# VOYAGER PAD

## Vascular Outcomes Study of ASA Along with Rivaroxaban in Endovascular or Surgical Limb Revascularizations for Peripheral Artery Disease

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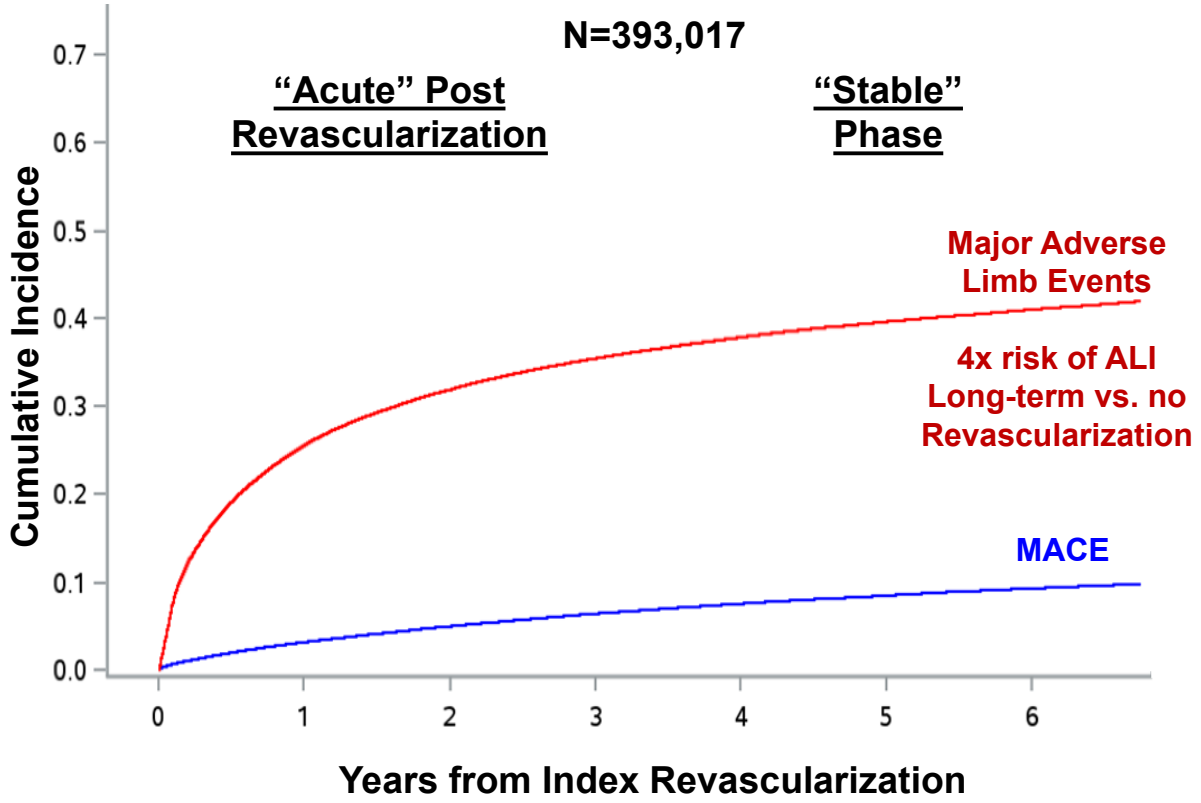
*American College of Cardiology Virtual Scientific Sessions 2020*
*Late-Breaking Clinical Trial*
*March 28, 2020*

University of Colorado Anschutz Medical Campus
*An Academic Research Organization Affiliated with the University of Colorado School of Medicine*

# Background

## Risk in Patients Undergoing Peripheral Revascularization




## Outcomes in Patients with Acute Limb Ischemia

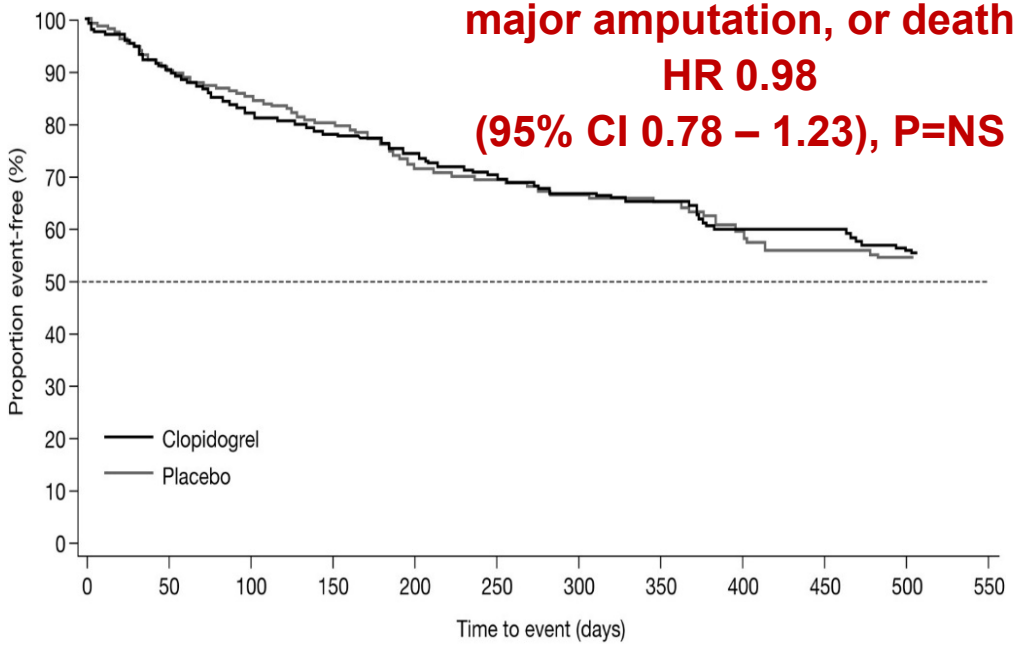
- Median hospitalization 8 days (IQR 5-15)
- ~4% die at presentation
- ~1/5 → major amputation
- ~1/3 → prolonged ICU stay
- ~3/4 → major surgery
- *Outcomes after hospitalization are poor with ~15% disabled or dead*


Hess…Hiatt et al. JACC 2020
Jones…Fowkes et al. Circulation 2017
Bonaca…Sabatine et al. JACC 2017
Bonaca…Morrow et al. Circulation 2016

