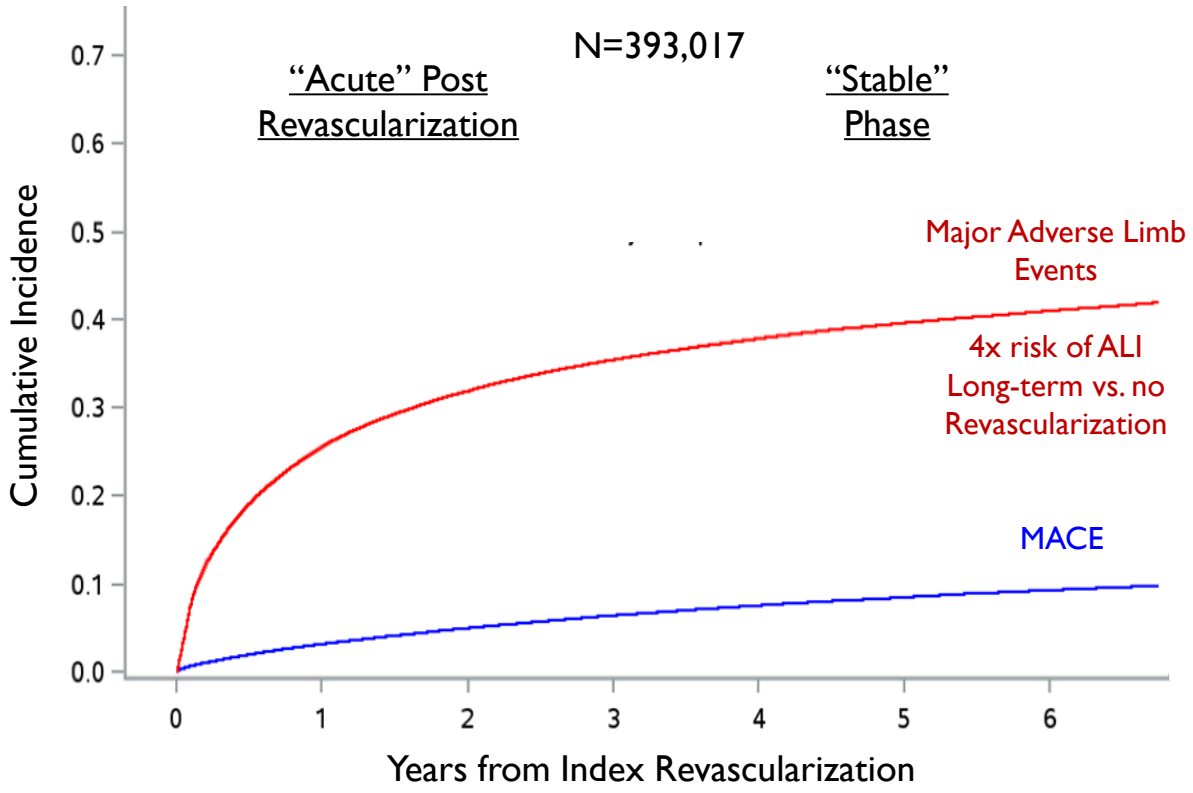
# RIVAROXABAN NELL'ARTERIOPATIA PERIFERICA SOTTOPOSTA A RIVASCOLARIZZAZIONE

## RISULTATI DEL TRIAL VOYAGER PAD

# 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*

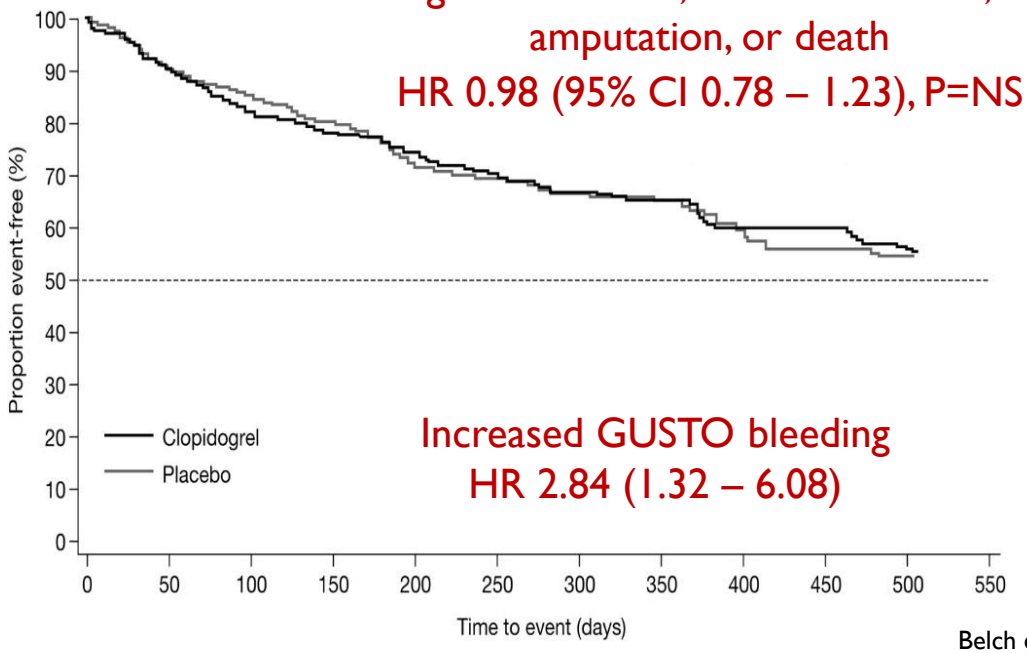

Hess…Hiatt et al. JACC 2020
Jones…Fowkes et al. Circulation 2017
Bonaca…Sabatine et al. JACC 2017
Bonaca…Morrow et al. Circulation 2016

# BACKGROUND

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

## DAPT with Aspirin and Clopidogrel

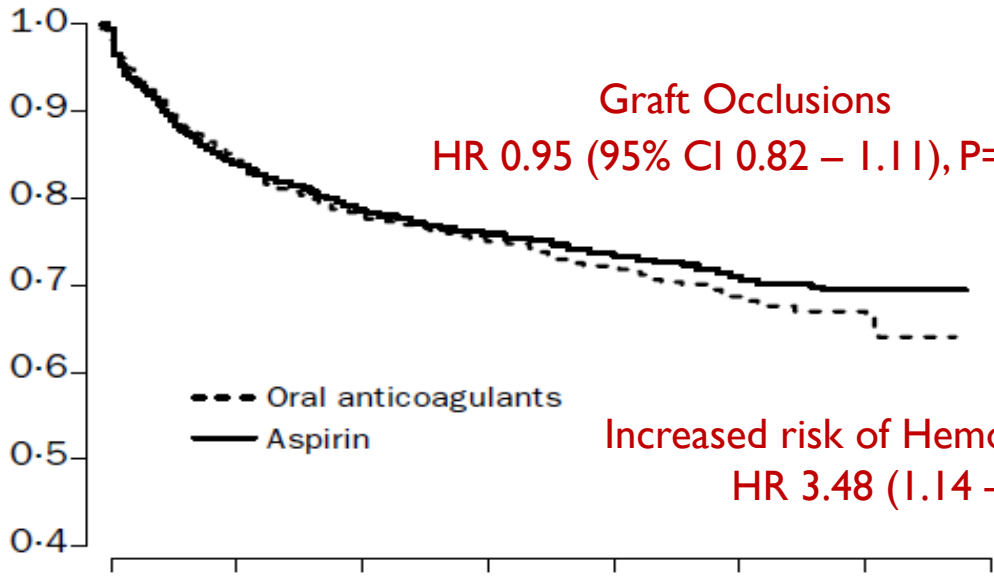
Index-graft occlusion, revascularization, major amputation, or death
HR 0.98 (95% CI 0.78 – 1.23), P=NS




Increased GUSTO bleeding
HR 2.84 (1.32 – 6.08)

## Full Intensity Oral anticoagulation

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




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

# DAPT RECOMMENDATIONS AFTER PAD INTERVENTION

| | | | |
|---|---|---|---|
| ACC-AHA: | IIb | C-LD | DAPT may be reasonable to reduce the risk of limb-related events after LER |
| ESC | IIa | C | DAPT is recommended for 1 month after intervention |
| Chest | Grade Ia | | SAPT (single antiplatelet therapy). Recommend against DAPT |
| Zilver PTX | | | DAPT for 2 months |
| IN.PACT SFA | | | DAPT for 1 month (without stent) or 3 months (with stent) |

