Evaluation of the Benefit of Rivaroxaban on the VOYAGER PAD Primary Composite of Irreversible Harm Events of the Limb, Heart and Brain Using the Global Rank and Win Ratio Methods

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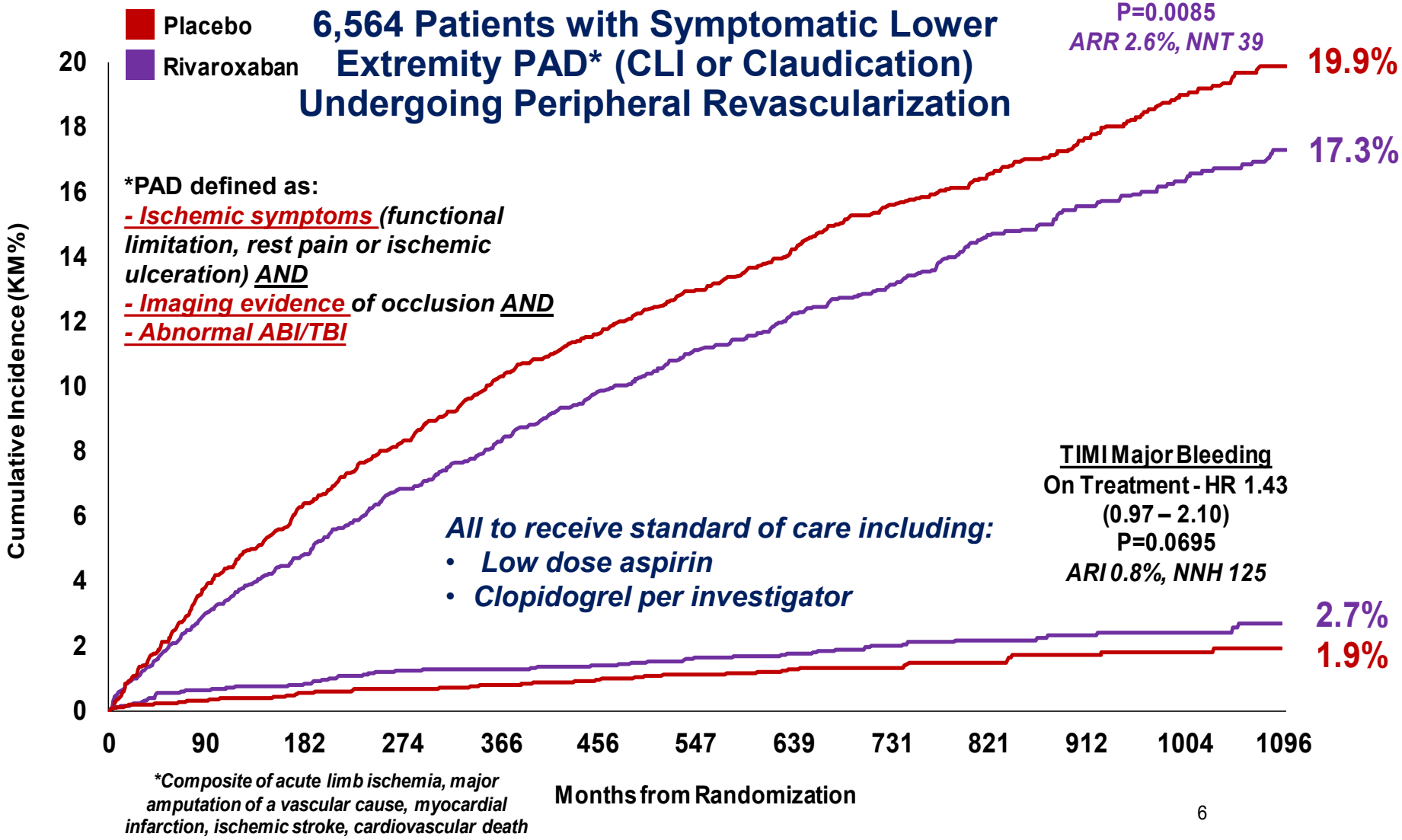
VOYAGER PAD Primary Results

