



Consistent Benefit of Rivaroxaban Early and Late after Lower Extremity Revascularization

Marc P. Bonaca MD MPH, Eike Sebastian Debus MD, PhD, Manesh R. Patel, MD, Mark R. Nehler, MD, Sonia S. Anand, MD, Connie N. Hess, MD, MHS, Judith Hsia MD, Michael Szarek, Jerrod Nelms, Eva Muehlhofer, MD, Lloyd P. Haskell, MD, MBA, Scott D. Berkowitz, MD, Rupert M. Bauersachs, MD

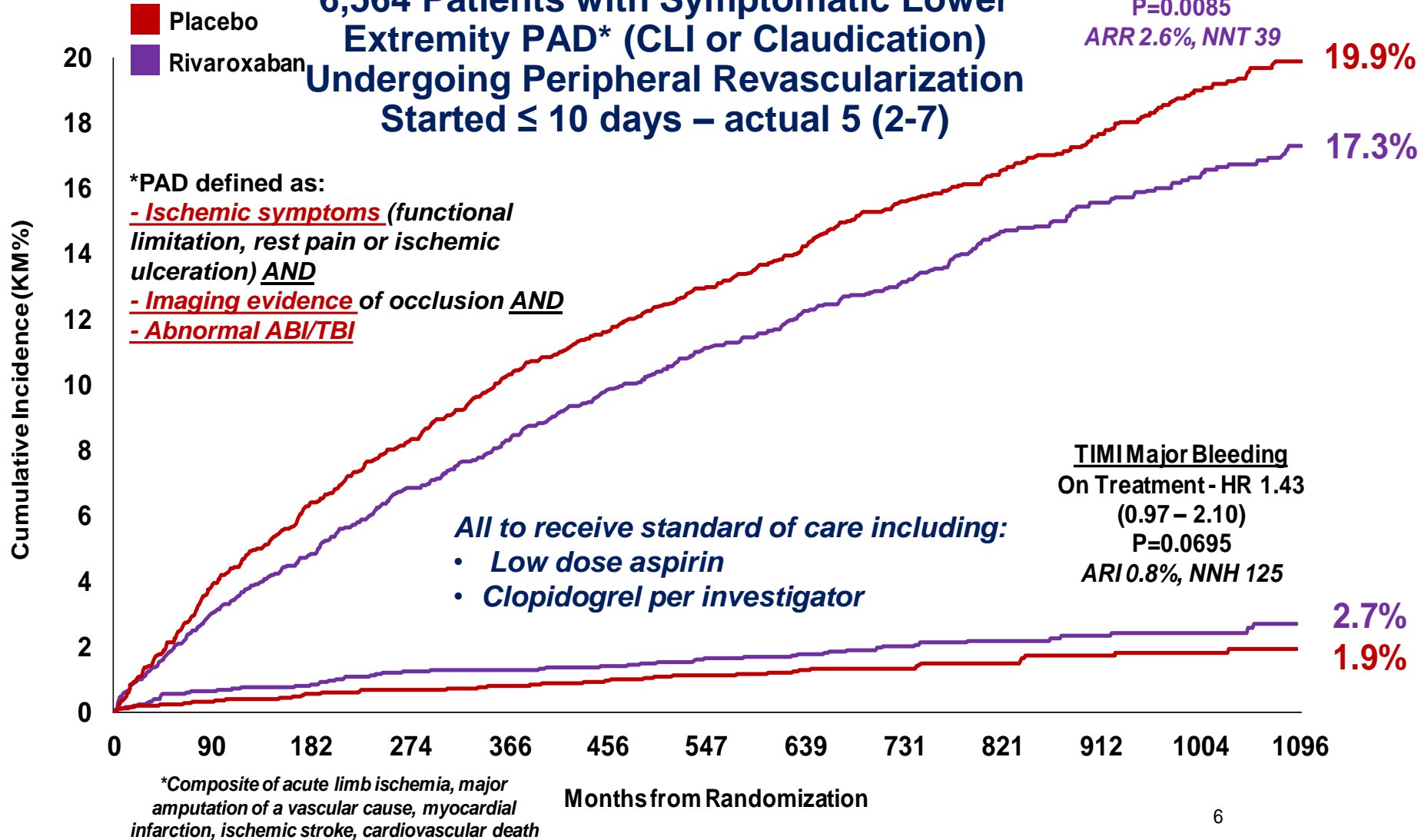
**American College of Cardiology
Scientific Sessions – March 2023**

Disclosures

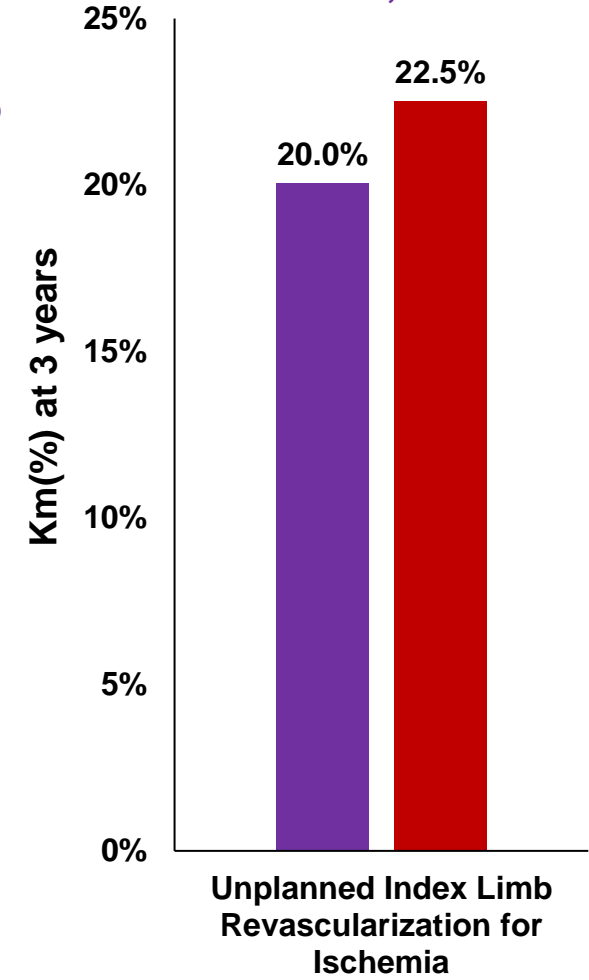
- **VOYAGER PAD funded through grants from Bayer and Janssen to CPC Clinical Research**
- **Dr. Bonaca is the Executive Director of CPC, a non-profit academic research organization affiliated with the University of Colorado, that receives research grant/consulting funding from: Abbott, Agios, Alexion Pharma, Anylam, Amgen, Angionetics, ARCA Biopharma, Array, AstraZeneca, Atentiv, Audentes, Bayer, Better Therapeutics, Brigham and Women's Hospital, Bristol-Myers Squibb, Cardiol Therapeutics, CellResearch, Cook Medical, Cook, CSL Behring, Eidos Therapeutics, EP Trading Co, Esperion Therapeutics, EverlyWell, Faraday, Fortress Biotech, HDL Therapeutics, Heartflow, Hummingbird Bioscience, Insmed, Janssen, Kowa Research, Lexicon, Merck, Medtronic, Moderna, Novate Medical, NovoNordisk, Pfizer, PhaseBio, PPD Development, Prairie Education and Research, Prothena Ciosciences, Regeneron, Regio Biosciences, Sanifit Therapeutics, Sanofi, Smith and Nephew, Stealth BioTherapeutics, University of Colorado, Worldwide Clinical Trials, Wraser, Yale Cardiovascular Research Group. Dr. Bonaca also reports stock in Medtronic and Pfizer and consulting fees from Audentes.**

VOYAGER PAD Primary Results

6,564 Patients with Symptomatic Lower Extremity PAD* (CLI or Claudication) Undergoing Peripheral Revascularization Started ≤ 10 days – actual 5 (2-7)