ORIGINAL ARTICLE

# Rivaroxaban in Peripheral Artery Disease after Revascularization

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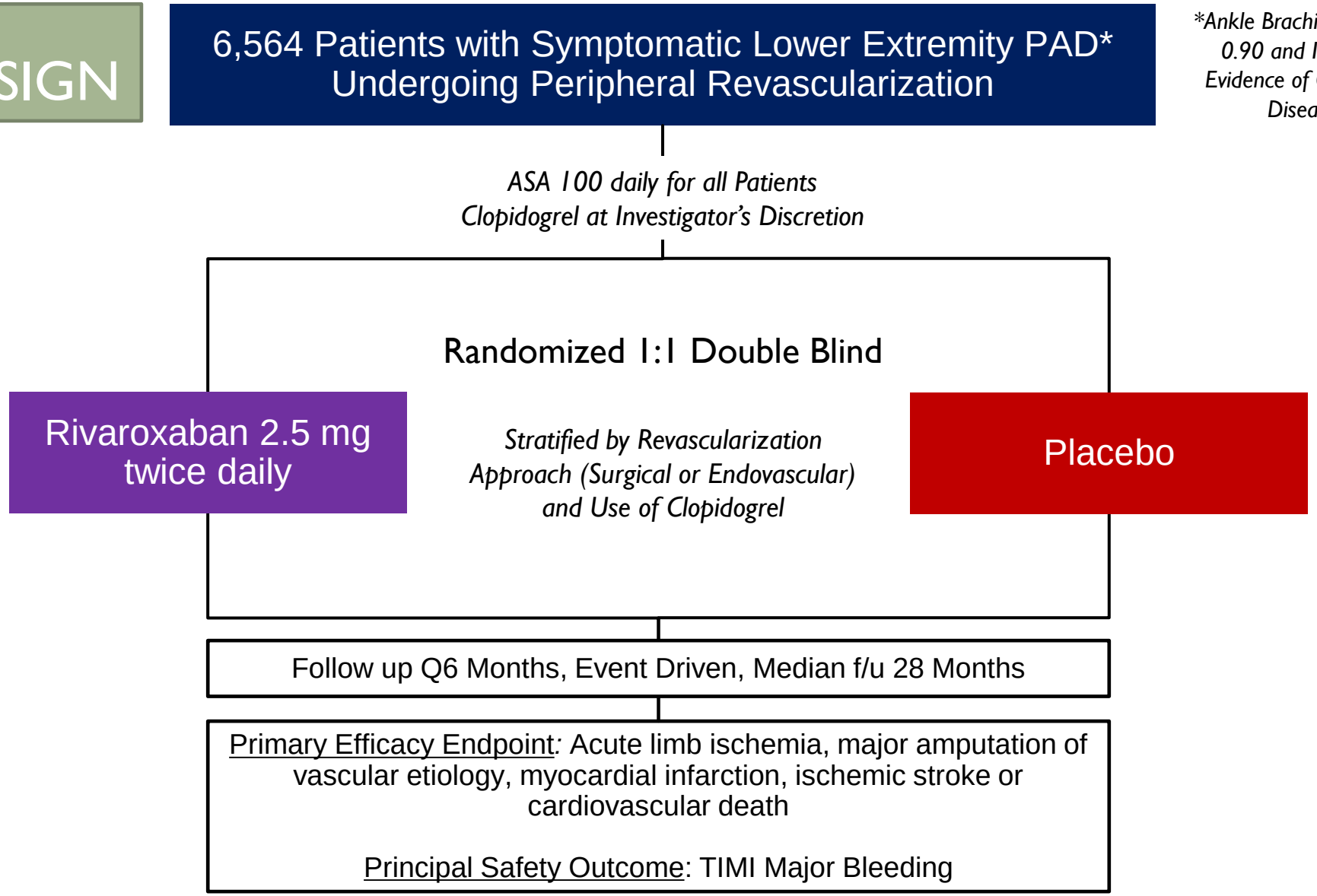
# OBJECTIVES

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

- 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)

Bonaca MP et al, NEJM 2020

## Efficacy

- **Primary**: acute limb ischemia (ALI), major amputation for vascular cause (amputation), myocardial infarction (MI), ischemic stroke or CV death
- **Secondary (hierarchical):**
  - ALI, amputation, MI, ischemic stroke or coronary heart death
  - Unplanned index limb revascularization for ischemia
  - Vascular hospitalization for a coronary or peripheral event of thrombotic nature
  - ALI, amputation, MI, ischemic stroke or all-cause mortality
  - ALI, amputation, MI, all stroke or CV death
  - All-cause mortality
  - Venous thromboembolism