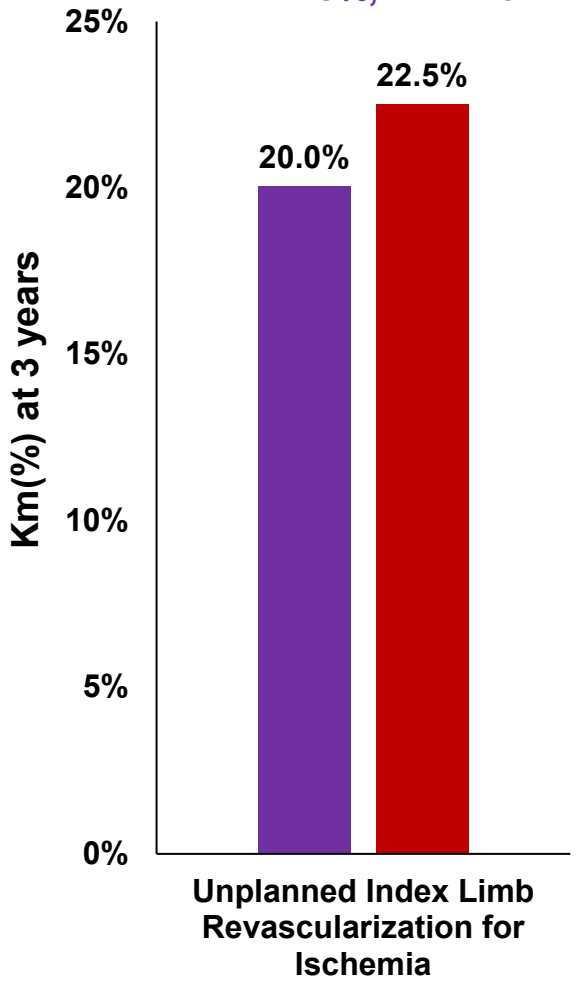


Primary Endpoint*
ITT - HR 0.85
(0.76 – 0.96)
P=0.0085
ARR 2.6%, NNT 39

TIMI Major Bleeding
On Treatment - HR 1.43
(0.97 – 2.10)
P=0.0695
ARI 0.8%, NNH 125

*Composite of acute limb ischemia, major amputation of a vascular cause, myocardial infarction, ischemic stroke, cardiovascular death

Unplanned Index Limb Revascularization
HR 0.88 (0.79 – 0.99)
P=0.028
ARR 2.5%, NNT 40

