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Andexanet in Life-Threatening or Uncontrolled Bleeding in Patients Receiving a Direct Oral Factor Xa Inhibitor

November 21, 2024

Cellular, Tissue and Gene Therapies Advisory Committee
AstraZeneca BioPharmaceuticals

Introduction

Jeffy John, MBA

Director, Regulatory Affairs
AstraZeneca BioPharmaceuticals

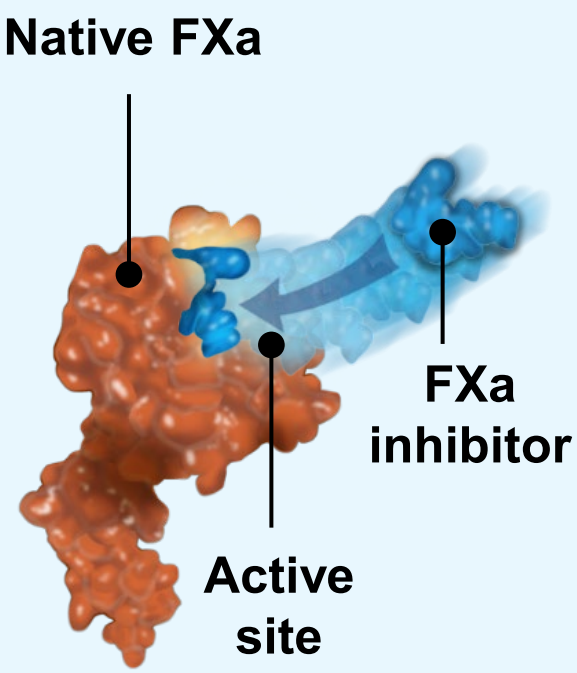
FXa Inhibitors Are Standard of Care for Anticoagulation in Many Clinical Situations, and Use Continues to Rise[1-3]

- FXa inhibitor specific reversal agents are needed to restore physiologic coagulation during major, life-threatening bleeds[4,5]
- Andexanet (ANDEXXA®) received accelerated approval in 2018
  - High unmet medical need
  - Evidence demonstrating potent reversal of FXa inhibition
- No other approved FXa inhibitor specific reversal therapies exist

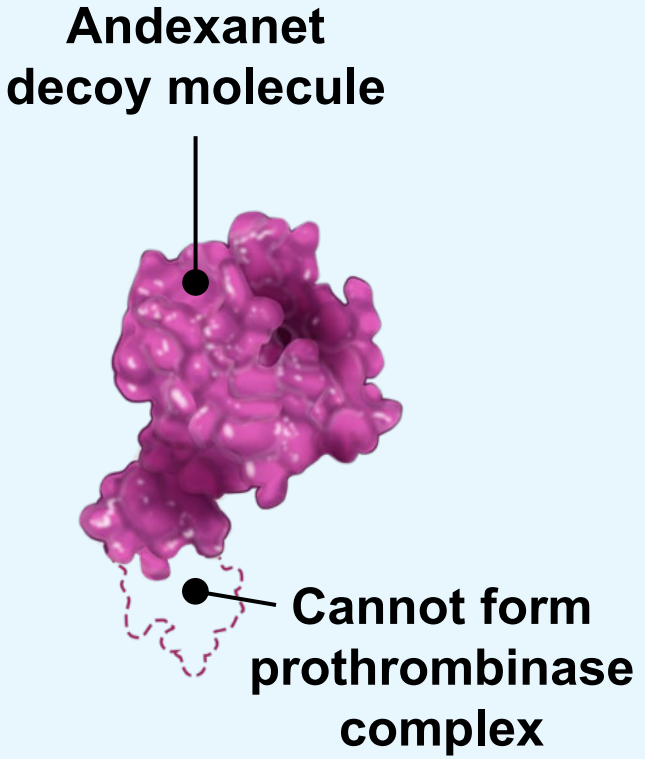
Andexanet is important component in bundle of care used to manage FXa inhibitor related uncontrolled, life-threatening bleeds

1. Troy, 2021; 2. Iyer, 2023; 3. Ansell, 2016; 4. Milling, 2017; 5. Kaatz, 2017

Andexanet Is a Modified Recombinant FXa Protein that Sequesters FXa Inhibitors



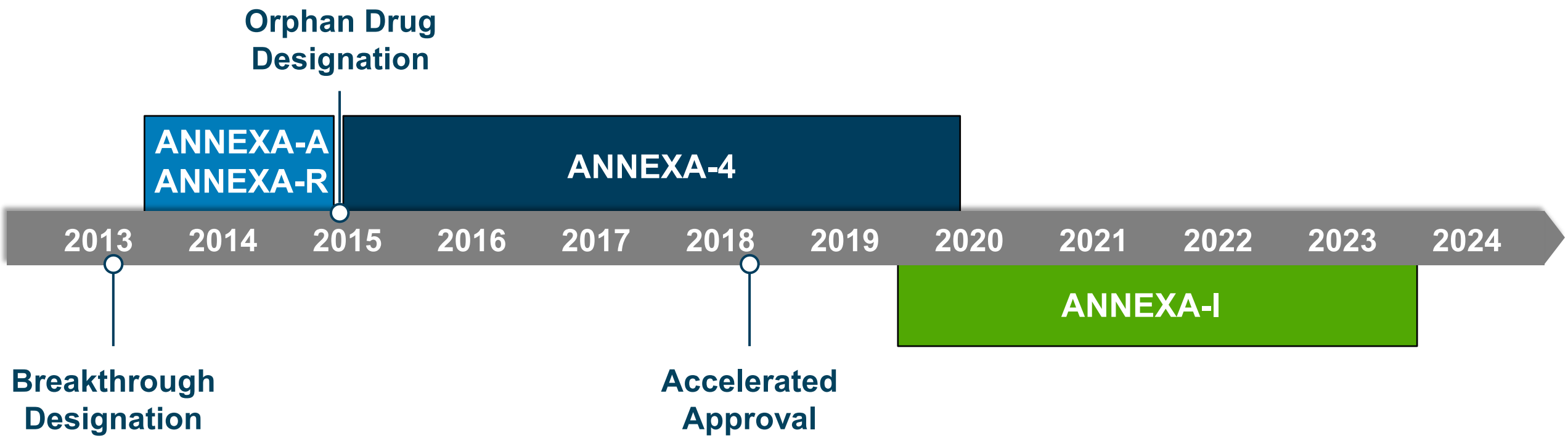
- FXa inhibitors target active site of FXa, blocking enzymatic activity and preventing thrombin generation



- Andexanet acts as a decoy and binds directly to FXa inhibitors

- Rapidly reduces free-plasma concentration
- Neutralizes anticoagulant effect

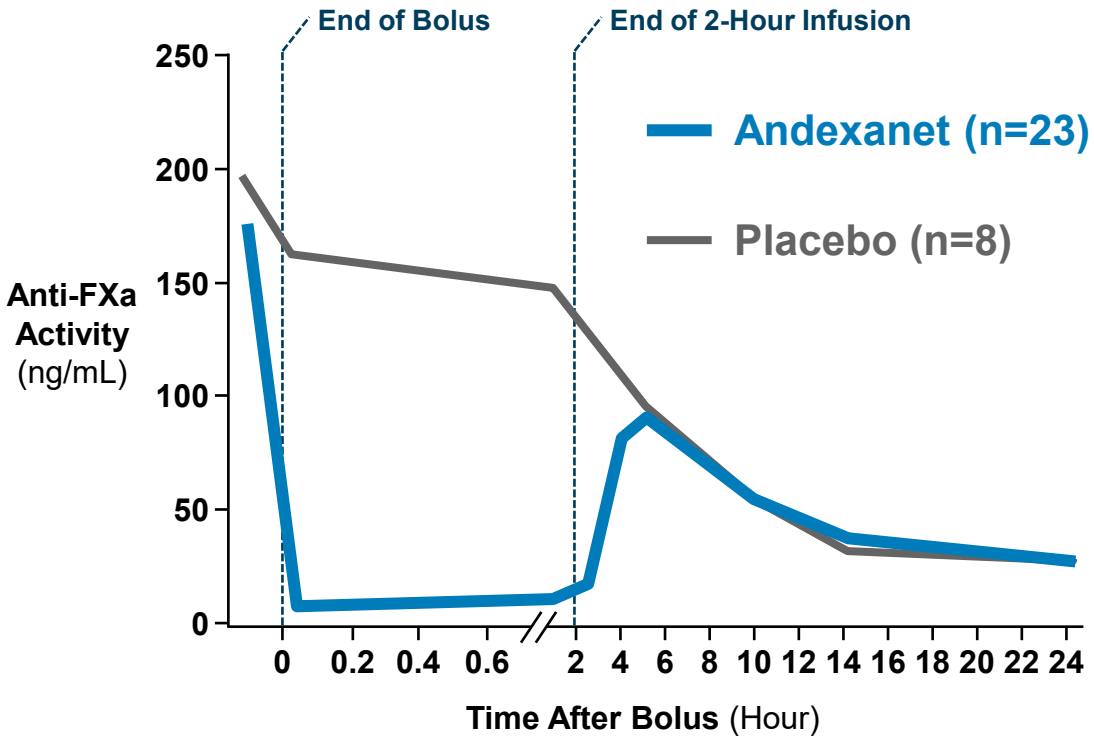
Clinical Development Program Includes 4 Studies Supporting the Benefit-Risk of Andexanet



PMR = Post-Marketing Requirement

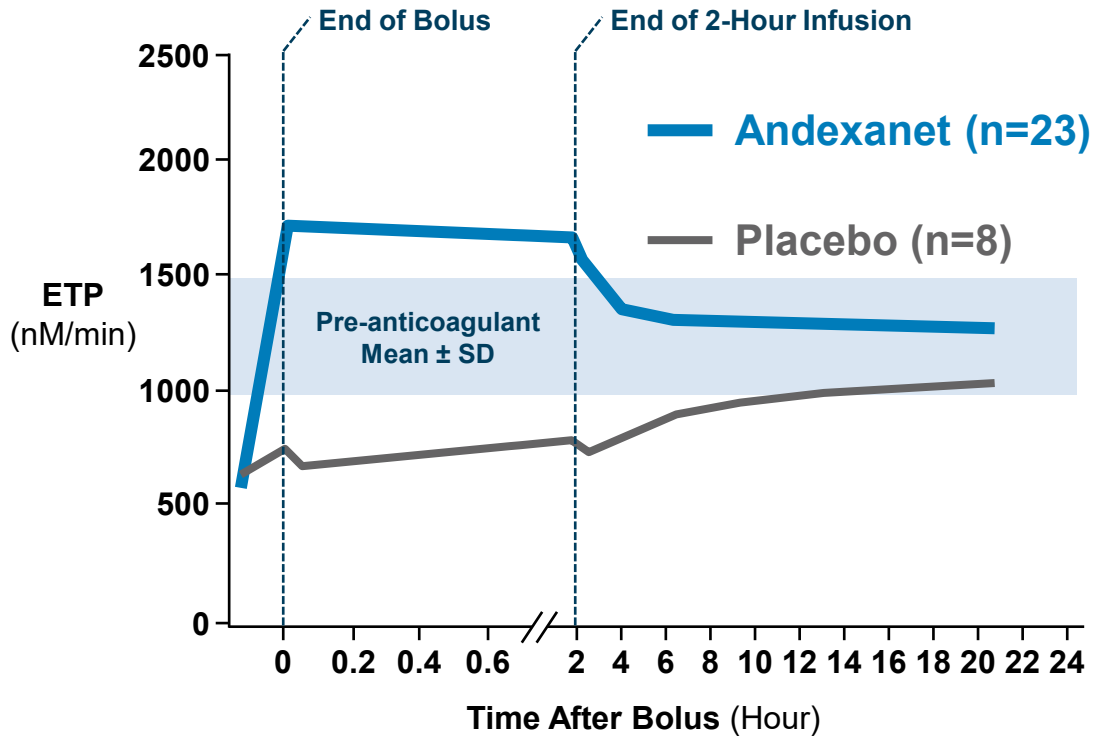
ANNEXA-A: Andexanet Reduced Anti-FXa Activity and Restored Thrombin Generation within 2 Minutes in Healthy Participants

Anti-FXa Activity



92% **Reduction in anti-FXa activity** from baseline to nadir ($p < 0.0001$)

Thrombin Generation



Rapid restoration of thrombin generation

ETP = Endogenous thrombin potential; ANNEXA-A = Apixaban-Treated Participants

ANNEXA-4 Clearly Demonstrated that Andexanet is an Effective Reversal Agent for FXa Inhibitors

ANNEXA-A & ANNEXA-R

- Two prospective, randomized, placebo-controlled Phase III studies of Andexanet
- Older, healthy volunteers

Evidence supporting accelerated approval

Demonstrated rapid reversal of FXa inhibitor activity

ANNEXA-4

- Multinational, prospective, single-arm, open-label Phase IIIb/IV study
- Patients presenting with acute major bleeding, including all bleeding locations, within 18 hours of taking an FXa inhibitor

