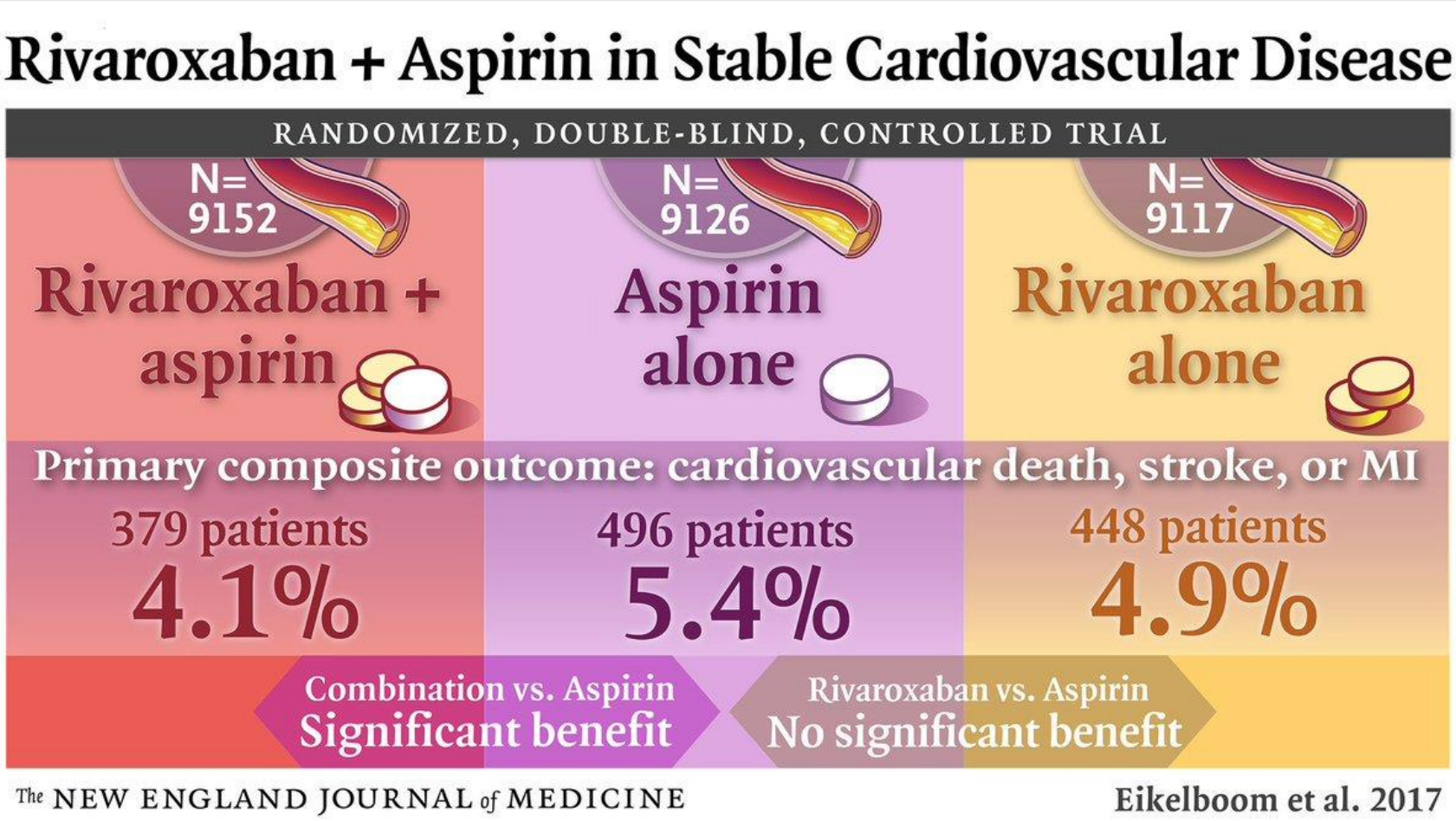
Terapia a lungo termine con Rivaroxaban e Aspirina nell'arteriopatia periferica e nelle sindromi coronariche croniche

