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Andexanet for Factor Xa Inhibitor-Associated Acute Intracerebral Hemorrhage

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Abstract:	Background Patients with acute intracerebral hemorrhage (ICH) on factor Xa (FXa) inhibitors have a risk of hematoma expansion. Andexanet rapidly reverses anticoagulation. Methods Patients with acute ICH on FXa inhibitors were randomly assigned (1:1) to receive andexanet or usual care. The primary outcome was hemostatic efficacy defined as ≤35% hematoma volume expansion, <7-point worsening in National Institutes of Health Stroke Scale score (range 0 to 42 with higher scores indicating greater neurologic deficit) at 12 hours, and no rescue therapy between 3 and 12 hours. Safety outcomes were thrombotic events and death. Efficacy analyses were performed on 452 patients in the pre-specified interim analysis and safety analyses on all 530 enrolled patients (extended population). Results Atrial fibrillation was the most common indication for FXa inhibitors. Most usual care patients (85.5%) received prothrombin complex concentrate. Hemostatic efficacy was achieved in 150/224 (67.0%) patients on andexanet and in 121/228 (53.1%) receiving usual care (difference, 13.4 percentage points; 95% confidence interval [CI], 4.6 to 22.2; P=0.003). Reduction in median anti-FXa activity was 94.5% with andexanet and 26.9% with usual care (P<0.001). Thrombotic events occurred in 27 (10.3%) patients receiving andexanet and in 15 (5.6%) receiving usual care (difference, 4.6 percentage points; 95% CI, 0.1 to 9.2; P=0.048). Ischemic stroke occurred in 17 (6.5%) patients receiving andexanet and

	in 4 (1.5%) receiving usual care. Conclusions In patients with ICH on FXa inhibitors, andexanet reduced the frequency of hematoma expansion compared to usual care but was associated with increased thrombotic events, including ischemic stroke.

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Andexanet for Factor Xa Inhibitor-Associated Acute Intracerebral Hemorrhage

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ABSTRACT

Background

Patients with acute intracerebral hemorrhage (ICH) on factor Xa (FXa) inhibitors have a risk of hematoma expansion. We tested the effect of the FXa reversal agent, andexanet, on ICH volume expansion.

Methods

Patients with acute ICH who had taken FXa inhibitors within 15 hours were randomly assigned in a 1:1 ratio to receive andexanet or usual care. The primary outcome was hemostatic efficacy defined as ≤35% hematoma volume expansion, <7-point worsening in National Institutes of Health Stroke Scale score (range 0 to 42 with higher scores indicating greater neurologic deficit) at 12 hours, and no rescue therapy between 3 and 12 hours. Safety outcomes were thrombotic events and death.

Results

A total of 263 patients were assigned to receive andexanet and 267 to receive usual care. Efficacy analyses were performed on 452 patients in an interim analysis, and safety was analyzed in all 530 enrolled patients. Atrial fibrillation was the most common indication for FXa inhibitors. Most usual care patients (85.5%) received prothrombin complex concentrate. Hemostatic efficacy was achieved in 150/224 (67.0%) patients on andexanet and 121/228 (53.1%) receiving usual care (adjusted difference, 13.4 percentage points; 95% confidence interval [CI], 4.6 to 22.2; P=0.003). Reduction in median anti-FXa activity was 94.5% with andexanet and 26.9% with usual care (P<0.001). Thrombotic events occurred in 27 (10.3%) patients receiving andexanet and in 15 (5.6%) receiving usual care (difference, 4.6 percentage points; 95% CI, 0.1 to 9.2; P=0.048) and ischemic stroke in 17 (6.5%) and 4 (1.5%),

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respectively. There were no appreciable differences in disability outcome or mortality between groups at 30 days.

Conclusions

In patients with ICH on FXa inhibitors, andexanet resulted in better control of hematoma expansion compared to usual care but was associated with thrombotic events, including ischemic stroke. (ClinicalTrials.gov number, NCT03661528)

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BACKGROUND

Factor Xa (FXa) inhibitors are widely used for prevention of thrombotic events but they increase the risk of hemorrhage (1). Acute intracerebral hemorrhage (ICH) is one of the potential consequences of their use and has high rates of morbidity and mortality (2-6). Furthermore, hematoma expansion is a predictor of poor outcome (7,8). ICH in the presence of oral anticoagulation has a poor prognosis (9), and rapid reversal of anticoagulation has the potential to reduce the risk of hematoma expansion. Andexanet is a modified recombinant inactive form of human FXa which binds and sequesters FXa inhibitor molecules, rapidly reducing anti-FXa activity and restoring thrombin generation (10,11). A previous trial, ANNEXA-4, the initial results of which were published in the *Journal*, was a single-arm cohort study of andexanet in patients with acute major bleeding at any site, reported that 80% of patients achieved effective hemostasis and 10% had a thrombotic event (12,13). We performed a randomized trial to assess the efficacy and safety of andexanet, compared to usual care in patients with acute ICH.