Evidence supporting accelerated approval

Demonstrated hemostatic benefit in indicated population

ANNEXA-I Initiated as PMR and Confirmed Hemostatic Benefit of Andexanet with Consistent Safety Profile

ANNEXA-A & ANNEXA-R

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- Older, healthy volunteers

Evidence supporting accelerated approval

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ANNEXA-4

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Evidence supporting accelerated approval

Demonstrated hemostatic benefit in indicated population

ANNEXA-I

- Randomized, open-label Phase IV study comparing Andexanet with usual care
- Patients presenting with acute intracerebral hemorrhage (ICH) within 15 hours of taking an FXa inhibitor

Post-marketing requirement trial to confirm superiority to usual care on effective hemostasis

Confirmed hemostatic benefit with acceptable and consistent safety profile

PMR Issued by FDA in 2018 Included Several Key Factors Which Were Reflected in ANNEXA-I Design

Post-Marketing Requirement for ANNEXA-I

- Include ≥ 440 adult patients
- Verify hemostatic effect in acute ICH
- Include assessments of NIHSS and CT / MRI at 12-hours post-randomization
- 30-day safety follow-up
- Hemostatic efficacy determined by blinded adjudication committee

NIHSS = National Institutes of Health Stroke Scale

ANNEXA-I Designed to Fulfill Regulatory Requirements Globally

	ANNEXA-I
FXa Inhibitors	**Apixaban** **Rivaroxaban** **Edoxaban**

- Enrollment aligned with approvals of Andexanet worldwide
- Sensitivity analyses of patients receiving Apixaban or Rivaroxaban supplement primary ITT results
  - Sensitivity analyses demonstrate consistent evidence of efficacy and safety

Timeline for Agency Feedback on Including Long-Term Neurological Functional Assessments in ANNEXA-I

- **June 2019:** First patient enrolled in ANNEXA-I
- **April 2020:** Sponsor prepared a protocol amendment with the addition of change in NIHSS and GCS through 24 hours as secondary endpoints
- **August 2020 & October 2020:** FDA feedback on amendment received
  - NIHSS and GCS through 24 hours do not translate to long-term outcomes
  - GOS and mRS at 90 Days represent valid functional outcome assessments
- **November 2020**: Sponsor responded to FDA feedback
  - Follow up timeline in ANNEXA-I remained through 30 days
  - GCS and NIHSS at 24H will be added as exploratory endpoints
  - Longer term follow up outside of scope for ANNEXA-I; goal is to confirm hemostatic efficacy

GCS = Glasgow Coma Scale; GOS = Glasgow Outcome Score; mRS = modified Rankin Scale

ANNEXA-I Demonstrates Positive Benefit-Risk Profile and Supports Conversion to Full Approval

Unmet Need

- Patients receiving FXa inhibitors who experience life-threatening bleeding event need reversal agents to restore physiologic coagulation and improve outcomes

Efficacy

- Andexanet provides statistically significant and clinically meaningful improvements hemostatic efficacy compared to usual care
- Andexanet rapidly reverses anticoagulation of FXa inhibitors

Safety

- Higher rate of thrombotic events compared to usual care in ANNEXA-I
- No new safety signals or adverse drug reactions were identified
- Acceptable and consistent safety profile in setting of life-threatening bleed

Proposed Indication Consistent with Accelerated Approval Indication

ANDEXXA® is indicated for patients treated with rivaroxaban or apixaban, when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding

Agenda

Unmet Need	**Paul A. Nyquist, MD, MPH** Professor of Neurology Co-Director, Johns Hopkins Bayview Neurocritical Care Unit Johns Hopkins School of Medicine
Andexanet Efficacy	**Per Ladenvall, MD, PhD** Global Clinical Head AstraZeneca BioPharmaceuticals
Andexanet Safety	**Rohit Narayan, MBCHB** Patient Safety Physician AstraZeneca BioPharmaceuticals
Clinical Perspective	**Ashkan Shoamanesh, MD, FRCPC** Marta and Owen Boris Chair in Stroke Research / Care Associate Professor, Medicine Department of Neurology McMaster University
Moderator for Q&A	**Matthew Roe, MD, MHS** Cardiologist, Adjunct Professor of Medicine Duke University Medical Center Vice President, Head of Early CVRM Clinical Development AstraZeneca BioPharmaceuticals

Additional Experts

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Anna Sundgren, PhD, MBA
Global Product Leader
AstraZeneca BioPharmaceuticals

Burden of Life-Threatening Bleeds Related to FXa Inhibitors and Need for Effective Reversal Agents

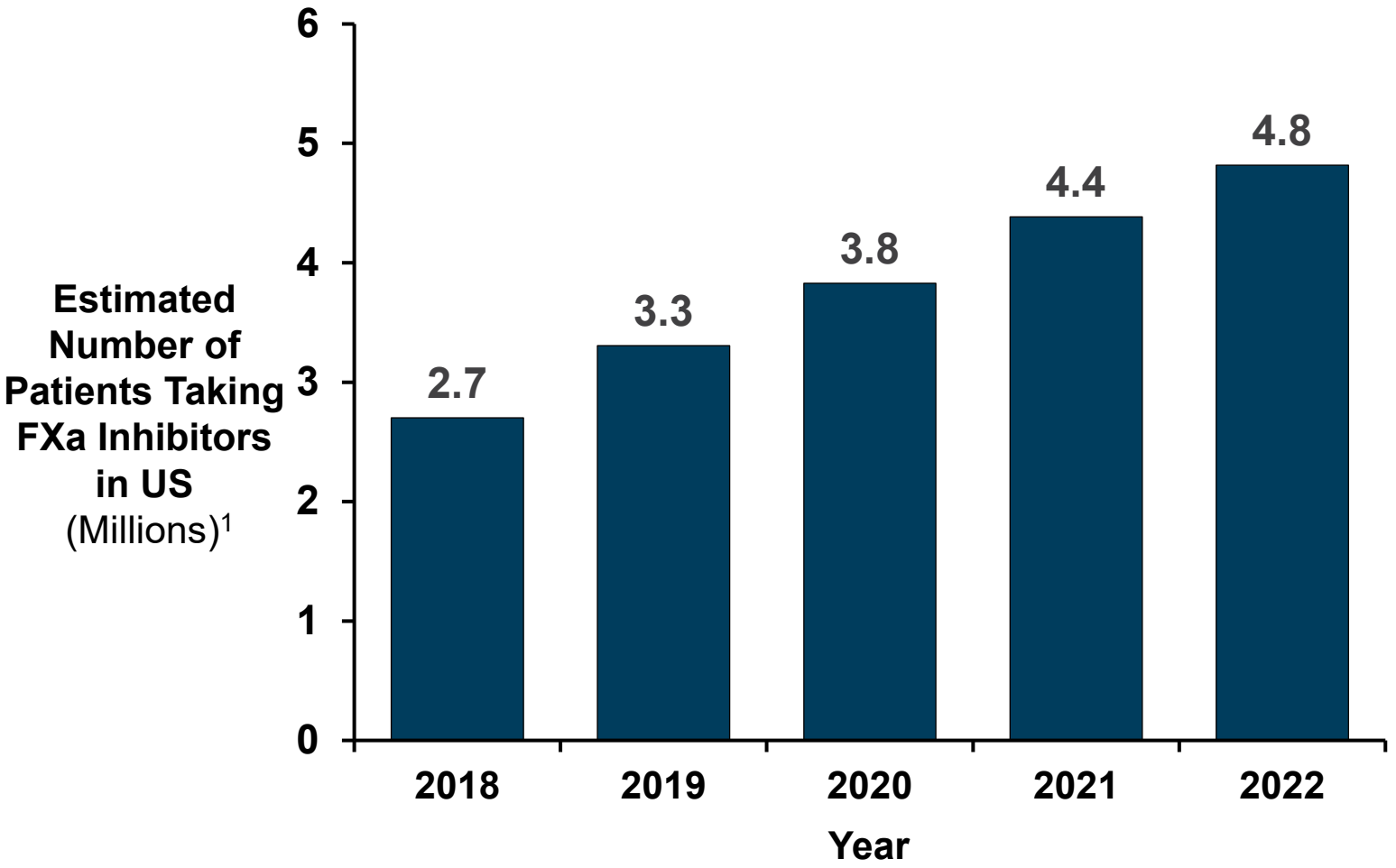
Paul A. Nyquist, MD, MPH

Professor of Neurology

Co-Director, Johns Hopkins Bayview Neurocritical Care Unit

Johns Hopkins School of Medicine

Use of FXa Inhibitors Increasing as They Become New Standard of Care for Anticoagulation



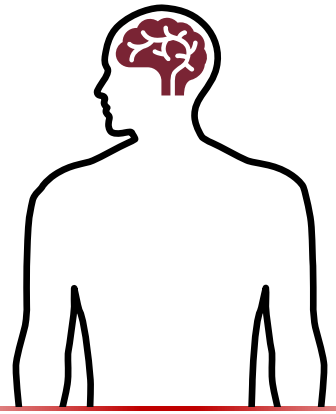
Guidelines recommend FXa inhibitors in patients with venous thromboembolism and patients with atrial fibrillation[2–5]

- American Heart Association
- American College of Cardiology
- National Institute for Health and Care Excellence
- Heart Rhythm Society
- European Heart Rhythm Association

3–5% of patients on FXa inhibitors require hospitalization due to life-threatening bleeding[2-4]

1. https://data.cms.gov/summary-statistics-on-use-and-payments/medicare-medicaid-spending-by-drug/medicare-part-d-spending-by-drug/data
2. January, 2019; 3. Joglar, 2023; 4. National Institute for Health and Care Excellence: NG196/NG158, 2024; 5. Steffel, 2021

FXa Inhibitor-Associated Major Bleeds Leading to Hospitalization Can Occur at Various Body Sites

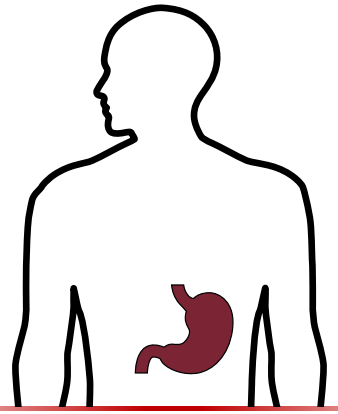


Intracranial Hemorrhage

- Intracerebral
- Subdural
- Subarachnoid

17%

Intracerebral

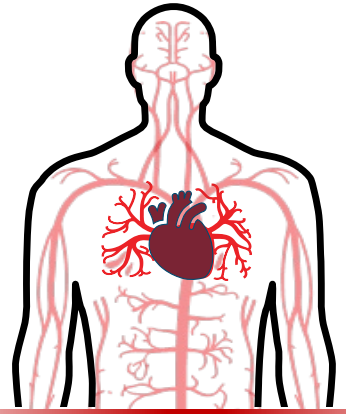


Major bleeding with hemodynamic instability

- Gastrointestinal
- Retroperitoneal
- Genitourinary tract

48%

Gastrointestinal

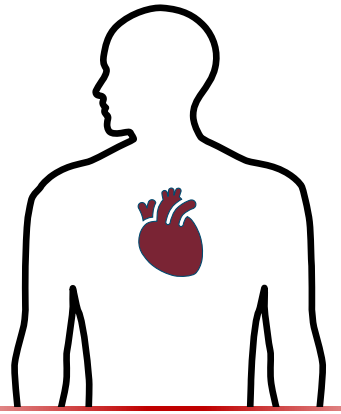


Major Trauma

- Blunt injury
- Penetrating injury

26%

Trauma Related



Bleeding at a Critical Site

- Intraocular
- Pericardial
- Intraspinal

Coleman, 2021 (US-based multicentre, retrospective, electronic medical record survey conducted between 2016 and 2019. N=45 hospitals and N=3030 hospitalizations)

In Emergency Setting, Primary Goal is to Stop Bleeding Event and Minimize Hematoma Expansion

Goal

Stop bleeding to reduce brain injury and death[1]

- **Door:** Stabilize patient, rapid imaging, coagulation tests
- **< 30 min:** Reverse anticoagulant, start intensive BP lowering
- **< 60 min:** SBP < 140 mmHg, consult neurosurgery, achieve temp < 37.5°C
- **7 days:** Maintain SBP < 140 mmHg, temp < 37.5°C, maintain normoglycemia