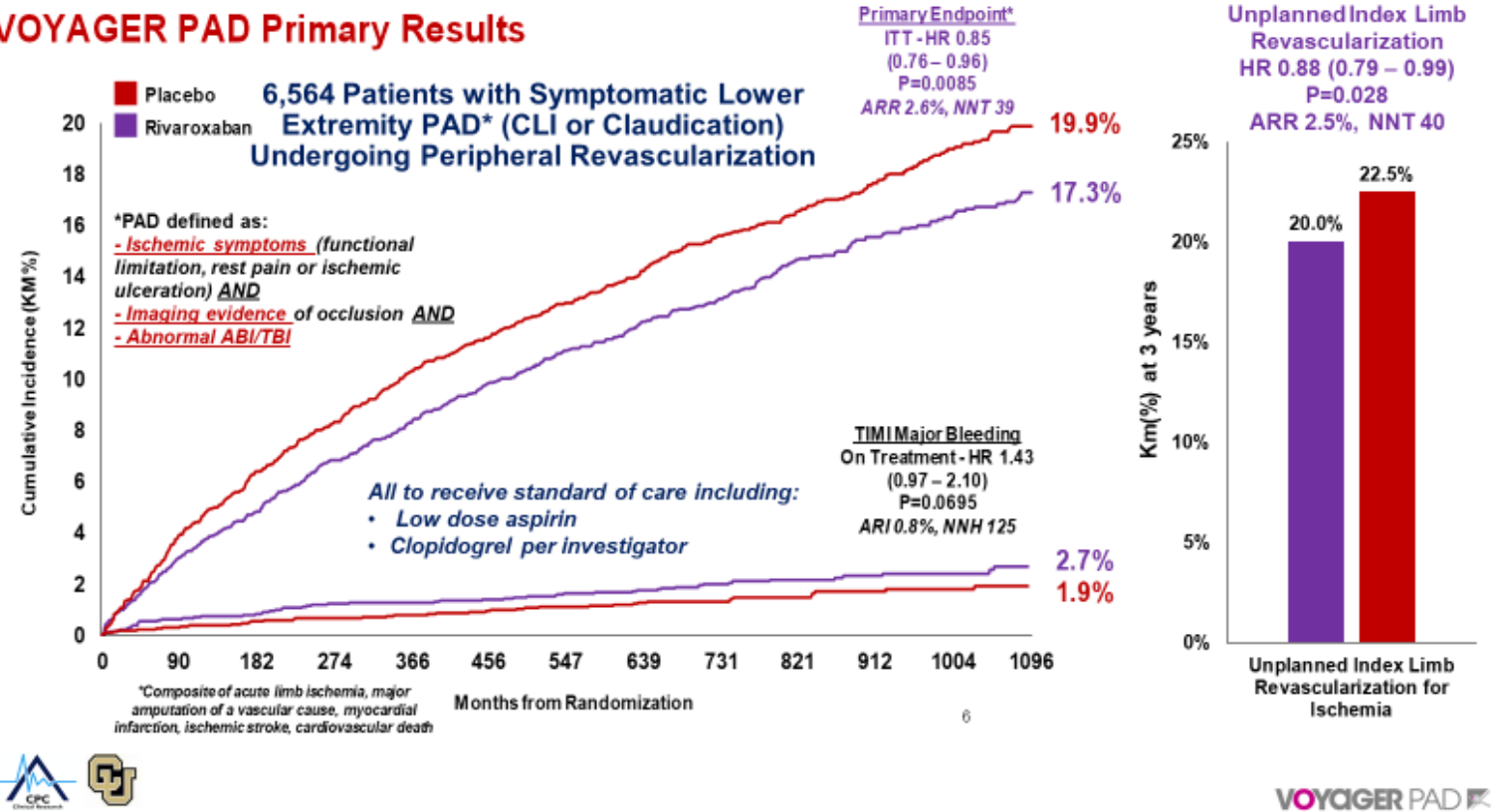
Unplanned Index Limb Revascularization
 HR 0.88 (0.79 – 0.99)
 P=0.028
 ARR 2.5%, NNT 40



Questions in Implementation

- How early to start?
- Transition after DAPT at 30 or 90 days?
- How long to continue?
- Is the benefit consistent early and late after LER?

VOYAGER PAD Primary Results



Objective

- *To evaluate whether the benefit and risk of rivaroxaban is consistent early and late after lower extremity revascularization*

Methods

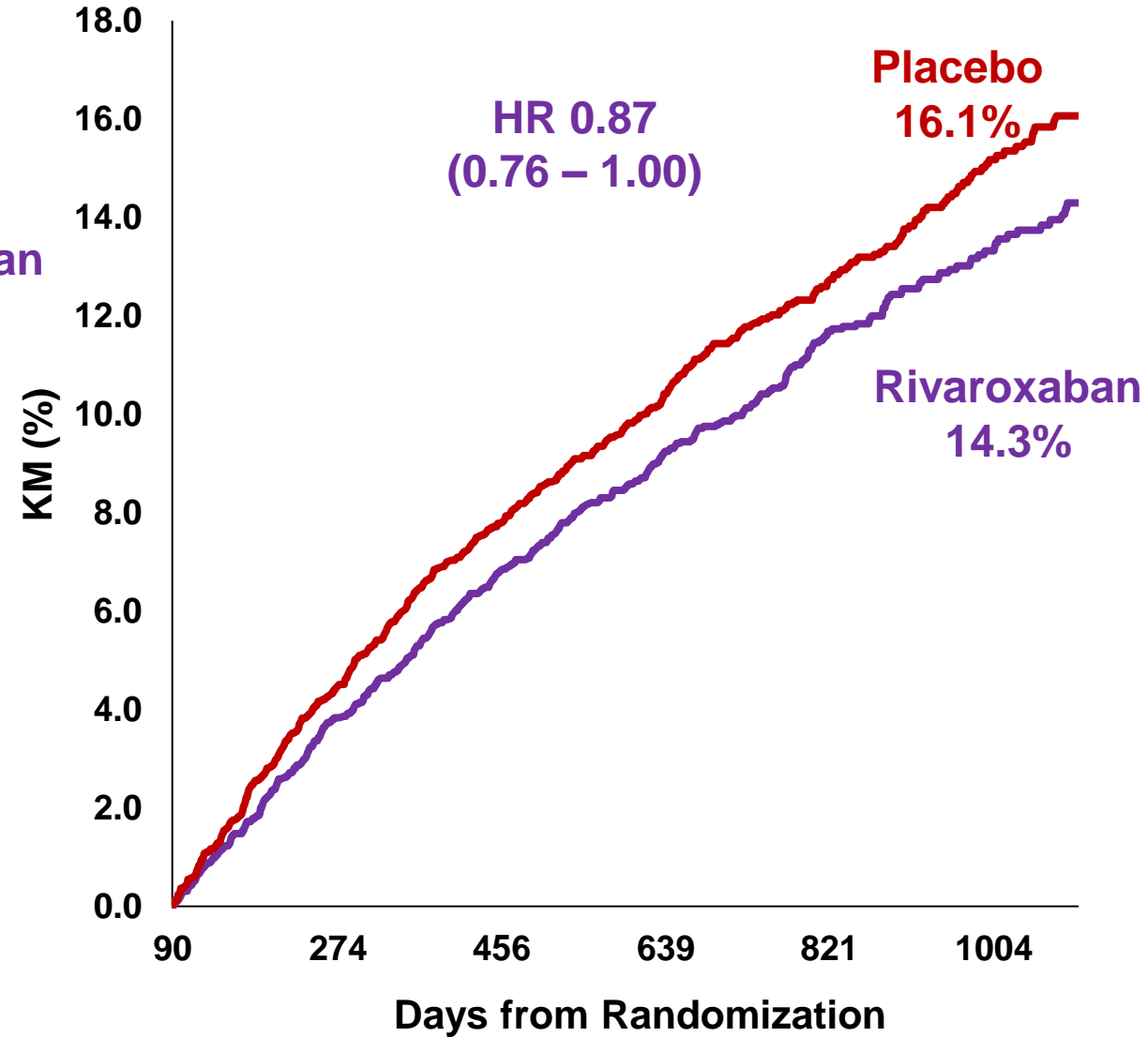
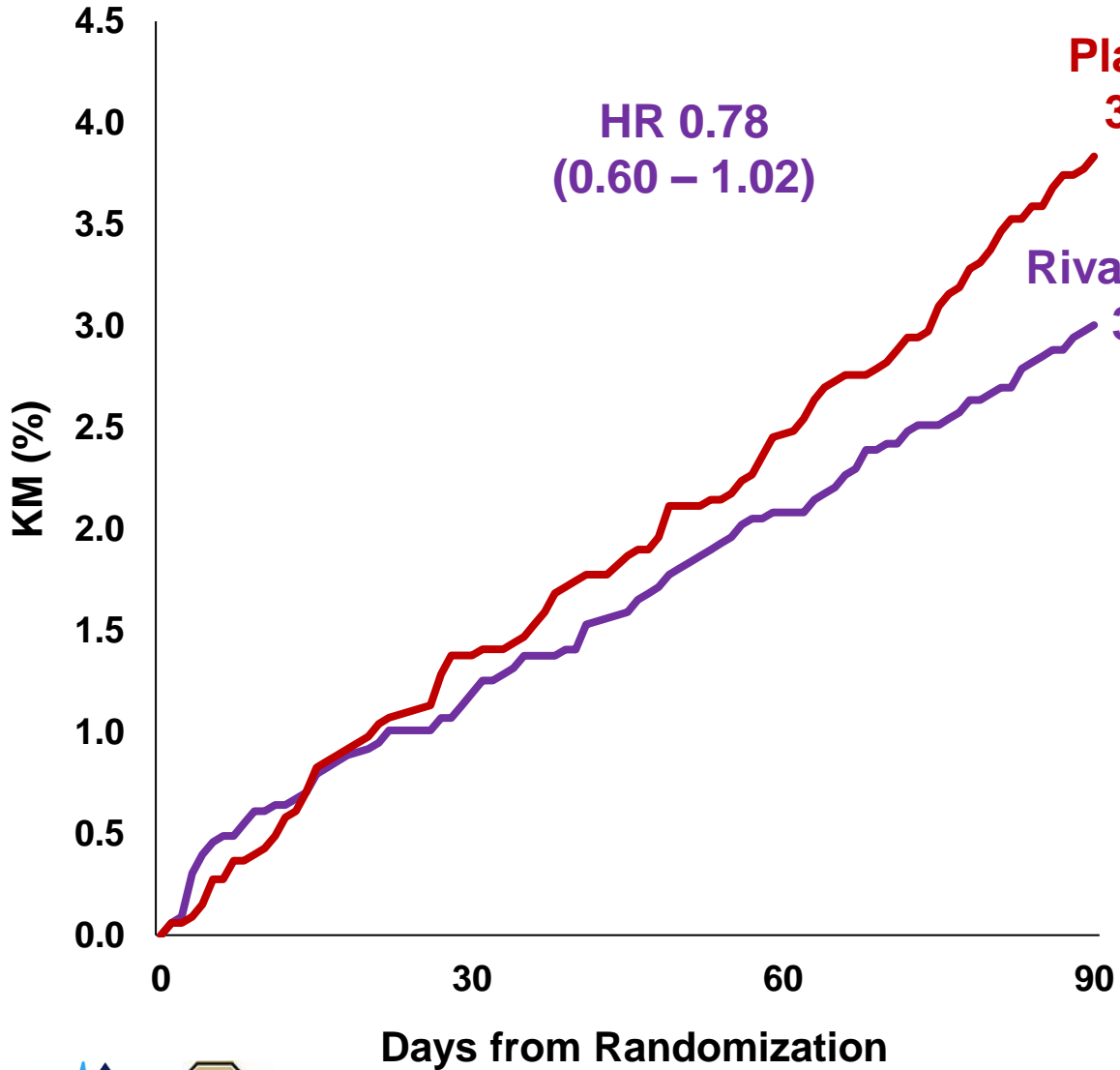
- **Prespecified analysis (Landmark) including primary & secondary outcomes overall and within the clopidogrel subgroup**
- **Outcomes adjudicated by a blinded CEC**
- **Primary analysis at 90 days (acute post revascularization period) and majority of clopidogrel use was completed by 90 days**
- **Efficacy – Intention to Treat**
 - **Primary composite of acute limb ischemia, major amputation of a vascular etiology, MI, ischemic stroke or CV death**
 - **Major adverse limb events – acute limb ischemia or major amputation of a vascular etiology**
 - **Acute limb ischemia**
- **Safety – On Treatment**
 - **Principal safety: TIMI major bleeding – safety scope/population**
- **Prespecified net clinical outcome – acute limb ischemia, major amputation of a vascular etiology, MI, ischemic stroke, CV death, or TIMI major bleeding in safety scope/population**

