

SUPPLEMENTAL MATERIAL

Content of online supplement belonging to the manuscript

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Note S1: Proportion of FXa bleeding likely to need acute reversal

The total FXa inhibitor major bleeding population is 80,000 per year in the U.S.⁷ This includes approximately 12%-16% percent intracranial bleeding (ICH) based on the Kcentra and ARISTOTLE studies.^{17,23} The higher acuity subset of bleeding patients enrolled in RE-VERSE AD,¹⁷ ANNEXA-4¹¹ and our cohort contained 34%-42% ICH. Assuming all ICHs remain in the higher acuity subset, this allows us to establish a proportional relationship between the larger group and the subset, which then allows us to calculate the size of the subset. At the low end, 12% divided by 34%, gives us 0.35 which multiplied by 80,000 is 28,000. At the high end, 16% divided by 42% is 0.38 multiplied by 80,000 is 30,400. Crossing the low and high ends (12/42 and 16/34) gives us 0.29 and 0.47 for a maximum estimated range of higher acuity major bleeding of 23,200 to 37,600.

Table S1. Medical centers included in the retrospective study

Medical Center	Investigator(s)	Type of Center	Patients
Seton Dell Medical School Stroke Institute	Truman J. Milling, MD	Level 1 Trauma	11
Beaumont Hospital-Royal Oak	Carol L. Clark, MD	Level 1 Trauma	13
Allegheny General Hospital	Charles Feronti, DO	Level 1 Trauma	12
Cedars-Sinai Medical Center	Shlee S. Song, MD; Sam S. Torbati, MD	Level 1 Trauma	14
University of Cincinnati College of Medicine	Gregory J. Fermann, MD	Level 1 Trauma	6
Total			56

Table S2. Demographics and characteristics of the retrospective study population and by bleeding location

Characteristic	Categories	Total	Gastrointestinal bleed	Intracranial hemorrhage	Other bleeding site
Patients – no. (%)	All	56 (100)	29 (52)	19 (34)	8 (14)
Age – years	Mean ± SD	75.6 ± 11.5	76.0 ± 10.3	75.5 ± 14.5	74.4 ± 8.7
	Median (IQR)	76.5 (70.3,84.2)	76.6 (70.3,82.2)	77.5 (68.7,85.8)	74.5 (70.3,77.9)
Gender – no. (%)	Male	33 (59)	16 (55)	12 (63)	5 (63)
	Female	23 (41)	13 (45)	7 (37)	3 (38)
Ethnicity – no. (%)	Caucasian	43 (77)	24 (83)	13 (68)	6 (75)
	Others [†]	8 (14)	3 (10)	5 (26)	0 (0)
	Unknown	5 (9)	2 (7)	1 (5)	2 (25)
Insurance type – no. (%)	Public	52 (93)	27 (93)	18 (95)	7 (88)
	Private	4 (7)	2 (7)	1 (5)	1 (13)
Charlson Comorbidity Index – score	Mean ± SD	1.8 ± 1.5	2.2 ± 1.5 [§]	1.0 ± 1.2 [§]	2.1 ± 1.2
	Median (IQR)	2.0 (0.0,3.0)	2.0 (2.0,3.0)	0.0 (0.0,2.0)	2.0 (1.8,3.0)
Anticoagulant – no. (%)	Apixaban	12 (21)	5 (17)	6 (32)	1 (13)
	Rivaroxaban	38 (68)	23 (79)	11 (58)	4 (50)
	Enoxaparin	6 (11)	1 (3)	2 (11)	3 (38)
Concomitant antiplatelets with DOACs [‡] – no. (%)	Concomitant antiplatelets	22 (44)	12 (43)	6 (35)	4 (80)
	DOAC alone	28 (56)	16 (57)	11 (65)	1 (20)

* Percentages may not total 100 because of rounding

[†] Other ethnicities include Asian, black and Hispanic

‡ Includes rivaroxaban or apixaban

§ Statistical difference: p=0.005

|| SD: Standard deviation; IQR: Interquartile range; DOAC: Direct-acting oral anticoagulant

Table S3. Bleeding and anticoagulant treatment timelines of the retrospective study population and by bleeding location

Characteristic	Categories	Total (n=56)	Gastrointestinal bleed (n=29)	Intracranial hemorrhage (n=19)	Other bleeding site (n=8)
Cause of major bleed – no. (%)	Spontaneous	34 (61)	17 (59)	10 (53)	7 (88)
	Trauma	6 (11)	0 (0)	6 (32)	0 (0)
	Procedure	1 (2)	0 (0)	0 (0)	1 (13)
	Unknown	15 (27)	12 (41)	3 (16)	0 (0)
Time on anticoagulant – no. (%)	Known	32 (57)	18 (62)	10 (53)	4 (50)
	Unknown	24 (43)	11 (38)	9 (47)	4 (50)
Time on anticoagulant prior to bleeding event – days	Median (IQR)	96.5 (19.8,209.8)	82.5 (17.8,196.8)	108.0 (85.0,152.0)	378.0 (19.0,918.0)
Time between bleeding event and admission – hr	Median (IQR)	8.2 (0.7,26.7)	24.1 (8.5,63.8) [‡]	1.8 (0.0,8.8) [‡]	0.7 (-1.7,5.2)
Blood loss ongoing at admission – no. (%)	Yes	46 (82)	28 (97) [§]	13 (68) [§]	5 (63)
	No	10 (18)	1 (3)	6 (32)	3 (38)
Bleeding intensity at admission [†] – no. (%)	Major	14 (25)	9 (31)	1 (5)	4 (50)
	Life-threatening	13 (23)	3 (10)	10 (53)	0 (0)
	Unknown	29 (52)	17 (59)	8 (42)	4 (50)

* Percentages may not total 100 because of rounding

† Based on American College of Surgeons Advanced Trauma Life Support (ATLS) classification of bleeding intensity

‡ Statistical difference: p=0.001; § Statistical difference: p=0.011

|| IQR: Interquartile range

Table S4. Length of stay of the retrospective study population and by bleeding location

Characteristic	Categories	Total	Gastrointestinal bleed	Intracranial hemorrhage	Other bleeding site
Total LOS – days	Mean ± SD	7.0 ± 7.4	5.9 ± 4.2	8.1 ± 11.2	8.4 ± 4.8
	Median (IQR)	5.0 (3.0,8.0)	4.5 (3.0,6.0)	4.0 (2.3,8.5)	7.3 (5.8,9.3)
ICU LOS – days	Mean ± SD	5.9 ± 8.4	3.5 ± 2.5	7.2 ± 11.2	7.8 ± 6.4
	Median (IQR)	3.5 (1.5,6.8)	2.0 (1.5,6.0)	3.5 (1.0,7.0)	5.0 (3.0,10.0)
Telemetry/stepdown LOS – days	Mean ± SD	4.4 ± 1.9	4.5 ± 2.2	3.5 ± 0.5	4.7 ± 1.5
	Median (IQR)	4.0 (3.0,5.1)	4.3 (3.3,5.4)	3.5 (3.3,3.8)	5.0 (4.0,5.5)

* LOS: Length of stay; ICU: Intensive care unit; SD: Standard deviation; IQR: Interquartile range