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Editor's Choice – External Applicability of the COMPASS and VOYAGER-PAD Trials on Patients with Symptomatic Lower Extremity Artery Disease in France: The COPART Registry

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1 **Short title**

2 Applicability of COMPASS and VOYAGER-PAD trials

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1 **What does this study add to the existing literature and how will it influence future**
2 **clinical practice?**

3 Only 30.1% of patients hospitalized for symptomatic lower extremity artery disease
4 are eligible to rivaroxaban 2.5 mg bid plus aspirin, based on the COMPASS or VOYAGER-
5 PAD criteria. These patients have higher rates of ischaemic events compared with those in
6 these trials. The one-year cumulative incidences were 6.0% (95%CI, 4.3-8.1) in the
7 COMPASS-eligible subset vs 3.5% (95%CI, 2.9-4.3) in the COMPASS control arm for major
8 adverse cardiovascular events, and 27.9% (95%CI, 19.9-38.3) in the VOYAGER-PAD-
9 eligible subset vs 6.0% (95%CI, 5.3-6.9) in the VOYAGER-PAD control arm for major
10 adverse limb events. This regimen may have greater benefits in the real-world population.

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1 **Abstract**

2 **Objectives:** The aim of this study is to examine the external applicability of the
3 COMPASS and the VOYAGER-PAD trials among patients with lower extremity artery
4 disease (LEAD) in the real-world.

5 **Design:** It is a multicenter, retrospective analysis of prospectively collected COPART
6 data, a French multicentre registry of patients hospitalized for symptomatic LEAD.

7 **Materials and Methods:** The proportion of patients eligible to the combination of
8 rivaroxaban 2.5 mg bid plus aspirin based on either COMPASS or VOYAGER-PAD criteria
9 is reported. The one-year cumulative incidence of outcomes between eligible vs non-eligible
10 patients, as well as eligible patients vs control arms of the COMPASS (LEAD patients
11 subgroup) and the VOYAGER-PAD trials are compared. Analyses were performed using Cox
12 models.

13 **Results:** Among 2 259 evaluable patients, only 679 (30.1%) were eligible for low-dose
14 rivaroxaban plus aspirin regimen. Others were non-eligible because of the need for
15 anticoagulant (respectively 48.5% and 38.9% of patients meeting COMPASS and
16 VOYAGER-PAD exclusion criteria) or dual antiplatelet therapy use (15.7% and 16.5%),
17 high-bleeding risk (14.4% and 11.6%), malignancy (26.1% and 21.0%), history of
18 ischaemic/haemorrhagic stroke (21.1% and 19.8%), and severe renal failure (13.2% and
19 10.5%). COMPASS and VOYAGER-PAD eligible and ineligible patients were at higher risk
20 of ischaemic events than participants in these trials. The one-year cumulative incidences were
21 6.0% (95%CI, 4.3-8.1) in the COMPASS-eligible subset vs 3.5% (95%CI, 2.9-4.3) in the
22 COMPASS control arm for MACE, and 27.9% (95%CI, 19.9-38.3) in the VOYAGER-PAD-
23 eligible subset vs 6.0% (95%CI, 5.3-6.9) in the VOYAGER-PAD control arm for major
24 adverse limb events.

1 **Conclusion:** Many patients hospitalized for symptomatic LEAD in France are not
2 eligible for the low-dose rivaroxaban plus aspirin combination. In turn, those eligible may
3 potentially have greater absolute benefit because of higher risk as compared to those enrolled
4 in those trials.

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6 **Keywords:** peripheral artery disease, rivaroxaban, cohort studies, mortality, amputation

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1 **Introduction**

2 Patients with lower extremity artery disease (LEAD) are at heightened risk of major
3 adverse cardiovascular events (MACE), including cardiovascular (CV) death, myocardial
4 infarction (MI), and stroke, and are also at increased risk of all-cause mortality. Despite
5 antithrombotic therapy, the one-year cumulative incidence of MACE is at least 12%, and is as
6 high as 16.8% after revascularization for chronic limb-threatening ischemia (CLTI) (1,2). The
7 limb-related events rates are also high. In a meta-analysis, during a 5-years follow up, 21% of
8 intermittent claudication (IC) patients were diagnosed as having CLTI, with 4-27%
9 undergoing amputation (3).

10 To improve both the general CV and limb outcome, guidelines recommend a medical
11 therapy including antiplatelet medication, as a pillar of CV prevention (4,5). However, even
12 when this therapy is well implemented, the residual risk in patients with LEAD is notable.
13 Hence, new antithrombotic strategies have been recently assessed with promising results
14 (6,7).

15 The COMPASS trial (Cardiovascular Outcomes for People Using Anticoagulation
16 Strategies) tested the combination of rivaroxaban 2.5 mg bid plus aspirin for long term
17 management of patients with stable atherosclerotic disease, and showed a significant
18 reduction of 24% of MACE with this combination as compared with the aspirin alone arm,
19 with consistent and significant results in the subgroup of patients with symptomatic LEAD
20 (6,8).

