

# **Supplemental Material**

**Table S1. APPRAISE-2 clinical endpoint definitions**

Clinical Endpoints	Definition
Myocardial infarction	Elevation of cardiac biomarkers (CK-MB, troponin T or troponin I) above the upper reference limit + one of the following: a. ischemic symptoms b. ECG changes: $\geq 1$ mm ST elevation in 2 leads, or $\geq 0.5$ mm ST depression in 2 leads dynamic horizontal or downsloping, or new and dynamic T wave inversion $> 0.1$ mm in 2 leads c. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality on echocardiography, radionuclide ventriculography, or MRI
Unstable angina	Worsening or recurrent severe or repetitive angina symptoms at rest lasting at least 10 minutes + at least 2 of the following: a. ECG changes: $\geq 1$ mm ST elevation in 2 leads, or $\geq 0.5$ mm ST depression in 2 leads dynamic horizontal or downsloping, or new and dynamic T wave inversion $> 0.1$ mm in 2 leads b. leading to inpatient hospitalization c. leading to an unplanned or urgent cardiac catheterization that shows evidence of hemodynamically and clinically significant stenosis, with or without revascularization
Stroke	A sudden onset of focal neurological deficit that lasted at least 24 hours, not related to another identifiable cause (i.e. brain tumor).
Bleeding (TIMI criteria)	Major: Fatal bleeding, intracranial hemorrhage, and clinically overt bleeding with a hemoglobin drop of $\geq 5$ g/dl, or $\geq 15\%$ absolute decrease in hematocrit. Minor: Observed blood loss with 3 g/dl decrease in hemoglobin concentration or 10% decrease in hematocrit; or no observed blood loss with 4 g/dl decrease in hemoglobin concentration or 12% decrease in hematocrit Minimal: any clinically overt or observed sign of hemorrhage that is associated with a $< 3$ g/dl decrease in hemoglobin concentration or $< 9\%$ decrease in hematocrit.

**Table S2. Rates of serious and non-serious clinical events**

Category of event	Serious	Non-serious
<b>Prespecified AEs</b>		
Heart failure	308 (71.8)	121 (28.2)
Pneumonia	87 (52.4)	79 (47.6)
Syncope	25 (48.1)	27 (51.9)
Atrial fibrillation	61 (30.5)	139 (69.5)
Chest pain	195 (22.3)	681 (77.7)
Urinary tract infection	27 (16.0)	142 (84.0)
Hypertension	45 (14.4)	268 (85.6)
Dizziness	18 (6.6)	254 (93.4)
Dyspnea	10 (3.6)	268 (96.4)
Headache	2 (0.9)	229 (99.1)
Bleed sent for coordinator review only	117 (9.1)	1173 (90.9)
<b>Site-Reported Endpoints</b>		
Myocardial infarction	391 (97.5)	10 (2.5)
Unstable angina	372 (82.9)	77 (17.1)
Ischemic stroke	71 (93.4)	5 (6.6)
Intracranial hemorrhage	17 (100.0)	0 (0.0)
Stroke (unknown type)	5 (83.3)	1 (16.7)
TIA	13 (68.4)	6 (31.6)
TIMI major bleeding	43 (81.1)	10 (18.9)
TIMI major or minor bleeding	53 (70.7)	22 (29.3)
ISTH major or clinically relevant non-major bleeding	151 (43.4)	197 (56.6)

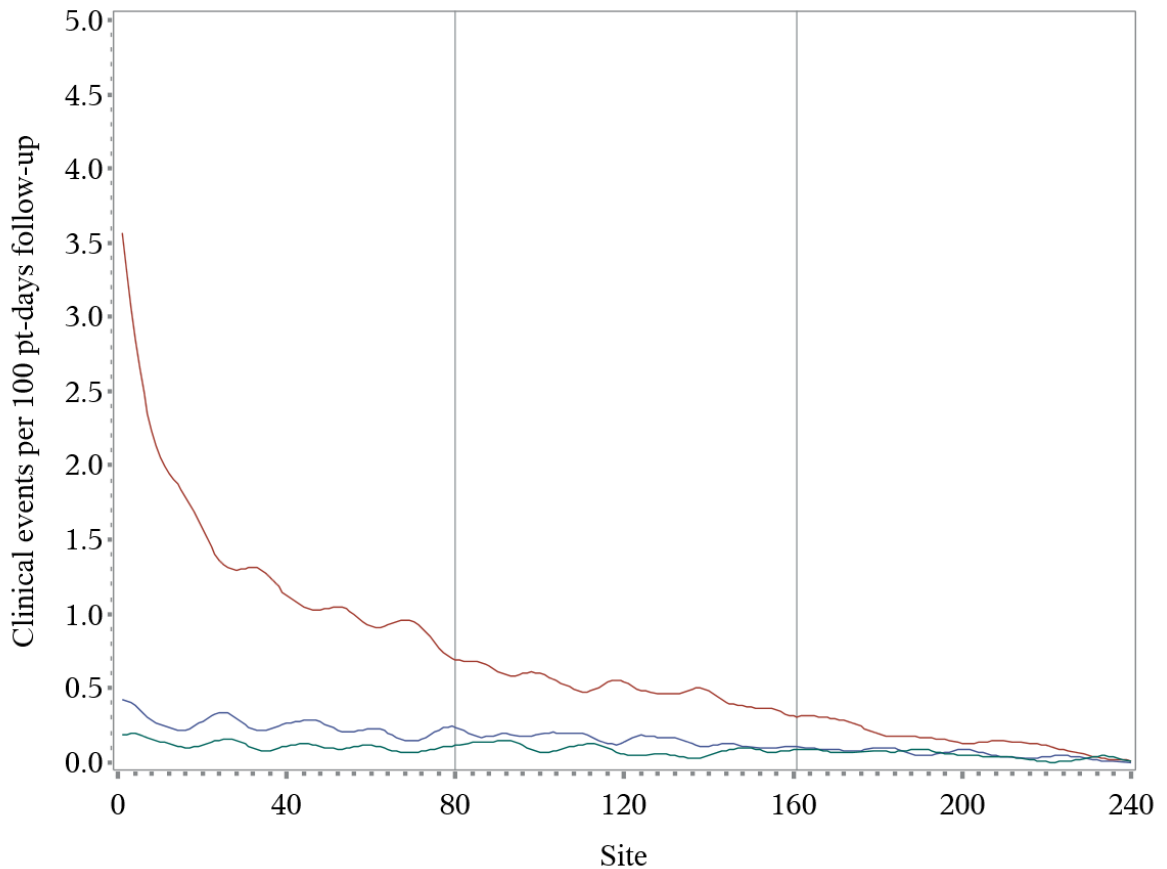
Abbreviations: AEs, adverse events; ISTH, International Society on Thrombosis and Haemostasis; TIA, transient ischemic attack; TIMI, Thrombolysis in Myocardial Infarction.

