Survival of HeartMate II Patients Despite Cessation of Anticoagulation
— Outcomes and Hemostatic Analysis —

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**Background:** In long-term left ventricular assist device (LVAD) therapy, recurrent bleeding events may justify cessation of anticoagulation therapy (AT). However, data about the safety and risks of AT cessation in LVAD patients are scarce.

**Methods and Results:** Between 2010 and 2015, 128 patients received a HeartMate II (HMII). Following recurrent bleeding events, we ceased vitamin K antagonist (VKA) therapy in 13 patients (10%) (no-VKA group). To characterize the hemostatic profile, we performed von Willebrand factor (vWF), platelet function (PF), and other hemostatic tests in all HMII patients. The incidence of pump thrombosis (PT), ischemic stroke (IS) and bleeding events in this HMII population was 4.7%, 6.2% and 36.7%, respectively. Median survival without VKA was 435 days. No cases of PT and only 1 of IS occurred after AT discontinuation. All patients had impaired PF and acquired von Willebrand syndrome (AvWS). However, the vWF collagen-binding activity to antigen ratio before and after VKA cessation was significantly lower in the no-VKA group compared with the HMII population (0.60±0.12 vs. 0.73±0.14, P=0.006). The thrombin-antithrombin III complex (TAT) value was significantly higher in the no-VKA group (P=0.0005).

**Conclusions:** We experienced good results with AT cessation in specific HMII patients. The simultaneous onset of AvWS and high TAT values could explain at least in part the low thromboembolic rate in HMII patients without VKA.

**Key Words:** Anticoagulation; Bleeding; HeartMate II; Left ventricular assist device; Pump thrombosis

Although continuous-flow left ventricular assist devices (CF-LVADs) show good durability and improved patient survival, bleeding and thromboembolic events remain the most common postoperative complications. With the growing use of CF-LVADs as destination therapy (DT), bleeding rates are increasing.\(^1\)\(^2\)\(^3\) The current anticoagulation recommendation for HeartMate II (HMII) is vitamin K antagonist (VKA) treatment with an international normalized ratio (INR) target of 2.5±0.5, together with daily antiplatelet therapy (APT) using acetylsalicylic acid (ASA: 81–325 mg).\(^4\) Considering the risk of thromboembolic events, the cessation of anticoagulation therapy (AT) may be the only viable option in patients with recurrent bleeding events during CF-LVAD support as DT.\(^5\)\(^6\) There is limited information regarding the hemostatic profile of HMII patients who survive despite cessation of VKA and APT without the development of thromboembolism.

Therefore, the present study assessed the safety of VKA therapy cessation in HMII patients by evaluating recurrent bleeding events and investigating a panel of coagulation assays.

**Methods**

**Patients and Data Collection**

This was a single-center combined retrospective and prospective observational study of HMII patients in whom VKA treatment and APT therapy were ceased for at least 30 days because of recurrent bleeding events. All patients who received HMII implantation from May 2010 until May 2015 were included and their data were analyzed. The institutional ethics committee waived the requirement of informed consent for retrospective data analysis. The prospective analysis was approved by the local ethics committee (EK 151/09). Written informed consent was given by each patient for the collection of blood samples.

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and clinical data. Data were collected from the electronic database of our clinic, and included patient demographics, medical history, laboratory assessments, adverse events (AEs), and rehospitalization. All LVAD patients are routinely followed up during which the device parameter (flow [L/min], power [Watts], pulse index [PI] and revolutions per minute [rpm]) are controlled and documented by the LVAD coordinator. In addition, all LVAD patients document their device parameters daily and send the document each month to the LVAD coordinator. All patients were routinely followed up in the outpatient clinic until April 2017.

Laboratory Tests
Besides the routine laboratory assessments, fibrinogen, plasma free hemoglobin (fHb), and D-dimer levels were routinely measured in all patients. In addition, as part of the routine laboratory evaluation of LVAD patients, von Willebrand (vWF) analysis, including measurement of vWF collagen-binding activity (vWF:CBA) and the vWF antigen (vWF:Ag) ratio and multimer analysis were performed, starting 1 month after implantation and then at 3-month intervals until transplantation or therapy end. Thrombin-antithrombin complex (TAT) as an indicator of the activation of the procoagulant pathway was measured in all 13 patients for whom AT was ceased and in 50 HMII patients who were treated with VKA and ASA. Pre-AT cessation TAT data were only available in 6 of the 13 patients, for whom AT was then ceased.