METHODS

Trial Design and Oversight

Independent ethics committees at each trial site approved the protocol. Consent was obtained directly from patients, by proxy, or was deferred where approved. The trial was conducted in accordance with ethical principles derived from the Declaration of Helsinki and the Council for International Organizations of Medical Sciences International Ethical Guidelines. An independent Data Safety Monitoring Board (DSMB) monitored the trial.

This trial was coordinated by Population Health Research Institute (PHRI), a joint institute of McMaster University and of Hamilton Health Sciences, and was initially funded by Portola Inc.,

which was purchased by Alexion, AstraZeneca Rare Disease. Portola Pharma Inc. and then Alexion was the trial sponsor and provided andexanet. There were confidentiality agreements between Portola/Alexion and the authors. The statistical analysis was done by LX. The trial was primarily designed by SC, together with PY and JC (employees of Portola). Trial data were collected by and analyzed at PHRI. SC composed the first draft of the manuscript and vouches for the accuracy and completeness of the data, adherence to the study protocol, and accurate reporting of adverse events. A medical writer, paid for by Alexion, assisted with the initial writing of the Methods section. Although the treatment was unblinded at the study sites, members of the steering committee were masked to treatment assignment, summary statistics, and trial results and outcomes were adjudicated by a committee masked to treatment assignment. There were 3 protocol amendments during the trial, which are described in the Protocol, available at NEJM.org and in Table S1.

Patients

Patients with ICH who had received a FXa inhibitor were eligible, with last dose ≤15 hours prior to randomization. No patients who had previously received andexanet were enrolled in the current trial. Initially, patients with any acute FXa-associated intracranial hemorrhage were eligible for enrollment but after protocol amendments, only patients with an acute intracerebral hemorrhage as the main bleeding event (not subdural, subarachnoid or intraventricular hemorrhage) with an estimated blood volume of ≥0.5 to ≤60 mL and maximum allowed National Institutes of Health Stroke Scale (NIHSS) score of 35 were eligible (range 0 to 42 with higher scores indicating greater neurological deficits); the time from onset of bleeding symptoms to baseline imaging scan was also reduced by amendment from ≤12 to ≤6 hours. The hemorrhage

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needed to be evident in the cerebrum by computerized tomography or magnetic resonance imaging within ≤2 hours prior to randomization. Patients were excluded if they had Glasgow Coma Scale score <7 at time of consent (range 3 to 15 with lower scores indicating poor neurologic function), NIHSS score >35 (range 0 to 42 with higher scores indicating greater neurologic deficits), planned surgery within 12 hours, or history of thrombotic event within 2 weeks. Hemorrhage volumes were estimated from cranial CT or MRI by site investigators using local protocols and adjudicated at a central site by readers masked to treatment assignment, using a semi-automated program (Quantomo, Cybertrials, Calgary, Canada). The same imaging method (CT or MRI) was used for baseline and final hematoma volume in each patient.

Randomization and Treatments

Patients were randomly assigned in a 1:1 ratio to andexanet or usual care, stratified (after amendment 1) by intention to use prothrombin complex concentrate (PCC) if randomized to usual care and by time from symptom onset to baseline imaging scan (<180 vs ≥180 minutes). The randomization scheme was generated by PHRI. There were 20 patients found before database lock and without unblinding to have not correctly consented; their data were removed from the database.

Patients assigned to the andexanet group received either high-dose or low-dose bolus over 15 to 30 minutes followed by continuous infusion over 2 hours. The andexanet formulation included 1 g mannitol. Dose selection followed the approved label and was based on the FXa inhibitor used, and the amount and timing of last dose (details of the algorithm for dose selection are in Table

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S1). Usual care was at the discretion of local physicians, but excluded andexanet, and could include PCC.

Endpoints

The primary efficacy endpoint of "effective hemostasis" was assessed at 12 hours post-randomization. The current trial, ANNEXA I, used a definition of effective hemostasis that was different from that used in ANNEXA 4, in which the determination of effective hemostasis relied almost entirely on hematoma volume change. In ANNEXA I, effective hemostasis was achieved if all of the following occurred: change in hematoma volume of ≤20% (excellent) or ≤35% (good) between baseline and 12 hours, increase in NIHSS score of <7 between baseline and 12 hours; and no rescue therapies such as andexanet, PCC, or surgery to decompress the hematoma within 3 to 12 hours from randomization. The 12-hour NIHSS assessment was done by trained health care professionals masked to treatment allocation. The secondary efficacy endpoint was percent change from baseline to nadir in anti-FXa activity during the first 2 hours post-randomization. There were additional outcomes in the protocol that have not been formally analyzed by the authors. In a post hoc analysis, we assessed modified Rankin Scale at 30 days post-randomization, dichotomized as 0 to 3 and > 3 (mRs, range 0 to 6 with 0 representing no deficit and 6, death) as this is considered of interest to the field and is used in cerebrovascular disease trials but is exploratory. Safety endpoints were assessed at 30 days and included thromboembolic events and death. An endpoint adjudication committee masked to treatment assignment reviewed all potential thrombotic events and assessments of hemostatic efficacy. Where there were missing brain scans or assessments of NIHSS, the committee assessed whether this lack was due to clinical reasons (such as patient death) or administrative reasons. A core lab

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masked to treatment assignment reviewed brain imaging to determine the change in hematoma volume.