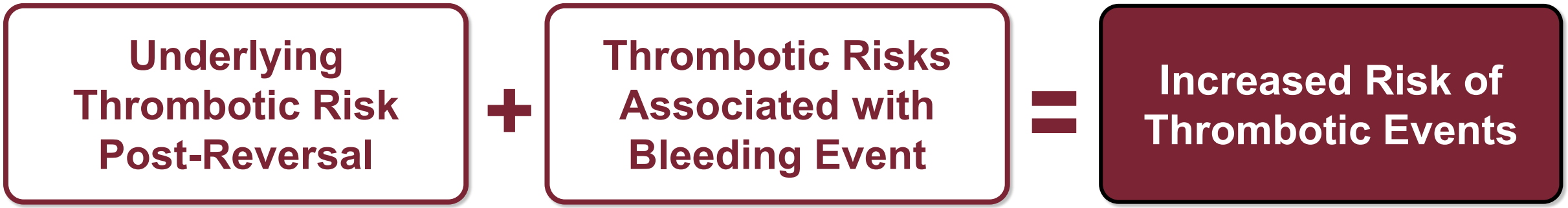
Bundle of Care

Multiple simultaneous, specific and fast-acting interventions required to stabilize patient and control the bleeding

- Blood pressure management
- Surgical procedures
- Targeted anticoagulant reversal agents

1. Parry-Jones, 2023

For Patients on Anticoagulant Therapies Thrombotic Events are a Known Risk Associated with Effective Reversal



TEs are Manageable in Acute Setting

- Emergency and critical care teams ensure appropriate measures in place to effectively manage in ICU

Minimizing TE Risk is Key Aspect of Early Secondary Prevention

- Early VTE prophylaxis per AHA guidelines[1] (24-48 hours from index event)
- Restart anticoagulant therapy as early as possible based on individualized risk benefit assessment

1. Greenberg, 2022

Reducing Hematoma Expansion is Critical Goal for Patients Experiencing a Life-Threatening Intracerebral Hemorrhage

Hematoma expansion predicts **Poor Clinical Outcomes**

Early Neurologic Deterioration[1]

OR (95% CI): 3.00 (2.05, 4.41), $p < 0.001$

Worsening Functional Outcomes[2]

Cumulative OR (95% CI): 0.84 (0.75, 0.92), $p < 0.001$

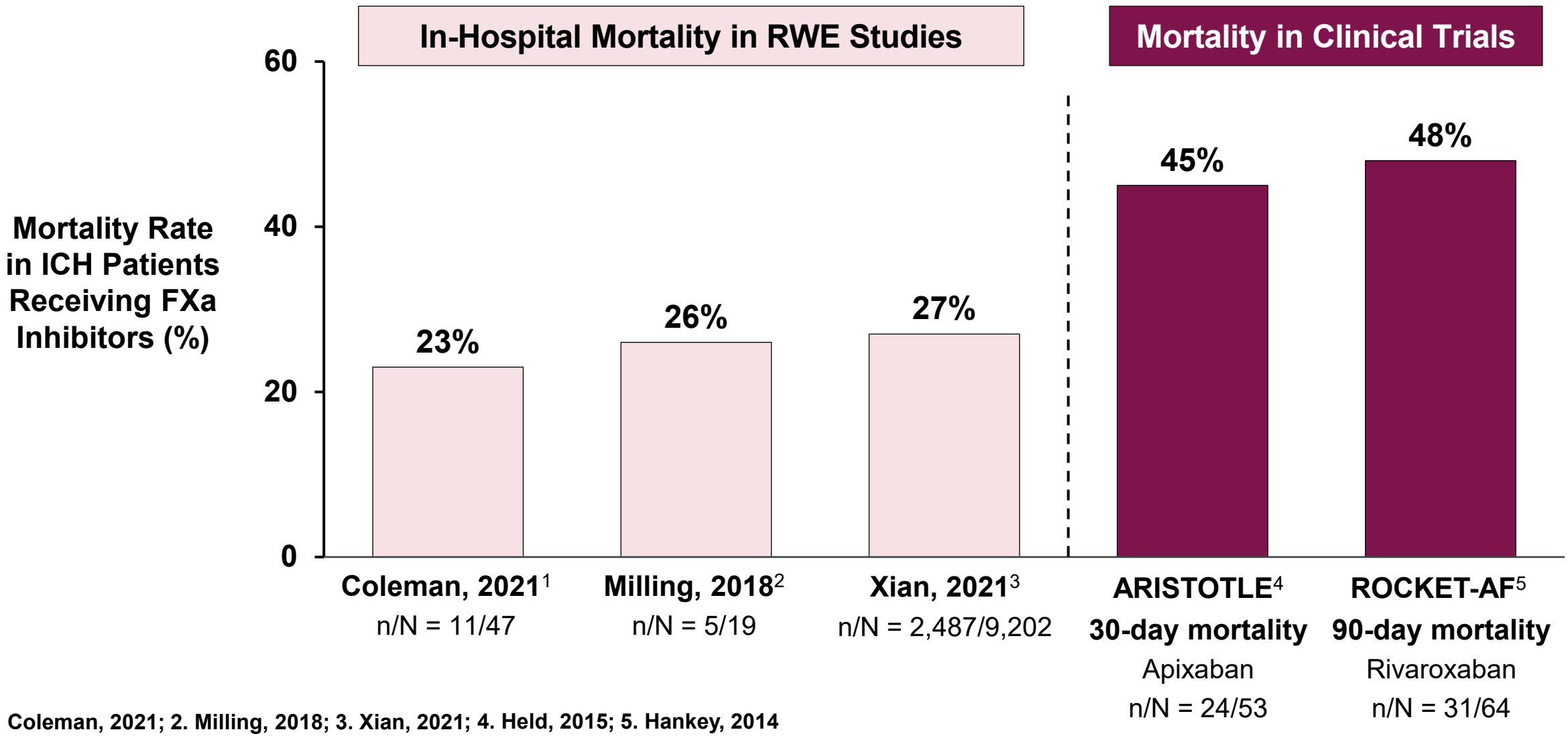
Increased Hazard of Death[2]

HR (95% CI): 1.05 (1.03, 1.08), $p < 0.001$

For every **1 mL** increase in hematoma volume,
there is a **5%** higher risk of death or dependency at 90 days[3]

1.Kuohn, 2022; 2.Davis, 2006; 3. Delcourt, 2012

Multiple Studies have Characterized Mortality Risk Associated with ICH in Patients Receiving FXa Inhibitors



1. Coleman, 2021; 2. Milling, 2018; 3. Xian, 2021; 4. Held, 2015; 5. Hankey, 2014

Andexanet is the Only Approved FXa-Inhibitor Specific Reversal Agent for Patients Taking Apixaban or Rivaroxaban[1]

Anticoagulant	Class	Intervention	Mechanism of action	Primary Endpoint
Apixaban Rivaroxaban	FXa inhibitor	Andexanet[1]	Reverses FXa inhibition	Anti-FXa Activity and Hemostatic Efficacy[2]
Warfarin	Vitamin K antagonist	4F-PCC[3,4]	Replaces factors II, VII, IX, and X	INR, Hemostatic Efficacy[5]
Dabigatran	Direct thrombin inhibitor	Idarucizumab[6]	Restores thrombin generation	ECT/dTT Normalization[7]

INR = international normalized ratio; ECT = ecarin clotting time; dTT = diluted thrombin time

1. ANDEXXA (andexanet alfa) USPI; 2. Milling, 2023; 3. KCENTRA (4F-PCC) USPI; 4. BALFAXAR (4F-PCC) USPI; 5. Ansell, 2008; 6. PRAXBIND (Idarucizumab) USPI; 7. Pollack, 2017

Multiple Guidelines Support Use of a Specific Reversal Agent for FXa Inhibitor-Related Major Bleeding Episodes

American Heart Association

American Stroke Association

Andexanet alfa is reasonable to reverse anticoagulant effect of FXa inhibitors in patients with direct FXa inhibitor-associated ICH (Class 2a recommendation)[1]

American College of Cardiology

Administer **andexanet alfa** first line for reversal of anticoagulation in patients taking FXa inhibitors with major critical site or major bleeding on oral direct FXa inhibitors; PCC or activated PCC is suggested only if andexanet is not available[2]

American College of Emergency Physicians

Andexanet alfa is a tier 1 recommendation for anticoagulation in reversal of apixaban- or rivaroxaban-treated patients experiencing life-threatening or critical site bleeds; PCC is suggested as a tier 2 recommendation if a tier 1 agent is not available[3]

1. Greenberg, 2022; 2. Tomaselli, 2020; 3. Baugh, 2020

Code ICH Protocol Bundled Care

Neurocritical Care Society, and Neurocritical Care Foundation

- Rapid neuroimaging
- Blood pressure control
- **Anticoagulant reversal** ❯❯❯
- Neurological assessments
- Surgical therapy
- Glucose control
- Temperature control

Anticoagulant Reversal Goals

Choose the right agent, and treat within 60 minutes:

- Vitamin K antagonists (warfarin, coumarins): IV vitamin K and 4F-PCC achieve INR ≤ 1.4
- Factor II inhibitor (dabigatran): Idarucizumab
- Factor Xa inhibitor (rivaroxaban, apixaban): Andexanet if available; 4F-PCC second line
- Antiplatelet agents (aspirin, clopidogrel): Desmopressin

Patients Experiencing an FXa Inhibitor-Related Life-Threatening Bleed Need Specific Reversal Agents

- Timely intervention is crucial to prevent complications
- Need amplified by increasing number of hospital admissions due to FXa inhibitor-related bleeding events
- Andexanet rapidly neutralizes effects of FXa inhibitors
  - Offering a targeted solution for managing bleeding events

Andexanet is vital component in bundle of care used to rapidly manage FXa inhibitor-related, life-threatening bleeding events

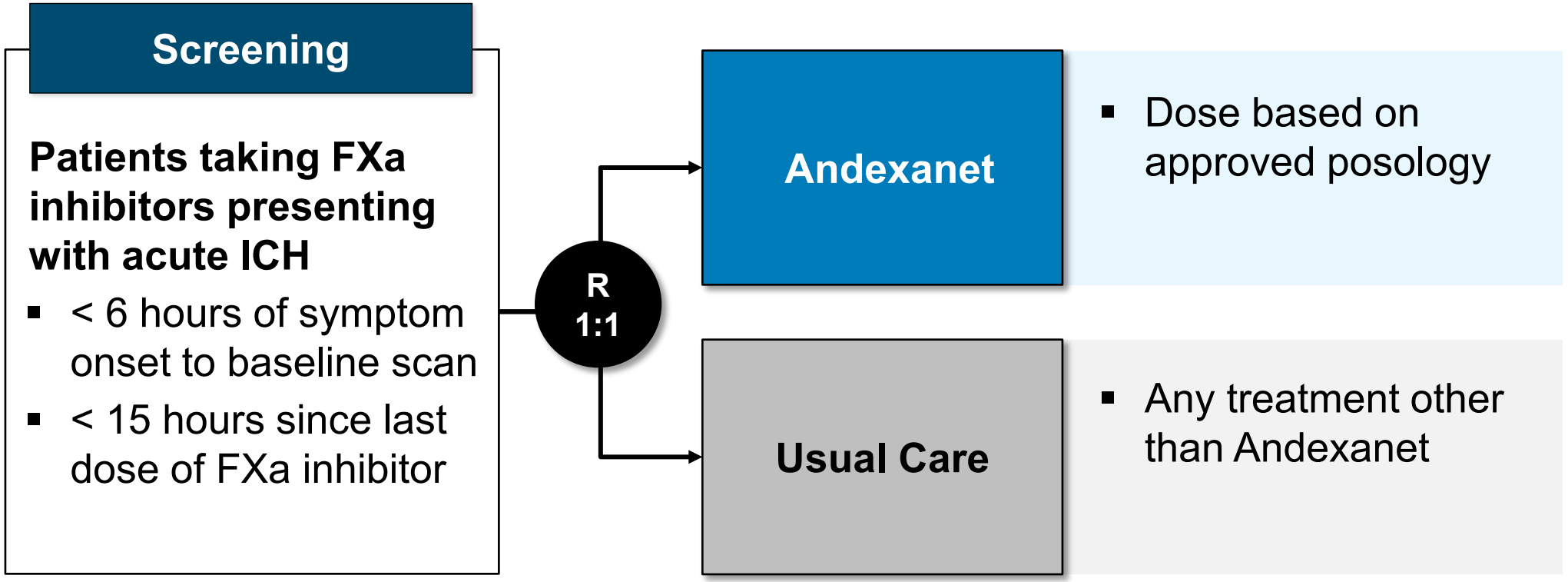
ANNEXA-I Efficacy

Per Ladenvall, MD, PhD

Global Clinical Head

AstraZeneca BioPharmaceuticals R&D

ANNEXA-I: Randomized, Open-Label, Multicenter, Clinical Phase IV Study



- Imaging performed at baseline and 12 hours following randomization
- Neurologic assessments (NIHSS) performed at baseline, 2, 3, 6, 12, 24, and 72 hours
- Safety follow-up for 30 days after treatment