Risultati dello studio di Open Label Extension
del COMPASS trial

Background: COMPASS trial



Long-term treatment with the combination of rivaroxaban and aspirin in patients with chronic coronary or peripheral artery disease: outcomes during the open label extension of the COMPASS trial

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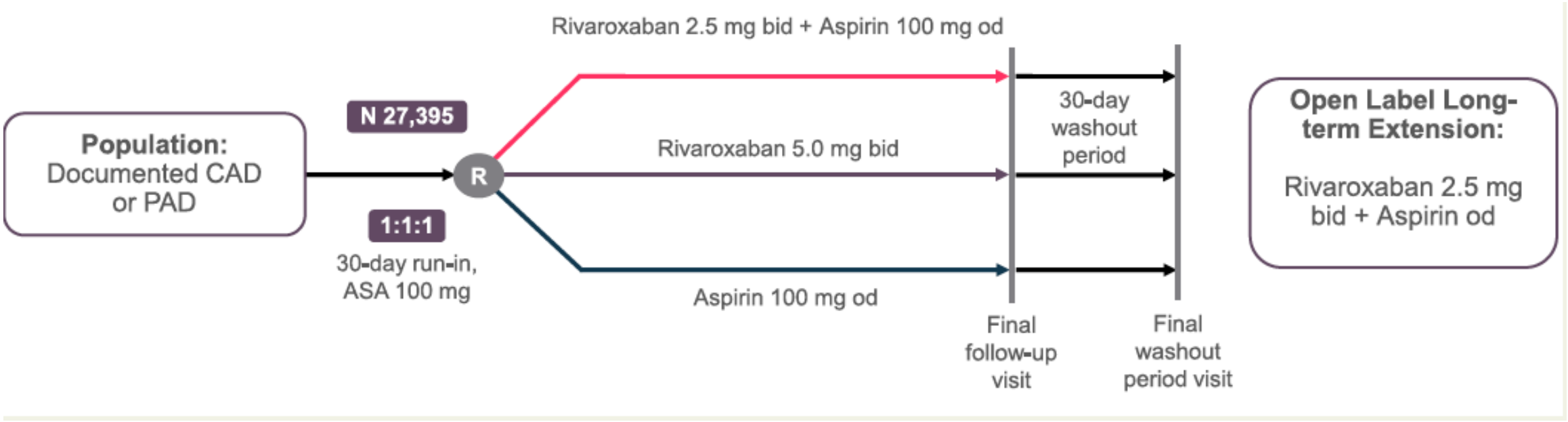
Methods

Of the 27 395 patients enrolled in COMPASS, 12 964 (mean age at baseline 67.2 years) from 455 sites in 32 countries were enrolled in LTOLE and treated with the combination of rivaroxaban and aspirin for a median of 374 additional days (range 1–1191 days).