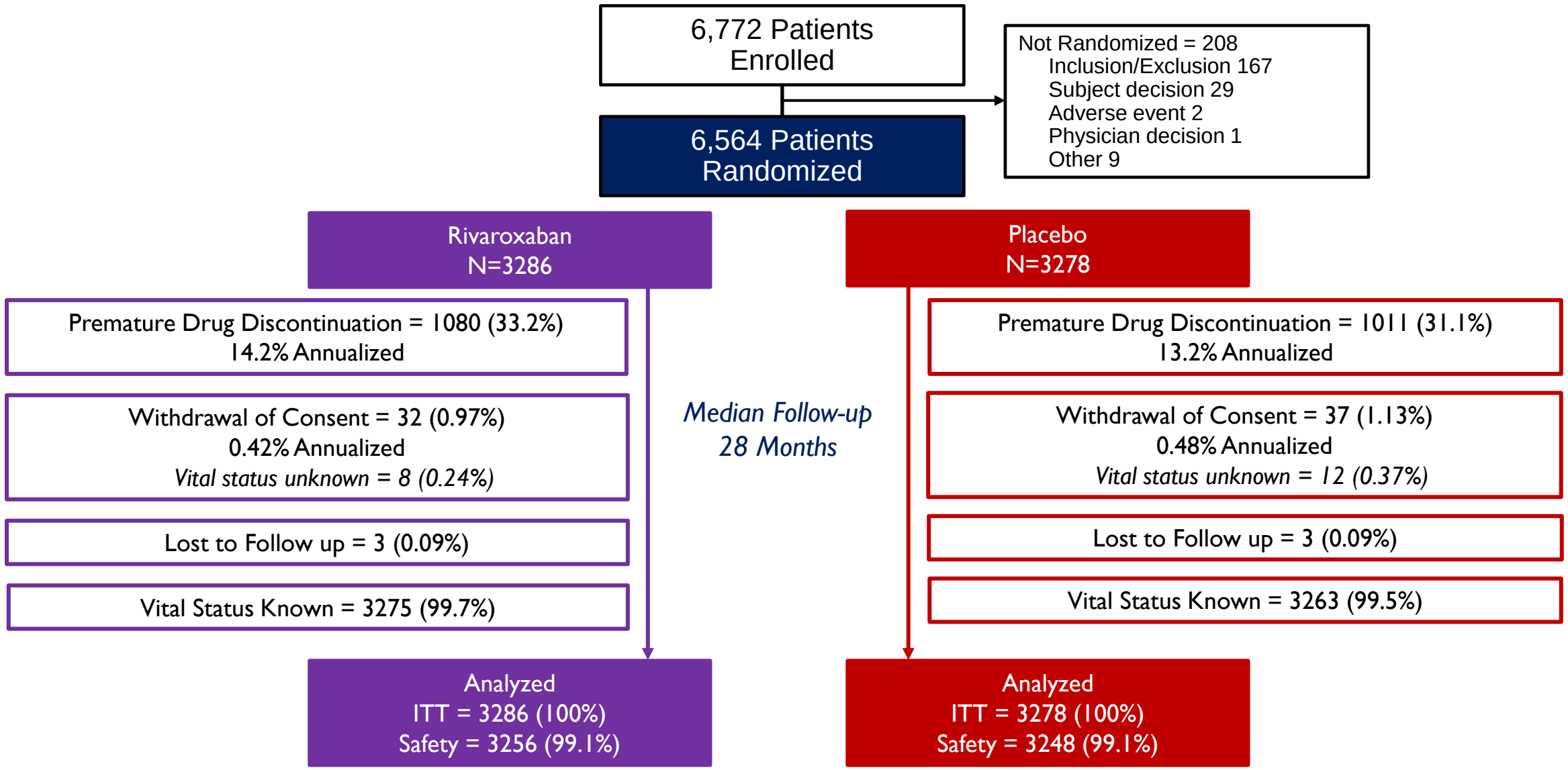
## Safety

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

OUTCOMES



Bonaca MP et al, NEJM 2020




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

Bonaca MP et al, NEJM 2020

| 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*

Bonaca MP et al, NEJM 2020

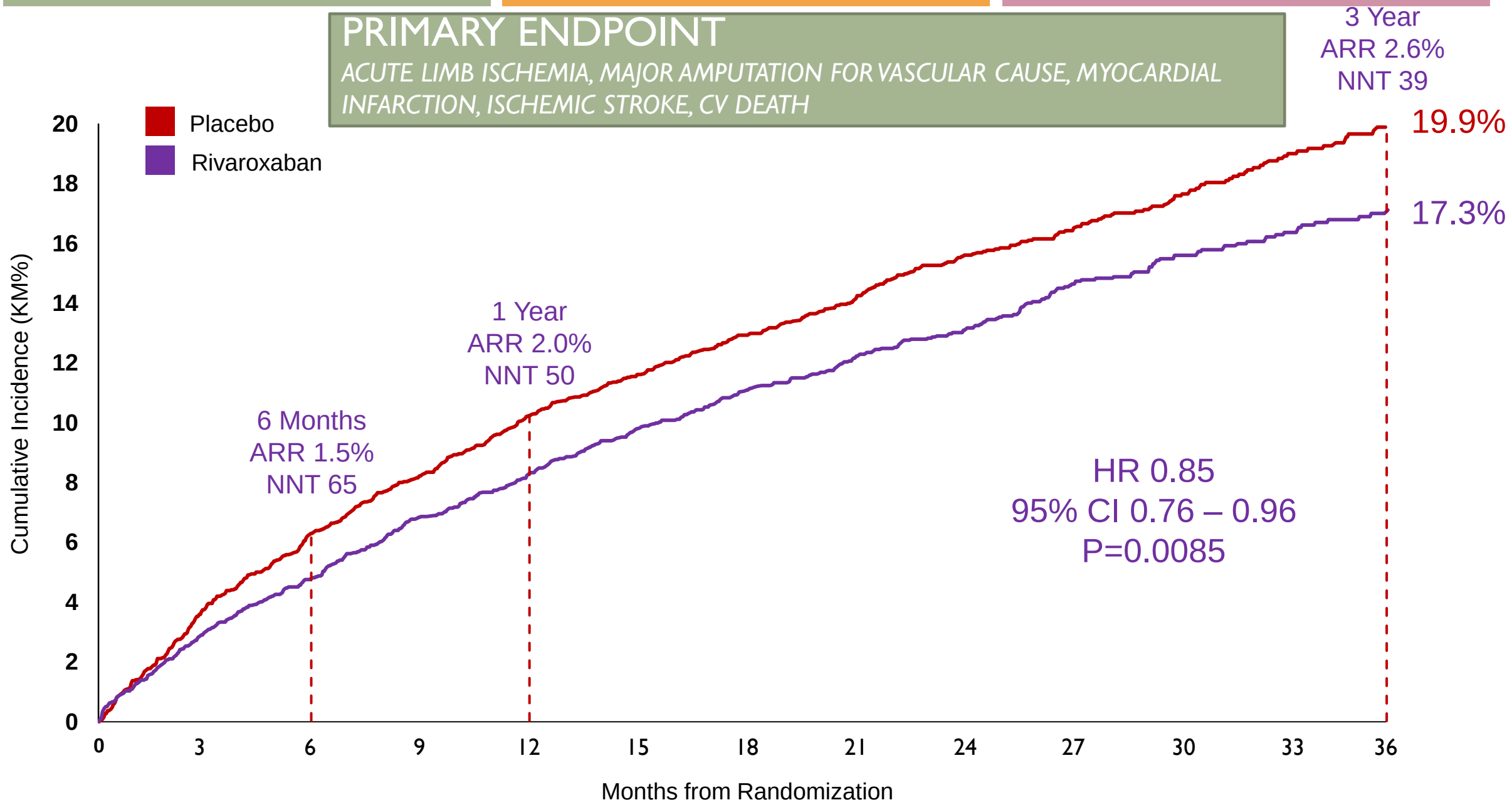
| Characteristics at Randomization | Rivaroxaban 2.5 mg twice daily + aspirin N=3286 % | Placebo + aspirin N=3278 % |
|---|---|---|
| *Prior Peripheral Artery Disease History* | | |
| History of Claudication | 95 | 96 |
| History of Revascularization | 36 | 35 |
| History of Amputation | 6 | 6 |
| Ankle 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*

Bonaca MP et al, NEJM 2020

# 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*

Bonaca MP et al, NEJM 2020

# 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) |

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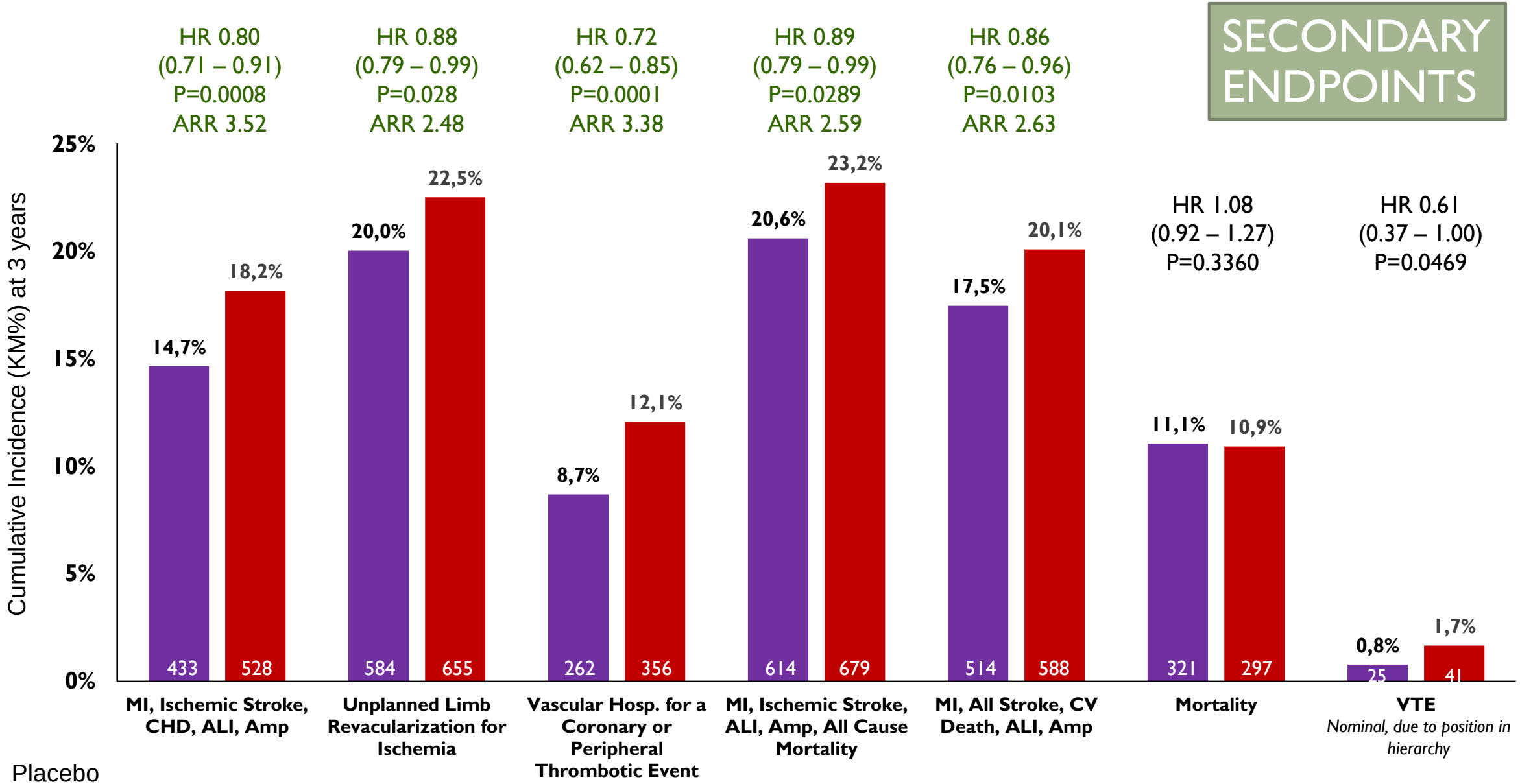
# SECONDARY ENDPOINTS




