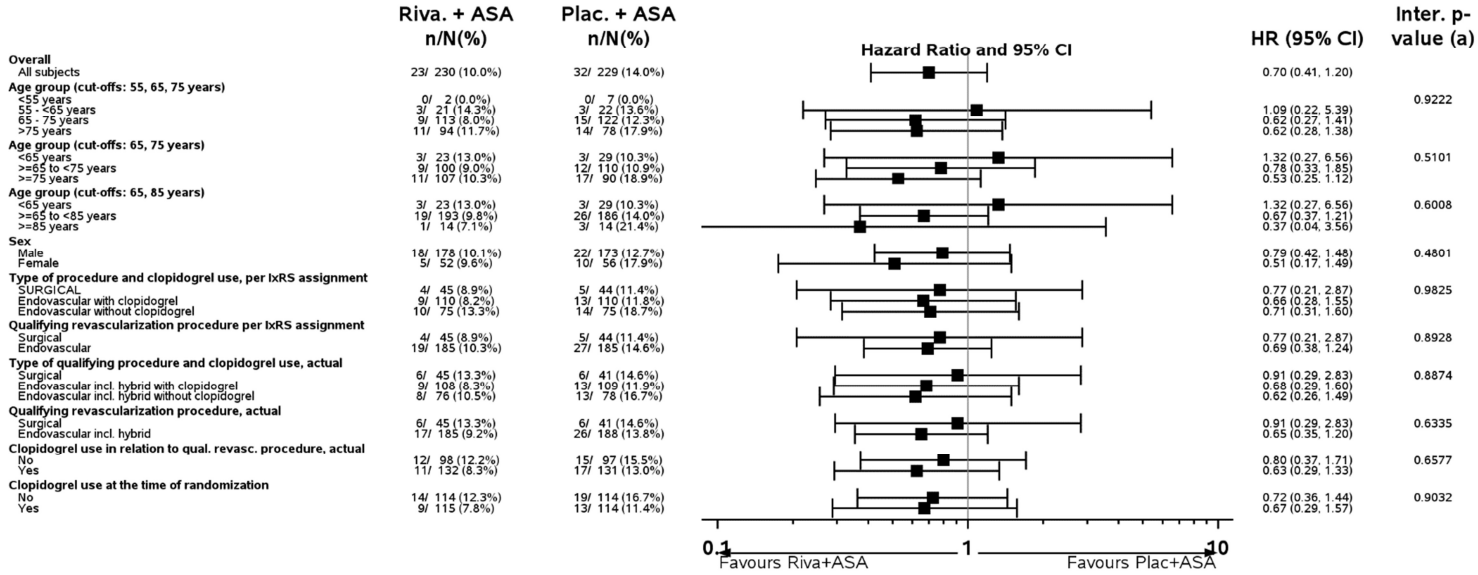
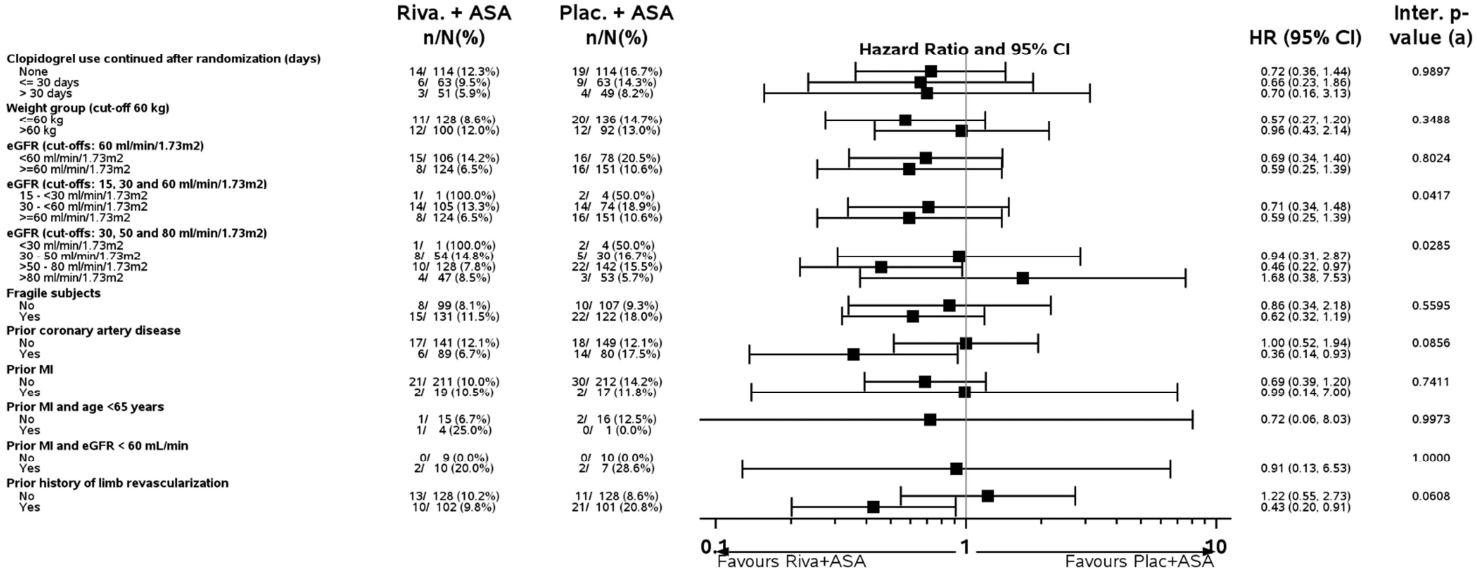
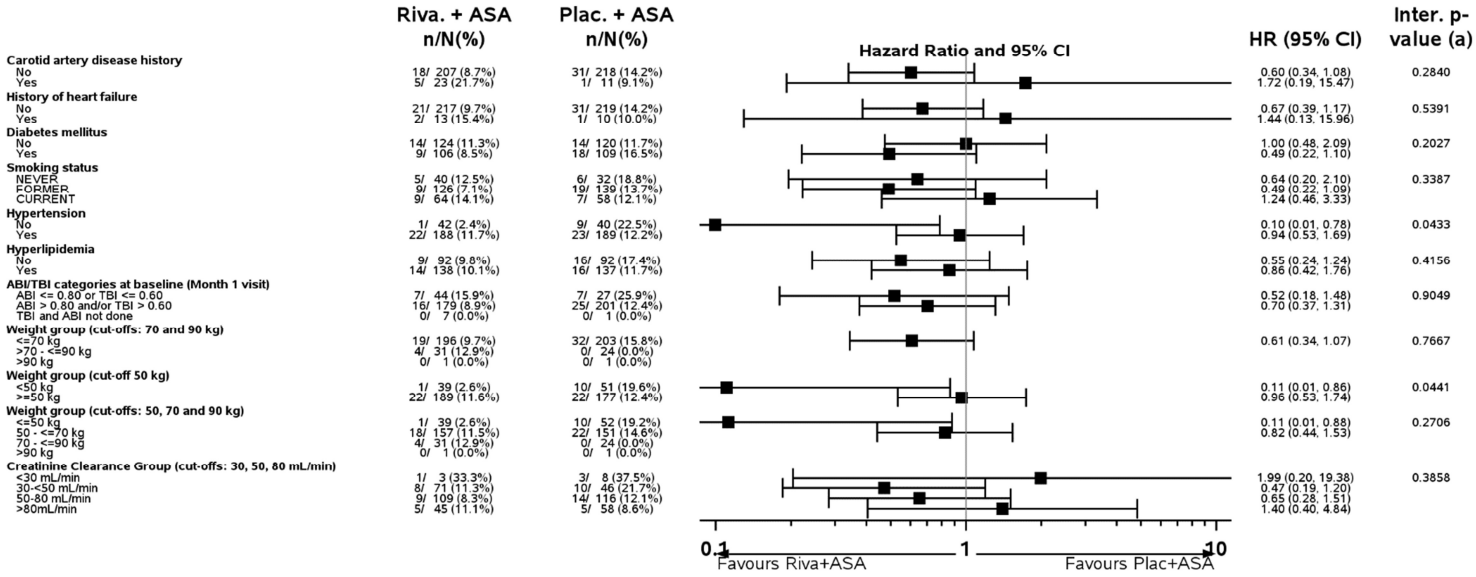
