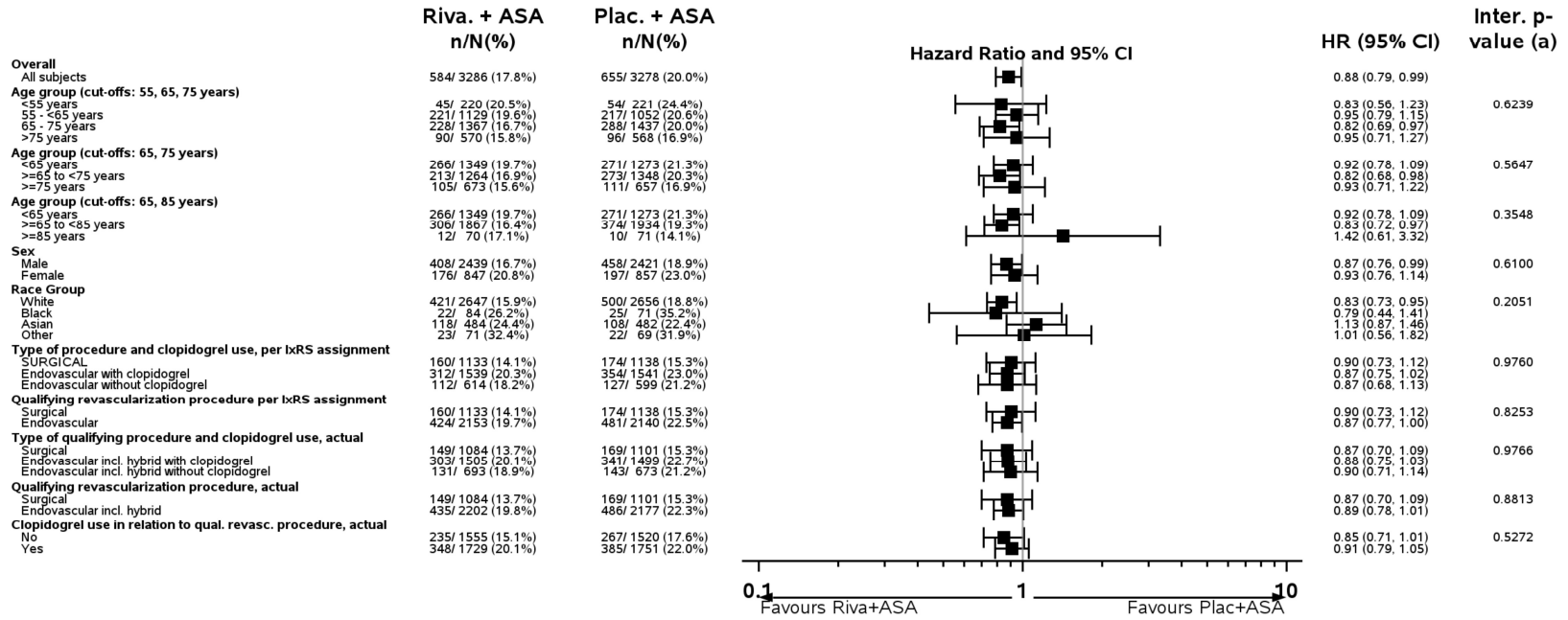
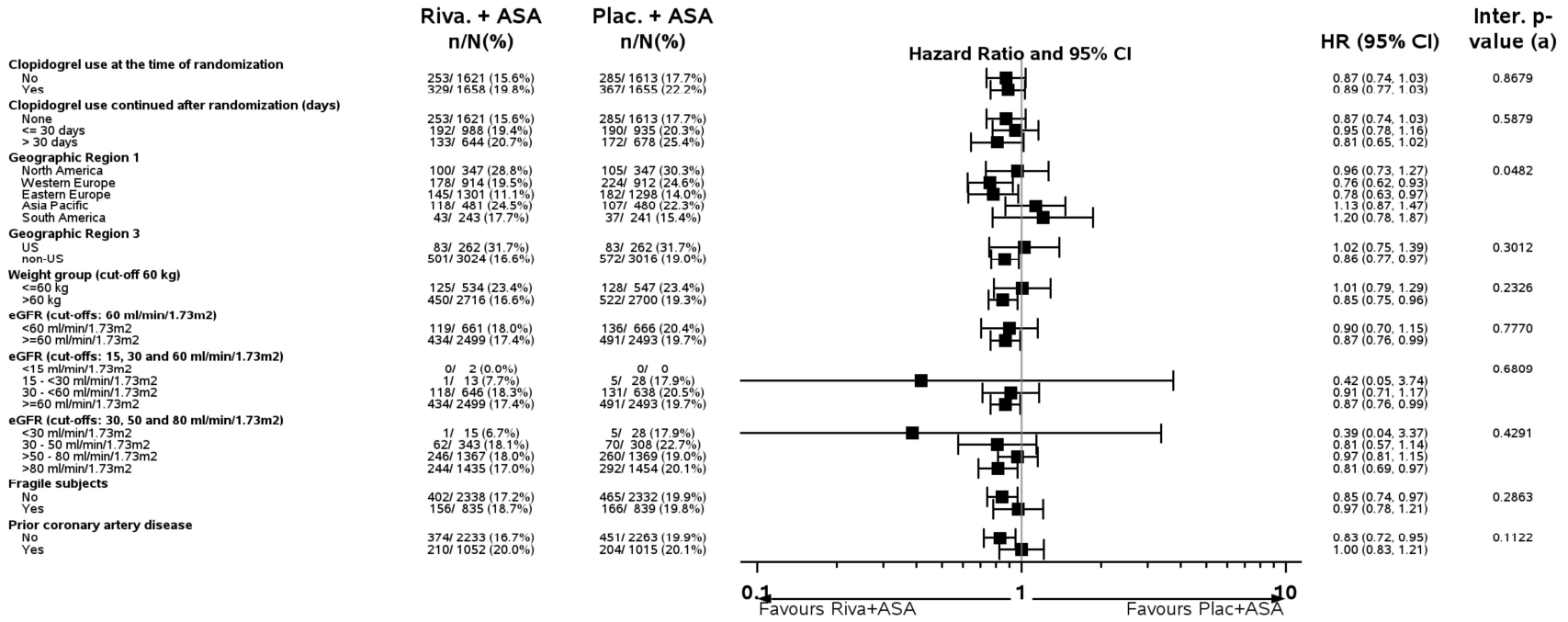
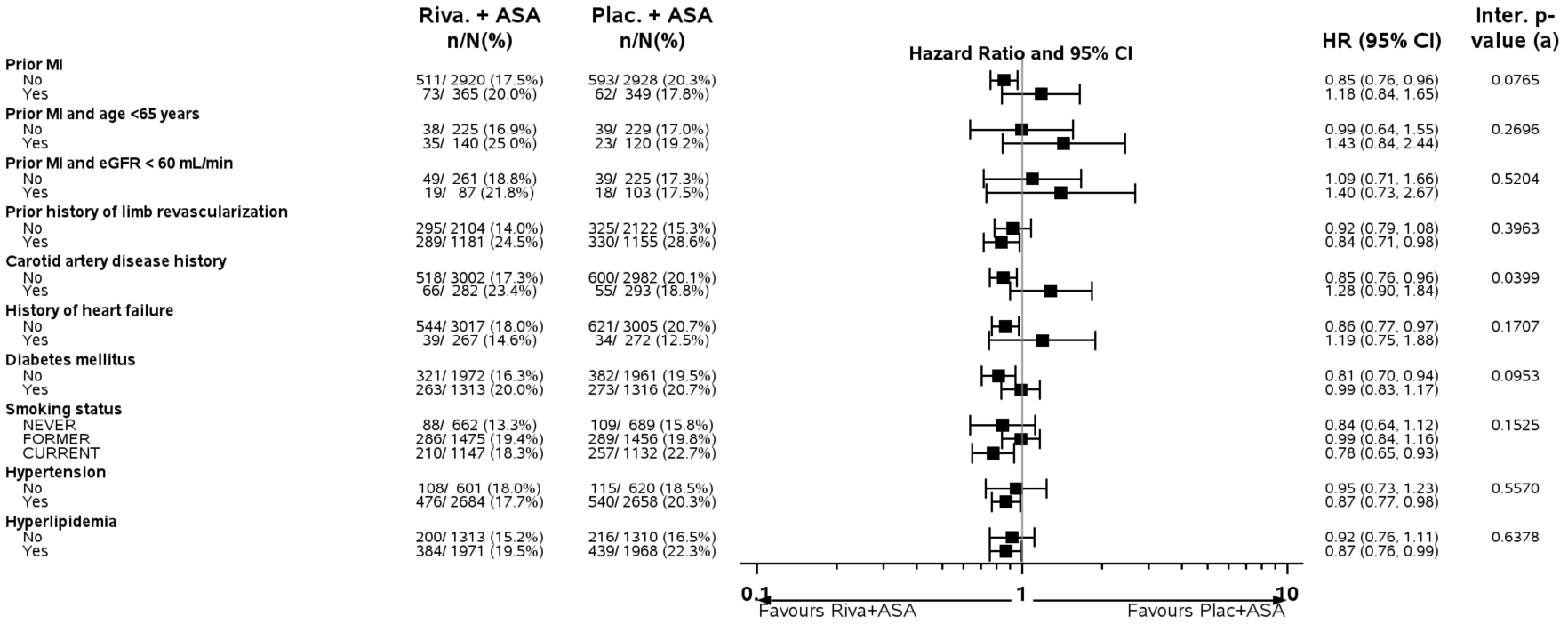
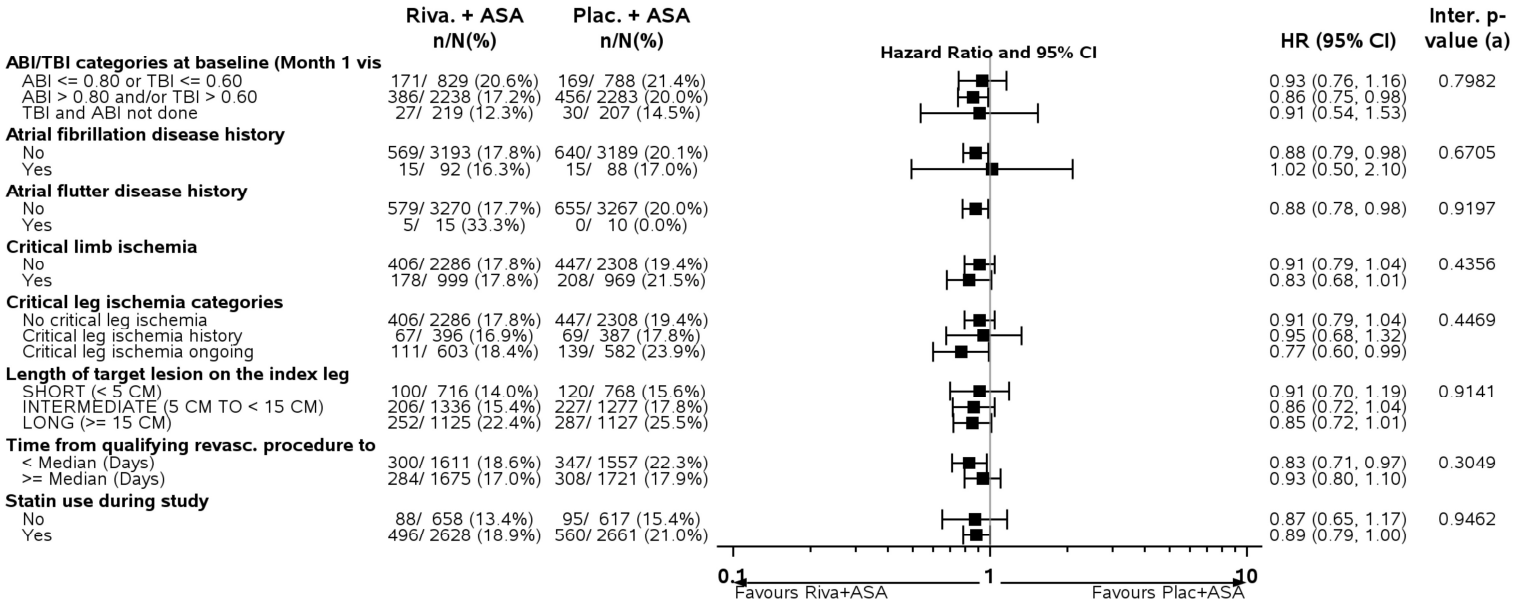
図 2.7.3.7-3 再発性肢虚血のために施行される、あらかじめ計画されていなかったインデックス肢に対する血行再建術の Forest プロット
〔試験 17454、全体集団、ITT、ECOD まで、治験責任（分担）医師判定〕




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 253/ 1621 (15.6%) 285/ 1613 (17.7%) 0.87 (0.74, 1.03) 0.8679
Yes 329/ 1658 (19.8%) 367/ 1655 (22.2%) 0.89 (0.77, 1.03)
Clopidogrel use continued after randomization (days)
None 253/ 1621 (15.6%) 285/ 1613 (17.7%) 0.87 (0.74, 1.03) 0.5879
<= 30 days 192/ 988 (19.4%) 190/ 935 (20.3%) 0.95 (0.78, 1.16)
> 30 days 133/ 644 (20.7%) 172/ 678 (25.4%) 0.81 (0.65, 1.02)
Geographic Region 1
North America 100/ 347 (28.8%) 105/ 347 (30.3%) 0.96 (0.73, 1.27) 0.0482
