Major Adverse Limb Events in Lower Extremity Peripheral Artery Disease: COMPASS Trial

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ABSTRACT

Background: Patients with lower extremity peripheral artery disease (PAD) are at increased risk of major adverse cardiovascular events (MACE) and major adverse limb events (MALE). There is limited information on the prognosis of patients who suffer MALE.

Objectives: Among participants with lower extremity PAD, we investigated: 1) if hospitalizations, MACE, amputations, and deaths are higher after first episode of MALE compared with PAD patients who do not experience MALE and 2) the impact of treatment with low dose rivaroxaban and aspirin compared to aspirin alone on the incidence of MALE, peripheral vascular interventions, and all peripheral vascular outcomes over a median follow-up of 21 months.

Methods: We analyzed outcomes in 6,391 patients with lower extremity PAD who were enrolled in the COMPASS trial - a randomized double blind placebo controlled trial of low dose rivaroxaban and aspirin combination, rivaroxaban alone, as compared to aspirin alone. MALE was defined as severe limb ischemia leading to an intervention or major vascular amputation.

Results: A total of 128 patients suffered an incident MALE. After MALE, the one year cumulative risk of a subsequent hospitalization was 95.4%, for vascular amputations it was 22.9%, for death it was 8.7%, and for MACE it was 3.8%. The MALE index event significantly increased the risk to experience subsequent hospitalizations (HR 7.21; P<0.0001), subsequent amputations (HR 197.5; P<0.0001) and death (HR 3.23; P<0.001). Compared with aspirin alone, the combination of rivaroxaban 2.5 mg twice daily and aspirin lowered the incidence of MALE by 43% (P=0.01), total vascular amputations by 58% (P=0.01), peripheral vascular interventions by 24% (P=0.03), and all peripheral vascular outcomes by 24% (P=0.02).

Summary: Among individuals with lower extremity PAD, the development of MALE is associated with a poor prognosis, making its prevention of utmost importance. The combination of rivaroxaban 2.5 mg bid and aspirin significantly lowers the incidence of MALE and its related complications and should be considered as an important therapy for patients with PAD.

Clinical trial: This is a subgroup analysis of a clinical trial called COMPASS registered on clinical trials.gov.

Key words: Peripheral Artery Disease, Major Adverse Limb Events, Amputation, Death, Antithrombotic Therapy

Condensed Abstract: Peripheral artery disease patients are at risk of suffering Major Adverse Limb Events (MALE) which are associated with a high risk of subsequent amputation and death. Prevention of MALE in PAD patients should be a high priority. Compared to aspirin alone, rivaroxaban 2.5 mg twice daily and aspirin used in combination is effective at reducing the incidence of MALE.

Abbreviations:

ACE: Angiotensin Converting Enzyme
CAD: Coronary Artery Disease
CAPRIE = Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events
COMPASS = Cardiovascular Outcomes for People Using Anticoagulation Strategies
CI: Confidence Interval
HR: Hazard Ratio

MACE: Major Adverse Cardiovascular Event
MALE: Major Adverse Limb Event
PAD: Peripheral Artery Disease

Introduction

About 200 million people in the world are estimated to suffer from lower extremity peripheral artery disease (PAD). (1) Patients with PAD are at high risk for the development of major adverse cardiovascular events (MACE) and major adverse limb events (MALE). (2) Recently, we showed in the COMPASS trial of 27,395 participants with coronary artery disease (CAD) and or PAD that compared with aspirin alone, rivaroxaban in combination with aspirin significantly reduced the risk of MACE by 24% (3). In the sub-population of patients with PAD from COMPASS, we showed that MALE including major amputation was reduced by 46%, as was the combined outcome of MACE or MALE by 31%. (4) Although the incidence of MALE is relatively low at 1% per year, the consequences of MALE can severely alter patients' prognosis (5).

In this analysis of lower extremity PAD patients from the COMPASS trial, we report the prognosis after MALE and the impact of a MALE index event on other outcomes, evaluate the baseline factors which predict the development of MALE, and evaluate the impact of the low dose rivaroxaban and aspirin combination, rivaroxaban alone, as compared with aspirin alone, on the outcomes of MALE, vascular interventions, and all vascular outcomes.

Methods

Population

COMPASS was a multi-centre, double-blind, randomized, placebo-controlled trial comparing rivaroxaban 2.5 mg bid with aspirin in combination or rivaroxaban 5 mg bid (with aspirin placebo) versus aspirin alone (with rivaroxaban placebo) for prevention of cardiovascular death, myocardial infarction (MI), or stroke (MACE) in patients with coronary artery disease (CAD) or PAD. The details of inclusion and exclusion criteria have been previously published

(3,6,7). For this analysis, we included participants with lower extremity PAD reported on their baseline case record forms as a history of prior aorto-femoral bypass surgery, limb bypass surgery, percutaneous transluminal angioplasty revascularization of the iliac or infra-inguinal arteries, limb or foot amputation for arterial vascular disease, intermittent claudication confirmed by objective measures (i.e., evidence of PAD by ankle brachial index (ABI), ultrasound, or angiogram), and we included participants with coronary artery disease who had an ABI <0.90 at baseline. Symptoms of limb ischemia were assessed using the Fontaine Classification at baseline (4).

