Appendix 1:

I: Bivalirudin for ECMO Titration Nomogram

Mechanical cardiac support/high-intensity nomogram, NON-CRRT (0.025 mg/kg/hr initial dose)	
Measured aPTT	Recommendation
< 45	Increase infusion by 0.01 mg/kg/hr. Repeat STAT aPTT every 3 hours after rate change
45 – 60	Increase infusion by 0.005 mg/kg/hr. Repeat STAT aPTT every 3 hours after rate change
61 – 75	No change. After three (3) consecutive aPTT are within therapeutic range, repeat STAT aPTT q6h if rate remains unchanged. After three (3) consecutive aPTT are within therapeutic range, decrease aPTT monitoring to twice daily
76 – 90	Decrease infusion by 0.005 mg/kg/hr. Repeat STAT aPTT every 3 hours after rate change
91 – 110	Hold infusion for 2 hours, then decrease infusion by 0.01 mg/kg/hr. Repeat STAT aPTT every 3 hours after rate change
> 110	Hold infusion for 2 hours, recheck aPTT every three hours until within goal range, then decrease by 0.01 mg/kg/hr. Repeat STAT aPTT every 3 hours after rate change

Abbreviations: aPTT, activated Partial Thromboplastin Time; CRRT, Continuous Renal Replacement Therapy

Mechanical cardiac support/high-intensity nomogram, CRRT (0.04 mg/kg/hr initial dose)	
Measured aPTT	Recommendation
< 45	Increase infusion by 0.01 mg/kg/hr. Repeat STAT aPTT every 3 hours after rate change
45 – 60	Increase infusion by 0.005 mg/kg/hr. Repeat STAT aPTT every 3 hours after rate change
61 – 75	No change. After three (3) consecutive aPTT are within therapeutic range, repeat STAT aPTT q6h if rate remains unchanged. After three (3) consecutive aPTT are within therapeutic range, decrease aPTT monitoring to twice daily
76 – 90	Decrease infusion by 0.005 mg/kg/hr. Repeat STAT aPTT every 3 hours after rate change
91 – 110	Hold infusion for 2 hours, then decrease infusion by 0.01 mg/kg/hr. Repeat STAT aPTT every 3 hours after rate change
> 110	Hold infusion for 2 hours, recheck aPTT every three hours until within goal range, then decrease by 0.01 mg/kg/hr. Repeat STAT aPTT every 3 hours after rate change

Abbreviations: aPTT, activated Partial Thromboplastin Time; CRRT, Continuous Renal Replacement Therapy

II: Heparin for VA-ECMO Titration Nomogram

Round Heparin Infusion Rate to nearest tenth.
Infusion = Heparin 25,000 units in 250 mL

Initial Heparin Infusion Rate = 8 units/kg/hr. Initial infusion rate not to exceed 1600 units/hr.

Heparin Stroke, EP, VAD, High Risk Bleed Nomogram		
If AntiXa	less than or equal to 0.2 units/mL	Increase current heparin infusion rate by 2 units/kg/hr Repeat STAT AntiXa 6 hours after rate change
	0.21–0.24 units/mL	Increase current heparin infusion rate by 1 units/kg/hr Repeat STAT AntiXa 6 hours after rate change
	0.25–0.35 units/mL	No change in heparin infusion rate/No bolus Repeat STAT AntiXa every 6 hours for 2 consecutive results After range reached for 2 consecutive results order AntiXa, Next 4AM, Daily, For 5 days Follow nomogram for each subsequent AntiXa result
	0.36–0.45 units/mL	Decrease current heparin infusion rate by 1 unit/kg/hr Repeat STAT AntiXa 2 hours after rate change
	0.46–0.69 units/mL	HOLD heparin infusion for 1 hour Decrease previous heparin infusion rate by 2 units/kg/hr after infusion has been held for 1 hour Repeat STAT AntiXa 2 hours after rate change
	greater than or equal to 0.7 units/mL	STOP heparin infusion and call physician for orders

III: VA-ECMO Cannulation Standards of Care

- Cannulation sites: Determined by cannulating physician
- Anticoagulation for initiation of VA-ECMO: Heparin (3,000 to 5,000 units intravenous bolus); Bivalirudin (0.3 mg/kg intravenous bolus)
- Initiation of continuous infusion anticoagulation was determined by patient's clinical status based on post-cannulation bleeding risks

IV: VA-ECMO Circuit/Oxygenator

- Oxygenator:
    - 2009-2010: Medtronic Affinity Oxygenator
    - 2010 – Present: Maquet Quadrox
        - Bioline used for Cardiohelp
        - Softline used for CentriMag
- Pump:
    - 2009: Biomedicus and Rotaflow
    - 2012 to Present: CardioHelp
    - 2015 to Present: CentriMag
- Tubing:
    - 2009 to 2017: Carmeda
    - 2017 to Present: X-Coated

