

Which Antiplatelet Therapy in Patients With Left Ventricular Assist Device and Aspirin Allergy?



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In patients with left ventricular assist device support and aspirin allergy, the choice of effective antiplatelet strategy remains a challenge. We compared the antithrombotic effect of clopidogrel vs ticagrelor in an LVAD patient with aspirin allergy by using a modified protocol of the thrombin generation test, accounting selectively for the platelet contribution on thrombin generation. Our results demonstrate enhanced antithrombotic efficacy offered by ticagrelor. Consistent with experimental results, the patient has passed more than 300 days without thromboembolic complications. This study provides additional mechanistic rationale supporting clinical evidence and opens the perspective to identify individual poor responsiveness to drugs by specifically evaluating drug-mediated platelet function.

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Left ventricular assist devices (LVADs) are rapidly emerging as the mainstay of therapy of patients with advanced systolic heart failure. Last-generation continuous-flow LVADs provided a progressive increase in patients' survival together with overall outcome improvement [1]. Nevertheless, an accompanying rise of adverse events, such as pump thrombosis and ischemic stroke, has been observed [2]. Pump-related issues—namely, altered hemodynamics and supraphysiologic shear stress—pose a significant post-implant thrombotic risk that requires routine antiplatelet therapy in addition to oral anticoagulation.

The Clinical Trial to Evaluate the HeartWare® Ventricular Assist System (ENDURANCE) confirmed that 325 mg/d aspirin associated with a vitamin K antagonist (eg, warfarin) targeted to international normalized ratio of 2 to 3 resulted in a reduction in thromboembolic complications in patients implanted with the HeartWare LVAD (HVAD; HeartWare Inc, Framingham, MA) [3].

However, no specific guidelines have been proposed for the management of patients with aspirin allergy or sensitivity.

Inhibitors of the adenosine 5'-diphosphate P2Y₁₂ platelet receptor are usually considered for these patients, despite the lack of consistent data. Effectiveness of anti-P2Y₁₂ agents is well documented in the settings of acute coronary syndrome, to prevent myocardial infarction, congestive heart failure, as well as percutaneous coronary interventions, but few data have been reported in the context of LVAD support. Moreover, the choice of the specific molecule (ie, clopidogrel, prasugrel, ticagrelor) is a challenge because a reliable diagnostic test of platelet function in response to different drugs has not been identified yet [4].

We present the first results obtained with an innovative experimental diagnostic test able to characterize the platelet response to antiplatelet agents that we used to evaluate antithrombotic effects mediated by clopidogrel vs ticagrelor in an HVAD patient with aspirin allergy.

The patient is a 57-year-old man in Interagency Registry for Mechanically Assisted Circulatory Support class 1 with ischemic end-stage heart failure. After HVAD implantation, he was managed with warfarin (international normalized ratio of 2 to 2.5) and clopidogrel (90 mg/d) because of aspirin allergy.

Recurrent thromboembolic events developed over the course of LVAD support; namely, three strokes after 108, 121, and 165 days of LVAD support, respectively, and a pump thrombosis after 484 days of support. The patient was managed to have a mean arterial pressure between 75 and 90 mm Hg. No aortic valve opening was observed. The patient had sinus rhythm. LVAD speed was equal to 2,560 rpm with corresponding LVAD flow between 3.5 and 4 L/min. At the occurrence of pump thrombosis, high flow was detected, with maximum flow equal to 5.4 L/min. After pump thrombosis, he was managed with intravenous thrombolytic therapy (no pump substitution). Because of his evident poor responsiveness to clopidogrel, he was then switched to ticagrelor (90 mg twice daily). No other management changes were introduced.

We compared the platelet prothrombotic profile as mediated by clopidogrel vs ticagrelor by properly modifying the experimental protocol of the thrombin generation test (TGT; Fig 1A), a validated biochemical assay that measures the prothrombotic tendency of a plasma sample [5].

Institutional Review Board approval was obtained for the test. The patient provided informed consent to participate in the study. To perform the test (see Appendix), the patient's purified platelets were obtained

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as previously described [6] and diluted in a platelet-free plasma pool. Thrombin generation was triggered by 0.5 pmol/L tissue factor in the reconstructed platelets + plasma preparation and measured according to the protocol described by Hemker and Kremers [5].

Five variables were extracted from the TGT curves (Fig 1) obtained from isolated (basal) and sonicated platelets: (1) lag time, the time to a thrombin concentration of 10 nmol; (2) endogenous thrombin potential, the total thrombin generated in the sample; (3) peak, the maximal velocity of thrombin generation; (4) time to peak, the time to maximal velocity of thrombin generation; and (5) acceleration, the change in velocity to peak velocity [5]. The basal-over-sonicated ratio was calculated to normalize basal thrombin generation against maximal prothrombinase activity of the sonicated

platelets [6]. The experiments were performed while the patient was receiving clopidogrel and were repeated 15 days after therapy with ticagrelor.

According to our results, ticagrelor markedly reduced platelet-mediated thrombin generation. Although endogenous thrombin potential was comparable (variation 8%), the marked increase of lag time (+42%) and time to peak (+75%) and the decrease of peak of thrombin generation (−24%) and acceleration (−61%) indicated a significantly lower platelet prothrombinase activity with ticagrelor. Consistent with these results, the patient has now passed 300 days without any further thromboembolic complications.

