SUPPLEMENTAL MATERIAL

Outcomes in High-risk Pulmonary Embolism Patients Undergoing FlowTriever Mechanical Thrombectomy or Other Contemporary Therapies: Results from the FLAME Study

Table of Contents

1. Supplemental Methods

1.1 The FlowTriever System Procedure Details

Treatment with the FlowTriever System could include use of the Triever aspiration catheter (16F, 20F, 24F) or the FlowTriever catheter for mechanical thrombus dislodgement and removal, or both, as previously described.[15] Following venous access, the Triever catheter is advanced over a 0.035" guidewire across the right heart to the pulmonary arteries. Volume-controlled aspiration is performed using a 60-cc large-bore syringe and repeated as needed. The FlowTriever Catheter may be used to engage the thrombus with self-expanding nitinol disks. Blood return using the FlowSaver Blood Return System (Inari Medical, Irvine, CA) could be used.

1.2 Eligibility Criteria and Primary Endpoint Component Definitions

Table S1. Inclusion and Exclusion Criteria

Inclusion Criteria	≥18 years of age
	Treatment team determined high-risk PE was cause of shock
	One or more of the following criteria: • Systolic blood pressure <90 mmHg for at least 15 minutes or systolic blood pressure decrease of >40 mmHg for at least 15 minutes • Need for vasopressor support • Resuscitation after cardiac arrest with <30 minutes of cardiopulmonary resuscitation and Glasgow Coma scale >8
Exclusion Criteria	Out-of-hospital cardiac arrest with Glasgow Coma Scale ≤8
	Witnessed cardiac arrest with ongoing cardiopulmonary resuscitation ≥30 minutes
	Contraindication to anticoagulants
	Hematocrit <28%
	Platelet count <25,000/μL
	International normalized ratio (INR) >8
	Intracardiac thrombus or clot in transit
	Known anaphylactic sensitivity to radiographic agents that cannot be pre-treated
	History of pulmonary hypertension with systolic pulmonary arterial pressure >70 mmHg
	Presence of chronic medical conditions with estimated <90 days of life expectancy per physician discretion and not including the current PE
	Current participation in another drug or device treatment study that would interfere with participation in FLAME
	Current active COVID-19

Table S2. Definitions

Primary Endpoint Component	Definition
All-cause mortality	All-cause mortality through hospital discharge.
Bailout to an alternate thrombus removal strategy	The need for mechanical circulatory support or another thrombus removal strategy after the primary treatment strategy was initiated. The additional treatment strategy was not an *a priori* part of the original treatment plan.
Clinical deterioration	The new need for cardiopulmonary resuscitation (CPR), starting intravenous vasopressors to keep systolic blood pressure >90 mmHg in a previously normotensive patient, mechanical ventilation in a previously spontaneously breathing patient, or noninvasive positive pressure ventilation in a patient previously on nasal cannula.
Major bleeding	3b, 3c, 5a, or 5b on the Bleeding Academic Research Consortium (BARC) scale.

1.3 Meta-Analysis Methods and Derivation of Performance Goal

The composite primary endpoint for the FlowTriever Arm was compared to a historical performance goal derived from a subset of 18 published studies (Table S3) from a recent systematic review and meta-analysis of high-risk PE outcomes.[4] Each of the 18 studies reported outcomes pertaining to at least 1 of the composite primary endpoint components and were therefore included in the development of the performance goal. The systematic review and meta-analysis were prospectively defined, compliant with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, and registered with PROSPERO (International Prospective Register of Systematic Reviews; CRD42020219695). Full methodological details and results of the systematic review and meta-analysis have been previously described.[4] Reported event rates in high-risk PE patients were averaged using a random-effects model to obtain the individual component rates for the composite performance goal calculation: in-hospital all-cause mortality (29.5%; 95% CI: 20.6%-37.9%), bailout to an alternate thrombus removal strategy (30.3%; 95% CI: 15.5%-50.7%), clinical deterioration (15.6%; 95% CI: 6.7%-32.5%), and BARC 3b/3c/5a/5b major bleeding (11.5%; 95% CI: 6.0%-21.0%) (Table S2). The performance goal was established at 32.0% by averaging the meta-analytic rates of the 4 individual primary endpoint components, rounding up to the nearest percent, and adding a 10% margin. A one-sided binomial proportion test with normal approximation and alpha = 0.05 was used to compare the primary endpoint to the performance goal.