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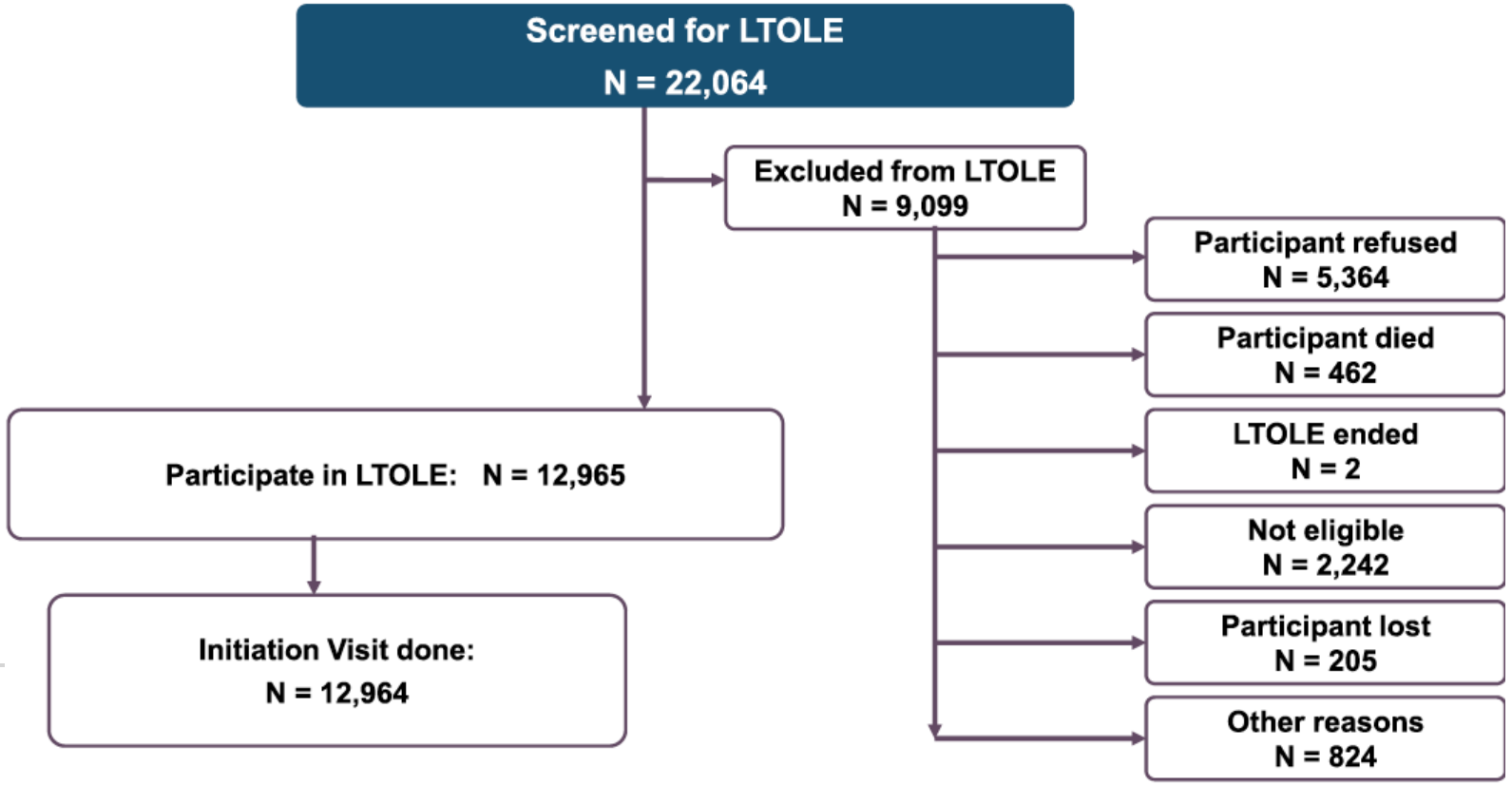
Patient flow diagram for long-term open-label extension entry (LTOLE)