Primary Endpoint

First 90 Days

P vs. constant HR 0.47

From day 91 through 3 Years

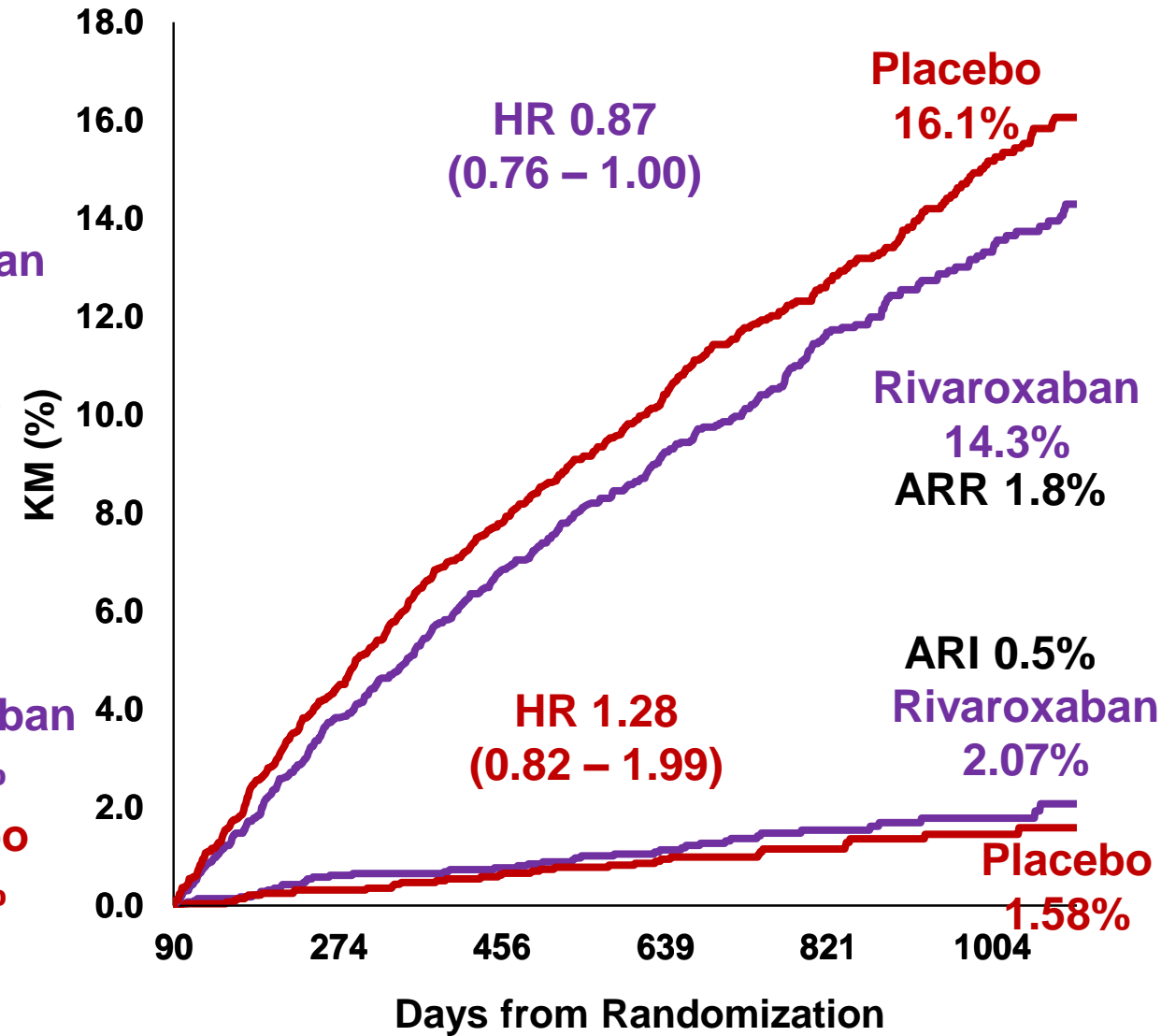
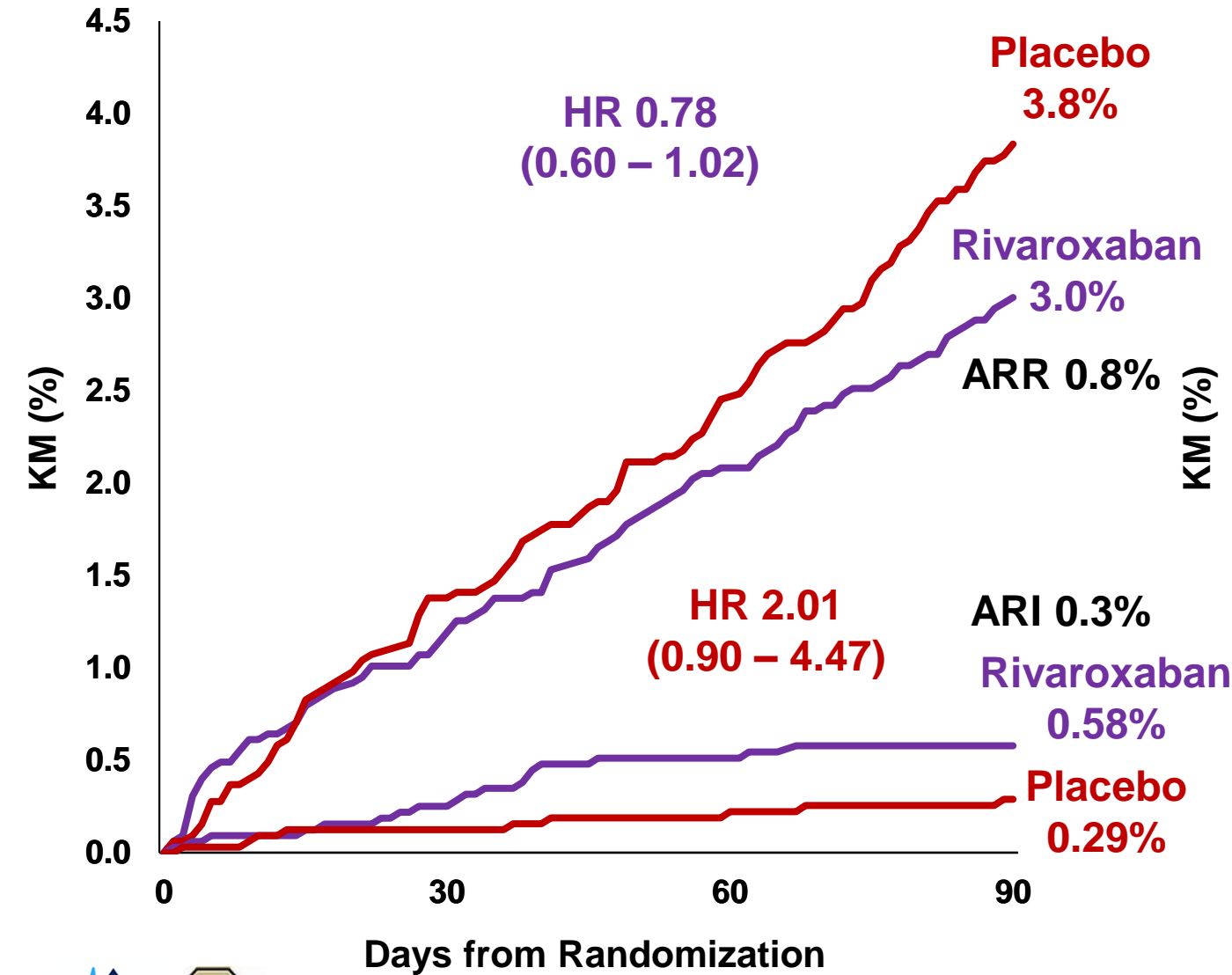