21 The VOYAGER-PAD trial (Vascular Outcomes Study of Acetylsalicylic acid Along
22 with Rivaroxaban in Endovascular or Surgical Limb Revascularization for Peripheral Artery
23 Disease) tested the same combination and doses of rivaroxaban and aspirin in selected
24 patients with symptomatic LEAD immediately after a successful revascularization procedure,
25 a setting with high risk for ischemic and bleeding complications. This trial showed a

1 significant reduction of 15% of the composite outcome of acute limb ischemia (ALI), major
2 amputation for vascular causes and MACE in the low-dose rivaroxaban plus aspirin arm as
3 compared with aspirin plus placebo arm (7). In both trials, while an excess in bleeding was
4 reported, the benefit/risk ratio was overall in favour of the use of this combined
5 antithrombotic strategy.

6 However, it is widely accepted that the results obtained in trials need further validation
7 in real-world clinical practice, as patients enrolled in CV trials are on average at lower risk
8 because of younger age and less comorbidities (1,9,10). Regarding patients with LEAD, the
9 number eligible for the low-dose rivaroxaban plus aspirin combination is uncertain. It is also
10 unclear whether the patients selected for treatment with the combination of low-dose
11 rivaroxaban plus aspirin will have similar risk in clinical practice than those enrolled in the
12 COMPASS and the VOYAGER-PAD trials.

13 Therefore, we examined the external applicability of the COMPASS and the
14 VOYAGER-PAD trials results by describing the proportion of COMPASS and VOYAGER-
15 PAD eligible patients in a cohort of consecutive patients hospitalized for symptomatic LEAD
16 in the vascular medicine departments in France. We also compared outcome rates between
17 eligible vs non-eligible patients for COMPASS and VOYAGER-PAD trials, and between
18 these eligible patients vs those randomized in the reference arm (i.e. aspirin arm) in those two
19 trials.

20

21 **Material and Methods**

22 *The COMPASS trial*

23 The COMPASS (Cardiovascular Outcomes for People Using Anticoagulation
24 Strategies) trial was a phase-3, double-blind randomized controlled trial (RCT), which
25 randomly assigned 27 395 patients with stable atherosclerotic vascular disease (coronary

1 artery disease [CAD], LEAD, or carotid artery disease) to receive rivaroxaban (2.5 mg bid)
2 plus aspirin (100 mg once daily), rivaroxaban (5 mg bid) plus placebo, or aspirin (100 mg
3 once daily) plus placebo (6). The detailed COMPASS inclusion and exclusion criteria are
4 described in Supplementary Material Table 1.

5

6 ***The VOYAGER-PAD trial***

7 The VOYAGER-PAD (Vascular Outcomes Study of Acetylsalicylic Acid along with
8 Rivaroxaban in Endovascular or Surgical Limb Revascularization for Peripheral Artery
9 Disease) trial was a phase 3, double-blind RCT, which randomly assigned 6 564 patients with
10 LEAD who had undergone revascularization to receive rivaroxaban (2.5 mg bid) plus aspirin
11 (100 mg once daily), or aspirin (100 mg once daily) plus placebo (7). Clopidogrel could be
12 additionally prescribed at the discretion of the investigator, but not for more than 6 months.
13 The detailed VOYAGER-PAD inclusion and exclusion criteria are described in
14 Supplementary Material Table 3.

15

16 ***The COPART registry***

17 The COPART (COhorte de Patients ARTériopathes) registry is an ongoing
18 multicentre, observational, cohort study, since 2006 prospectively collecting data on
19 consecutive patients hospitalized for symptomatic LEAD in the vascular medicine
20 departments of 4 French academic centres (Bordeaux, Limoges, Paris, and Toulouse). Patients
21 may have been hospitalized for scheduled surgery following a consultation, or for emergency
22 care, or transferred from other hospitals or from others departments of the same hospital.
23 Patients requiring only outpatient care for LEAD are not included in the COPART registry.
24 Details on the study protocol have been published elsewhere (11). Patient care was provided
25 according to usual practice. After the initial hospitalization, patients were followed for at least

1 12 months. Data were prospectively collected by trained medical COPART investigators,
2 following a computerized standardized case report form, and using all records available
3 during hospitalization and follow-up. Patients, their families and/or their physicians were
4 systematically contacted one year after hospital discharge. The patients gave their informed
5 consent to participate. The study complies with the declaration of Helsinki and was approved
6 by the Ethic Committee of Toulouse University Hospital. The current report is based on a
7 database locked in October 2017, including patients recruited from 2006 to 2015.

8 Each patient required the following criteria to be included in COPART registry: age
9 ≥ 18 years, consent to participate, and specifically hospitalized for treatment and/or
10 management of symptomatic LEAD of atherosclerotic origin. Clinical presentations included
11 either an intermittent claudication, associated with abnormal ABI < 0.90 or > 1.30 , or, in the
12 case of normal ABI at rest, a positive treadmill test (Strandness protocol, 3.2 km/h on a 10%
13 slope), arterial stenosis $> 50\%$ on duplex ultrasound or angiography computerized tomography
14 or angiography, or ischemic rest pain, ulceration or gangrene or an ALI related to a
15 documented LEAD with significant arterial stenosis.

16 Patients for whom follow-up was improbable (i.e. patients who cannot be contacted
17 after hospitalization, follow-up carried out in a foreign country), those with arterial occlusive
18 disease not related to atherosclerosis, those with ALI without LEAD and those refusing to
19 participate were not included.