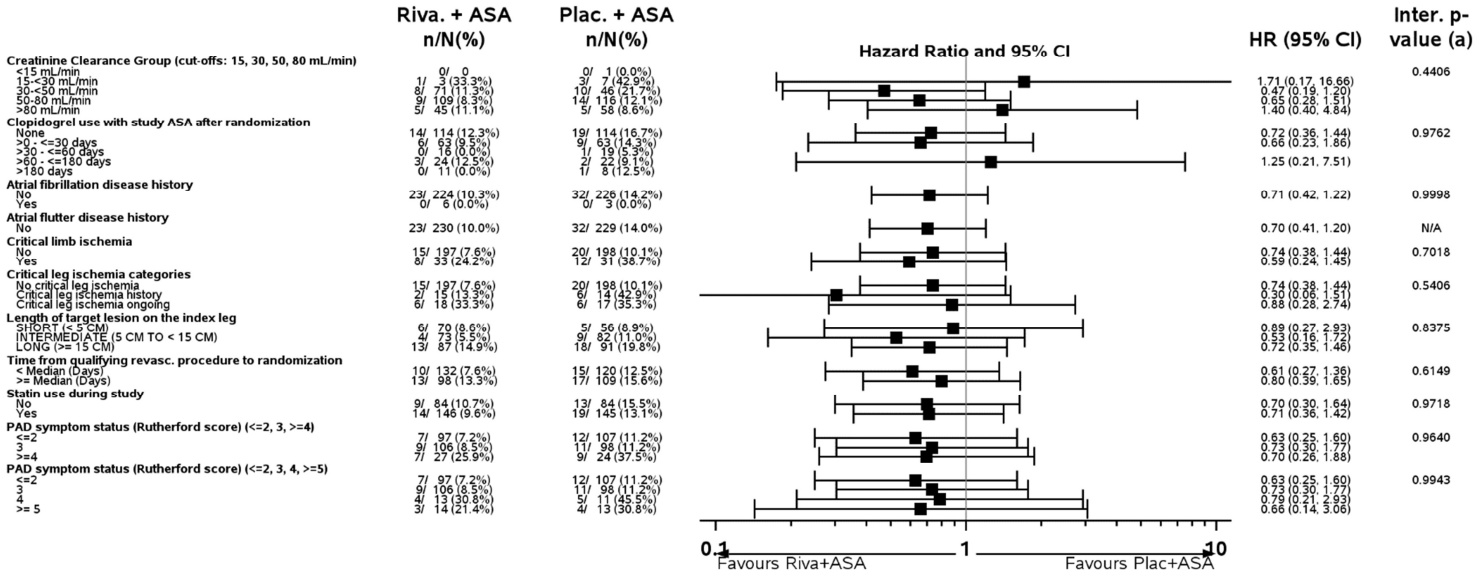
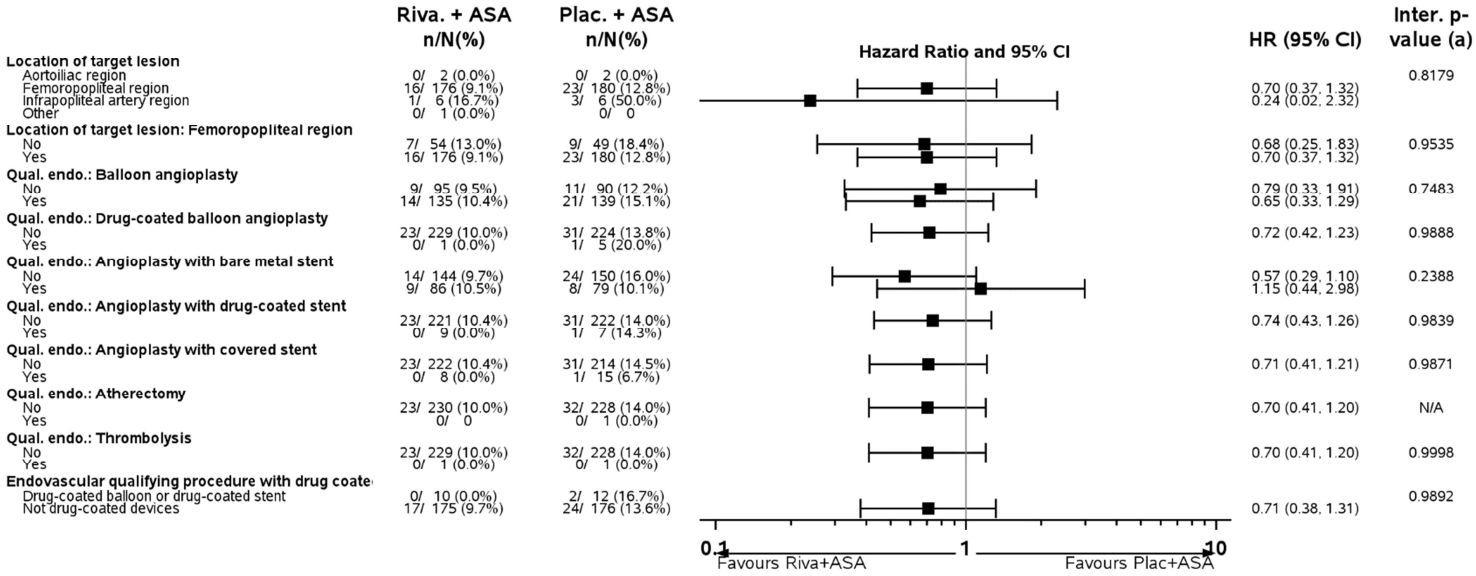
図 2.7.3.7-11 MI、全脳卒中、心血管死、ALI、又は血管系の原因による大切断の複合エンドポイントの Forest プロット
（試験 17454、日本人集団、ITT、ECOD まで、ICAC 判定）




