SUPPLEMENTAL MATERIAL

Definitions of Thrombotic Events

Arterial Systemic Embolism

Systemic arterial embolism is defined as abrupt vascular insufficiency associated with clinical and other objective evidence of arterial occlusion in the absence of other likely mechanisms. Clinical signs and symptoms must be consistent with embolic arterial occlusion, and there must be clear evidence of abrupt occlusion of a systemic artery, with at least one type of supporting evidence, such as surgical report indicating evidence of arterial embolism, pathological specimens related to embolism removal, imaging evidence consistent with arterial embolism, or autopsy report.

Myocardial Infarction

The term acute myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia.

Under these conditions any one of the following criteria meets the diagnosis for MI:

1. Detection of a rise and/or fall of cardiac biomarker values [preferably cardiac troponin (cTn)] with at least one value above the upper limit of normal (ULN) and with at least one of the following:
   - Symptoms of ischemia
   - New or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB)
   - Development of pathological Q waves in the electrocardiogram (ECG)
   - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
   - Identification of an intracoronary thrombus by angiography or autopsy.
2. Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased.
3. Percutaneous coronary intervention (PCI)–related MI is arbitrarily defined by elevation of cTn values (>5×ULN) in patients with normal baseline values or a rise of cTn values >20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischemia or (ii) new ischemic ECG changes or (iii) angiographic findings consistent with a procedural complication or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.
4. Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarker values with at least one value above the ULN.
5. Coronary artery bypass grafting (CABG)–related MI is arbitrarily defined by elevation of cardiac biomarker values (>10×ULN) in patients with normal baseline cTn values. In addition, either (i) new pathological Q waves or new LBBB or (ii) angiographic documented new graft or new native coronary artery occlusion or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Stroke

Stroke is an acute episode of neurological dysfunction consistent with a vascular cause. Stroke is defined as the rapid onset of signs and/or symptoms of a new persistent neurological deficit consistent with an obstruction to cerebral blood flow or with cerebral hemorrhage with no apparent nonvascular cause (eg, trauma, tumor, or infection). Signs or symptoms must last at least 24 hours or, if symptoms last less than 24 hours, have neuroimaging evidence of new infarct. Available neuroimaging studies will be considered, to support the clinical impression and to determine if there is a demonstrable lesion compatible with an acute stroke. Strokes will be classified as ischemic, hemorrhagic, or unknown. Ischemic stroke with hemorrhagic transformation will be primarily classified with ischemic stroke etiology. Although all strokes will be adjudicated, only strokes that are ischemic will be considered thrombotic events. Strokes that are primarily hemorrhagic are adverse outcomes but not thrombotic events.

For the diagnosis of stroke, the following 4 criteria should be fulfilled:

1. Rapid onset* of a focal/global neurological deficit with at least one of the following:
    a. Change in level of consciousness
    b. Hemiplegia
    c. Hemiparesis
    d. Numbness or sensory loss affecting one side of the body
    e. Dysphasia/Aphasia
    f. Hemianopia (loss of half of the field of vision of one or both eyes)
    g. Amaurosis fugax (transient complete/partial loss of vision of one eye)
    h. Other new neurological sign(s)/symptom(s) consistent with stroke

*If the mode of onset is uncertain, a diagnosis of stroke may be made provided that there is no plausible non-stroke cause for the clinical presentation

2. Duration of a focal/global neurological deficit ≥24 hours
   OR
   The neurological deficit results in death
   OR
   Neuroimaging evidence of new infarct
3. No other readily identifiable non-stroke cause for the clinical presentation (eg, brain tumor, trauma, infection, hypoglycemia, peripheral lesion)
4. Confirmation of the diagnosis by at least one of the following:
    a. Specialist evaluation (consult notes)
    b. Brain imaging procedure (at least one of the following)
        i. CT scan
        ii. MRI scan
        iii. Cerebral vessel angiography
    c. Lumbar puncture (ie, spinal fluid analysis diagnostic of intracranial hemorrhage)

If the acute focal signs represent a worsening of a previous deficit, these signs must have either:

1. Persisted for more than 1 week, or
2. Persisted for more than 24 hours and were accompanied by an appropriate new CT or MRI finding.

