SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods

INTERMACS Definitions

- Ischemic stroke is defined as a new acute neurologic deficit of any duration associated with acute infarction on imaging corresponding anatomically to the clinical deficit.

- Hemorrhagic stroke (acute symptomatic intracranial hemorrhage) is defined as new acute neurologic deficit attributable to intracranial hemorrhage.

Table S1. Variables considered for inclusion into all endpoint models.

Demographics
Age
Body Mass Index (BMI)
Sex
Race
Medical History
Smoking status
History of non-compliance
History of alcoholism
History of drug abuse
History of arrhythmia
History of atrial fibrillation
History of cancer
History of chronic coagulopathy
History of pulmonary disease
History of pulmonary hypertension
History of Peripheral Vascular Disease
History of renal disease
History of stroke
Diabetes
Current Implantable Cardioverter Defibrillator (ICD)
New York Heart Association classification (NYHA)
Blood pressure
INTERMACS profile

Type of LVAD (axial or centrifugal) Destination therapy Year of implant
Laboratory Measurements
Hemoglobin Sodium Platelets White Blood Cells Blood Urea Nitrogen (BUN) Bilirubin Creatinine Lactate Dehydrogenase (LDH) International Normalized Ratio (INR)
Medications
Antiplatelet therapy Warfarin Inotropes Baseline use of PDE-5 inhibitors
Interventions within 48 hours of implant
Ventilator Intra-Aortic Balloon Pump (IABP) Extracorporeal Membrane Oxygenation (ECMO) Dialysis

LVAD: Left Ventricular Assist Device, INTERMACS: Interagency Registry for Mechanically Assisted Circulatory Support

Table S2. Significant variables included in logistic model for administration of PDE-5 inhibitors (Propensity score model)*

Demographics
Age
Sex
Race
Medical History
Smoking status
History of non-compliance
History of chronic coagulopathy
History of pulmonary disease
History of pulmonary hypertension
History of renal disease
Current Implantable Cardioverter Defibrillator (ICD)
New York Heart Association classification (NYHA)
Type of LVAD (axial or centrifugal)
Laboratory Measurements
Hemoglobin
Bilirubin
Medications
Antiplatelet therapy
Warfarin
Interventions within 48 hours of implant
Ventilator

LVAD: Left Ventricular Assist Device

**** All variables listed in Table S1 were considered and variables with a P<0.05 were included in logistic model.***

Table S3. Significant variables included in final adjusted models for each endpoint.

Endpoint	**Variables included in final adjusted model***
Pump thrombosis or ischemic stroke	Age Sex Body Mass Index (BMI) Race Smoking status History of non-compliance History of pulmonary disease History of pulmonary hypertension Pre-implant hemoglobin Pre-implant bilirubin Patient INTERMACS profile Year of implant
Pump thrombosis	Age Sex Body Mass Index (BMI) Race History of non-compliance History of pulmonary disease Pre-implant hemoglobin Type of continuous flow LVAD (centrifugal, axial)
Ischemic stroke	Age Smoking status

	History of pulmonary disease Type of continuous flow LVAD (centrifugal, axial) Dialysis within last 48 hours Systolic blood pressure Pre-implant antiplatelet therapy Pre-implant creatinine History of diabetes History of arrhythmia
All-cause mortality, pump thrombosis or ischemic stroke	Age Body Mass Index (BMI) Sex Race Smoking status History of non-compliance Log (Blood Urea Nitrogen) History of pulmonary disease Type of continuous flow LVAD (centrifugal, axial) LVAD as destination therapy History of cancer Patient INTERMACS profile Dialysis within last 48 hours

Table S3. Significant variables included in final adjusted models for each endpoint

(Continued)

Endpoint	**Variables included in final adjusted model***
All-cause Mortality	Age Smoking status Hemoglobin, g/dL Log (Blood Urea Nitrogen) Platelets (x10/L) History of pulmonary disease Type of continuous flow LVAD (centrifugal, axial) LVAD as destination therapy History of cancer History of Peripheral Vascular Disease Patient INTERMACS profile Systolic Blood Pressure Dialysis within last 48 hours Race
Hemorrhagic stroke	Type of continuous flow LVAD (centrifugal, axial) Sex Patient INTERMACS profile Body Mass Index (BMI) Intra-Aortic Balloon Pump (IABP) within last 48 hours