Riva. + ASA n/N(%)
Plac. + ASA n/N(%)
Hazard Ratio and 95% CI
HR (95% CI)
Inter. p-value (a)
Clopidogrel use continued after randomization (days)
None 14/ 114 (12.3%) 19/ 114 (16.7%) 0.72 (0.36, 1.44) 0.9897
<= 30 days 6/ 63 (9.5%) 9/ 63 (14.3%) 0.66 (0.23, 1.86)
> 30 days 3/ 51 (5.9%) 4/ 49 (8.2%) 0.70 (0.16, 3.13)
Weight group (cut-off 60 kg)
<=60 kg 11/ 128 (8.6%) 20/ 136 (14.7%) 0.57 (0.27, 1.20) 0.3488
>60 kg 12/ 100 (12.0%) 12/ 92 (13.0%) 0.96 (0.43, 2.14)
eGFR (cut-offs: 60 ml/min/1.73m2)
<60 ml/min/1.73m2 15/ 106 (14.2%) 16/ 78 (20.5%) 0.69 (0.34, 1.40) 0.8024
>=60 ml/min/1.73m2 8/ 124 (6.5%) 16/ 151 (10.6%) 0.59 (0.25, 1.39)
eGFR (cut-offs: 15, 30 and 60 ml/min/1.73m2)
15 - <30 ml/min/1.73m2 1/ 1 (100.0%) 2/ 4 (50.0%) 0.0417
30 - <60 ml/min/1.73m2 14/ 105 (13.3%) 14/ 74 (18.9%) 0.71 (0.34, 1.48)
>=60 ml/min/1.73m2 8/ 124 (6.5%) 16/ 151 (10.6%) 0.59 (0.25, 1.39)
eGFR (cut-offs: 30, 50 and 80 ml/min/1.73m2)
<30 ml/min/1.73m2 1/ 1 (100.0%) 2/ 4 (50.0%) 0.0285
30 - 50 ml/min/1.73m2 8/ 54 (14.8%) 5/ 30 (16.7%) 0.94 (0.31, 2.87)
>50 - 80 ml/min/1.73m2 10/ 128 (7.8%) 22/ 142 (15.5%) 0.46 (0.22, 0.97)
>80 ml/min/1.73m2 4/ 47 (8.5%) 3/ 53 (5.7%) 1.68 (0.38, 7.53)
Fragile subjects
No 8/ 99 (8.1%) 10/ 107 (9.3%) 0.86 (0.34, 2.18) 0.5595
Yes 15/ 131 (11.5%) 22/ 122 (18.0%) 0.62 (0.32, 1.19)
Prior coronary artery disease
No 17/ 141 (12.1%) 18/ 149 (12.1%) 1.00 (0.52, 1.94) 0.0856
Yes 6/ 89 (6.7%) 14/ 80 (17.5%) 0.36 (0.14, 0.93)
Prior MI
No 21/ 211 (10.0%) 30/ 212 (14.2%) 0.69 (0.39, 1.20) 0.7411
Yes 2/ 19 (10.5%) 2/ 17 (11.8%) 0.99 (0.14, 7.00)
Prior MI and age <65 years
No 1/ 15 (6.7%) 2/ 16 (12.5%) 0.72 (0.06, 8.03) 0.9973
Yes 1/ 4 (25.0%) 0/ 1 (0.0%)
Prior MI and eGFR < 60 mL/min
No 0/ 9 (0.0%) 0/ 10 (0.0%) 1.0000
Yes 2/ 10 (20.0%) 2/ 7 (28.6%) 0.91 (0.13, 6.53)
Prior history of limb revascularization
No 13/ 128 (10.2%) 11/ 128 (8.6%) 1.22 (0.55, 2.73) 0.0608
Yes 10/ 102 (9.8%) 21/ 101 (20.8%) 0.43 (0.20, 0.91)
0.1
1
10
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)
Carotid artery disease history
No 18/ 207 (8.7%) 31/ 218 (14.2%) 0.60 (0.34, 1.08) 0.2840
Yes 5/ 23 (21.7%) 1/ 11 (9.1%) 1.72 (0.19, 15.47)
History of heart failure
No 21/ 217 (9.7%) 31/ 219 (14.2%) 0.67 (0.39, 1.17) 0.5391
Yes 2/ 13 (15.4%) 1/ 10 (10.0%) 1.44 (0.13, 15.96)
Diabetes mellitus
No 14/ 124 (11.3%) 14/ 120 (11.7%) 1.00 (0.48, 2.09) 0.2027
Yes 9/ 106 (8.5%) 18/ 109 (16.5%) 0.49 (0.22, 1.10)
Smoking status
NEVER 5/ 40 (12.5%) 6/ 32 (18.8%) 0.64 (0.20, 2.10) 0.3387
FORMER 9/ 126 (7.1%) 19/ 139 (13.7%) 0.49 (0.22, 1.09)
CURRENT 9/ 64 (14.1%) 7/ 58 (12.1%) 1.24 (0.46, 3.33)
Hypertension
No 1/ 42 (2.4%) 9/ 40 (22.5%) 0.10 (0.01, 0.78) 0.0433
Yes 22/ 188 (11.7%) 23/ 189 (12.2%) 0.94 (0.53, 1.69)
Hyperlipidemia
No 9/ 92 (9.8%) 16/ 92 (17.4%) 0.55 (0.24, 1.24) 0.4156
Yes 14/ 138 (10.1%) 16/ 137 (11.7%) 0.86 (0.42, 1.76)
ABI/TBI categories at baseline (Month 1 visit)
ABI <= 0.80 or TBI <= 0.60 7/ 44 (15.9%) 7/ 27 (25.9%) 0.52 (0.18, 1.48) 0.9049
ABI > 0.80 and/or TBI > 0.60 16/ 179 (8.9%) 25/ 201 (12.4%) 0.70 (0.37, 1.31)
TBI and ABI not done 0/ 7 (0.0%) 0/ 1 (0.0%)
Weight group (cut-offs: 70 and 90 kg)
<=70 kg 19/ 196 (9.7%) 32/ 203 (15.8%) 0.61 (0.34, 1.07) 0.7667