# Background

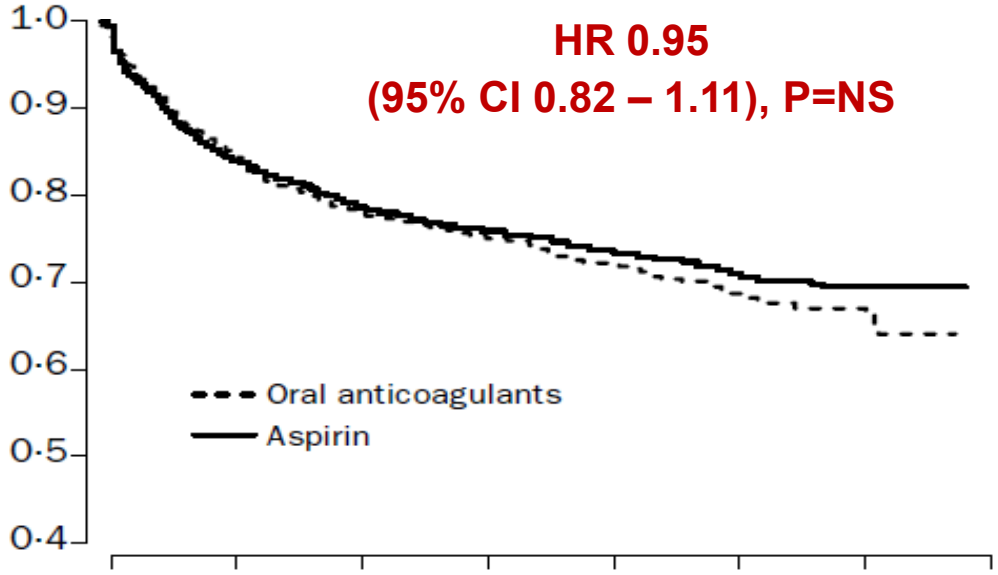
**Despite the high risk, currently <u>there is no proven antithrombotic strategy</u> that has demonstrated efficacy for <u>reducing major adverse limb and cardiovascular events after peripheral intervention for ischemia</u>**

**Index-graft occlusion, revascularization, major amputation, or death**
**HR 0.98**
**(95% CI 0.78 – 1.23), P=NS**




**DAPT with Aspirin and Clopidogrel**
**Increased GUSTO bleeding**
**HR 2.84 (1.32 – 6.08)**

**Graft Occlusions**
**HR 0.95**
**(95% CI 0.82 – 1.11), P=NS**




**Full Intensity Oral anticoagulation**
**Increased risk of Hemorrhagic Stroke**
**HR 3.48 (1.14 – 10.60)**


Belch et al. Journal of Vascular Surgery. 2010
Dutch Bypass Oral anticoagulants or Aspirin (BOA) Study Group. Lancet. 2000

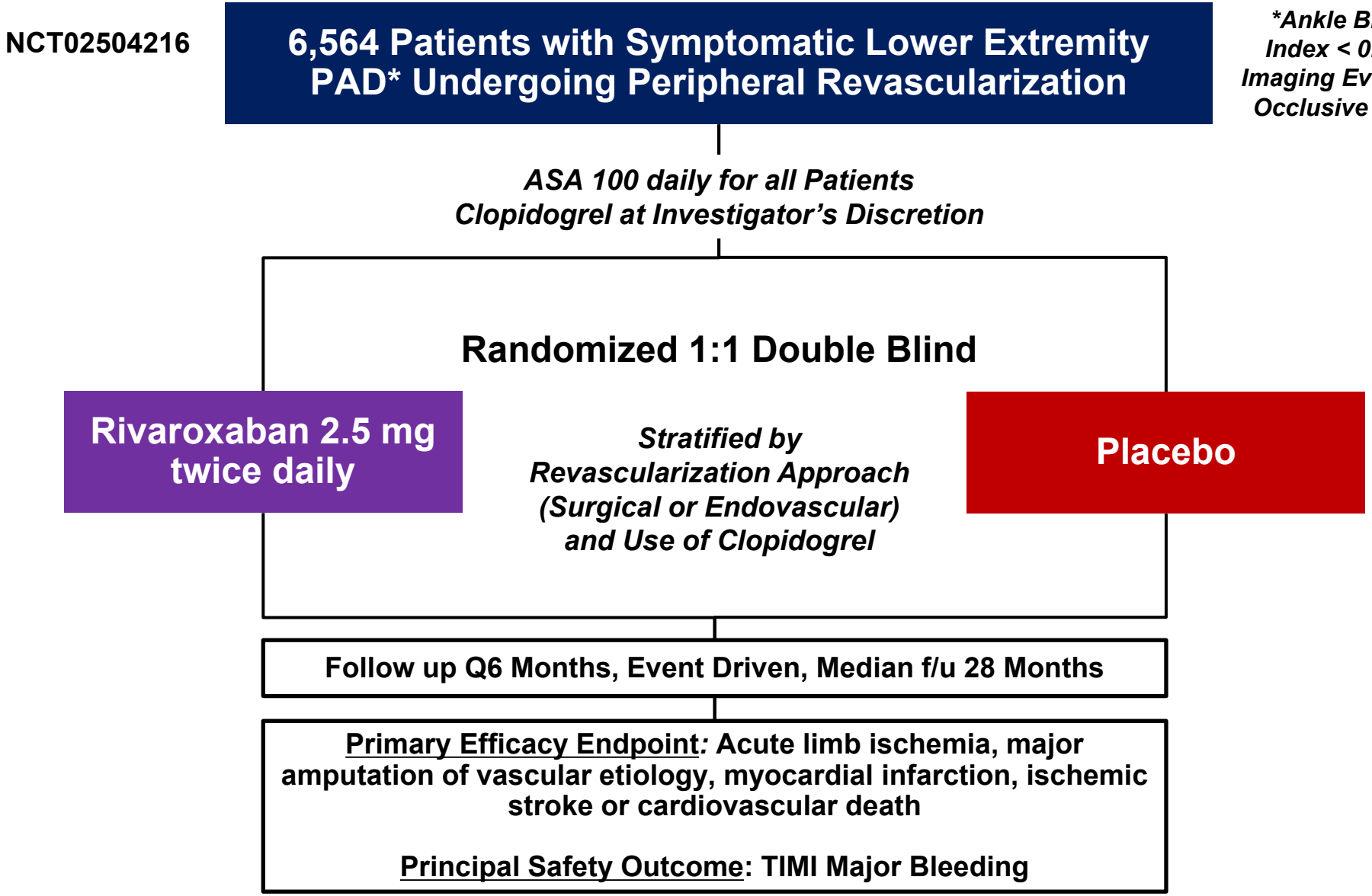
# Objectives

## In PAD patients undergoing lower extremity revascularization for ischemic symptoms:

- Test whether rivaroxaban 2.5 mg twice daily added to low dose aspirin reduces the risk of major adverse limb and cardiovascular events compared to aspirin alone

