Changes in Coagulation and Platelet Activation Markers Following Transcatheter Left Atrial Appendage Closure

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The recommendations for antithrombotic treatment after left atrial appendage closure (LAAC) remain empirical, and no data exist on the changes in hemostatic markers associated with LACC. The objective of the present study is to determine the presence, degree, and timing of changes in the markers of platelet and coagulation activation after LAAC. Forty-three patients (mean age 76 ± 9 years, 23 men) with atrial fibrillation who underwent successful LACC with the Watchman (n = 27) or Amplatzer Cardiac Plug (n = 16) devices were included in the study. Patients received antiplatelet therapy after LAAC (aspirin + clopidogrel: 27 patients; single antiplatelet therapy with aspirin or clopidogrel: 16 patients). Prothrombin fragment 1+2 and thrombin-antithrombin III were used as markers of coagulation activation, and soluble P-selectin and soluble CD40 ligand were used as markers of platelet activation. Measurements of all hemostatic markers were performed at baseline just before the procedure, followed by days 7, 30, and 180 after LAAC. Prothrombin fragment 1+2 and thrombin-antithrombin levels increased from 0.27 nmol/L and 4.68 ng/ml, respectively, at baseline to peak values of 0.43 nmol/L and 9.76 ng/ml, respectively, at 7 days, partially returning to baseline levels at days 30 and 180 after LAAC ($p < 0.001$ for both markers). No clinical or procedural factors were associated with a greater increase in the markers of coagulation activation after LAAC. Levels of soluble P-selectin and soluble CD40 ligand did not change at any time after LAAC. In conclusion, transcatheter LAAC is associated with significant activation of the coagulation system, yet without evidence of significant platelet activation. **(Am J Cardiol 2017;■:■−■)**

Transcatheter left atrial appendage closure (LAAC) has emerged as an alternative to anticoagulation for preventing thromboembolic events in patients with atrial fibrillation.[1] Although most complications associated with LAAC have decreased with time, the occurrence of device thrombosis remains a concern, with an incidence of 4% to 6%.[2,3] The type and duration of antithrombotic therapies after LAAC have evolved empirically. Although transient (6 weeks) anticoagulation therapy has been recommended in some studies,[4,5] others have used dual antiplatelet therapy within the 3 to 6 months after the procedure.[3,5,6] More recently, single antiplatelet therapy immediately after LAAC has also been suggested.[7] However, there is currently no biologic basis supporting a specific approach, and deciphering specific alternations of platelet and coagulation activation after LAAC could be useful for guiding the type and duration of antithrombotic therapy after LAAC. Soluble P-selectin (sPselectin) and CD40 ligand (CD40L) have been well validated as markers of platelet activation,[8,9] and prothrombin fragment 1+2 (F1+2) and thrombin-antithrombin III (TAT) as markers of coagulation activation.[10] The purpose of the present study is to determine the presence, degree, and timing of the changes in the markers of platelet (sPselectin, sCD40L) and coagulation (F1+2, TAT) activation after LAAC.

Methods

A total of 43 patients with atrial fibrillation who underwent LAAC because of contraindications to anticoagulation therapy were included in the study. The procedures were performed through the transfemoral approach, under general anesthesia with transesophageal echocardiographic guidance. Details specific to the LAAC procedure have been detailed elsewhere.[4−6] The device (Watchman [Boston Scientific, Natick, MA] or Amplatzer Cardiac Plug [ACP; St Jude Medical, Minneapolis, MN]) was selected according to left atrial appendage anatomy and physician's preference. Dual antiplatelet therapy (aspirin 80 mg/day + clopidogrel 75 mg/day) for 45 days and then aspirin indefinitely was the standard therapy after LAAC, but single antiplatelet therapy was an alternative option in those patients at very high risk of recurrent bleeding (HAS-BLED score >3). The final decision was left at the discretion of the physician responsible for the patient. A control transesophageal echocardiography (TEE) was performed at 6 weeks after LAAC, and patients underwent clinical follow-up at 6 and 12 months after the procedure, and

Department of Cardiology, Quebec Heart & Lung Institute, Laval University, Quebec City, Quebec, Canada. Manuscript received January 28, 2017; revised manuscript received and accepted March 16, 2017.

See page 5 for disclosure information.

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0002-9149/17/$ - see front matter
http://dx.doi.org/10.1016/j.amjcard.2017.03.253

Table 1
Baseline, procedural, and in-hospital characteristics of the study population