Strokes are subclassified as follows:

1. Ischemic (non-hemorrhagic): a stroke caused by an arterial obstruction due to either a thrombotic (eg, large vessel disease/atherosclerotic or small vessel disease/lacunar) or embolic etiology. This category includes ischemic stroke with hemorrhagic transformation.
2. Hemorrhagic: a stroke due to a hemorrhage in the brain as documented by neuroimaging or autopsy. This category will include strokes due to primary intracerebral hemorrhage (intraparenchymal or intraventricular), and primary subarachnoid hemorrhage.
3. Subdural hematoma will be classified as intracranial hemorrhage but will not be classified as either stroke or as intracerebral hemorrhage.
4. Unknown: the stroke type could not be determined by imaging or other means and no imaging was performed.

Transient Ischemic Attack (TIA)

A transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, with signs or symptoms lasting <24 hours and no evidence of new infarct on neuroimaging if performed.

Venous Thromboembolism

Venous thromboembolism is defined as symptomatic deep vein thrombosis or pulmonary embolism confirmed by objective testing.

Criteria for the objective confirmation of deep vein thrombosis include:

- A constant filling defect in two or more views on contrast venography in one or more proximal venous segments (iliac, common femoral, superficial femoral, popliteal)
- New or previously undocumented non-compressibility of one or more venous segments on compression ultrasound
- A clearly defined intraluminal filling defect on contrast-enhanced computed tomography

Criteria for the objective diagnosis of pulmonary embolism include:

- An intraluminal filling defect on pulmonary angiography
- Sudden contrast cutoff of one or more vessels more than 2.5 mm in diameter on a pulmonary angiogram
- A high probability VQ scan (one or more segmental perfusion defects with corresponding normal ventilation)
- An abnormal non-high VQ scan plus criteria for the diagnosis of DVT
- An unequivocal, intra-arterial, un-enhancing filling defect in the central pulmonary vasculature (pulmonary trunk, main pulmonary arteries, anterior trunk, right and left interlobar and lobar arteries) on CT

Table I. Hemostatic Efficacy Criteria

Excellent[*] (effective)	• Intracranial hemorrhage:
	  • Intracerebral hemorrhage: ≤20% increase in hematoma volume compared to baseline on a repeat CT or MRI scan performed at both the 1- and 12-hour post-infusion time points.
	  • Subarachnoid bleeding: ≤20% increase in maximum thickness using the most dense area on the follow-up versus baseline at both the 1- and 12-hour post-infusion time points.
	  • Subdural hematoma: ≤20% increase in maximum thickness at both the 1- and 12-hour post-infusion assessments compared to baseline.

Good[†] (effective)	• Intracerebral hematoma: >20% but ≤35% increase in hematoma volume compared to baseline on a repeat CT or MRI scan at +12-hour time point. • Subarachnoid bleeding: >20% but <35% increase in maximum thickness using the most dense area on the follow-up at +12 hours versus baseline. • Subdural hematoma: >20% but <35% increase in maximum thickness at +12 hours compared to baseline.
Poor/None[‡] (not effective)	• Intracerebral hematoma: >35% increase in hematoma volume on a CT or MRI compared to baseline on a repeat CT or MRI scan at +12-hour time point. • Subarachnoid bleeding: >35% increase in maximum thickness using the most dense area on the +12 hours versus at baseline. • Subdural hematoma: >35% increase in maximum thickness at +12 hours compared to baseline.

CT indicates computed tomography and MRI, magnetic resonance imaging.

*No additional plasma, blood products (whole blood products not including packed red blood cells [PRBCs]) and/or coagulation factor products required after initial treatment with andexanet.

†No more than two additional units of plasma or blood products and/or coagulation factor products required after initial treatment with andexanet. “Blood products” include whole blood but not PRBCs.

‡More than two additional units of plasma or blood products and/or coagulation factor products required after initial treatment with andexanet. “Blood products” include whole blood but not PRBCs.