- To evaluate the safety of rivaroxaban 2.5 mg twice daily added to low dose aspirin compared to aspirin alone

# Trial Design




Capell WH, Bonaca MP, Nehler MR…Hiatt WR. AHJ 2018

# Inclusion & Exclusion

## Inclusion

- Age ≥ 50
- Documented PAD including:
  - *Ischemic symptoms (functional limitation, rest pain or ischemic ulceration)* ***AND***
  - *Imaging evidence of occlusion* ***AND***
  - *Abnormal ABI*
- Successful lower extremity revascularization for ischemia

## Exclusion

- Revascularization for asymptomatic disease
- Recent revascularization (within 10 days) or ALI (2 weeks) or ACS (30 days)
- Current major tissue loss
- Need for antiplatelet or anticoagulant other than aspirin and/or clopidogrel
- Need for long-term DAPT (intended > 6 months)
- High risk for bleeding (significant bleeding in last 6 months, prior stroke or other high-risk condition)

# Outcomes

## Efficacy

**Primary**: acute limb ischemia (ALI), major amputation for vascular cause (amputation), myocardial infarction (MI), ischemic stroke or CV death

**Secondary (hierarchical)**:

1. ALI, amputation, MI, ischemic stroke or coronary heart death
2. Unplanned index limb revascularization for ischemia
3. Vascular hospitalization for a coronary or peripheral event of thrombotic nature
4. ALI, amputation, MI, ischemic stroke or all-cause mortality
5. ALI, amputation, MI, all stroke or CV death
6. All-cause mortality
7. Venous thromboembolism

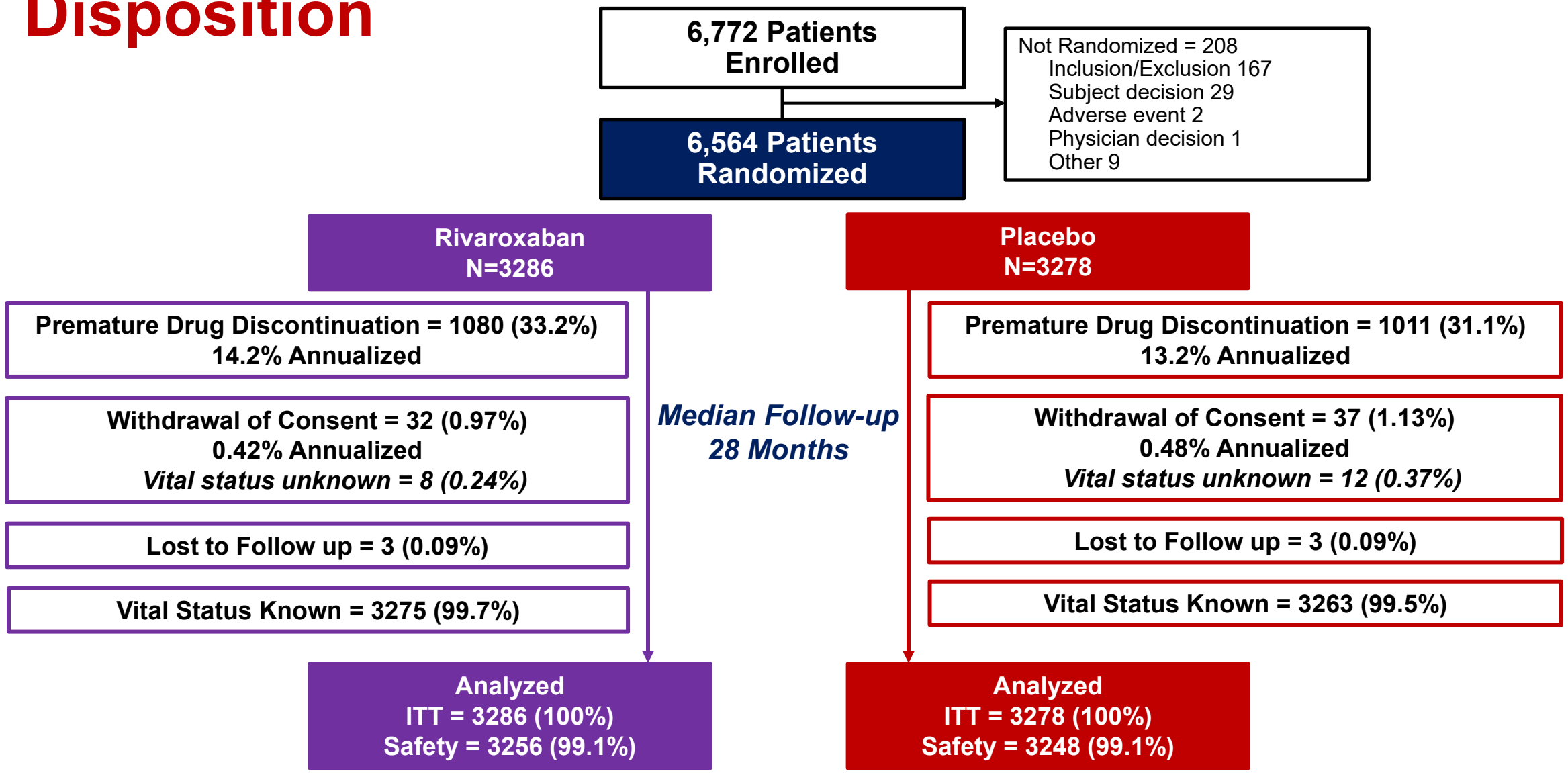
## Safety

**Principal**: TIMI major bleeding

**Secondary**: ISTH major bleeding, BARC 3b or above

*CPC Clinical Events Committee (CEC) adjudicated all efficacy and safety events*

# Disposition




***Complete primary efficacy and principal safety outcome ascertainment in 98.8% of potential patient-years of follow up***