20

21 ***“COMPASS-eligible” and “VOYAGER-PAD-eligible” study populations***

22 Patients with missing data regarding eligibility criteria for COMPASS or VOYAGER-
23 PAD were excluded. Then, the analysis started with COMPASS inclusion and exclusion
24 criteria (Supplementary Material Table 1). A detailed list of adjustments made in these criteria

1 for the analysis of the COPART registry is provided in Supplementary Material Table 2. First,
2 patients meeting any adapted COMPASS exclusion criteria were excluded; the main reasons
3 for exclusion were reported. Second, remaining patients were included in the “COMPASS-
4 eligible” subset if they fulfilled adapted COMPASS inclusion criteria. The analysis continued
5 with VOYAGER-PAD inclusion and exclusion criteria (Supplementary Material Table 3). A
6 detailed list of adjustments made in these criteria for the analysis of the COPART registry is
7 provided in Supplementary Material Table 4. First, patients not undergoing limb
8 revascularization were excluded. Second, patients meeting any adapted VOYAGER-PAD
9 exclusion criteria were excluded; the main reasons for these exclusions were reported. Third,
10 remaining patients were included in the “VOYAGER-PAD-eligible” subset if they fulfilled
11 adapted VOYAGER-PAD inclusion criteria. Patients excluded from VOYAGER-PAD and
12 those of the “VOYAGER-PAD-eligible” subset were included in the “COMPASS-eligible”
13 subset if they fulfilled adapted COMPASS inclusion criteria without meeting any adapted
14 COMPASS exclusion criteria.

15

16 *Primary and secondary outcomes*

17 For this study, the primary outcome is MACE, a composite of CV death, MI, and
18 stroke, similar to the primary outcome of the COMPASS trial. The primary outcome of
19 VOYAGER-PAD trial was the composite of MACE, ALI, and major amputation for vascular
20 causes. ALI during the follow-up is not specifically recorded in COPART registry, however
21 major amputation and limb revascularization are recorded, so ALI is included in the
22 composite of limb revascularization or major amputation. Secondary outcomes also available
23 in the COPART, COMPASS and VOYAGER-PAD databases were also analysed: all-cause
24 death, CV death, non-CV death, MI, stroke, major amputation, and major adverse limb events
25 (MALE), a composite of major amputation and limb revascularization. Revascularization

1 could be achieved by percutaneous angioplasty (with or without stenting), subintimal
2 recanalization, endarterectomy, embolectomy, surgical vein or prosthetic bypass. Amputation
3 above the ankle level was considered major, and minor when below.

4

5 *Statistical analysis*

6 Baseline characteristics of the following subgroups are described using mean \pm
7 standard deviation or median \pm interquartile range for continuous variables and frequencies
8 and percentages for categorical variables:

- 9 - COMPASS-eligible subset: COPART patients with all the COMPASS inclusion
10 criteria and none of the COMPASS exclusion criteria,
- 11 - COMPASS-non eligible subset: COPART patients without all the COMPASS
12 inclusion criteria and/or with at least one COMPASS exclusion criteria,
- 13 - COMPASS participants with symptomatic LEAD of the aspirin alone arm: patients
14 with symptomatic LEAD randomized in the aspirin alone group of the COMPASS
15 trial (8),
- 16 - VOYAGER-PAD-eligible subset: COPART patients with limb revascularization, with
17 all the VOYAGER-PAD inclusion criteria and none of the VOYAGER-PAD
18 exclusion criteria,
- 19 - VOYAGER-PAD-non eligible subset: COPART patients with limb revascularization,
20 without all the VOYAGER-PAD inclusion criteria and/or with at least one
21 VOYAGER-PAD exclusion criteria,
- 22 - VOYAGER-PAD participants of the placebo arm: patients randomized in the aspirin
23 group of the VOYAGER-PAD trial, with clopidogrel which can be additionally
24 prescribed up to 6 months of limb revascularization (7).

1 Proportions of COMPASS exclusion criteria and VOYAGER-PAD exclusion criteria
2 were reported.

3 Since in COMPASS trial rivaroxaban was given to patients with stable LEAD, the index
4 date for COMPASS-eligible and non-eligible subsets is the date of discharge from the index
5 hospitalization. For VOYAGER-PAD-eligible and non-eligible subsets, the index date is the
6 date of the qualifying revascularization procedure.

7 Comparisons between subgroups are made using Chi-2 test for categorical variables or
8 Fisher exact test when appropriate, while Student's t-test and Mann-Whitney test are used for
9 continuous variables. Z-test was used to compare continuous variables between COMPASS-
10 eligible subset and COMPASS participants with symptomatic LEAD of the aspirin arm. The
11 Kaplan-Meier method is used to estimate cumulative incidence of outcomes at one year, with
12 95% confidence interval (95%CI). Patients were censored at the date of the first considered
13 outcome. If they did not develop the outcome during the year of follow-up, they were
14 censored at the date of the one-year final record completion or at the date of loss of follow-up.
15 In order to allow statistical comparisons of outcomes between COMPASS participants with
16 symptomatic LEAD and COMPASS-eligible subset, and between VOYAGER-PAD
17 participants and VOYAGER-PAD-eligible subset, estimations of p-value based on 95%CI are
18 given according to Krzywinski and Altman graphs (12).