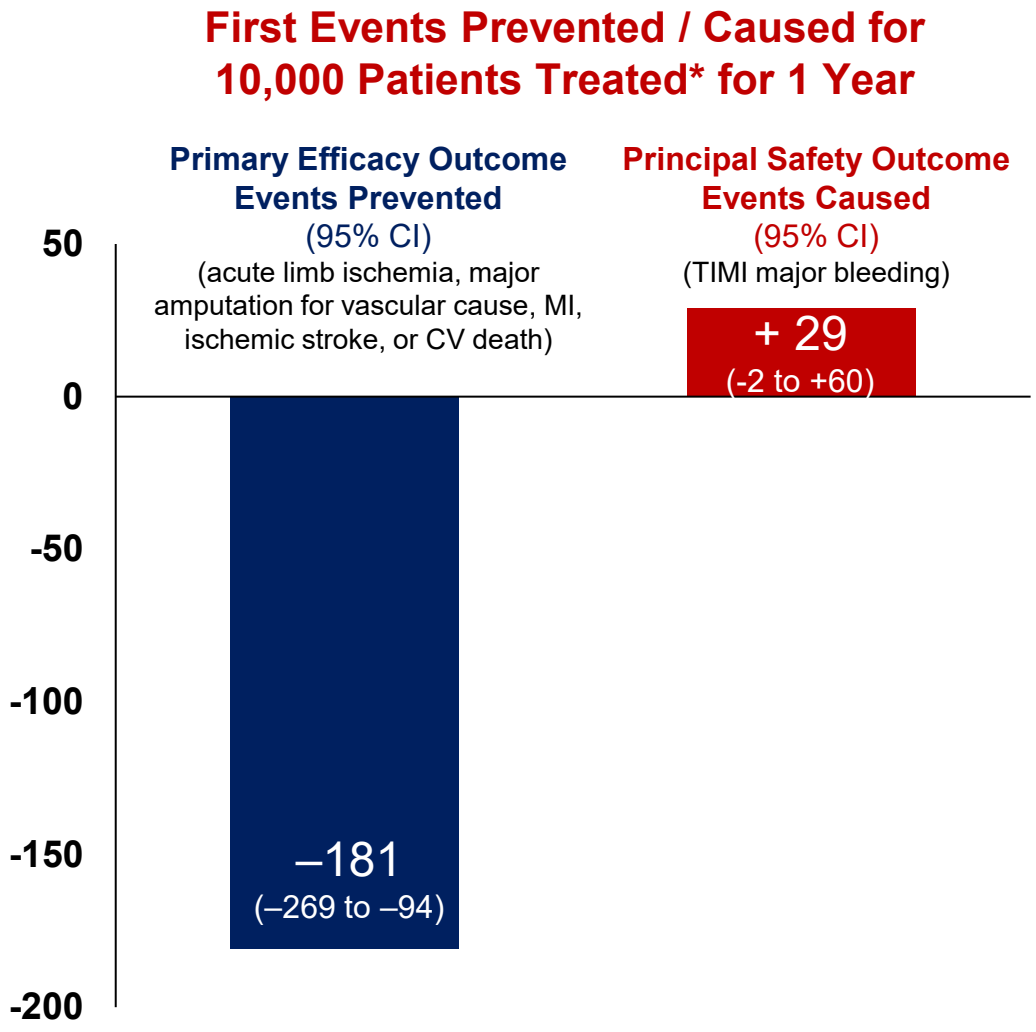


ITT population & data scope

CPC Clinical Research

VOYAGER PAD

Background



- **VOYAGER PAD demonstrated that rivaroxaban reduced the composite endpoint of acute limb ischemia (ALI), major amputation of a vascular etiology, myocardial infarction, ischemic stroke, or CV death**
- **The introduction of major adverse limb events (MALE) into primary endpoints with MACE is novel and the relative severity of components may be unfamiliar**
- **The primary analysis was performed as time to first event with equal weighting of components including fatal and non-fatal events**
- **Analyses evaluating outcomes using ranking of events may provide clinicians a mechanism to interpret the robustness of results when considering the clinical importance of specific components**
- **For therapies with safety considerations analyses of net outcome may provide clinicians another manner to understand benefit-risk**

**Efficacy and safety on treatment*

Bonaca MP…Hiatt WR *et al*. *N Engl J Med* 2020;382:1994–2004
Bonaca MP *et al*. Presented at ACC 2020. Slides available at https://cpcclinicalresearch.org/wp-content/uploads/2020/03/CPC-VOYAGER-PAD-Primary-Results-Slide-Presentation-by-Marc-P.-Bonaca.pdf

Aims and Methods

- ***To evaluate the robustness of the VOYAGER PAD primary composite endpoints using methods incorporating ranking of components and to evaluate net benefit including composites of efficacy and safety endpoints***
- **Global rank method**
  - **Rank all components of the composite by order of clinical importance with a *primary and alternative ranking* prespecified**
  - **Each patient assigned a rank with the worse rank for worse outcome and for patients with the same outcome, those occurring earlier assigned the worse rank. Van Elteren test for differences between groups was applied stratified by type of procedure and clopidogrel use consistent with the primary trial analysis.**
- **Win ratio method**
  - **Unmatched win ratio method according to Pocock's rule which ranked CV death higher than non-fatal events and then compared pairs of subjects, one from each treatment group for wins and losses.**
  - **Finkelstein and Schoenfeld statistics were utilized for the p-value with confidence intervals provided from bootstrapping**
- **Net benefit – prespecified composites of efficacy and safety events**

Results – Global Rank Method

Global Rank Method		
	Primary Hierarchy	*Alternative Hierarchy*
1	CV death	CV death
2	Ischemic Stroke	Ischemic Stroke
3	Acute limb ischemia	Acute limb ischemia
4	Major amputation of a vascular etiology	Myocardial Infarction
5	Myocardial Infarction	Major amputation of a vascular etiology
	Subjects experience a worse event according to the hierarchy are assigned a worse rank. Among subjects with the same type of event, those having the event earlier are assigned a worse rank	

