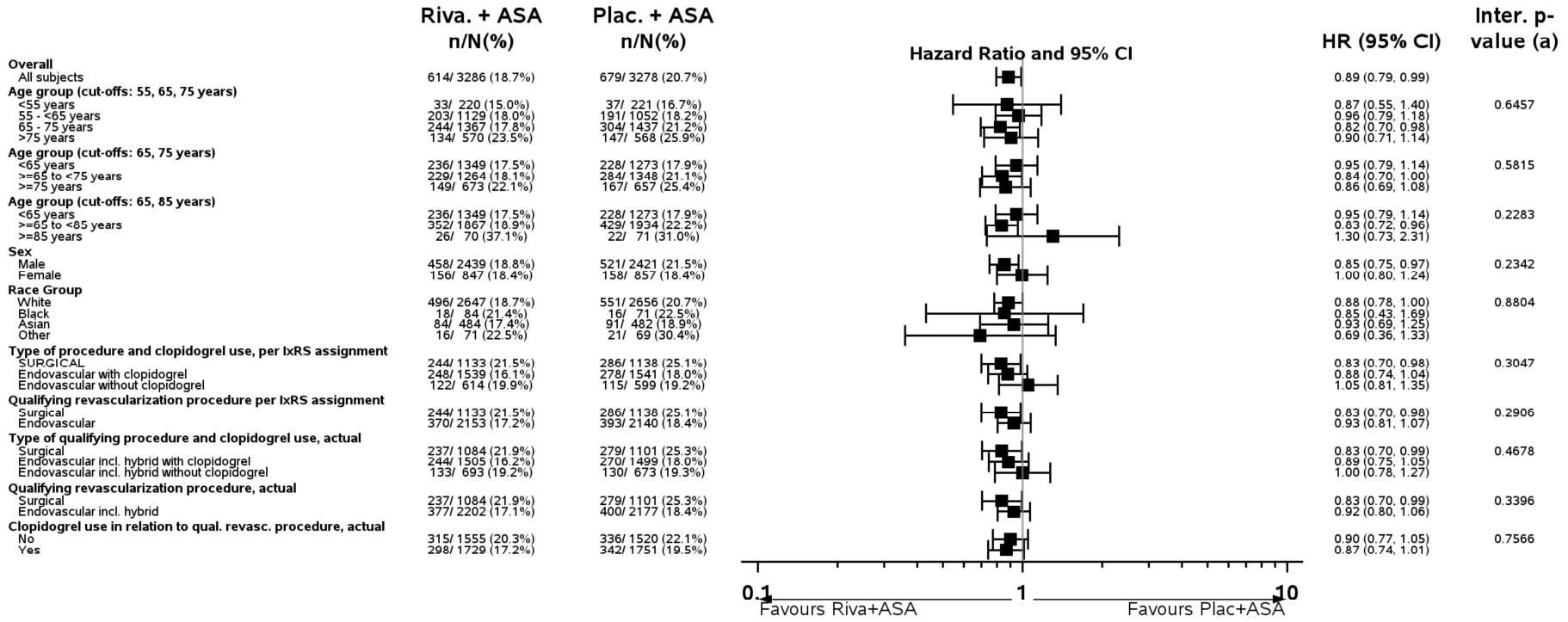
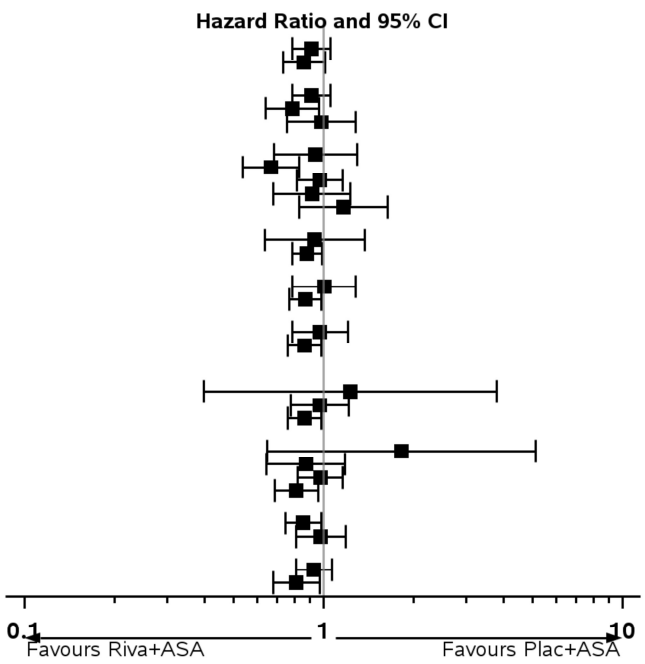
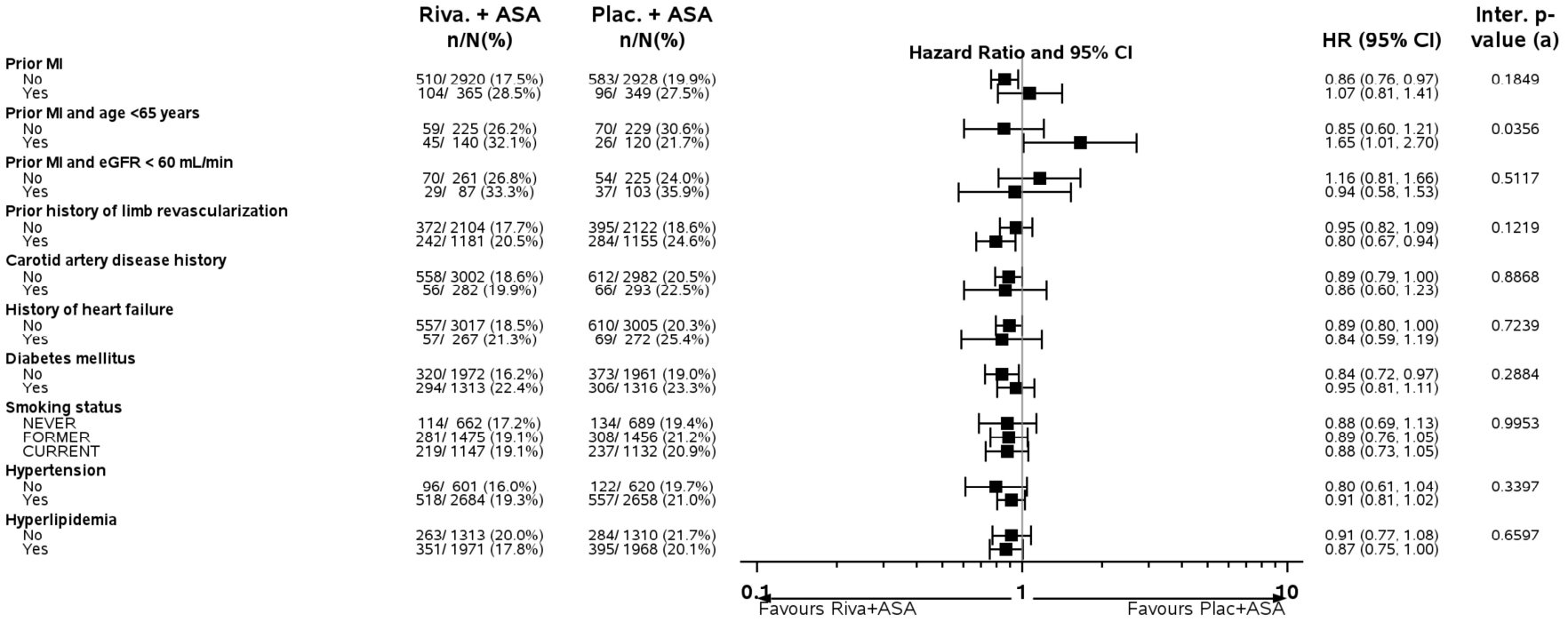
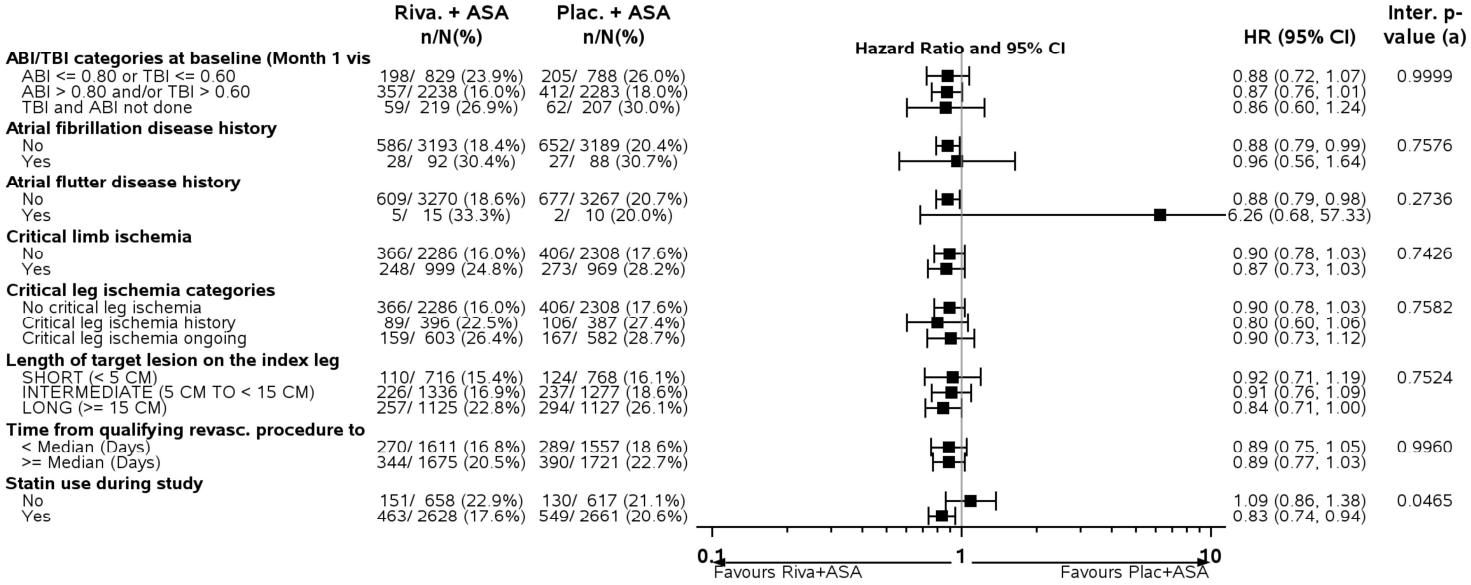
図 2.7.3.7-5 MI、虚血性脳卒中、全死亡、ALI、又は血管系の原因による大切断の複合エンドポイントの Forest プロット
（試験 17454、全体集団、ITT、ECOD まで、ICAC 判定）



	Riva. + ASA n/N(%)	Plac. + ASA n/N(%)	HR (95% CI)	Inter. p-value (a)
Clopidogrel use at the time of randomization				
No	335/ 1621 (20.7%)	360/ 1613 (22.3%)	0.91 (0.78, 1.06)	0.6115
Yes	278/ 1658 (16.8%)	317/ 1655 (19.2%)	0.86 (0.73, 1.01)	
Clopidogrel use continued after randomization (days)				
None	335/ 1621 (20.7%)	360/ 1613 (22.3%)	0.91 (0.78, 1.06)	0.3733
<= 30 days	170/ 988 (17.2%)	197/ 935 (21.1%)	0.79 (0.64, 0.97)	
> 30 days	106/ 644 (16.5%)	115/ 678 (17.0%)	0.98 (0.75, 1.28)	
Geographic Region 1				
North America	73/ 347 (21.0%)	77/ 347 (22.2%)	0.94 (0.68, 1.29)	0.0382
Western Europe	138/ 914 (15.1%)	197/ 912 (21.6%)	0.67 (0.54, 0.83)	
Eastern Europe	249/ 1301 (19.1%)	252/ 1298 (19.4%)	0.97 (0.81, 1.16)	
Asia Pacific	83/ 481 (17.3%)	91/ 480 (19.0%)	0.91 (0.68, 1.23)	
South America	71/ 243 (29.2%)	62/ 241 (25.7%)	1.16 (0.83, 1.64)	
Geographic Region 3				
US	50/ 262 (19.1%)	54/ 262 (20.6%)	0.93 (0.63, 1.37)	0.7799
non-US	564/ 3024 (18.7%)	625/ 3016 (20.7%)	0.88 (0.79, 0.99)	
Weight group (cut-off 60 kg)				
<=60 kg	128/ 534 (24.0%)	129/ 547 (23.6%)	1.00 (0.79, 1.28)	0.2912
>60 kg	481/ 2716 (17.7%)	540/ 2700 (20.0%)	0.87 (0.77, 0.98)	
eGFR (cut-offs: 60 ml/min/1.73m2)				