Platelet function was evaluated with light transmission aggregometry (LTA) and PFA-100, at 3 and 6 months after implantation. Further coagulation analysis was carried out in patients for whom AT was ceased and who survived until April 2016. Coagulation was assessed in whole blood by performing extrinsic- and intrinsic-activated thromboelastometry (EXTEM and INTEM, respectively). Thrombin generation in plasma was measured using the calibrated automated thrombogram (CAT; Thrombinoscope, Maastricht, The Netherlands). For detailed information about blood sampling and hemostatic analysis, please refer to Supplementary File 1.

AT After HMII Implantation
When chest tube drainage was <50 mL/h, continuous infusion of heparin was initiated within the 24-h postoperative period in order to achieve an activated partial thromboplastin time (aPTT) of 50–60 s. For platelet inhibition, ASA (100 mg/day) was added to the medication regimen on postoperative day (POD) 1. At POD 3, VKA (Phenprocoumon, Pheno-hipropharm® 3 mg) was administered orally with a target INR of 1.8–2.2.

Patient Groups
AT was ceased in patients who had more than 4 bleeding events or hemorrhagic stroke (HS) and 1 further bleeding event within a period of 6 months during HMII support, and they resisted ICU readmission, and transfusion of blood products. After stabilization, all patients underwent repeated endoscopic diagnostic tests, such as upper and lower endoscopy or capsule endoscopy or computer tomography with angiography, and no definitive source of bleeding, which would have enabled intervention, could be identified.

Patients then received only ASA (100 mg/day) without VKA. This definition was a consensus among experts from cardiac surgery, cardiology and gastroenterology based on our experience with HMII and other LVAD devices during the past decade in our institution.

These 13 patients formed the no-VKA group. The rest of the population HMII (115 patients) formed the VKA group. After termination of AT, we frequently performed transeosophageal echocardiography, CT angiography, laboratory tests, and HMII-VAD device reading to detect thromboembolic disorders or events.

AE Monitoring
Each patient’s AE history was evaluated during hospital stay and at every outpatient visit. AEs were defined according to the 2013 Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) Version 2.2 definitions for ischemic stroke (IS), HS, transient ischemic attack (TIA), pump thrombosis (PT), and bleeding.

Statistical Analysis
Continuous variables are presented as mean±standard deviation (SD) or median with interquartile range [IQR] as appropriate, and categorical variables are described in absolute numbers and percentages. Owing to non-normal distribution of data, continuous variables were analyzed using the Wilcoxon signed-rank test for paired or repeated measurements and the Mann-Whitney U test for unpaired measurements. Categorical variables were analyzed using the chi-square test or, if appropriate, Fisher’s exact test. To compensate for the small sample number (n=6) of available TAT measurements in the no-VKA group prior to AT cessation and to perform a comparison with the VKA group, we performed propensity matching. Propensity scores were calculated for each patient using multivariate logistic regression based on the following preoperative covariates: age, sex, body mass index (BMI), INTERMACS level. The 6 no-VKA patients were then paired with 6 patients in the no-VKA group to compare TAT values before AT cessation.

The 6 no-VKA patients were also paired with 6 patients in the no-VKA group to compare TAT values before AT cessation between groups.

Events per patient-years were analyzed using Poisson regression. Kaplan-Meier analyses were performed to determine survival, freedom from AEs and to evaluate time-related outcomes using the log-rank test. All data analyses were performed using SPSS 23 (IBM Corp., Armonk, NY, USA). P<0.05 was considered statistically significant.

Results
Demographics and Medical History
The study included 128 patients, with a median follow-up of 562 [IQR: 28, 1021] days. An overview of patient demographics is presented in Table 1. AT was ceased in 13 patients (10%) (no-VKA group), and these patients were older than the rest of the HMII population (VKA group) (68±7 vs. 61±9 years, P=0.003). Among these patients, 84% were treated as DT. In the no-VKA group, 100% of the patients had ischemic heart failure, 61% had INTERMACS IV at implantation, and 46% had a history of atrial fibrillation.