Outcomes

Definitions of PAD outcomes in COMPASS have been previously published. (4) Briefly, MALE was defined as acute or chronic limb ischemia, and in this analysis includes all major vascular amputations. Acute limb ischemia (ALI) was defined as limb-threatening ischemia which is confirmed by limb hemodynamics or imaging and leads to an acute vascular intervention (i.e. pharmacologic [heparin, thrombolysis], peripheral artery surgery/reconstruction, peripheral angioplasty/stent, or amputation) within 30 days of onset of symptoms. Chronic limb ischemia (CLI) was defined as continuing ischemic limb, foot or digit pain leading to hospitalization and intervention and not meeting the definition of acute limb ischemia, or participants with Fontaine Classification Stage 3 or 4 at baseline who had a peripheral intervention over the course of the trial. Major vascular amputation was defined as was defined as an amputation due to a vascular event above the forefoot. Peripheral vascular interventions were defined as interventions including peripheral angioplasty, vascular surgery or amputation, not meeting the definition for ALI or CLI. Total peripheral vascular outcomes were defined as acute or chronic limb ischemia, a peripheral vascular intervention, or a hospitalization

for other vascular reason. The PAD outcome definitions were specified in advance, and acute limb ischemia events were verified using an algorithm, and if the algorithm did not confirm acute limb ischemia, events were formally adjudicated by a vascular disease expert physician (4).

Statistical considerations

To predict the development of MALE, the baseline factors significant at an alpha level of 0.10 were tested in a multivariable model. The multivariable model was constructed using a stepwise selection method with entry level of significance of 0.10 and a selection stay level of significance of 0.10. In the final multivariable model, a factor was deemed significant if its P value was < 0.05. To describe the prognosis of individuals who experienced an index MALE outcome on subsequent events of interest, i.e. hospitalizations, MACE, vascular amputations, and death, the time to event from the date of the index MALE to the date of the event of interest was used to estimate the cumulative incidence risk by Kaplan-Meier estimates. Among participants who suffered more than one MALE event, the first MALE event was considered as the index event. To estimate the incidence rate of outcomes that occured between randomization and the occurrence of MALE or end-of-follow-up (whichever occured first), the time to event from the date of randomization to the date of the event of interest was used. For participants who experienced a MALE, only those events that occurred prior to the MALE were considered, otherwise they were censored at the day of the MALE index event. Participants without the event of interest and who did not experience a MALE were censored at the end of follow-up. The impact of the MALE index event on other events of interest, i.e. hospitalizations, MACE, vascular amputations, and death, was assessed using stratified Cox proportional hazards models with the MALE index event modelled as a time-dependent covariate. If the interaction between antithrombotic treatment and the time-dependent covariate MALE index event was significant

at an alpha level of 0.10, the impact of the MALE index event was modelled separately by treatment group. The comparison of treatment effect of rivaroxaban and aspirin combination, rivaroxaban alone, versus aspirin on the outcomes of MALE, peripheral vascular interventions and all peripheral vascular outcomes were calculated using separate log-rank tests. Kaplan-Meier estimates of the cumulative risk were used to evaluate the timing of event occurrences in each of the treatment groups. Hazard ratios and corresponding 95% CIs were obtained from stratified Cox proportional-hazards models. No adjustments for multiple testing were made.

Results

Baseline Characteristics of PAD participants

6,391 participants with PAD of the lower extremity were included (**Table 1**). This cohort was generally well treated for secondary atherosclerosis prevention with lipid lowering medications and angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blocker (ARB) medications (**Table 1**). 1.4% of participants developed atrial fibrillation or atrial flutter during the course of the follow-up, and 2.7% of participants suffered a major bleeding complication. Furthermore 82% of participants did not permanently discontinue randomized study drug over the course of the 21 month follow-up of participants in the trial.

The characteristics of participants who suffered a MALE

The independent predictors of MALE included severe ischemia symptoms at baseline (Fontaine classification 3 or 4), prior limb or foot amputation at baseline, prior history of peripheral revascularization surgery or angioplasty, and randomization to the aspirin arm of trial. Diabetes, current or former smoking, female sex, and history of CAD were not independently predictive of MALE. (Table 2) The incidence of MALE was 3.8% in PAD patients with a prior history of intervention (i.e. peripheral revascularization or amputation), compared to 1.37%

among those PAD patients with intermittent claudication with no prior intervention, and lowest (0.5%) among those with asymptomatic PAD defined as an ABI < 0.90.

Prognosis after MALE

A total of 128 (2.0%) participants suffered MALE, and the median follow-up of patients after MALE was 360 days (interquartile range: 188-518). was 95.4%. The cumulative incidence one-year risk after MALE of a subsequent hospitalization was 95.4%, for total vascular amputations it was 22.9%, for death it was 8.7% and for MACE it was 3.8% (**Table 3A, Figure 1, Figure 2**). The MALE index event significantly increased the risk to experience subsequent hospitalization (HR 7.21, 95% CI: 5.51-9.43, P<0.0001), total vascular amputations (HR 197.5, 95% CI: 97.33-400.8, P<0.0001), death (HR 3.23, 95% CI: 1.87-5.56, P<0.001) and the composite of MACE or total vascular amputations (HR 7.56, 95% CI: 5.14-11.12). (**Table 3B**).

In addition, the increase risk due to MALE for the outcomes death and the MACE or total vascular amputations composite, was different in the participants randomized to receive rivaroxaban and aspirin combination compared to those randomized to aspirin alone. While the risk of death did not change after a MALE event in participants randomized to receive rivaroxaban and aspirin combination, there was a 6-fold risk (HR 5.97, 95% CI: 3.19-11.19) of death after a MALE event for participants randomized to receive aspirin alone. Likewise for the composite MACE or total vascular amputation, the risk in participants randomized to receive aspirin alone was 10-fold (HR 10.24; 95% CI: 6.28-16.70) after the MALE event, acknowledging that the follow-up time after the MALE index event for participants randomized to receive rivaroxaban and aspirin combination was shorter since antithrombotic treatment prevents MALE index events.