Primary Endpoint & TIMI major Bleeding

First 90 Days

P vs. constant HR 0.47

From day 91 through 3 Years

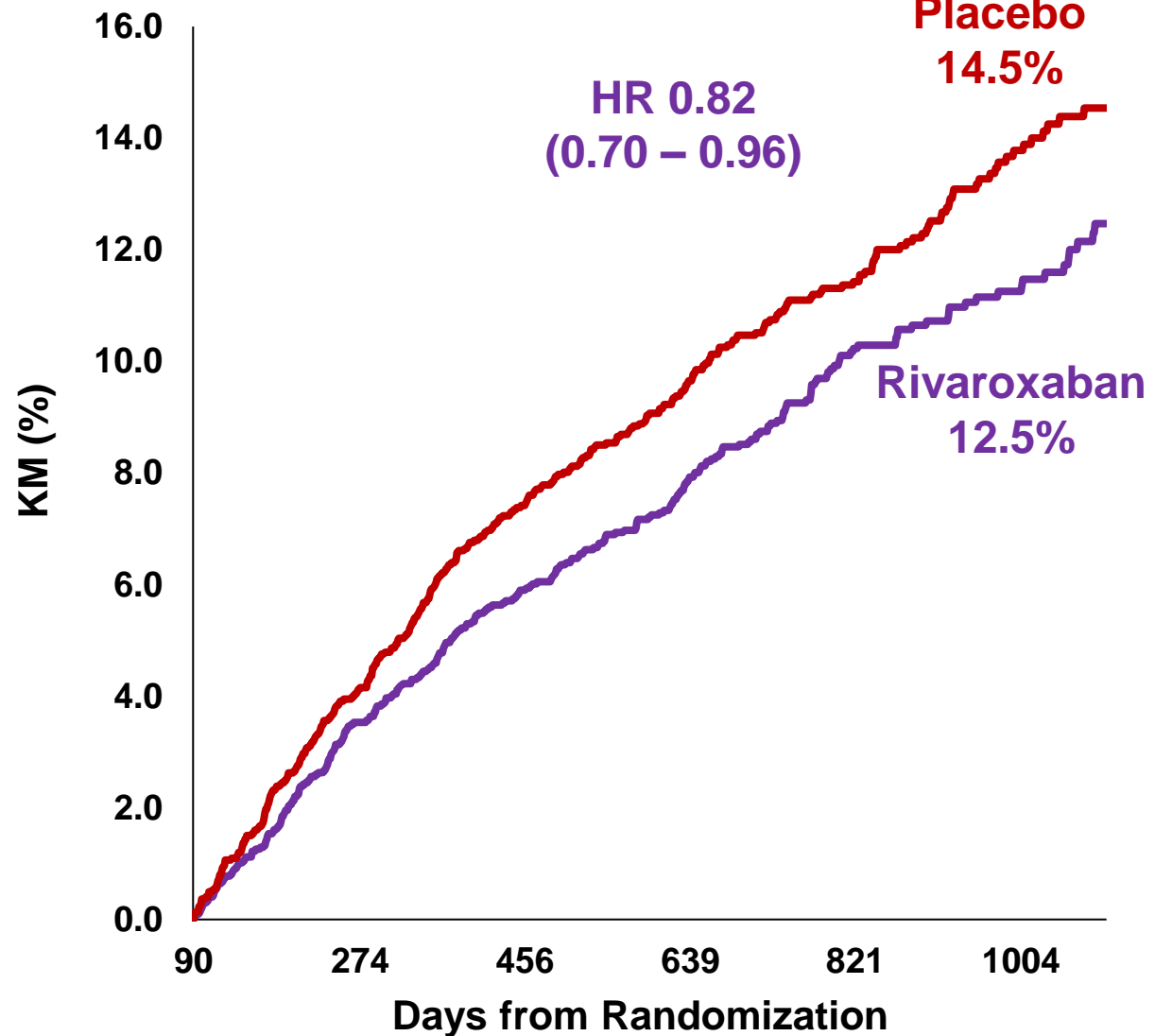
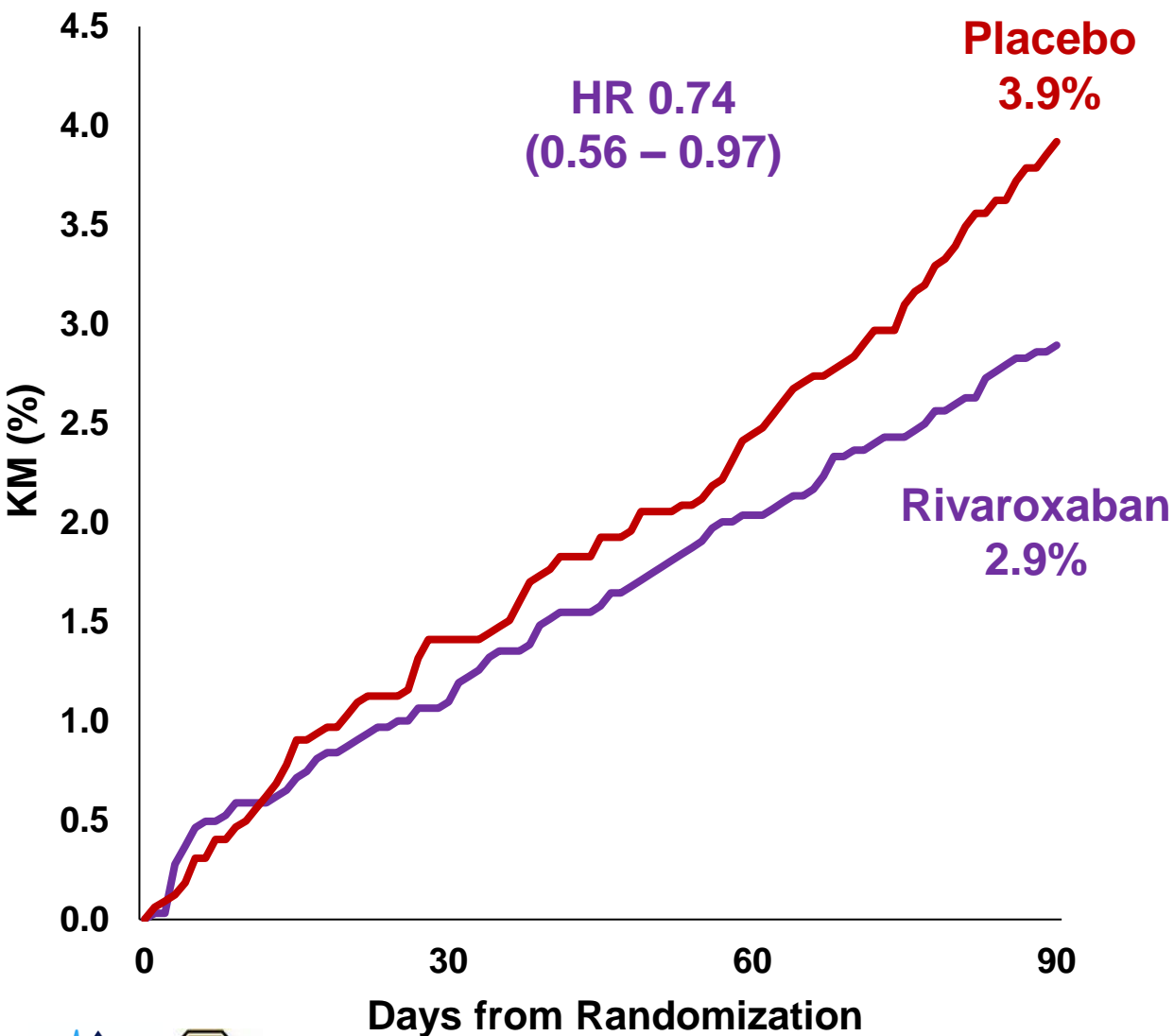


Net Clinical Benefit*

P vs. Constant HR 0.52
Overall HR 0.80
(0.70 – 0.92, p=0.0012)

First 90 Days

From day 91 through 3 Years



*MI, ischemic stroke, ALI, major vascular amputation, CV death, TIMI major bleeding 8