<60 ml/min/1.73m2	163/ 661 (24.7%)	170/ 666 (25.5%)	0.97 (0.78, 1.21)	0.3471
>=60 ml/min/1.73m2	425/ 2499 (17.0%)	477/ 2493 (19.1%)	0.86 (0.76, 0.98)	
eGFR (cut-offs: 15, 30 and 60 ml/min/1.73m2)				
<15 ml/min/1.73m2	2/ 2 (100.0%)	0/ 0		0.5293
15 - <30 ml/min/1.73m2	5/ 13 (38.5%)	11/ 28 (39.3%)	1.23 (0.40, 3.79)	
30 - <60 ml/min/1.73m2	156/ 646 (24.1%)	159/ 638 (24.9%)	0.97 (0.78, 1.21)	
>=60 ml/min/1.73m2	425/ 2499 (17.0%)	477/ 2493 (19.1%)	0.86 (0.76, 0.98)	
eGFR (cut-offs: 30, 50 and 80 ml/min/1.73m2)				
<30 ml/min/1.73m2	7/ 15 (46.7%)	11/ 28 (39.3%)	1.82 (0.65, 5.13)	0.2844
30 - 50 ml/min/1.73m2	84/ 343 (24.5%)	85/ 308 (27.6%)	0.87 (0.65, 1.18)	
>50 - 80 ml/min/1.73m2	248/ 1367 (18.1%)	256/ 1369 (18.7%)	0.97 (0.82, 1.16)	
>80 ml/min/1.73m2	249/ 1435 (17.4%)	295/ 1454 (20.3%)	0.81 (0.69, 0.96)	
Fragile subjects				
No	386/ 2338 (16.5%)	436/ 2332 (18.7%)	0.86 (0.75, 0.98)	0.2449
Yes	207/ 835 (24.8%)	214/ 839 (25.5%)	0.98 (0.81, 1.18)	
Prior coronary artery disease				
No	395/ 2233 (17.7%)	425/ 2263 (18.8%)	0.93 (0.81, 1.06)	0.2361
Yes	219/ 1052 (20.8%)	254/ 1015 (25.0%)	0.81 (0.68, 0.97)	



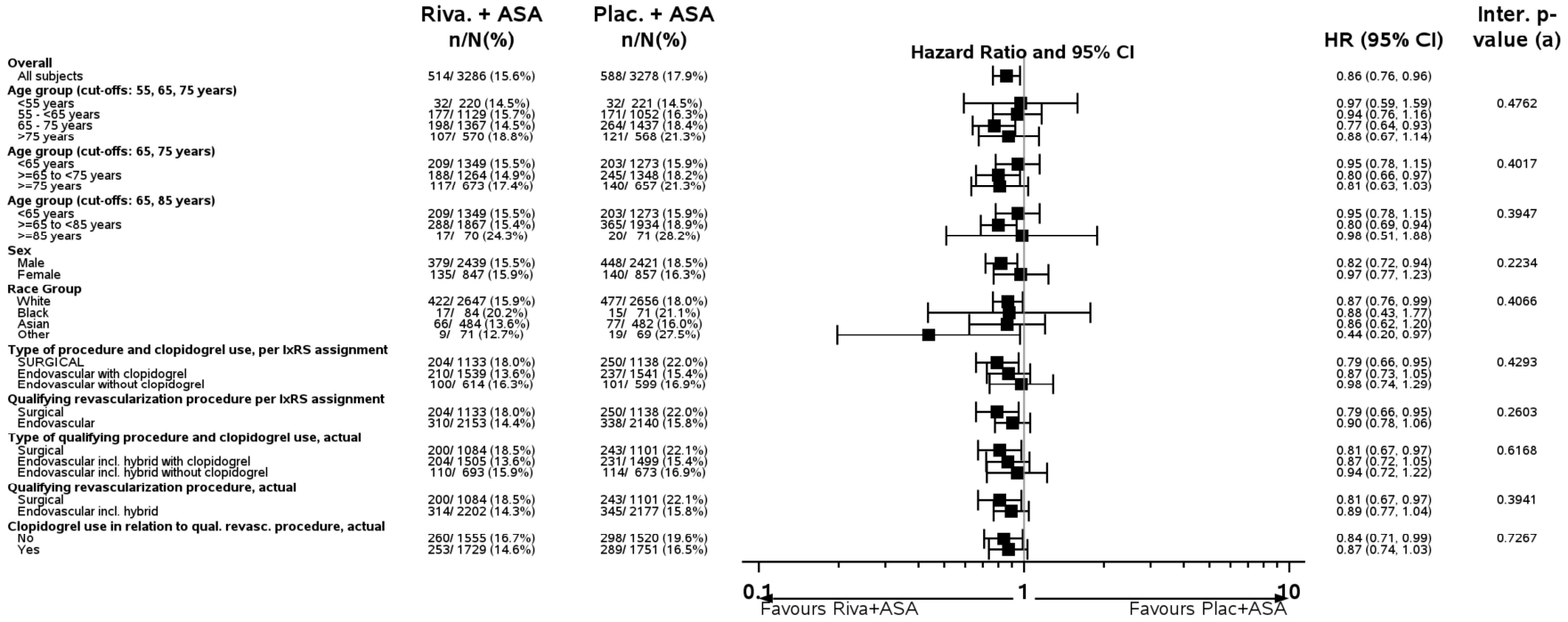

Riva. + ASA n/N(%)
Plac. + ASA n/N(%)
Hazard Ratio and 95% CI
HR (95% CI)
Inter. p-value (a)
Prior MI
No 510/ 2920 (17.5%) 583/ 2928 (19.9%) 0.86 (0.76, 0.97) 0.1849
Yes 104/ 365 (28.5%) 96/ 349 (27.5%) 1.07 (0.81, 1.41)
Prior MI and age <65 years
No 59/ 225 (26.2%) 70/ 229 (30.6%) 0.85 (0.60, 1.21) 0.0356
Yes 45/ 140 (32.1%) 26/ 120 (21.7%) 1.65 (1.01, 2.70)
Prior MI and eGFR < 60 mL/min