*Presented in order of hierarchy from left to right

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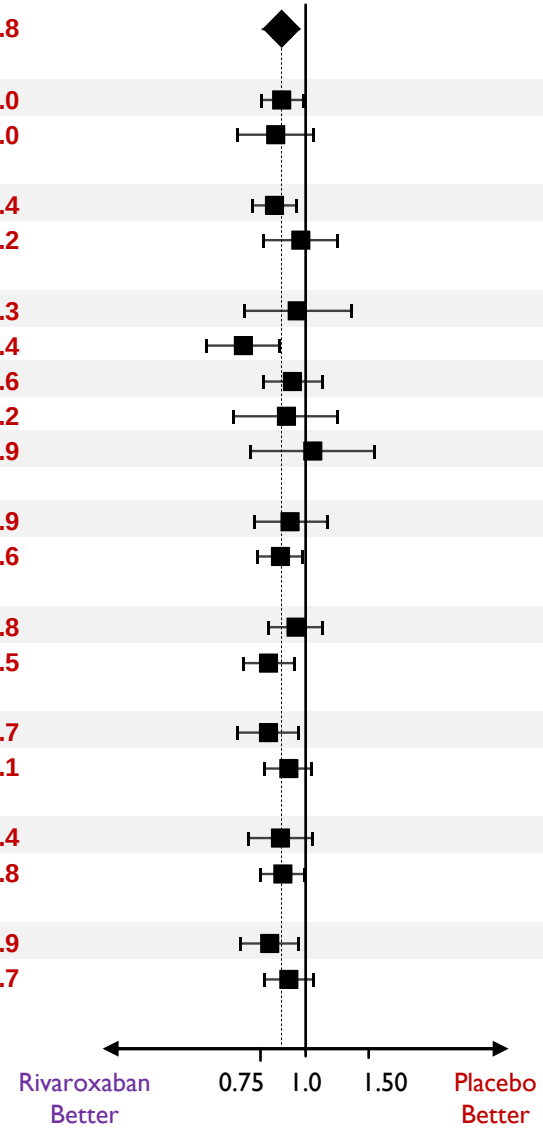
# PRIMARY EFFICACY OUTCOME IN SELECTED SUBGROUPS

| *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) | |

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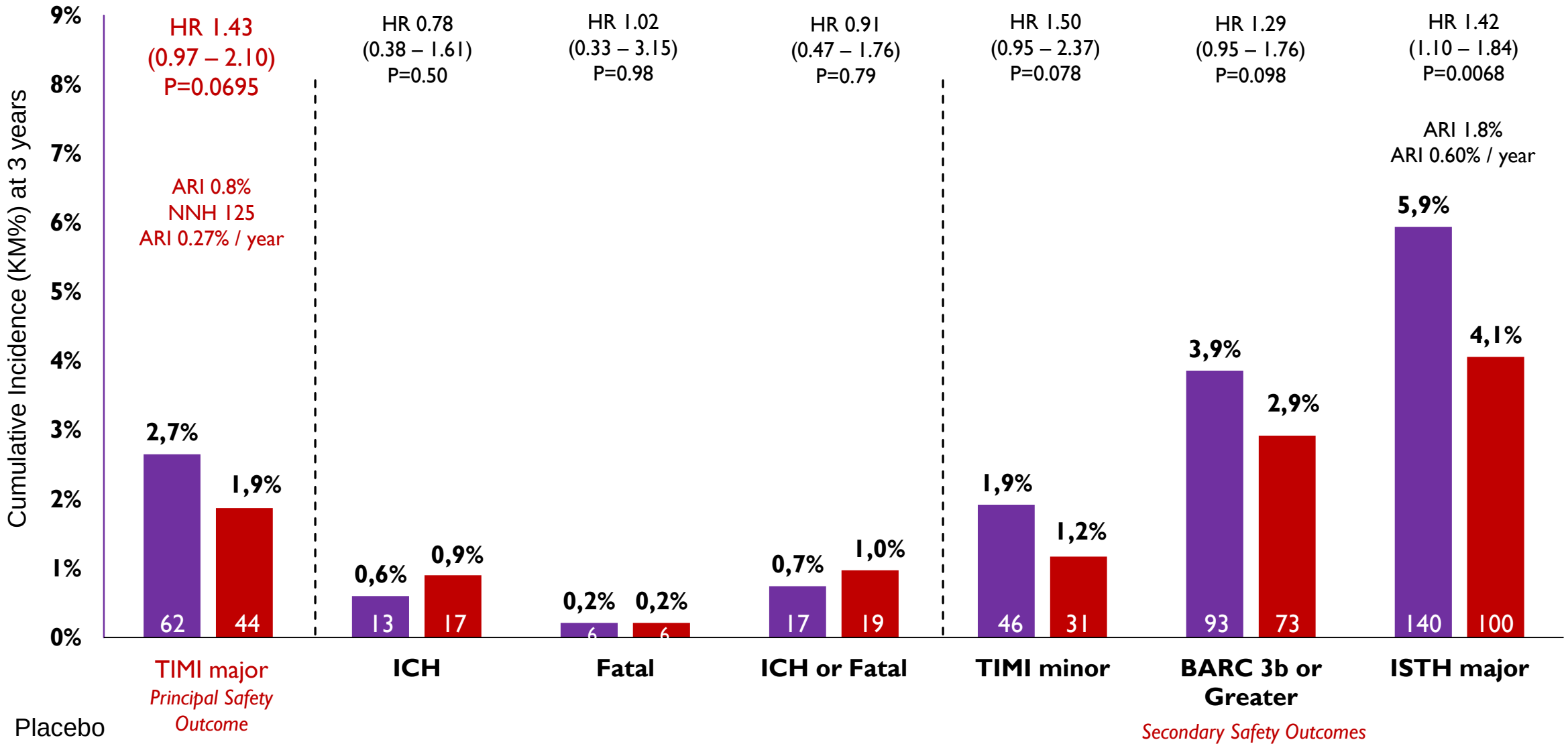
# SAFETY