By definition participants with a MALE underwent an intervention, and the types and frequency of MALE-associated interventions are shown in **Figure 3**. The most common procedures associated with MALE were peripheral artery angioplasty (35.9%), amputation (23.4%), and bypass surgery (21.1%). Of the 128 participants with MALE, 48 (37.5%) discontinued study drugs after the index MALE, and, 17/128 (13.3%) were placed on a single antiplatelet agent, 13/128 (10.2%) received dual antiplatelet therapy, 3/128 participants (2.3%) were placed on an oral anticoagulant, whereas 15/128 participants (11.7%) received neither an antiplatelet nor anticoagulant (**Figure 3B**).

Treatment impact of low dose rivaroxaban versus aspirin on MALE and peripheral vascular outcomes

Compared with those participants randomized to aspirin alone, participants randomized to receive rivaroxaban and aspirin combination were less likely to suffer a MALE (2.6% vs 1.5%; HR 0.57; 95% CI: 0.37-0.88; P=0.01). Total and major amputations were also reduced by 58% (95% CI: 15-79%) and 67% (95% CI: 8-88%) respectively. Vascular interventions were reduced by 24% (95% CI: 3-40%), and total peripheral vascular outcomes were reduced by 24% (95% CI: 4-39%) (**Table 4, Figure 4**). Rivaroxaban alone compared to aspirin alone showed only a nominally significant reduction in MALE, and no significant reduction in total or major amputations due to a vascular cause (**Table 4**).

Discussion

We demonstrate that the prevention of MALE is of paramount importance among individuals with lower extremity PAD (**Central Illustration)**. The prognosis after MALE is dire with a 3-fold increase in death, and 200-fold increase in the risk of subsequent vascular amputation. Further, MALE is more common in those with a prior history of peripheral

revascularization, amputation, severe symptomatic limb ischemia at baseline, or treatment with single antiplatelet therapy. Consistent with the overall COMPASS trial result, we show that use of rivaroxaban 2.5 mg bid and aspirin is superior to aspirin alone in reducing MALE, peripheral vascular interventions, and all peripheral vascular outcomes among individuals with lower extremity PAD.

Our work supports prior studies showing the poor prognosis after a MALE. Data from the TRA2P-TIMI 50 - vorapaxar trial showed that after acute limb ischemia, the risk of amputation was 27% and mortality was 14% after a median follow-up of 2 years. (5) A recent retrospective cohort study from 1,085 American acute care hospitals which included 31,538 PAD patients with chronic limb ischemia who underwent peripheral artery revascularization, reported that 21.3% of patients had unplanned hospital readmission within 30 days of being discharged, and among those readmitted, 25% had repeat revascularization or amputation, and 5.2% had died. (8) Common reasons for readmission included procedure-related complications, complications from diabetes, sepsis, and on-going limb ischemia. Furthermore readmission to hospital was costly and priced at $12,394 US dollars (8).

Predictors of MALE: Individuals who had severe or progressive PAD were the highest risk for suffering a MALE. Specifically risk predictors of severe PAD including severe limb ischemia (Fontaine class 3 or 4) at baseline, prior peripheral bypass surgery or angioplasty, and prior vascular amputation. Our findings are consistent with prior reports from other PAD trials including the EUCLID trial and the PEGASUS PAD subgroup analysis in which a prior history of peripheral revascularization was associated with a 4 fold increase in the risk of MALE (9,10).

Therapies to reduce MALE and interventions: Aspirin therapy is the most commonly used antiplatelet agent in patients with chronic stable PAD although the limb complication event

rate remains relatively high, as noted by the international REACH Registry (11). In our analysis we show that randomization to the aspirin alone arm of the trial is a "risk factor" for MALE, and the outcomes for patients after MALE receiving aspirin alone were worse compared to those receiving rivaroxaban and aspirin combination. Given the effectiveness of low dose rivaroxaban and aspirin, this combination therapy should be considered for patients with PAD to prevent MALE, and to reduce peripheral vascular interventions. Prior to COMPASS, other antiplatelet or antithrombotic agents alone or in combination have produced ambiguous results in PAD patients. Compared with aspirin, more potent antiplatelet agents such as clopidogrel alone have not shown superiority for preventing MALE or its components (acute limb ischemia or amputation) (12, 13). Dual antiplatelet therapy with clopidogrel and aspirin compared with single antiplatelet therapy also did not show significantly different limb outcomes in the CHARISMA trial (14). In contrast, the PEGASUS trial of 21,612 post-myocardial infarction patients showed that combination ticagrelor with aspirin compared with aspirin alone reduced acute limb ischemia or revascularization for peripheral ischemia after 3 years of follow-up (0.46% vs 0.71%; HR: 0.65; 95% CI: 0.44 to 0.95; p= 0.026) (15). These effects were directionally consistent but were not significant in the 1,143 subset of patients with concomitant PAD over 3 years of follow-up (5.75% vs 7.3%; P=NS). (10) Some promise was observed with use of a protease-activated receptor-1 antagonist, vorapaxar used on top of dual antiplatelet agents, compared with dual antiplatelet therapy alone in reducing hospitalization for acute limb ischemia and peripheral revascularization (16), although the significant increase in moderate/severe bleeding has impeded its widespread use. For oral anticoagulants such as warfarin, life-threatening bleeding rates are high, and no benefit has been observed in reducing MACE or severe limb ischemia in the chronic stable PAD population included in the WAVE trial (17) or in

reducing graft occlusion, amputation or vascular interventions in post infra-inguinal bypass surgery patients in the DUTCH BOA trial (18).