No 70/ 261 (26.8%) 54/ 225 (24.0%) 1.16 (0.81, 1.66) 0.5117
Yes 29/ 87 (33.3%) 37/ 103 (35.9%) 0.94 (0.58, 1.53)
Prior history of limb revascularization
No 372/ 2104 (17.7%) 395/ 2122 (18.6%) 0.95 (0.82, 1.09) 0.1219
Yes 242/ 1181 (20.5%) 284/ 1155 (24.6%) 0.80 (0.67, 0.94)
Carotid artery disease history
No 558/ 3002 (18.6%) 612/ 2982 (20.5%) 0.89 (0.79, 1.00) 0.8868
Yes 56/ 282 (19.9%) 66/ 293 (22.5%) 0.86 (0.60, 1.23)
History of heart failure
No 557/ 3017 (18.5%) 610/ 3005 (20.3%) 0.89 (0.80, 1.00) 0.7239
Yes 57/ 267 (21.3%) 69/ 272 (25.4%) 0.84 (0.59, 1.19)
Diabetes mellitus
No 320/ 1972 (16.2%) 373/ 1961 (19.0%) 0.84 (0.72, 0.97) 0.2884
Yes 294/ 1313 (22.4%) 306/ 1316 (23.3%) 0.95 (0.81, 1.11)
Smoking status
NEVER 114/ 662 (17.2%) 134/ 689 (19.4%) 0.88 (0.69, 1.13) 0.9953
FORMER 281/ 1475 (19.1%) 308/ 1456 (21.2%) 0.89 (0.76, 1.05)
CURRENT 219/ 1147 (19.1%) 237/ 1132 (20.9%) 0.88 (0.73, 1.05)
Hypertension
No 96/ 601 (16.0%) 122/ 620 (19.7%) 0.80 (0.61, 1.04) 0.3397
Yes 518/ 2684 (19.3%) 557/ 2658 (21.0%) 0.91 (0.81, 1.02)
Hyperlipidemia
No 263/ 1313 (20.0%) 284/ 1310 (21.7%) 0.91 (0.77, 1.08) 0.6597
Yes 351/ 1971 (17.8%) 395/ 1968 (20.1%) 0.87 (0.75, 1.00)
0.1
1
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Favours Riva+ASA
Favours Plac+ASA

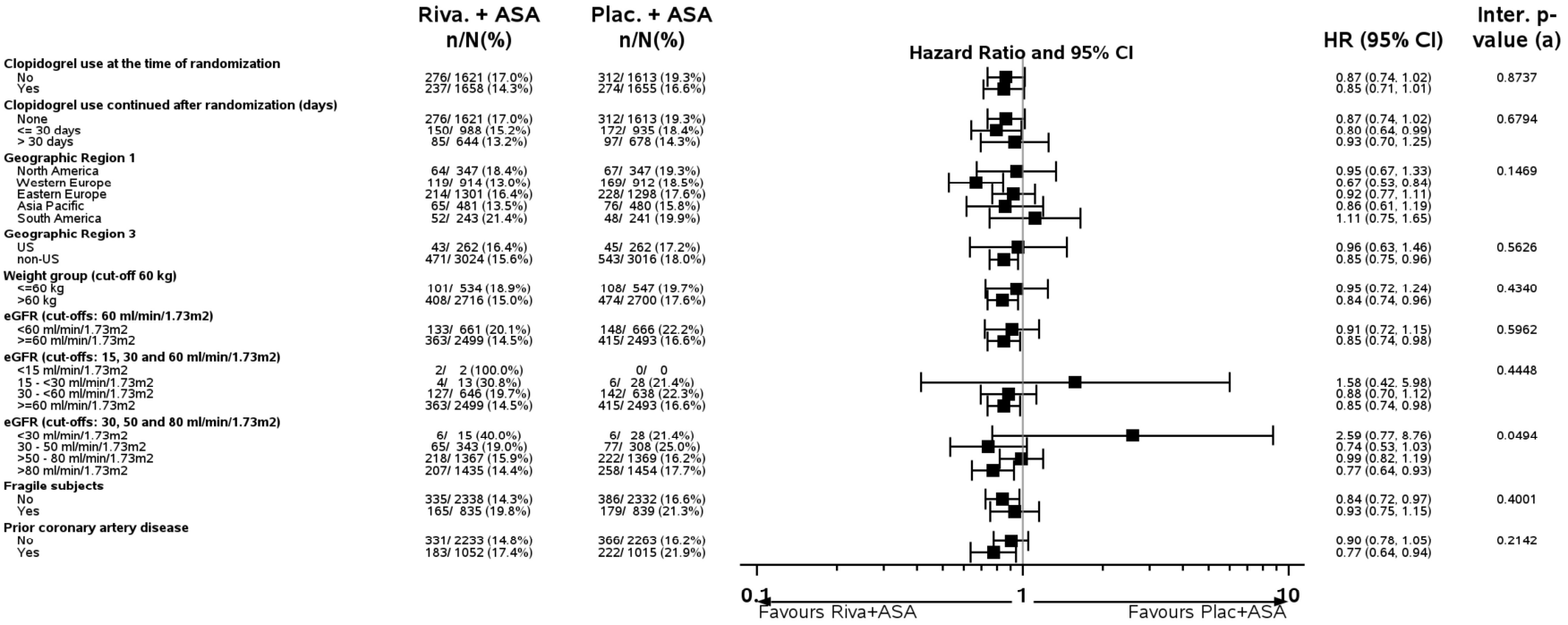


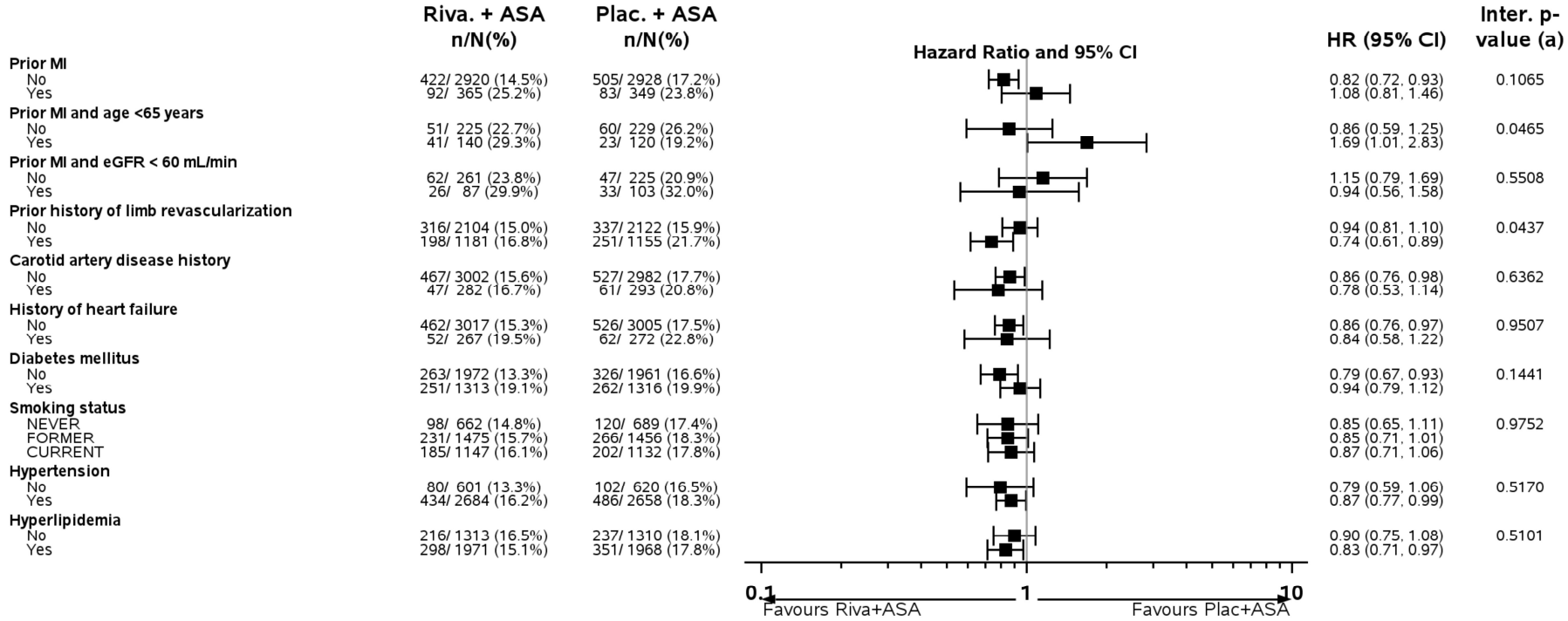
The ITT analysis set includes all randomized subjects. The ITT data scope includes outcome events observed from randomization date until efficacy cut-off date. Subgroup variables from Atrial fibrillation disease history and below are added post-hoc.