Statistical Analysis

Based on an observed hemostatic efficacy rate of 80% for patients treated with andexanet in ANNEXA-4, a total sample size of 900 patients was estimated to be required for 90% power to detect a 10% absolute difference in the rate of effective hemostasis with a 2-sided type I error rate of 5%. The primary efficacy analysis compared the proportion of patients with effective hemostasis between the andexanet and usual care groups using a Cochran-Mantel-Haenszel test stratified by time from symptom onset to baseline imaging scan (<180 vs ≥180 minutes). The secondary endpoint of percent change in anti-FXa activity was assessed using analysis of covariance (ANCOVA) on the ranked data, including intended-usual-care agent, time from symptom onset to baseline imaging scan, and baseline anti-FXa activity as covariates. Both the efficacy and safety analyses are based on intention-to-treat analysis and included a few patients with subdural and subarachnoid hemorrhages who were recruited before a change in the protocol that excluded them.

Following protocol amendment 1, total enrollment was increased from 440 to 900 patients and an interim analysis of efficacy at 450 patients was planned. For the interim analysis or the final analysis, a hierarchical testing procedure was to be used to test the primary and secondary endpoints to control the overall family-wise type I error rate at 5%. The methods for handling missing data are contained in the Protocol. The masked adjudication committee was able to

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assess cases with missing scans or missing NIHSS as non-assessable, poor, good or excellent based on their complete review of all clinical information.

Prior to amendment 1, there was an interim analysis which would potentially lead to early stopping of the trial if a p value of <0.001 occurred in favor of treatment for the primary outcome. With amendment 1, total patient enrollment in the trial was increased from 440 to 900 patients and an interim analysis with a different stopping rule was introduced to occur at 450 patients to assess efficacy. This change was made without any knowledge of treatment effect. At this interim analysis, the primary endpoint was to be tested at a significance level of 0.0310; if the primary endpoint was statistically significant at this level, the secondary endpoint would be tested at a significance level of 0.0310. The interim analysis was performed by the unmasked statistician at PHRI and reviewed by the DSMB, which made the final recommendation whether to stop the trial or not based on the totality of the efficacy and safety data available and on the interim p value <0.031 for superiority of andexanet in hemostatic efficacy. The statistical analysis plan is available at NEJM.org.

RESULTS

Between June 6, 2019 and May 27, 2023 the trial enrolled and randomly assigned 550 patients to a treatment group at 131 sites in 23 countries (Figure 1). Irregularities related to deferred and emergency consent were discovered in 20 patients and their data were removed from the database. On May 31, 2023, the pre-specified interim analysis of efficacy, based on the first 452 patients enrolled, met the criterion for efficacy and the DSMB recommended that the trial be stopped. There were 78 patients enrolled during the period lasting from database lock for the interim analysis until the time of the stopping recommendation by the DSMB. The interim

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analysis including 452 patients was designated as the primary analysis of efficacy, whereas all 530 patients in the database were included in the safety analyses. Of the patients assigned to usual care, 195 (85.5%) received PCC in the first 3 hours after randomization (median dose 3000 IU [Q1, Q3 2000, 3500 IU]). The type of PCC used was known in 119 patients (4-factor in 110 [92%] patients, 3-factor in 4 [3%], and activated PCC or factor eight bypassing activity [FEIBA] in 5 [4%]).

For patients assigned to receive andexanet, 174 (77.7%) received the low-dose regimen and the remainder, the high dose regimen. Four patients randomized to andexanet did not receive it (2 received PCC), and 4 patients randomized to usual care received andexanet. There were 9 patients in whom hemostatic efficacy was non-assessable due to lack of essential data, such as follow-up brain scan or NIHSS score. These were adjudicated as due to administrative reasons (no clinical reason found for lack of data). In 5 patients (2 on andexanet), hemostatic efficacy was non-assessable due to clinical deterioration, such as death or withdrawal of care All non-assessable patients were included in the primary efficacy analysis as failing to have hemostatic efficacy (poor efficacy).

The characteristics of the 2 treatment groups were similar with several exceptions including more patients in the andexanet group with atrial fibrillation (90% vs 84% in andexanet and usual care groups, respectively) and slightly fewer with intracerebral hemorrhage (as differentiated from all types of intracranial hemorrhage). Prior to amendment 1, 34 patients (11% in the andexanet and 6% in the usual care groups, respectively) in whom the primary site of bleeding was subdural or subarachnoid hematoma were enrolled. Subsequently, only patients with

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intracerebral hematoma were eligible. Baseline characteristics were also similar to those of registries of patients with direct oral anticoagulant-associated intracranial hemorrhage within the literature (Table S7).

The most frequently used FXa inhibitor was apixaban (62.5% and 59.2% in the andexanet and usual care groups, respectively). The baseline median hematoma volumes were 10.5 (IQR, (4.1, 24.9) and 9.0 mL (IQR, 3.1 to 22.8), on andexanet and usual care, respectively. Participants had prior stroke in 21.4% on andexanet and 21.1% on usual care, myocardial infarction in 10.7% and 14.5%, pulmonary embolism in 7.1% and 9.2%, and deep vein thrombosis in 8.0% and 9.6%, respectively on andexanet on usual care (Table 1). Bleeding was preceded by trauma in 11.6% on andexanet and in 14.5% on usual care. Median baseline NIHSS score was 9.0 in both groups. Median time from symptom onset to baseline scan was 2.3 and 2.4 hours and from scan to randomization was 1.1 and 1.2 hours in the andexanet and usual care groups, respectively.