ANNEXA-I: Primary Efficacy Endpoint Covering Different Aspects of Hemostasis

Primary Endpoint: Effective hemostasis 12 hours post-randomization

Hematoma Expansion: ≤ 35% increase in hematoma volume

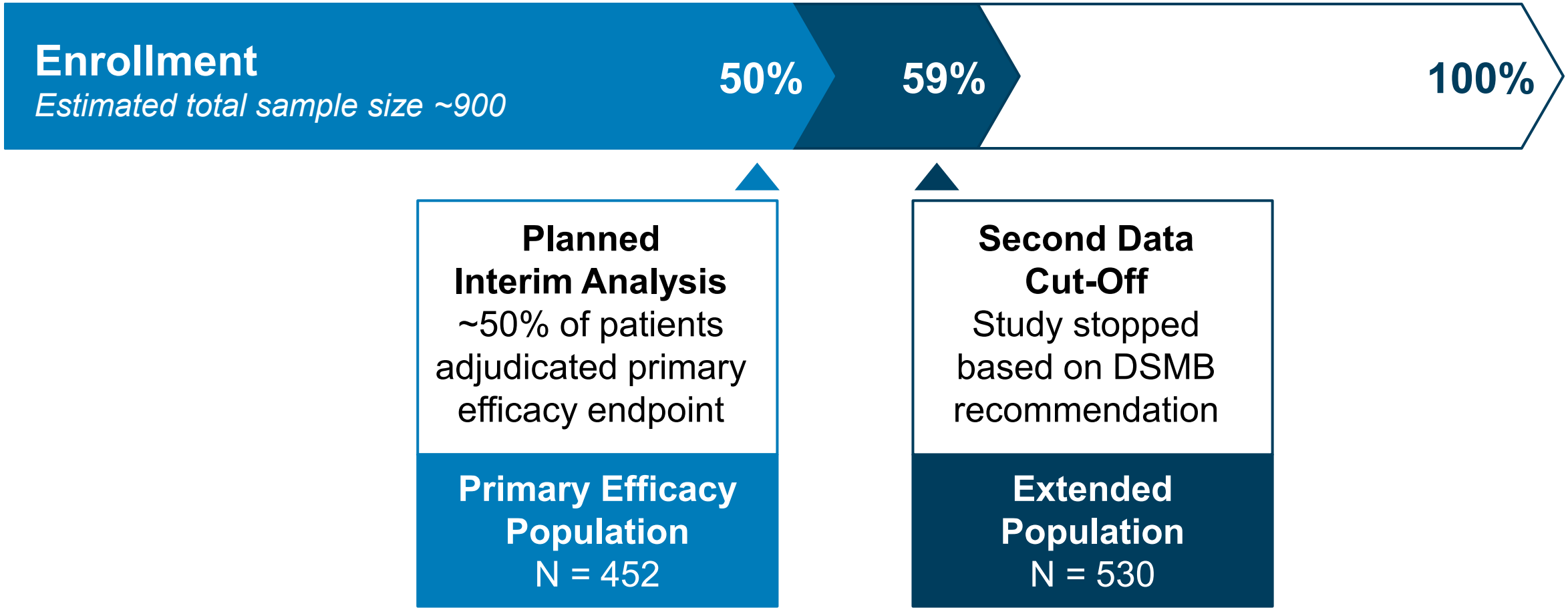
AND

Neurological Deterioration: < 7-point change in NIHSS

AND

No Rescue Therapy: Between 3- and 12-hours post-randomization

ANNEXA-I: DSMB Recommended Study be Stopped Based on Results from Planned Interim Analysis



DSMB = Data Safety Monitoring Board

ANNEXA-I: Baseline Demographics

Primary Efficacy Population

		Andexanet N = 224	Usual Care N = 228
Age (years), **Mean** (SD)		**78.9** (8.5)	**78.9** (8.5)
Male		**58%**	**50%**
Race	**Black/ African American**	**2%**	**1%**
	White	**93%**	**94%**
Ethnicity	**Hispanic or Latino**	**6%**	**5%**
	Not Hispanic or Latino	**85%**	**90%**
Region	**Europe**	**88%**	**89%**
	North America	**12%**	**11%**

ANNEXA-I: Disease Characteristics

Primary Efficacy Population

	Andexanet N = 224	Usual Care N = 228
FXa inhibitor		
Apixaban	**63%**	**59%**
Rivaroxaban	**29%**	**29%**
Edoxaban	**9%**	**11%**
Hematoma volume (mL), median (Q1, Q3)	**10.6** (4.1, 24.6)	**9.0** (3.3, 22.8)
Baseline NIHSS, median (Q1, Q3)	**9.0** (6.0, 16.0)	**9.0** (4.0, 14.0)
Symptom onset to baseline scan (hours), median (min, max)	**2.3** (0.2, 11.4)	**2.4** (0.3, 11.9)
Symptom onset to treatment (hours), median (min, max)	**4.0** (1.3, 12.6)	**4.1** (1.2, 13.5)
Baseline scan to treatment (hours), median (min, max)	**1.5** (0.2, 4.5)	**1.7** (0.2, 4.0)

ANNEXA-I: Baseline Medical History

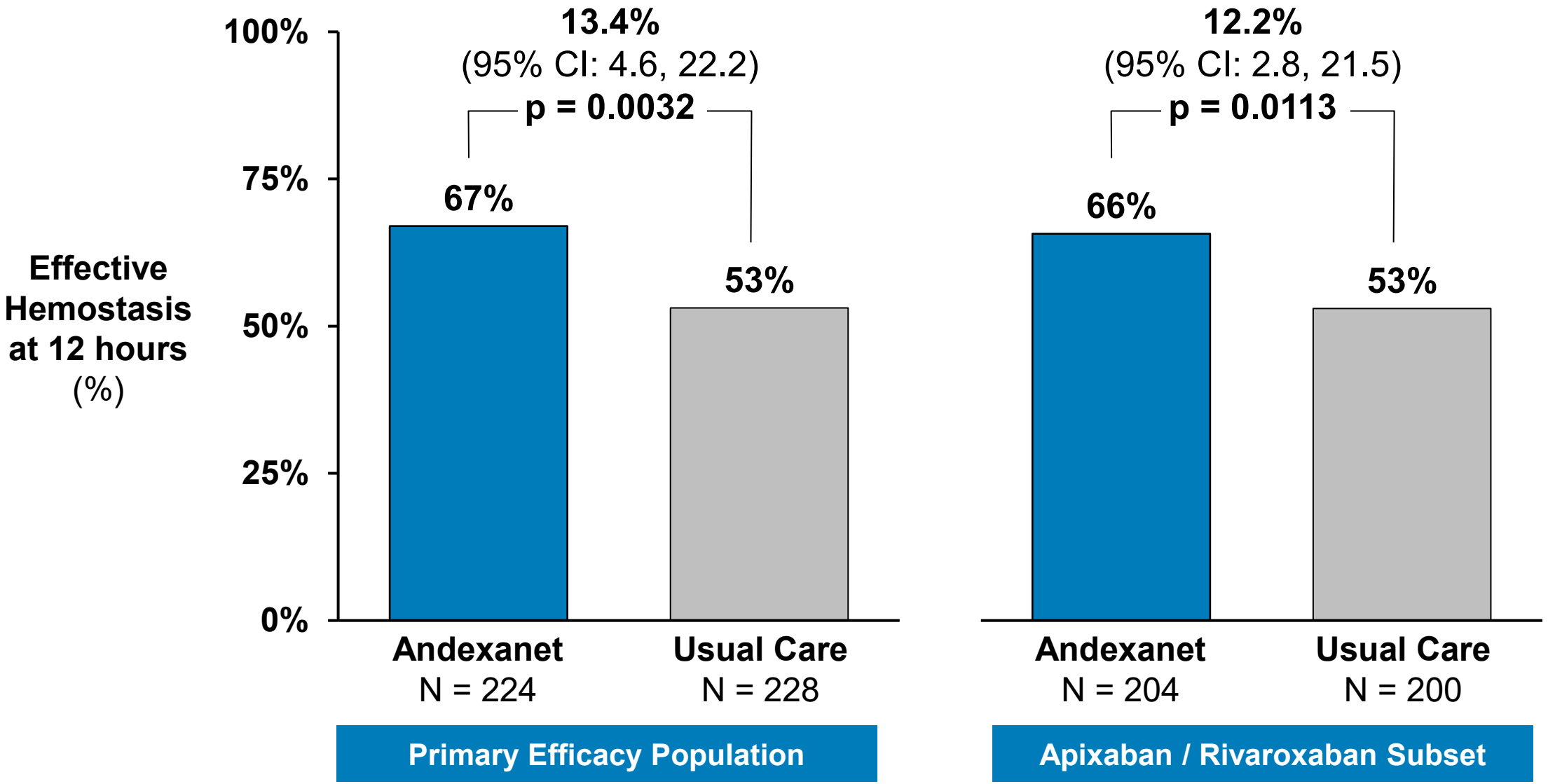
Primary Efficacy Population – Safety Set

Medical History	Andexanet N = 223	Usual Care N = 226
Atrial fibrillation	90%	85%
Diabetes	37%	26%
Stroke	21%	21%
Congestive heart failure	13%	20%
Myocardial infarction	10%	14%
Deep vein thrombosis	8%	10%
Pulmonary embolism	8%	9%
CHA_2DS_2-VASC score, median	4	4

CHA_2DS_2-VASC score – stratification of risk of stroke in patients with AF estimated using the Congestive heart failure, Hypertension, Age, Diabetes mellitus, prior Stroke or TIA or thromboembolism, VAscular disease, Sex Category score

ANNEXA-I Efficacy

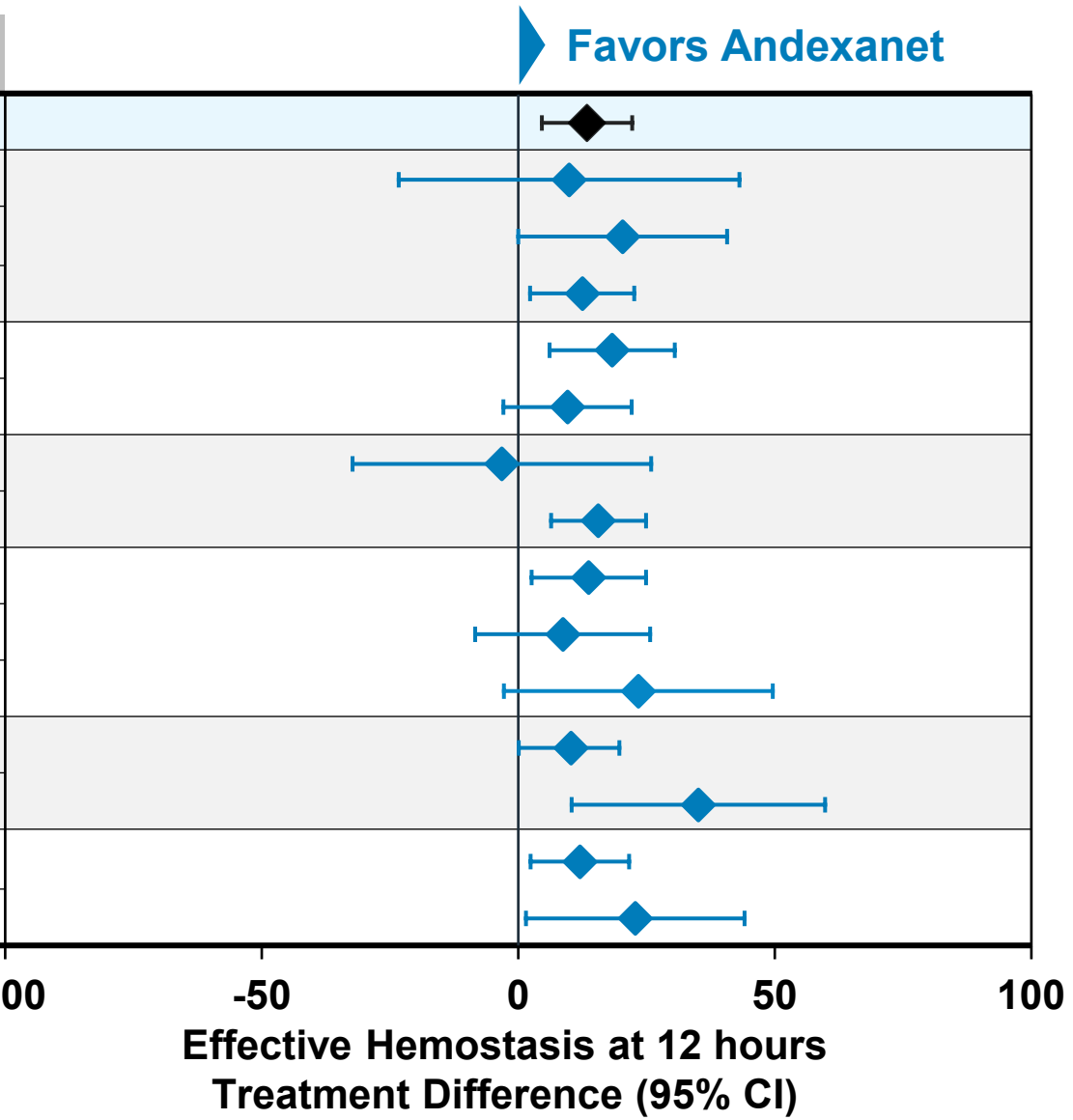
ANNEXA-I: Primary Efficacy Endpoint Established Hemostatic Benefit of Andexanet vs Usual Care



