Multicenter Evaluation of Octreotide as Secondary Prophylaxis in Patients With Left Ventricular Assist Devices and Gastrointestinal Bleeding

BACKGROUND: Gastrointestinal (GI) bleeding is one of the most common complications after continuous-flow left ventricular assist device implantation. More than one third of patients with incident bleed go on to develop recurrent GI bleeding. Octreotide, a somatostatin analog, is proposed to reduce the risk of recurrent GI bleeding in this population.

METHODS AND RESULTS: This multicenter, retrospective analysis evaluated 51 continuous-flow left ventricular assist device patients who received secondary prophylaxis with octreotide after their index GI bleed from 2009 to 2015. All patients had a hospitalization for GI bleed and received octreotide after discharge. Patient demographics, medical and medication history, and clinical characteristics of patients who rebled after receiving octreotide were compared with non–rebleeders. These data were also compared with matched historical control patients previously enrolled in the HMII (HeartMate II) clinical trials, none of whom received octreotide, to provide a context for the bleeding rates. Twelve patients (24%) who received secondary octreotide prophylaxis developed another GI bleed, whereas 39 (76%) did not. There were similar intergroup demographics; however, significantly more bleeders had a previous GI bleeding history before left ventricular assist device placement (33% versus 5%; P=0.02) and greater frequency of angiodysplasia confirmed during endoscopy (58% versus 23%; P=0.03). Fewer patients in this study experienced a recurrent GI bleed compared with a matched historical control group that did not receive octreotide (24% versus 43%; P=0.04).

CONCLUSIONS: Patients with continuous-flow left ventricular assist device receiving secondary prophylaxis with octreotide had a significantly lower GI bleed recurrence compared with historical controls not treated with octreotide. Additional prospective studies are needed to confirm these data.

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WHAT IS NEW?

- In patients who experienced gastrointestinal bleeding with a continuous-flow left ventricular assist device, we observed a significant reduction of rebleeding after treatment with octreotide when compared with a matched historical control group.
- These are the first comparative data suggesting an effective therapy for the secondary prevention of left ventricular assist device–related gastrointestinal bleeding.

WHAT ARE THE CLINICAL IMPLICATIONS?

- Somatostatin analogs, which have been used previously to effectively treat angiodysplasia and von Willebrand disease–related bleeding, may have a role in the treatment for left ventricular assist device–related gastrointestinal bleeding.
- Prospective studies are necessary to definitively define risk and benefit of octreotide treatment in this population.

Gastrointestinal (GI) bleeding is a frequent complication after continuous-flow left ventricular assist device (CF-LVAD) implantation.[1,2] In some reports, over a third of patients with CF-LVAD implantation will experience a significant GI bleeding episode at some time point after implantation.[3] The causes and sources of bleeding are multifactorial.[4–6] The only consistently reported demographic risk factor for LVAD-related GI bleeding seems to be age >65 years[5]; however, other clinical correlates include a history of previous GI bleeding, preoperative use of antiplatelet or anticoagulant medications, poor kidney function, and device strategy for LVAD implantation (destination therapy [DT] versus bridge-to-transplantation. The cause of bleeding is found in ≈75% of the patients. Of those who rebleed, ≈75% have similar symptoms, and the cause of rebleeding is the same as the index bleeding episode in 50% of the patients. The anatomic location of bleeding is predominantly upper GI in origin, and most of them are from angiodysplastic lesions.[7]

Acquired von Willebrand Syndrome has been shown to develop in patients with CF-LVADs presumably because of high shear forces resulting in destruction of high–molecular weight von Willebrand factor multimers by the LVAD impeller.[8,9] It has been shown that these patients have a higher than normal occurrence of GI angiodysplasia. Whether these arteriovenous malformations are preexisting or result from de novo angiogenesis from the gut mucosa is unknown. It is thought that the loss of pulsatility and potential hypoxia result in upregulation of angiogenic mediators, such as vascular endothelial growth factor and angiopoietin-2, may contribute to the development of angiodysplasia.[10–12] Consequently, appropriate primary and secondary bleeding prophylaxis is essential in improving long-term outcomes after LVAD implantation.