Supplemental Table 1: Anticoagulation Parameters

Variable	Bivalirudin (n=54)	UFH (n=89)	P-value
Time in Therapeutic Range (percentage)[a]	50 [36-80]	40 [0-50]	<0.001
Time to first consecutive aPTT or anti-Xa (hours)[a]	21 [9-28]	28 [20-38]	0.001
Achieved therapeutic range, N(%)	47 (87)	64 (71)	0.02

[a]median [IQR]

Supplemental Table 2: Complete Multivariate Cox Regression: Factors Influencing Time to Thrombotic Event During ECMO

Model #	Variable	B	Exp(B)	95% CI for Exp(B)	P-value
Model 1	Bivalirudin	1.34	3.81	1.5 to 9.7	0.01
	Hypertension	0.03	1.03	0.438 to 2.41	0.95
	DVT/PE	-0.17	0.85	0.286 to 2.497	0.76
	Cannulation Strategy	-0.01	0.99	0.446 to 2.197	0.98
	Anticoagulated within 24 hours	0.58	1.79	0.728 to 4.391	0.21
	BMI	0.02	1.02	0.98 to 1.07	0.29
	Diabetes	-0.63	0.54	0.262 to 1.091	0.09
	Previous Major Bleeding	0.30	1.36	0.239 to 7.683	0.73
	ACT	0.00	1.00	0.995 to 1.006	0.77
	Age	0.01	1.01	0.981 to 1.032	0.64
Model 2	Bivalirudin	1.34	3.80	1.512 to 9.568	0.01
	Hypertension	0.02	1.03	0.457 to 2.299	0.95
	DVT/PE	-0.17	0.85	0.289 to 2.482	0.76
	Anticoagulated within 24 hours	0.58	1.79	0.737 to 4.35	0.20
	BMI	0.02	1.02	0.98 to 1.07	0.29
	Diabetes	-0.63	0.54	0.262 to 1.091	0.09
	Previous Major Bleeding	0.31	1.36	0.24 to 7.674	0.73
	ACT	0.00	1.00	0.996 to 1.006	0.77

	Age	0.01	1.01	0.981 to 1.032	0.63
Model 3	Bivalirudin	1.34	3.83	1.552 to 9.432	0.00
	DVT/PE	-0.16	0.85	0.293 to 2.467	0.77
	Anticoagulated within 24 hours	0.58	1.78	0.747 to 4.25	0.19
	BMI	0.02	1.02	0.98 to 1.07	0.28
	Diabetes	-0.62	0.54	0.269 to 1.074	0.08
	Previous Major Bleeding	0.31	1.36	0.24 to 7.686	0.73
	ACT	0.00	1.00	0.996 to 1.006	0.77
	Age	0.01	1.01	0.982 to 1.031	0.63
Model 4	Bivalirudin	1.35	3.87	1.581 to 9.485	0.00
	DVT/PE	-0.16	0.85	0.295 to 2.473	0.77
	Anticoagulated within 24 hours	0.58	1.78	0.745 to 4.236	0.20
	BMI	0.02	1.02	0.981 to 1.07	0.28
	Diabetes	-0.63	0.53	0.267 to 1.052	0.07
	Previous Major Bleeding	0.32	1.37	0.245 to 7.709	0.72
	Age	0.01	1.01	0.983 to 1.031	0.59
Model 5	Bivalirudin	1.35	3.84	1.57 to 9.404	0.00
	Anticoagulated within 24 hours	0.56	1.76	0.74 to 4.169	0.20
	BMI	0.02	1.02	0.981 to 1.069	0.28
	Diabetes	-0.63	0.53	0.268 to 1.054	0.07
	Previous Major Bleeding	0.22	1.25	0.252 to 6.2	0.79

	Age	0.01	1.01	0.983 to 1.031	0.57
Model 6	Bivalirudin	1.39	4.02	1.729 to 9.351	0.00
	Anticoagulated within 24 hours	0.58	1.79	0.758 to 4.205	0.19
	BMI	0.02	1.02	0.98 to 1.067	0.30
	Diabetes	-0.62	0.54	0.272 to 1.062	0.07
	Age	0.01	1.01	0.983 to 1.031	0.59
Model 7	Bivalirudin	1.37	3.94	1.698 to 9.149	0.00
	Anticoagulated within 24 hours	0.60	1.82	0.772 to 4.273	0.17
	BMI	0.02	1.02	0.981 to 1.067	0.29
	Diabetes	-0.64	0.53	0.267 to 1.032	0.06
Model 8	Bivalirudin	1.41	4.10	1.743 to 9.626	0.00
	Anticoagulated within 24 hours	0.51	1.67	0.716 to 3.882	0.24
	Diabetes	-0.65	0.52	0.266 to 1.024	0.06
Model 9	Bivalirudin	1.34	3.81	1.652 to 8.782	0.00
	Diabetes	-0.63	0.53	0.271 to 1.043	0.07

Supplemental Figure 1: Patient Exclusion Flowchart