# Baseline Characteristics

| Characteristics at Randomization | Rivaroxaban 2.5 mg twice daily + aspirin N=3286 % | Placebo + aspirin N=3278 % |
|---|---|---|
| Age, Yrs Median | 67 | 67 |
| Female | 26 | 26 |
| Caucasian | 81 | 81 |
| Diabetes Mellitus | 40 | 40 |
| Current Smoking | 35 | 35 |
| COPD | 11 | 11 |
| eGFR < 60 ml/min/1.73m$^2$ | 20 | 20 |
| Coronary Artery Disease | 32 | 31 |
| Prior MI | 11 | 11 |
| Known Carotid Stenosis | 9 | 9 |
| Clopidogrel | 51 | 51 |
| Statin | 79 | 81 |
| ACEi or ARB | 64 | 63 |

***P>0.05 for all comparisons***

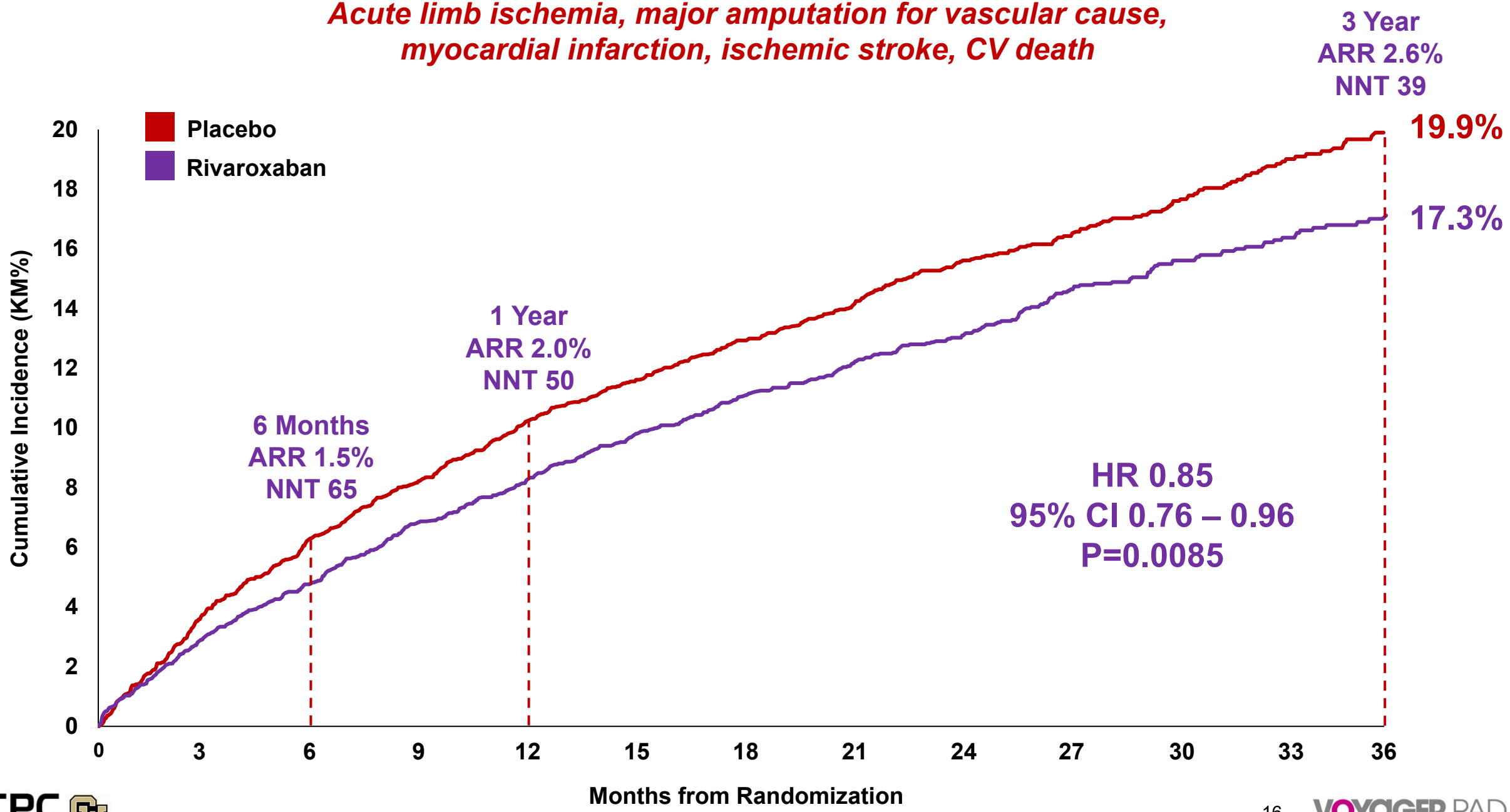
# PAD & Procedural Characteristics

| Characteristics at Randomization | Rivaroxaban 2.5 mg twice daily + aspirin N=3286 % | Placebo + aspirin N=3278 % |
|---|---|---|
| *Prior Peripheral Artery Disease History* | | |
| History of Claudication | 95 | 96 |
| History of Revascularization | 36 | 35 |
| History of Amputation | 6 | 6 |
| Ankle Brachial Index, Median (IQR) | 0.56 (0.42 – 0.67) | 0.56 (0.42 – 0.67) |
| *Indication for Revascularization* | | |
| Critical limb ischemia | 23 | 24 |
| Claudication | 77 | 76 |
| *Type of Revascularization* | | |
| Surgical | 35 | 35 |
| Endovascular or Hybrid | 66 | 65 |
| Days from Procedure to Randomization, Median (IQR) | 5 (2 – 7) | 5 (2 – 7) |