ANNEXA-I: Treatment Effect of Andexanet Consistent Across Key Patient Subgroups

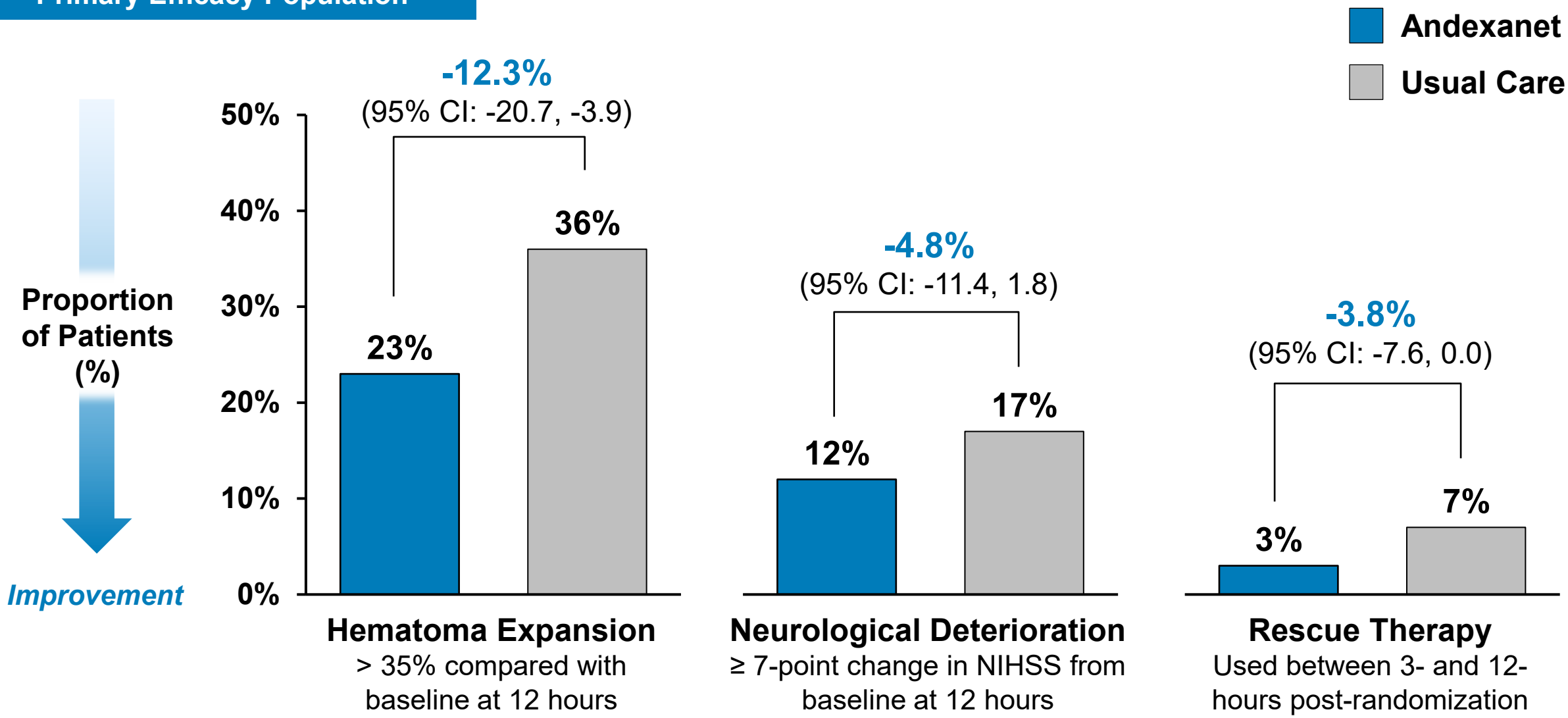
Primary Efficacy Population

		Andexanet		Usual Care	
Overall		**67%**	(150/224)	**53%**	(121/228)
Age	**< 65**	**77%**	(10/13)	**67%**	(10/15)
	65 – 74	**62%**	(28/45)	**41%**	(19/46)
	≥ 75	**67%**	(112/166)	**55%**	(92/167)
Sex	**Male**	**63%**	(82/130)	**44%**	(51/115)
	Female	**72%**	(68/94)	**62%**	(70/113)
Location	**North America**	**50%**	(13/26)	**52%**	(13/25)
	Europe	**69%**	(137/198)	**53%**	(108/203)
FXa Inhibitor	**Apixaban**	**70%**	(98/140)	**56%**	(76/135)
	Rivaroxaban	**56%**	(36/64)	**46%**	(30/65)
	Edoxaban	**80%**	(16/20)	**56%**	(14/25)
ICH Score	**< 3**	**67%**	(130/195)	**56%**	(112/199)
	≥ 3	**69%**	(20/29)	**31%**	(9/29)
Hematoma Volume	**< 30 mL**	**69%**	(125/180)	**57%**	(109/192)
	≥ 30 mL	**57%**	(25/44)	**34%**	(12/35)



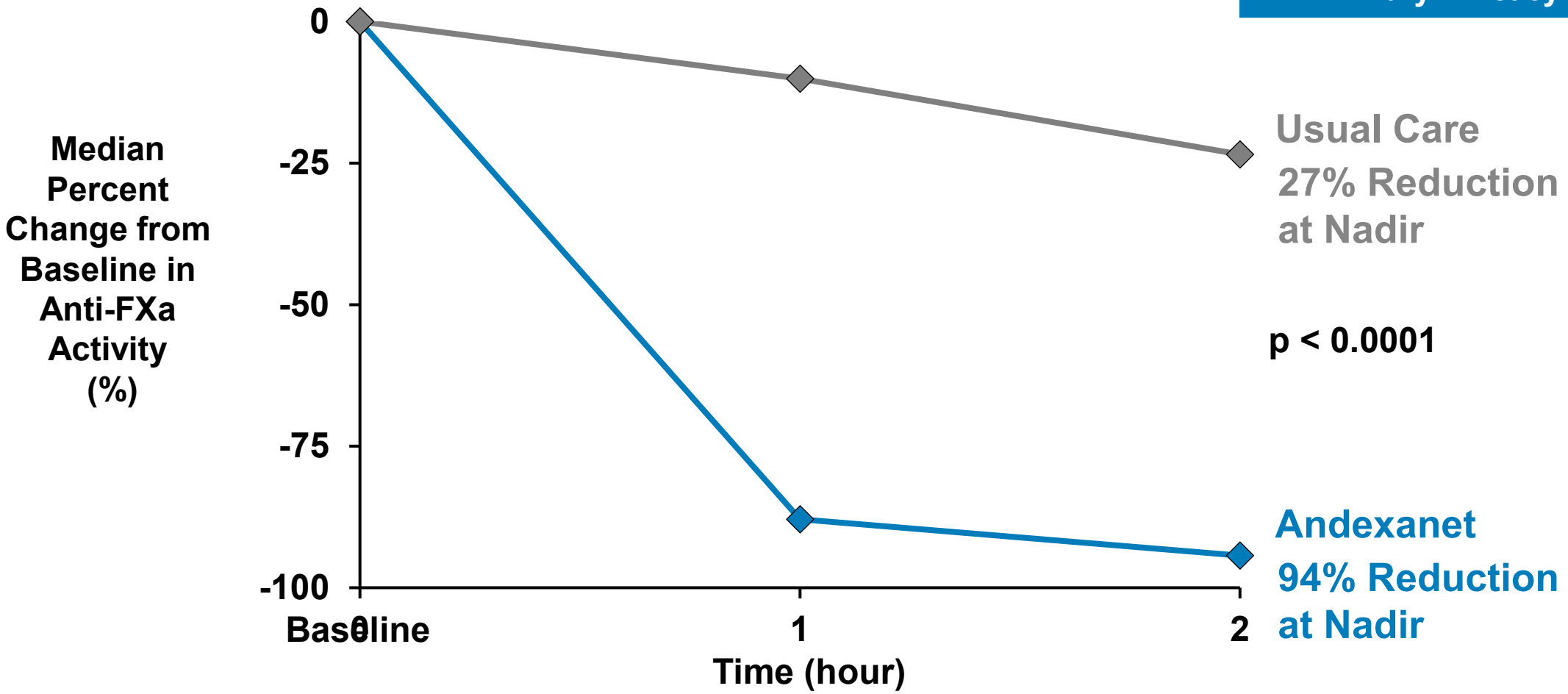
ANNEXA-I: Andexanet Showed Numerical Improvements vs Usual Care in All Components of Primary Endpoint

Primary Efficacy Population



ANNEXA-I: Andexanet Rapidly Reduced Anti-FXa Activity

Primary Efficacy Population



Andexanet	209	198	195
Usual care	204	189	193

ANNEXA-I: Confirmed Hemostatic Benefit of Andexanet Compared to Usual Care

- Statistically significant reduction in anti-FXa activity vs usual care
- Statistically significant and clinically meaningful improvement in effective hemostasis vs usual care
  - Consistent benefit across sensitivity analyses and exploratory patient subgroup analyses
- Improvement in all aspects of effective hemostasis
  - Hematoma expansion, neurological function, use of rescue therapy

ANNEXA-I confirms findings from ANNEXA-4 supporting benefit for patients with life-threatening, uncontrolled bleeding

ANNEXA-I Safety

Rohit Narayan, MBCHB

Patient Safety Physician

AstraZeneca BioPharmaceuticals

Andexanet Has a Well-Established Safety Profile

	Healthy Volunteers	ANNEXA-4	ANNEXA-I Safety Set	
	Andexanet	Andexanet	Andexanet	Usual Care
Patients (N)	**553**	**479**	**262**	**265**

- Estimated* cumulative global post-marketing exposure includes 70,158 patients
  - 36,597 patients in United States
- No new safety signals identified in clinical trials or post-marketing use

*Based on sales data

ANNEXA-I: Overall Summary of Treatment-Emergent Adverse Events

% (n)	Safety Set		Apixaban and Rivaroxaban	
	Andexanet N = 262	Usual Care N = 265	Andexanet N = 239	Usual Care N = 232
TEAE	**85.1%** (223)	**82.6%** (219)	**85.8%** (205)	**81.9%** (190)
TESAE	**45.8%** (120)	**36.2%** (96)	**46.4%** (111)	**37.1%** (86)
TEAE leading to withdrawal of study drug	**0**	**0**	**0**	**0**
TEAE leading to interruption of study drug	**0.4%** (1)	**0**	**0.4%** (1)	**0**
TEAE leading to death	**24.4%** (64)	**20.4%** (54)	**24.7%** (59)	**21.1%** (49)
All-cause mortality (30-days)	**28.2%** (74)	**26.4%** (70)	**28.0%** (67)	**26.3%** (61)

ANNEXA-I: Treatment-Emergent SAEs Occurring in ≥ 2% of Patients

Safety Set

% (n)	Andexanet N = 262	Usual Care N = 265
TESAE	**46%** (120)	**36%** (96)
Nervous system disorders	**19%** (49)	**19%** (51)
Ischemic stroke	**5%** (13)	**0.8%** (2)
Hemorrhage intracranial	**3%** (8)	**4%** (11)
Cerebral hemorrhage	**3%** (7)	**4%** (11)
Hydrocephalus	**3%** (7)	**2%** (4)
Neurological decompensation	**0.8%** (2)	**3%** (7)
Infections and infestations	**16%** (43)	**11%** (28)
Pneumonia	**5%** (14)	**6%** (16)
Pneumonia aspiration	**5%** (14)	**3%** (7)
Sepsis	**2%** (6)	**0.8%** (2)
Cardiac disorders	**8%** (22)	**3%** (7)
Myocardial infarction	**3%** (8)	**0.4%** (1)
Respiratory, thoracic and mediastinal disorders	**6%** (17)	**5%** (12)
Pulmonary embolism	**0.8%** (2)	**3%** (7)