Variables	n=43
Baseline Characteristics	
Age (years)	76±9
Men	23 (54%)
Body mass index (kg/m2)	28±6
Hypertension	41 (95%)
Diabetes mellitus	16 (37%)
Coronary artery disease	21 (49%)
Previous heart failure	12 (28%)
LEVF (%)	54±11
Chronic renal failure	17 (40%)
Previous liver disease	3 (7%)
Atrial fibrillation type	
Paroxysmal	20 (47%)
Persistent/Permanent	23 (54%)
Thromboembolic events	
Stroke	15 (35%)
Transient ischemic attack	7 (16%)
Prior bleeding	39 (91%)
Labile INR*	1 (2%)
$CHADS_2$ score	3 (2-4)
CHA_2DS_2-VASc score	4 (3-6)
HAS-BLED score	4 (3-5)
Procedural Characteristics and In-Hospital Outcomes	
LAA Closure Device Implanted	
ACP	16 (37%)
Watchman	27 (63%)
In-hospital events	
Stroke	0
Major bleeding	0
Minor bleeding	1 (2%)
Pericardial effusion requiring intervention	1 (2%)
Prosthesis embolization	0
Hospital stay, days	1 [1-2]
Antithrombotic treatment at discharge	
Aspirin	13 (30%)
Clopidogrel	3 (7%)
Aspirin + clopidogrel	27 (63%)

Variables are presented as %, mean (SD), or median (IQR).

ACP = Amplatzer cardiac plug; ASD = atrial septal defect; INR = international normalized ratio; IQR = interquartile range; LAA = left atrial appendage; LVEF = left-ventricle ejection fraction; PFO = patent foramen ovale; TIA = transitory ischemic attack.

* Labile INR was define as <60% time in therapeutic range (INR 2-3 inclusive).

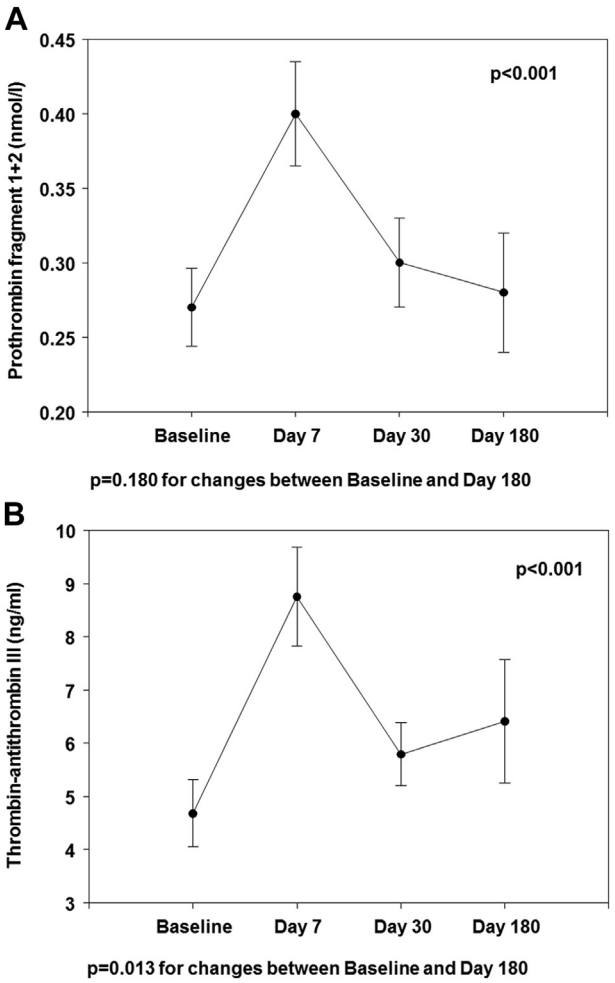

Figure 1. Changes in the markers of coagulation activation after LAAC. *(A)* Changes in F1+2 levels after LAAC. *(B)* Changes in TAT levels after LAAC.

yearly thereafter. The study protocol was approved by the local Ethics Committee and all patients provided signed informed consent.

Fasting blood samples were collected before the procedure on the same day of LAAC and at 7, 30, and 180 days after the procedure. Blood was collected into 4 Vacutainer tubes prefilled with 0.5 ml of 3.2% buffered sodium citrate (Becton Dickinson) that were kept on ice for a maximum of 2 hours before centrifugation at 2000g at 4°C for 15 minutes. Plasma and serum were pipetted into plastic vials in aliquots and stored at −70°C until analysis. Enzyme immunoassays were used for determining laboratory levels of F1+2 (Stago), TAT (Stago), sPselectin (R&D Systems), and sCD40 L (R&D Systems).

Categorical data are expressed as percentages, and continuous variables as mean (SD) or median (interquartile range). Comparisons between groups were performed using the chi-square test for categorical variables and the student *t* test for numerical variables. An ANOVA for repeated measures was performed to test for equal means at different times. Posteriori comparisons were performed using the Tukey's method. Statistical significance was assumed with a p value ≤0.05. Statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, North Carolina).

Results

The main baseline and procedural characteristics of the study population are listed in Table 1. The results of coagulation system activation (as assessed by F1+2 and TAT) are listed in Figure 1. Mean baseline levels of F1+2 and TAT were 0.27 nmol/L and 4.68 ng/ml, respectively. There was a significant change in both F1+2 and TAT levels after LAAC (p <0.001 for both markers). F1+2 levels increased by 68% at day 7 (95% confidence interval [CI] 46 to 90) and gradually decreased, yet remained 20% higher than baseline by day 30 (95% CI 8 to 32) and 16%