***P>0.05 for all comparisons***

# Primary Endpoint

***Acute limb ischemia, major amputation for vascular cause, myocardial infarction, ischemic stroke, CV death***

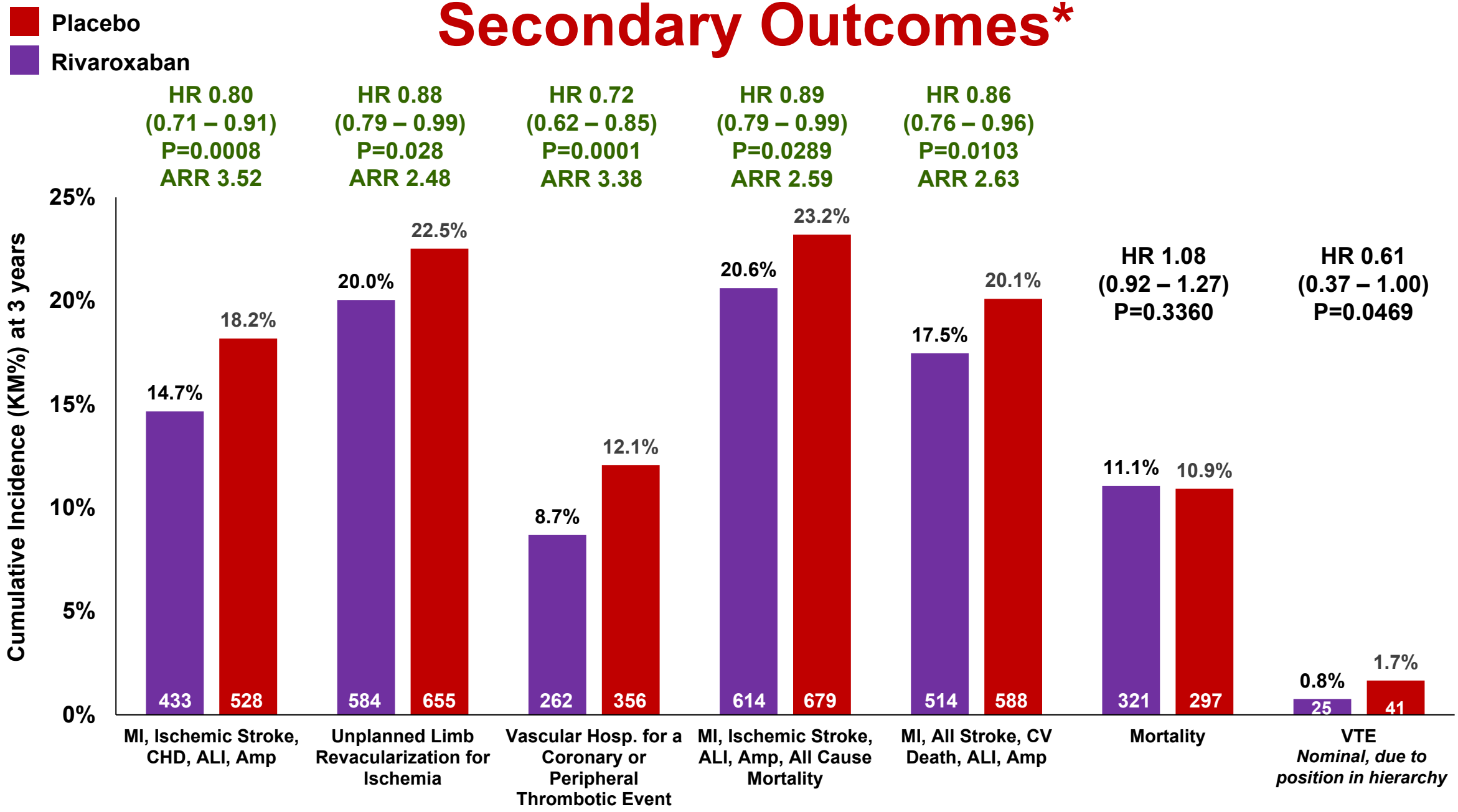



*ARR – absolute risk reduction, NNT number needed to treat*

# Primary Endpoint & Components

| | KM% 3 Years (n) Rivaroxaban N=3286 | KM% 3 Years (n) Placebo N=3278 | HR (95% CI) |
|---|---|---|---|
| Primary Efficacy Outcome | 17.3 | 19.9 | 0.85 (0.76 – 0.96) |
| Acute Limb Ischemia | 5.24 | 7.74 | 0.67 (0.55 – 0.82) |
| Major Vascular Amputation | 3.42 | 3.87 | 0.89 (0.68 – 1.16) |
| Ischemic Stroke | 2.70 | 3.01 | 0.87 (0.63 – 1.19) |
| Myocardial Infarction | 4.55 | 5.22 | 0.88 (0.70 – 1.12) |
| CV Death | 7.05 | 6.43 | 1.14 (0.93 – 1.40) |