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Efficacy

The primary efficacy outcome, effective hemostasis, occurred in 150/ 224 (67.0%) patients in the andexanet arm and in 121/ 228 (53.1%) in the usual care arm (difference, 3.4 percentage points; 95% confidence interval [CI], 4.6 to 22.2; P=0.003) (Table 2). Of the 3 components of the primary outcome, ≤ 35% hematoma expansion was achieved in 76.7% vs 64.6%; <7 point change in NIHSS, in 87.9% vs 83.0%; and rescue therapy, in 2.7% vs 6.6% with andexanet vs usual care, respectively. Most of the effective hemostasis outcomes had ≤20% hematoma volume expansion. Very large hematoma expansion (as defined as ≥12.5 mL, as used in other studies), or death within 12 hours occurred in 24/ 216 (11.1%) patients on andexanet and in 36/ 214 (16.8%)

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with usual care. The proportion of patients with modified Rankin scale scores ≤3 at 30 days was 69/246 (28.0%) and 79/255 (31.0%) for andexanet and usual care, respectively,

The secondary outcome of change in median FXa activity between baseline and 1-hour nadir was -94.5% (interquartile range [IQR], -96.6% to -88.9%) with andexanet and was -26.9% (IQR -54.2% to -9.5%) with usual care (p<0.001) (Figure S1). Results at 2 hours were similar to those at 1 hour.

Thrombotic Events and Death Within 30 Days (Table 3)

There were 27 (10.3%) patients on andexanet with a thrombotic event compared to 15 (5.6%) patients receiving usual care (difference, 4.6 percentage points; 95% CI, 0.1 to 9.2; P=0.048). Ischemic stroke occurred in 17 (6.5%) patients on andexanet and in 4 (1.5%) patients receiving usual care (difference, 5.0 percentage points; 95% CI, 1.5 to 8.8). Death occurred in 73/ 263 (27.8%) patients receiving andexanet and in 68/ 267 (25.5%) patients receiving usual care (difference, 2.5 percentage points; 95% CI, -5.0 to 10.0; P=0.51). The trial does not have sufficient information or power to draw conclusions about the effect of treatment on death. Thrombotic events in the extended population, which assigns patients to the treatment arms based on treatment received, were similar and are presented in Table S5. Figure 2 shows a forest plot for pre-specified subgroups for the primary outcome of hemostatic efficacy. The trial was not powered for conclusions about subgroups.

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DISCUSSION

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In patients with acute ICH who had received a FXa inhibitor, andexanet compared to usual care resulted in a larger proportion of patients who attained hemostatic efficacy, defined in the trial as ≤35% expansion of hematoma volume at 12 hours, <7-point worsening in NIHSS score, and absence of rescue therapy. This encompasses the trial definitions of "good" and "excellent" hemostatic efficacy, the latter requiring <20% hematoma expansion. The difference in the primary outcome between the treatment arms was apparently driven by differences in hematoma volume expansion as the two other components of the primary outcome were not appreciably different between trial groups. Hematoma expansion is considered a modifiable risk factor in patients with acute ICH that has an influence on morbidity and mortality. In the INTERACT1 trial (8), each 1 mL of hematoma growth was associated with a 5% higher chance of death or dependency at 90 days. Hematoma expansion of ≥12.5 mL has also been associated with poor outcome in patients with ICH, with an 80% positive predictive value for significant disability or death. (14,15) However, in the current trial multiplicity unadjusted results for mortality and good outcome on the modified Rankin scale did not differ appreciably between groups; the trial was not designed to have sufficient power to detect differences in these outcomes.

There was rapid reduction in anti-FXa activity with andexanet compared to minimal reduction with usual care. This effect is consistent with the mechanism of action of the drug, which is to rapidly sequester FXa inhibitor molecules to allow normalization of natural hemostatic mechanisms (11). The small amount of mannitol in the drug diluent was unlikely to affect outcomes.

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The rate of thrombotic events in the andexanet arm of approximately 10% was similar to the rate observed with andexanet in patients in the single-arm ANNEXA 4 study (12). Possible mechanisms by which andexanet increases the risk of thrombotic events include rapid reversal of anticoagulation in patients at risk of cardio-embolic stroke. It is also possible that andexanet has a direct pro-coagulant effect through binding of tissue factor pathway inhibitor, an endogenous inhibitor of factors Xa and VIIa that transiently increases D-dimer and prothrombin fragment levels (16). No thrombotic events were reported in older healthy volunteers who received andexanet in other studies (10,17). The mechanism of thrombotic events with andexanet is uncertain.

The reduction in hematoma expansion with andexanet compared to usual care was accompanied by an increase in thrombotic events, including stroke. Determining the potential net benefit of andexanet treatment in acute ICH is challenging because the relative clinical impacts are difficult to assess.