	Log (creatinine) Hemoglobin, g/dL
Gastrointestinal bleeding	Age Hemoglobin History of pulmonary disease Race Log (Blood Urea Nitrogen) Dialysis within last 48 hours History of Peripheral Vascular Disease Smoking status History of cancer Body Mass Index (BMI) Antiplatelet therapy History of atrial fibrillation

**** All variables listed in Table S1 were considered for each endpoint and variables with a P<0.05 were retained in the final adjusted model***

LVAD: Left Ventricular Assist Device, INTERMACS: Interagency Registry for Mechanically Assisted Circulatory Support

Table S4. Risk estimates for PDE-5 inhibitor within six months post-implant and after six months post-implant.

Endpoint	**PDE-5 Inhibitor vs No PDE-5 Inhibitor**	
	Adjusted Hazard Ratio (95% CI)*	P Value
Pump thrombosis or ischemic stroke (primary endpoint)		
< 6 months post-implant	0.81 (0.72-0.91)	0.003
≥ 6 months post-implant	0.88 (0.78-0.99)	0.042
Pump thrombosis		
< 6 months post-implant	0.70 (0.61-0.81)	<0.001
≥ 6 months post-implant	0.93 (0.81-1.06)	0.258
Ischemic stroke		
< 6 months post-implant	0.94 (0.79-1.12)	0.458
≥ 6 months post-implant	0.72 (0.57-0.90)	0.003
All-cause mortality		
<6 month post-implant	0.73 (0.65-0.82)	<0.001
≥ 6 month post-implant	0.98 (0.88-1.10)	0.755
All-cause mortality, pump thrombosis or ischemic stroke		
<6 month post-implant	0.76 (0.70-83)	<0.001
≥ 6 month post-implant	0.95 (0.87-1.04)	0.247

*Each model weighted by the inverse probability of treatment and adjusted for the variables listed in ***Table S3.*** Dummy variables were created to represent PDE-5i use prior to 6 months and PDE-5i use after 6 months.

Table S5. Relationship between the timing of use of PDE-5 inhibitor (pre-implant, post-implant) and the primary endpoint.

Variable	Adjusted Hazard Ratio* (95% CI)	P Value
No PDE-5i (n=8399)	ref	N/A
Pre-implant PDE-5i (n=423)	0.92 (0.72-1.16)	0.478
Post-implant PDE-5i (n=3998)	0.82 (0.75-0.90)	<0.001

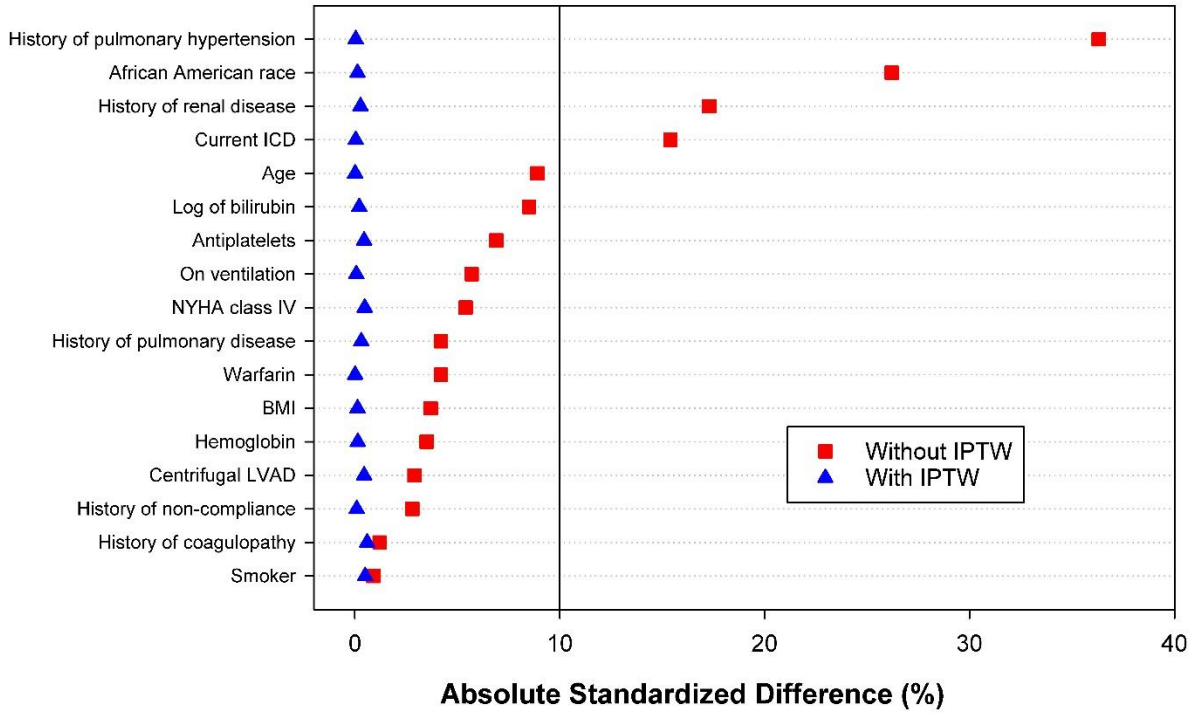
** **Adjusted for the variables listed in Table S3 for the primary endpoint.***