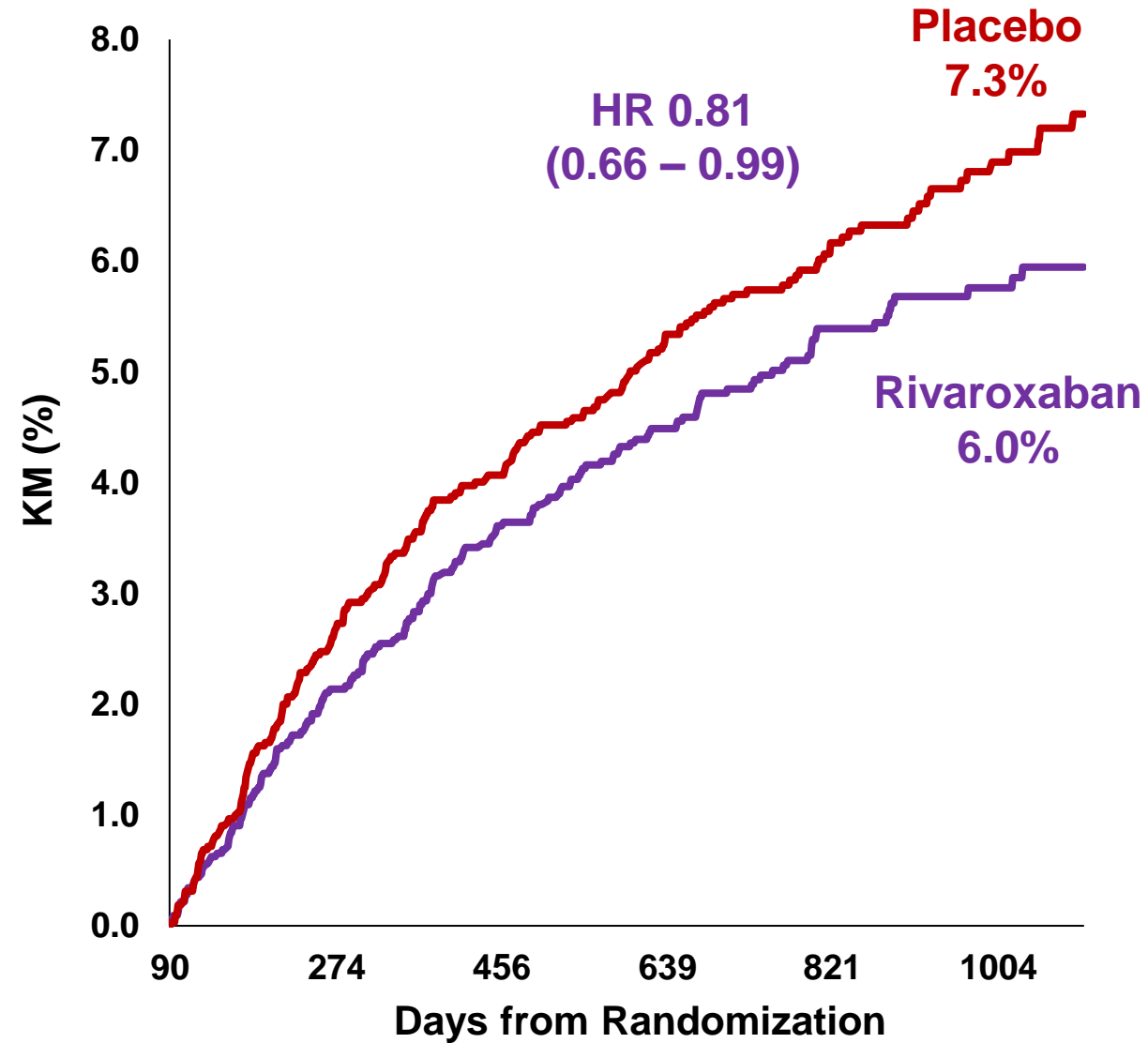
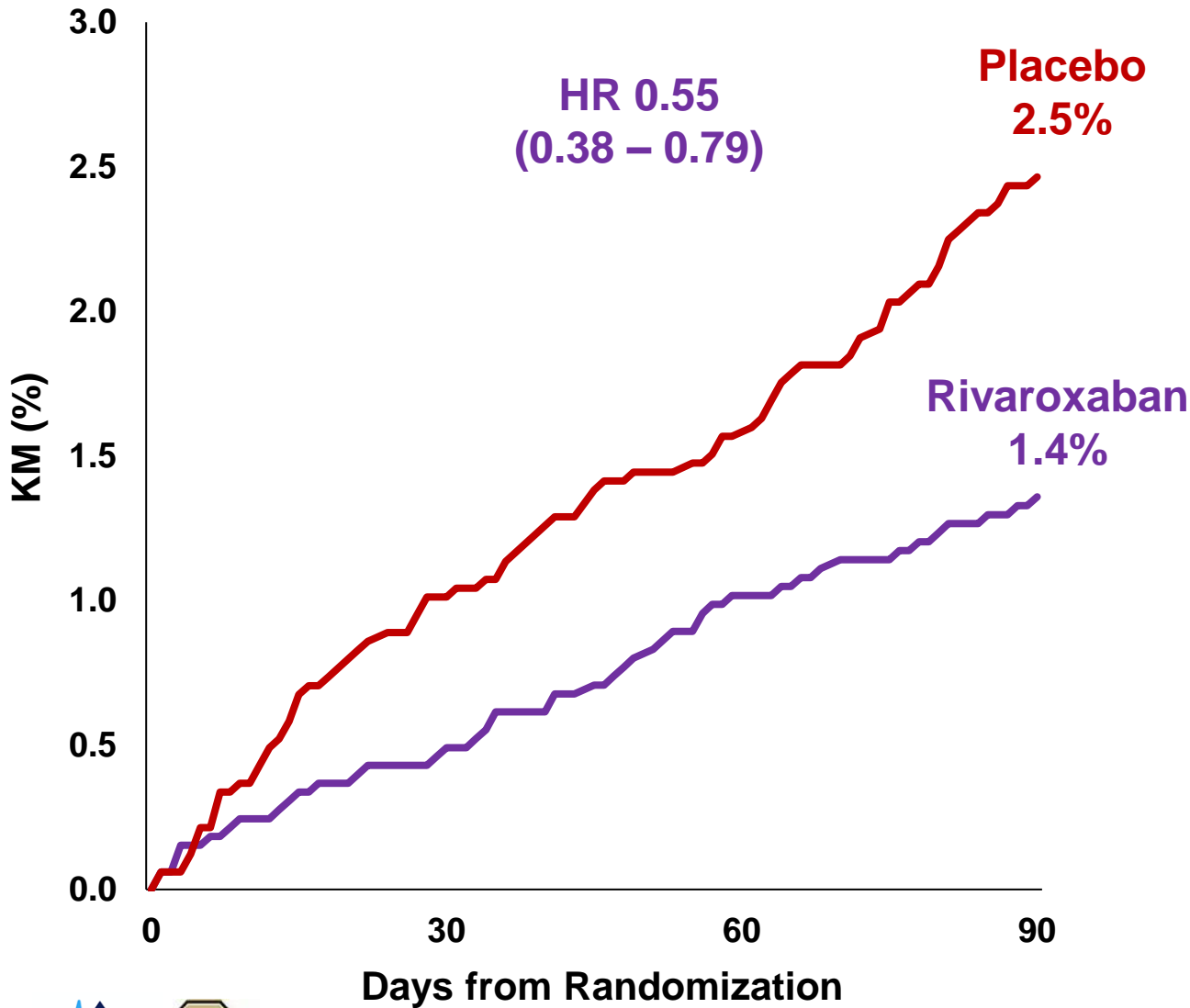