Primary Hierarchy Result

- Rivaroxaban superior to placebo
- P-value 0.0158

Alternative Hierarchy Result

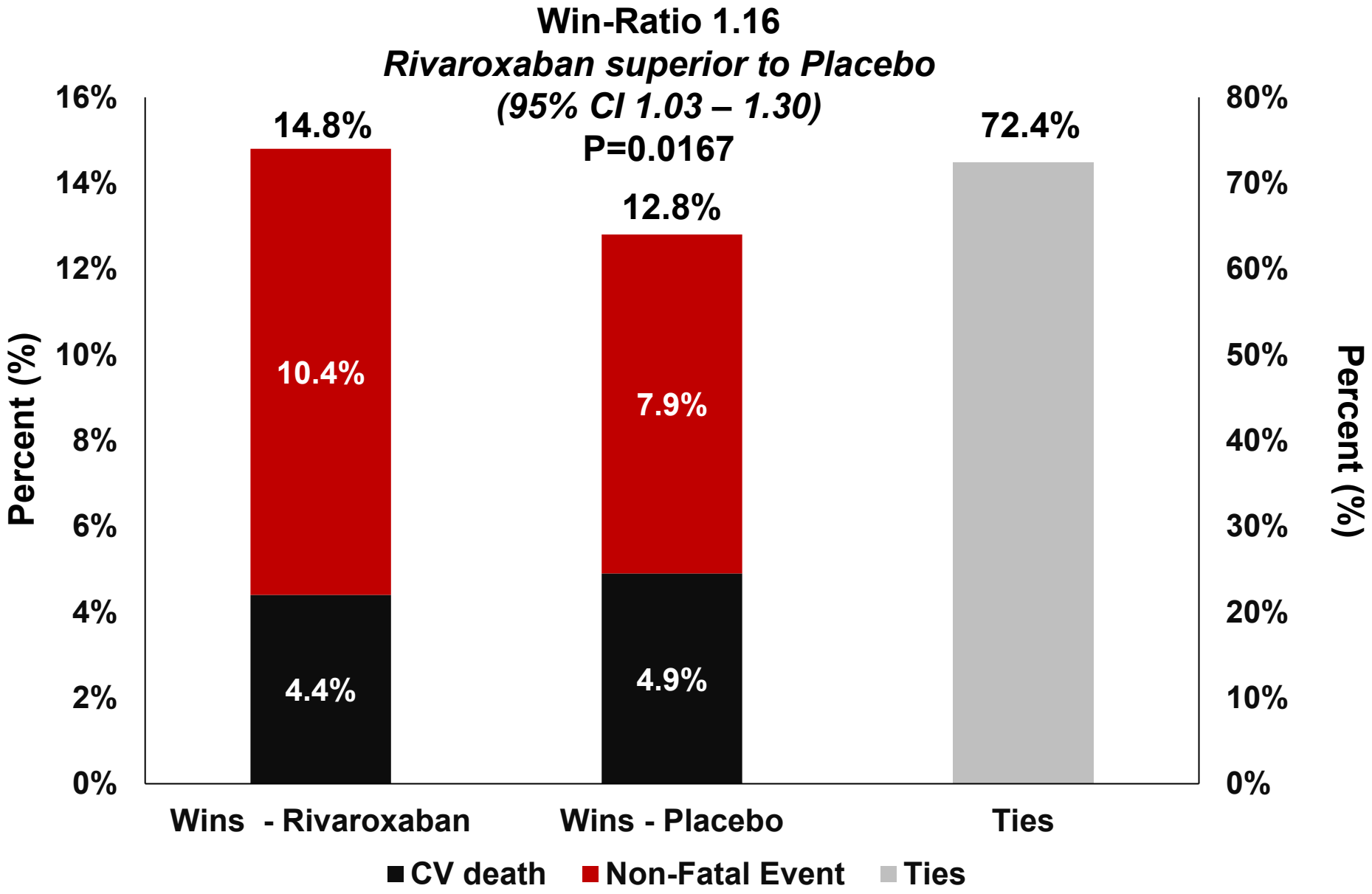
- Rivaroxaban superior to placebo
- P-value 0.0155