Table S6. Time to occurrence (months) of the primary endpoint to both groups stratified by LDH at 1-month post LVAD implant.

Any PDE-5 inhibitor use post-implant	LDH (U/L) 1-month post implant	Number of observations	Mean (months)	Median (months)
No	<400	762	10.49	7.00
	400-700	285	7.55	3.00
	>700	174	4.91	2.00
Yes	<400	388	10.32	7.00
	400-700	196	9.88	5.00
	>700	73	5.82	2.00

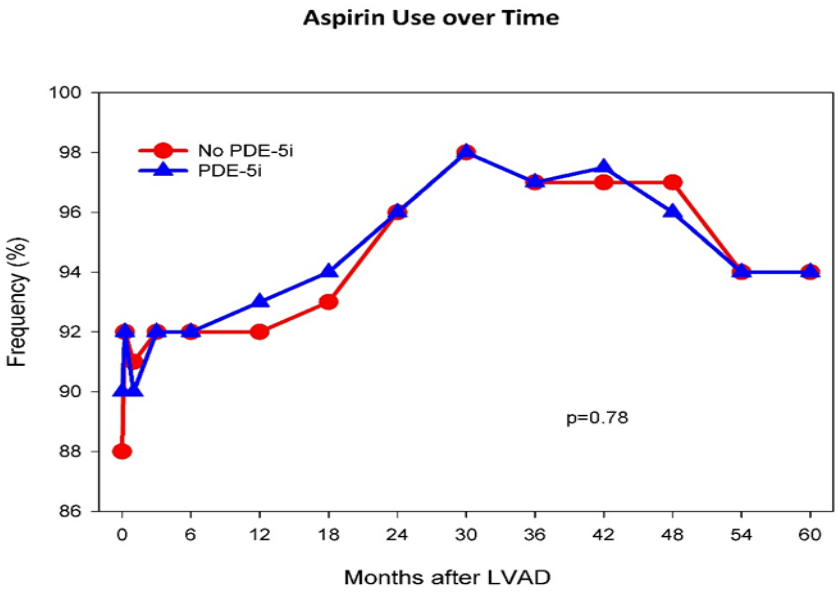
LDH: Lactate Dehydrogenase

Figure S1. Symbols indicate the absolute standardized differences for each variable.



