affected bleeding events in this time period. Moreover, platelet function measurement was conducted 48 h after LAAC. Therefore, especially bleeding events in the early time period after LAAC might be associated with the represented values of clopidogrel induced platelet inhibition. However, a strict affirmation that clopidogrel response is directly associated with the occurrence of bleeding is limited based on the results of this study. This is due to the lack of power to differences in clinical events, to the occurring major bleeding evens in patients with sufficient response to clopidogrel and to the revealed influence of CHA2DS2-VASc and CHADS2 in the multivariate analysis after three months follow-up.

Furthermore, thresholds for HTPR and LTPR have been obtained for patients with coronary artery disease and it is not proven that the same thresholds have validity for other situations. Additionally, it has been shown, that HTPR to clopidogrel decrease over time [49]. In this study, measurements of platelet reactivity were conducted cross-sectionally during hospital course and not during time-series measurements. Moreover, several patients could not be on their steady-state phase of clopidogrel treatment at the time of pharmacodynamic measurement. Hence, rate of HTPR to clopidogrel might be overestimated. Finally, there is a multiplicity of tests available to measure platelet function. In this study, we referred to LTA and VASP as frequently and reliably used methods. However, other platelet function assays could have provided valuable confirmation of the findings of this study.

5. Conclusion

In this study, HTPR to clopidogrel was very frequent after LAAC. However, no occluder thrombosis or stroke occurred during one year follow-up. Additionally, patients with LTPR to clopidogrel showed more minor bleeding events. Therefore, this study rises the hypothesis that aspirin monotherapy might be safe and efficient after LAAC. To this affect, clinical trials are needed addressing this hypothesis.

Acknowledgments

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Ethics committee approval

The study conformed to the Declaration of Helsinki and was approved by the University of Düsseldorf Ethics Committee.

Authors' contributions

L.D. and P.M. designed the study, analyzed and interpreted data and wrote the manuscript. D.N., R.M., K.T., D.K., G.W., and M.B. collected data and revised the manuscript. V.S., B.L., T.H., T.Z., M.K., and A.P. supervised the study and revised the manuscript.

Disclosures

No conflicts to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.10.040.

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