19 No imputation was made on missing data. A p-value <0.05 was considered as statistically
20 significant. Analyses were performed on STATA Statistical software (release 14.2, StataCorp
21 LLC®, College Station, Texas).

22

23 **Results**

24 *Rivaroxaban plus aspirin eligible patients in COPART registry*

1 Among 2 520 patients in COPART registry, 261 were excluded because missing data in
2 COMPASS or VOYAGER-PAD exclusion or inclusion criteria (Figure 1).

3 Among the remaining 2 259 evaluable patients, 679 (30.1%) were eligible for COMPASS.
4 Among the 1 580 evaluable patients not eligible for COMPASS, 1 374 had at least one
5 COMPASS exclusion criteria; the main reasons for exclusion were indication for full-dose oral
6 anticoagulant treatment, known malignancy and history of haemorrhagic or ischemic stroke
7 (Figure 2).

8 Among the 1 073 evaluable patients undergoing limb revascularization, 101 (9.4%) were
9 eligible for VOYAGER-PAD. Among the 972 evaluable patients undergoing limb
10 revascularization not eligible for VOYAGER-PAD, 868 had at least one VOYAGER-PAD
11 exclusion criteria; the main reasons for exclusion were indication for full-dose oral
12 anticoagulant treatment, major tissue loss and known malignancy (Figure 3).

13 All the VOYAGER-PAD-eligible patients were also eligible for COMPASS, therefore,
14 only 30.1% of the entire COPART evaluable cohort was eligible for rivaroxaban 2.5 mg bid
15 plus aspirin 100 mg once daily regimen, based on either COMPASS or VOYAGER-PAD
16 criteria. The proportion of patients eligible for this regimen varied according to the year of
17 inclusion in the COPART registry, between 21.2% and 38.1% based on COMPASS criteria
18 and between 3.6% and 16.0% based on VOYAGER-PAD criteria, with a trend toward a
19 decrease over the most recent years.

20

21 *Comparison of baseline characteristics and outcomes of COMPASS-eligible and* 22 *COMPASS-non eligible subsets*

23 As compared with other COPART patients, COMPASS-eligible patients are younger,
24 with lower prevalence of diabetes, history of CAD, stroke, heart failure and renal failure

1 (Table 1). The clinical presentation of LEAD was less severe and use of statin more frequent.
2 Regarding outcome, the cumulative incidences of MACE and all-cause mortality were lower
3 than those non eligible for COMPASS (Figure 4, Supplemental Table 5).

4

5 ***Comparison of baseline characteristics and outcomes of COMPASS-eligible subset and***
6 ***COMPASS participants with symptomatic LEAD in the aspirin alone arm***

7 As compared with participants with symptomatic LEAD randomized in the aspirin
8 alone arm of COMPASS, proportions of diabetes, history of CAD and heart failure are higher
9 in the COMPASS-eligible subset, but LEAD is less severe (Table 2). Cumulative incidence of
10 MACE is higher in COMPASS-eligible subset (Figure 4, Supplemental Table 6). One-year
11 cumulative incidence of MALE in COMPASS participants with symptomatic LEAD of the
12 aspirin alone arm is not available, but the risk of MALE in COMPASS-eligible subset is
13 higher, given the 30-month Kaplan-Meier incidence risk in the former group (8).

14

15 ***Comparison of baseline characteristics and outcomes of VOYAGER-PAD-eligible and***
16 ***VOYAGER-PAD-non eligible subsets***

17 As compared with other COPART revascularized patients, proportions of
18 hypertension, history of CAD, heart failure and renal failure are lower in the VOYAGER-
19 PAD-eligible subset (Table 3). There was no statistically significant difference between the
20 two groups regarding cumulative incidences of outcomes (Figure 5, Supplemental Table 7).

21

22 ***Comparison of baseline characteristics and outcomes differences between VOYAGER-***
23 ***PAD-eligible subset and VOYAGER-PAD participants of the placebo arm***

1 As compared with VOYAGER-PAD participants randomized in the placebo arm,
2 LEAD presentation is more severe in the VOYAGER-PAD-eligible subset and qualifying
3 revascularization required more often surgery (Table 4). Compared with VOYAGER-PAD
4 placebo arm, VOYAGER-PAD-eligible patients from COPART have a higher risk of major
5 amputation (Figure 5, Supplemental Table 8). Cumulative incidence of overall mortality is
6 higher in VOYAGER-PAD-eligible subset than in the VOYAGER-PAD placebo arm, but the
7 difference is driven by non-CV death (Figure 5, Supplemental Table 8).