Comment

The present work introduces an innovative and clinically reliable diagnostic tool to spot the platelet response to antiplatelet agents in patients requiring antithrombotic therapy. The diagnostic methodology we developed allows the characterization of how different drugs modulate the platelet thrombin generation profile, accounting selectively for the platelet contribution on thrombin generation in the plasma and excluding any influence of oral anticoagulants (warfarin) on the test.

We show that ticagrelor might offer better enhanced antiplatelet efficacy than clopidogrel in the context of LVAD support. Our results are in agreement with previous studies reporting thrombotic episodes in LVAD clopidogrel-treated patients and further expand previous findings that showed optimal antithrombotic efficacy offered by aspirin, dipyridamole, and ticagrelor combined therapy [7]. Here, we suggest that ticagrelor alone might represent a valid antiplatelet strategy for LVAD patients with aspirin allergy who exhibit poor responsiveness to thienopyridines. Indeed, whatever the specific triggering mechanism of diagnosed thrombotic events (ie, particular angulation of inflow/outflow LVAD cannula, patient-specific predisposition associated with arrhythmias, atrial/ventricular fibrillation, aortic valve opening, etc), attenuation of the platelet prothrombotic tendency, as mediated by ticagrelor, contributed to limit the occurrence of further complications.

Our data provide additional mechanistic rationale supporting clinical evidence and corroborate the need for individualized antiplatelet strategies based on platelet function diagnostic tests, such as the one proposed here. These tests might provide more clinically useful data than genetic tests to identify and manage variability in the platelet response to drugs. Indeed, previous studies reported that the identification of the cytochrome P450 2C19 (CYP2C19) polymorphism was not univocally associated with clopidogrel resistance [8].

Prospectively, our platelet function test might be further explored in the clinic to spot the platelet response to antiplatelets before LVAD implant to promptly identify individual poor responsiveness to drugs and to facilitate the tailoring of individualized pharmacologic strategies preventing thromboembolic complications over the time of support.

1. Isolation of PLATELETS

2. PLATELETS + Platelet-free-Plasma + 0.5 pmol/L Tissue Factor

3. FLUOROGENIC ASSAY platelet-mediated thrombin production rate

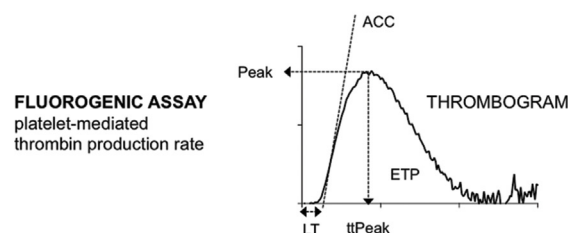
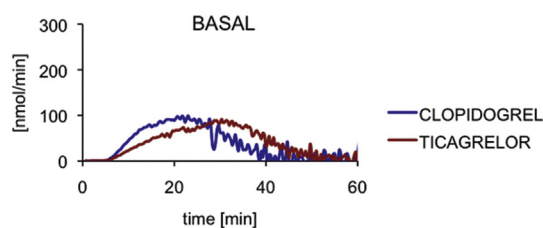
**A****B**

Fig 1. (A) Schematics of the three-step protocol for the thrombin generation test. (B) Comparison of platelet-mediated thrombin generation as modulated by clopidogrel (blue line) vs ticagrelor (red line). The test was performed on basal (top) and sonicated (bottom) platelet samples to normalize basal thrombin generation against maximal prothrombinase activity of sonicated platelets. (ACC = acceleration, the change in velocity to peak velocity; ETP = endogenous thrombin potential; LT = lag time; Peak = maximal velocity of thrombin generation; ttPeak = time to peak.)

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Appendix

Experimental Protocol of the Thrombin Generation Test

To perform the Thrombin Generation Test (TGT), patient's purified platelets were obtained from whole blood collected in ACD (ratio 10:1) via gentle centrifugation and gel-column filtration, as described in [6], and diluted in a platelet-free plasma pool (PFP) at a final concentration of 50,000platelets/ μ L. To obtain PFP, whole blood was collected from n=15 donors in sodium citrate with addition of corn trypsin inhibitor (Hematologic Technologies, USA) to avoid contact phase activation of factor XII resulting in undesired thrombin generation not-related to platelet function.

Thrombin generation was triggered by 0.5 pmol/L Tissue Factor in the reconstructed platelets+PFP preparation and measured according to the protocol described in [5]. Briefly, thrombin generation was monitored for 60min at 37°C (Fluoroskan Ascent plate reader, Thermo Labsystem, Finland; excitation filter 390 nm, emission filter 460 nm) and the fluorescent signal converted to a thrombin concentration by comparison with the signal generated by a thrombin calibrator (Thrombin Calibrator, Diagnostica Stago, Inc., USA) added to a separate PFP sample [5].

Five parameters were extracted from the TGT curves (Fig. 1A) obtained from isolated (basal) and sonicated platelets: i) Lag Time (LT), i.e., the time to a thrombin concentration of 10-nmol; ii) Endogenous Thrombin Potential (ETP), i.e., the total thrombin generated in the sample; iii) Peak, i.e., the maximal velocity of thrombin generation; iv) Time to Peak (ttPeak), i.e., the time to maximal velocity of thrombin generation; v) Acceleration (ACC), i.e., the change in velocity to peak velocity. The basal-over-sonicated ratio was calculated to normalize basal thrombin generation against maximal pro-thrombinase activity of sonicated platelets (sonication conditions: 10W, 10sec; Misonix Microson XL200, Qsonica LLC, USA) [6].