Supplementary Table II: Baseline and Demographic Characteristics of Safety Population

Patients with Spontaneous & Traumatic Intracranial Hemorrhages

	Safety Population		
	Overall (N=227)	**Spontaneous ICrH (N=128)**	**Traumatic ICrH (N=99)**
Age (years), mean ± SD	79.3±8.8	78.0±9.2	80.9±7.9
Male, n (%)	117 (51.5%)	70 (54.7%)	47 (47.5%)
Indication of FXa Inhibition*			
Atrial fibrillation	193 (85.0%)	106 (82.8%)	87 (87.9%)
Venous thromboembolic disease	29 (12.8%)	18 (14.1%)	11 (11.1%)
Other	9 (4.0%)	5 (3.9%)	4 (4%)
FXa inhibitor therapy, n (%)			
Rivaroxaban	69 (30.4%)	47 (36.7%)	22 (22.2%)
Apixaban	140 (61.7%)	68 (53.1%)	72 (72.7%)
Edoxaban	7 (3.1%)	6 (4.7%)	1 (1%)
Enoxaparin	11 (4.8%)	7 (5.5%)	4 (4%)
Time from onset of symptoms to baseline scan (hours), median (IQR)	3.3 (1.4, 6.8)	2.6 (1.0, 3.9)	4.1 (1.6, 7.1)
Time from baseline scan to andexanet alfa treatment (hours), median (IQR)	2.0 (1.3, 3.3)	1.8 (1.2, 2.7)	2.4 (1.5, 3.7)
Glasgow Coma Scale score			
N	220	122	98
Median (IQR)	15.0 (14.0, 15.0)	14.0 (13.0, 15.0)	15.0 (14.0, 15.0)
NIHSS			
N	95	53	42
Median (IQR)	3.0 (1.0, 9.0)	6.0 (2.0, 12.0)	1.0 (0.0, 4.0)
Modified Rankin Score			
N	225	127	98
Median (IQR)	3.0 (1.0, 4.0)	4.0 (2.0, 4.0)	3.0 (1.0, 4.0)

FXa: factor Xa; ICrH: intracranial hemorrhage; IQR: interquartile range; NIHSS: National Institutes of Health Stroke Scale; SD: standard deviation. *Patients may have multiple Indication of FXa Inhibition †NIHSS implemented midway through study.

Supplemental Table III: Characteristics stratified by mortality status in follow-up (to 30 days)

	Safety Population	
Variable	**Alive (N=193)**	**Died (N=34)**
Age (years), mean±SD	78.7±8.6	82.6±9.0
Thrombotic event, n (%)	15 (7.8%)	6 (17.6%)
Bleeding type, n (%)	193	34
Spontaneous ICrH	104 (53.9%)	24 (70.6%)
Traumatic ICrH	89 (46.1%)	10 (29.4%)
Volume of Hemorrhage for Traumatic ICrH at 12 hour		
ICH and/or IVH: Volume (n)	12	2
Volume (mL): mean±SD	13.1±24.7	6.3±8.8
Multiple: Volume (n)	17	6
Volume (mL): mean±SD	26.4±23.4	76.5±41.8
Volume of Hemorrhage for Spontaneous ICrH at 12 hour		
ICH and/or IVH: Volume (n)	78	15
Volume (mL): mean±SD	16.3±17.7	24.1±22.1
ICH and SAH only: Volume (n)	0	2
Volume (mL): mean±SD	N/A	28.9±31.5
ICH and SDH only: Volume (n)	3	1
Volume (mL): mean±SD	33.1±43.3	43.0*

Percentage based on number of subjects in the corresponding category. *SD not applicable as n=1. ICrH, intracranial hemorrhage; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; SAH, subarachnoid hemorrhage; SD, standard deviation; and SDH, subdural hemorrhage