ANNEXA-I: TEAEs Leading to Death in > 2 Patients

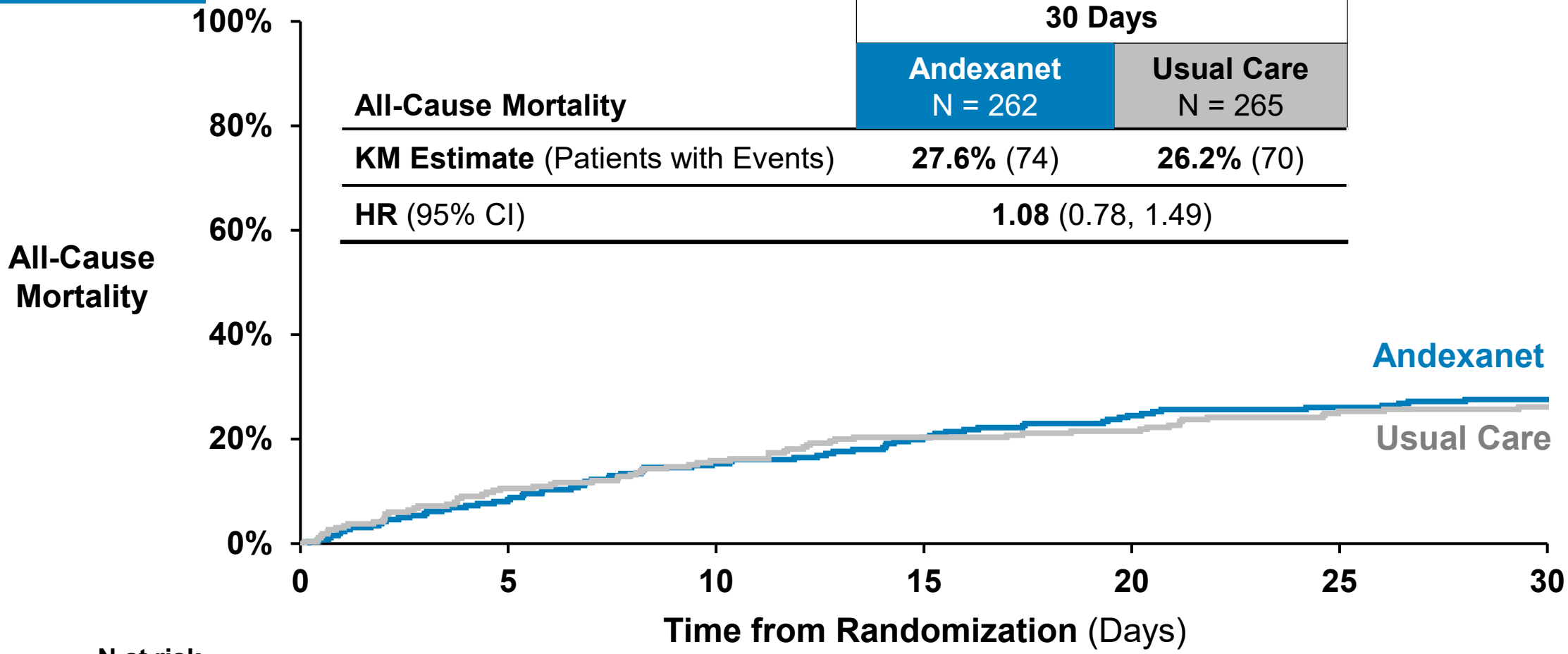
Safety Set

% (n)	Andexanet N = 262	Usual Care N = 265
TEAE leading to death	**24%** (64)	**20%** (54)
Nervous system disorders	**9%** (24)	**10%** (26)
Cerebral hemorrhage	**2%** (6)	**3%** (9)
Hemorrhage intracranial	**2%** (5)	**2%** (4)
Ischemic stroke	**1%** (3)	**0**
Infections and infestations	**7%** (18)	**6%** (15)
Pneumonia	**3%** (7)	**2%** (6)
Pneumonia aspiration	**3%** (7)	**2%** (5)
Sepsis	**1%** (3)	**0.4%** (1)
Respiratory, thoracic and mediastinal disorders	**4%** (11)	**2%** (5)
Respiratory failure	**2%** (4)	**2%** (4)
Cardiac disorders	**3%** (8)	**0.8%** (2)
Cardiac failure	**1%** (3)	**0**

ANNEXA-I: All-Cause Mortality at 30 Days Similar Between Treatment Groups

Safety Set

All-Cause Mortality	30 Days	
	Andexanet N = 262	Usual Care N = 265
KM Estimate (Patients with Events)	**27.6%** (74)	**26.2%** (70)
HR (95% CI)	**1.08** (0.78, 1.49)	



N at risk

Andexanet	262	239	221	208	197	193	132
Usual Care	265	237	223	211	207	195	145

AESI: Thrombotic Events

USPI contains boxed warning about risk of thrombotic events with Andexanet

Adjudication of Thrombotic Events in ANNEXA-I

Multiple sources identified potential thrombotic events for adjudication

1. Site reported event of special interest
2. Identified by medical review
3. Identified by adverse event code matching

Blinded Endpoint Adjudication Committee
Followed prespecified charter determined whether events were thrombotic

	Safety Set		Apixaban / Rivaroxaban Subset	
% (n)	**Andexanet** N = 262	**Usual Care** N = 265	**Andexanet** N = 239	**Usual Care** N = 232
Blinded EAC Adjudicated Thrombotic Events	**10.3%** (27)	**5.7%** (15)	**10.9%** (26)	**5.6%** (13)

Difference Between Independently Adjudicated Thrombotic Event Rates and FDA Assessment

Apixaban / Rivaroxaban Subset

Andexanet (N = 239)	
Blinded EAC Adjudicated TEs	**10.9% (26)**
Total FDA TE Count	**14.6% (35)**
Atrial thrombosis	+1
Troponin increased	-1
Ischaemic stroke	+2
Cerebrovascular accident	+2
Cerebral infarction	+1
Pulmonary embolism	+3
Embolism arterial	+1

Usual Care (N = 232)	
Blinded EAC Adjudicated TEs	**5.6% (13)**
Total FDA TE Count	**6.9% (16)**
Sudden cardiac death	+1
Central venous thrombosis	+1
Pulmonary embolism	+1

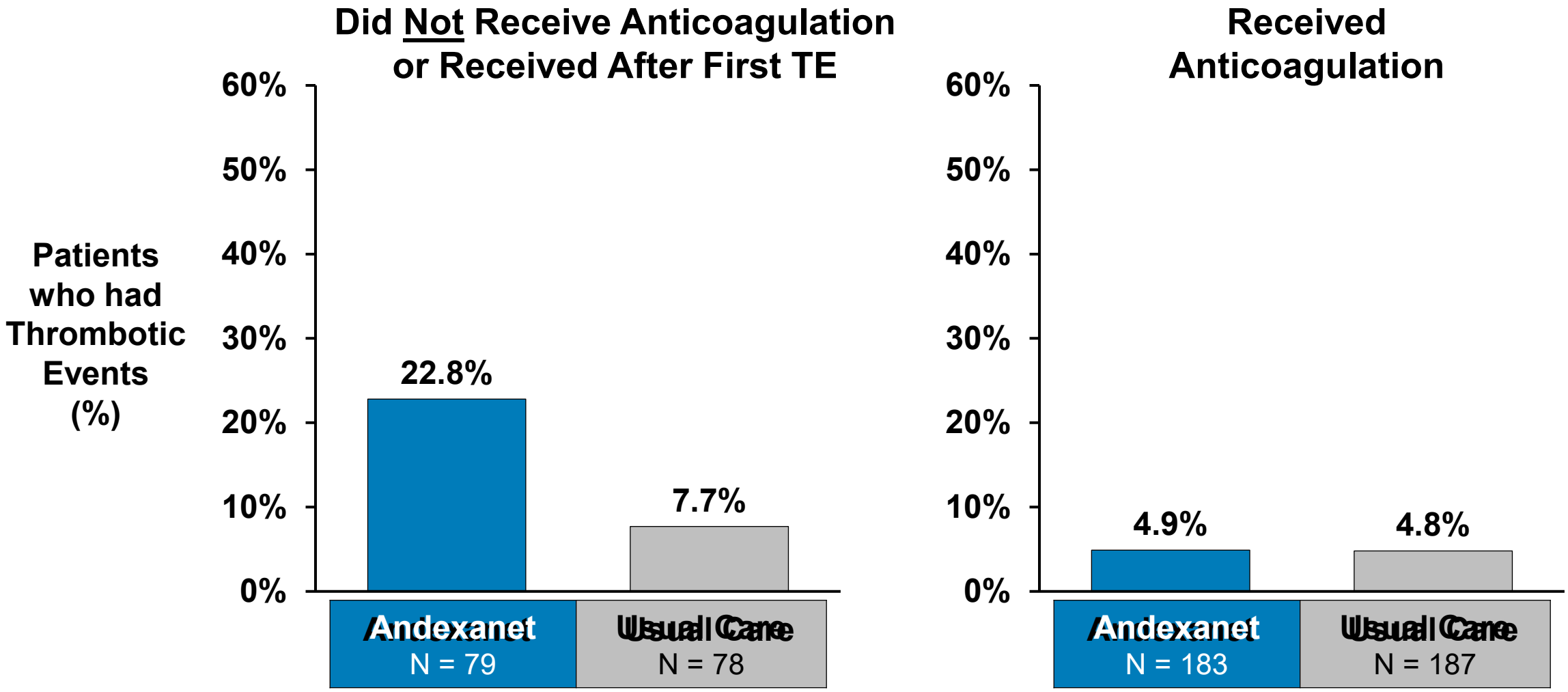
ANNEXA-I: Adjudicated Thrombotic Events

Safety Set

% (n)	Andexanet N = 262	Usual Care N = 265
Any thrombotic event	**10.3%** (27)	**5.7%** (15)
Ischemic stroke	**6%** (17)	**2%** (4)
Myocardial infarction	**4%** (11)	**2%** (4)
Arterial systemic embolism	**1%** (3)	**0.8%** (2)
Pulmonary embolism	**0.4%** (1)	**2%** (6)
Deep vein thrombosis	**0.4%** (1)	**0.8%** (2)
Thrombotic event leading to death	**2%** (6)	**0.8%** (2)

ANNEXA-I: Relationship Between Re-anticoagulation and Thrombotic Events

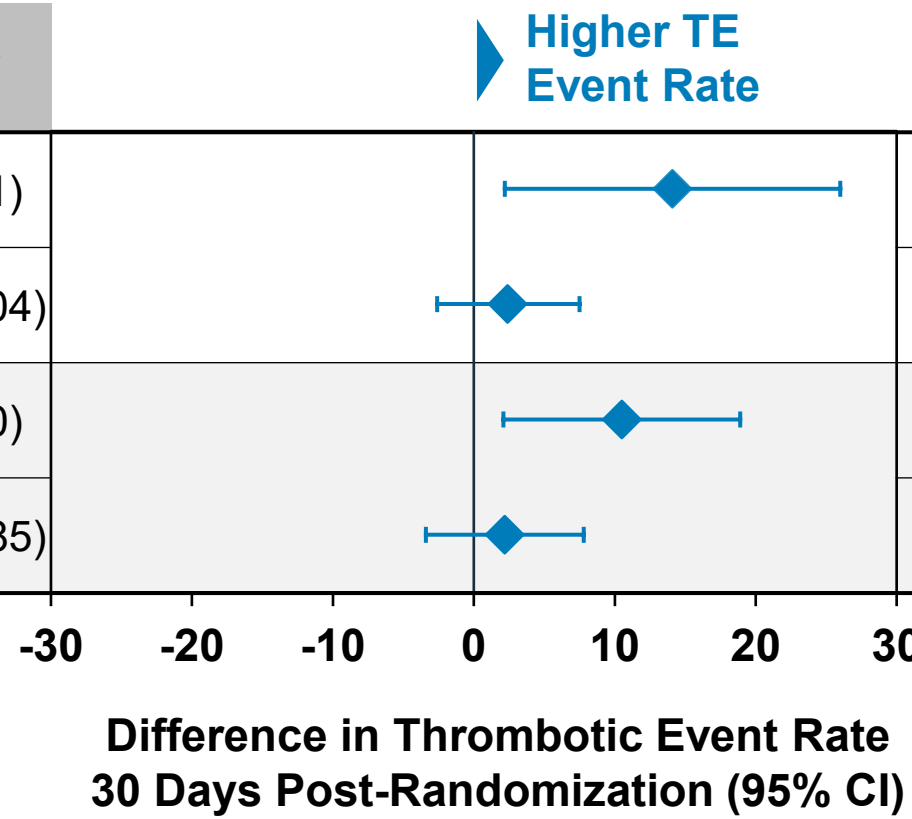
Safety Set



ANNEXA-I: Subgroup Analyses to Delineate Update to USPI Informing Use in Patients at High Baseline Thrombotic Risk

Safety Set

Medical History		Andexanet % (n/N)		Usual Care % (n/N)		Difference (95% CI)
Cardiac Failure	Yes	**17.4%**	(8/46)	**3.3%**	(2/61)	**14.1%** (2.2, 26.0)
	No	**8.8%**	(19/216)	**6.4%**	(13/204)	**2.4%** (-2.6, 7.5)
Stroke or MI	Yes	**12.8%**	(10/78)	**2.5%**	(2/80)	**10.5%** (2.1, 18.9)
	No	**9.2%**	(17/184)	**7.0%**	(13/185)	**2.2%** (-3.4, 7.8)



ANNEXA-I Supports Acceptable Safety Profile of Andexanet In The Setting of Uncontrolled and Life-Threatening Bleeding