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In a trial of patients with intracerebral hematoma who had taken a factor Xa inhibitor within the previous 15 hours, andexanet rapidly reduced anti-FXa activity and resulted in better control of hematoma expansion on a composite measure than usual care but was associated with thrombotic events.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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Table 1. Baseline Characteristics.

Parameter	Statistics	Andexanet (N=224)	Usual care (N=228)
Age	Mean (SD)	78.9 (8.5)	78.9 (8.5)
Female	n(%)	94 (42.0%)	113 (49.6%)
BMI (kg/m^2)	Mean (SD)	26.9 (5.3)	26.3 (4.6)
Medical History			
Myocardial Infarction	n(%)	24 (10.7%)	33 (14.5%)
Stroke	n(%)	48 (21.4%)	48 (21.1%)
Deep Vein Thrombosis	n(%)	18 (8.0%)	22 (9.6%)
Pulmonary Embolism	n(%)	16 (7.1%)	21 (9.2%)
Atrial Fibrillation	n(%)	202 (90.2%)	192 (84.2%)
Congestive Heart Failure	n(%)	34 (15.2%)	44 (19.3%)
Diabetes	n(%)	82 (36.6%)	59 (25.9%)
Creatinine clearance <30 mL/min	n(%)	10 (4.5%)	9 (3.9%)
FXa inhibitor used			
Treatment with Apixaban	n(%)	140 (62.5%)	135 (59.2%)
Treatment with Rivaroxaban	n(%)	64 (28.6%)	65 (28.5%)

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Parameter	Statistics	Andexanet (N=224)	Usual care (N=228)
Treatment with Edoxaban	n(%)	20 (8.9%)	25 (11.0%)
Site of bleeding and clinical presentation			
- ICH	n(%)	198 (88.4%)	214 (93.9%)
- Intraventricular Hemorrhage	n(%)	3 (1.3%)	1 (0.4%)
- Subarachnoid	n(%)	9 (4.0%)	8 (3.5%)
- Subdural	n(%)	13 (5.8%)	4 (1.8%)
Bleed preceded by trauma	n(%)	26 (11.6%)	33 (14.5%)
Systolic blood pressure (ICH patients)* (mm Hg)	Mean (SD)	161.2 (27.0)	159.8 (27.7)
Hematoma volume (mL)	Median (Q1, Q3)	10.5 (4.1, 24.9)	9.0 (3.1, 22.8)
Baseline Glasgow Coma Scale score	Median (Q1, Q3)	15.0 (13.0, 15.0)	15.0 (13.0, 15.0)
Baseline NIHSS score	Median (Q1, Q3)	9.0 (5.0, 16.0)	9.0 (4.0, 14.0)
Time from symptom onset to baseline scan (hours)	Median (Q1, Q3)	2.3 (1.5, 4.0)	2.4 (1.4, 3.8)
Time from baseline scan to randomization (hours)	Median (Q1, Q3)	1.1 (0.7, 1.5)	1.2 (0.7, 1.7)

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Parameter	Statistics	Andexanet (N=224)	Usual care (N=228)
Door to needle time (hours)†	Median (Q1, Q3)	2.1 (1.5, 2.9)	2.3 (1.7, 3.1)
Andexanet patients receiving high dose (800 mg)	n(%)	45 (20.1%)	-
Andexanet patients receiving low dose (400 mg)	n(%)	175 (78.1%)	-
Usual care patients receiving PCC (within 3 hours)	n(%)	-	195 (85.5%)

Abbreviations: BMI = body mass index, FXa = Factor Xa; ICH = intracerebral hemorrhage, NIHSS = National Institutes of Health Stroke Scale, PCC = prothrombin complex concentrate, SD = standard deviation.
***Patients with ICH, 236 on andexanet and 251 on usual care.**
†Time to treatment with andexanet or to PCC, excludes usual care patients not receiving PCC.

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Table 2. Efficacy Outcomes.

Parameter	Andexanet (N=224) n/N (%)	Usual Care (N=228) n/N (%)	Difference per 100 patients (percentage points) (95% CI)*	P value*
Hemostatic efficacy	150/ 224 (67.0%)	121/ 228 (53.1%)	13.4 (4.6, 22.2)	0.003
Hemostatic efficacy according only to hematoma volume change ≤35%†	165/ 215 (76.7%)	137/ 212 (64.6%)	12.1 (3.6, 20.5)	
Hemostatic efficacy according to NIHSS score change <7 points	188/ 214 (87.9%)	181/ 218 (83.0%)	4.6 (-2.0, 11.2)	
Use of rescue therapy between 3-12 hours	6/ 224 (2.7%)	15/ 228 (6.6%)	-3.8 (-7.6, 0.0)	
Hematoma increase ≥12.5 mL‡	24/ 216 (11.1%)	36/ 214 (16.8%)	-5.6 (-12.0, 0.8)	
Hemostatic efficacy, excluding patients non-evaluable for administrative reasons	150/ 218 (68.8%)	121/ 225 (53.8%)	14.5 (5.7, 23.4)	

Abbreviations: CI = confidence interval, NIHSS = National Institutes of Health Stroke Scale.
***The proportion difference, P value, and 95% CI are from Cochran-Mantel-Haenszel test stratified by time from symptom onset to baseline imaging scan (<180 vs ≥180 minutes).**
†Patients with hematoma volume change non-evaluable are excluded.
‡Including patients dead within 12 hours without follow-up brain imaging.