Western Europe 178/ 914 (19.5%) 224/ 912 (24.6%) 0.76 (0.62, 0.93)
Eastern Europe 145/ 1301 (11.1%) 182/ 1298 (14.0%) 0.78 (0.63, 0.97)
Asia Pacific 118/ 481 (24.5%) 107/ 480 (22.3%) 1.13 (0.87, 1.47)
South America 43/ 243 (17.7%) 37/ 241 (15.4%) 1.20 (0.78, 1.87)
Geographic Region 3
US 83/ 262 (31.7%) 83/ 262 (31.7%) 1.02 (0.75, 1.39) 0.3012
non-US 501/ 3024 (16.6%) 572/ 3016 (19.0%) 0.86 (0.77, 0.97)
Weight group (cut-off 60 kg)
<=60 kg 125/ 534 (23.4%) 128/ 547 (23.4%) 1.01 (0.79, 1.29) 0.2326
>60 kg 450/ 2716 (16.6%) 522/ 2700 (19.3%) 0.85 (0.75, 0.96)
eGFR (cut-offs: 60 ml/min/1.73m2)
<60 ml/min/1.73m2 119/ 661 (18.0%) 136/ 666 (20.4%) 0.90 (0.70, 1.15) 0.7770
>=60 ml/min/1.73m2 434/ 2499 (17.4%) 491/ 2493 (19.7%) 0.87 (0.76, 0.99)
eGFR (cut-offs: 15, 30 and 60 ml/min/1.73m2)