>70 - <=90 kg 4/ 31 (12.9%) 0/ 24 (0.0%)
>90 kg 0/ 1 (0.0%) 0/ 1 (0.0%)
Weight group (cut-off 50 kg)
<50 kg 1/ 39 (2.6%) 10/ 51 (19.6%) 0.11 (0.01, 0.86) 0.0441
>=50 kg 22/ 189 (11.6%) 22/ 177 (12.4%) 0.96 (0.53, 1.74)
Weight group (cut-offs: 50, 70 and 90 kg)
<=50 kg 1/ 39 (2.6%) 10/ 52 (19.2%) 0.11 (0.01, 0.88) 0.2706
50 - <=70 kg 18/ 157 (11.5%) 22/ 151 (14.6%) 0.82 (0.44, 1.53)
70 - <=90 kg 4/ 31 (12.9%) 0/ 24 (0.0%)
>90 kg 0/ 1 (0.0%) 0/ 1 (0.0%)
Creatinine Clearance Group (cut-offs: 30, 50, 80 mL/min)
<30 mL/min 1/ 3 (33.3%) 3/ 8 (37.5%) 1.99 (0.20, 19.38) 0.3858
30-<50 mL/min 8/ 71 (11.3%) 10/ 46 (21.7%) 0.47 (0.19, 1.20)
50-80 mL/min 9/ 109 (8.3%) 14/ 116 (12.1%) 0.65 (0.28, 1.51)
>80mL/min 5/ 45 (11.1%) 5/ 58 (8.6%) 1.40 (0.40, 4.84)
0.1
1
10
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)
Creatinine Clearance Group (cut-offs: 15, 30, 50, 80 mL/min)
<15 mL/min 0/ 0 0/ 1 (0.0%) 0.4406
15-<30 mL/min 1/ 3 (33.3%) 3/ 7 (42.9%) 1.71 (0.17, 16.66)
30-<50 mL/min 8/ 71 (11.3%) 10/ 46 (21.7%) 0.47 (0.19, 1.20)
50-80 mL/min 9/ 109 (8.3%) 14/ 116 (12.1%) 0.65 (0.28, 1.51)
>80 mL/min 5/ 45 (11.1%) 5/ 58 (8.6%) 1.40 (0.40, 4.84)
Clopidogrel use with study ASA after randomization
None 14/ 114 (12.3%) 19/ 114 (16.7%) 0.72 (0.36, 1.44) 0.9762
>0 - <=30 days 6/ 63 (9.5%) 9/ 63 (14.3%) 0.66 (0.23, 1.86)
>30 - <=60 days 0/ 16 (0.0%) 1/ 19 (5.3%) 1.25 (0.21, 7.51)
>60 - <=180 days 3/ 24 (12.5%) 2/ 22 (9.1%)
>180 days 0/ 11 (0.0%) 1/ 8 (12.5%)
Atrial fibrillation disease history
No 23/ 224 (10.3%) 32/ 226 (14.2%) 0.71 (0.42, 1.22) 0.9998
Yes 0/ 6 (0.0%) 0/ 3 (0.0%)
Atrial flutter disease history
No 23/ 230 (10.0%) 32/ 229 (14.0%) 0.70 (0.41, 1.20) N/A
Critical limb ischemia
No 15/ 197 (7.6%) 20/ 198 (10.1%) 0.74 (0.38, 1.44) 0.7018
Yes 8/ 33 (24.2%) 12/ 31 (38.7%) 0.59 (0.24, 1.45)
Critical leg ischemia categories
No critical leg ischemia 15/ 197 (7.6%) 20/ 198 (10.1%) 0.74 (0.38, 1.44) 0.5406
Critical leg ischemia history 2/ 15 (13.3%) 6/ 14 (42.9%) 0.30 (0.05, 1.51)
Critical leg ischemia ongoing 6/ 18 (33.3%) 6/ 17 (35.3%) 0.88 (0.28, 2.74)
Length of target lesion on the index leg
SHORT (< 5 CM) 6/ 70 (8.6%) 5/ 56 (8.9%) 0.89 (0.27, 2.93) 0.8375
INTERMEDIATE (5 CM TO < 15 CM) 4/ 73 (5.5%) 9/ 82 (11.0%) 0.53 (0.16, 1.72)
LONG (>= 15 CM) 13/ 87 (14.9%) 18/ 91 (19.8%) 0.72 (0.35, 1.46)
Time from qualifying revasc. procedure to randomization
< Median (Days) 10/ 132 (7.6%) 15/ 120 (12.5%) 0.61 (0.27, 1.36) 0.6149
>= Median (Days) 13/ 98 (13.3%) 17/ 109 (15.6%) 0.80 (0.39, 1.65)
Statin use during study
No 9/ 84 (10.7%) 13/ 84 (15.5%) 0.70 (0.30, 1.64) 0.9718
Yes 14/ 146 (9.6%) 19/ 145 (13.1%) 0.71 (0.36, 1.42)
PAD symptom status (Rutherford score) (<=2, 3, >=4)
<=2 7/ 97 (7.2%) 12/ 107 (11.2%) 0.63 (0.25, 1.60) 0.9640
3 9/ 106 (8.5%) 11/ 98 (11.2%) 0.73 (0.30, 1.77)
>=4 7/ 27 (25.9%) 9/ 24 (37.5%) 0.70 (0.26, 1.88)
PAD symptom status (Rutherford score) (<=2, 3, 4, >=5)
<=2 7/ 97 (7.2%) 12/ 107 (11.2%) 0.63 (0.25, 1.60) 0.9943
3 9/ 106 (8.5%) 11/ 98 (11.2%) 0.73 (0.30, 1.77)
4 4/ 13 (30.8%) 5/ 11 (45.5%) 0.79 (0.21, 2.93)
>= 5 3/ 14 (21.4%) 4/ 13 (30.8%) 0.66 (0.14, 3.06)
0.1
1
10
Favours Riva+ASA
Favours Plac+ASA