The current treatment for LVAD-associated GI bleeding is primarily focused on identifying the location of bleeding with subsequent endoscopic intervention, along with adjustments to a lower intensity of anticoagulation and antiplatelet therapy. Beyond that, the policies to manage these patients continue to be institution specific. There is a dearth of evidence-based data on how to prevent the risk of recurrent GI bleeds post-LVAD placement. These patients may also receive supportive treatment with blood product transfusion, cryoprecipitate, and desmopressin; however, these approaches do not prevent recurrent hospitalizations and are associated with high costs and morbidity. Importantly, patients receiving multiple transfusions can develop antibodies that make subsequent cardiac transplantation more difficult.

Octreotide acetate, a somatostatin analog, has been thoroughly studied in various conditions and has a known safety profile. It is currently used to control active GI hemorrhage and can also be used for secondary bleeding prophylaxis for vascular ectasias in non-LVAD patients. There are meta-analysis–level data showing decreased need for transfusion in patients with arteriovenous malformations treated with octreotide.[13] However, the data supporting the use of octreotide for bleeding prophylaxis in LVAD patients are sparse and limited to case reports and single-center experiences.[13–16] A recent prospective study was conducted with octreotide in stable LVAD patients and was noted to be well tolerated with no drug-related side effects or GI bleeding events observed.[17]

To further elucidate the potential role of octreotide in preventing recurrent LVAD-associated GI bleeding, we conducted a retrospective, multicenter cohort study to determine the incidence of rebleeding in patients receiving secondary octreotide prophylaxis. Herein, we report the demographics and clinical characteristics associated with rebleeding versus non–rebleeding and further compare these data to a historical control group comprised patients who experienced GI bleeding in the original clinical trial of the HMII (HeartMate II) LVAD.

METHODS

Patients and Selection Criteria

This retrospective multicenter study was conducted at Virginia Commonwealth University, The Ohio State University, Columbia University, The University of Chicago, and Allegheny General Hospital. Each site received institutional review board approval before study initiation. The study inclusion criteria included age >18 years, the placement of an HMII LVAD, hospitalization for GI bleeding and subsequent receipt of standard-of-care treatment, and receipt of octreotide acetate

given as either monthly depot injection or twice daily subcutaneous injection on hospital discharge. Patients who received octreotide for primary GI bleeding prophylaxis or for another medical indication were excluded.

Data Sources and Collection

Fifty-one patients meeting inclusion criteria at the 5 centers from the years 2009 to 2015 were identified using *International Classification of Diseases*, Ninth Revision, billing codes and queries of local health system databases. Chart reviews were completed to confirm LVAD placement, GI bleed, and receipt of octreotide treatment for secondary bleeding prophylaxis on hospital discharge. The patients who met these criteria had their anonymized data entered into a secure, Health Insurance Portability and Accountability Act compliant research electronic data capture (REDCap) database. To ensure data entry validity, each center recollected data on 3 patients randomly selected by the coordinating site, and data congruency was analyzed to ensure that the collection strategies were robust. The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

In addition to demographics, the clinical characteristics for each patient were collected, which included past and concurrent medical history, medications, LVAD system settings, laboratory data (kidney function, hemoglobin, international normalized ratio [INR]), and interventions performed in response to GI bleed.

These interventions included blood products received (eg, packed red blood cells, fresh frozen plasma, cryoprecipitate) and platelet transfusions. In addition, endoscopy procedures and medication interventions were documented.

Historical Control Group

As a reference for comparing GI rebleeding rates, a historical control group of HMII LVAD patients who had experienced a GI bleed in the original combined HMII bridge-to-transplantation and DT clinical trials (NCT00121472 and NCT00121485, respectively) was identified as a subgroup of the 956 patient cohort previously published by Boyle et al.[18] The clinical bridge-to-transplantation and DT studies enrolled 1302 patients who received an HMII between March 2005 and January 2010. After excluding patients who were implanted for compassionate use or rescue exchange for HeartMate XVE, a total of 956 patients were successfully discharged from the hospital. In this group, there were 240 patients who suffered a GI bleed. Because of the differences in baseline characteristics, each patient in the octreotide study group was matched to a patient experiencing GI bleeding in the HMII clinical trial with the same indication and the closest LVAD support time at the time of the reference GI bleed. Any ties were then broken by matching to the same sex and if needed the closest age at time of the reference GI bleed.