<15 ml/min/1.73m2 0/ 2 (0.0%) 0/ 0 0.6809
15 - <30 ml/min/1.73m2 1/ 13 (7.7%) 5/ 28 (17.9%) 0.42 (0.05, 3.74)
30 - <60 ml/min/1.73m2 118/ 646 (18.3%) 131/ 638 (20.5%) 0.91 (0.71, 1.17)
>=60 ml/min/1.73m2 434/ 2499 (17.4%) 491/ 2493 (19.7%) 0.87 (0.76, 0.99)
eGFR (cut-offs: 30, 50 and 80 ml/min/1.73m2)
<30 ml/min/1.73m2 1/ 15 (6.7%) 5/ 28 (17.9%) 0.39 (0.04, 3.37) 0.4291
30 - 50 ml/min/1.73m2 62/ 343 (18.1%) 70/ 308 (22.7%) 0.81 (0.57, 1.14)
>50 - 80 ml/min/1.73m2 246/ 1367 (18.0%) 260/ 1369 (19.0%) 0.97 (0.81, 1.15)
>80 ml/min/1.73m2 244/ 1435 (17.0%) 292/ 1454 (20.1%) 0.81 (0.69, 0.97)
Fragile subjects
No 402/ 2338 (17.2%) 465/ 2332 (19.9%) 0.85 (0.74, 0.97) 0.2863
Yes 156/ 835 (18.7%) 166/ 839 (19.8%) 0.97 (0.78, 1.21)
Prior coronary artery disease