Bleeding and Thromboembolic Events
All HMII Patients
The cumulative risk of PT was 2.3%, 3.1% and 4.7% at 1, 3 and 4 years, respectively (0.03 events
Table 1. Demographic, Peri- and Postoperative Data for Study Patients on HeartMate II Support

| Variable                        | VKA (n=115) | No-VKA (n=13) | P value |
|---------------------------------|-------------|---------------|---------|
| **Preoperative data**           |             |               |         |
| Age, years                      | 60.7±8.7    | 68.3±7.0      | 0.003   |
| Female, n (%)                   | 18 (15.6)   | 1 (7.7)       | 0.690   |
| BMI, kg/m²                      | 26.7±3.8    | 24.5±3.9      | 0.037   |
| Prior cardiac surgery, n (%)    | 21 (18.3)   | 1 (7.7)       | 0.461   |
| Prior PCI                       | 28 (24.3)   | 4 (30.8)      | 0.735   |
| ICM, n (%)                      | 87 (75.6)   | 13 (100)      | 0.070   |
| DCM, n (%)                      | 28 (24.4)   | 0             | 0.070   |
| DM                              | 34 (29.6)   | 5 (38.5)      | 0.533   |
| PAD                             | 26 (22.6)   | 5 (38.5)      | 0.302   |
| HT                              | 79 (68.7)   | 11 (84.1)     | 0.342   |
| Dialysis                        | 8 (6.9)     | 0             | 1.000   |
| CVA, n (%)                      | 6 (5.2)     | 0             | 1.000   |
| COPD, n (%)                     | 31 (26.9)   | 3 (23.7)      | 1.000   |
| PHT                             | 56 (48.7)   | 6 (46.1)      | 1.000   |
| DT                              | 87 (75.6)   | 11 (84.6)     | 0.731   |
| BTT                             | 28 (24.4)   | 2 (15.4)      | 0.731   |
| **INTERMACS**                   |             |               |         |
| I                               | 18 (15.6)   | 2 (15.4)      | 1.000   |
| II                              | 20 (17.4)   | 1 (7.7)       | 0.692   |
| III                             | 21 (18.3)   | 2 (15.4)      | 1.000   |
| IV                              | 56 (48.7)   | 8 (61.5)      | 0.560   |
| **Laboratory data**             |             |               |         |
| Hb, g/dL                        | 12.3±2.3    | 12.1±2.1      | 0.732   |
| Platelet count, /nL             | 220.3±90.3  | 229.6±84.3    | 0.783   |
| LDH, U/L                        | 332.3±415   | 229.1±67      | 0.323   |
| AST, U/L                        | 60.8±86.3   | 40.3±35.8     | 0.277   |
| ALT, U/L                        | 60.9±105.4  | 32.9±26.4     | 0.042   |
| Creatinine, mg/dL               | 1.1±1.5     | 1.1±0.3       | 0.855   |
| Pre-op ECMO                     | 18 (15.6)   | 2 (15.4)      | 1.000   |
| **Peri- and postoperative data**|             |               |         |
| LVAD alone                      | 55 (47.8)   | 3 (23.1)      | 0.140   |
| LVAD+CABG                       | 36 (31.1)   | 7 (53.8)      | 0.125   |
| LVAD+TVR                        | 16 (13.9)   | 2 (15.4)      | 1.000   |
| LVAD+AVR                        | 8 (6.9)     | 1 (7.7)       | 1.000   |
| CBP time, min                   | 141±65      | 143±65        | 0.711   |
| PRBCs, Units                    | 3.7±3.4     | 3.5±2.6       | 0.995   |
| FFPs, Units                     | 3.2±2.8     | 3.2±2.2       | 0.630   |
| PC, Units                       | 1.8±1.2     | 1.8±1.7       | 0.918   |
| PRBCs 30 POD, Units             | 6.7±6.1     | 6.9±6.7       | 0.978   |
| FFPs 30 POD, Units              | 2.5±3.6     | 1.7±2.4       | 0.641   |
| PC 30 POD, Units                | 0.7±1.2     | 0.5±0.7       | 0.991   |
| Pneumonia, n (%)                | 43 (37.4)   | 5 (38.5)      | 1.000   |
| Dialysis                        | 30 (26.1)   | 4 (30.8)      | 0.744   |
| ICU stay, days                  | 12.7±14.2   | 15.1±21.9     | 0.932   |
| Hospital LOS, days              | 25.8±41.1   | 37.4±32.9     | 0.052   |