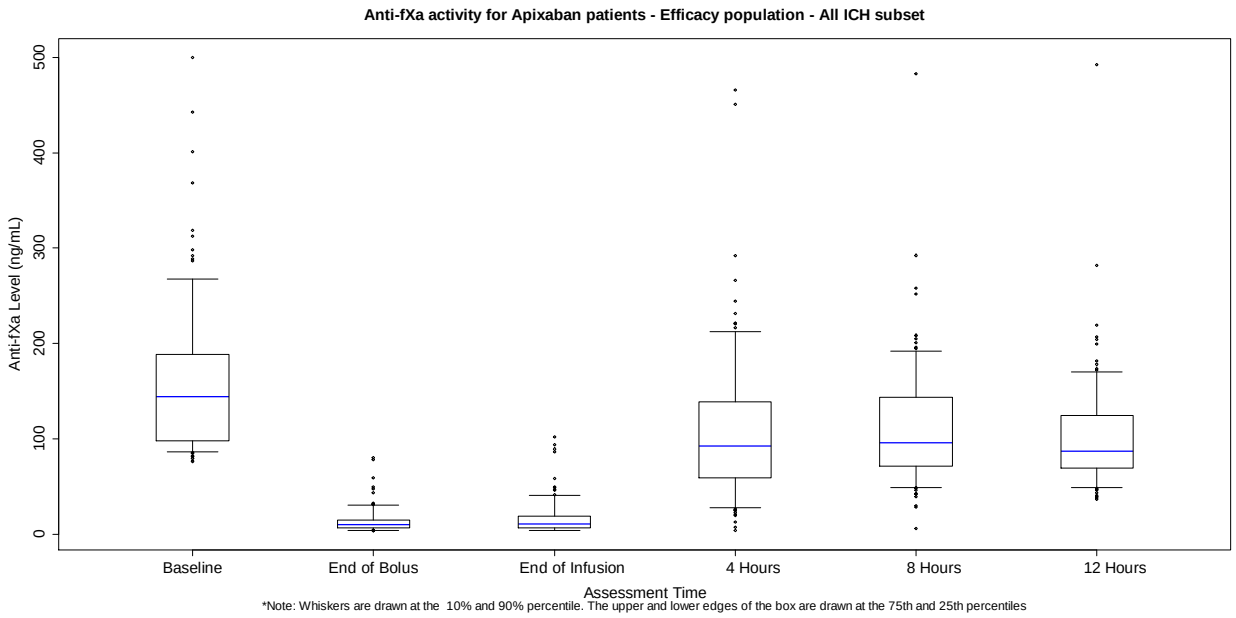


Figure IA. Anti-fXa activity over time for patients with either spontaneous and traumatic intracranial hemorrhage who had received apixaban. The horizontal lines represent the median values; upper and lower edges of the boxes represent the 75th and 25th percentiles; upper and lower whiskers represent the 90th and 10th percentiles. FXa indicates factor Xa. Median baseline anti-fXa activity levels were 144.2 ng/mL at baseline and 9.6 ng/mL at the lowest value post-andexanet treatment. The median percentage decrease from baseline to nadir was -93.8% (95% CI: -94.6% to -92.6%).