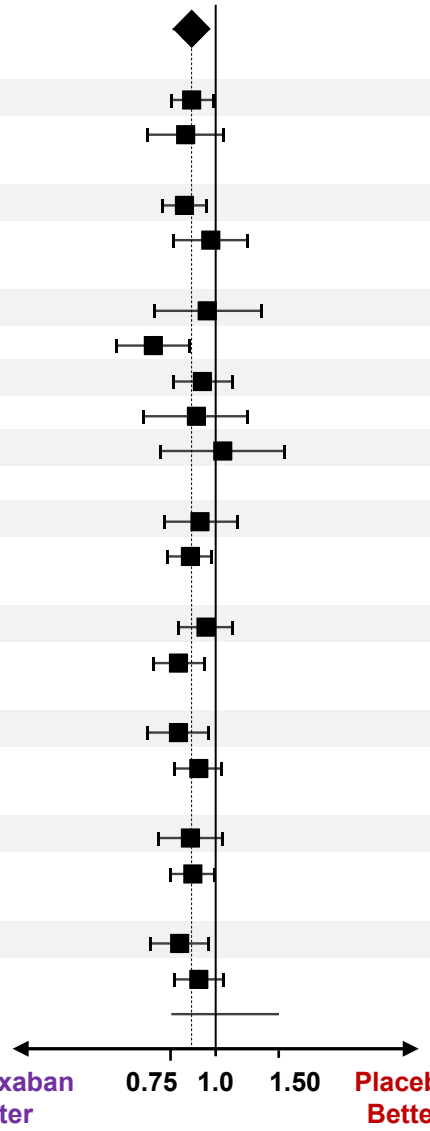
# Secondary Outcomes*



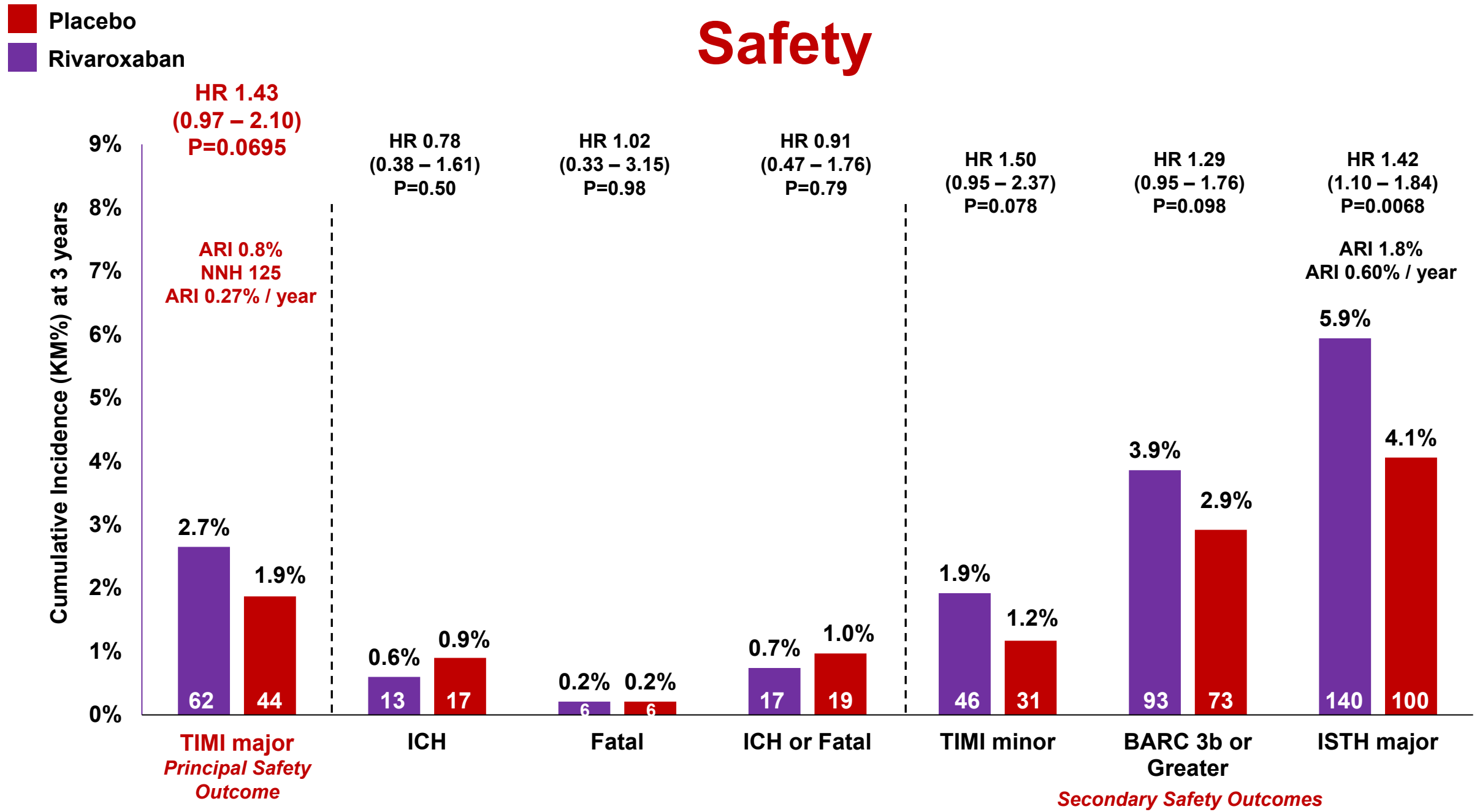

*Presented in order of hierarchy from left to right

# Primary Efficacy Outcome in Selected Subgroups

| *Characteristic* | | Rivaroxaban 2.5 mg bid plus ASA daily n/N (%) | Placebo bid plus ASA daily n/N (%) | HR (95% CI) | *P-interaction* |
|---|---|---|---|---|---|
| *All subjects* | | 15.5 | 17.8 | 0.85 ( 0.76, 0.96) | |
| Age | | | | | |
| | < 75 | 15.0 | 17.0 | 0.86 ( 0.75, 0.98) | 0.8314 |
| | ≥ 75 | 17.4 | 21.0 | 0.82 ( 0.64, 1.05) | |
| Sex | | | | | |
| | Male | 15.4 | 18.4 | 0.82 ( 0.71, 0.94) | 0.2385 |
| | Female | 15.7 | 16.2 | 0.97 ( 0.76, 1.23) | |
| Region | | | | | |
| | North America | 18.4 | 19.3 | 0.95 ( 0.67, 1.33) | 0.2286 |
| | Western Europe | 12.9 | 18.4 | 0.67 ( 0.53, 0.84) | |
| | Eastern Europe | 16.4 | 17.6 | 0.92 ( 0.76, 1.11) | |
| | Asia Pacific | 13.3 | 15.2 | 0.88 ( 0.63, 1.23) | |
| | South America | 20.2 | 19.9 | 1.04 ( 0.70, 1.56) | |
| eGFR (ml/min/1.73m$^2$) | | | | | |
| | < 60 | 19.7 | 21.9 | 0.90 ( 0.71, 1.15) | 0.6177 |
| | ≥ 60 | 14.4 | 16.6 | 0.85 ( 0.73, 0.97) | |
| Diabetes mellitus | | | | | |
| | Yes | 18.9 | 19.8 | 0.94 ( 0.79, 1.11) | 0.1588 |
| | No | 13.2 | 16.5 | 0.79 ( 0.67, 0.93) | |
| Coronary Artery Disease | | | | | |
| | Yes | 17.4 | 21.7 | 0.78 ( 0.64, 0.95) | 0.2872 |
| | No | 14.6 | 16.1 | 0.89 ( 0.77, 1.04) | |
| Critical Limb Ischemia | | | | | |
| | Yes | 20.9 | 24.4 | 0.85 ( 0.69, 1.05) | |
| | No | 13.8 | 15.8 | 0.86 ( 0.74, 0.99) | |
| Qualifying Procedure | | | | | |
| | Surgical | 17.9 | 21.9 | 0.79 ( 0.66, 0.95) | 0.2896 |
| | Endovascular | 14.2 | 15.7 | 0.90 ( 0.77, 1.05) | |