8

9 **Discussion**

10 Randomized-controlled trials constitute the highest level of evidence for new drug
11 applications, line extensions, and recommendations for treatment. In 2018, the Committee for
12 Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA)
13 issued a favourable opinion about the use of low-dose rivaroxaban on top of aspirin in patients
14 with CAD or symptomatic LEAD at high risk of ischemic events. Multiple international
15 agencies also granted low-dose rivaroxaban approval. Since then, this combination is being
16 incorporated into international guidance statements: this association is suggested in patients
17 with CAD or LEAD, including CLTI (13–15). However, patients samples in RCTs, including
18 those focused on LEAD, are highly selected with a lower risk profile than real-world
19 populations, and are not broadly representative of patients encountered in daily practice
20 (1,9,10). Moreover, new therapies may be used in a broader patient population in clinical
21 practice than that enrolled in the RCTs, and the regulatory approval may also extend beyond
22 the inclusion and exclusion criteria of the trials (16). Application of real-world data (RWD),
23 mostly drawn from registries, to support drug approvals is now accepted by regulatory
24 authorities as the EMA and the United States Food and Drug Administration (FDA) (17).
25 RWD can complement the results of phase 3 RCTs by providing insight into their

1 applicability to clinical practice and informing health technology assessment bodies and
2 payers (16).

3 In the present study, only 30.1% of the COPART evaluable cohort was eligible for
4 rivaroxaban 2.5 mg bid plus aspirin regimen. VOYAGER-PAD criteria did not allow more
5 patients to be eligible to this regimen than COMPASS criteria alone.

6 To date, no other registry assessed the external applicability of the VOYAGER-PAD
7 trial. Concerning the external applicability of the COMPASS trial, in the REACH registry
8 (Reduction of Atherothrombosis for Continued Health), 59.3% of CAD or peripheral artery
9 disease (PAD) patients were eligible to secondary prevention with low-dose rivaroxaban plus
10 aspirin: 68.4% of PAD alone patients, 60.4% of PAD + CAD patients, and 48.7% of CAD
11 alone patients (18). Only CAD patients are included in other cohorts, with 14.9% to 44.2% of
12 them eligible for combined low-dose rivaroxaban and aspirin treatment (19–22).

13 As found in the REACH registry, indication for full-dose anticoagulant or DAPT, and
14 high bleeding risk, are among the main reasons for being ineligible for low-dose rivaroxaban
15 plus aspirin regimen (18). Severe renal failure and major tissue loss are exclusion criteria
16 respectively in about 10% of ineligible patients in COMPASS and VOYAGER subsets, and in
17 a third in the VOYAGER-PAD subset. These patients are at high-risk of ischemic events.
18 Indeed, in the COMPASS trial, patients with symptomatic LEAD with high-risk limb
19 presentations (prior amputation, Fontaine III or IV symptoms, previous peripheral artery
20 revascularization) or high-risk comorbidities (kidney dysfunction, heart failure, diabetes,
21 polyvascular disease) had a higher incidence of MACE and MALE than those with neither
22 high-risk limb presentation nor high-risk comorbidities (8). Moreover, after MALE, one-year
23 cumulative incidences of MACE, all-cause mortality, and amputation were high (23). Since
24 this non-eligible population is likely to be among those who will benefit the most from
25 combination therapy, further studies are needed to explore the applicability of this strategy.

1 ALI is found in 13% of ineligible patients in the VOYAGER-PAD subset; even if low-dose
2 rivaroxaban plus aspirin has not primarily been investigated after ALI, a small subgroup of
3 patients within the COMPASS trial who had ALI also had a marked reduction in amputation
4 and mortality rate, as highlighted in the European Society for Vascular Surgery (ESVS)
5 guidelines (24). Finally, malignancy is another major reason for ineligibility, found in about
6 20% of ineligible patients.

7 In the COPART registry, VOYAGER-PAD eligible patients had the same risk of
8 MACE than VOYAGER-PAD participants in the reference arm and even higher risks of non-
9 CV death, MALE, and major amputation. COMPASS eligible patients had higher risks of
10 MACE and MALE than COMPASS LEAD participants in the reference arm. These results
11 support the fact that the COMPASS and VOYAGER-PAD inclusion criteria define high-risk
12 patients, which may derive particular benefit from low-dose rivaroxaban plus aspirin regimen.

13 However, COMPASS ineligible patients had an even higher risk of MACE than
14 COMPASS eligible patients, which advocates for further studies enrolling these high-risk
15 patients to clarify the benefit of this intervention in more representative populations. This is
16 an aim of the prospective post-approval XATOA registry study (Xarelto plus Acetylsalicylic
17 acid: Treatment patterns and Outcomes in patients with Atherosclerosis) (16).

18 There are limitations to this analysis. Because the COPART registry recruited patients
19 from 2006 to 2015 (recent data being entered), the management and prognosis of some
20 patients could be different from what is currently observed. The differences found in event
21 rates between the registry and the RCT may, at least partially, reflect the developments of
22 revascularization procedures and secondary prevention during this period. The population
23 from the COPART registry represents a nationwide sample of patients hospitalized for LEAD
24 in university hospitals in France but cannot necessarily be extrapolated to patients
25 hospitalized in non-university hospitals, outpatients or patients from other countries. Of note,

1 results from the main COMPASS trial demonstrated different results by geographical
2 location, with high efficacy seen in the Asia-Pacific and Eastern European regions (6). A few
3 COMPASS and VOYAGER-PAD eligibility criteria were not collected as part of the
4 COPART registry, and others required adjustment. For example, the exclusion criteria of a
5 high bleeding risk was not captured in the COPART registry, so it was approached by the
6 composite of any medical history of major bleeding and/or platelet count less than 100 G/L.
7 Moreover, the date of major bleeding during follow-up was not captured in the registry so the
8 Cox analysis was not available for this outcome. Finally, the cost of rivaroxaban is not
9 considered when it could be a factor limiting the use of the treatment.