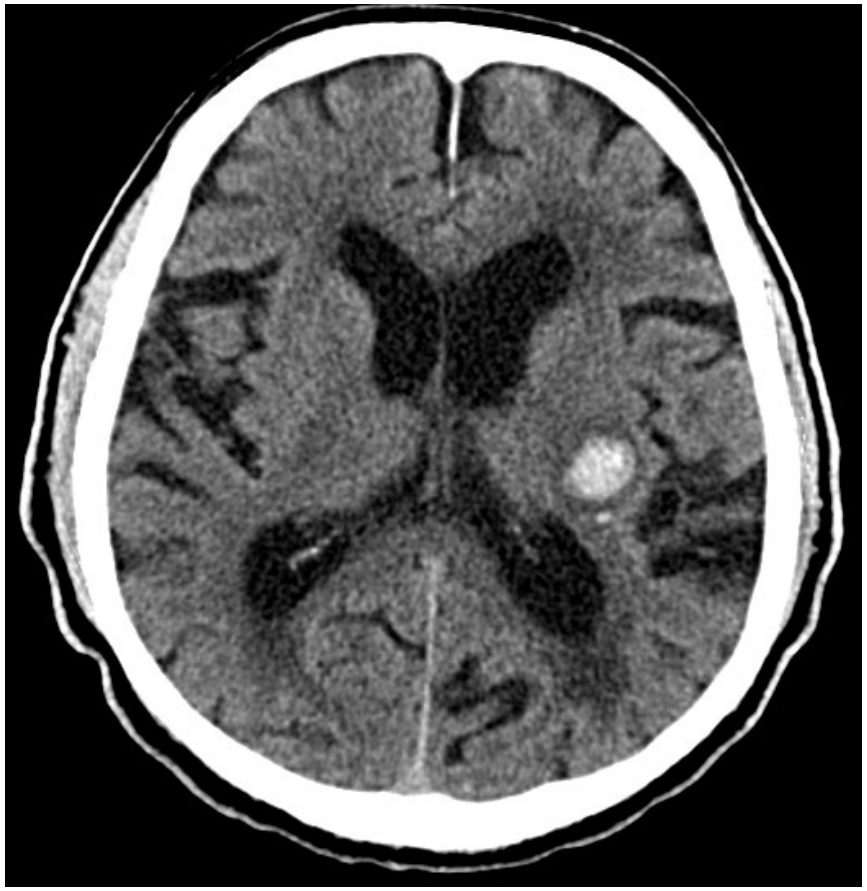
- Higher rate of thrombotic events with andexanet
  - Known risk when restoring physiologic coagulation in patients with an underlying thrombotic risk who are bleeding
  - Proposed USPI update informing use in specific patients with high baseline thrombotic risk
- 30-day mortality rates were similar between treatment groups
  - Causes of death in ANNEXA-I are in line with other studies
- Safety profile in ANNEXA-I is consistent with results from the clinical development program and consistent with MoA
- No new safety signals or adverse drug reactions identified

Clinical Perspective

Ashkan Shoamanesh, MD, FRCPC

Marta and Owen Boris Chair in Stroke Research and Care
Associate Professor, Medicine Department of Neurology
McMaster University

Treatment of Patients with ICH Requires Rapid Decisions in Emergency Setting to Minimize Risk of Death



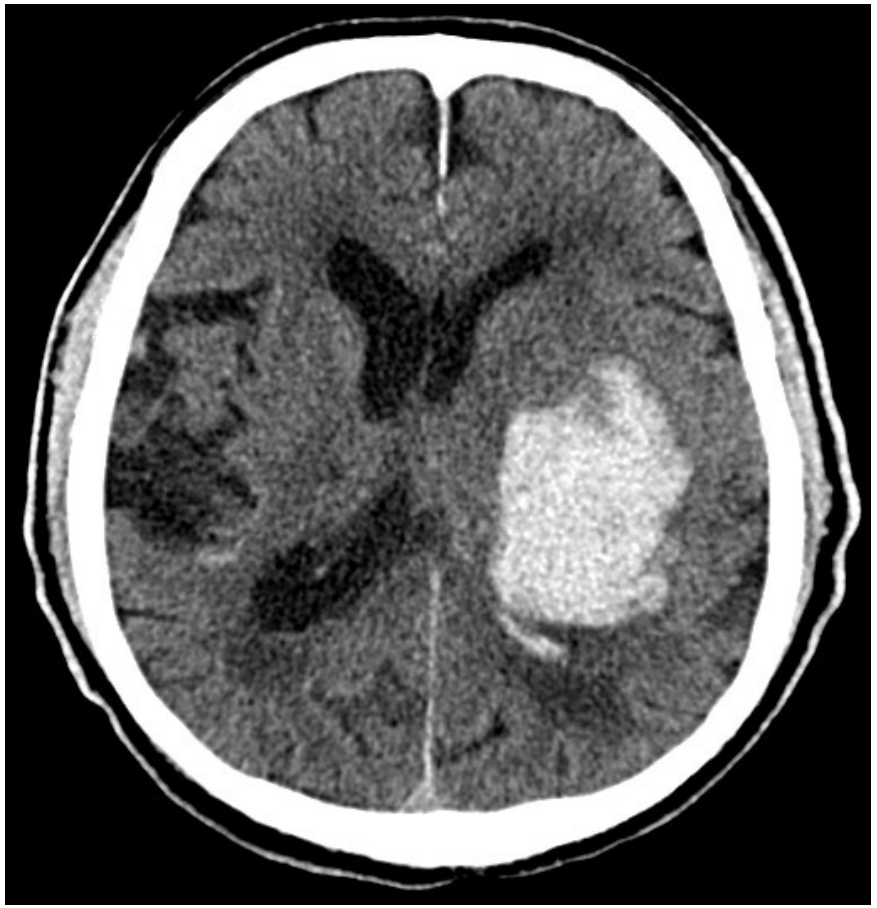
3 cc

ICH Score: 0

0% mortality

5 hours

Anticoagulated
77-year-old
Male



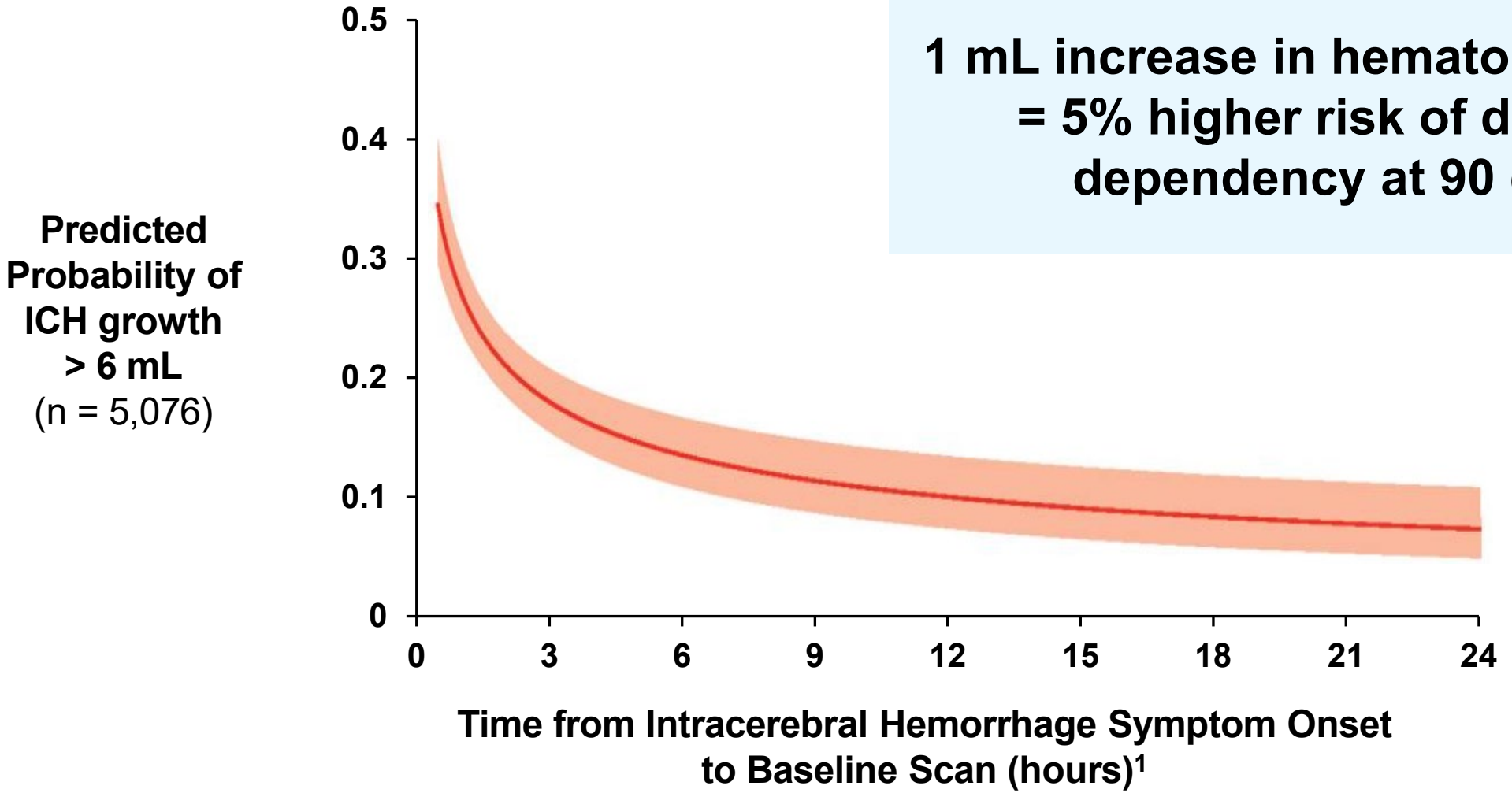
42 cc

ICH Score: 3

72% mortality

Time is Brain: Therapies that Assist with our Rapid Response in These Settings are Critical

1 mL increase in hematoma volume = 5% higher risk of death or dependency at 90 days



1. Adapted from Al-Shahi Salman, 2018

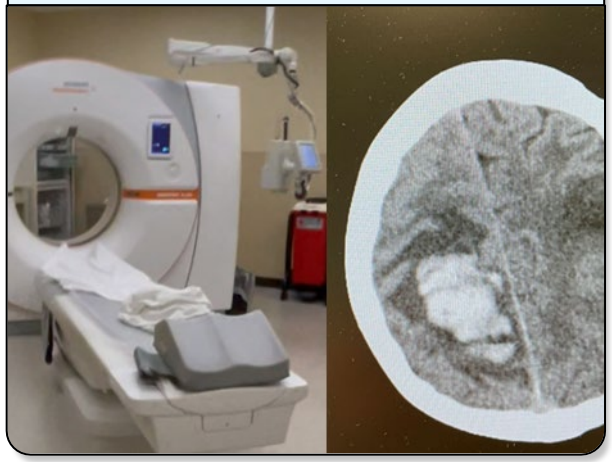
Reversing Anticoagulation is Only One Aspect in Bundle of Care for Patients with ICH

EMS

- Symptom onset
- Vitals
- Glucose
- NIHSS
- Anticoagulant use (dose, time)
- eGFR
- Trauma vs spontaneous