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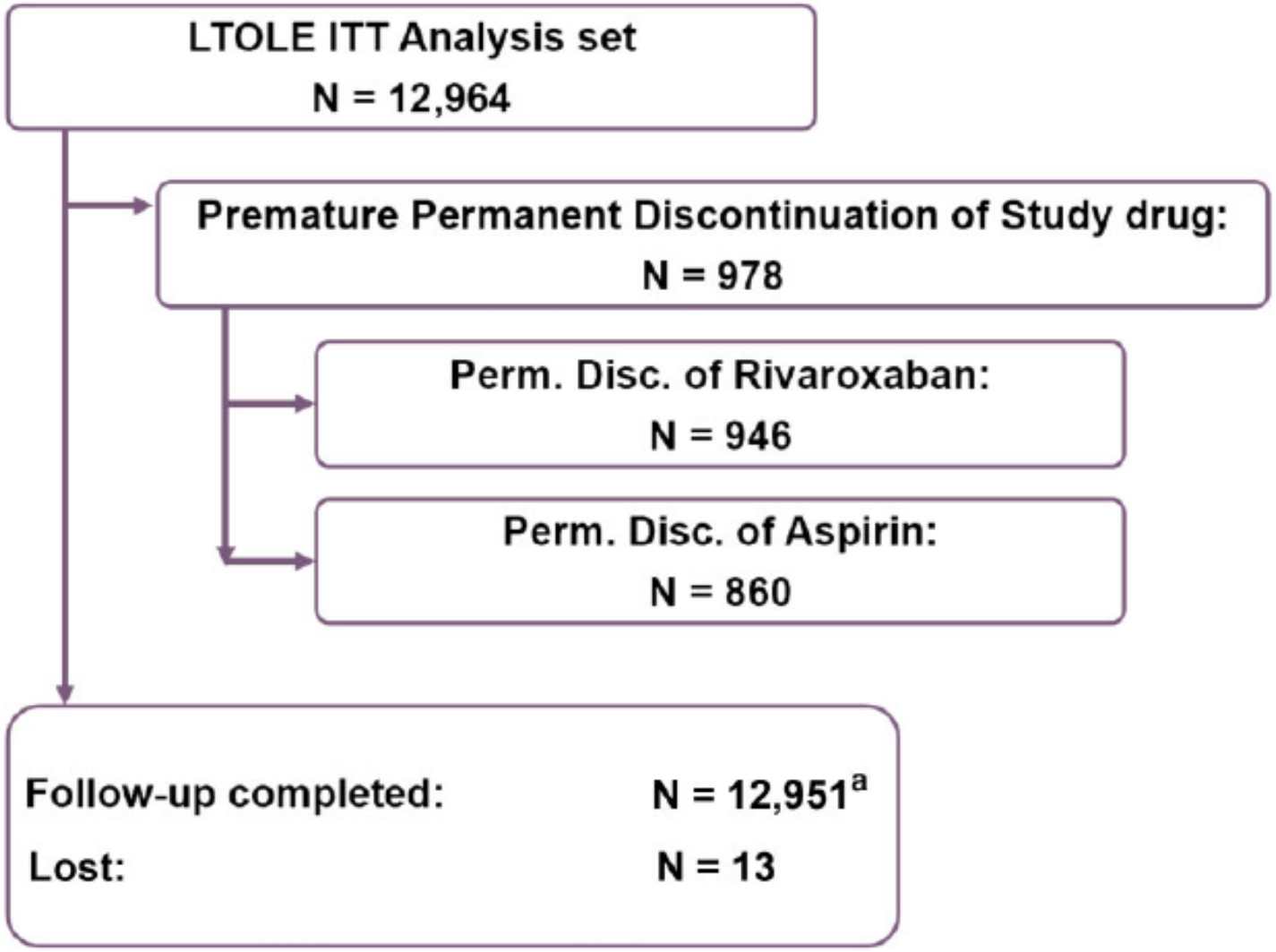
Patient disposition during LTOLE

- [a]Includes 18 patients who refused further follow up; their most recent visit was counted as their final visit.



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Baseline characteristics at entry into the COMPASS trial of patients treated with the combination of rivaroxaban and aspirin during LTOLE, during randomized evaluation, and patients not enrolled in LTOLE