10

11 **Conclusion**

12 Based on the COMPASS or VOYAGER-PAD criteria, patients eligible to low-dose
13 rivaroxaban plus aspirin represent only a third of patients with LEAD hospitalized in vascular
14 departments of 4 tertiary-care hospitals in France. The higher rates of MALE and major
15 amputation in these patients compared with those in the VOYAGER-PAD trial, and the
16 higher rates of MACE compared with those in the COMPASS trial, may result in greater
17 benefits from this regimen in the real-world population. However, ineligible patients represent
18 a higher risk population, who could have benefited more from this regimen, requiring further
19 research. There is a need for further clinical trials assessing the LEAD population that may
20 benefit from this treatment in routine clinical practice.

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1 **Conflicts of interest**

2 Dr. Lapébie reports personal fees from Bayer healthcare SAS, outside the submitted work. Dr.
3 Aboyans reports personal fees from Bayer Healthcare, BMS/Pfizer, Novartis, and Sanofi,
4 outside the submitted work. Dr. Lacroix, Dr. Constans, Dr. Boulon, Dr. Messas and Dr.
5 Ferrières have nothing to disclose. Dr. Bongard reports personal fees from Sanofi outside the
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9

10 **Author contributions**

11 Conception and design: FXL, VA, ABR

12 Analysis and interpretation: FXL, VA, PL, JC, CB, EM, JF, VB, ABR

13 Data collection: FXL, VA, PL, JC, CB, EM, ABR

14 Writing the article: FXL, VA, ABR

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16 Final approval of the article: FXL, VA, PL, JC, CB, EM, JF, VB, ABR

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19 Overall responsibility: ABR

20

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25

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5

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2 Copy editors: please note that only the critical style editing has been made to these tables. Full copy
 3 editing is still needed including setting up the italics and indentations in the first column. I have used
 4 green background color to highlight the edits that should be repeated in the following rows in the
 5 same column / following columns in the same row

6

7 Please note that the deletion of total no of patients for each variable originates from the earlier
 8 instructions by the EiC - if necessary, the total number of patients can be calculated by the
 9 percentage, and that's why their publication is not needed.

10

11 **Table I: Baseline characteristics of 2 259 COMPASS-eligible and COMPASS-non**
 12 **eligible patients from COPART registry at the time of hospital discharge.**

Characteristics	COMPASS-eligible (n = 679)	COMPASS non- eligible (n = 1 580)	<i>p</i> *
<i>Demographic data</i>			
Age – years	66.7 ± 12.9	72.6 ±12.3	< .001
Men	523 (77.1)	1168 (74.3)	.15
<i>Cardiovascular risk factors</i>			
Diabetes	282 /679 (41.5)	842 /1580 (53.3)	< .001
Dyslipidemia	540 /679 (79.5)	1171 /1578 (74.2)	.007
Hypertension	564 /679 (83.1)	1385 /1579 (87.7)	.003
Current smokers	250 /676 (37.0)	303 /1553 (19.5)	< .001
Obesity	119 /636 (18.7)	305 /1438 (21.2)	.19
<i>Medical history</i>			
CAD	211 /677 (31.2)	632 /1571 (40.2)	< .001
Ischemic stroke	23 /679 (3.4)	337 /1569 (21.5)	< .001
Heart failure	35 /674 (5.2)	252 /1549 (16.3)	< .001
Atrial fibrillation	0 /668 (0)	502 /1556 (32.3)	< .001
COPD or asthma	124 /665 (18.7)	300 /1532 (19.6)	.61
Cancer	0 /679 (0)	359 /1580 (22.7)	< .001
Renal failure	186 /679 (27.4)	774 /1580 (49.0)	< .001
Hepatic failure	0 /679 (0)	21 /1580 (1.3)	.003
<i>Laboratory exams</i>			
eGFR – mL/min/1.73 m ²	77.6 ±32.4	59.2 ±25.2	< .001
<i>LEAD at hospital admittance</i>			
Prior revascularization	287 /675 (42.5)	464 /1564 (29.7)	< .001
Prior amputation	90 /673 (13.4)	220 /1564 (14.1)	.66
LEAD classification			< .001

Rutherford 0	4 /677 (0.6)	13 /1575 (0.8)	
Rutherford 1, 2 or 3	261 /677 (38.6)	319 /1575 (20.3)	
Rutherford 4	80 /677 (11.8)	150 /1575 (9.5)	
Rutherford 5 or 6	285 /677 (42.1)	965 /1575 (61.3)	
Acute limb ischemia	47 /677 (6.9)	128 /1575 (8.1)	
Gangrene	59 /664 (8.9)	216 /1536 (14.1)	.001
<i>Medical treatment at hospital discharge</i>			
Aspirin or clopidogrel	637 /679 (93.8)	1033 /1390 (74.3)	< .001
Oral anticoagulant	0 /679 (0)	432 /1575 (27.4)	< .001
Statin	542 /679 (79.8)	994 /1392 (71.4)	< .001
ACEI or ARB	417 /673 (62.0)	812 /1359 (59.8)	.34
Beta-blockers	170 /677 (25.1)	487 /1365 (35.7)	< .001

- 1 Data are presented as n (%) or mean \pm standard deviation. CAD = coronary artery disease;
- 2 COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate;
- 3 LEAD = lower extremity artery disease; ACEI = angiotensin-converting enzyme inhibitors;
- 4 ARB = angiotensin receptor blockers.
- 5 * p-value of difference between COMPASS-eligible and COMPASS-non eligible subsets.