No 374/ 2233 (16.7%) 451/ 2263 (19.9%) 0.83 (0.72, 0.95) 0.1122
Yes 210/ 1052 (20.0%) 204/ 1015 (20.1%) 1.00 (0.83, 1.21)
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 511/ 2920 (17.5%) 593/ 2928 (20.3%) 0.85 (0.76, 0.96) 0.0765
Yes 73/ 365 (20.0%) 62/ 349 (17.8%) 1.18 (0.84, 1.65)
Prior MI and age <65 years
No 38/ 225 (16.9%) 39/ 229 (17.0%) 0.99 (0.64, 1.55) 0.2696
Yes 35/ 140 (25.0%) 23/ 120 (19.2%) 1.43 (0.84, 2.44)
Prior MI and eGFR < 60 mL/min
No 49/ 261 (18.8%) 39/ 225 (17.3%) 1.09 (0.71, 1.66) 0.5204
Yes 19/ 87 (21.8%) 18/ 103 (17.5%) 1.40 (0.73, 2.67)
Prior history of limb revascularization
No 295/ 2104 (14.0%) 325/ 2122 (15.3%) 0.92 (0.79, 1.08) 0.3963
Yes 289/ 1181 (24.5%) 330/ 1155 (28.6%) 0.84 (0.71, 0.98)
Carotid artery disease history