Characteristic	Patients treated with rivaroxaban 2.5 mg twice daily + aspirin once daily: During LTOLE ($n = 12964$)	Patients treated with rivaroxaban 2.5 mg twice daily + aspirin once daily: During randomized treatment ($n = 9152$)	Patients not enrolled in LTOLE ($n = 14431$)
Age (years), mean (SD)	67.2 (7.8)	68.2 (7.9)	69.1 (8.0)
Female sex, *n* (%)	2879 (22.2%)	2059 (22.5%)	3138 (21.7%)
Cholesterol (mmol/L), mean (SD)	4.19 (1.07)	4.19 (1.08)	4.19 (1.06)
Tobacco use, *n* (%)	2878 (22.2%)	1944 (21.2%)	2990 (20.7%)
Hypertension, *n* (%)	9575 (73.9%)	6907 (75.5%)	11 072 (76.7%)
CAD, *n* (%)	11 753 (90.7%)	8313 (90.8%)	13 072 (90.6%)
Prior MI, *n* (%)	8324 (64.2%)	5654 (61.8%)	8703 (60.3%)
PAD, *n* (%)	3421 (26.4%)	2492 (27.2%)	4053 (28.1%)
Prior stroke, *n* (%)	441 (3.4%)	351 (3.8%)	595 (4.1%)
BMI (kg/m^2), mean (SD)	28.6 (4.6)	28.3 (4.8)	28.1 (4.8)
Systolic blood pressure (mmHg), mean (SD)	134.9 (17.0)	135.5 (17.5)	136.1 (18.0)
Diastolic blood pressure (mmHg), mean (SD)	77.6 (9.7)	77.4 (9.9)	77.5 (10.2)
eGFR (mL/min/1.73 m^2), mean (SD)	74.7 (17.2)	73.9 (17.9)	73.0 (18.6)
<30	63 (0.5%)	77 (0.8%)	180 (1.2%)
30 to ≤60	2641 (20.4%)	1977 (21.6%)	3393 (23.5%)
≥60	10 260 (79.1%)	7094 (77.5%)	10 851 (75.2%)
Ethnicity, *n* (%)			
White or Caucasian	8691 (67.0%)	5673 (62.0%)	8337 (57.8%)
Black/African American	115 (0.9%)	76 (0.8%)	146 (1.0%)
Asian	1147 (8.8%)	1451 (15.8%)	3122 (21.6%)
Other	3011 (23.2%)	1952 (21.3%)	8337 (57.8%)
Cancer	737 (5.7%)	596 (6.5%)	998 (6.9%)
CV risk categories			
Polyvascular disease, *n* (%)	2796 (21.6%)	6204 (22.6%)	3415 (23.6%)
Heart failure, *n* (%)	3074 (23.7%)	1963 (21.4%)	2825 (19.6%)
[a]Chronic kidney disease, *n* (%)	2704 (20.9%)	2054 (22.4%)	3573 (24.8%)
Diabetes, *n* (%)	4502 (34.7%)	3448 (37.7%)	5847 (40.5%)

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Antithrombotic therapies after completion of randomized antithrombotic treatment and prior to start of LTOLE, and concomitant therapies at the time of LTOLE start

Treatments	Patients enrolled in LTOLE ($n = 12964$)
Antithrombotic therapies prior to LTOLE enrolment	
Antiplatelet	
Aspirin	12228 (94.3%)
Clopidogrel	682 (5.3%)
Prasugrel	27 (0.2%)
Ticagrelor	38 (0.3%)
Ticlopidine	25 (0.2%)
Dipyridamole	25 (0.2%)
Other	47 (0.4%)
Anticoagulant	
Parenteral	54 (0.4%)
Rivaroxaban (non-study)	110 (0.8%)
Apixaban	14 (0.1%)
Dabigatran	14 (0.1%)
Vitamin K antagonist	24 (0.2%)
Other	12 (<0.1%)
Non-antithrombotic therapies at time of LTOLE enrolment	
Proton pump inhibitor (non-study)	3938 (30.4%)
NSAID	578 (4.5%)
ACE inhibitor/ARB	9661 (74.5%)
Alpha blocker or another vasodilator	1671 (12.9%)
Diuretic	3936 (30.4%)
Lipid-lowering agent	11732 (90.5%)
Calcium channel blocker	3608 (27.8%)
Beta blocker	9095 (70.2%)
Hypoglycaemic agent	4146 (32.0%)
Selective serotonin reuptake inhibitor	533 (4.1%)

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Efficacy outcomes in patients treated with the combination of rivaroxaban and aspirin during LTOLE or during randomized evaluation