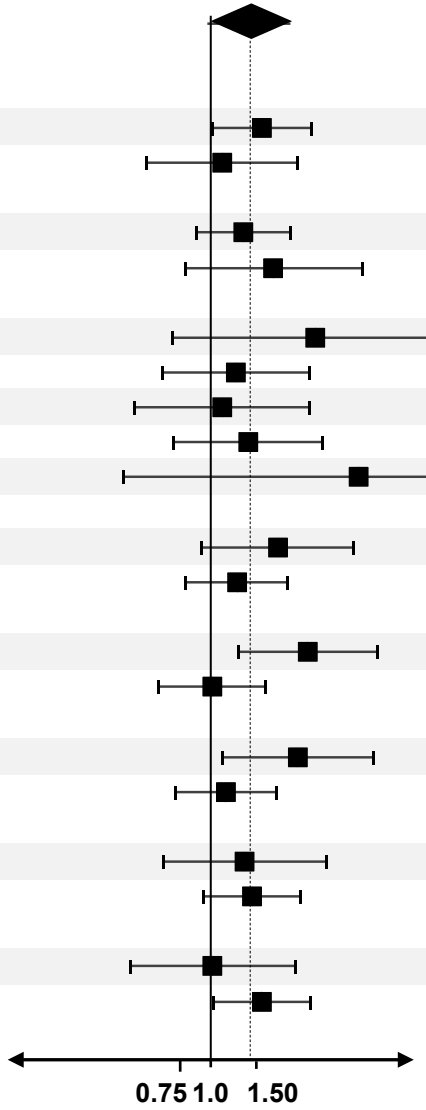
# Safety



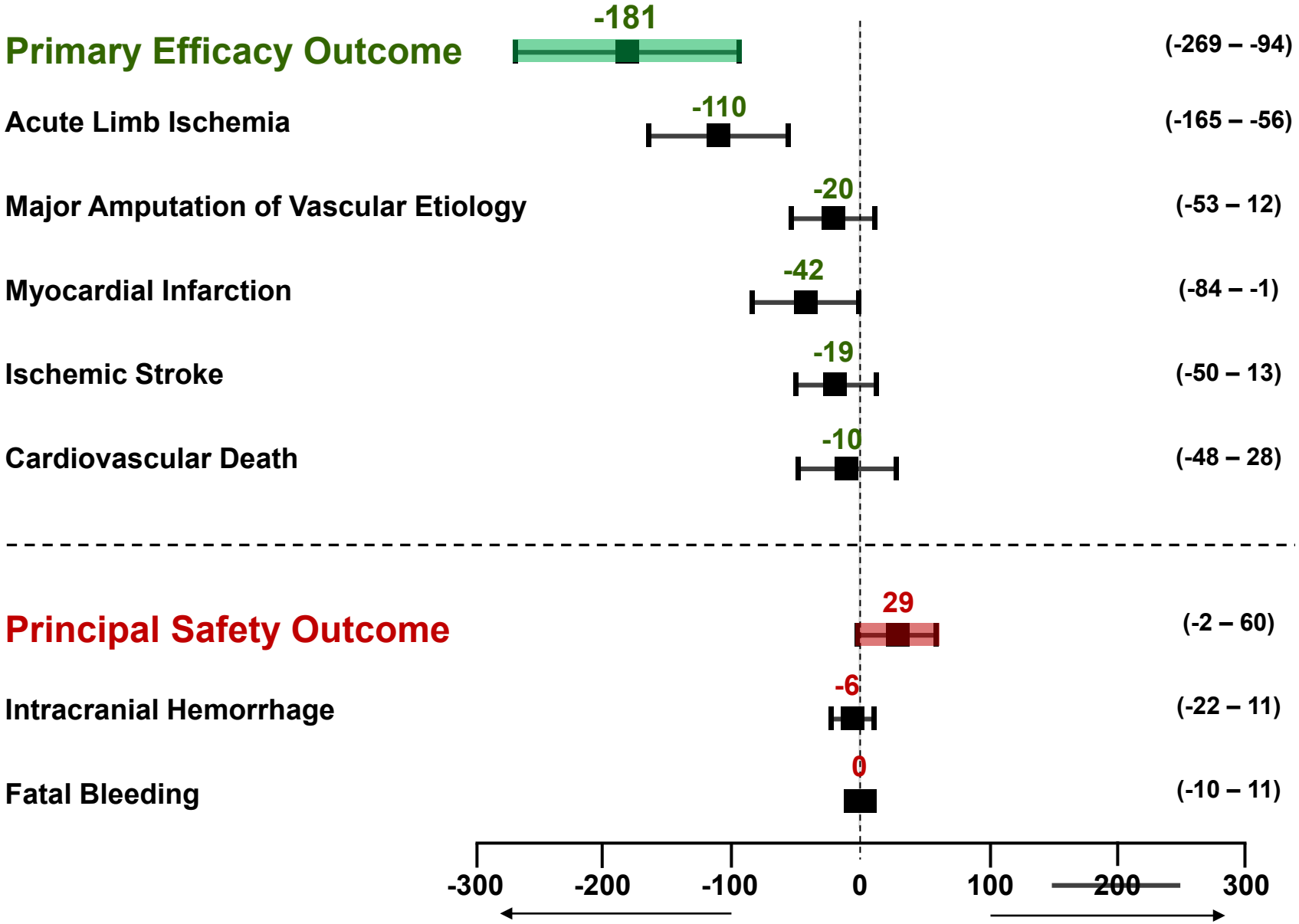

*ARI – absolute risk increase, NNH number needed to harm*

# Principal Safety Outcome in Selected Subgroups

| *Characteristic* | | Rivaroxaban 2.5 mg bid plus ASA daily n/N (%) | Placebo bid plus ASA daily n/N (%) | HR (95% CI) | *P-Interaction* |
|---|---|---|---|---|---|
| All subjects | | 1.9 | 1.4 | 1.43 ( 0.97, 2.10) | |
| Age | | | | | |
| | < 75 | 1.8 | 1.1 | 1.60 ( 1.01, 2.55) | 0.3807 |
| | ≥ 75 | 2.4 | 2.3 | 1.11 ( 0.55, 2.26) | |
| Sex | | | | | |
| | Male | 1.9 | 1.5 | 1.35 ( 0.87, 2.10) | 0.5974 |
| | Female | 1.8 | 1.1 | 1.79 ( 0.78, 4.09) | |
| Region | | | | | |
| | North America | 2.4 | 0.9 | 2.65 ( 0.70, 9.99) | 0.9858 |
| | Western Europe | 2.1 | 1.7 | 1.26 ( 0.64, 2.48) | |
| | Eastern Europe | 0.9 | 0.9 | 1.10 ( 0.49, 2.50) | |
| | Asia Pacific | 4.0 | 2.9 | 1.41 ( 0.71, 2.81) | |
| | South America | 1.7 | 0.4 | 3.95 ( 0.44, 35.38) | |
| eGFR (ml/min/1.73m$^2$) | | | | | |
| | < 60 | 3.2 | 1.8 | 1.86 ( 0.92, 3.79) | 0.3726 |
| | ≥ 60 | 1.5 | 1.2 | 1.27 ( 0.79, 2.05) | |
| Diabetes mellitus | | | | | |
| | Yes | 2.4 | 1.0 | 2.45 ( 1.28, 4.69) | 0.0334 |
| | No | 1.6 | 1.6 | 1.01 ( 0.61, 1.66) | |
| Coronary artery disease | | | | | |
| | Yes | 2.4 | 1.1 | 2.24 ( 1.10, 4.56) | 0.1245 |
| | No | 1.7 | 1.5 | 1.15 ( 0.72, 1.84) | |
| Critical Limb Ischemia | | | | | |
| | Yes | 2.0 | 1.6 | 1.37 ( 0.64, 2.94) | |
| | No | 1.9 | 1.3 | 1.47 ( 0.94, 2.30) | |
| Qualifying procedure | | | | | |
| | Surgical | 1.2 | 1.1 | 1.02 ( 0.47, 2.19) | 0.3155 |
| | Endovascular | 2.3 | 1.5 | 1.60 ( 1.02, 2.51) | |



# First Events Prevented / Caused for 10,000 Patients Treated* for 1 Year




*Efficacy and safety on-treatment

# Summary & Conclusion

- **In symptomatic PAD after revascularization, ~1 in 5 have acute limb ischemia, major amputation of vascular etiology, MI, ischemic stroke or cardiovascular death at 3 years**

- **In this population and setting, rivaroxaban 2.5 mg twice daily with aspirin compared to aspirin alone:**

  - ✓ ***Significantly reduces this risk with…***