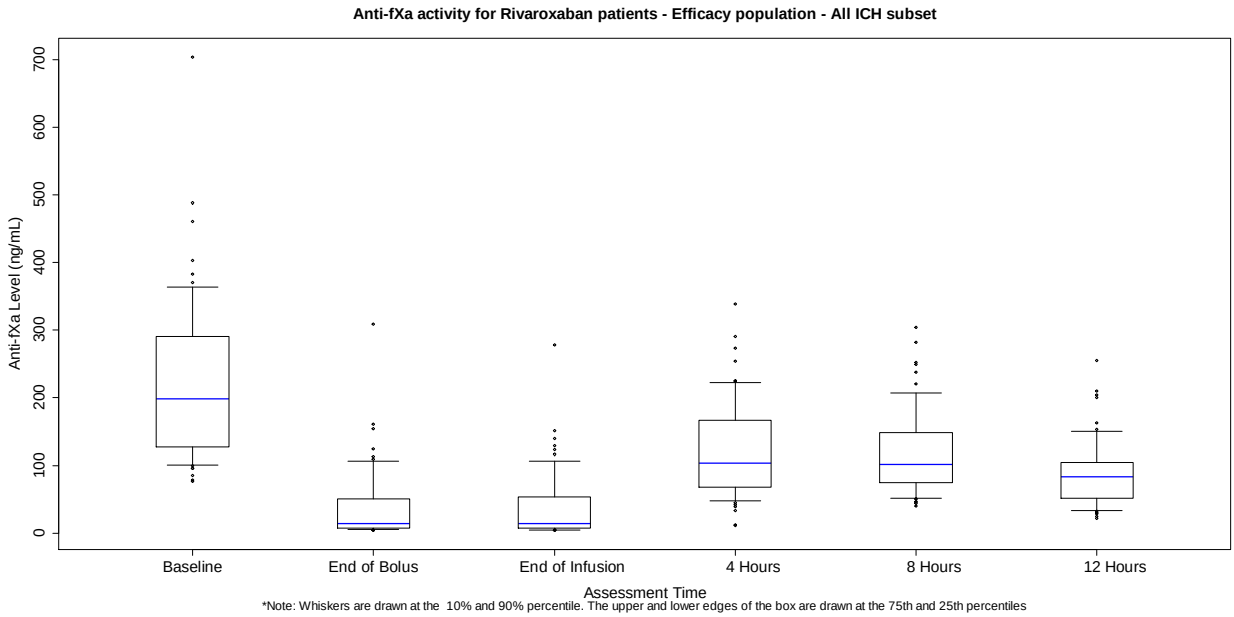
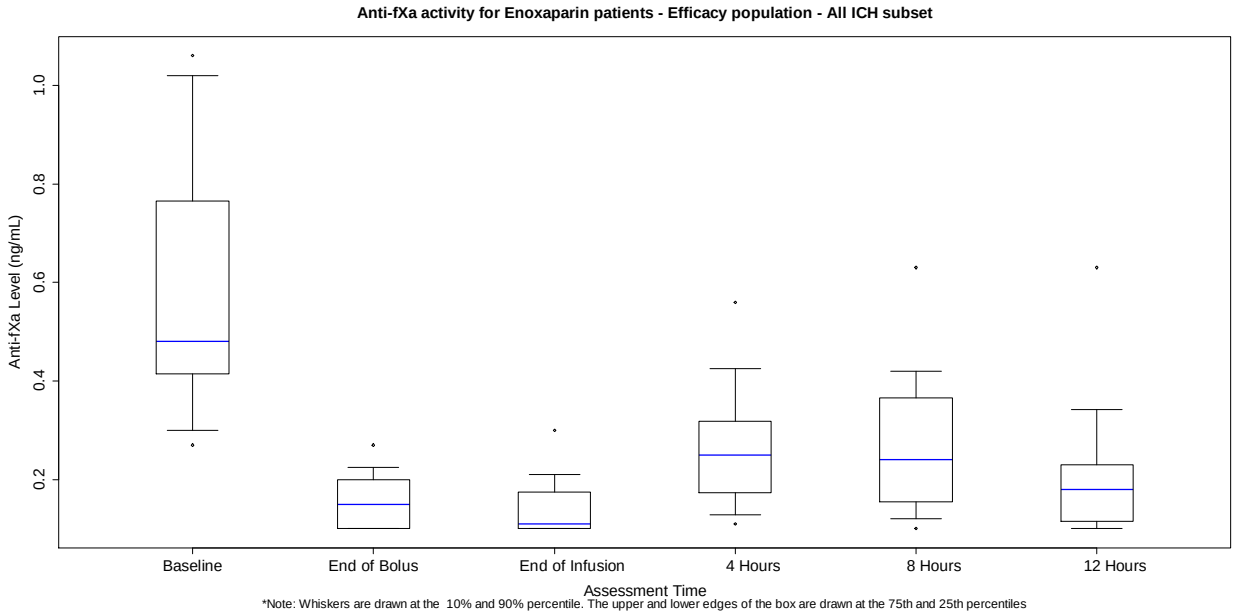


Figure IB. Anti-fXa activity over time for patients with spontaneous and traumatic intracranial hemorrhage who had received rivaroxaban. The horizontal lines represent the median value; upper and lower edges of the box represent the 75th and 25th percentiles; upper and lower whiskers represent the 90th and 10th percentiles. FXa indicates factor Xa. Median baseline anti-fXa activity levels were 198.1 ng/mL at baseline and 10.8 ng/mL at the lowest value post-andexanet treatment. The median percentage decrease from baseline to nadir was -92.6% (95% CI: -95.1% to -90.0%).


Anti-fXa activity for Enoxaparin patients - Efficacy population - All ICH subset
Anti-fXa Level (ng/mL)
0.2
0.4
0.6
0.8
1.0
Baseline
End of Bolus
End of Infusion
4 Hours
8 Hours
12 Hours
Assessment Time
*Note: Whiskers are drawn at the 10% and 90% percentile. The upper and lower edges of the box are drawn at the 75th and 25th percentiles