	Patients treated with rivaroxaban 2.5 mg twice daily + aspirin once daily			
	During LTOLE ($N = 12964$)[a]		During randomized treatment ($N = 9152$)[b]	
Outcome	***n***	***N*/100 p-yrs**	***N***	***N*/100 p-yrs**
Primary				
CV death, stroke, MI	353	2.35 (2.11–2.61)	379	2.18 (1.97–2.41)
Mortality	282	1.87 (1.65–2.10)	313	1.78 (1.58–1.98)
CV death	166	1.10 (0.94–1.28)	160	0.91 (0.77–1.06)
Non-CV death	116	0.77 (0.63–0.92)	153	0.87 (0.74–1.02)
Stroke	94	0.62 (0.50–0.76)	83	0.47 (0.38–0.59)
MI	153	1.02 (0.86–1.19)	178	1.02 (0.88–1.18)
Severe limb ischaemia	21	0.14 (0.09–0.21)	22	0.12 (0.08–0.19)
Hospitalization	1664	11.83 (11.27–12.41)	2600	17.76 (17.09–18.46)

SIMILAR INCIDENCE OF ISCHEMIC EVENTS

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Events per 100 patient years for cardiovascular death, stroke, or myocardial infarction in key subgroups of patients treated with the combination of rivaroxaban and aspirin

	Patients treated with rivaroxaban 2.5 mg twice daily + aspirin once daily			
	During LTOLE (n = 12 964)[a]		During randomized treatment (n = 9152)[b]	
Subgroup	***N***	***N*/100 p-yrs (95% CI)**	***N***	***N*/100 p-yrs (95% CI)**
CAD				
Yes	310	2.31 (2.06–2.58)	347	2.17 (1.95–2.41)
No	43	2.71 (1.95–3.65)	32	2.28 (1.56–3.22)
PAD				
Yes	115	2.85 (2.35–2.42)	126	2.82 (2.35–3.36)
No	238	2.17 (1.90–2.46)	253	1.96 (1.72–2.21)
CAD plus PAD				
Yes	72	2.93 (2.29–3.69)	94	3.06 (2.47–3.75)
No	281	2.24 (1.98–2.51)	285	1.99 (1.77–2.24)
Polyvascular disease, *n* (%)				
Yes	90	2.83 (2.28–3.48)	114	3.01 (2.48–3.61)
No	263	2.22 (1.96–2.51)	265	1.95 (1.72–2.20)
Heart failure, *n* (%)				
Yes	108	3.15 (2.59–3.81)	108	3.13 (2.57–3.78)
No	245	2.11 (1.86–2.39)	271	1.94 (1.72–2.19)
Chronic kidney disease, *n* (%)†				
Yes	95	3.03 (2.45–3.70)	132	3.41 (2.85–4.04)
No	258	2.17 (1.91–2.45)	247	1.83 (1.61–2.07)
Diabetes, *n* (%)				
Yes	171	3.26 (2.79–3.79)	179	2.74 (2.35–3.17)
No	182	1.86 (1.60–2.15)	200	1.84 (1.60–2.12)
Polyvascular disease, heart failure, chronic kidney disease, or diabetes				
0	79	1.57 (1.24–1.95)	63	1.10 (0.84–1.40)
1	135	2.26 (1.90–2.68)	155	2.26 (1.92–2.65)
2	97	3.11 (2.53–3.80)	112	3.04 (2.51–3.66)
3 or 4	42	4.67 (3.37–6.31)	49	4.40 (3.26–5.82)

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Bleeding outcomes in patients treated with the combination of rivaroxaban and aspirin

	Patients treated with rivaroxaban 2.5 mg twice daily + aspirin once daily			
	During LTOLE ($n = 12\,964$)[a]		During randomized treatment ($n = 9152$)[b]	
Outcome	***N***	***N*/100 p-yrs**	***N***	***N*/100 p-yrs**
Major modified ISTH	152	1.01 (0.86–1.19)	288	1.67 (1.48–1.87)
Fatal	9	0.06 (0.03–0.11)	15	0.09 (0.05–0.14)
Critical organ bleeding (non-fatal)	40	0.27 (0.19–0.36)	73	0.42 (0.33–0.52)
Requiring reoperation (non-fatal and non-critical organ)	12	<0.1 (0.04–0.14)	15	0.09 (0.05–0.14)
Hospitalization (non-fatal, non-critical organ, not leading to reoperation)	90	0.60 (0.48–0.73)	259	1.50 (1.32–1.69)
Site of major bleeding				
Gastrointestinal	45	0.30 (0.22–0.40)	140	0.80 (0.67–0.95)
Intracranial	16	0.11 (0.06–0.17)	28	0.16 (0.11–0.23)
Minor bleeding	370	2.49 (2.24–2.75)	838	5.11 (4.77–5.47)