    - ***Benefits apparent early and continued over time***
    - ***Consistent benefit across major subgroups***
    - ***Broad benefits including reductions in unplanned index limb revascularization***

  - ✓ ***Increases bleeding: in VOYAGER PAD, there was a numerical increase in TIMI major bleeding and significantly increased ISTH major bleeding but no excess in intracranial or fatal bleeding***

  - ✓ ***Prevents ~6 times as many ischemic events relative to bleeds caused in PAD patients after revascularization***

The NEW ENGLAND JOURNAL of MEDICINE

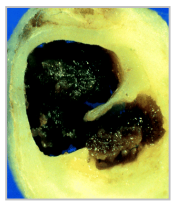
ORIGINAL ARTICLE

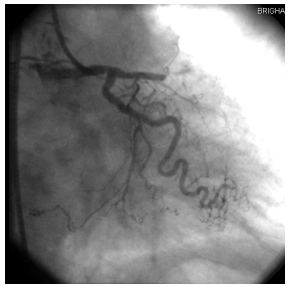
# Rivaroxaban in Peripheral Artery Disease after Revascularization

Marc P. Bonaca, M.D., M.P.H., Rupert M. Bauersachs, M.D., Sonia S. Anand, M.D., Eike S. Debus, M.D., Ph.D., Mark R. Nehler, M.D., Manesh R. Patel, M.D., Fabrizio Fanelli, M.D., Warren H. Capell, M.D., Lihong Diao, , Nicole Jaeger, , Connie N. Hess, M.D., M.H.S., Akos F. Pap, , John M. Kittelson, Ph.D., Ivan Gudz, M.D., Ph.D., Lajos Mátyás, M.D., Dainis K Krievins, M.D., Rafael Diaz, M.D., Marianne Brodmann, M.D., Eva Muehlhofer, M.D., Lloyd P. Haskell, M.D., Scott D. Berkowitz, M.D., and William R. Hiatt, M.D.

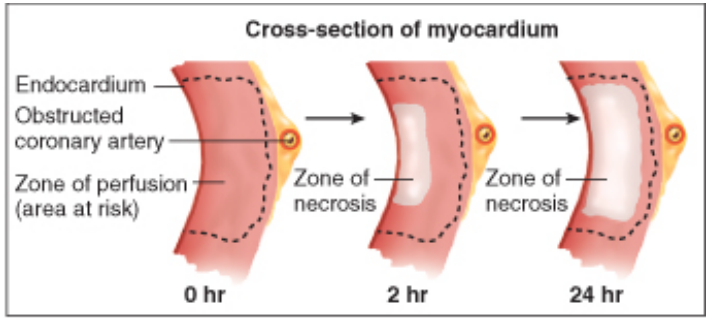
**Slides for Download at:**
**https://cpcclinicalresearch.org/ @cpcresearch**

# STEMI





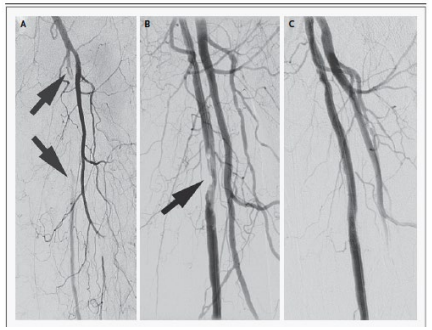
- Acute thrombotic occlusion of an artery threatening tissue loss
- "Time Is Muscle"
- Outcomes determined by time to acute reperfusion
- Reperfusion injury is a complication






- Mortality at 1 year 8.1%[1]
- Recurrent MACE at 1 year 3.4%[1]
- HF at 1 year 7.4%[1]

# ALI



- Acute thrombotic occlusion of an artery threatening tissue loss
- "Time Is Muscle"
- Outcomes determined by time to acute reperfusion
- Reperfusion injury is a complication

0 Hour → 24 Hour

- Mortality at 1 year 12.1%[2]
- MACE 11.7%, Recurrent ALI 24% (1 yr) [2]
- Amputation at 1-year 27%[2]

1. Zeymer et al. EORP EU STEMI Registry 2019

2. Bonaca et al. Circulation 2016