The variable management of patients who suffered MALE in the COMPASS trial is consistent with the lack of robust evidence regarding the optimal antithrombotic treatment after a MALE occurs. We observed significant variability in the antithrombotic therapy management of patients after MALE with 62.5% of patients continuing on randomized blinded study drug, whereas the most common non-study drug therapy patients were placed on was single antiplatelet agent, followed by dual antiplatelet therapy. The use of oral anticoagulants was very low, and importantly 11.7% of patients received neither study drug nor any other antithrombotic therapy after MALE (**Figure 3B**). The optimal antithrombotic treatment after a MALE requires further investigation.

In contrast to the mixed results of other antithrombotic treatments in PAD patients, the COMPASS data demonstrate prevention of both MACE and MALE outcomes with a combination low dose oral anticoagulant rivaroxaban with aspirin. Further, in this analysis we demonstrate that among patients with PAD of the lower extremity, the total number of peripheral vascular interventions and outcomes are also significantly reduced by this combination treatment which is likely to result in significant cost savings for the health care system (19). This strengthens the vascular protective role of combination low dose oral rivaroxaban used with aspirin as the most effective therapy in this population (2).

There are both strengths and limitations of the current analysis that should be considered. Strengths include the relatively large number of PAD participants analyzed, reporting and adjudication of incident events within the context of a double blind trial, participants were well treated for secondary atherosclerotic risk and thus reflect contemporary therapy, and this analysis

of lower extremity PAD was pre-specified. Limitations include the fact that this is a subgroup analysis of a larger trial (which showed similar results overall) despite MALE being a pre-specified endpoint, and that there was a relatively low total number of MALE cases. The MALE incidence, however, is consistent with other large trials which have included stable PAD patients, and prospective evaluation in COMPASS overcomes many of the potential biases of retrospective cohorts.

Conclusions

Among individuals with stable lower extremity PAD, the development of MALE is associated with a dire prognosis, making its prevention of utmost importance. The combination of rivaroxaban 2.5 mg bid and aspirin significantly lowers the incidence of both MALE and MACE and its related complications. It should therefore be considered as an important therapy to improve prognosis among lower extremity PAD patients.

Clinical Perspectives

Competencies in Patient Care: Prevention of MALE in patients with PAD of the lower extremity improves their survival. Compared to aspirin alone rivaroxaban 2.5 mg twice daily and aspirin combination is an effective therapy to prevent MALE.

Translational Outlook: Further research is required to optimize the medical and surgical management of patients who suffer a MALE.

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Figure Legends

Central Illustration: **Major Adverse Limb Events in lower extremity peripheral artery disease**. A. The cumulative incidence risk of death following MALE and the cumulative incidence risk of total vascular amputation following MALE (line graph). B. The bar graphs show the Pre-MALE and Post MALE incidence rate for death and the pre-MALE and post-MALE incidence rate for vascular amputation, with the Hazard Ratios (95% confidence intervals) for the index MALE.

Figure 1: A. The cumulative incidence risk of death following MALE (line graph). This shows the cumulative incidence risk of death following index MALE in PAD patients who suffered a MALE. B. The bar graph shows Pre-MALE and Post MALE incidence rates for death with the Hazard Ratio (95% confidence interval) for the index MALE.

Figure 2: A. The cumulative incidence of subsequent total vascular amputation following MALE (line graph)B. The bar graph shows Pre-MALE and Post MALE incidence rates for vascular amputation with the Hazard Ratio (95% confidence interval) for the index MALE.

Figure 3A: Major Adverse Limb Event-associated procedures. The types of interventions patients who developed major adverse limb events underwent at the time of diagnosis with severe limb ischemia. **Figure 3B: Antithrombotic Therapy used after the diagnosis of a major adverse limb event (MALE).** The patients with MALE (62.5%) remained on their randomized drug therapy in the COMPASS trial, whereas the 37.5% stopped randomized treatment, and the percent of patients who received either no antithrombotic therapy or a different type of treatment regimen.

Figure 4: The cumulative incidence risk of peripheral artery outcomes in trial participants treated with rivaroxaban and aspirin compared to aspirin alone. The cumulative incidence

risk of total peripheral artery outcomes in patients by randomized treatment group. Patients who received the rivaroxaban and aspirin combination have a significantly lower incidence of all types of peripheral artery outcomes.

Table 1: Characteristics of participants with lower extremity PAD

	All Lower Extremity PAD	MALE	No MALE	P-Value univariable predictor of MALE
Randomized	6391	128	6263	
Age (SD)	67.6 (8.5)	67.6 (8.3)	67.6 (8.5)	0.66
Women (%)	1786 (27.9)	24 (18.8)	1762 (28.1)	0.03
Body Mass Index (SD)	28.4 (4.9)	27.9 (4.3)	28.4 (4.9)	0.19
Intermittent Claudication with Fontaine Classification 3 or 4 (%)	234 (3.7)	22 (17.2)	212 (3.4)	<0.0001
History of coronary artery disease (%)	4145 (64.9)	68 (53.1)	4077 (65.1)	0.0007
History of peripheral revascularization surgery or angioplasty (%)	2045 (32)	74 (57.8)	1971 (31.5)	<0.0001
Prior amputation at baseline (%)	335 (5.2)	26 (20.3)	309 (4.9)	<0.0001