CT-Scan

- Ischemic
- Hemorrhagic
- Tumor/cancer
- Trauma



Bundle of Care

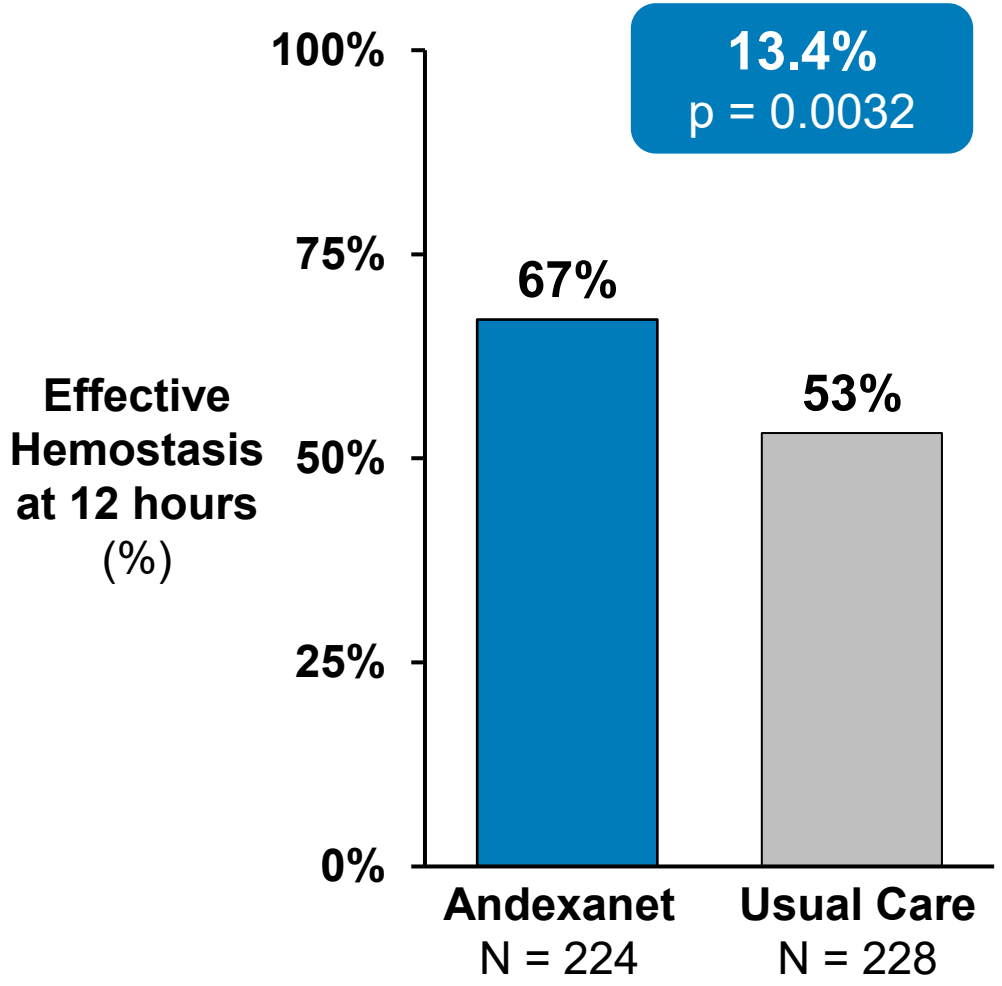
- Anticoagulation reversal, agent specific
- BP control
- Glucose control
- Surgical evacuation
- Normothermia

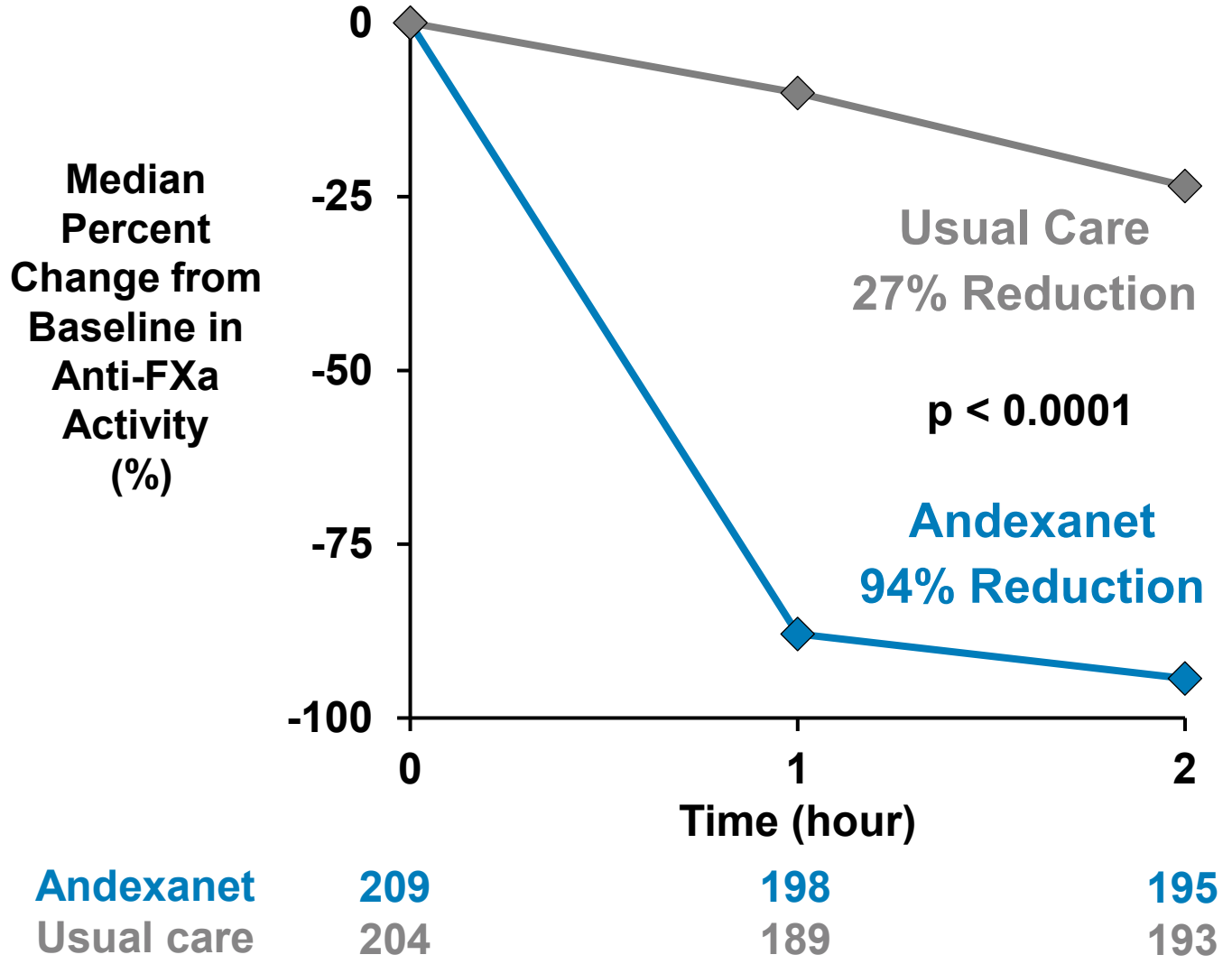
In-hospital Care and Secondary Prevention

- BP management
- Risk factor management
- Re-initiation of anticoagulants
- Infection control measures
- Early rehabilitation

Ma, 2023; Li, 2024; Greenberg, 2022; Parry-Jones, 2023

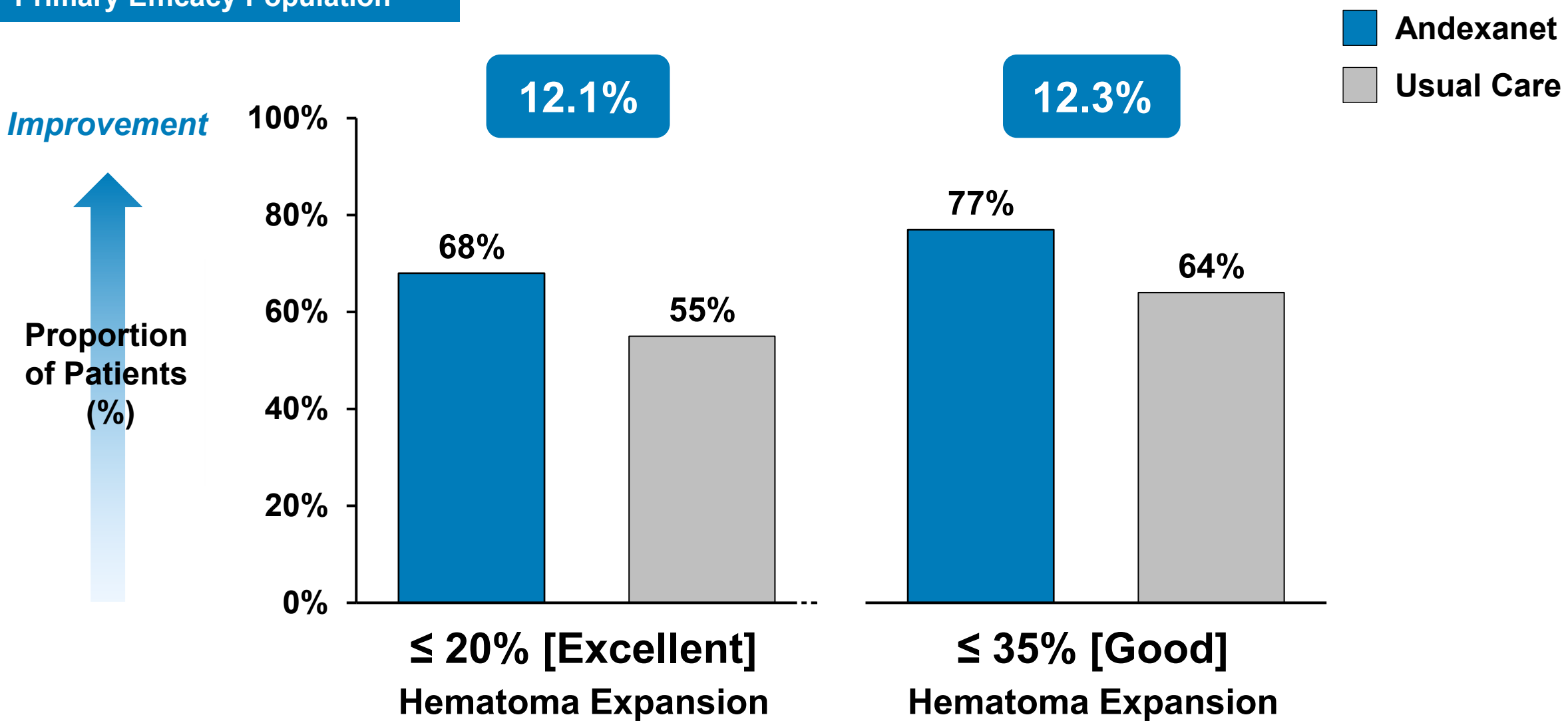
ANNEXA-I: Primary Efficacy Endpoint Established Hemostatic Benefit of Andexanet vs Usual Care





Minimizing Hematoma Expansion is Critical Outcome in FXa Inhibitor-Related Life-Threatening Bleeds

Primary Efficacy Population



Minimizing Door to Needle Time for ICH Treatment is Key Goal

Time (hours), Median (Q1, Q3)	ANNEXA-I		
	Andexanet N = 224	Usual care N = 228	Get With The Guidelines Stroke Registry (USA, N = 9,492)[1]
Symptom onset to baseline scan	**2.3** (1.5, 4.0)	**2.4** (1.4, 3.8)	-
Symptom onset to hospital arrival (door)	-	-	**2.6** (1.1, 7.0)
Baseline scan to randomization	**1.1** (0.7, 1.5)	**1.2** (0.7, 1.7)	-
Door-to-needle	**2.1** (1.5, 2.9)	**2.3** (1.7, 3.1)	**1.4** (1.0, 2.0)*

- Door-to-needle time is a predictor of treatment effect

1. Sheth, 2024

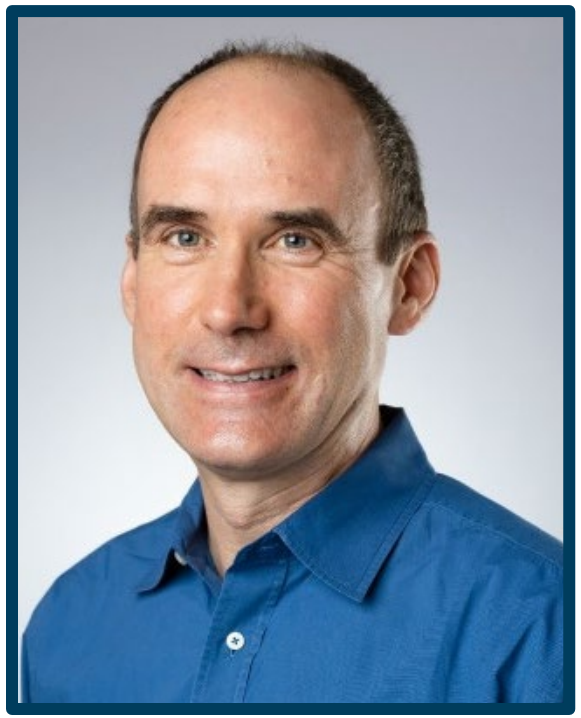
*N = 5,224

Andexanet Has Well-Established Safety Profile

- Andexanet increased risk of TE in ANNEXA-I
  - Consistent with label and boxed warning in USPI
  - Similar rate as observed in ANNEXA-4
- TE risk must be assessed in context of management of life-threatening or uncontrolled bleeding event
  - Primary goal is to stop the bleed to limit brain injury
  - Well-equipped to monitor and manage TEs
  - Once patient stabilizes, focus shifts to managing long-term risks
  - Need to reinitiate anticoagulation therapy as soon as medically appropriate

Reducing Hematoma Expansion is the Primary Goal of Medical Interventions in Acute ICH Setting

- Time is brain!
- ANNEXA-I supports that andexanet fills an important medical need as an effective, rapid reversal agent for FXa inhibitors
- Balancing reductions in hematoma expansion vs. increase in thrombotic risk indicate overall benefit of andexanet



Moderator for Q&A

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Andexanet in Life-Threatening or Uncontrolled Bleeding in Patients Receiving a Direct Oral Factor Xa Inhibitor

November 21, 2024

Cellular, Tissue and Gene Therapies Advisory Committee
AstraZeneca