MI, stroke, mortality, ALI, major amputation of vascular etiology and events leading to hospitalization are adjudicated by Independent Clinical Adjudication Committee (ICAC), index limb revascularization and venous thromboembolic events are reported by investigator only. Index limb revascularization is defined as subsequent index leg revascularization that was not planned or considered as part of the initial treatment plan at the time of randomization, CV death = Cardiovascular death and unknown cause, MI = Myocardial infarction, ALI = Acute limb ischemia, CHD = coronary heart disease. Efficacy cut-off date = 08SEP2019,
Subjects will be considered fragile if age >75 years or weight <=50 kg or baseline eGFR <50 mL/min/1.73m2.
bid = twice daily, od = once daily, ASA = acetylsalicylic acid, CI = confidence interval, Riva. + ASA = Rivaroxaban 2.5 mg bid + ASA 100 mg od, Plac. + ASA = Rivaroxaban placebo bid + ASA 100 mg od
n = number of subjects with events, N = number of subjects at risk, % = 100 * n/N. Inter. = Interaction
HR (95% CI) is based on the Cox proportional hazards model stratified by type of procedure and clopidogrel use (per IxRS) (except for subgroups related to qualifying revascularization procedure or clopidogrel use), with treatment as the only covariate.
(a) P-value for interaction is based on the Cox proportional hazards model stratified by type of procedure and clopidogrel use (per IxRS) by adding the corresponding treatment interaction term.