aHT, arterial hypertension; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AVR, aortic valve replacement; BMI, body mass index; BTT, bridge to transplantation; CABG, coronary artery bypass graft; CBP, cardiopulmonary bypass; COPD, chronic obstructive pulmonary disease; CVA, cardiovascular accident; DCM, dilative cardiomyopathy; DM, diabetes mellitus; DT, destination therapy; ECMO, extracorporeal membrane oxygenation; FFP, fresh frozen plasma; Hb, hemoglobin; IABP, intra-aortic balloon pump; ICM, ischemic cardiomyopathy; ICU, intensive care unit; LDH, lactate dehydrogenase; LOS, length of stay; LVAD, left ventricular assist device; Op, operation; PAD, peripheral arterial disease; PC, platelet concentrate; PCI, percutaneous coronary intervention; PHT, pulmonary hypertension; PRBCs, packed red blood cells; TVR, tricuspid valve replacement.
definitive arteriovenous malformation (AVM) in 37%; suspected AVM in 14%; ulcer in 10%; gastric angioectasia in 4%; and 4% diverticulosis.

Cessation of AT and Outcomes

The median duration of HMII support before AT cessation was 394 [IQR: 127, 861] days. After AT was ceased, during the follow-up period none of the patients in the no-VKA group had PT or HS; 2 patients had a TIA at 4 and 13 months, respectively, after AT cessation and 1 patient had IS at 9 months post-AT cessation; 1 patient had 2 GIB events during the first year after AT cessation. On comparing the rate of GIB before and after AT cessation (Table 2), per patient-year [eppy]); of IS it was 3.9%, 5.5%, and 6.2% at 1, 3 and 4 years, respectively (0.04 eppy); of HS was 2.3%, 3.1% and 3.1% at 1, 3 and 4 years, respectively (0.02 eppy). The incidence of all gastrointestinal bleeding (GIB) was 25.8%, 35.1% and 35.7% at 1, 3 and 4 years, respectively (0.65 eppy). The distribution of bleeding events was as follows: 81.4% GIB; 10.9% epistaxis; bleeding from the urinary tract 4.6% and 3.1% HS. Eppy of all AEs in both groups are presented in Table 2.

**Table 2. Bleeding and Thromboembolic Events in Study Patients on HeartMate II Support**

| Adverse events | All HMII patients (n=128) | VKA group (n=115) | No-VKA before cessation (n=13) | P values | No-VKA after cessation (n=13) | No-VKA before cessation (n=13) | P values | No-VKA after cessation (n=13) | P values
|----------------|--------------------------|-------------------|------------------------------|----------|-------------------------------|-------------------------------|----------|-------------------------------|----------|
| IS events, n (eppy) | 8 (0.036) | 8 (0.039) | 0.467 | 0.467 | 1 (0.045) | 0.999 |
| TIA events, n (eppy) | 11 (0.050) | 7 (0.039) | 1 (0.051) | 0.739 | 0.325 | 2 (0.091) | 1 (0.051) | 0.700 |
| HS events, n (eppy) | 4 (0.018) | 2 (0.011) | 2 (0.10) | 0.006 | 0.814 | 0 | 2 (0.10) | 0.2184 |
| GIB events, n (eppy) | 143 (0.65) | 73 (0.40) | 69 (3.58) | <0.001 | 0.111 | 2 (0.091) | 69 (3.58) | <0.001 |
| PT events, n (eppy) | 6 (0.027) | 6 (0.022) | 0 | 0.540 | 0.497 | 0 | 0 | – |
| Mean INR at event | 1.98±0.65 | 2.1±0.7 | 2.2±0.6 | 0.964 | 0.001 | 1.1±0.2 | 2.2±0.6 | 0.001 |

**Source of GIB** All patients suffering GIB underwent either upper and lower endoscopy or capsule endoscopy or CT angiography. According to the results of the tests, the source of GIB was no active bleeding site detected in 31%; definitive arteriovenous malformation (AVM) in 37%; suspected AVM in 14%; ulcer in 10%; gastric angioectasia in 4%; and 4% diverticulosis.