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Table 3. Thrombotic Events and Deaths Within 30 Days

Parameter	Andexanet (N=263)	Usual care (N=267)	Increase per 100 patients (percentage points) (95% CI)*	P value*
No. of patients with ≥1 Thrombotic event, n(%)	27 (10.3%)	15 (5.6%)	4.6 (0.1, 9.2)	0.048
Transient Ischemic Attack, n(%)	0 (0%)	0 (0%)	-	
Ischemic Stroke, n(%)	17 (6.5%)	4 (1.5%)	5.0 (1.5, 8.8)	
Myocardial Infarction, n(%)	11 (4.2%)	4 (1.5%)	2.7 (-0.2, 6.1)	
Deep Vein Thrombosis, n(%)	1 (0.4%)	2 (0.7%)	-0.4 (-2.4, 1.5)	
Pulmonary Embolism, n(%)	1 (0.4%)	6 (2.2%)	-1.9 (-4.5, 0.2)	
Arterial Systemic Embolism, n(%)	3 (1.1%)	2 (0.7%)	0.4 (-1.7, 2.7)	
Death, n(%)	73 (27.8%)	68 (25.5%)	2.5 (-5.0, 10.0)	0.51

Abbreviation: CI = confidence interval.
***For death event, the estimated increase with andexanet per 100 patients, 95% CI, and the p-value are from Cochran-Mantel-Haenszel test stratified by time from symptom onset to baseline imaging scan (<180 vs ≥180 minutes). For number of patients with ≥1 thrombotic event, the increase with andexanet per 100 patients is estimated from the proportion difference, the 95% CI is Wald CI, and the P value is from Chi-square test. The CI for component of thrombotic event is calculated using exact CIs.**
The analysis is based on the intention to treat, using the extended population.

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Figure Legends

Figure 1. CONSORT Diagram.

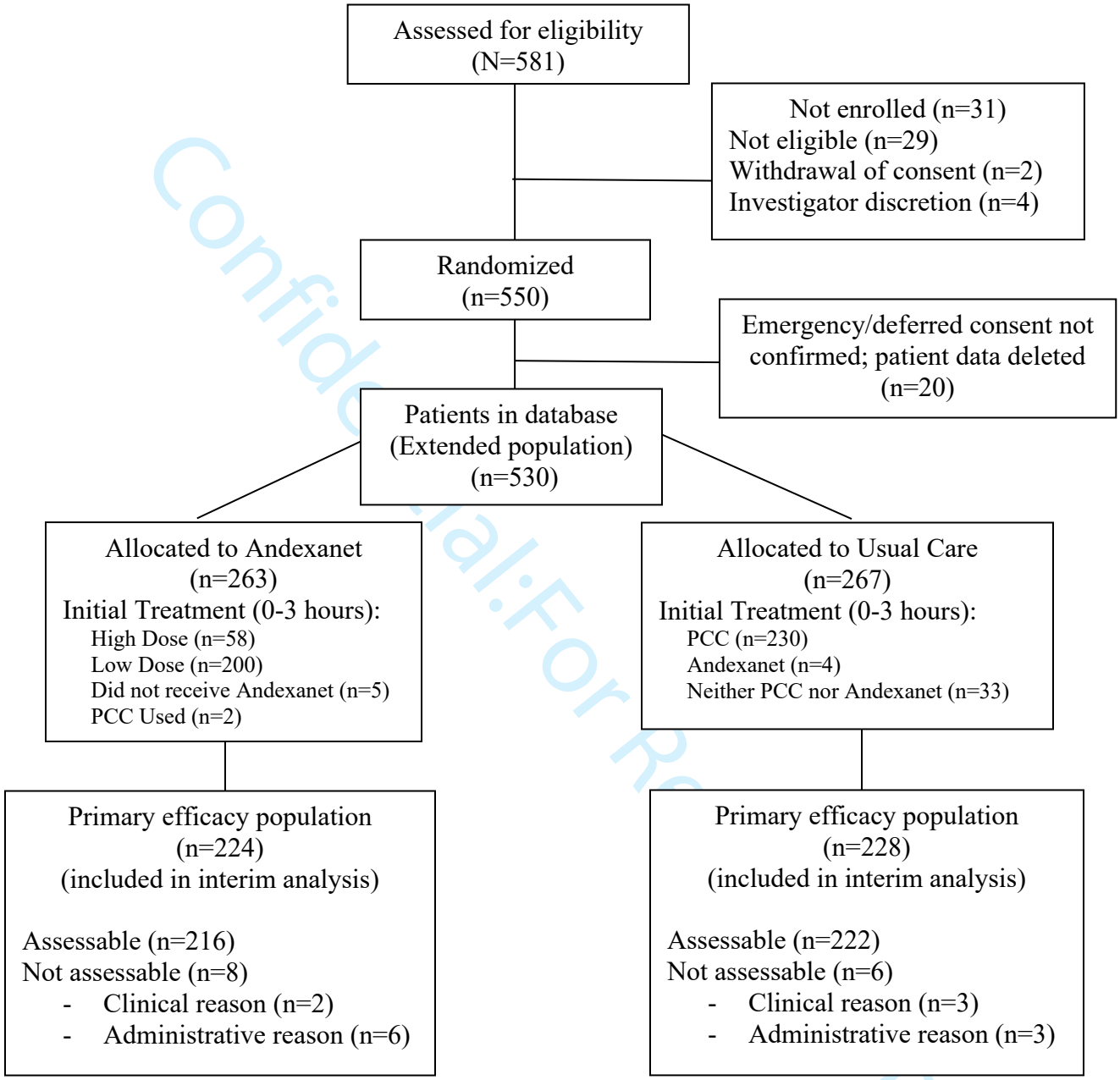
Abbreviation: PCC = prothrombin complex concentrate.