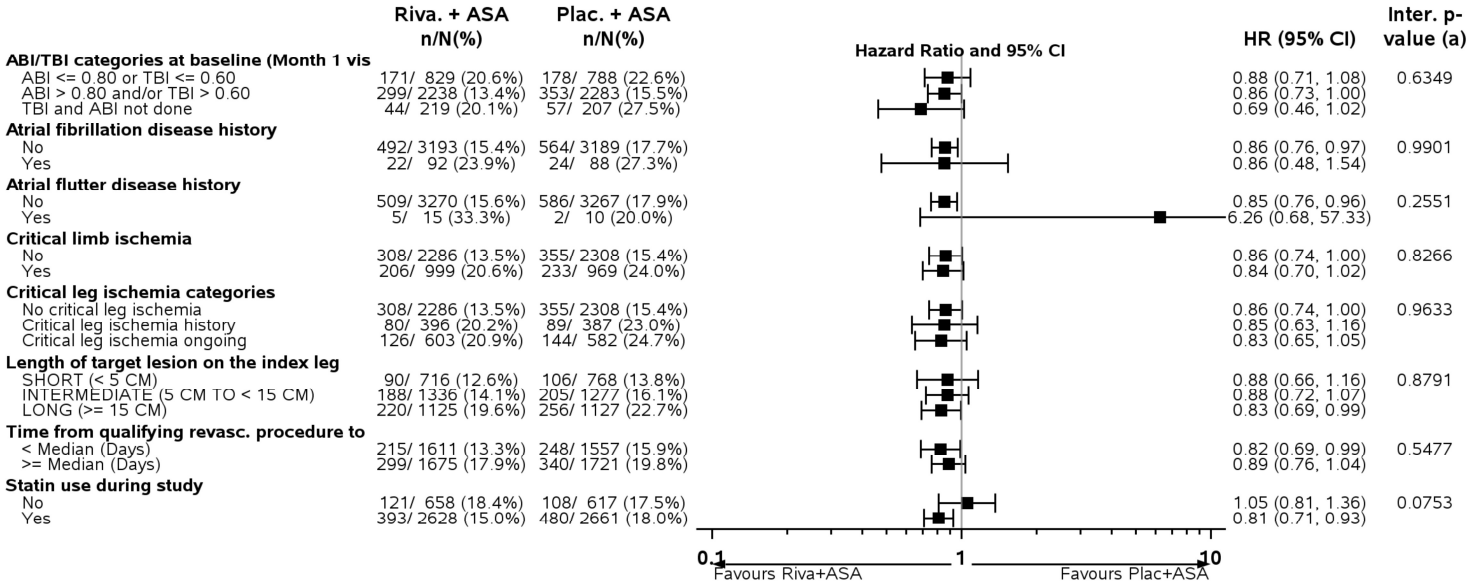
Source: 5.3.5.1.1 PH-40164/Figure 14.2.5.2/5

図 2.7.3.7-6 MI、全脳卒中、心血管死、ALI、又は血管系の原因による大切断の複合エンドポイントの Forest プロット
（試験 17454、全体集団、ITT、ECOD まで、ICAC 判定）




Riva. + ASA n/N(%)
Plac. + ASA n/N(%)
Hazard Ratio and 95% CI
HR (95% CI)
Inter. p-value (a)
Clopidogrel use at the time of randomization
No 276/ 1621 (17.0%) 312/ 1613 (19.3%) 0.87 (0.74, 1.02) 0.8737
Yes 237/ 1658 (14.3%) 274/ 1655 (16.6%) 0.85 (0.71, 1.01)
Clopidogrel use continued after randomization (days)
None 276/ 1621 (17.0%) 312/ 1613 (19.3%) 0.87 (0.74, 1.02) 0.6794
<= 30 days 150/ 988 (15.2%) 172/ 935 (18.4%) 0.80 (0.64, 0.99)
> 30 days 85/ 644 (13.2%) 97/ 678 (14.3%) 0.93 (0.70, 1.25)
Geographic Region 1
North America 64/ 347 (18.4%) 67/ 347 (19.3%) 0.95 (0.67, 1.33) 0.1469
Western Europe 119/ 914 (13.0%) 169/ 912 (18.5%) 0.67 (0.53, 0.84)
Eastern Europe 214/ 1301 (16.4%) 228/ 1298 (17.6%) 0.92 (0.77, 1.11)
Asia Pacific 65/ 481 (13.5%) 76/ 480 (15.8%) 0.86 (0.61, 1.19)
South America 52/ 243 (21.4%) 48/ 241 (19.9%) 1.11 (0.75, 1.65)
Geographic Region 3
US 43/ 262 (16.4%) 45/ 262 (17.2%) 0.96 (0.63, 1.46) 0.5626
non-US 471/ 3024 (15.6%) 543/ 3016 (18.0%) 0.85 (0.75, 0.96)
Weight group (cut-off 60 kg)
<=60 kg 101/ 534 (18.9%) 108/ 547 (19.7%) 0.95 (0.72, 1.24) 0.4340
>60 kg 408/ 2716 (15.0%) 474/ 2700 (17.6%) 0.84 (0.74, 0.96)
eGFR (cut-offs: 60 ml/min/1.73m2)
<60 ml/min/1.73m2 133/ 661 (20.1%) 148/ 666 (22.2%) 0.91 (0.72, 1.15) 0.5962