Ankle Brachial Index at baseline (SD)	0.90 (0.20)	0.89 (0.24)	0.90 (0.20)	0.25
Ankle Brachial Index <0.50 (%)	99 (1.5)	3 (2.3)	96 (1.5)	0.31
Current/former smoker (%)	4789 (74.9)	110 (85.9)	4679 (74.7)	0.008
Diabetes (%)	2854 (44.7)	69 (53.9)	2785 (44.5)	0.04
Hypertension (%)	5024 (78.6)	106 (82.8)	4918 (78.5)	0.28
Renal insufficiency: eGFR <60% (%)	1783 (27.9)	37 (28.9)	1746 (27.9)	0.84
Total Cholesterol mmol/L (SD)	4.39 (1.15)	4.39 (1.15)	4.49 (1.13)	0.24
Lipid lowering agent (%)	5262 (82.3)	102 (79.7)	5160 (82.4)	0.26
ACE inhibitor or ARB (%)	4452 (69.7)	96 (75)	4356 (69.6)	0.28
Heart Failure (%)	1186	16	1170	0.13

	(18.6)	(12.5)	(18.7)	
Atrial Fibrillation/Atrial Flutter during follow-up (%)	87 (1.4)	0 (0)	87 (1.4)	0.98
Hospitalization other than for MALE during study (%)	1876 (29.4)	38 (29.7)	1838 (29.3)	0.61
Major Bleeding during study (%)	172 (2.7)	4 (3.1)	168 (2.7)	0.91
Did not permanently discontinue study medications (Rivaroxaban and/or Aspirin) (%)	5241 (82)	109 (85.2)	5132 (81.9)	0.19
Randomization to Aspirin (%)	2123 (33.2)	56 (43.8)	2067 (33)	0.01

Data are mean (SD) or n (%). Legend: BMI: Body Mass Index; ABI: Ankle Brachial Index; eGFR: estimated Glomerular filtration rate; ACE: Angiotensin converting enzyme; ARB: Angiotensin receptor blocker, MALE: Major Adverse Limb Event

Table 2: Predictors of MALE

	# Participants	MALE Event N (%)	Univariable Hazard Ratio	P Value	Multivariable Hazard ratio	P Value
Women	1786	24 (1.3)	0.61 (0.39-0.96)	0.032	0.64 (0.40-1.01)	0.06
Intermittent Claudication Fontaine 3 or 4 Classification	234	22 (9.4)	6.07 (3.83-9.62)	<0.0001	4.79 (2.99-7.69)	<0.0001
History of Coronary Artery Disease	4145	68 (1.6)	0.55 (0.39-0.78)	0.0007	0.71 (0.49-1.02)	0.06
History of peripheral revascularization surgery or angioplasty	2045	74 (3.6)	2.89 (2.03-4.10)	<0.0001	2.44 (1.71-3.50)	<0.0001
Prior amputation at baseline	335	26 (7.8)	5.05 (3.28-7.77)	<0.0001	3.77 (2.40-5.93)	<0.0001
Current/Former smoker	4789	110 (2.3)	1.96 (1.19-3.23)	0.008	1.59 (0.94-2.67)	0.08

Randomization to Aspirin arm of trial	2123	56 (2.6)	1.57 (1.11-2.23)	0.01	1.63 (1.15-2.31)	0.006
History of Diabetes	2854	69 (2.4)	1.44 (1.02-2.04)	0.038	N/A	N/A

N/A: In the stepwise selection History of Diabetes was not selected for the final model

Table 3a: Outcomes in Patients after a MALE and O**utcomes in patients before a MALE**

	Risk for subsequent outcomes in patients AFTER MALE Outcome Event during the study (N=128)				**Risk for outcomes between randomization and the occurrence of MALE or end-of-followup (whichever came first) (N=6391)**		
	# patient years	**N (%)**	**Rate /100-pers yrs**	**1 year incidence risk**	**# patient years**	**N (%)**	**Rate /100-pers yrs**
Outcome							
Any Hospitalization	65.59	79 (61.7)	120.5	95.41	9346.09	1903 (29.8)	20.4
Total Vascular Amputation	113.74	25 (19.5)	22.0	22.95	11409.48	15 (0.2)	0.1
All-cause mortality	132.8	14 (10.9)	10.5	8.72	11421.72	351 (5.5)	3.1
CV death, MI or Stroke	130.63	7 (5.5)	5.4	3.78	11202.87	386 (6.0)	3.4
CV Hospitalization	71.42	71 (55.5)	99.4	85.85	10320.46	1060 (16.6)	10.3

	Risk for subsequent outcomes in patients AFTER MALE Outcome Event during the study (N=128)				**Risk for outcomes between randomization and the occurrence of MALE or end-of-followup (whichever came first) (N=6391)**		
	# patient years	**N (%)**	**Rate /100-pers yrs**	**1 year incidence risk**	**# patient years**	**N (%)**	**Rate /100-pers yrs**
CV Death, MI, Stroke, Total Vascular Amputation	111.56	29 (22.7)	26.0	25.33	11190.78	399 (6.2)	3.6
CV Death, MI, Stroke, Major Amputation	120.63	18 (14.1)	14.9	12.95	11202.87	386 (6.0)	3.4

Table 3b – Impact of MALE index event on Outcomes of Interest (using MALE as time-dependent covariate in Cox Model)