Statistical Analysis

Continuous variables were presented as mean and SD or median and interquartile range. Intergroup differences between rebleeders and non–rebleeders in the current study were assessed using the Student *t* test for continuous data. For nominal data, a χ^2 test was performed unless the frequencies in the contingency table were ≤5, in which case the Fisher Exact test was used. Freedom from rebleeding within 6 months after the index event was estimated by the Kaplan–Meier method. The reference time zero in the treatment group was the occurrence of the GI bleeding event first treated with octreotide regardless of prior GI bleeding events on LVAD support, and for the historical control, it was the occurrence of the first GI bleeding event after LVAD implantation. Comparison of freedom from rebleeding was performed with the log-rank test. Statistical significance was defined as $P<0.05$. All data summaries and analyses were conducted using SPSS statistical software.

RESULTS

Table 1 shows the patient demographics and clinical features of the 51 subjects who received octreotide. Approximately half of the patients were implanted with a CF-LVAD as DT, and 41% had experienced a prior GI bleed on the device. Twelve of the 51 subjects (24%) in this study experienced a rebleed within 6 months of beginning octreotide treatment.

When comparing subject demographics between those who rebled to non–rebleeders, there were no statistically significant differences. There were also few differences in the clinical characteristics between these subgroups. Fewer of the rebleed subjects had atrial fibrillation compared with the nonbleeders (8% versus 44%, respectively; P=0.04); however, the rebleeding subjects had a greater prevalence of a history of GI bleeding before LVAD placement (33% versus 5%, respectively; P=0.02).

Table 2 shows the patients' clinical characteristics on their initial admission for GI bleed. There were no statistically significant intergroup differences in LVAD parameters (speed, power, pulsatility), nor were there differences in kidney function or hemoglobin values. Most patients (41%) were taking 81 mg aspirin daily. Similarly, 84% of patients were on warfarin therapy with the target INR ≈2.3 in both groups. There was a trend toward significance in the mean INR at the time of bleeding, with the rebleed group having a lower INR compared with the non–rebleeders (INR, 2.0±0.6 versus 3.0±1.9; P=0.08). At the time of GI bleed, very few patients were on dipyridamole, low–molecular weight heparin, or a novel oral anticoagulant, whereas 67% in both groups were receiving proton pump inhibitor therapy.

The clinical interventions performed in the octreotide-treated group are provided in Table 3. The majority of patients (72%) received the monthly octreotide depot formulation after experiencing an LVAD-related GI bleed. There were no statistically significant differences in the amount of packed red blood cells used nor the percentage of patients who received fresh frozen plasma. During the reference bleeding hospitalization, there was a trend toward more patients in the rebleeding group receiving both cryoprecipitate and platelet transfusions compared with non–rebleeders (17% versus 0%, respectively; P=0.05). Nearly all of the population (92%) had

Table 1. Patient Demographics at the Time of Index Bleed for the Octreotide-Treated Group

Variables	Rebleed at 6 mo (n=12)	No Rebleed at 6 mo (n=39)	*P* Value
Age, y	65±11	64±10	0.9
Sex (male)	58%	72%	0.5
Race			0.2
White	50%	67%	
Black	42%	31%	
Other	8%	3%	
Median time from LVAD implant (IQR)	262 (45–1275)	166 (69–551)	0.4
INTERMACS profile			0.2
Profile 1	9%	24%	
Profile 2	55%	40%	
Profile 3	9%	24%	
Profile 4 or 5	27%	13%	
Destination therapy	50%	51%	1.0
Medical history			
Gastrointestinal bleed before LVAD	33%	5%	0.02
Diabetes mellitus	58%	48%	0.7
Atrial fibrillation	8%	44%	0.04
Hypertension	75%	62%	0.5
CKD stage III or greater	33%	44%	0.7
Peripheral vascular disease	8%	10%	1.0
COPD	25%	18%	0.7
Ischemic heart disease	75%	62%	0.5
Prior LVAD-related complications			
Superficial driveline infection	0%	16%	0.3
Pump infection	0%	5%	1.0
Bacteremia	33%	28%	0.7
Pump thrombosis	17%	13%	0.7
Ischemic CVA	0%	13%	0.3
Hemorrhagic CVA	0%	3%	1.0
Peripheral arterial embolic event	8%	5%	0.6

CKD indicates chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; IQR, interquartile range; and LVAD, left ventricular assist device.

an endoscopic procedure performed, with significantly more rebleed patients having confirmed angiodysplasia compared with non–rebleeders (58 versus 23%, respectively; *P*=0.03). Most of the patients (57%) had a warfarin dose reduction in response to the bleed.