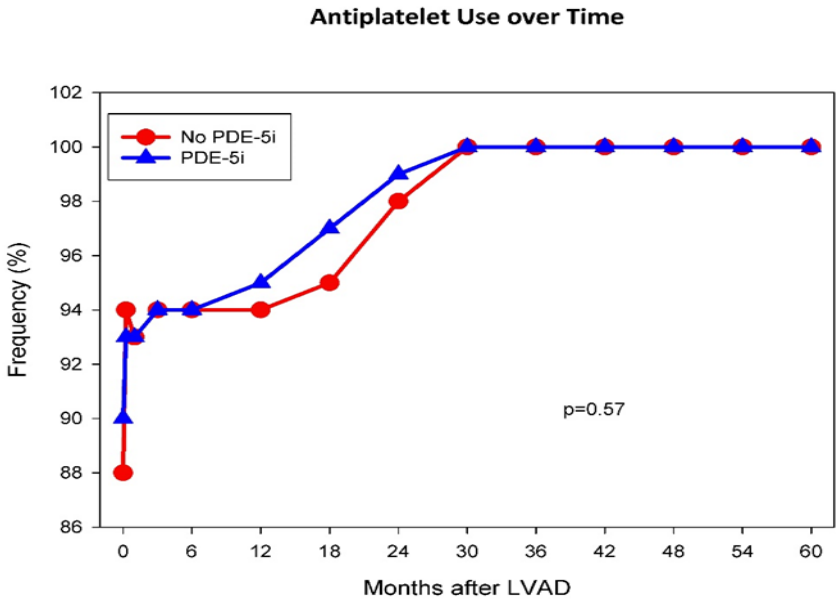
Absolute standardized differences are the absolute value of the difference in mean values between treatments groups divided by the square root of [(standard deviation of mean1 + standard deviation of mean2) ÷2]. Larger standardized difference indicates greater imbalance between treatment groups. ***IPTW:*** *inverse probability treatment weighting;* ***ICD:*** *Implantable Cardioverter Defibrillator;* ***NYHA:*** New York Heart Association; **BMI:** Body Mass Index; ***LVAD:*** Left Ventricular Assist Device

Figure S2. Comparison of the frequency of aspirin use with time post-LVAD implantation between PDE-5 and no-PDE-5 inhibitor group.



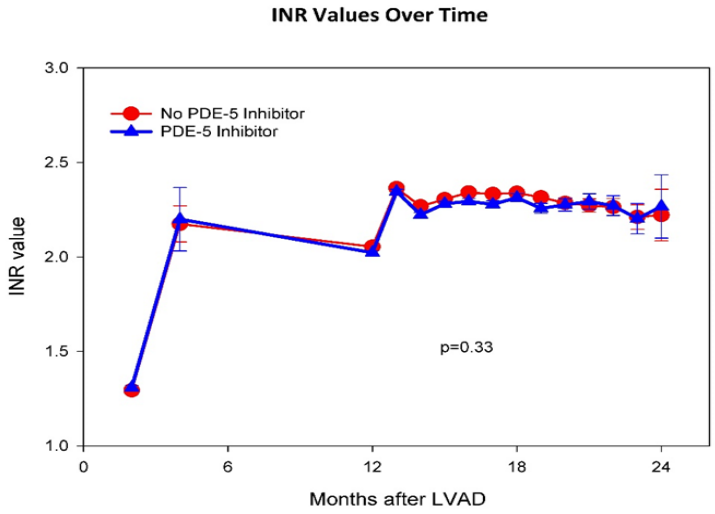
No difference was observed (p=0.78).

Figure S3. Comparison of the frequency of antiplatelet treatment use (including aspirin) with time post-LVAD implantation between PDE-5 and no-PDE-5 inhibitor group.



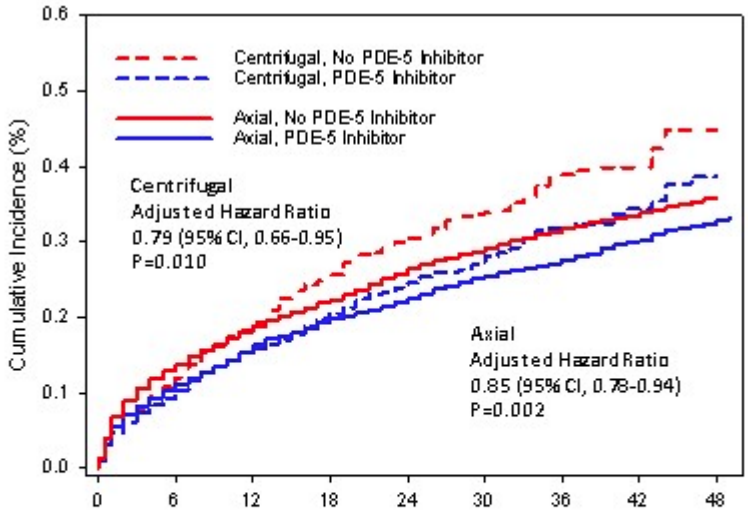
No difference was observed (p=0.57).