HIGHER INCIDENCE OF BLEEDING EVENTS DURING RANDOMIZED TREATMENT

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Incidence rates for cardiovascular death, stroke, or myocardial infarction and modified ISTH major bleeding

Event	Rivaroxaban 2.5 mg twice daily + aspirin 100 mg once daily (*n* = 4399)	Rivaroxaban 5 mg twice daily (*n* = 4292)	Aspirin 100 mg once daily (*n* = 4273)
CV death, stroke, or MI			
During randomized treatment	2.27 (2.12, 2.42)	2.71 (2.55, 2.88)	2.98 (2.81, 3.16)
During LTOLE	2.47 (2.06, 2.94)	2.46 (2.04, 2.93)	2.12 (1.73, 2.57)
ISTH modified major bleeding			
During randomized treatment	1.62 (1.45, 1.82)	1.45 (1.28, 1.63)	0.98 (0.84, 1.13)
During LTOLE	0.79 (0.56, 1.07)	1.12 (0.85, 1.45)	1.13 (0.85, 1.47)

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Limitations

- Only 47% of the original COMPASS cohort (12 964/27 395) entered LTOLE
- Patients who entered LTOLE are not directly comparable with those who were originally randomized in the COMPASS trial because the two cohorts are overlapping and patients enrolled in LTOLE are several years older.
- COMPASS LTOLE did not include a control group.
- Unlike during the randomized phase of COMPASS, we did not adjudicate outcomes during LTOLE.
  - Adjudication refuted 10–15% of the efficacy events reported by the sites because there was insufficient evidence to confirm that they met the definition.
  - Overall bleeding event rates were not affected by adjudication because we did not refute any bleeds (they could only be reclassified).

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Conclusions

- COMPASS LTOLE demonstrated that among patients who agreed to participate after successfully completing follow-up during the randomized phase, treatment with the combination of rivaroxaban 2.5 mg twice daily and aspirin 100 mg once daily for up to a further 3 years was associated with incidence rates for CV death, stroke, or MI that were similar to those seen during the randomized phase, and with similar or lower incidence rates for bleeding, including gastrointestinal and intracranial bleeding.
- These data provide further support for guideline recommendations for the long-term use of the combination of rivaroxaban and aspirin in high-risk patients with chronic CAD and/or PAD.