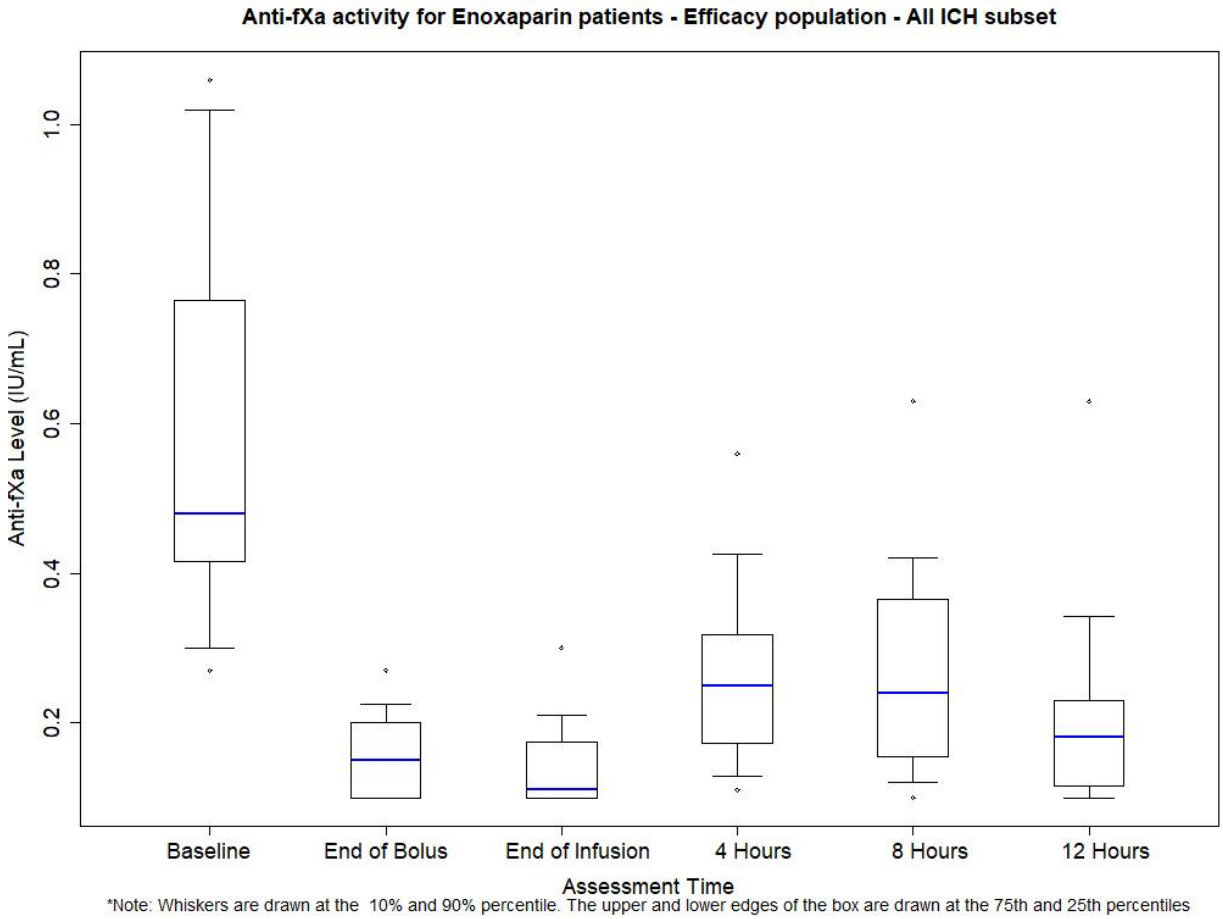

Anti-fXa activity for Enoxaparin patients - Efficacy population - All ICH subset
Anti-fXa Level (IU/mL)
0.2
0.4
0.6
0.8
1.0
Baseline
End of Bolus
End of Infusion
4 Hours
8 Hours
12 Hours
Assessment Time
*Note: Whiskers are drawn at the 10% and 90% percentile. The upper and lower edges of the box are drawn at the 75th and 25th percentiles

Figure IC. Anti-fXa activity over time for patients with spontaneous and traumatic intracranial hemorrhage who had received enoxaparin. The horizontal lines represent the median value; upper and lower edges of the box represent the 75th and 25th percentiles; upper and lower whiskers represent the 90th and 10th percentiles. FXa indicates factor Xa. Median baseline anti-fXa activity levels were 0.5 IU/mL at baseline and 0.1 IU/mL at the lowest value post-andexanet treatment. The median percentage decrease from baseline to nadir was -75.4% (95% CI: -79.4% to -66.7%).