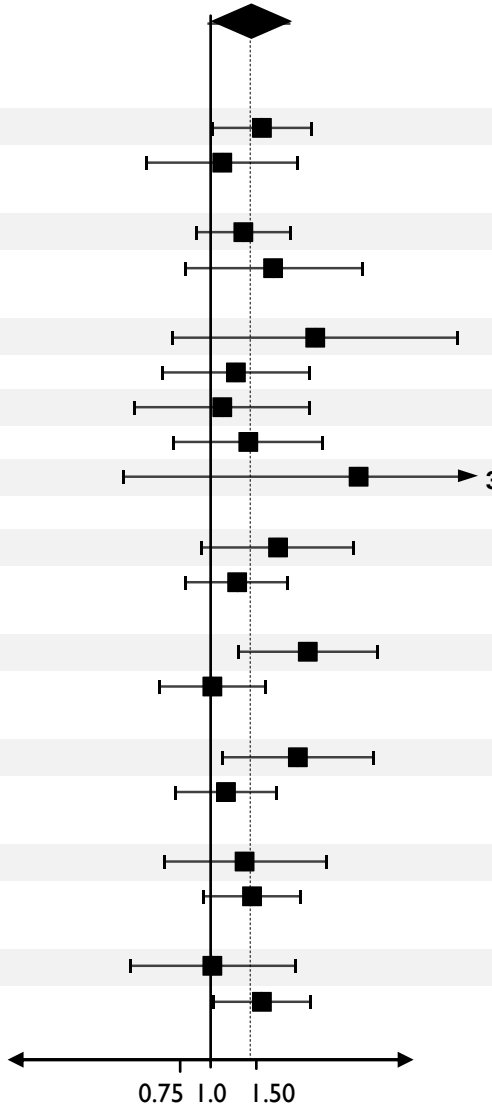



*ARI – absolute risk increase, NNH number needed to harm*

Bonaca MP et al, NEJM 2020

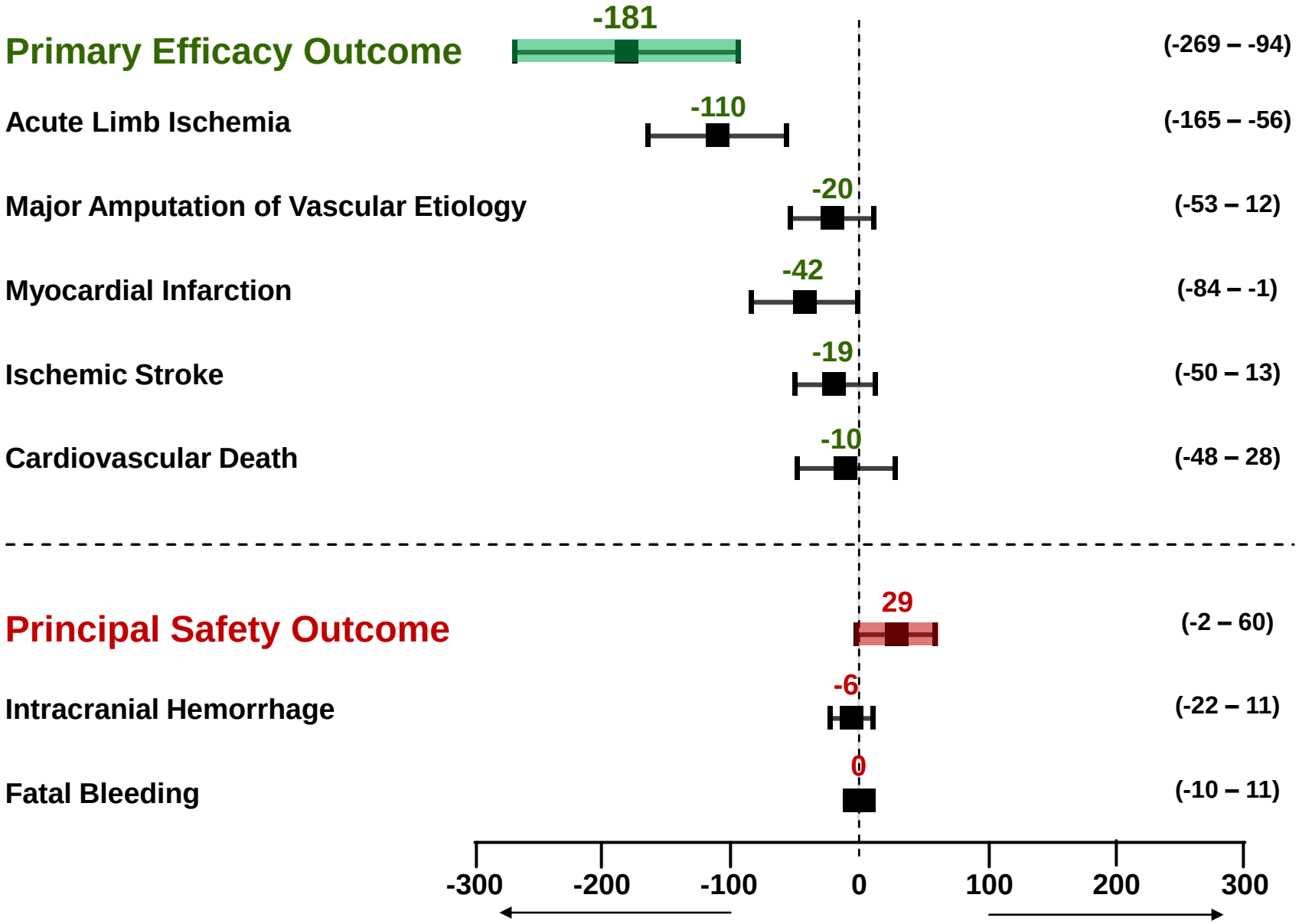
# PRINCIPAL SAFETY OUTCOME IN SELECTED SUBGROUPS

| *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) | |




Bonaca MP et al, NEJM 2020

# FIRST EVENTS PREVENTED / CAUSED FOR 10,000 PATIENTS TREATED* FOR 1 YEAR




*Efficacy and safety on-treatment*

Bonaca MP et al, NEJM 2020

# LIMITATIONS

- The percentage of patients who discontinued treatment prematurely, although relatively balanced between the groups, was higher than anticipated
  - Annualized discontinuation rates in the rivaroxaban group (approximately 14% per year) similar to those observed in other recent trials in stable atherosclerosis and lower than those in some trials in acute coronary syndrome.

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# 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: 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*

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# SUBANALYSIS WITH AND WITHOUT CLOPIDOGREL

# PAD & PROCEDURAL CHARACTERISTICS

| | Yes Clopidogrel N=3313 % | No Clopidogrel N=3234 % | P-value |
|---|---|---|---|
| ***PAD Indication and History*** | | | |
| **Indication: Claudication** | **80** | **73** | 0.7826 |
| **Indication: Critical limb threatening ischemia** | **20** | **27** | **<0.0001** |
| **Prior limb revascularization** | **40** | **31** | **<0.0001** |
| **Prior major amputation** | **1.2** | **0.8** | 0.1287 |
| **ABI at Screening (Median – IQR)** | **0.58 (0.46-0.70)** | **0.52 (0.40-0.64)** | **< 0.0001** |
| ***Type of Revascularization*** | | | **<0.0001** |
| **Surgical** | **9** | **58** | |
| **Endovascular** | **91** | **42** | |

Hiatt, ACC 2020

# BASELINE CHARACTERISTICS

| Characteristic at Randomization | Yes Clopidogrel N=3313 % | No Clopidogrel N=3234 % | P-value |
|---|---|---|---|
| Age, years (Median-IQR) | 67 (61-73) | 67 (61-73) | 0.3519 |
| Female n | 28 | 24 | <0.0001 |
| White Caucasian | 80 | 82 | <0.0001 |
| Hypertension | 82 | 80 | 0.0265 |
| Diabetes Mellitus (type 2) | 43 | 34 | <0.0001 |
| Hyperlipidemia | 65 | 55 | <0.0001 |
| Current smoking | 34 | 35 | 0.1013 |
| COPD | 10 | 12 | 0.0477 |
| eGFR < 60 ml/min/1.73m$^2$ | 22 | 19 | 0.0028 |
| Coronary artery disease | 34 | 29 | <0.0001 |
| Prior CABG | 9 | 7 | 0.0399 |
| Prior coronary intervention | 16 | 10 | <0.0001 |
| Carotid stenosis ≥ 50% | 9 | 7 | 0.0035 |