MALE – Acute Limb Ischemia or Major Vascular Amputation

P vs. constant HR 0.06

First 90 Days

From day 91 through 3 Years

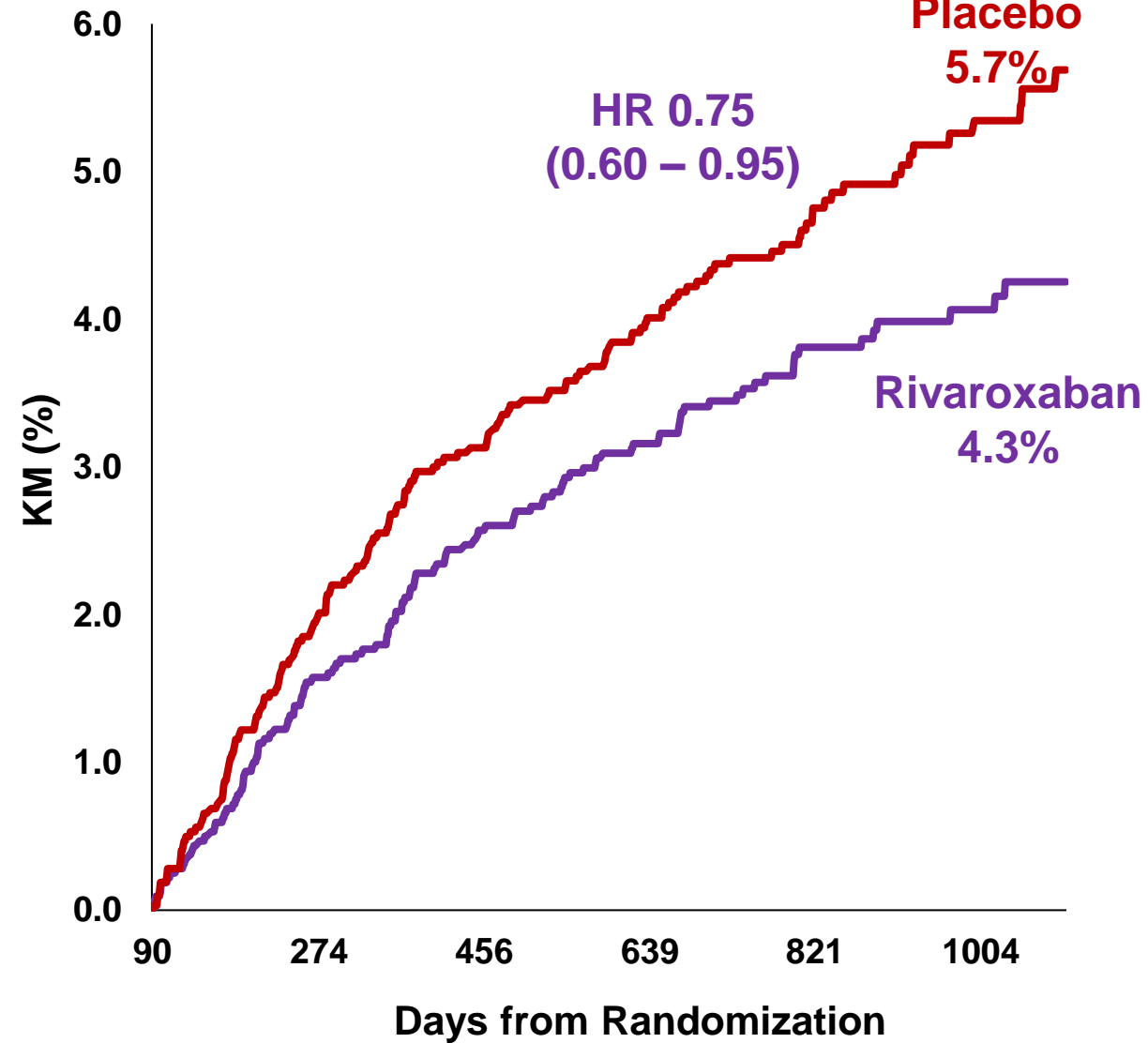
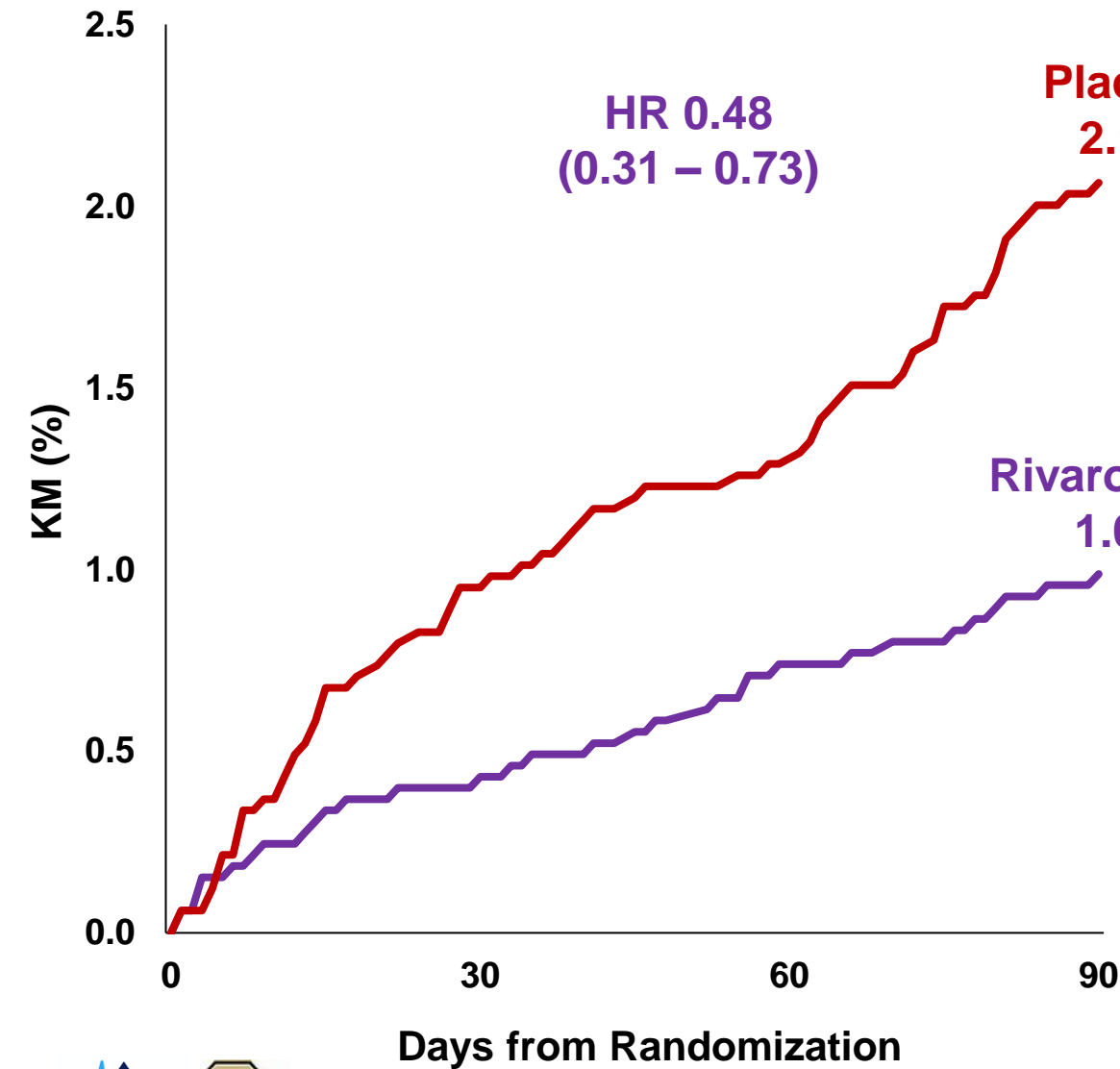