**Table S3. Associations between region and patient characteristics and event reporting**

	Clinical endpoints			Serious AEs			Non-serious AEs		
	RR (95% CI)	F	p	RR (95% CI)	F	p	RR (95% CI)	F	p
<b>Region (ref: East Europe)</b>		5.82	0.0001		10.33	<.0001		3.03	0.0167
<b>Asia Pacific</b>	0.62 (0.42, 0.92)			0.97 (0.64, 1.47)			1.36 (0.89, 2.08)		
<b>North America</b>	1.26 (0.93, 1.71)			1.85 (1.32, 2.59)			1.78 (1.25, 2.53)		
<b>South America</b>	1.74 (1.20, 2.51)			1.58 (1.03, 2.43)			1.18 (0.76, 1.83)		
<b>West Europe</b>	1.39 (1.03, 1.88)			2.65 (1.91, 3.68)			1.53 (1.08, 2.17)		
<b>Age (per 10y)</b>	1.21 (1.10, 1.33)	16.15	<.0001	1.07 (1.00, 1.15)	3.75	0.0528	1.03 (1.00, 1.07)	4.62	0.0317
<b>Female sex</b>	1.17 (0.99, 1.39)	3.52	0.0608	1.13 (0.99, 1.28)	3.43	0.0640	1.26 (1.19, 1.34)	62.91	<.0001
<b>Peripheral vascular disease</b>	1.17 (0.96, 1.44)	2.40	0.1217	1.45 (1.26, 1.68)	25.43	<.0001	1.09 (1.01, 1.17)	4.98	0.0257
<b>Depression</b>	1.28 (0.92, 1.77)	2.19	0.1391	1.77 (1.45, 2.17)	30.39	<.0001	1.27 (1.14, 1.42)	17.90	<.0001
<b>Hypertension</b>	1.25 (0.99, 1.59)	3.52	0.0605	1.16 (0.99, 1.37)	3.28	0.0701	1.05 (0.98, 1.13)	1.72	0.1900
<b>Cardiovascular disease</b>	1.08 (0.84, 1.39)	0.35	0.5535	0.92 (0.76, 1.12)	0.66	0.4177	1.02 (0.93, 1.11)	0.13	0.7139
<b>Atrial fibrillation</b>	1.30 (0.98, 1.72)	3.28	0.0703	1.25 (1.01, 1.55)	4.22	0.0400	1.21 (1.10, 1.34)	13.78	0.0002
<b>Diabetes</b>	1.30 (1.10, 1.53)	9.33	0.0023	1.35 (1.19, 1.53)	21.28	<.0001	1.07 (1.01, 1.13)	4.68	0.0306
<b>Heart failure</b>	1.19 (1.01, 1.40)	4.22	0.0401	1.93 (1.70, 2.18)	106.50	<.0001	1.10 (1.03, 1.16)	9.26	0.0024
<b>Renal dysfunction</b>	1.13 (0.94, 1.37)	1.63	0.2020	1.30 (1.12, 1.50)	12.12	0.0005	1.11 (1.04, 1.19)	9.83	0.0017

Abbreviations: AEs, adverse events; CI, confidence interval; RR, relative risk.

**Figure S1. Rates of site-reported clinical endpoints, serious adverse events, and non-serious adverse events per 100 patient-days of follow-up at site level (sites with 10 or more patients, n=241)**



The median (IQR) rate of clinical events per 100 patient-days of follow-up for high-reporting, middle-reporting and low-reporting sites were: 0.20 (0.10,0.35), 0.13 (0.06,0.23), 0.04 (0.00,0.07) for serious adverse events; 1.15 (0.94,1.56), 0.52 (0.38,0.62), 0.14 (0.06,0.23) for non-serious adverse events; and 0.09 (0.04,0.17), 0.06 (0.03,0.12), 0.04 (0.00,0.08) for site-reported endpoints.