	MALE as Time-Dependent Covariate	
Outcome	**HR (95% CI)**	**P Value**
Any Hospitalization*	7.21 (5.51 - 9.43)	<0.0001
Total Vascular Amputation*	197.5 (97.33 - 400.8)	<0.0001
All-Cause Mortality	3.23 (1.87 - 5.56)	<0.0001
CV death, MI, Stroke	1.52 (0.72 - 3.24)	0.27
CV Hospitalization*	11.72 (9.04 - 15.21)	<0.0001
MACE or Vascular Amputation*	7.56 (5.14 - 11.12)	<0.0001
MACE or Major Amputation*	4.23 (2.62 - 6.84)	<0.0001

*considering only those outcomes that did not occur on the same day as the index MALE

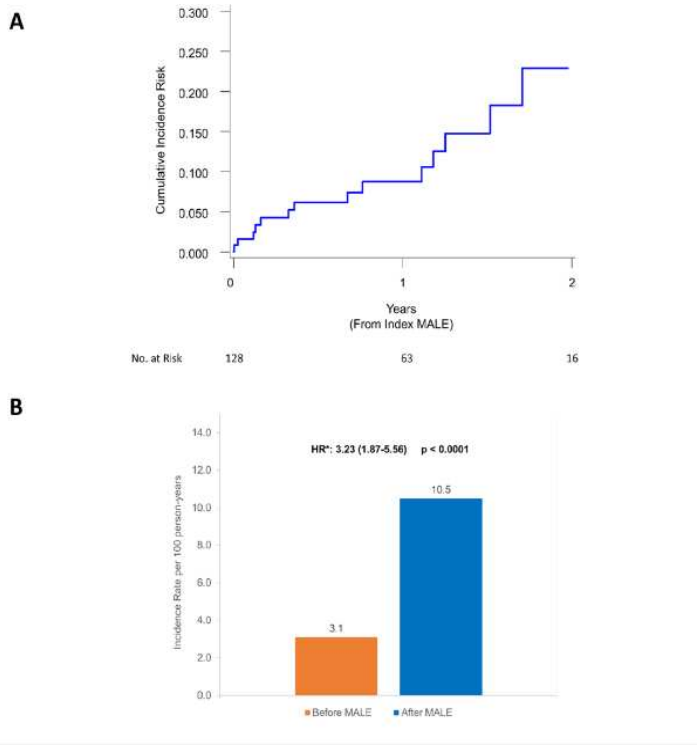
Table 4: Peripheral vascular disease outcomes and treatment effect with rivaroxaban and aspirin, rivaroxaban alone as compared with aspirin alone

	Rivaroxaban 2.5 mg bid plus aspirin 100 mg (N=2,139)	Rivaroxaban 5 mg bid plus aspirin placebo (N=2,129)	Aspirin 100 mg plus rivaroxaban placebo (N=2,123)	Rivaroxaban 2.5 bid plus aspirin 100 mg		Rivaroxaban 5 mg bid vs. aspirin 100 mg once-daily	
N	**N(%)**	**N(%)**	**N (%)**	**HR (95% CI)**	**P Value**	**HR (95% CI)**	**P Value**
MALE*	32 (1.5)	40 (1.9)	56 (2.6)	0.57 (0.37-0.88)	0.01	0.71 (0.47-1.06)	0.07
Total Vascular Amputation	11 (0.5)	17 (0.8)	26 (1.2)	0.42 (0.21-0.85)	0.01	0.65 (0.35-1.19)	0.16
Major Vascular Amputation	5 (0.2)	8 (0.4)	15 (0.7)	0.33 (0.12-0.92)	0.03	0.52 (0.22-1.22)	0.13
All Amputations	19	24	36	0.52	0.02	0.66	0.11

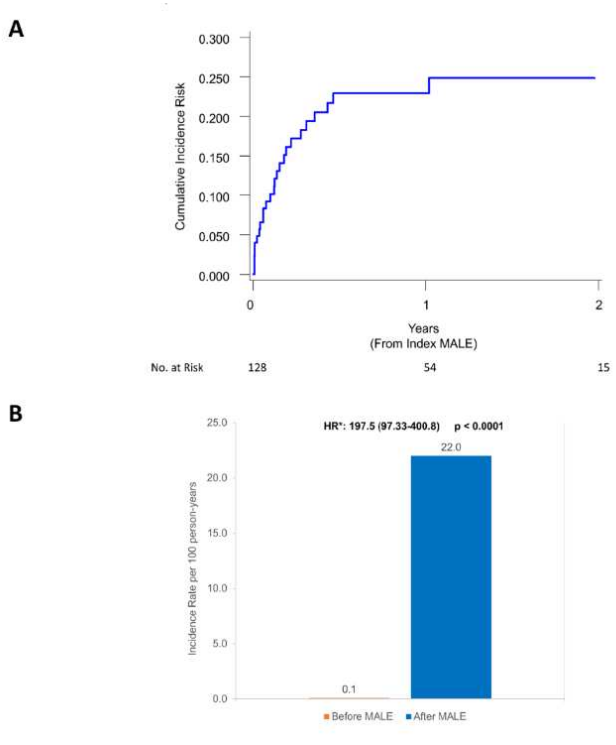
	(0.9)	(1.1)	(1.7)	(0.30-0.91)		(0.39-1.10)	
Vascular Interventions †	117 (5.5)	119 (5.6)	150 (7.1)	0.76 (0.60-0.97)	0.03	0.78 (0.62-1.00)	0.05
Total Outcomes for peripheral artery disease complications‡	132 (6.2)	138 (6.5)	169 (8.0)	0.76 (0.61-0.96)	0.02	0.81 (0.64-1.01)	0.06
Major Bleeding	68 (3.2)	66 (3.1)	42 (2.0)	1.61 (1.09-2.36)	0.01	1.60 (1.09-2.36)	0.02
Severe Bleeding**	24 (1.1)	23 (1.1)	18 (0.8)	1.32 (0.71-2.42)	0.38	1.30 (0.70-2.40)	0.41