No 518/ 3002 (17.3%) 600/ 2982 (20.1%) 0.85 (0.76, 0.96) 0.0399
Yes 66/ 282 (23.4%) 55/ 293 (18.8%) 1.28 (0.90, 1.84)
History of heart failure
No 544/ 3017 (18.0%) 621/ 3005 (20.7%) 0.86 (0.77, 0.97) 0.1707
Yes 39/ 267 (14.6%) 34/ 272 (12.5%) 1.19 (0.75, 1.88)
Diabetes mellitus
No 321/ 1972 (16.3%) 382/ 1961 (19.5%) 0.81 (0.70, 0.94) 0.0953
Yes 263/ 1313 (20.0%) 273/ 1316 (20.7%) 0.99 (0.83, 1.17)
Smoking status
NEVER 88/ 662 (13.3%) 109/ 689 (15.8%) 0.84 (0.64, 1.12) 0.1525
FORMER 286/ 1475 (19.4%) 289/ 1456 (19.8%) 0.99 (0.84, 1.16)
CURRENT 210/ 1147 (18.3%) 257/ 1132 (22.7%) 0.78 (0.65, 0.93)
Hypertension
No 108/ 601 (18.0%) 115/ 620 (18.5%) 0.95 (0.73, 1.23) 0.5570
Yes 476/ 2684 (17.7%) 540/ 2658 (20.3%) 0.87 (0.77, 0.98)
Hyperlipidemia
No 200/ 1313 (15.2%) 216/ 1310 (16.5%) 0.92 (0.76, 1.11) 0.6378