Hiatt, ACC 2020

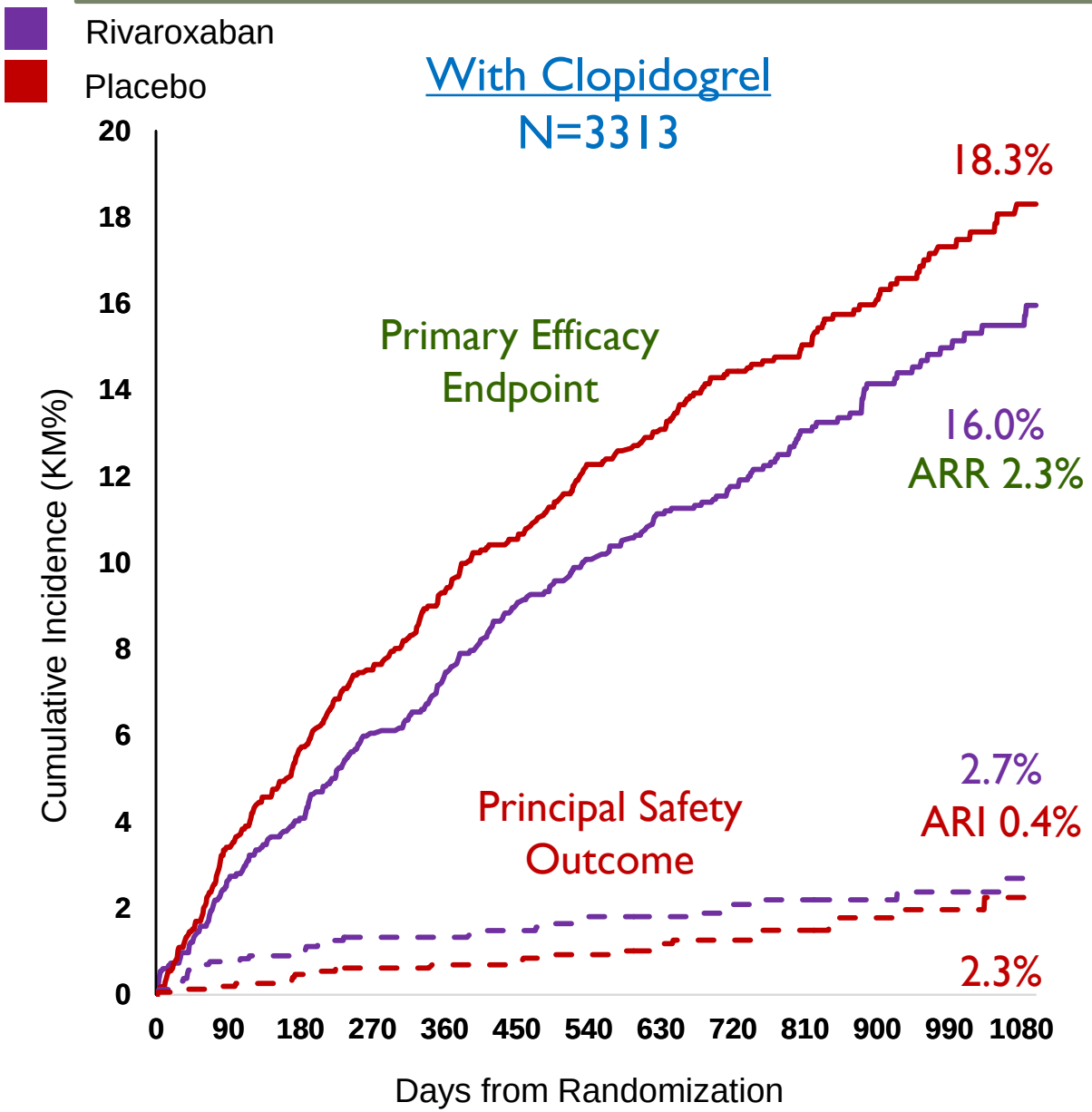
# CLOPIDOGREL USE

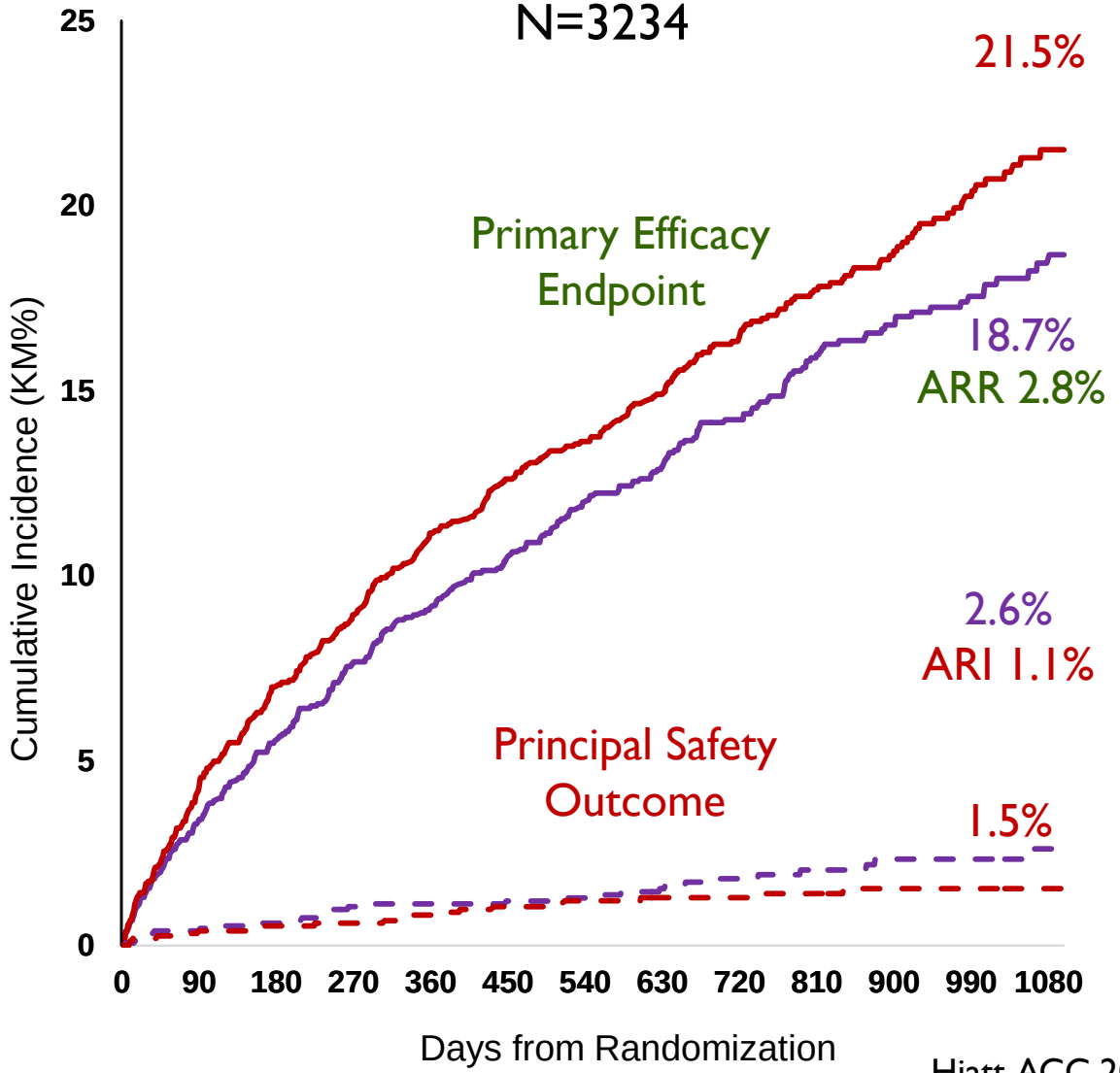
| | Rivaroxaban 2.5 mg twice daily + aspirin N=3286 % | Placebo + aspirin N=3278 % | P-value |
|---|---|---|---|
| **Clopidogrel use at randomization** | 50.5 | 50.5 | 0.7926 |
| | | | |
| **Median duration days (IQR)** | 29.0 (25.0-49.5) | 29.0 (26.0-50.0) | 0.0700 |
| **≤ 30 days** | 59.6 | 56.5 | |
| **31- 90 days** | 29.0 | 31.7 | |
| **91-180 days** | 6.3 | 6.3 | |
| **Median duration days (IQR) for drug-coated products*** | 31.0 (27.0-59.0) | 32.0 (27.5-59.0) | 0.9311 |

*38% of endovascular procedures with clopidogrel were for drug coated products

Hiatt, ACC 2020

# RISK AND BENEFIT OF RIVAROXABAN WITH AND WITHOUT CLOPIDOGREL

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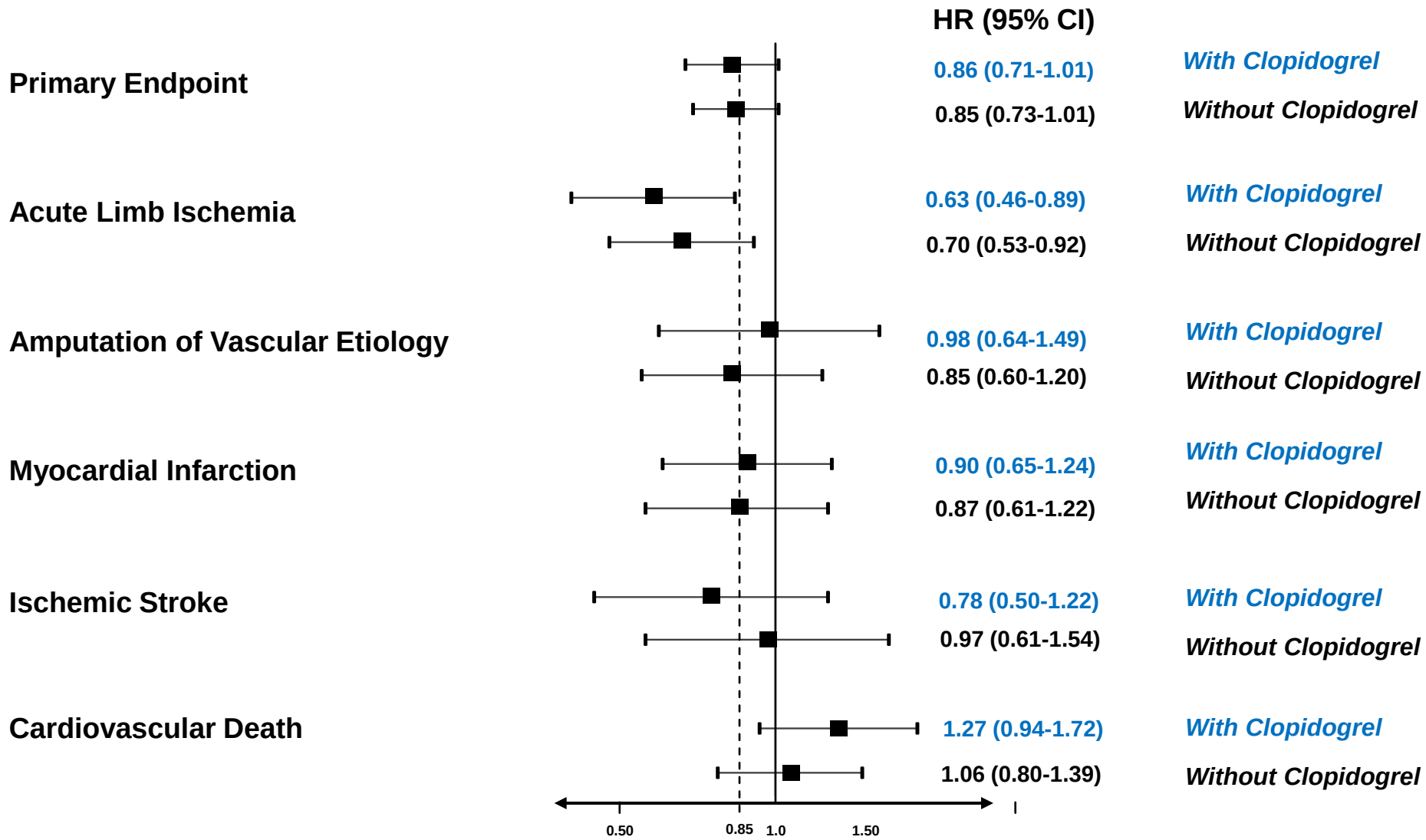
# Benefit of Rivaroxaban for the Primary Outcome and Components with and without Background Clopidogrel