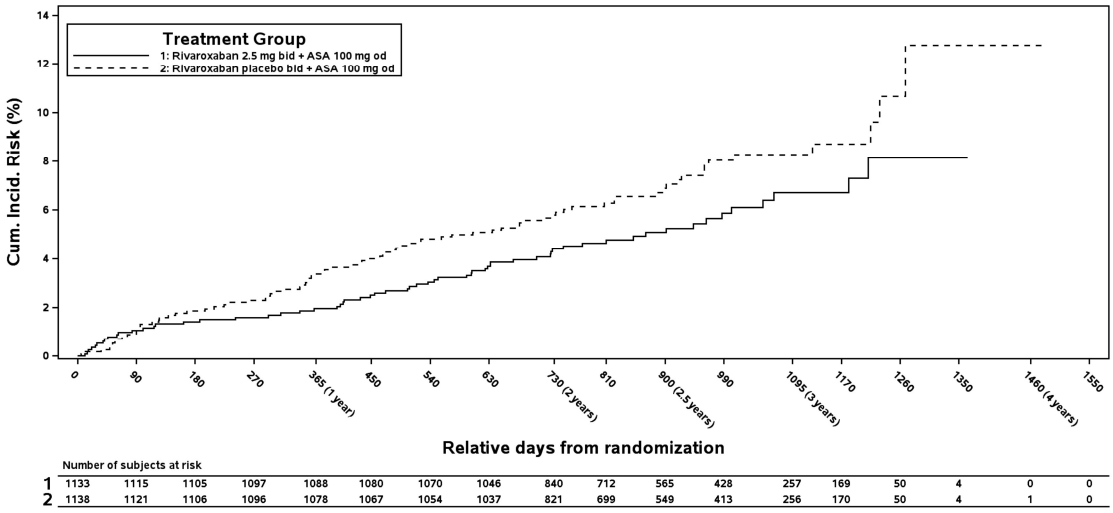


The ITT analysis set includes all randomized subjects. The ITT data scope includes outcome events observed from randomization date until efficacy cut-off date. Subgroup variables from Atrial fibrillation disease history and below are added post-hoc.
MI, stroke, mortality, ALI, major amputation of vascular 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 unstratified Cox proportional hazards model, with treatment as the only covariate
(a) P-value for interaction is based on the corresponding Cox proportional hazards model by adding the corresponding treatment interaction term.

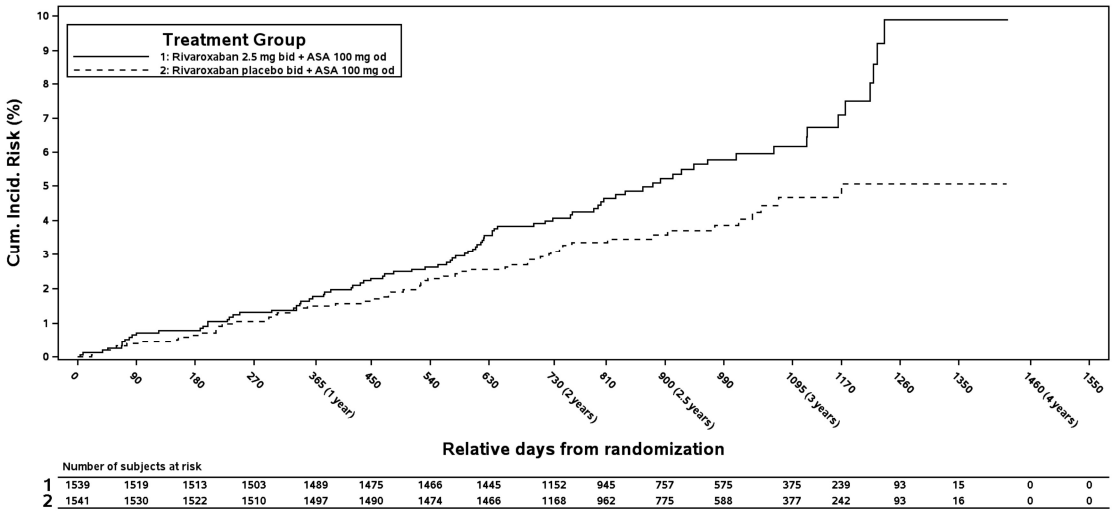
Source: 5.3.5.1.2 17454_J_analysis/Figure 14.2.5.2/49