Figure S4. Comparison of the INR values post-LVAD implantation with time between PDE-5 and no-PDE-5 inhibitor group.



No difference was observed (p=0.33).

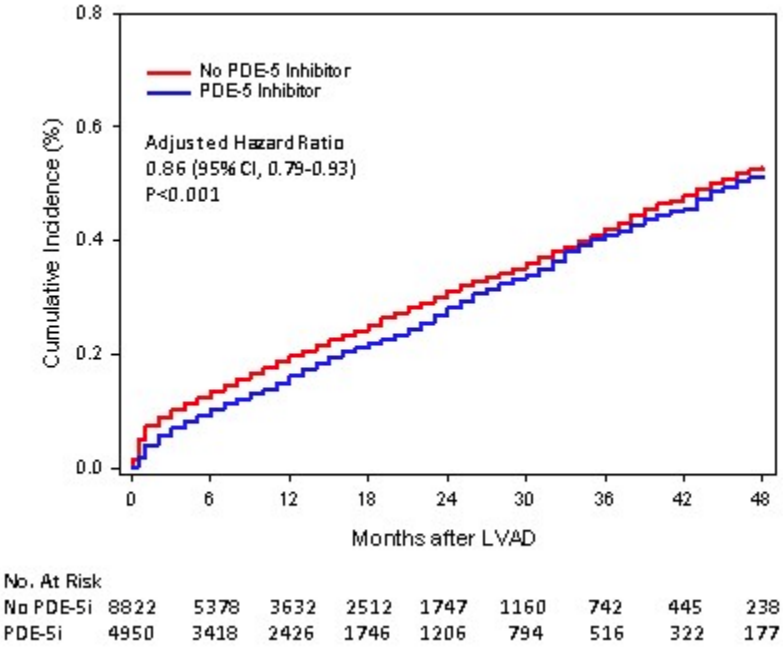
Figure S5. Cumulative incidence curves for the primary endpoint by LVAD type.



No. At Risk									
Centrifugal									
No PDE-5i	2224	1129	642	383	243	130	62	28	6
PDE-5i	1330	787	480	317	193	117	58	26	14
Axial									
No PDE-5i	6469	4065	2801	1965	1383	945	620	384	209
PDE-5i	3620	2495	1804	1303	928	617	426	274	149

Patients on PDE-5 inhibitors (both with axial and centrifugal LVADs) exhibit significantly lower risk compared with those not on PDE-5 inhibitors at 48 months.

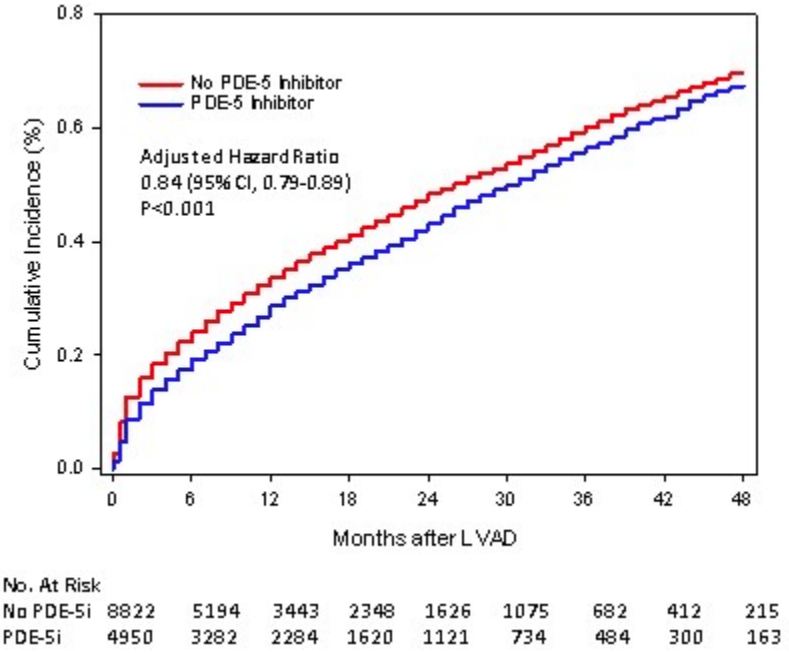
Figure S6. Cumulative incidence curves for all-cause mortality.