ITT population & data scope

Results – Win Ratio Method

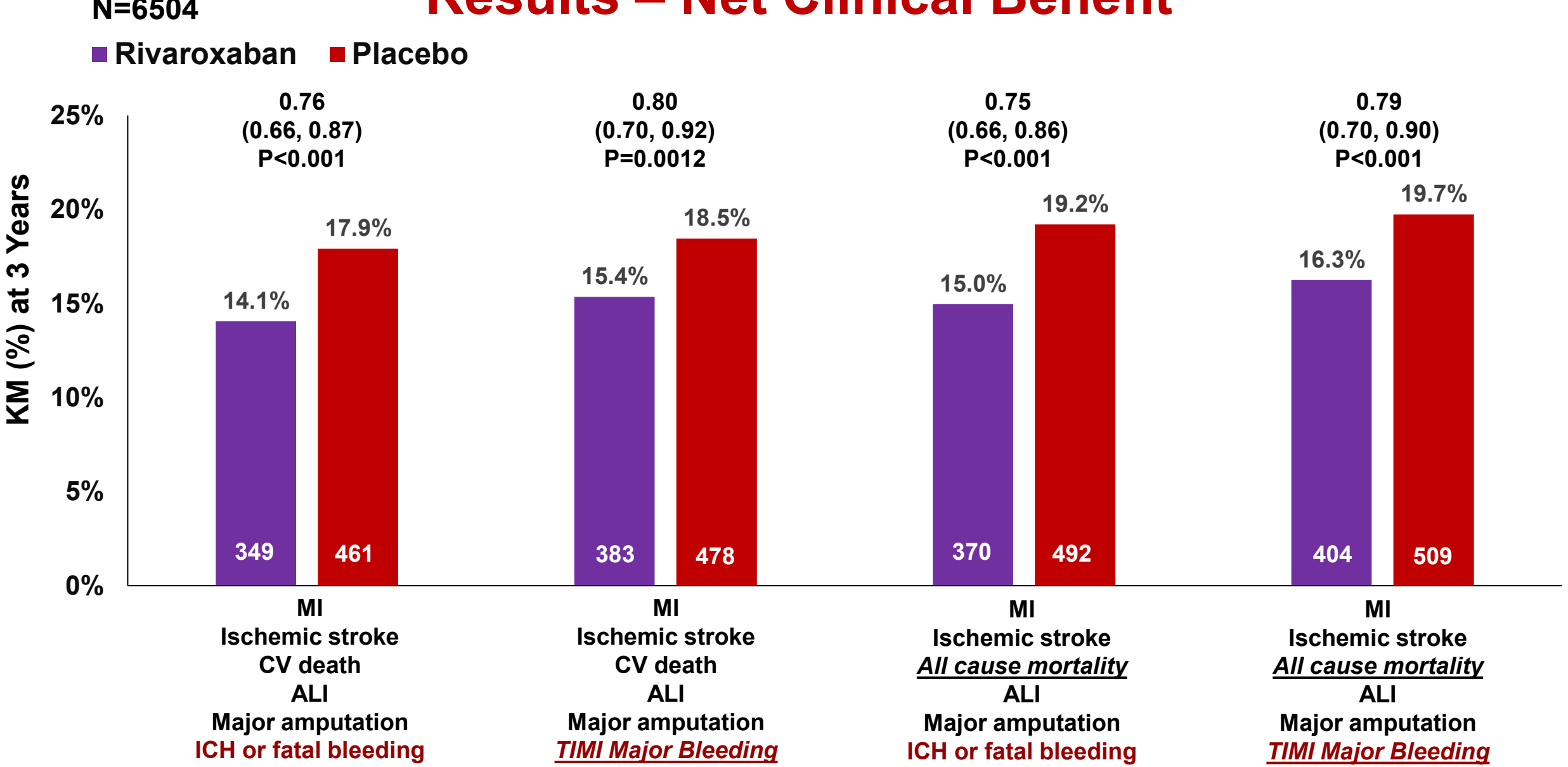
Outcomes	Outcome Category	
Patient in Rivaroxaban arm had CV Death first	A Placebo win	CV Death – fatal event so counted first (worst)
Patient in placebo arm had CV death first	B Rivaroxaban win	
Patient in Rivaroxaban arm had non-fatal primary efficacy event first	C Placebo win	Non-fatal components of the primary endpoint
Patient in Placebo arm had non-fatal primary efficacy event first	D Rivaroxaban win	
No CV death or non-fatal primary efficacy events	None of the 4 Categories	
Win Ratio: [(b+d)/(a+c)]		

Results – Win Ratio Method



ITT population & data scope

Results – Net Clinical Benefit



Includes all randomized subjects who received at least one dose of study treatment and includes events through 2 days following treatment discontinuation

Summary & Conclusions

- **Rivaroxaban significantly reduces acute limb ischemia, amputation, MI, ischemic stroke or CV death in PAD after lower extremity revascularization and increases bleeding but with a favorable benefit-risk profile**

- **Novel analytic approaches utilizing ranking, weighting, and net outcomes enable clinicians to understand the robustness of results and relative impacts of fatal and non-fatal events to evaluate benefit-risk**

- **Exploratory analyses of the VOYAGER PAD results show consistent superiority and net benefit when considered as:**
  - ***Ranked hierarchy of outcomes with CV death as the worst event***
  - ***Win-ratio approach ranking CV death as the worst event***
  - ***Net outcomes including ischemic events, bleeding and mortality***

- **These findings support the utilization of rivaroxaban in appropriate patients after peripheral revascularization for symptomatic PAD**