Yes 384/ 1971 (19.5%) 439/ 1968 (22.3%) 0.87 (0.76, 0.99)
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

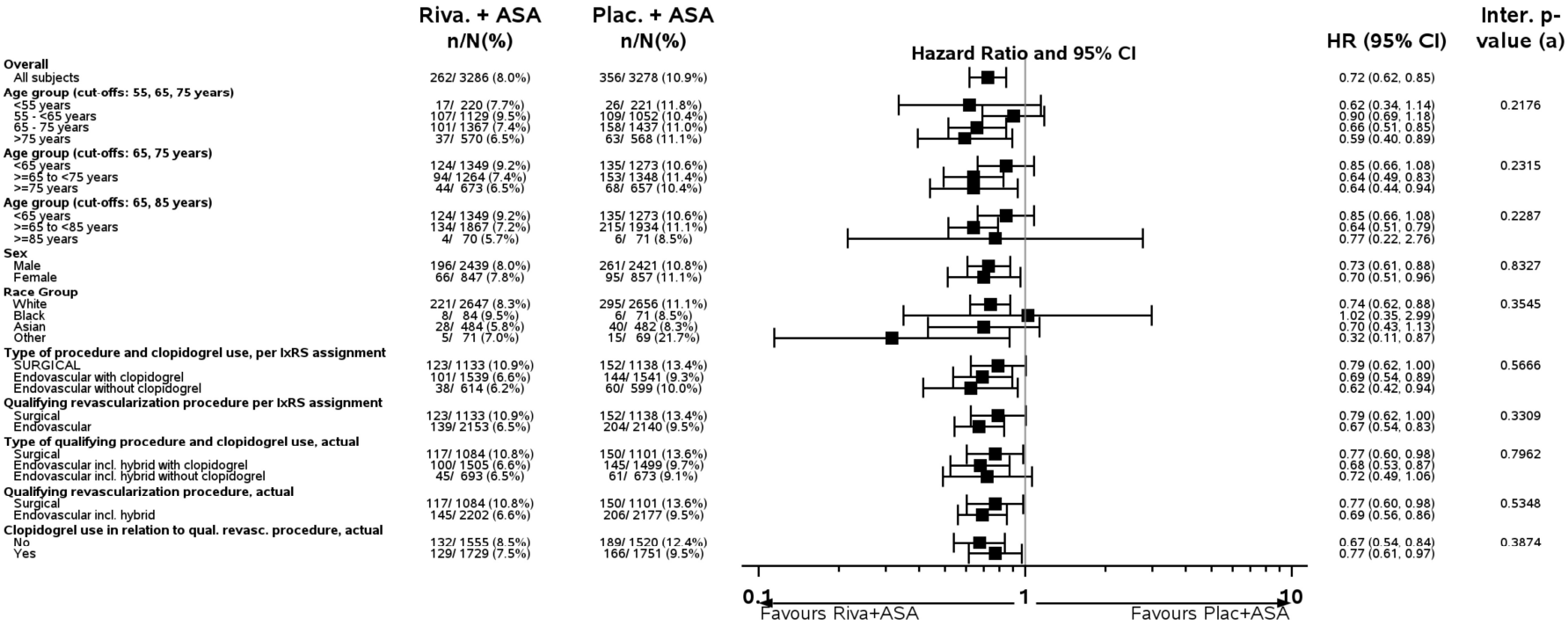
n = number of subjects with events, N = number of subjects at risk, % = 100 * n/N. Inter. = Interaction

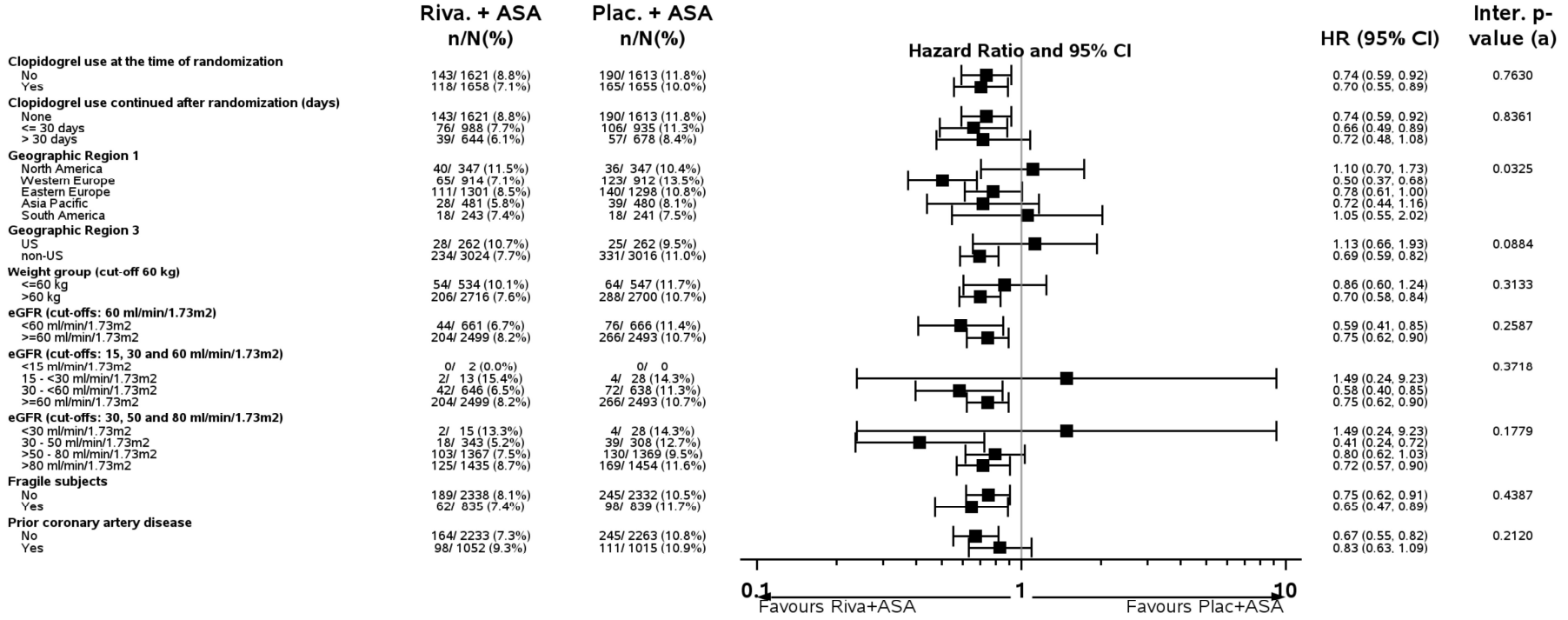
HR (95% CI) is based on the Cox proportional hazards model stratified by type of procedure and clopidogrel use (per IxRS) (except for subgroups related to qualifying revascularization procedure or clopidogrel use), with treatment as the only covariate.

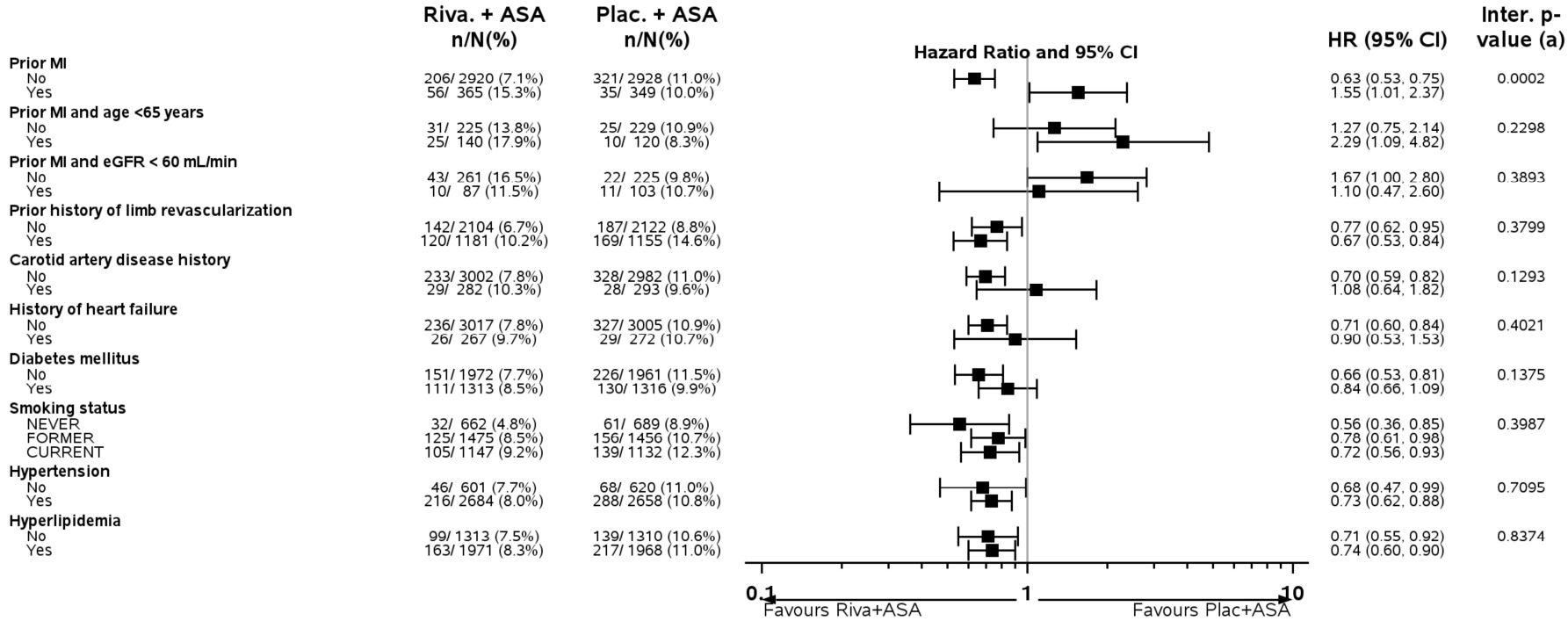
(a) P-value for interaction is based on the Cox proportional hazards model stratified by type of procedure and clopidogrel use (per IxRS) by adding the corresponding treatment interaction term.