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1 **Table II: Baseline characteristics of 2 038 COMPASS-eligible patients in COPART and**
2 **actual subgroup of COMPASS participants with symptomatic lower extremity artery**
3 **disease (LEAD) from aspirin alone reference arm**

Characteristics	COMPASS-eligible in COPART (n = 679)	Actual COMPASS participants with symptomatic LEAD of aspirin alone arm (n = 1 359)	p *
<i>Demographic data</i>			
Age – years	66.7 ± 12.9	66.7 ± 8.8	1.0
Men	523 (77.1)	960 (70.6)	.002
<i>Risk factors and coexisting conditions</i>			
Diabetes	282 /679 (41.5)	644 /1359 (47.4)	.012
Current smokers	250 /676 (37.0)	442 /1359 (32.5)	.046
Coronary artery disease	211 /677 (31.2)	725 /1359 (53.3)	< .001
Ischemic stroke	23 /679 (3.4)	65 /1359 (4.8)	.14
Heart failure	35 /674 (5.2)	226 /1359 (16.6)	< .001
Renal failure	186 /679 (27.4)	371 /1359 (27.3)	.96
<i>LEAD history</i>			
Previous revascularization	287 /675 (42.5)	563 /1359 (41.4)	.64
Previous amputation	90 /673 (13.4)	103 /1359 (7.6)	< .001
LEAD classification			
Rutherford 1, 2 or 3	261 /677 (38.6)	943 /1359 (69.4)	< .001
Rutherford 4	80 /677 (11.8)	44 /1359 (3.2)	< .001
Rutherford 5 or 6	285 /677 (42.1)	12 /1359 (.9)	< .001
<i>Medication</i>			
Aspirin or clopidogrel	637 /679 (93.8)	1359 /1359 (100.0)	< .001
Aspirin	497 /679 (73.2)	1359 /1359 (100.0)	< .001
Clopidogrel	140 /679 (20.6)	0 /1359 (0)	< .001
Statin	542 /679 (79.8)	1051 /1359 (77.3)	.20
ACEI and/or ARB	417 /673 (62.0)	920 /1359 (67.7)	.010

4 Data are presented as n (%) or mean ± standard deviation. ACEI = angiotensin-converting
5 enzyme inhibitors; ARB = angiotensin receptor blockers.

6 * p-value of difference between COMPASS-eligible subset and COMPASS participants with
7 symptomatic LEAD in the aspirin alone arm.

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1 **Table III: Baseline characteristics of 1 073 VOYAGER-PAD-eligible and VOYAGER-**
2 **PAD-non eligible patients revascularized from COPART at the time of index**
3 **revascularization**

Characteristics	VOYAGER-PAD-eligible (n = 101)	VOYAGER-PAD non-eligible (n = 972)	p *
<i>Demographic data</i>			
Age – years	69.2 ± 11.7	70.2 ± 12.7	.41
Men	78 (77.2)	725 (75.1)	.64
<i>Cardiovascular risk factors</i>			
Diabetes	41 /101 (40.6)	491 /972 (50.5)	.058
Dyslipidemia	80 /101 (79.2)	750 /971 (77.2)	.65
Hypertension	78 /101 (77.2)	850 /971 (87.5)	.004
Current smokers	34 /101 (33.7)	232 /967 (24.0)	.032
Obesity	14 /95 (14.7)	189 /937 (20.2)	.20
<i>Medical history</i>			
CAD	30 /101 (29.7)	389 /967 (40.2)	.039
Ischemic stroke	0 /101 (.0)	163 /972 (16.8)	< .001
Heart failure	4 /101 (4.0)	128 /960 (13.3)	.007
Atrial fibrillation	0 /101 (.0)	238 /964 (24.7)	< .001
COPD or asthma	22 /100 (22.0)	185 /952 (19.4)	.54
Cancer	0 /101 (.0)	182 /972 (18.7)	< .001
Renal failure	30 /101 (29.7)	412 /972 (42.4)	.014
Hepatic failure	0 /101 (.0)	9 /972 (.9)	1.0
<i>Laboratory exams</i>			
eGFR – mL/min/1.73 m ²	75.3 ± 23.3	63.8 ± 31.9	.001
<i>LEAD at hospital admittance</i>			
Prior revascularization	41 /101 (40.6)	317 /968 (32.8)	.11
Prior amputation	7 /101 (6.9)	99 /963 (10.3)	.29
LEAD classification			< .001
Rutherford 0	0 /101 (.0)	3 /970 (.3)	
Rutherford 1, 2 or 3	30 /101 (29.7)	276 /970 (28.5)	
Rutherford 4	27 /101 (26.7)	79 /970 (8.1)	
Rutherford 5 or 6	44 /101 (43.6)	496 /970 (51.1)	
Acute limb ischemia	0 /101 (.0)	116 /970 (12.0)	
Gangrene	7 /99 (7.1)	93 /957 (9.7)	.39
<i>Medical treatment at hospital discharge</i>			
Aspirin or clopidogrel	98 /101 (97.0)	723 /894 (80.9)	< .001
Oral anticoagulant	0 /101 (.0)	237 /972 (24.4)	< .001
Statin	83 /101 (82.2)	713 /896 (79.6)	.54

