

Supplementary material

Table S1. Definition and Counts of Patient Characteristics for Inclusion in Exposure–Response Models.

Covariate	Categories	Exposure–Efficacy Models		Exposure–Safety Models	
		Patients (<i>N</i> = 15 167)	Percent	Patients (<i>N</i> = 15 350)	Percent
Patient characteristics included in the exposure–response models regardless of significance level					
Age	<65 years	9640	63.6	9769	63.6
	65–75 years	4434	29.2	4480	29.2
	>75 years	1093	7.2	1101	7.2
Baseline renal function (CrCl)	>80 mL/min	8825	58.2	8884	57.9
	50–80 mL/min	5296	34.9	5389	35.1
	<50 mL/min	1046	6.9	1077	7.0
Patient characteristics for potential inclusion in the exposure–response models					
Baseline antiplatelet use	Aspirin plus thieno	14 133	93.2	14 313	93.2
	Aspirin	1034	6.8	1037	6.8
Hospital region	Eastern Europe	6048	39.9	6048	39.4
	Asia	2974	19.6	3157	20.6
	Western Europe	2182	14.4	2182	14.2
	South America	1656	10.9	1656	10.8
	Others	1441	9.5	1441	9.4

	North America	866	5.7	866	5.6
History of stroke/TIA	No	14 767	97.4	14 948	97.4
	Yes	400	2.6	402	2.6
Weight	≥60 to <90 kg	10 128	66.8	10 247	66.8
	≥90 kg	3675	24.2	3677	24.0
	<60 kg	1364	9.0	1426	9.3
Sex	Male	11 330	74.7	11 471	74.7
	Female	3837	25.3	3879	25.3
Low baseline hemoglobin (<13 g/dL for male and <12 g/dL for female)	No	12 210	80.5	12 321	80.3
	Yes	2957	19.5	3029	19.7
History of GI bleeding	No	Not evaluated	Not evaluated	15 216	99.1
	Yes	Not evaluated	Not evaluated	134	0.9
Baseline type of ACS	STEMI	7636	50.3	7725	50.3
	NSTEMI	3917	25.8	3929	25.6
	UA	3614	23.8	3696	24.1
History of MI	No	11 061	72.9	11 202	73.0
	Yes	4106	27.1	4148	27.0
History of diabetes mellitus	No	10 328	68.1	10 442	68.0
	Yes	4839	31.9	4908	32.0
History of heart failure	No	13 488	88.9	13 671	89.1
	Yes	1679	11.1	1679	10.9
History of hypertension	Yes	10 288	67.8	10 362	67.5
	No	4879	32.2	4988	32.5
Elevated cardiac enzymes	Yes	12 488	82.3	12 600	82.1

	No	2679	17.7	2750	17.9
Smoking status (current/other)	No	Not evaluated	Not evaluated	9017	58.7
	Yes	Not evaluated	Not evaluated	6333	41.3
Alcohol use	Abstinent	Not evaluated	Not evaluated	8075	52.6
	Light	Not evaluated	Not evaluated	6086	39.6
	Moderate	Not evaluated	Not evaluated	1104	7.2
	Heavy	Not evaluated	Not evaluated	85	0.6
Previous revascularization (CABG or PCI)	Yes	9239	60.9	9252	60.3
	No	5928	39.1	6098	39.7

Abbreviations: ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; CrCl, estimated creatinine clearance; GI, gastrointestinal; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; TIA, transient ischemic attack; UA, unstable angina.

Table S2. Results of the Likelihood Ratio Test for the Final Models for Efficacy Outcomes.

Variable	Degrees of Freedom	AIC	P Value (LRT)
MI, ischemic stroke, and nonhemorrhagic CV death			
None (null model)	NA	15851.42	NA
C _{max}	1	15858.80	0.0022
Age	2	15871.10	0.00001
CrCl	2	15859.79	0.00206
Type of ACS	2	15857.48	0.00656
History of MI	1	15918.19	<0.00001
Previous revascularization	1	15890.09	<0.00001
History of diabetes mellitus	1	15858.19	0.00306
History of heart failure	1	15875.68	<0.00001
Elevated cardiac enzymes	1	15861.06	0.00065
Baseline hemoglobin	1	15869.51	0.00001
MI, ischemic stroke, and death from all causes			
None (null model)	NA	16324.40	NA
C _{max}	1	16331.20	0.00302
Age	2	16343.68	0.00001
CrCl	2	16335.37	0.00056

History of MI	1	16395.67	<0.00001
Previous revascularization	1	16363.01	<0.00001
History of diabetes mellitus	1	16331.73	0.00226
History of heart failure	1	16346.10	<0.00001
Elevated cardiac enzymes	1	16385.59	<0.00001
Baseline hemoglobin	1	16339.89	0.00003

Abbreviations: ACS, acute coronary syndrome; AIC, Akaike information criterion; C_{\max} steady-state maximum plasma concentration; CrCl, estimated creatinine clearance; CV, cardiovascular; LRT, likelihood ratio test; MI, myocardial infarction; NA, not applicable.

Table S3. Results of the Likelihood Ratio Test for the Final Models for Safety Outcomes.

Variable	Degrees of Freedom	AIC	P Value (LRT)
TIMI major bleeding			
None (null model)	NA	3249.459	NA
C _{max}	1	3275.479	<0.00001
Age	2	3254.442	0.0112
CrCl	2	3246.607	0.56322
Sex	1	3256.331	0.0029
Previous revascularization	1	3255.595	0.00434
Clinically significant bleeding			
None (null model)	NA	30052.66	NA
C _{max}	1	30237.35	<0.00001
Age	2	30077.10	<0.00001
CrCl	2	30050.33	0.43262
Hospital region	5	30180.86	<0.00001
Previous revascularization	1	30065.07	0.00015
History of hypertension	1	30067.45	0.00004
Baseline alcohol intake	3	30064.99	0.00038
Baseline hemoglobin	1	30062.24	0.00067

Abbreviations: AIC, Akaike information criterion; C_{\max} steady-state maximum plasma concentration; CrCl, estimated creatinine clearance; LRT, likelihood ratio test; NA, not applicable.