図 2.7.3.7-12 心血管死の ECOD までの累積イベント発現率に関する Kaplan-Meier 曲線（試験 17454、全体集団、ITT、IxRS の層別、ICAC 判定）

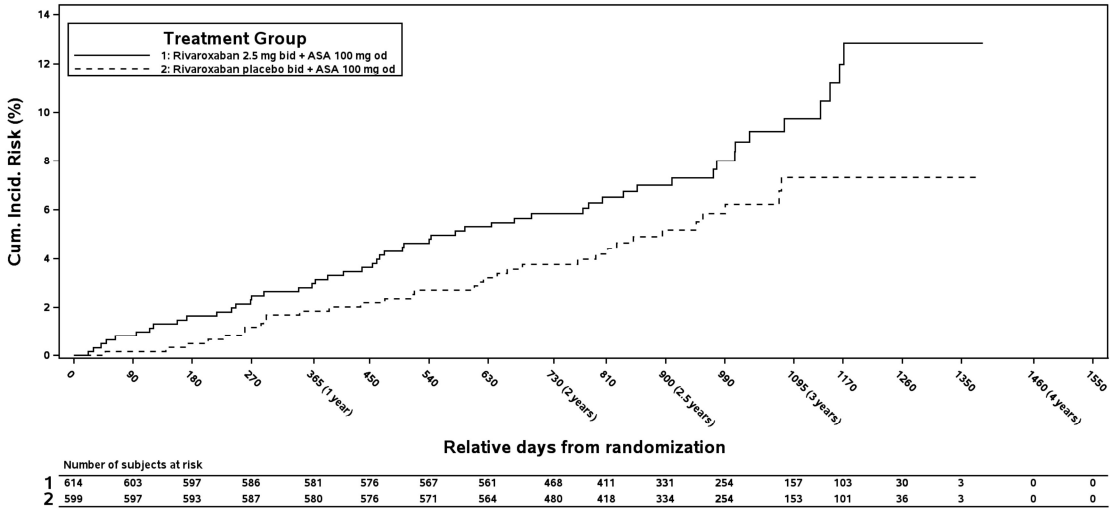
外科的血行再建術



血管内血行再建術でクロピドグレル使用あり



血管内血行再建術でクロピドグレル使用なし

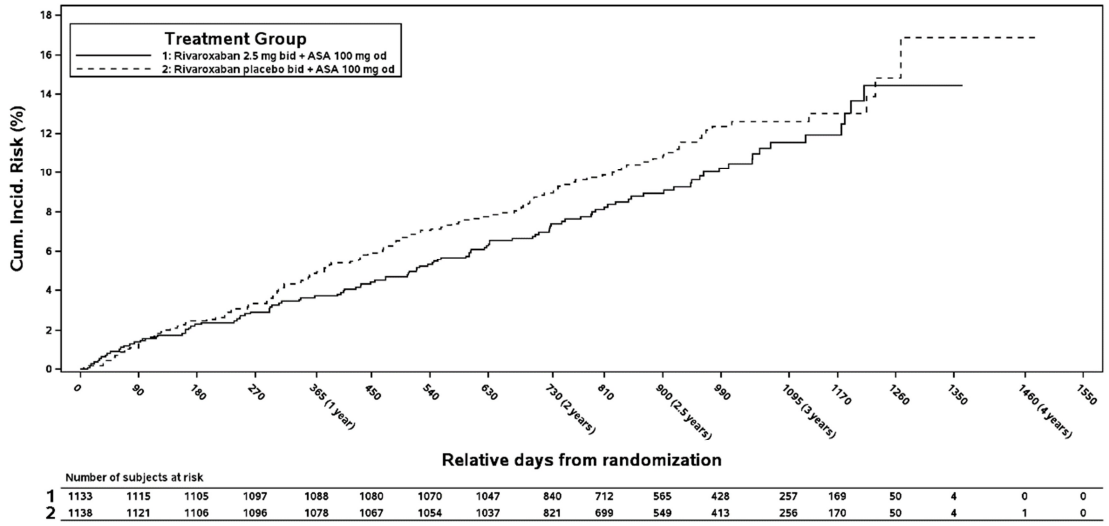


At-risk subject counts were calculated as at end of timepoint.
Figure displays outcome events meeting the definition as adjudicated by Independent Clinical Adjudication Committee (ICAC).
The ITT analysis set includes all randomized subjects. The ITT data scope includes outcome events observed from randomization date until efficacy cut-off date.
Efficacy cut-off date = 08SEP2019
CV death = Cardiovascular death and unknown cause
bid = twice daily, od = once daily, ASA = acetylsalicylic acid
K-M = Kaplan-Meier, Cum. Incid. Risk (%) = K-M estimates of the cumulative incidence for an event, calculated as 100 * (1 minus the K-M estimates of the survival function).
Only the first occurrence of the outcome event under analysis within the data scope from a subject is considered.

