Purpose: TRACE (sTudy of Reduced Anti-Coagulation/Anti-platelet Therapy in Patients with the HeartMate II LVAS) is a multi-center study in standard anti-thrombotic therapies of warfarin plus aspirin. To assess the long term safety of such approaches, TRACE (sTudy of Reduced Anti-Coagulation/Anti-platelet Therapy in Patients with the HeartMate II LVAS) was initiated in the US and Europe.

Methods: The TRACE-US enrolled HMII outpatients who at enrollment or as of Jan 1, 2011 were on a reduced anti-thrombotic (RT) regimen: warfarin only (RT-w), aspirin only (RT-a), or no anticoagulant or anti-platelet therapy (RT-n). The indication for RT, subsequent anti-thrombotic changes, as well as any bleeding, stroke, or pump thrombosis after RT were documented. Patients were prospectively followed for up to 24 months post-enrollment. 100 outpatients on RT were enrolled in the TRACE-US Study from 9 sites. In this report we present adverse events in patients on RT for 2 years.

Results: At 2 years post initiation of RT therapy, freedom from bleeding, hemorrhagic stroke, ischemic stroke and pump thrombosis were respectively 86±5%, 96 ± 3%, 93 ± 3%, 93 ± 3%. Freedom from ischemic stroke, hemorrhagic stroke, and pump thrombosis at two years were 93±3%, 93±3%, 93±3%, respectively.

Conclusion: This preliminary analysis of the TRACE study suggests that patients may be safely managed on a single vitamin K antagonist (AVK) with a target INR greater than 2.0, without anti-platelet therapy. Further prospective studies are needed to confirm if these results are applicable to a larger patient population.

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Chronic Management With Reduced Anti-Thrombotic Therapy in HeartMate II Patients With Persistent Bleeding - Results From the US-TRACE Study

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Purpose: Persistent bleeding in LVAD patients often requires a reduction in standard anti-thrombotic therapies of warfarin plus aspirin. To assess the long term safety of such approaches, TRACE (Study of Reduced Anti-Coagulation/Anti-platelet Therapy in Patients with the HeartMate II LVAS) was initiated in the US and Europe.

Methods: The TRACE-US enrolled HMII outpatients who at enrollment or as of Jan 1, 2011 were on a reduced anti-thrombotic (RT) regimen: warfarin only (RT-w), aspirin only (RT-a), or no anticoagulant or anti-platelet therapy (RT-n). The indication for RT, subsequent anti-thrombotic changes, as well as any bleeding, stroke, or pump thrombosis after RT were documented. Patients were prospectively followed for up to 24 months post-enrollment. 100 outpatients on RT were enrolled in the TRACE-US Study from 9 sites. In this report we present adverse events in patients on RT for 2 years.

Results: As of September 2014, 75 patients had been on RT for at least 24 months (n=58) or reached an outcome (n=17). The median age was 65 years (36-80), 87% were male, 64% had ischemic etiology and 71% were DT. The primary reason for RT (79% of pts) was to control bleeding (GI or epistaxis). RT-w, RTa and RT-n, were used in 33%, 29%, and 37% of the patients. At enrollment the median INR of the RT-w group was 2.1 (IQR 1.7-2.5). The median age was 65 years (24-72) years, 93% were male, 54% had ischemic etiology and 71% were DT. The primary reason for RT (79% of pts) was to control bleeding (GI or epistaxis). RT-w, RTa and RT-n, were used in 33%, 29%, and 37% of the patients. At enrollment the median INR of the RT-w group was 2.1 (IQR 1.7-2.5). The median INR at follow-up was 2.31 [range: 0.73-5.2] which was higher than the median INRs of patients in the HMII clinical trial (median of 2.0). Only 4% of the INR measurements were below 1.5. Median LDH was 365 U/L [range: 66-3020].

At 2 years post initiation of RT therapy, freedom from bleeding, hemorrhagic stroke, ischemic stroke and pump thrombosis were respectively 86±5%, 96 ± 3%, 93 ± 3%, 93 ± 3%.

Conclusion: This preliminary analysis of the TRACE study suggests that patients may be safely managed on a single vitamin K antagonist (AVK) with a target INR greater than 2.0, without anti-platelet therapy. Further prospective studies are needed to confirm if these results are applicable to a larger patient population.
LVAD-Associated von Willebrand Factor Degradation Alters Angiogenesis: A Mechanistic Link Between LVAD Support, Gastrointestinal Angiodyplasia, and Bleeding


Purpose: Gastrointestinal (GI) bleeding occurs frequently in patients with a left ventricular assist device (LVAD). Evidence suggests a major role for von Willebrand Factor (vWF). However, a mechanistic link between vWF degradation and GI angiodyplasia has not been explored. We investigated whether LVAD-associated vWF degradation fragments generated by shear stress and ADAMTS-13 (the vWF protease) affected angiogenesis in vitro.

Methods: Purified human vWF protein and/or recombinant human ADAMTS-13 protein was exposed to LVAD-like shear stress (4 hours, ~175 dynes/cm²). Human umbilical vein endothelial cells (15,000 cells, n=8/condition) were cultured with: 1. vWF, 2. Small vWF multimers generated from shear stress, 3. vWF + ADAMTS-13, 4. vWF fragments from ADAMTS-13 cleavage during shear stress. Small vWF multimers and vWF fragments were characterized by gel electrophoresis and immunoblotting. Endothelial angiogenesis was quantified with a Matrigel assay (vacular tube formation), a scratch assay (migration), 5-ethyl-2'-deoxyuridine uptake (proliferation), and terminal transferase dUTP nick-end labeling (apoptosis).