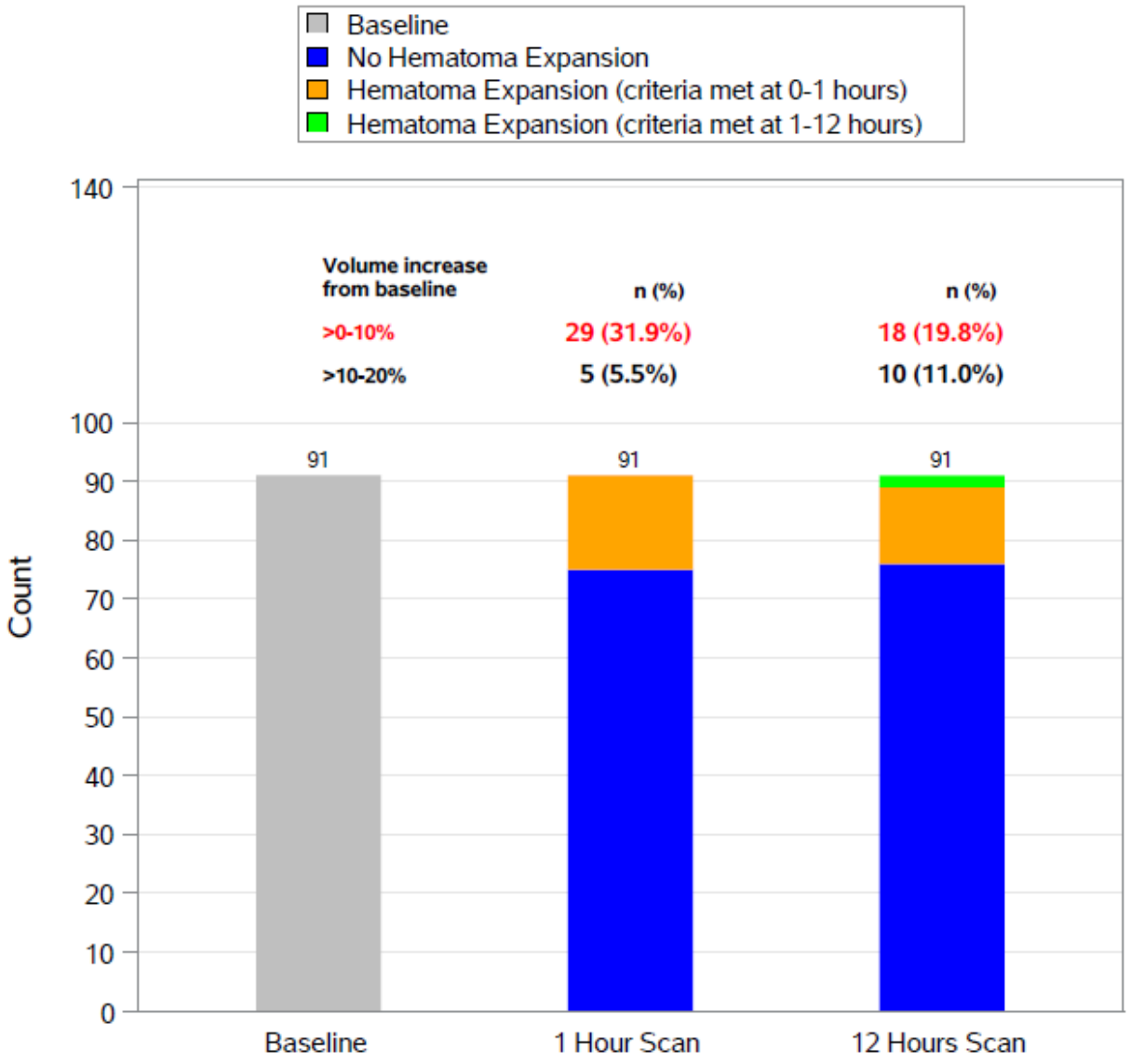
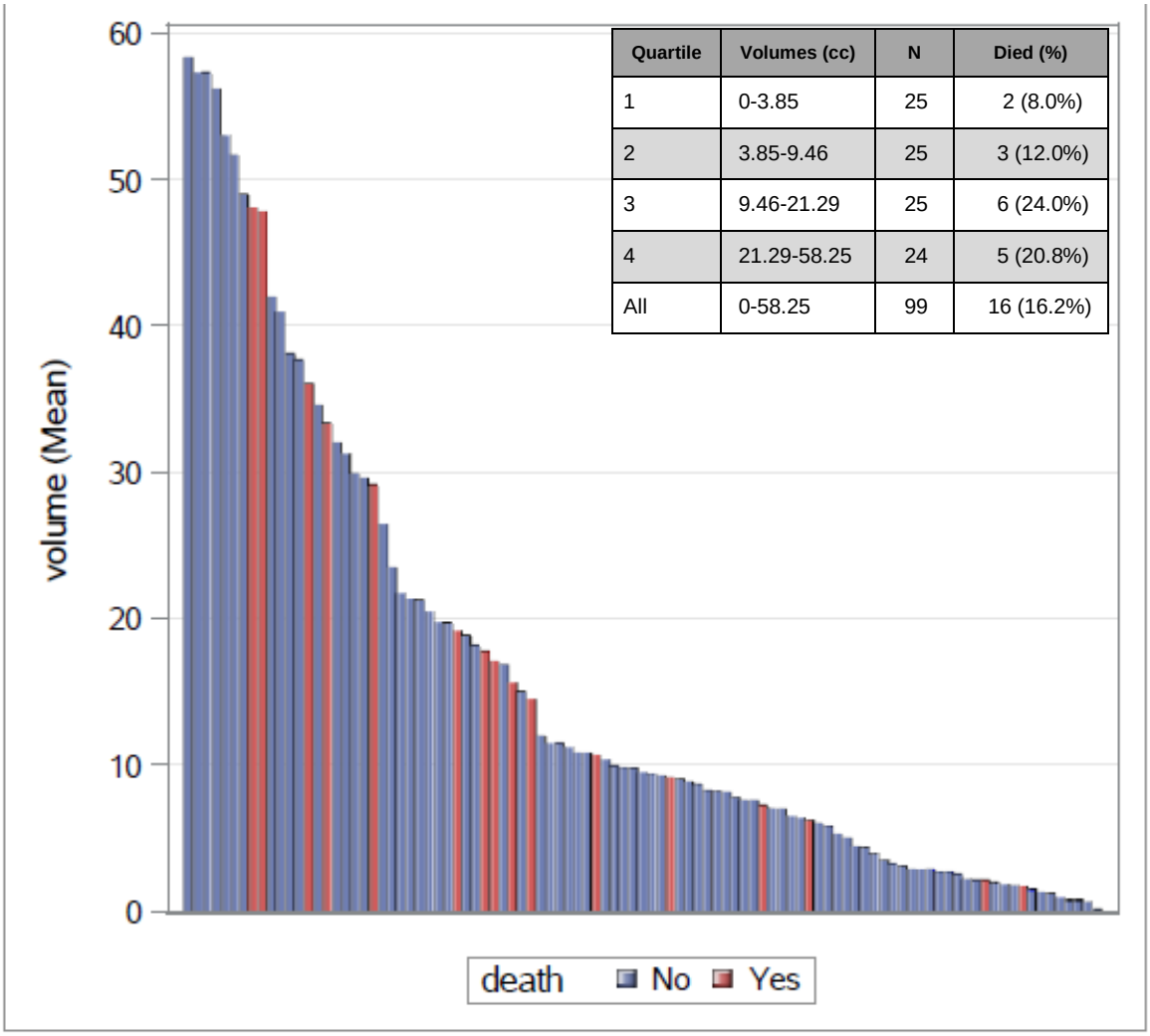


Figure II. Hematoma expansion in spontaneous intracerebral/intraventricular bleeds (safety population).

Hematoma expansion defined as greater than 35% increase in hematoma volume relative to baseline at the specific time indicated in the figure. The plot only includes subjects with no missing values at baseline, 1 hour, and 12 hours scan. Eight patients were excluded due to missing data.



Quartile	Volumes (cc)	N	Died (%)
1	0-3.85	25	2 (8.0%)
2	3.85-9.46	25	3 (12.0%)
3	9.46-21.29	25	6 (24.0%)
4	21.29-58.25	24	5 (20.8%)
All	0-58.25	99	16 (16.2%)

Figure III. Patients with spontaneous intracerebral/intraventricular bleeding, ordered by baseline hematoma volume. Patients surviving 30 days are indicated by the blue bars; patients dying within 30 days are indicated by the red bars. *P* for effect of baseline hematoma volume on death = 0.293 (logistic regression, univariate analysis).