Table S3. Studies included in Performance Goal Derivation

Reference	Study Type	Subjects	In-hospital all-cause mortality	Bailout to alternate thrombus removal strategy	Clinical deterioration (within 24 hours)	Major Bleeding (BARC 3b/3c/5a/5b)
Avgerinos 2018[16]	Retrospective	90	15/90, 16.6%	NS	NS	24/90, 26.6%
Barrett 2010[17]	Retrospective	SE: 9	6/9, 66.6%	NS	NS	NS
		TL: 10	6/10, 60.0%			
		AC: 14	5/14, 35.7%			
Carvalho 2010[18]	Retrospective	16	7/16, 43.8%	NS	NS	NS
Cho 2016[19]	Retrospective	TL: 19	NS	4/19, 21.0%	NS	NS
		SE: 26		NS		
de Winter 2019[20]	Retrospective	33	NS	8/33, 24.2%	NS	NS
George 2018[21]	Retrospective	32	15/32, 46.9%	NS	5/32, 15.6%	NS
Kuo 2015[22]	Prospective, observational	28	4/28, 14.3%	NS	NS	0/28, 0.0%
Minakawa 2018[23]	Retrospective	63	23/63, 36.5%*	NS	NS	NS
Moon 2018[24]	Retrospective	Without ECMO: 9	7/9, 77.8%	NS	NS	NS
		ECMO: 14	8/14, 57.1%			7/14, 50.0%
Munakata 2012[25]	Retrospective	10	3/10, 30.0%†	NS	NS	2/10, 20.0%
Neely 2015[26]	Retrospective	49	5/49, 10.2%*	NS	NS	1/49, 2.0%
Pasrija 2018[27]	Retrospective	SE: 27	5/27, 18.5%	NS	NS	3/27, 11.1%
		SE/ECMO: 29	1/29, 3.4%			4/29, 13.8%
Secemsky 2018[1]	Prospective, observational	46	15/46, 32.6%	NS	NS	11/46, 23.9%
Senturk 2016[28]	Prospective, observational	186	NS	NS	NS	10/186, 5.4%
Sharifi 2016[29]	Prospective, observational	23	2/23, 8.7%	NS	NS	0/23, 0.0%
Shiomi 2017[30]	Retrospective	31	4/31, 12.9%	NS	NS	NS
Ucar 2013[31]	Retrospective	107	18/107, 16.8%	NS	NS	4/107, 3.7%
Wang 2015[32]	Prospective, randomized	TL group 1: 20	NS	12/20, 60.0%	NS	NS
		TL group 2: 20		4/20, 20.0%		
Total		**911**	**149/607**	**28/92**	**5/32**	**66/609**
Weighted Average [95% CI]			**28.5% [20.6%, 37.9%]**	**30.3% [15.5%, 50.7%]**	**15.6% [6.7%, 32.5%]**	**11.5% [6.0%, 21.0%]**

Studies shown are a subset of a systematic review and meta-analysis published separately.[4] These studies reported data for one or more of the primary endpoint components and, therefore, were used to determine the performance goal. The weighted averages were calculated using a random-effects model. AC, anticoagulation; BARC, Bleeding Academic Research Consortium; ECMO, extracorporeal membrane oxygenation; NA, not applicable; NS, not specified; SE, surgical embolectomy; TL, thrombolytic therapy.
*Operative mortality was reported. Only patients in refractory shock were included in the analysis.
†All patients died within 15 hours of the procedure.

Table S4. Demographics, Medical History, and Clinical Presentation Reported in Studies included in Performance Goal Derivation