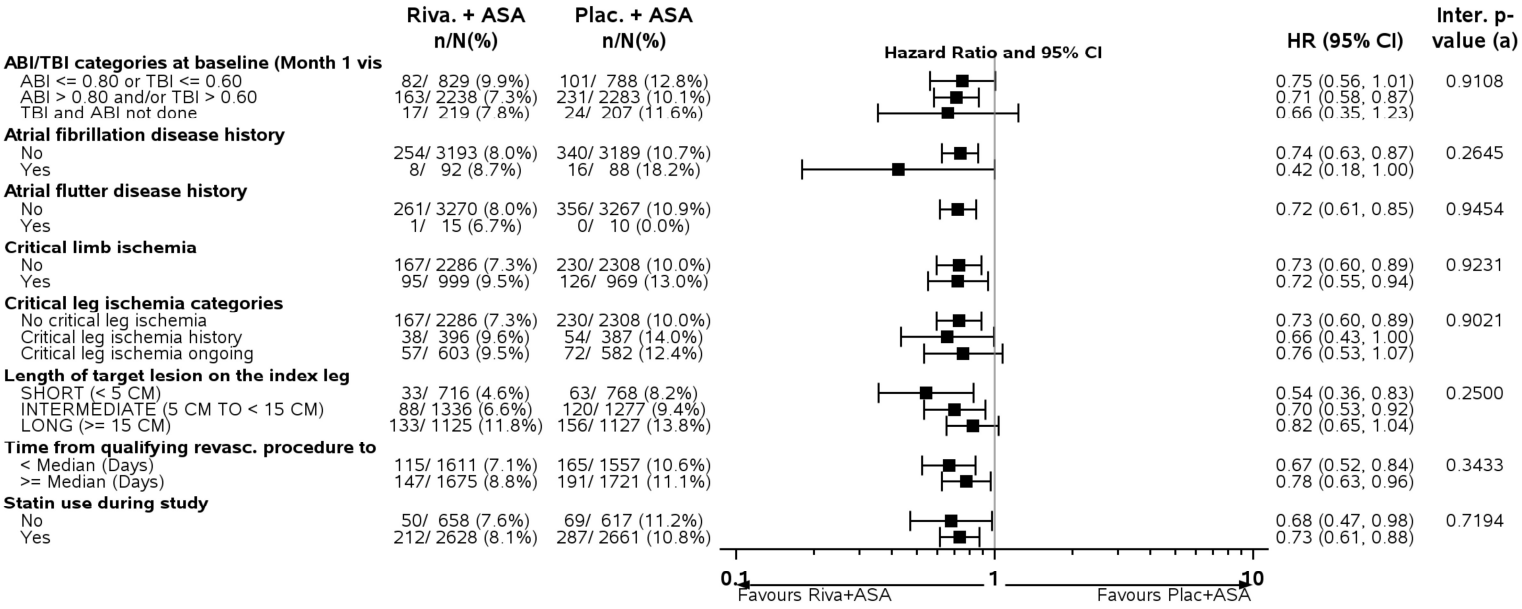
Source: 5.3.5.1.1 PH-40164/Figure 14.2.5.2/3

図 2.7.3.7-4 冠動脈又は末梢血管（いずれかの下肢）の血栓性イベントによる入院の 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 143/ 1621 (8.8%) 190/ 1613 (11.8%) 0.74 (0.59, 0.92) 0.7630
Yes 118/ 1658 (7.1%) 165/ 1655 (10.0%) 0.70 (0.55, 0.89)
Clopidogrel use continued after randomization (days)
None 143/ 1621 (8.8%) 190/ 1613 (11.8%) 0.74 (0.59, 0.92) 0.8361
<= 30 days 76/ 988 (7.7%) 106/ 935 (11.3%) 0.66 (0.49, 0.89)
> 30 days 39/ 644 (6.1%) 57/ 678 (8.4%) 0.72 (0.48, 1.08)
Geographic Region 1
North America 40/ 347 (11.5%) 36/ 347 (10.4%) 1.10 (0.70, 1.73) 0.0325
Western Europe 65/ 914 (7.1%) 123/ 912 (13.5%) 0.50 (0.37, 0.68)
Eastern Europe 111/ 1301 (8.5%) 140/ 1298 (10.8%) 0.78 (0.61, 1.00)
Asia Pacific 28/ 481 (5.8%) 39/ 480 (8.1%) 0.72 (0.44, 1.16)
South America 18/ 243 (7.4%) 18/ 241 (7.5%) 1.05 (0.55, 2.02)
Geographic Region 3
US 28/ 262 (10.7%) 25/ 262 (9.5%) 1.13 (0.66, 1.93) 0.0884
non-US 234/ 3024 (7.7%) 331/ 3016 (11.0%) 0.69 (0.59, 0.82)
Weight group (cut-off 60 kg)
<=60 kg 54/ 534 (10.1%) 64/ 547 (11.7%) 0.86 (0.60, 1.24) 0.3133
>60 kg 206/ 2716 (7.6%) 288/ 2700 (10.7%) 0.70 (0.58, 0.84)
eGFR (cut-offs: 60 ml/min/1.73m2)
<60 ml/min/1.73m2 44/ 661 (6.7%) 76/ 666 (11.4%) 0.59 (0.41, 0.85) 0.2587
>=60 ml/min/1.73m2 204/ 2499 (8.2%) 266/ 2493 (10.7%) 0.75 (0.62, 0.90)
eGFR (cut-offs: 15, 30 and 60 ml/min/1.73m2)
<15 ml/min/1.73m2 0/ 2 (0.0%) 0/ 0 0.3718
15 - <30 ml/min/1.73m2 2/ 13 (15.4%) 4/ 28 (14.3%) 1.49 (0.24, 9.23)
30 - <60 ml/min/1.73m2 42/ 646 (6.5%) 72/ 638 (11.3%) 0.58 (0.40, 0.85)
>=60 ml/min/1.73m2 204/ 2499 (8.2%) 266/ 2493 (10.7%) 0.75 (0.62, 0.90)
eGFR (cut-offs: 30, 50 and 80 ml/min/1.73m2)
<30 ml/min/1.73m2 2/ 15 (13.3%) 4/ 28 (14.3%) 1.49 (0.24, 9.23) 0.1779
30 - 50 ml/min/1.73m2 18/ 343 (5.2%) 39/ 308 (12.7%) 0.41 (0.24, 0.72)
>50 - 80 ml/min/1.73m2 103/ 1367 (7.5%) 130/ 1369 (9.5%) 0.80 (0.62, 1.03)