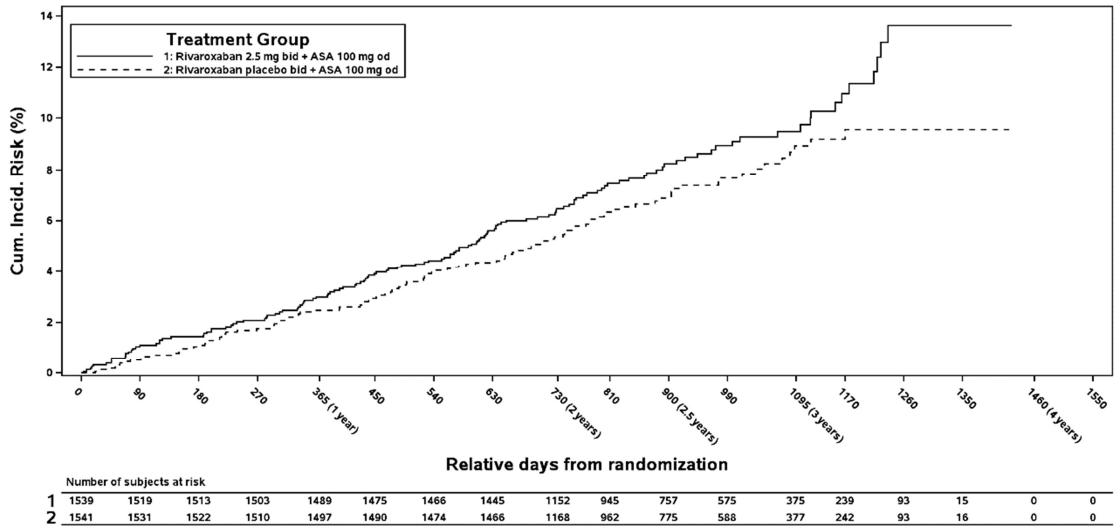
Source: 5.3.5.1.1 PH-40164/Figure 14.2.1/20

図 2.7.3.7-13 全死亡の ECOD までの累積イベント発現率に関する Kaplan-Meier 曲線（試験 17454、全体集団、ITT、IxRS の層別、ICAC 判定）

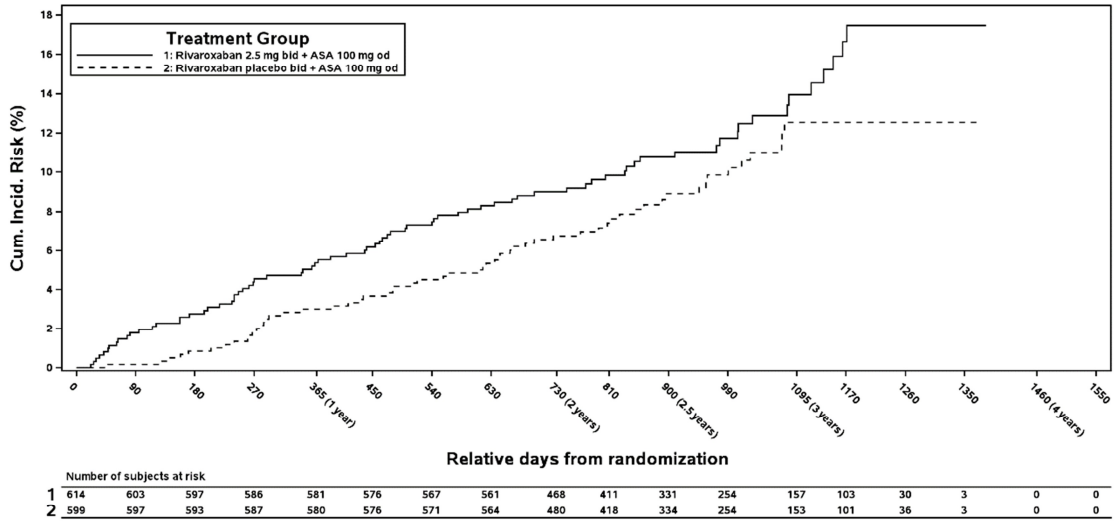
外科的血行再建術



血管内血行再建術でクロピドグレル使用あり



血管内血行再建術でクロピドグレル使用なし



At-risk subject counts were calculated as at end of timepoint.
The ITT analysis set includes all randomized subjects. The ITT data scope includes outcome events observed from randomization date until efficacy cut-off date.
Efficacy cut-off date = 08SEP2019
All-cause mortality is adjudicated by Independent Clinical Adjudication Committee (ICAC).
bid = twice daily, od = once daily, ASA = acetylsalicylic acid
K-M = Kaplan-Meier, Cum. Incid. Risk (%) = K-M estimates of the cumulative incidence for an event, calculated as 100 * (1 minus the K-M estimates of the survival function).
Only the first occurrence of the outcome event under analysis within the data scope from a subject is considered.

Source: 5.3.5.1.1 PH-40164/Figure 14.2.2/23