Figure 2. Subgroup Analysis for Hemostatic Efficacy.

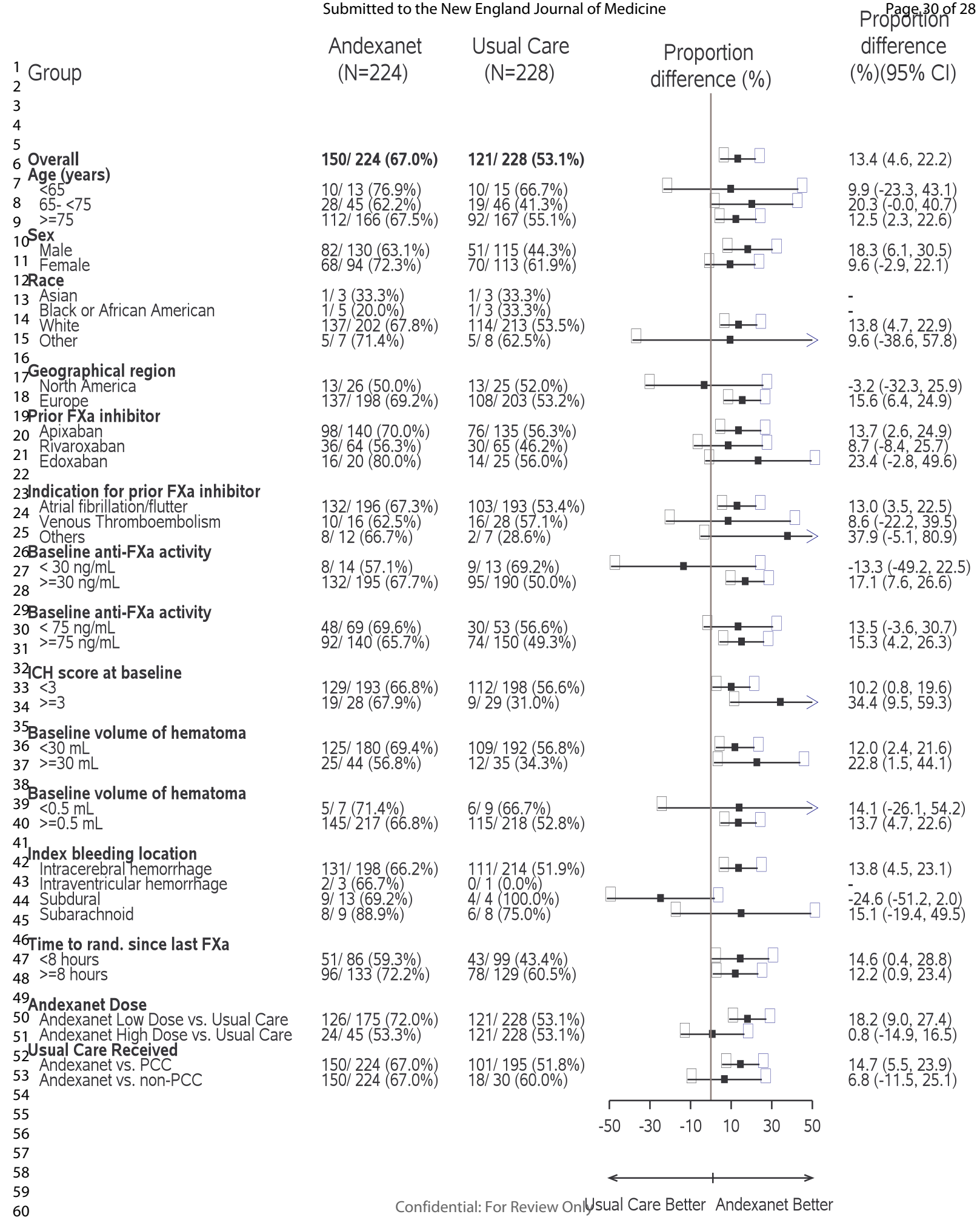
Abbreviations: CI = confidence interval, FXa = factor Xa, ICH = intracerebral hemorrhage, PCC = prothrombin complex concentrate.

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Figure 1. CONSORT Diagram.