>80 ml/min/1.73m2 125/ 1435 (8.7%) 169/ 1454 (11.6%) 0.72 (0.57, 0.90)
Fragile subjects
No 189/ 2338 (8.1%) 245/ 2332 (10.5%) 0.75 (0.62, 0.91) 0.4387
Yes 62/ 835 (7.4%) 98/ 839 (11.7%) 0.65 (0.47, 0.89)
Prior coronary artery disease
No 164/ 2233 (7.3%) 245/ 2263 (10.8%) 0.67 (0.55, 0.82) 0.2120
Yes 98/ 1052 (9.3%) 111/ 1015 (10.9%) 0.83 (0.63, 1.09)
0.1
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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 206/ 2920 (7.1%) 321/ 2928 (11.0%) 0.63 (0.53, 0.75) 0.0002
Yes 56/ 365 (15.3%) 35/ 349 (10.0%) 1.55 (1.01, 2.37)
Prior MI and age <65 years
No 31/ 225 (13.8%) 25/ 229 (10.9%) 1.27 (0.75, 2.14) 0.2298
Yes 25/ 140 (17.9%) 10/ 120 (8.3%) 2.29 (1.09, 4.82)
Prior MI and eGFR < 60 mL/min
No 43/ 261 (16.5%) 22/ 225 (9.8%) 1.67 (1.00, 2.80) 0.3893
Yes 10/ 87 (11.5%) 11/ 103 (10.7%) 1.10 (0.47, 2.60)
Prior history of limb revascularization
No 142/ 2104 (6.7%) 187/ 2122 (8.8%) 0.77 (0.62, 0.95) 0.3799
Yes 120/ 1181 (10.2%) 169/ 1155 (14.6%) 0.67 (0.53, 0.84)
Carotid artery disease history
No 233/ 3002 (7.8%) 328/ 2982 (11.0%) 0.70 (0.59, 0.82) 0.1293
Yes 29/ 282 (10.3%) 28/ 293 (9.6%) 1.08 (0.64, 1.82)
History of heart failure
No 236/ 3017 (7.8%) 327/ 3005 (10.9%) 0.71 (0.60, 0.84) 0.4021
Yes 26/ 267 (9.7%) 29/ 272 (10.7%) 0.90 (0.53, 1.53)
Diabetes mellitus
No 151/ 1972 (7.7%) 226/ 1961 (11.5%) 0.66 (0.53, 0.81) 0.1375
Yes 111/ 1313 (8.5%) 130/ 1316 (9.9%) 0.84 (0.66, 1.09)
Smoking status
NEVER 32/ 662 (4.8%) 61/ 689 (8.9%) 0.56 (0.36, 0.85) 0.3987
FORMER 125/ 1475 (8.5%) 156/ 1456 (10.7%) 0.78 (0.61, 0.98)
CURRENT 105/ 1147 (9.2%) 139/ 1132 (12.3%) 0.72 (0.56, 0.93)
Hypertension
No 46/ 601 (7.7%) 68/ 620 (11.0%) 0.68 (0.47, 0.99) 0.7095
Yes 216/ 2684 (8.0%) 288/ 2658 (10.8%) 0.73 (0.62, 0.88)
Hyperlipidemia
No 99/ 1313 (7.5%) 139/ 1310 (10.6%) 0.71 (0.55, 0.92) 0.8374
Yes 163/ 1971 (8.3%) 217/ 1968 (11.0%) 0.74 (0.60, 0.90)
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 14.2.5.2/4