ACEI or ARB	64 /100 (64.0)	533 /875 (60.9)	.55
Beta-blockers	20 /101 (19.8)	316 /882 (35.8)	.001

1 Data are presented as n (%) or mean ± standard deviation. CAD = coronary artery disease;
2 COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate;
3 LEAD = lower extremity artery disease; ACEI = angiotensin-converting enzyme inhibitors;
4 ARB = angiotensin receptor blockers.
5 * p-value of difference between VOYAGER-PAD-eligible and VOYAGER-PAD-non eligible
6 subsets.

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1 **Table IV: Baseline characteristics of 3 379 VOYAGER-PAD-eligible patients in**
 2 **COPART and actual VOYAGER-PAD participants from aspirin reference arm**

Characteristics	VOYAGER-PAD-eligible in COPART (n = 101)	Actual VOYAGER-PAD participants (aspirin reference arm) (n = 3 278)	p *
Age – years	69.2 ± 11.7	67.0 ± 12.0	NA
Men	78 (77.2)	2421 (73.9)	.45
Body mass index – kg/m ²	24.6 ±4.3	26.0 ±5.9	NA
<i>Risk factors and coexisting conditions</i>			
Diabetes	41 /101 (40.6)	1316 /3278 (40.1)	.93
Dyslipidemia	80 /101 (79.2)	1968 /3278 (60.0)	< .001
Hypertension	78 /101 (77.2)	2658 /3278 (81.1)	.33
Current smokers	34 /101 (33.7)	1132 /3278 (34.5)	.86
Coronary artery disease	30 /101 (29.7)	1015 /3278 (31.0)	.787
Renal failure	30 /101 (29.7)	666 /3278 (20.3)	.022
<i>LEAD history</i>			
Prior revascularization	41 /101 (40.6)	1155 /3278 (35.2)	.27
Prior amputation	7 /101 (6.9)	196 /3278 (6.0)	.69
<i>Qualifying revascularization</i>			
Performed for claudication	30 /101 (29.7)	2504 /3278 (76.4)	< .001
Performed for critical limb ischemia	71 /101 (70.3)	771 /3278 (23.5)	< .001
Endovascular	35 /101 (34.7)	2140 /3278 (65.3)	< .001
Surgical	66 /101 (65.3)	1138 /3278 (34.7)	< .001
<i>Medication</i>			
Aspirin at randomization	76 /101 (75.3)	3248 /3278 (99.1)	< .001
Clopidogrel at randomization	22 /101 (21.8)	1655 /3278 (50.5)	< .001
Statin	83 /101 (82.2)	2641 /3278 (80.6)	.69
ACEI or ARB	64 /100 (64.0)	2063 /3278 (62.9)	.83

3 Data are presented as n (%) or median ± interquartile range. LEAD = lower extremity artery
 4 disease; ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor
 5 blockers.

6 * p-value of difference between VOYAGER-PAD-eligible subset and VOYAGER-PAD
 7 participants in the aspirin reference arm.

8

1 **Figure legend**

2 Figure 1: Flow chart for identification of COMPASS and VOYAGER-PAD eligible patients
3 with lower extremity artery disease in COPART registry. Among the VOYAGER-PAD non
4 eligible patients, 277 were eligible for COMPASS and 695 were not. All the VOYAGER-
5 PAD-eligible patients were also eligible for COMPASS.

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7 Figure 2: Main reasons for exclusion of patients with lower extremity artery disease in
8 COPART registry, according to the exclusion criteria in COMPASS trial

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10 Figure 3: Main reasons for exclusion of patients revascularized for lower extremity artery
11 disease in COPART registry, according to the exclusion criteria in VOYAGER-PAD trial

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13 Figure 4: Comparison of one-year cumulative incidences (95% confidence intervals) of
14 outcomes for the COMPASS eligible and non-eligible subsets from COPART, and
15 COMPASS participants with symptomatic lower extremity artery disease of the aspirin alone
16 arm. CV = cardiovascular; MI = myocardial infarction. The *p* values: * <.05; § <.010; **
17 <.001; and † >.05.

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19 Figure 5: Comparison of one-year cumulative incidences (95% confidence intervals) of
20 outcomes for the VOYAGER-PAD eligible and non-eligible subsets from COPART, and
21 VOYAGER-PAD participants of the placebo arm with lower extremity artery disease. CV =
22 cardiovascular; MI = myocardial infarction. ;The *p* values * <.05; ** <.001; and † >.05.