No. At Risk									
No PDE-5i	8822	5378	3632	2512	1747	1160	742	445	238
PDE-5i	4950	3418	2426	1746	1206	794	516	322	177

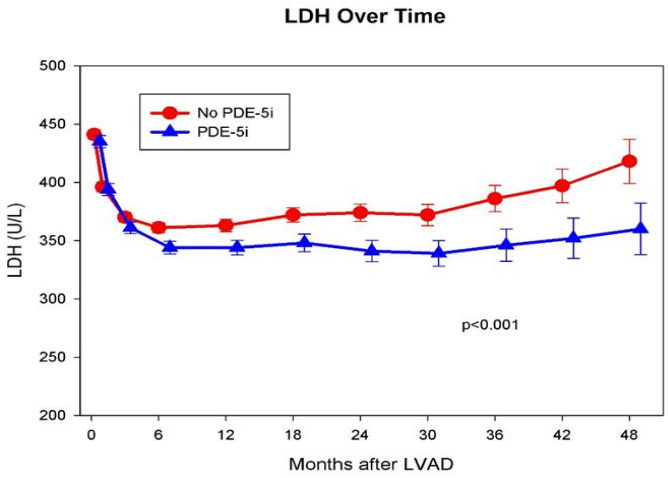
Patients on PDE-5 inhibitors have 14% lower risk for all-cause mortality compared to those not on PDE-5 inhibitors at 48 months.

Figure S7. Cumulative incidence curves for all-cause mortality, pump thrombosis or ischemic stroke.



The use of PDE-5 inhibitors is associated with 16% lower risk for adverse events.

Figure S8. Comparison of LDH values with time between the PDE-5 and no-PDE-5 inhibitor groups.



Patients on PDE-5 inhibitors exhibited significantly lower LDH values

Figure S9. Comparison of LDH as a continuous variable 1-month post LVAD implantation between PDE-5 and no-PDE-5 inhibitors.