	Available Data from 18 Meta-analyzed Studies (N=911)		
	Value from available data	Pooled sample size	Number of studies with data available
Age, years	60.3	n=495	13
Female	55.6%	n=495	13
BMI, kg/m^2	31.2	n=144	5
Race			
American Indian or Alaskan Native	NR		
Asian	NR		
Black or African American	35.7%	n=56	1
Native Hawaiian or Pacific Islander	NR		
White	68.2%	n=88	2
Other	NR		
Not provided	NR		
History			
Congestive Heart Failure	4.7%	n=258	5
Chronic Obstructive Pulmonary Disease	9.5%	n=242	4
Systemic Hypertension	42.2%	n=348	8
Pulmonary Hypertension	NR		
Diabetes Mellitus	21.6%	n=348	8
Cancer	19.2%	n=454	11
Pulmonary Embolism	12.5%	n=16	1
Deep Vein Thrombosis	48.4%	n=273	6
Contraindication to thrombolytics	59.7%	n=124	4
Prior COVID-19	NR		
Clinical Presentation at Admission or Time of High-risk PE Diagnosis			
SCAI shock stage	NR		
Systolic BP, mmHg	97.2	n=163	2
Diastolic BP, mmHg	57.0	n=107	1
Heart Rate, bpm	117.9	n=76	2
Tachycardia, >100 bpm	66.7%	n=69	2
Respiration Rate, breaths/min	27.5	n=56	1
Peripheral O_2 Sat (SpO_2), %	NR		
Supplemental O_2			
Nasal cannula	NR		
Face mask	NR		
Intubated	47.1%	n=87	2
Hypotension*	80.4%	n=112	3
Need for vasopressor support	57.5%	n=87	2
Resuscitation after cardiac arrest**	42.7%	n=351	11
Lactate ≥2 mmol/L	NR		
RV/LV Ratio	1.33	n=55	2
Location of PE	NR		

Presented as weighted averages or percentages.

*Hypotension defined as systolic BP <90 mmHg, systolic BP <100 mmHg or a decline of >40 mmHg, or sustained (>15 minutes) systolic BP<90 mmHg.

**Includes in-hospital and out-of-hospital cardiac arrest or resuscitation.

BMI, body mass index; BP, blood pressure; LV, left ventricle; NR, not reported; PE, pulmonary embolism; RV, right ventricle; SCAI, Society for Cardiovascular Angiography and Interventions.

Table S4 reports all pooled data available on demographic, medical history, and clinical presentation details from the 18 meta-analyzed studies included in Table S3 that informed the derivation of the performance goal. Many variables were not systematically reported for high-risk PE patients in these studies. Due to this high degree of missingness, there is low confidence that the pooled data is reflective of the overall population of high-risk PE patient included in the 18 meta-analyzed studies. These results are furnished for informational purposes only to partially contextualize the characteristics of high-risk PE patients included in the meta-analyzed studies.

1.4 Sample Size Calculation and Early Stopping Criteria for Success

The maximum sample size of 71 FlowTriever Arm patients was calculated using a two-stage group sequential design, where the in-hospital composite primary endpoint of all-cause mortality, bailout to an alternate thrombus removal strategy, clinical deterioration, and major bleeding (BARC 3b/3c/5a/5b) was expected to occur in 18% of FlowTriever Arm patients, based on the consensus from a steering committee of expert clinicians. This expected frequency of the primary endpoint in the FlowTriever Arm was compared to the historical performance goal, which was established at 32.0% by averaging the rates of the 4 individual primary endpoint components from the meta-analysis shown in Table S3, rounding up to the nearest percent, and adding a 10% margin. A one-sided binomial proportion test with normal approximation was used against the historical performance goal with a power of 80% and alpha = 0.05. The O'Brien-Fleming method was implemented to determine the early stopping boundary for 50 subjects enrolled in the FlowTriever Arm. This interim analysis constitutes the first stage of the design, while the second stage is the final analysis performed at N = 71 FlowTriever Arm subjects.

At the final analysis of 71 FlowTriever Arm subjects, the Z-score threshold was -1.7116 and the *P* value threshold was 0.0435 for success, meaning that a maximum of 16 patients out of 71 patients could reach the primary endpoint in order for the study to succeed. While the protocol specified a maximum sample size of 71 FlowTriever Arm patients, the study was stopped after the interim analysis stopping criterion was reached at 50 FlowTriever Arm patients enrolled. At the interim analysis, the Z-score threshold was -2.0311 and the *P* value threshold was 0.0211 for success. The interim analysis was intended to determine whether the study should be stopped early due to success. There was no futility threshold specified for the interim analysis.