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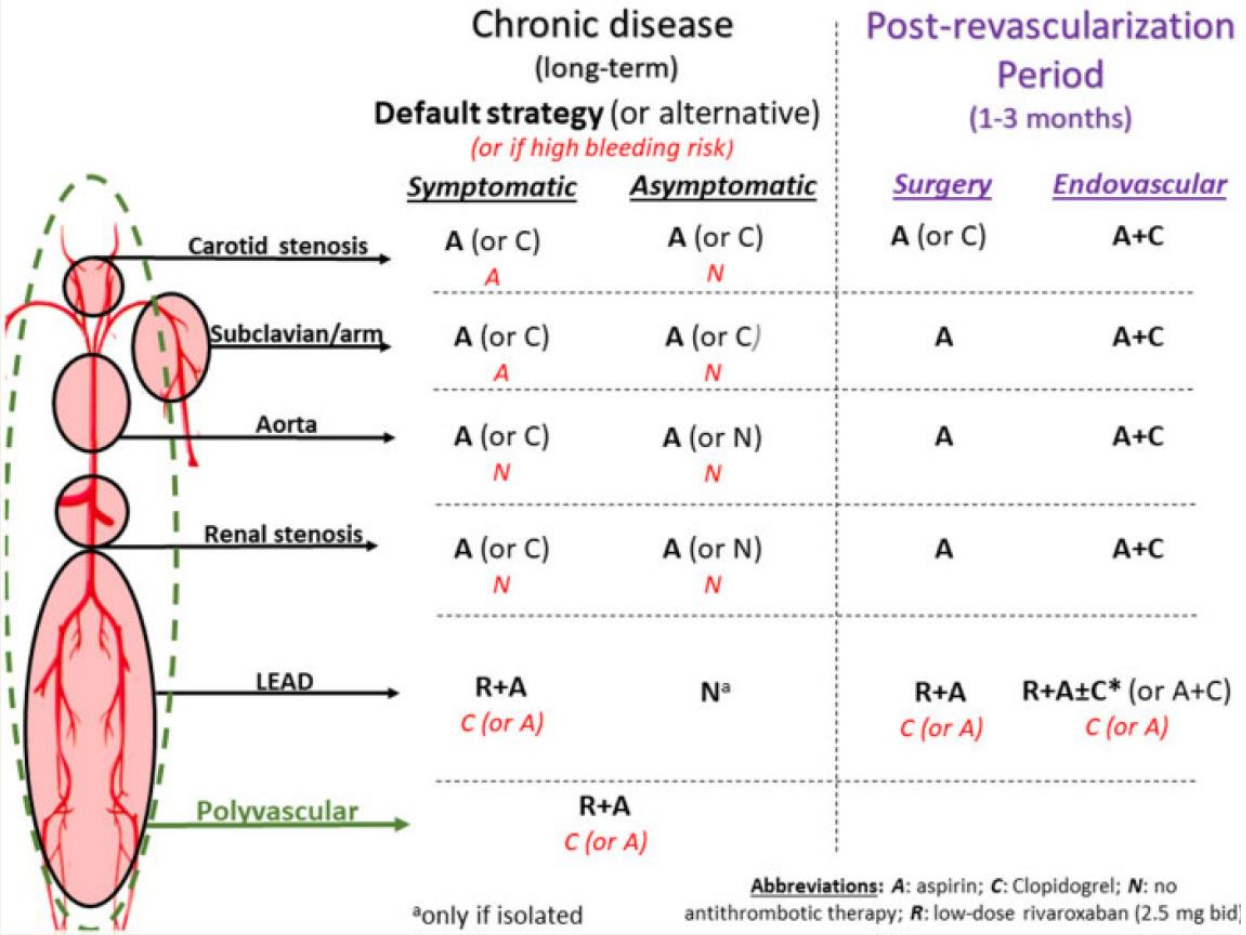
Consensus ESC 2021



	Chronic disease (long-term) Default strategy (or alternative) (or if high bleeding risk)		Post-revascularization Period (1-3 months)	
	Symptomatic	*Asymptomatic*	*Surgery*	*Endovascular*
Carotid stenosis	A (or C) *A*	A (or C) *N*	A (or C)	A+C
Subclavian/arm	A (or C) *A*	A (or C) *N*	A	A+C
Aorta	A (or C) *N*	A (or N) *N*	A	A+C
Renal stenosis	A (or C) *N*	A (or N) *N*	A	A+C
LEAD	R+A *C (or A)*	N[a]	R+A *C (or A)*	R+A±C* (or A+C) *C (or A)*
Polyvascular	R+A *C (or A)*			

[a]only if isolated

Abbreviations: ***A***: aspirin; ***C***: Clopidogrel; ***N***: no antithrombotic therapy; ***R***: low-dose rivaroxaban (2.5 mg bid)

Antiplatelet therapy is the mainstay of antithrombotic strategy in patients with symptomatic LEAD.
Rivaroxaban 2.5mg bid should be proposed on top of low-dose aspirin in stable patients with chronic symptomatic LEAD, without conditions at high risk of bleeding.*

*History of intra-cranial haemorrhage or ischaemic stroke, or other intracranial pathology, recent gastrointestinal bleeding or anaemia due to possible gastrointestinal blood loss, other gastrointestinal pathology associated with increased bleeding risk, liver failure, bleeding diathesis or coagulopathy, extreme old age or frailty, or renal failure with eGFR <15 mL/min/1.73 m2.