Comparison to Historical Control Group

The octreotide cohort was compared with appropriately matched patients in the HMII clinical trials. There were 240 patients in the clinical trials who experienced a GI bleed on HMII support, and 40% of them had a rebleeding event. However, the majority of these 240 patients (73%) were implanted as DT compared with 49% of the octreotide-treated group, and the median LVAD support duration at the time of the reference GI bleed was also shorter compared with the octreotide-treated patients (91 versus 197 days). To control for differences in baseline characteristics, each octreotide-treated patient was matched (1:1) to a patient experiencing GI bleeding from the historical cohort with the same indication and a similar support duration on device. Comparison of baseline characteristics between the octreotide-treated group and the matched historical control group is shown in Table 4. Patients in the octreotide-treated group have a lower rate of rebleeding compared with matched patients enrolled in the HMII clinical trials (24% versus 43%; *P*=0.04). Kaplan–Meier curves

Table 2. Characteristics During Admission for Acute Gastrointestinal Bleed for Patients Receiving Octreotide

Variable	Rebleed at 6 mo (n=12)	No Rebleed at 6 mo (n=39)	*P* Value
First episode of bleeding on LVAD	50%	62%	0.5
Mean arterial pressure, mm Hg	75±12	76±14	0.8
Heart rate, beats per minute	80±14	86±19	0.3
Aortic valve completely closed	50%	43%	0.7
LVAD parameters			
Speed, rpm	9231±281	9224±407	1.0
Power, W	6.4±0.6	6.0±0.8	0.1
Pulsatility index	5.2±1.0	4.7±1.0	0.2
Laboratory data			
eGFR, mL min^{-1} 1.73 m^{-2}	62±25	58±24	0.7
Baseline hemoglobin, g/dL	10.0±1.7	9.6±2.0	0.5
Admission hemoglobin, g/dL	6.6±2.1	7.1±1.6	0.3
Medications before bleeding			
Aspirin			0.8
None	25%	36%	
81 mg 3× per wk	8%	8%	
81 mg daily	42%	41%	
>81 mg daily	25%	16%	
Dipyridamole	0%	5%	1.0
Warfarin	75%	87%	0.3
Target INR	2.2±0.4	2.3±0.4	0.5
INR at time of bleed	2.0±0.6	3.0±1.9	0.08
LMWH	8%	8%	1.0
Novel oral anticoagulant	0%	3%	1.0
Proton pump inhibitor	67%	67%	1.0

eGFR indicates estimated glomerular filtration rate; INR, international normalized ratio; LMWH, low molecular weight heparin; and LVAD, left ventricular assist device.

Table 3. Interventions in Patients Receiving Octreotide

Variable	Rebleed at 6 mo (n=12)	No Rebleed at 6 mo (n=39)	*P* Value
Octreotide formulation			0.7
LAR depot	67%	74%	
Subcutaneous daily	33%	26%	
Blood products			
Packed red blood cells (% patients)	83%	77%	1.0
Packed red blood cells (mean±SD units)	4.7±2.6	3.4±2.3	0.1
Fresh frozen plasma (% patients)	33%	18%	0.2
Cryoprecipitate (% patients)	17%	0%	0.05
Platelets (% patients)	17%	0%	0.05
Endoscopy			
Any endoscopic procedure	92%	92%	1.0
No. of endoscopies per patient	1.9±1.3	1.2±0.6	0.09
EGD	75%	58%	0.3
Push enteroscopy	8%	18%	0.7
Deep enteroscopy	17%	5%	0.2
Flexible sigmoidoscopy	8%	3%	0.4
Colonoscopy	58%	28%	0.09
Capsule	25%	10%	0.3
Active bleeding seen	67%	41%	0.2
Source of bleeding (can be multiple)			
Confirmed angiodysplasia	58%	23%	0.03
Vascular bleeding	0%	13%	0.3
Bleeding polyp	25%	13%	0.4
Ulcer/mucosal disruption	17%	18%	1.0
Other	8%	10%	1.0
Source not located	16%	36%	0.3
Additional clinical interventions			
Reduction in aspirin dose	17%	18%	1.0
Reduction in warfarin dose	58%	56%	1.0
Reduction in LVAD speed	17%	8%	0.5