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**Figure 1.** Cumulative freedom from adverse events in the no-VKA group after anticoagulation cessation. (A) Ischemic stroke, (B) transitory ischemic attack, (C) pump thrombosis, (D) gastrointestinal bleeding, and (E) hemorrhagic stroke. VKA, vitamin K antagonist.
Anticoagulation Cessation in HeartMate II Patients

Rates of HS and GIB in the no-VKA group (0.10 and 3.58, respectively) before AT cessation were significantly higher than in the VKA group (P=0.006 and P<0.001, respectively) (Table 2). The median time until the first bleeding event after discharge that led to rehospitalization was 8.5 [IQR: 5, 19].

the bleeding rate was significantly lower after AT cessation than before cessation (0.09 eppy vs. 3.58 eppy, P<0.001). The mean INR after AT cessation during follow-up was 1.0±0.2. There was no significant difference in the rates of IS, PT and TIA within the no-VKA group before and after cessation (Table 2).

Figure 2. Cumulative freedom from adverse events in the VKA group after HMII implantation. (A) Ischemic stroke, (B) transitory ischemic attack, (C) pump thrombosis, (D) gastrointestinal bleeding, and (E) hemorrhagic stroke. HMII, HeartMate II; VKA, vitamin K antagonist.

Figure 3. Ratio of von Willebrand factor (vWF) collagen-binding activity (CBA) to vWF antigen (Ag) and thrombin-antithrombin (TAT) III complex. The dotted line indicates the normal cutoff values. (A) Comparison between the vitamin K antagonist (VKA) and no-VKA groups before anticoagulation cessation. (B) Comparison between VKA and no-VKA groups after anticoagulation cessation. (C) Comparison within the no-VKA group before and after anticoagulation cessation. (D) Comparison of TAT III complex between the no-VKA group (after cessation) and 50 patients from the VKA group. (E) Comparison of TAT III complex between 6 patients matched from the no-VKA group (before cessation) and VKA group.
before AT cessation to 12 values (within 6–9 months) after AT cessation (Figure 4). The mean fibrinogen levels during the 3–9 months after AT cessation did not differ significantly between the no-VKA and VKA groups (3.3 ± 0.2 vs. 3.4 ± 0.3 g/L, P=0.357, respectively). Additionally, there were no significant differences between the VKA and no-VKA groups in the 12-month values of LDH, D-dimer, and fHb before and after AT cessation (Figure 5).

vWF Factor
Loss of high-molecular-weight multimers (HMWM) of vWF was detected 3 months after implantation with western blot analysis in all HMII patients, indicating the occurrence of acquired vWF syndrome (AvWS) after HMII implantation (Figures S1, S2 demonstrate the loss of HMWM in western blotting). Patients in the no-VKA group had significantly lower vWF:CBA to vWF:Ag ratio (vWF ratio) before AT cessation when compared with the rest of the HMII patients (cutoff 0.7) (0.60 ± 0.12 vs. 0.73 ± 0.14, P=0.006). The vWF ratio was also significantly lower in the no-VKA group after AT cessation than in the VKA group (0.57 ± 0.11 vs. 0.73 ± 0.14, P=0.006, respectively). No significant change was detected on comparing the vWF ratio before and after AT cessation within the no-VKA group (Figure 3).

Platelet Function
LTA with adenosine diphosphate (ADP) 10 µmol/L, before AT cessation to 12 values (within 6–9 months) after AT cessation (Figure 4). The mean fibrinogen levels during the 3–9 months after AT cessation did not differ significantly between the no-VKA and VKA groups (3.3 ± 0.2 vs. 3.4 ± 0.3 g/L, P=0.357, respectively). Additionally, there were no significant differences between the VKA and no-VKA groups in the 12-month values of LDH, D-dimer, and fHb before and after AT cessation (Figure 5).

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Anticoagulation Cessation in HeartMate II Patients

Echocardiographic Findings
Transthoracic echocardiography (TTE) was performed in all LVAD patients at hospital discharge and at each outpatient visit. The following parameters were routinely measured: left ventricular (LV) systolic diameter, LV diastolic diameter, LV sphericity index (SI) (SI was calculated as the ratio of the major (in 4-chamber view) to the minor axis (in parasternal view) of LV dimensions), and tricuspid annular plane systolic excursion (TAPSE) and aortic valve (AV) opening status was also evaluated.