Acute Limb Ischemia

First 90 Days

P vs. constant HR 0.059

From day 91 through 3 Years

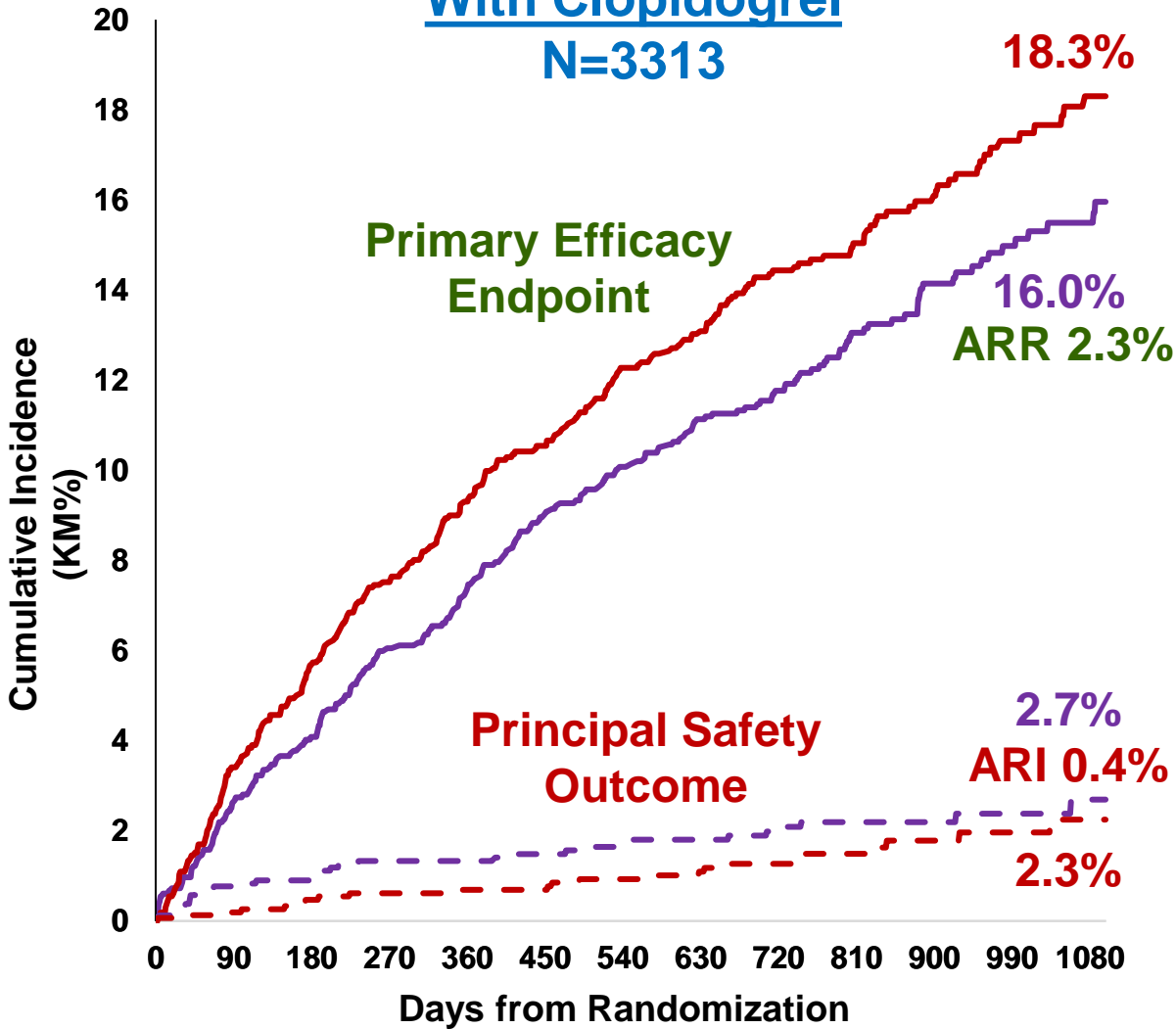


Benefit – Risk Consistent Regardless of DAPT

■ Placebo
■ Rivaroxaban

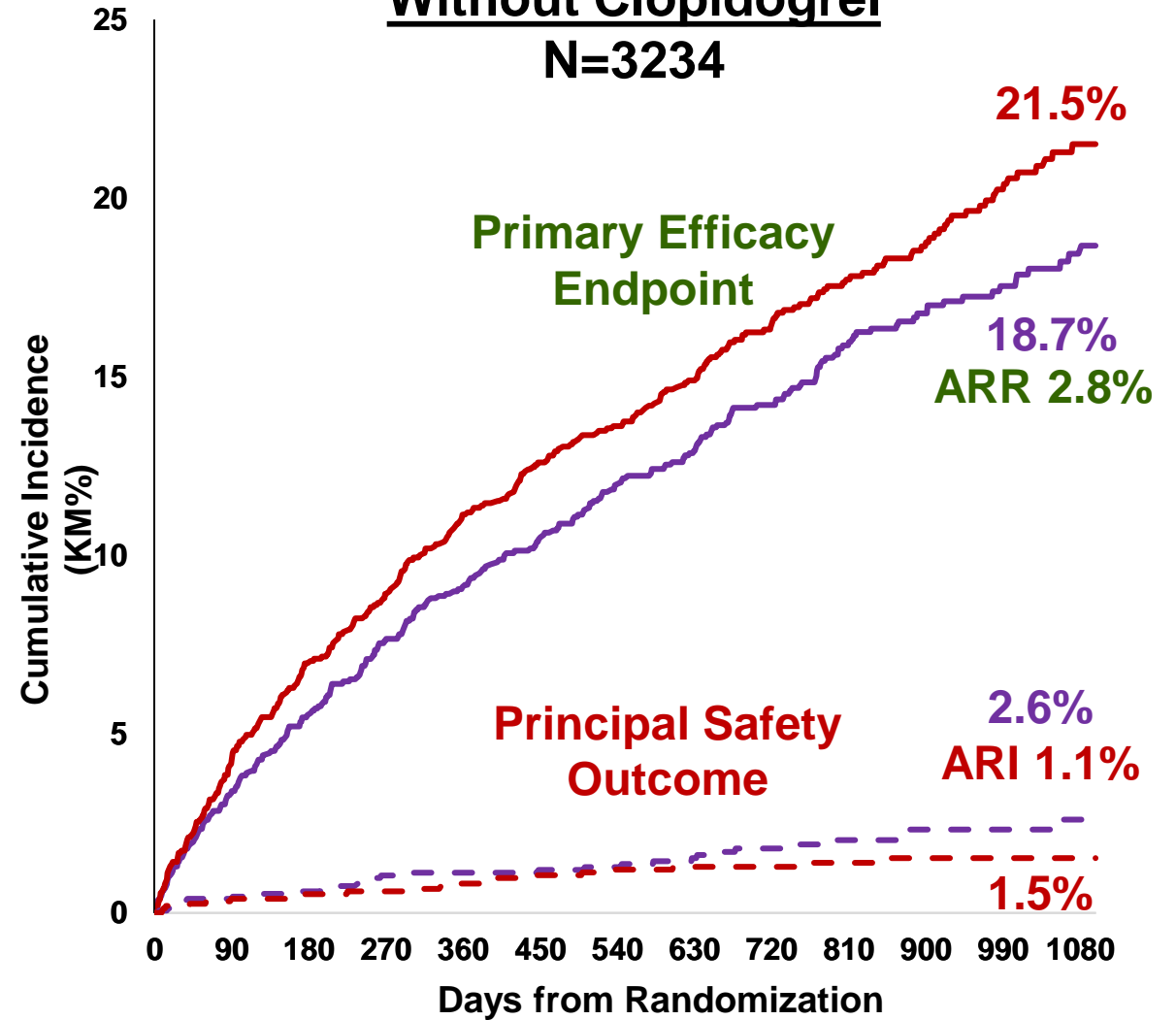
With Clopidogrel

N=3313



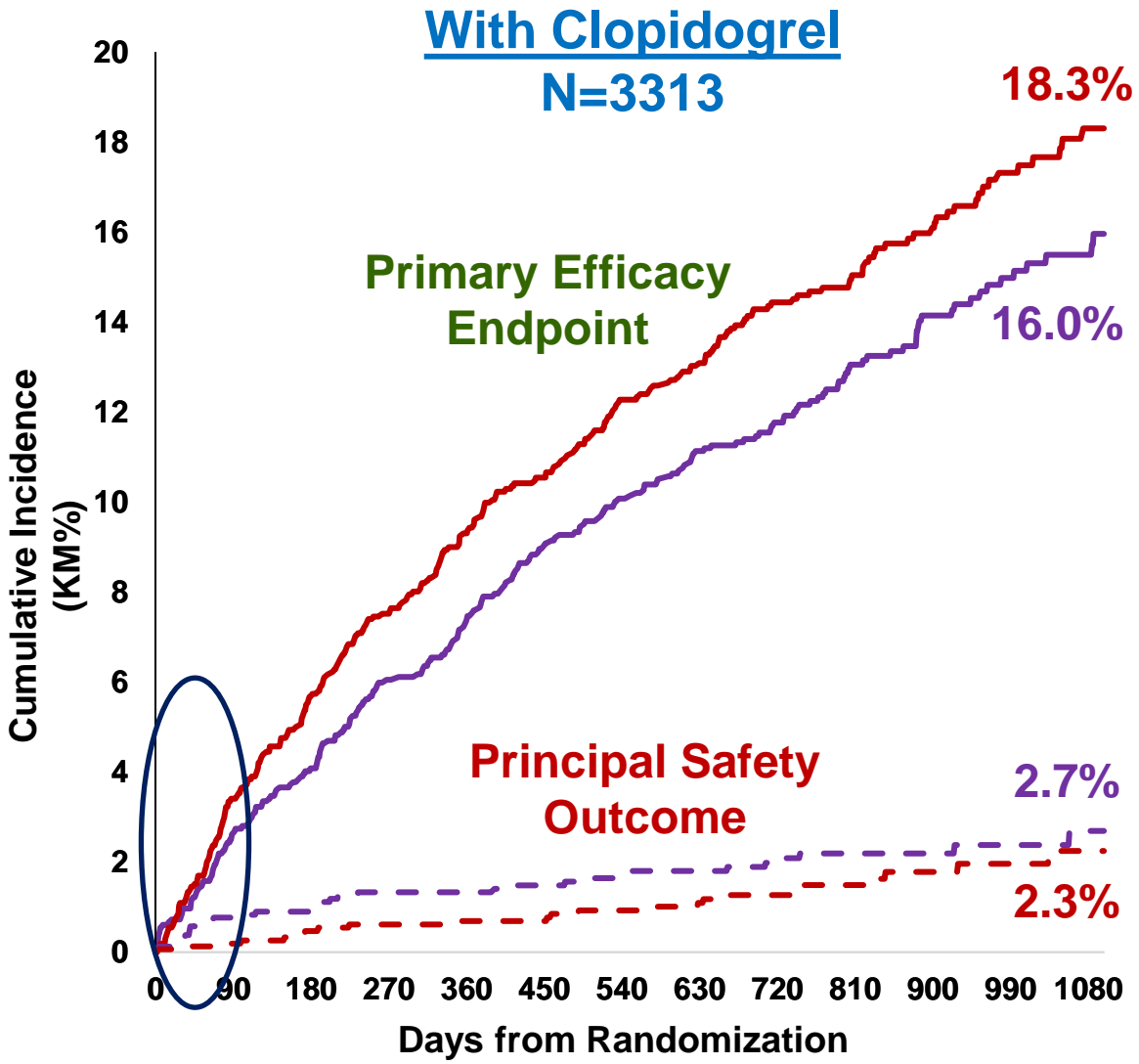
Without Clopidogrel

N=3234



Is DAPT Alone Enough for Early Limb Events?