EGD indicates esophagogastroduodenoscopy; LAR, long-acting release; and LVAD, left ventricular assist device.

showing freedom from GI rebleed curves for both groups are shown in Figure. Patients in the octreotide-treated group had a significantly higher freedom from GI rebleed compared with patients in the matched historical control (75±6% versus 52±8%; $P<0.01$).

DISCUSSION

Even with more than a decade of clinical experience with CF-LVADs, GI bleeding remains a prevailing complication after device implantation. In contemporary clinical trials, irrespective of device design, the rates of GI bleeding in patients in the short term or bridge-to-transplantation population are 15% at 6 months of follow-up.[19,20] For patients implanted without the intention of transplantation, GI bleeding rates exceed 30% at 1 year, even in less sick ambulatory patients implanted before becoming inotrope dependent.[21,22] To put this further into context, the event rate of GI bleeding in patients with CF-LVADs at 65 per 100 patient-years is much higher compared with 2.60 to 4.6 per 100 patient-years in patients with mechanical valves (on aspirin and warfarin), and 8% in patients receiving triple antithrombotic therapy (aspirin, clopidogrel, and warfarin). In fact, no studies have investigated the optimal anticoagulation management in the cohort of patients with CF-LVADs and GI bleeding. Efforts to understand this adverse event need to extend beyond single-center analyses and focus on therapeutic options targeting different mechanistic causes of bleeding.

Studies such as ours present an important insight into the multifactorial mechanisms that come together to result in GI bleed in patients with CF-LVADs. This is the first multicenter study to evaluate rebleeding from the GI tract in LVAD patients after treatment with octreotide for secondary prophylaxis. After treatment, 24% of the LVAD patients experienced a GI rebleed, which was <43% from the matched historical control patients from the HMII clinical trial. Compared with the bleeding data from the HMII clinical trials,[18] our data appear similar with respect to demographics and clinical characteristics.

Because of the limited number of events in the octreotide-treated group, we can only qualitatively characterize patients who rebled after octreotide. Patients who rebled after treatment with octreotide had clinical interventions suggestive of more severe bleeding during the index bleed, including trends toward a greater number of blood product transfusions and a higher number of endoscopic procedures and were more likely to have a history of GI bleeding before LVAD implantation. Given that nearly all patients with assist devices who experienced GI bleeding had therapeutic or subtherapeutic INR at the time of their bleeding events, it is clear the antithrombotic therapy alone does not account for the higher rate of bleeding in CF-LVADs. Indeed, those that rebled were more likely to have confirmed angiodysplasia on endoscopy, and these patients underwent more endoscopic procedures to identify sources of bleeding, likely indicators of more diffuse disease in this group.

A few previously published retrospective, single-center studies have examined the reoccurrence of GI bleeding in CF-LVAD patients. In HMII patients with GI bleeding, Jabbar et al[23] reported a rebleed rate of 43% (19/44 patients), whereas Morgan et al[24] observed a rebleed rate of 21% (4/19 patients). Goldstein et al[19] described a 34% rebleed rate (20/59) in CF-LVAD

Table 4. Comparison of Key Variables of Octreotide Study Group With the Matched Historical Control Group

Variable	Octreotide Study Group (n=51)	Matched Historical Control Group (n=51)	*P* Value
Demographics			
Sex, n (%)			0.8
Male	35 (69)	36 (71)	
Female	16 (31)	15 (29)	
Indication, n (%)			1.0
BTT	26 (51)	26 (51)	
DT	25 (49)	25 (49)	
Age at reference bleed, y	65 [60–71]	65 [59–72]	0.8
Ischemic cause, n (%)	33 (65)	33 (65)	1.0
History of stroke, n (%)	6 (12)	9 (18)	0.4
LVAD support and events before reference GI bleed			
LVAD support duration at reference GI bleed, d	197 [66–761]	190 [63–708]	0.9
Bleed before reference GI bleed, n (%)	21 (41)	0 (0)	<0.01
Rebleeding rates			
Rebleed within 6 mo of reference GI bleed, n (%)	12 (24)	22 (43)	0.04

Values are n (%) and median [interquartiles]. BTT indicates bridge-to-transplantation; DT, destination therapy; GI, gastrointestinal; and LVAD, left ventricular assist device.

patients with a history of previous GI bleeding. In this study, the rebleed rate was 40% in the 240 patients enrolled in the HMII clinical trials, which represents the largest studied cohort of patients with a CF-LVAD–related GI bleed.