Results: All indices of angiogenesis were abnormal when endothelial cells were grown with LVAD-associated vWF degradation fragments. Endothelial migration (450±49 vs. 277±53 µm, p = 0.01), vascular tube formation (36.8±4.0 vs. 19.7±3.6 mm, p < 0.001), and proliferation (12±3 vs. 6±1%, p=0.08) decreased with LVAD degradation fragments. Similarly, endothelial proliferation decreased with small vWF multimers (10±2 vs. 1±1%, p=0.002). Endothelial apoptosis increased with small vWF multimers (12±2 vs. 36±2%, p < 0.001) and with vWF fragments (15±2 vs. 23±2%, p = 0.03).

Conclusion: For the first time, these data suggest that LVAD-associated vWF degradation fragments alter angiogenesis. These data support our novel hypothesis for LVAD-associated GI angiodyplasia. Abnormal angiogenesis in bowel mucosa, which proliferates continuously, may promote GI angiodyplasia and predispose LVAD patients to bleeding events.

Association of Warfarin Genotype With Thrombosis and Bleeding Events in Continuous-Flow Left Ventricular Assist Device (CF-LVAD) Patients

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Purpose: Previous studies have suggested an association between rare variants in Warfarin metabolism genes with anticoagulation and an increased risk of bleeding events. The effect of rare variants on frequency of bleeding and thrombosis events in CF-LVAD patients remains unknown.

Methods: Patients who underwent CF-LVAD implantation at our center and had Warfarin genotype data were included in this analysis. DNA was extracted from peripheral blood. Genotypes tested were rs1799853 (c430C>T), rs10946832 (c455G>A), rs6993779 (c1075A>G), rs1057910 (c1075A>G), and rs9923231 (-1639G>C) in CYP2C9 genes and rs9923231 (-1639G>C) in VKORC1 gene. Patients were categorized based on presence or absence of any rare variants in CYP2C9 and VKORC1 genes. Groups were then comparatively analyzed for LVAD-related complications.

Results: 77 patients with Warfarin genotype data were identified. 19 patients (24.6%) carried at least one rare variant in CYP2C9 gene whereas 22 patients (28.6%) carried at least one rare variant in VKORC1 gene. INR variability was increased in patients carrying the rare VKORC1 genotype (0.692 vs. 0.557 p = 0.0001) or the rare CYP2C9 genotype (0.709 vs. 0.58, p = 0.0001). Carrying a rare genetic variant in CYP2C9 (OR 0.69, p = 0.568) or VKORC1 (OR 0.62, p = 0.462) genes did not alter the risk of GI Bleeding Events. Rare variants in CYP2C9 gene also did not have an effect on risk of device thrombosis (OR 1.27, p = 0.717). However, patients carrying a rare variant in VKORC1 gene which increases sensitivity to Warfarin had significantly higher risk of device thrombosis compared to patients with wild-type only alleles (27.0% vs. 7.7% at 1 year, respectively, OR 4.76, p = 0.030, Figure). Post-LVAD survival was not different between different genotype groups.

Conclusion: Our findings suggest an association between rare VKORC1 variants that increase sensitivity to Warfarin, increased INR variability, and risk of device thrombosis. Genotype specific warfarin dosing algorithms to reduce INR variability should be explored.

Thrombophilias Prospective Detection Tailored Anticoagulation Protocol Without Antiplatelet Therapy in Patients With Axial-Flow Ventricular Assist Device

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Purpose: Current recommendations for antithrombotic therapy for patients with the HeartMate II (HMII) left ventricular assist device (LVAD) include the use of both an anticoagulant (Warfarin) and an antiplatelet agent. In order to reduce the risk of bleeding, device induced abnormalities such as acquired von Willebrand syndrome have been reflected in recent trials using protocols without anti-platelet therapy in HMII patients. On the other hand, an impact of patient related factors as thrombophilias mutations to the bleeding and thrombotic complications still remain chronically overlooked.

Methods: 119 HMII consecutive patients have been prospectively screened for major thrombophilias mutations (Factor II Prothrombin, Factor V Leiden and homozygote MTHFR). Subsequently, consistently anti-platelet free protocol with individualized Warfarin anticoagulation with target INR of 2.5-3.0 in thrombophilia positive and INR of 1.8-2.2 in negative patients have been conducted.

Results: Mean age was 51±12 years, 83% were male and total follow-up on LVAD reached 111 pt/years. Mean HMII support duration was 342±301 days. At 1 year post implant in major thrombophilias positive cohort, freedom from bleeding, hemorrhagic stroke, ischemic stroke and pump thrombosis were 97±3%, 100%, 84±4% and 94±4% respectively. Whereas, at 1 year endpoint in thrombophilias negative group, freedom from bleeding, hemorrhagic stroke, ischemic stroke and pump thrombosis were 91± 3%, 94±3%, 93±4% and 94±3% respectively. Statistical analysis did not identify any significant differences between corresponding groups.

Conclusion: To the best of our knowledge this is a first reported consecutive cohort of this individualized approach. Data suggest that managing HMII patients without aspirin may help to reduce the incidence of major bleeding without increasing the risk of thromboembolic events including ischemic stroke and device thrombosis as compared to recent clinical series. Importantly, individualized thrombophilias based antithrombotic protocol may lead to a safe incremental decrease of target INR level to 1.8-2.2 in negative population while keeping a risk of bleeding events in thrombophilic group with more aggressive anticoagulation regimen in impeccably low rates. Further, prospective randomized studies are needed.