* Acute or chronic limb ischemia and Includes all major amputations; †Vascular Interventions defined as any vascular intervention of the lower extremity including bypass surgery, peripheral angioplasty/stenting, amputation or revision; not captures in acute or chronic limb ischemia leading to an intervention; ‡Total outcome for peripheral artery disease complications defined as a composite of acute or chronic limb ischemia, a peripheral vascular intervention, or other vascular reason. ** Bleeding leading to death or symptomatic bleeding into a critical organ or surgical site bleeding requiring re-operation.

Death



Vascular Amputation



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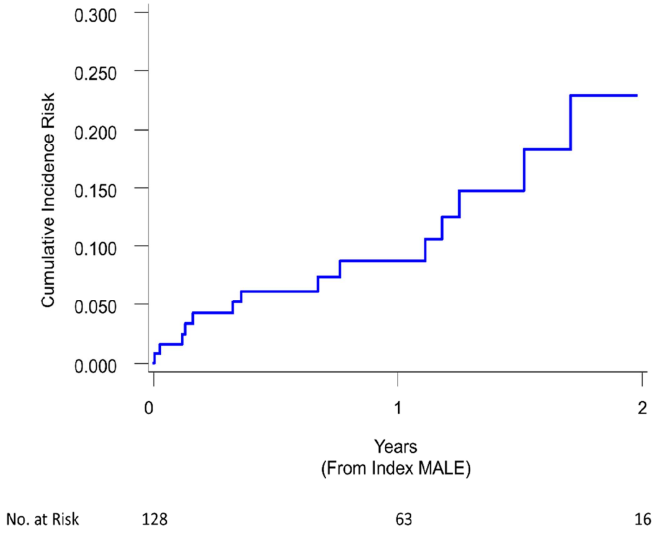
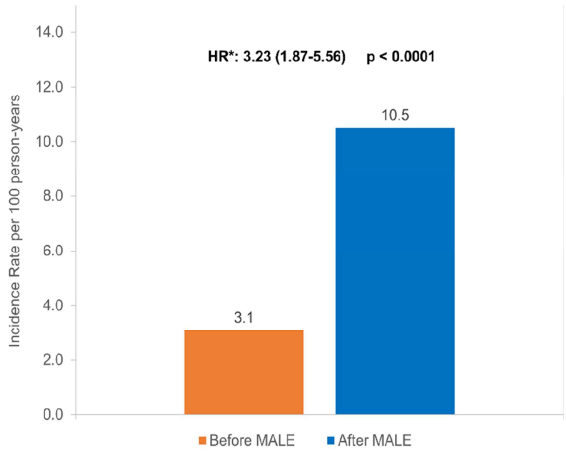
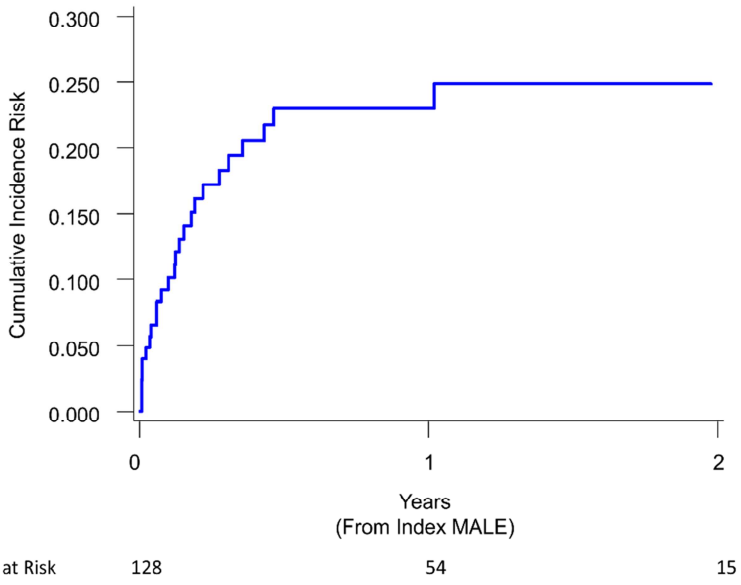

0.300
0.250
0.200
0.150
0.100
0.050
0.000
Cumulative Incidence Risk
0
1
2
Years
(From Index MALE)
No. at Risk
128
63
16