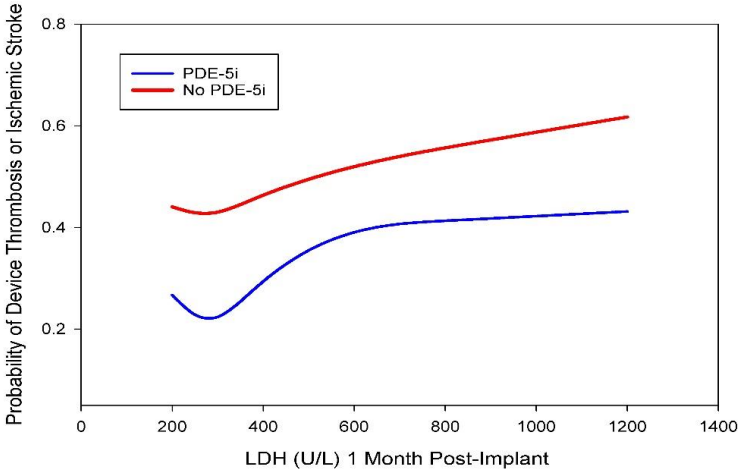
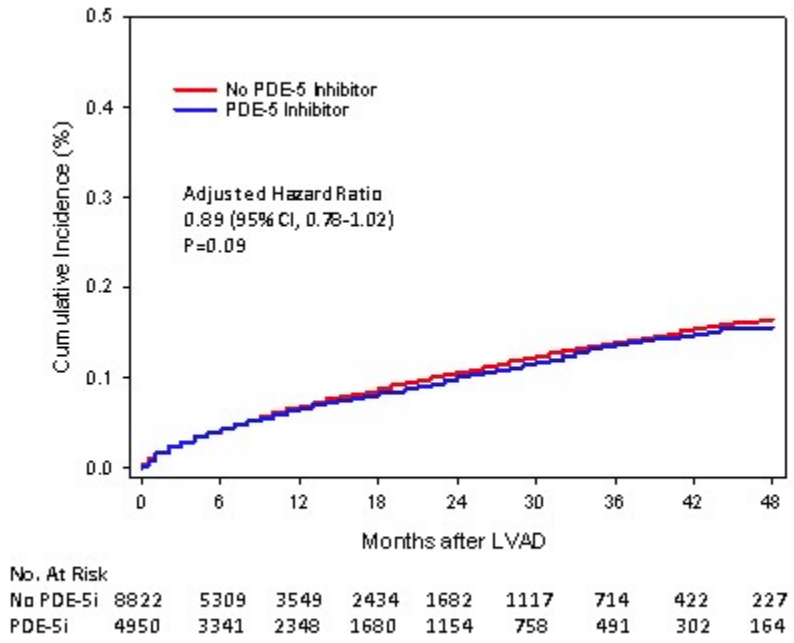
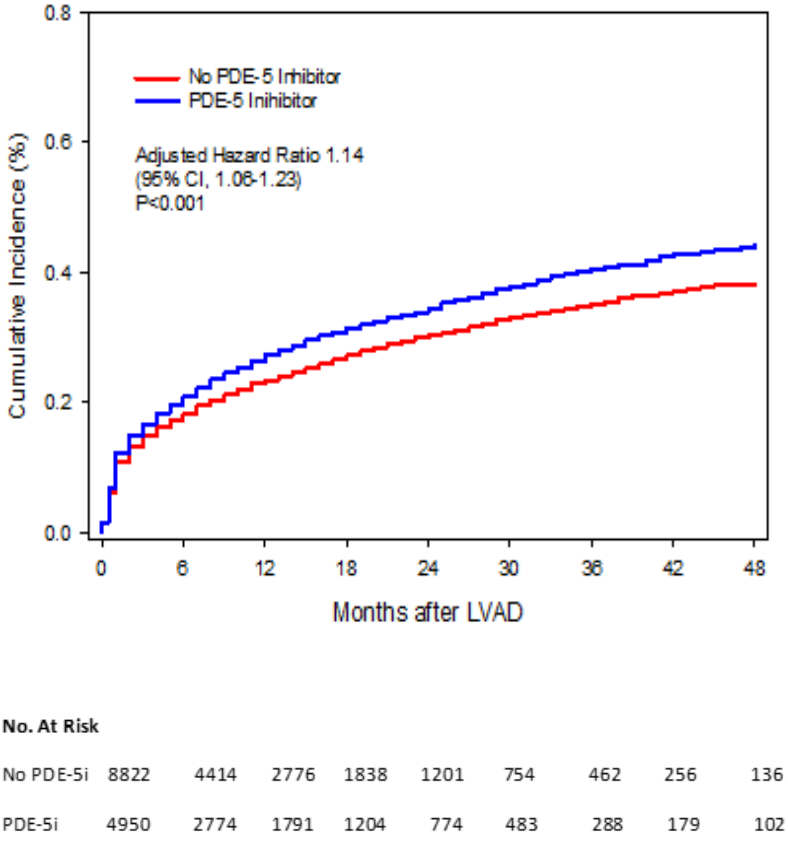


Figure S10. Cumulative incidence curves for hemorrhagic stroke.



There was no significant difference between the 2 groups (PDE-5 inhibitor versus no PDE-5 inhibitor).

Figure S11. Cumulative incidence curves for gastrointestinal bleeding.



Patients on PDE-5 inhibitors had 14% increased risk for gastrointestinal bleeding compared to those not on PDE-5 inhibitors