Table S1 shows the last available TTE parameters measured in the no-VKA group before AT cessation and the TTE parameters 3 months after AT cessation. No significant changes could be detected in LV diameter (LV inner adrenalin 50 µmol/L, and arachidonic acid as agonists and PFA-100 tests demonstrated impaired platelet function in all HMII patients (Figure 5). The measured values did not show any significant changes within the no-VKA group on comparing values from at least one test before and one after AT cessation (Figure 5). On comparing the LTA and PFA-100 tests between the no-VKA group before cessation and the VKA group, only activation involving collagen/ADP differed significantly between the groups (VKA vs. no-VKA: 268±47.5 vs. 220.5±59.8, P=0.040) (Figure 5). This can be explained by the lower vWF:CBA ratio in the no-VKA group.

Other Hemostatic Tests
Of the patients in the no-VKA group, 5 who were on HMII support without AT until April 2017 underwent further analysis with TEM. We could not detect any specific characteristics or significant changes on comparing the findings to the cutoff values of a healthy population. A detailed overview of the measured parameters and results is presented in Supplementary File 1.

Echocardiographic Findings
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20.8±21.1 months. Over the study period, 12 (9.3%) patients underwent heart transplantation, and 64 (50%) patients died. Of the 128 patients, 12 (9.3%) died before discharge after LVAD implantation.

In the no-VKA group, 8 patients had a mean survival of 14.1±12.6 months on HMII support without AT. Overall survival without AT in the no-VKA group was 19.8±15 months (5 patients still on HMII support without AT).

The causes of death in the 8 patients were not related to thromboembolic events: 3 patients died of multi-organ failure as a result of pneumonic septic shock; 2 patients had septic shock caused by recurrent driveline infection; 3 patients had right heart failure with decompensation.

Discussion
Despite improved survival with CF-LVADs, recurrent bleeding events, especially GIB, may justify AT cessation. Some patients can tolerate AT cessation without increased risk of thromboembolic events, as presented in our study of a reasonable number of patients from a single center who had AT ceased after HMII implantation following recurrent GIB. Our data indicated that patients with a HMII had increased thrombin generation as indicated by high TAT values, which has been confirmed by Spanier et al.8 HMII patients in our study who did not receive VKA...
because of recurrent bleeding events but survived without increased thromboembolic risk seemed to have a balance between bleeding risk, because of a low vWF:CBA/vWF:Ag ratio, and the thromboembolic risk, represented by high TAT values indicating activated procoagulant pathways. These findings are similar to those of Spanier et al., who described a phenomenon of “compensated coagulopathy” underlying the apparent auto-anticoagulation in recipients of textured-surface LVADs. They also found low thromboembolic rates in LVAD patients with simultaneous increased thrombin generation and fibrinolysis. All of the present HMII patients in whom AT was measured had higher values than the laboratory cutoff value (<4 μg/L), but the patients in the no-VKA group had significantly higher TAT values than the rest of this HMII population. Our comparison might not be appropriate because the 115 HMII patients were receiving a VKA, which in turn inhibits thrombin among other coagulation factors. This will lead to lower TAT values in the HMII patients who received VKA. TAT values were available in 6 patients in the no-VKA group before their VKA was ceased. However, TAT values in the no-VKA group before and after AT cessation were significantly higher than the values in the other HMII patients. These findings demonstrate that the balance between the procoagulant pathway and the bleeding risk from AvWS could explain, at least in part, the low thromboembolic rate in our no-VKA group.

Many factors contribute to the high incidence of bleeding after CF-LVAD implantation. AvWS is among the most discussed factor, and it results from mechanical destruction and proteolysis of the HMWM of vWF, induced by shear stress.4,10–12 In accordance with Heilmann et al.,6 our entire HMII population showed loss of the HMWM of vWF, indicating AvWS; however, not all patients showed bleeding. The 13 patients with the most number of recurrent bleeding events, which necessitated AT cessation, had significantly lower vWF:CBA/vWF:Ag ratio than the rest of our HMII patients. These findings are consistent with those of Klovstevet et al.,13 who found that all HMII patients with a low vWF:CBA/vWF:Ag ratio (<0.7) showed bleeding and that patients with a very low vWF ratio value (<0.6) showed recurrent major bleeding events. In addition to AvWS, platelet dysfunction was present in all our CF-LVAD patients because of the high shear forces induced by the pump; this might contribute to the high bleeding incidence after CF-LVAD implantation.14 In concordance with results from Steinlechner et al.14 and Baghali et al.,15 our LTA and PFA-100 tests demonstrated impaired platelet function in all HMII patients; however, we identified no significant changes during the time course of AT cessation or on comparing the values before and after AT cessation.