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Group
Andexanet (N=224)
Usual Care (N=228)
Proportion difference (%)
Proportion difference (%)(95% CI)
Overall 150/ 224 (67.0%) 121/ 228 (53.1%) 13.4 (4.6, 22.2)
Age (years)
<65 10/ 13 (76.9%) 10/ 15 (66.7%) 9.9 (-23.3, 43.1)
65- <75 28/ 45 (62.2%) 19/ 46 (41.3%) 20.3 (-0.0, 40.7)
>=75 112/ 166 (67.5%) 92/ 167 (55.1%) 12.5 (2.3, 22.6)
Sex
Male 82/ 130 (63.1%) 51/ 115 (44.3%) 18.3 (6.1, 30.5)
Female 68/ 94 (72.3%) 70/ 113 (61.9%) 9.6 (-2.9, 22.1)
Race
Asian 1/ 3 (33.3%) 1/ 3 (33.3%) -
Black or African American 1/ 5 (20.0%) 1/ 3 (33.3%) -
White 137/ 202 (67.8%) 114/ 213 (53.5%) 13.8 (4.7, 22.9)
Other 5/ 7 (71.4%) 5/ 8 (62.5%) 9.6 (-38.6, 57.8)
Geographical region
North America 13/ 26 (50.0%) 13/ 25 (52.0%) -3.2 (-32.3, 25.9)
Europe 137/ 198 (69.2%) 108/ 203 (53.2%) 15.6 (6.4, 24.9)
Prior FXa inhibitor
Apixaban 98/ 140 (70.0%) 76/ 135 (56.3%) 13.7 (2.6, 24.9)
Rivaroxaban 36/ 64 (56.3%) 30/ 65 (46.2%) 8.7 (-8.4, 25.7)
Edoxaban 16/ 20 (80.0%) 14/ 25 (56.0%) 23.4 (-2.8, 49.6)
Indication for prior FXa inhibitor
Atrial fibrillation/flutter 132/ 196 (67.3%) 103/ 193 (53.4%) 13.0 (3.5, 22.5)
Venous Thromboembolism 10/ 16 (62.5%) 16/ 28 (57.1%) 8.6 (-22.2, 39.5)
Others 8/ 12 (66.7%) 2/ 7 (28.6%) 37.9 (-5.1, 80.9)
Baseline anti-FXa activity
< 30 ng/mL 8/ 14 (57.1%) 9/ 13 (69.2%) -13.3 (-49.2, 22.5)
>=30 ng/mL 132/ 195 (67.7%) 95/ 190 (50.0%) 17.1 (7.6, 26.6)
Baseline anti-FXa activity
< 75 ng/mL 48/ 69 (69.6%) 30/ 53 (56.6%) 13.5 (-3.6, 30.7)
>=75 ng/mL 92/ 140 (65.7%) 74/ 150 (49.3%) 15.3 (4.2, 26.3)
ICH score at baseline
<3 129/ 193 (66.8%) 112/ 198 (56.6%) 10.2 (0.8, 19.6)
>=3 19/ 28 (67.9%) 9/ 29 (31.0%) 34.4 (9.5, 59.3)
Baseline volume of hematoma
<30 mL 125/ 180 (69.4%) 109/ 192 (56.8%) 12.0 (2.4, 21.6)
>=30 mL 25/ 44 (56.8%) 12/ 35 (34.3%) 22.8 (1.5, 44.1)
Baseline volume of hematoma
<0.5 mL 5/ 7 (71.4%) 6/ 9 (66.7%) 14.1 (-26.1, 54.2)
>=0.5 mL 145/ 217 (66.8%) 115/ 218 (52.8%) 13.7 (4.7, 22.6)
Index bleeding location
Intracerebral hemorrhage 131/ 198 (66.2%) 111/ 214 (51.9%) 13.8 (4.5, 23.1)
Intraventricular hemorrhage 2/ 3 (66.7%) 0/ 1 (0.0%) -
Subdural 9/ 13 (69.2%) 4/ 4 (100.0%) -24.6 (-51.2, 2.0)
Subarachnoid 8/ 9 (88.9%) 6/ 8 (75.0%) 15.1 (-19.4, 49.5)
Time to rand. since last FXa
<8 hours 51/ 86 (59.3%) 43/ 99 (43.4%) 14.6 (0.4, 28.8)
>=8 hours 96/ 133 (72.2%) 78/ 129 (60.5%) 12.2 (0.9, 23.4)
Andexanet Dose
Andexanet Low Dose vs. Usual Care 126/ 175 (72.0%) 121/ 228 (53.1%) 18.2 (9.0, 27.4)
Andexanet High Dose vs. Usual Care 24/ 45 (53.3%) 121/ 228 (53.1%) 0.8 (-14.9, 16.5)
Usual Care Received
Andexanet vs. PCC 150/ 224 (67.0%) 101/ 195 (51.8%) 14.7 (5.5, 23.9)
Andexanet vs. non-PCC 150/ 224 (67.0%) 18/ 30 (60.0%) 6.8 (-11.5, 25.1)
-50 -30 -10 10 30 50
Usual Care Better
Andexanet Better