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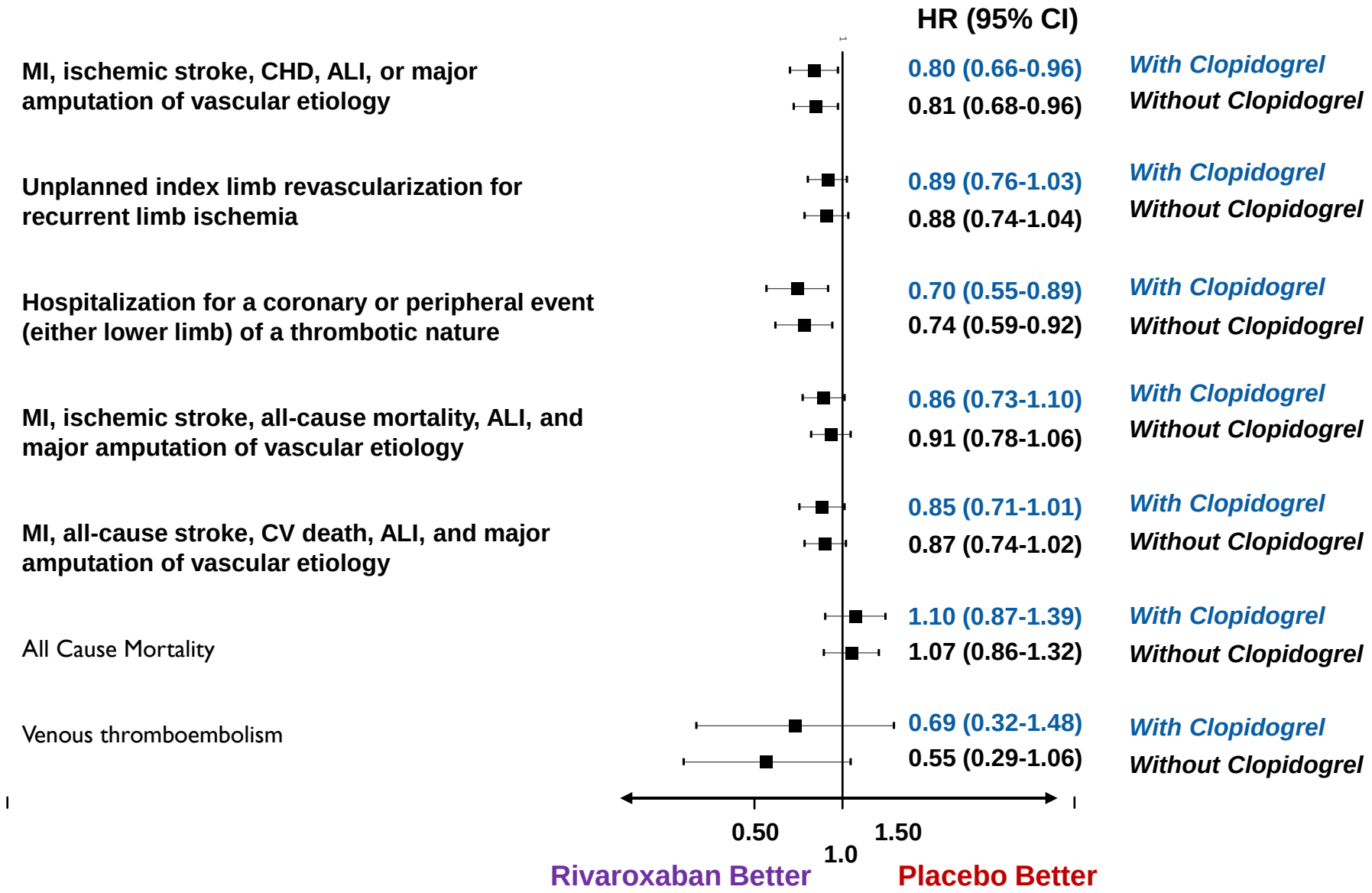
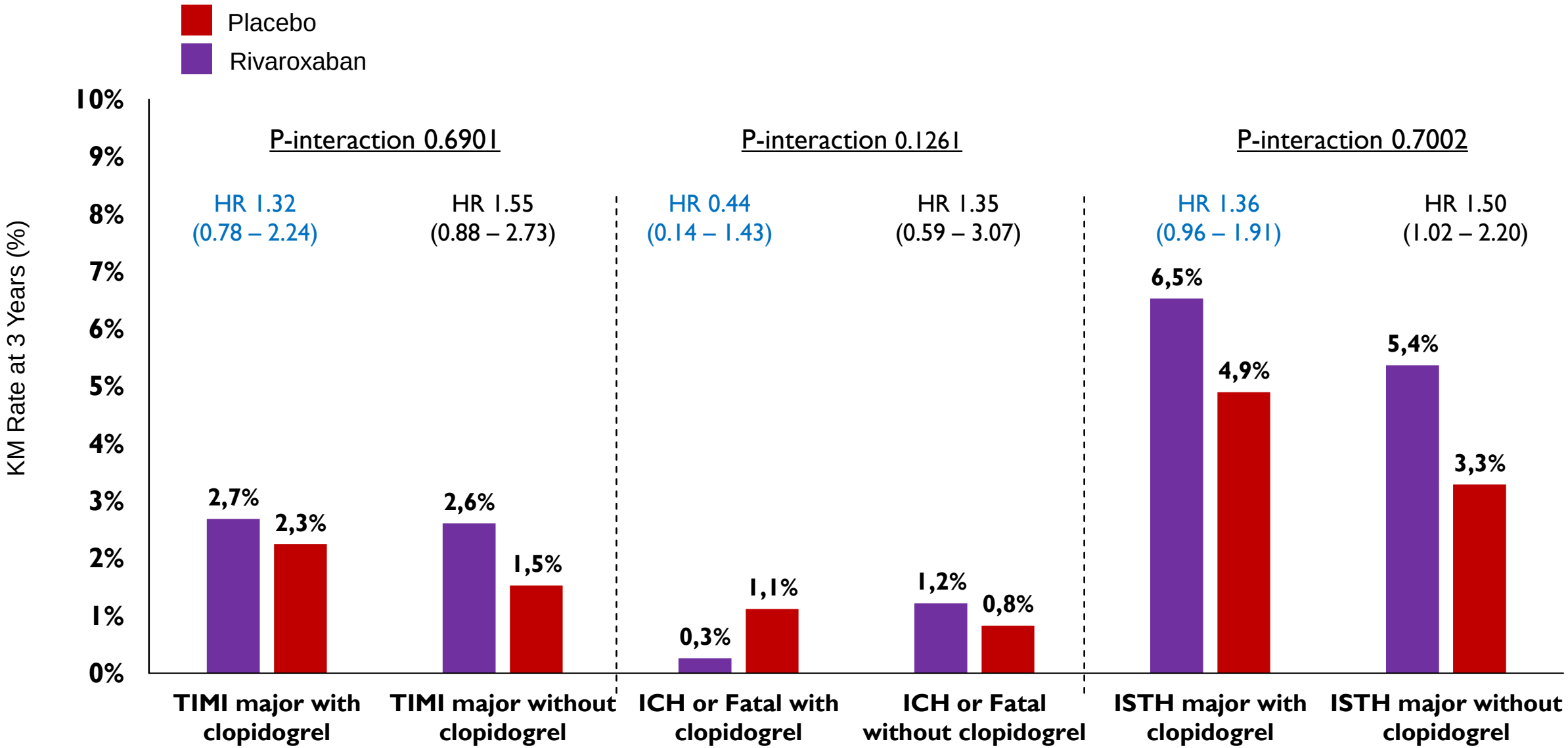
# Benefit of Rivaroxaban for Secondary Outcome with and without Background Clopidogrel