2. Supplemental Results

2.1 Interim Analysis Results

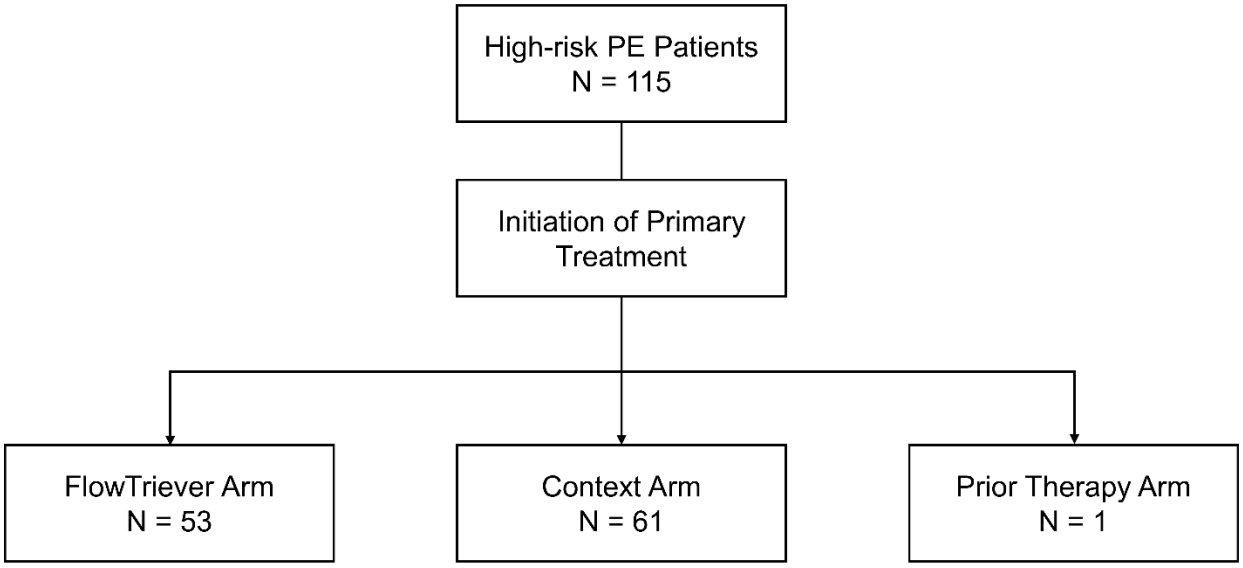
Table S5. Interim Analysis Results

	FlowTriever Arm (Interim analysis population, n = 50)	Performance Goal	*P* value
Primary endpoint	9 (18.0%)	32.0%	0.0169*

*The pre-specified interim analysis was performed after 50 FlowTriever patients were enrolled to determine whether the study should be stopped early due to success. The primary endpoint analysis met the pre-specified criterion for early stoppage of the study, having achieved $P<0.0211$.

2.2 Enrollment Flow

Figure S1. Enrollment Flow for High-risk Patients in the FLAME Study



The FLAME study is a prospective, non-randomized, parallel group, observational study. High-risk pulmonary embolism (PE) patients were enrolled concurrently into 1 of 3 parallel registries (FlowTriever Arm, Context Arm, or Prior Therapy Arm) based on physician selection of the primary treatment approach.

2.3 Prior Therapy Arm

One patient was enrolled in the Prior Therapy Arm who was initially treated for a non-high-risk PE with anticoagulation, systemic thrombolytics, and catheter-directed thrombolysis with the EkoSonic Endovascular System (Boston Scientific, Maple Grove, MN). The patient deteriorated later the same day, becoming high-risk, and was treated with the FlowTriever System as the primary treatment for the high-

risk PE. The patient subsequently developed hypotension and septic shock and expired 3 days post-procedure.

2.4 All-cause Mortality Stratified by SCAI Shock Stage

Table S6. All-cause Mortality Stratified by SCAI Shock Stage: FlowTriever Arm

SCAI Shock Stage	FlowTriever Arm (n = 53)
A	0/2 (0%)
B	1/11 (9.1%)
C	0/29 (0%)
D	0/5 (0%)
E	0/6 (0%)
Total all-cause mortality	1/53 (1.9%)

SCAI, Society for Cardiovascular Angiography and Interventions.

Table S7. All-cause Mortality Stratified by SCAI Shock Stage: Context Arm

SCAI Shock Stage	Context Arm (n = 61)
A	0/1 (0%)
B	1/6 (16.7%)
C	2/22 (9.1%)
D	5/12 (41.7%)
E	10/20 (50.0%)
Total all-cause mortality	18/61 (29.5%)

SCAI, Society for Cardiovascular Angiography and Interventions.