>=60 ml/min/1.73m2 363/ 2499 (14.5%) 415/ 2493 (16.6%) 0.85 (0.74, 0.98)
eGFR (cut-offs: 15, 30 and 60 ml/min/1.73m2)
<15 ml/min/1.73m2 2/ 2 (100.0%) 0/ 0 0.4448
15 - <30 ml/min/1.73m2 4/ 13 (30.8%) 6/ 28 (21.4%) 1.58 (0.42, 5.98)
30 - <60 ml/min/1.73m2 127/ 646 (19.7%) 142/ 638 (22.3%) 0.88 (0.70, 1.12)
>=60 ml/min/1.73m2 363/ 2499 (14.5%) 415/ 2493 (16.6%) 0.85 (0.74, 0.98)
eGFR (cut-offs: 30, 50 and 80 ml/min/1.73m2)
<30 ml/min/1.73m2 6/ 15 (40.0%) 6/ 28 (21.4%) 2.59 (0.77, 8.76) 0.0494
30 - 50 ml/min/1.73m2 65/ 343 (19.0%) 77/ 308 (25.0%) 0.74 (0.53, 1.03)
>50 - 80 ml/min/1.73m2 218/ 1367 (15.9%) 222/ 1369 (16.2%) 0.99 (0.82, 1.19)
>80 ml/min/1.73m2 207/ 1435 (14.4%) 258/ 1454 (17.7%) 0.77 (0.64, 0.93)
Fragile subjects
No 335/ 2338 (14.3%) 386/ 2332 (16.6%) 0.84 (0.72, 0.97) 0.4001
Yes 165/ 835 (19.8%) 179/ 839 (21.3%) 0.93 (0.75, 1.15)
Prior coronary artery disease
No 331/ 2233 (14.8%) 366/ 2263 (16.2%) 0.90 (0.78, 1.05) 0.2142
Yes 183/ 1052 (17.4%) 222/ 1015 (21.9%) 0.77 (0.64, 0.94)
0.1
1
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Favours Riva+ASA
Favours Plac+ASA


Riva. + ASA n/N(%)
Plac. + ASA n/N(%)
Hazard Ratio and 95% CI
HR (95% CI)
Inter. p-value (a)
Prior MI
No 422/ 2920 (14.5%) 505/ 2928 (17.2%) 0.82 (0.72, 0.93) 0.1065
Yes 92/ 365 (25.2%) 83/ 349 (23.8%) 1.08 (0.81, 1.46)
Prior MI and age <65 years
No 51/ 225 (22.7%) 60/ 229 (26.2%) 0.86 (0.59, 1.25) 0.0465
Yes 41/ 140 (29.3%) 23/ 120 (19.2%) 1.69 (1.01, 2.83)
Prior MI and eGFR < 60 mL/min