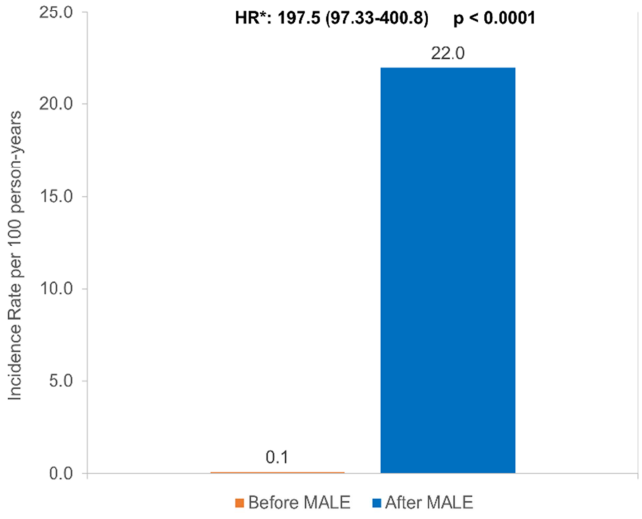
B

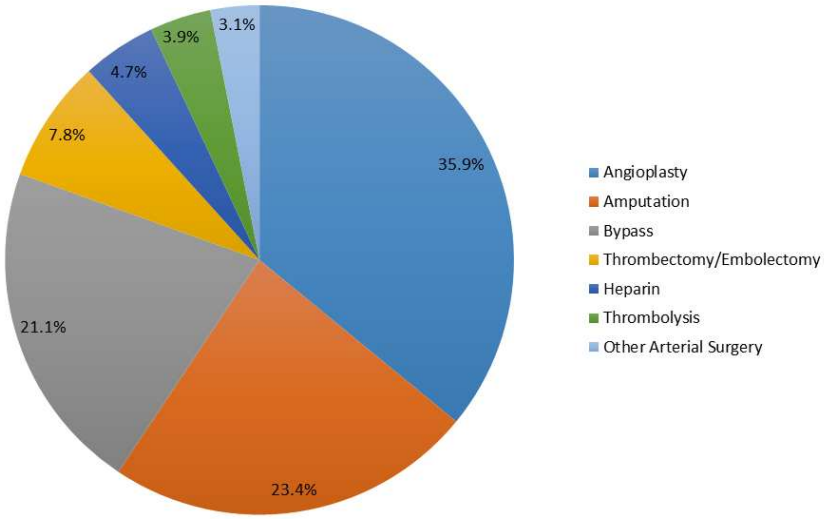

HR*: 3.23 (1.87-5.56)
p < 0.0001
14.0
12.0
10.0
8.0
6.0
4.0
2.0
0.0
Incidence Rate per 100 person-years
10.5
3.1
Before MALE
After MALE

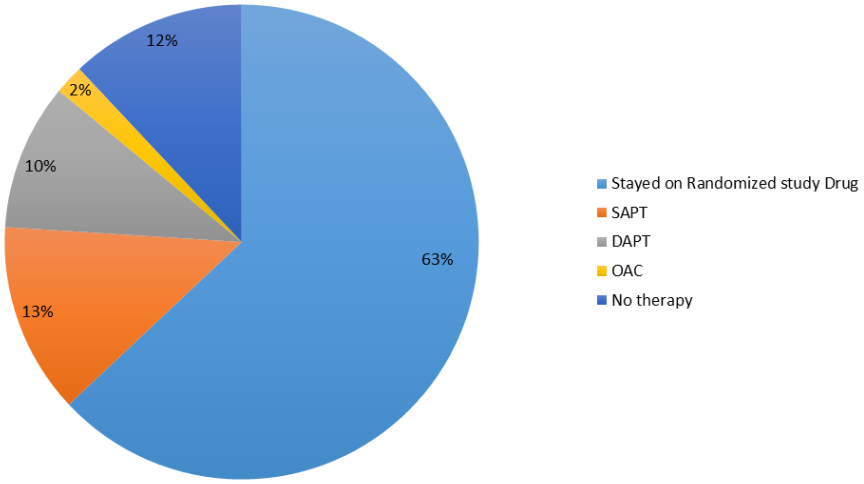
A

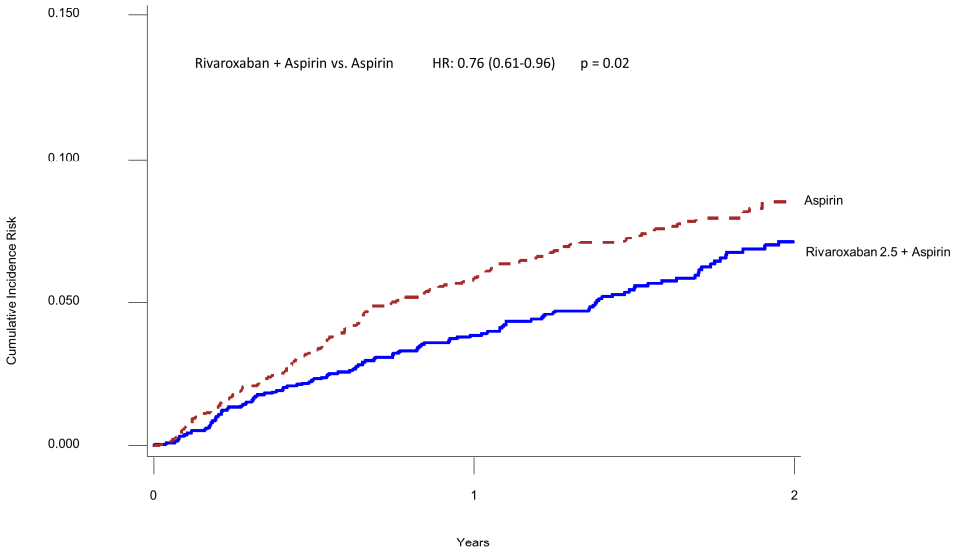

0.300
0.250
0.200
0.150
0.100
0.050
0.000
Cumulative Incidence Risk
0
1
2
Years
(From Index MALE)
No. at Risk
128
54
15

B


HR*: 197.5 (97.33-400.8) p < 0.0001
25.0
20.0
15.0
10.0
5.0
0.0
Incidence Rate per 100 person-years
22.0
0.1
Before MALE
After MALE







No. at Risk			
Rivaroxaban 2.5 + Aspirin	2139	1741	740
Aspirin	2123	1670	751