2.5 Additional Secondary Endpoints and Serious Adverse Event Incidence

Table S8. Additional Secondary Endpoints and Serious Adverse Event Incidence: FlowTriever Arm

Additional Secondary Safety Endpoints	FlowTriever Arm (n = 53)
Stroke	1 (1.9%), (0.0%-10.1%)
Ischemic	1
Hemorrhagic	0
Subjects with device-related complication[*]	12 (22.6%), (12.3%-36.2%)
Related to primary treatment device/therapy[†,‡]	12
Related to bailout	1
Related to ECMO only	0
Subjects with access site injury requiring intervention[†]	4 (7.5%), (2.1%-18.2%)
Serious Adverse Events	
Subjects with Serious Adverse Events (SAEs)	16 (30.2%)
Subjects with SAEs related to primary treatment device or therapy[†,‡]	10 (18.9%)
Related to thrombolytic therapy	0 (0.0%)
Related to ECMO only	0 (0.0%)
Subjects with SAEs related to subsequent bailout therapy	1 (1.9%)
Utility Measures	
Length of post-treatment hospital stay, nights[§]	7.0 [3.0-12.5], (7.5-14.3), n = 52
Length of post-treatment ICU stay, nights[§]	2.0 [1.0-4.0], (2.9-8.1), n = 52
ECMO use	3 (5.7%), (1.2%-15.7%)
Time to extubation, days[§,‖]	1.6 [1.2-4.3], n = 4
Discharge location	
Expired prior to discharge	1 (1.9%), (0.0%-10.1%)
Home	26 (49.1%), (35.1%-63.2%)
Home with home healthcare	6 (11.3%), (4.3%-23.0%)
Care facility or skilled nursing home	13 (24.5%), (13.8%-38.3%)
Not discharged (in hospital ≥45 days)	4 (7.5%), (2.1%-18.2%)
Other	3 (5.7%), (1.2%-15.7%)

Values are n (%), (95% Confidence Interval) or median [IQR], (95% Confidence Interval). SAEs and secondary safety endpoints were adjudicated by an independent Clinical Events Committee. ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; SAE, serious adverse event. Denominator is 53 for the FlowTriever Arm unless otherwise noted.

[*]Device-related complications included primary treatment devices, bailout devices, and ECMO if it was part of the primary treatment strategy. A subject could have more than 1 device-related complication.

[†]One patient with a hemoglobin decrease adjudicated as related to FlowTriever had a pericardial drain placed and a failed PCI prior to the thrombectomy procedure. One patient with anemia adjudicated as related to FlowTriever had a high baseline hemoglobin likely due to hemoconcentration and a low follow-up reading noted by the site to be likely due to lab error, but no overt bleeding. One patient with a vascular access site hemorrhage adjudicated as related to FlowTriever was treated with 10 minutes of manual pressure without further intervention.

[‡]One patient with a vascular access site hemorrhage adjudicated as related to FlowTriever was treated with manual pressure without further intervention. One patient with a vascular access site hematoma adjudicated as related to FlowTriever was treated with manual pressure and a femoral compression system without further intervention.

[§]Assessed in patients who survived to discharge or study exit.

[‖]Assessed in patients who were intubated prior to initiation of primary treatment and who were extubated prior to discharge or study exit.

Table S9. Additional Secondary Endpoints and Serious Adverse Event Incidence: Context Arm

Additional Secondary Safety Endpoints	Context Arm (n = 61)
Stroke	4 (6.6%), (1.8%-15.9%)
Ischemic	2
Hemorrhagic	2
Subjects with device-related complication[*]	10 (16.4%), (8.2%-28.1%)
Related to primary treatment device/therapy	9
Related to bailout	7
Related to ECMO only	3
Subjects with access site injury requiring intervention[†]	5 (8.2%), (2.7%-18.1%)
Serious Adverse Events	
Subjects with Serious Adverse Events (SAEs)	37 (60.7%)
Subjects with SAEs related to primary treatment device or therapy	23 (37.7%)
Related to thrombolytic therapy	17 (27.9%)
Related to ECMO only	1 (4.3%)
Subjects with SAEs related to subsequent bailout therapy	6 (9.8%)
Utility Measures	
Length of post-treatment hospital stay, nights[‡]	8.0 [6.0-15.0], (9.0-14.2), n = 43
Length of post-treatment ICU stay, nights[‡]	3.0 [1.0-7.0], (3.4-7.2), n = 43
ECMO use	7 (11.5%), (4.7%-22.2%)
Time to extubation, days[†,‡]	1.8 [1.5-3.1], n = 6
Discharge location	
Expired prior to discharge	18 (29.5%), (18.5%-42.6%)
Home	23 (37.7%), (25.6%-51.0%)
Home with home healthcare	3 (4.9%), (1.0%-13.7%)
Care facility or skilled nursing home	11 (18.0%), (9.4%-30.0%
Not discharged (in hospital ≥45 days)	0 (0%), --
Other	6 (9.8%), (3.7%-20.2%)

Values are n (%) or median [IQR]. SAEs and secondary safety endpoints were adjudicated by an independent Clinical Events Committee. ECMO, extracorporeal membrane oxygenation; SAE, serious adverse event. Denominator is 61 for the Context Arm unless otherwise noted. ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit.