We could not characterize the hemostatic profile of HMII patients in whom AT can be safely discontinued. These findings are consistent with those of Pereira et al.,6 who performed diverse hemostatic tests on HMII patients who survived without VKA and thromboembolic events. However, we demonstrated that HMII patients who had a low vWF:CBA/vWF:Ag ratio and experienced recurrent bleeding events benefited from ASA and/or only VKA cessation without an increased risk of thromboembolic events and had a very low bleeding rate. These findings are consistent with those of Kamdar et al.,1 who discontinued VKA in 14 of 213 HMII patients and found no additional adverse thromboembolic, hemolytic, or neurologic events after warfarin cessation in these patients.

Despite controversies regarding anticoagulation regimens in HMII patients,16,17 our departmental protocol for HMII patients has not changed from 2010 until now, with an INR target range of 1.8–2.2 and daily ASA 100 mg. Despite the low INR target, we demonstrated no increase in the rate of thromboembolic events. The incidence of both PT and IS was lower than the incidences reported by Starling et al.,18 Stulak et al.19 and McIlvennan et al.,1 and comparable to the incidence reported in the PREVEntion study.1

Data on the safety, risks, and hemostatic profile of HMII patients in whom AT can be safely discontinued are scarce. The TRACE study20,21 evaluated the benefits and risks of reduced APT and/or AT in HMII patients, but did not include any hemostatic analysis. Netuka et al.22 found in the European arm of the TRACE study that managing HMII patient with a reduced INR target of 2.3 without antiplatelet therapy was safe and reduced the risk of bleeding without increasing the thromboembolic risk. At the other hand the US arm of the TRACE study23 included HMII patients in whom VKA (28%) or VKA and ASA (34%) were completely discontinued and they found that despite AT cessation the bleeding risk might persist and there was a higher risk of DT. The lower thromboembolic rate in our HMII population could not be explained by our anticoagulation regimen or by the hemostatic analysis. Important factors besides hemostatic changes in LVAD patients that can contribute to PT are the surgical technique and the angle of the IC, as described by Taghavi et al.24 Data on the IC angle and outflow cannula were not available in our study.

There is still a lack of experience on balancing the risks and benefits associated with reduced AT in patients with CF-LVADs. Hence, the hemostatic profile and characteristics of patients in whom AT can be safely reduced or even discontinued are still unknown.

**Study Limitations**

Our study was limited by the usual shortcomings of a small cohort, single-center study. Owing to the absence of randomization and the partly retrospective nature of our study, our data were subjected to potential bias with regard to patient selection and data acquisition; therefore, caution should be taken when interpreting our results. Bleeding complications in LVAD patients are multifactorial, and as a result we cannot exclude the possibility that unmeasured confounders influenced our results. An important limitation to the study was the self-defined criteria for cessation of AT, which was determined by a consensus group of experts from cardiac surgery, cardiology and gastroenterology in our institution. However, currently no internationally accepted consensus or guidelines exist, and, given the rare number of cases of patients with LVAD implantation and cessation of AT, may justify such a retrospective analysis, which has relevance for many clinicians with comparable problems and limited experience in this field.

Another limitation was the relatively small number and the heterogeneity of the patients, which may limit generalization of the results.

**Conclusions**

We experienced good results with AT cessation in specific HMII patients. The simultaneous onset of AvWS and high TAT values could explain at least in part the low thromboembolic rate in these HMII patients without VKA. Despite
a reduced INR target (1.8–2.2), no increase in the thromboembolic rate was noted in our HMII patients. Further studies in a larger number of patients are needed to identify the hemostatic profile of patients who would benefit from anticoagulation cessation and those who would not.

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**Disclosures**

None declared.

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**Supplementary Files**

**Supplementary File 1**

**Supplementary Methods**

- Figure S1. Thrombin generation.
- Figure S2. Thromboelastometry.
- Figure S3. Exemplary results from western blot analysis of HMII patients, demonstrating the loss of high-molecular-weight multimers of von Willebrand factor.

**Table S1.** Comparison of last available echocardiographic parameters in the no-VKA group pre-AT cessation with the 3 months post-AT cessation parameters

**Table S2.** Comparison of device parameters 4 months pre- and 4 months post-AT cessation

Please find supplementary file(s): http://dx.doi.org/10.1253/circj.CJ-17-0897