No 62/ 261 (23.8%) 47/ 225 (20.9%) 1.15 (0.79, 1.69) 0.5508
Yes 26/ 87 (29.9%) 33/ 103 (32.0%) 0.94 (0.56, 1.58)
Prior history of limb revascularization
No 316/ 2104 (15.0%) 337/ 2122 (15.9%) 0.94 (0.81, 1.10) 0.0437
Yes 198/ 1181 (16.8%) 251/ 1155 (21.7%) 0.74 (0.61, 0.89)
Carotid artery disease history
No 467/ 3002 (15.6%) 527/ 2982 (17.7%) 0.86 (0.76, 0.98) 0.6362
Yes 47/ 282 (16.7%) 61/ 293 (20.8%) 0.78 (0.53, 1.14)
History of heart failure
No 462/ 3017 (15.3%) 526/ 3005 (17.5%) 0.86 (0.76, 0.97) 0.9507
Yes 52/ 267 (19.5%) 62/ 272 (22.8%) 0.84 (0.58, 1.22)
Diabetes mellitus
No 263/ 1972 (13.3%) 326/ 1961 (16.6%) 0.79 (0.67, 0.93) 0.1441
Yes 251/ 1313 (19.1%) 262/ 1316 (19.9%) 0.94 (0.79, 1.12)
Smoking status
NEVER 98/ 662 (14.8%) 120/ 689 (17.4%) 0.85 (0.65, 1.11) 0.9752
FORMER 231/ 1475 (15.7%) 266/ 1456 (18.3%) 0.85 (0.71, 1.01)
CURRENT 185/ 1147 (16.1%) 202/ 1132 (17.8%) 0.87 (0.71, 1.06)
Hypertension
No 80/ 601 (13.3%) 102/ 620 (16.5%) 0.79 (0.59, 1.06) 0.5170
Yes 434/ 2684 (16.2%) 486/ 2658 (18.3%) 0.87 (0.77, 0.99)
Hyperlipidemia
No 216/ 1313 (16.5%) 237/ 1310 (18.1%) 0.90 (0.75, 1.08) 0.5101
Yes 298/ 1971 (15.1%) 351/ 1968 (17.8%) 0.83 (0.71, 0.97)
0.1
1
10
Favours Riva+ASA
Favours Plac+ASA



The ITT analysis set includes all randomized subjects. The ITT data scope includes outcome events observed from randomization date until efficacy cut-off date. Subgroup variables from Atrial fibrillation disease history and below are added post-hoc.