[*]Device-related complications included primary treatment devices, bailout devices, and ECMO if it was part of the primary treatment strategy. A subject could have more than 1 device-related complication.

[†]Assessed in patients who were intubated prior to initiation of primary treatment and who were extubated prior to discharge or study exit.

[‡]Assessed in patients who survived to discharge or study exit.

2.6 Most Common Device-related Complications

Table S10. Most Common Device-related Complications: FlowTriever Arm

Complication	FlowTriever Arm (n = 53)
Hemoglobin decrease or anemia*	8
Vascular access site hemorrhage/hematoma	4

Complications occurring in more than 1 patient.

*6/8 (75%) of the complications related to hemoglobin decrease or anemia occurred in patients whose procedures did not include use of the FlowSaver blood return device.

Table S11. Most Common Device-related Complications: Context Arm

Complication	Context Arm (n=61)
Vascular access site hemorrhage/hematoma	4
Hemoglobin decrease or anemia	3
Hypotension	3

Complications occurring in more than 1 patient.

2.7 Listing of Serious Adverse Events Related to the Primary Treatment Device or Therapy

Serious adverse events were defined as fatal or life-threatening, resulting in persistent or significant disability or incapacity, resulted in permanent impairment of a body function or permanent damage to a body structure, resulted in hospitalization or prolonged a hospitalization, or necessitated medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure. Serious adverse events were adjudicated by the CEC for severity and relatedness to the primary treatment device or therapy or subsequent bailout therapy.

Table S12. Listing of Serious Adverse Events Related to the Primary Treatment Device or Therapy: FlowTriever Arm

Serious Adverse Event Term	FlowTriever Arm* (n = 53)
Anemia	3
Anemia postoperative	1
Arterial hemorrhage	1
Arterial repair	1†
Hemoglobin decreased	3
Hypotension	1
Obstructive shock	1
Right ventricular failure	1
Swelling	1
Vascular access site hematoma	1
Vascular access site hemorrhage	1

Serious adverse event terms follow Medical Dictionary for Regulatory Activities (MedDRA) terminology.

*All FlowTriever Arm serious adverse events were also reported as device-related complications. One patient with a hemoglobin decrease adjudicated as related to FlowTriever had a pericardial drain placed and a failed PCI prior to the thrombectomy procedure. One patient with anemia adjudicated as related to FlowTriever had a high baseline hemoglobin likely due to hemoconcentration and a low follow-up reading noted by the site to be likely due to lab error, but no overt bleeding. One patient with a vascular access site hemorrhage adjudicated as related to FlowTriever was treated with 10 minutes of manual pressure without further intervention. One patient with a vascular access site hematoma adjudicated as related to FlowTriever was treated with manual pressure and a femoral compression system without further intervention.

†Related to extracorporeal membrane oxygenation use.

Table S13. Listing of Serious Adverse Events Related to the Primary Treatment Device or Therapy: Context Arm

Serious Adverse Event Term	Context Arm (n = 61)
Acute kidney injury	1
Acute respiratory failure	1
Anemia	4
Arterial occlusive disease	1*
Breast hematoma	1
Cardio-respiratory arrest	1
Chest wall hematoma	1
Gastrointestinal hemorrhage	1
Hematoma	3
Hematuria	1
Hemodynamic instability	1
Hemoglobin decreased	3
Hemorrhage	1
Hemorrhage intracranial	1
Hypotension	2
Orbital hematoma	1
Peripheral ischemia	1
Pharyngeal hemorrhage	1
Pulmonary embolism	1
Pulmonary hemorrhage	1
Pulseless electrical activity	1
Shock hemorrhagic	2
Subdural hemorrhage	1
Thrombosis	1
Tooth socket hemorrhage	1
Vascular access site hematoma	1
Vascular access site hemorrhage	4

Serious adverse event terms follow Medical Dictionary for Regulatory Activities (MedDRA) terminology.
*Related to extracorporeal membrane oxygenation use.