Hiatt, ACC 2020

# SAFETY OF RIVAROXABAN WITH AND WITHOUT CLOPIDOGREL

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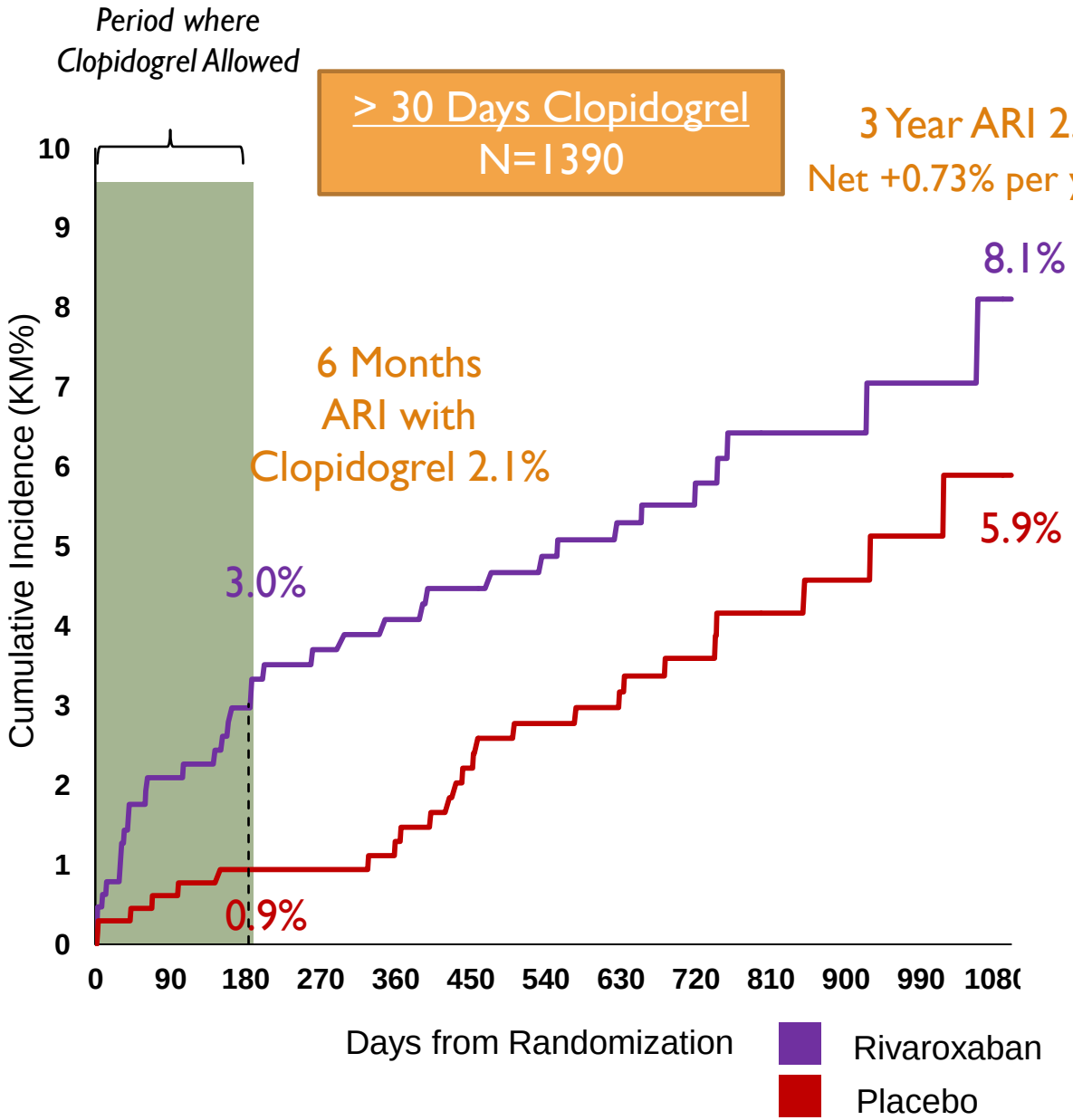
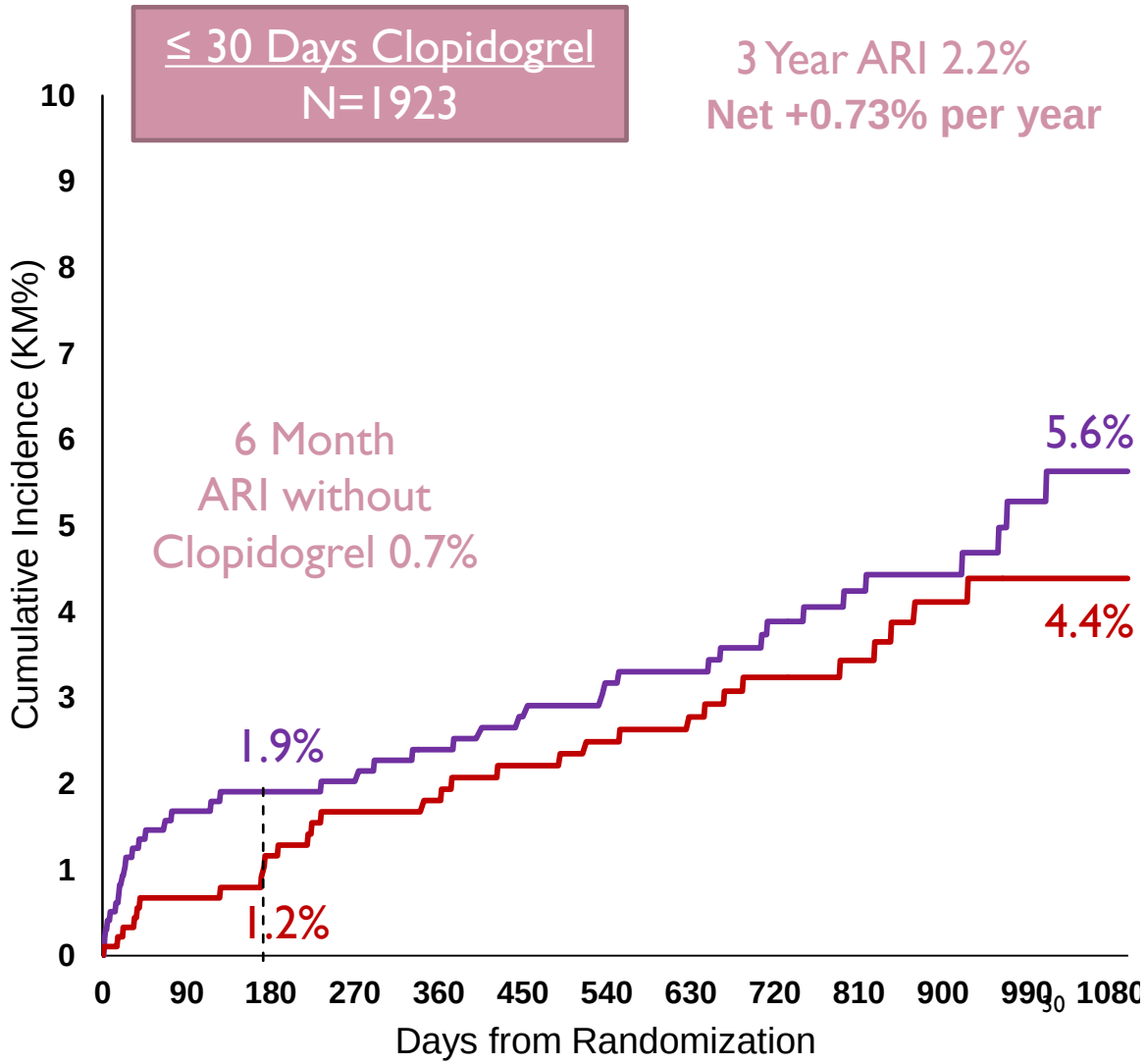
# ISTH MAJOR BLEEDING BY CLOPIDOGREL DURATION




ARI = Absolute Risk Increase

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# SUMMARY

- In patients with symptomatic PAD undergoing revascularization:
  - The benefit of rivaroxaban plus aspirin versus aspirin alone is consistent regardless of background clopidogrel
    - *Primary efficacy endpoint HR ~0.85 with rivaroxaban regardless of clopidogrel with NNT < 50 with or without clopidogrel*
  - The safety of rivaroxaban plus aspirin versus aspirin alone is consistent regardless of background clopidogrel
    - *Principal safety outcome TIMI major bleeding HR ~1.3-1.5 regardless of clopidogrel with NNH > 90 with or without clopidogrel*
  - Clopidogrel exposure was associated with higher rates of bleeding overall, particularly with longer durations (e.g. > 30 days)

Hiatt, ACC 2020

# CONCLUSIONS & PERSPECTIVE

## In patients with symptomatic PAD undergoing revascularization:

- The benefit of DAPT is uncertain, with the only RCT in surgical bypass showing no benefit and significantly increased bleeding
- Rivaroxaban added to aspirin significantly reduces limb and cardiovascular risk with consistent benefits regardless of clopidogrel
- The safety and risk/benefit of rivaroxaban plus aspirin are consistent regardless of background clopidogrel
- In patients receiving rivaroxaban, the addition of clopidogrel as a third agent, is associated with higher rates of bleeding during exposure
- *More bleeding with background clopidogrel, even if not severe by adjudication, may be associated with broad consequences, including discontinuation of therapies. In the absence of clear benefit, clopidogrel exposure along with aspirin and rivaroxaban should be minimized or avoided to reduce this risk*

Hiatt, ACC 2020