One inherent limitation of our study is the use of a historical control group. Although the 1:1 matching has resulted in well-balanced patient groups with similar baseline characteristics, it did not control for potential effects of time era associated variables such as changes in clinical practice. However, considering that the rates of GI bleeding have not decreased in more contemporary clinical studies over a variety of CF-LVAD platforms,[19–23] one might argue that any changes in clinical practice between the time eras of the groups have minimal impact on GI bleeding rates. Furthermore, within the 6-year time period of the HMII clinical trials, we found no significant impact of implant era on GI rebleeding (Figures I and II in the Data Supplement). The findings in the present study should be considered to be hypothesis generating and highlight the need for a randomized controlled clinical trial which would more definitively define the risks and benefits of octreotide therapy.

The study has additional limitations related to the retrospective study design that precludes definitive conclusions on the efficacy of octreotide. First, the patients treated with octreotide did not receive a standard formulation, dose or duration of therapy. This is important because octreotide has different formulations including an immediate-release injection given twice daily, and a long-acting release depot injection given monthly. The monthly injection theoretically should increase patient adherence compared with the immediate-release formulation. However, adherence to therapy could not be measured in this study nor could the administered octreotide dose. It is possible that those patients who bled were receiving suboptimal dosing compared with the nonbleeders. Moreover, the medical record in many cases did not capture date of drug discontinuation, or whether patients were unable to reliably obtain the drug because of financial constraints. Second, although the comparison of rebleed rates in the octreotide treatment group to the HMII clinical trials is provocative and further posits the benefits of octreotide, the 2 groups

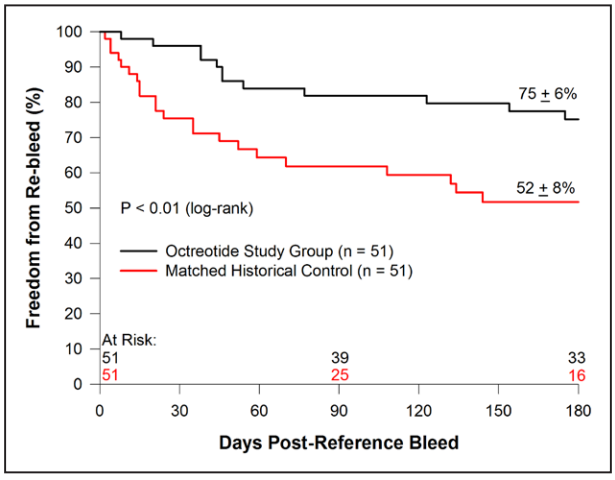

Figure. Kaplan–Meier curves showing freedom from rebleeding for the octreotide-treated group and the matched historical control group.

have notable differences. The clinical trial cohort was studied from the time of the first GI bleed after LVAD, whereas the octreotide group was studied at the time of their octreotide-treated bleed. Therefore, the octreotide group selected for patients who survived longer from their LVAD and patients who already suffered a GI bleed on the device. Furthermore, it was not possible to effectively control for all possible confounding variables because the HMII clinical trial patients had limited data collected at the time of the GI bleed.

In conclusion, we observed that the rate of rebleeding in CF-LVAD patients treated with octreotide after a GI bleed was noticeably less than previous clinical trial data. These results are encouraging and support the need for defining the efficacy and safety of octreotide in a prospective, randomized, clinical trial.

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FOOTNOTES

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Circ Heart Fail is available at http://circheartfailure.ahajournals.org.