MI, stroke, mortality, ALI, major amputation of vascular etiology and events leading to hospitalization are adjudicated by Independent Clinical Adjudication Committee (ICAC), index limb revascularization and venous thromboembolic events are reported by investigator only. Index limb revascularization is defined as subsequent index leg revascularization that was not planned or considered as part of the initial treatment plan at the time of randomization, CV death = Cardiovascular death and unknown cause, MI = Myocardial infarction, ALI = Acute limb ischemia, CHD = coronary heart disease. Efficacy cut-off date = 08SEP2019,
Subjects will be considered fragile if age >75 years or weight <=50 kg or baseline eGFR <50 mL/min/1.73m2.
bid = twice daily, od = once daily, ASA = acetylsalicylic acid, CI = confidence interval, Riva. + ASA = Rivaroxaban 2.5 mg bid + ASA 100 mg od, Plac. + ASA = Rivaroxaban placebo bid + ASA 100 mg od
n = number of subjects with events, N = number of subjects at risk, % = 100 * n/N. Inter. = Interaction
HR (95% CI) is based on the Cox proportional hazards model stratified by type of procedure and clopidogrel use (per IxRS) (except for subgroups related to qualifying revascularization procedure or clopidogrel use), with treatment as the only covariate.
(a) P-value for interaction is based on the Cox proportional hazards model stratified by type of procedure and clopidogrel use (per IxRS) by adding the corresponding treatment interaction term.

Source: 5.3.5.1.1 PH-40164/Figure 14.2.5.2/6