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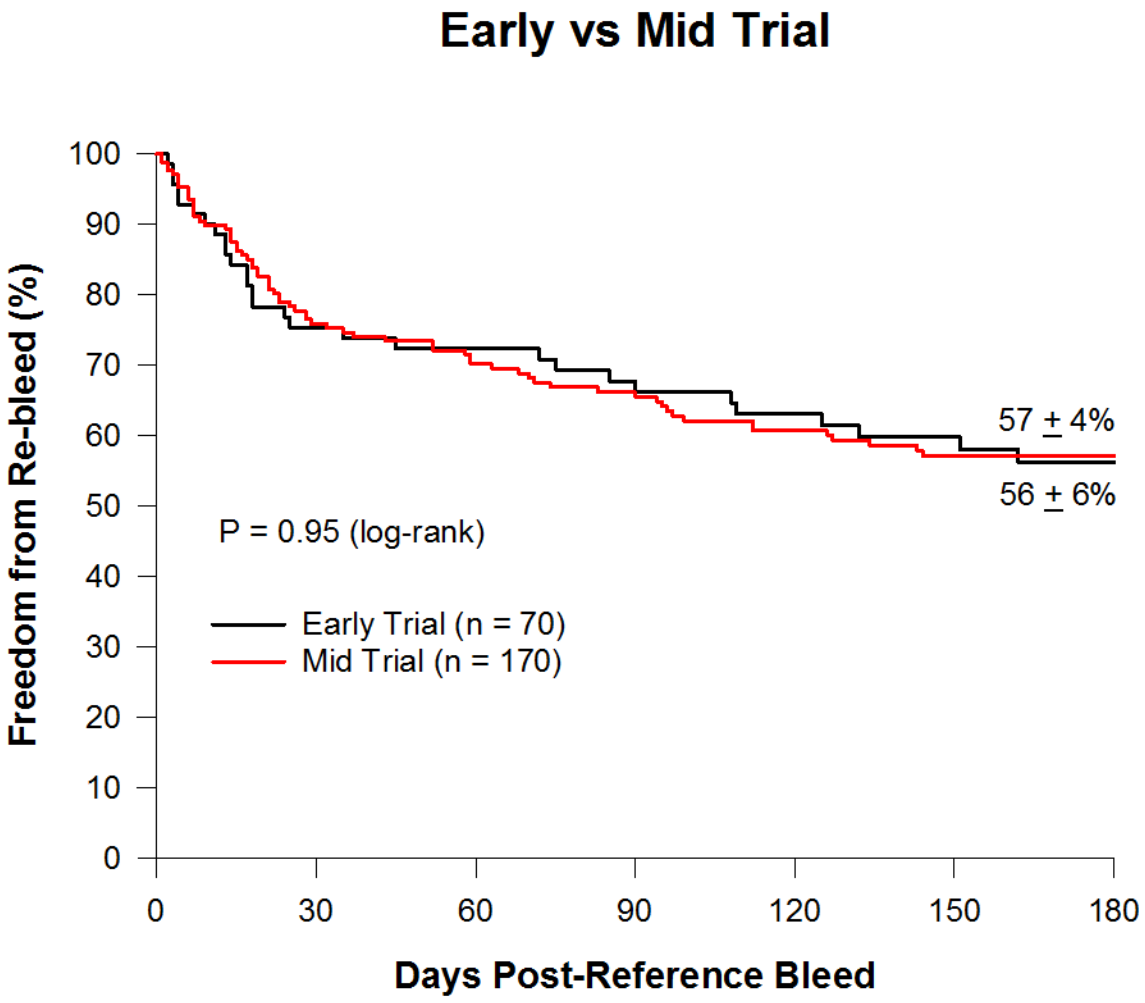
SUPPLEMENTAL MATERIAL

Stratification by Implant Era

Supplemental Figure 1 shows freedom from re-bleeding in patients implanted during the early and mid time periods of the clinical trial. The BTT trial's early and mid-implant periods were March 2005-May 2006 and May 2006-April 2008 respectively. The DT trial's early and mid-implant periods were March 2005-May 2007 and May 2007-March 2009 respectively. Figure 2 shows freedom from re-bleeding in the 1st half of implants vs the 2nd half of implants.

Supplemental Figure 1. Freedom from re-bleeding in patients implanted during the early and mid time periods of the HMII clinical trials.



Supplemental Figure 2. Freedom from re-bleeding in the 1st half of patients vs the 2nd half implanted during the HMII clinical trials.