■ Placebo
■ Rivaroxaban



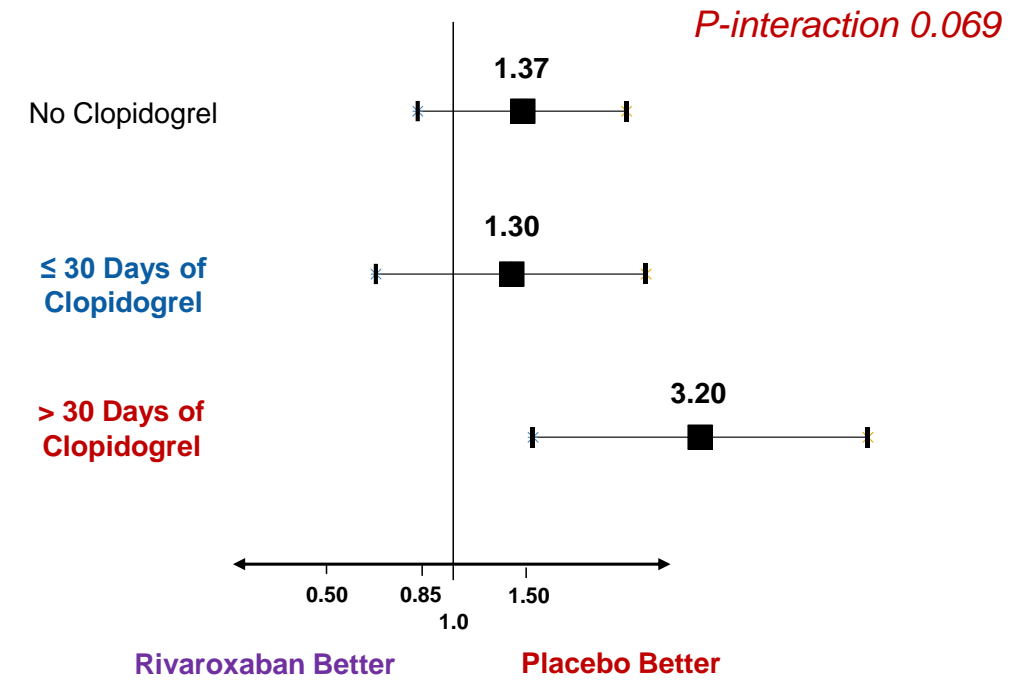
DAPT Only

DAPT + Rivaroxaban

ARR 2.3%
ARI 0.4%

6:1 Benefit Risk Ratio for Adding Rivaroxaban on top of DAPT

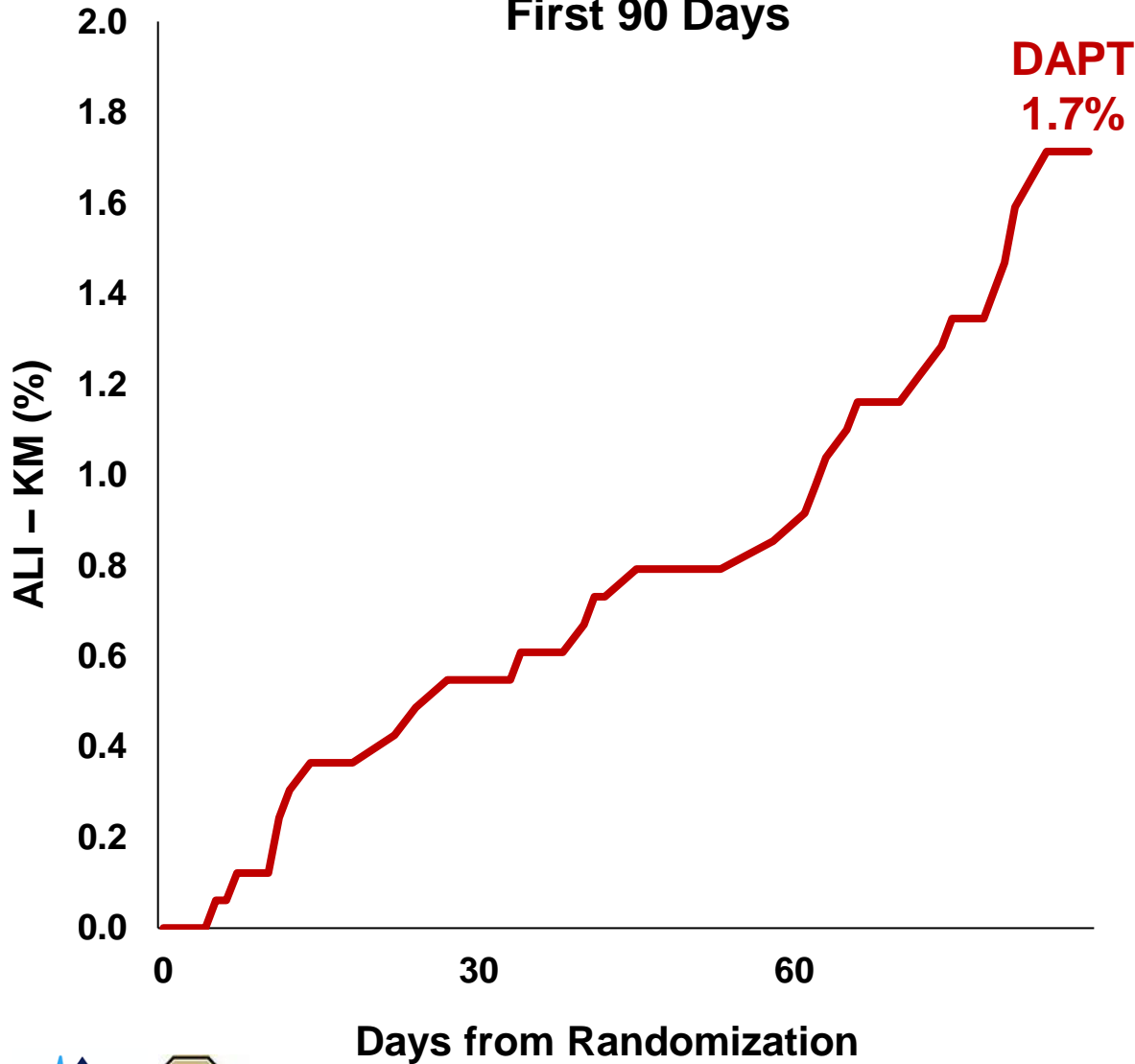
Bleeding Risk based on Duration of DAPT



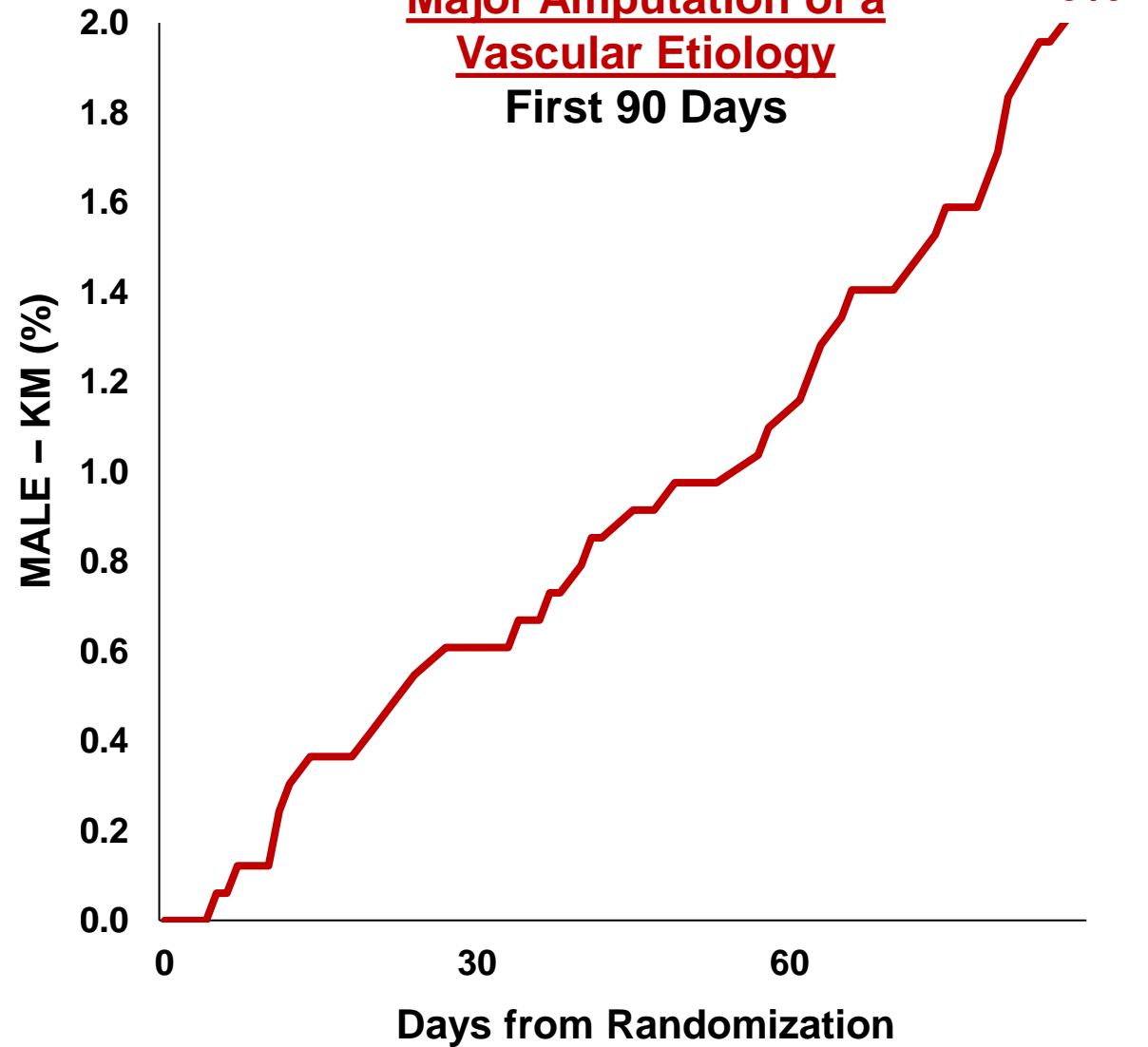
Hiatt WR et al. Circulation 2020

MALE and ALI in those Receiving DAPT – First 90 Days

Acute Limb Ischemia
First 90 Days

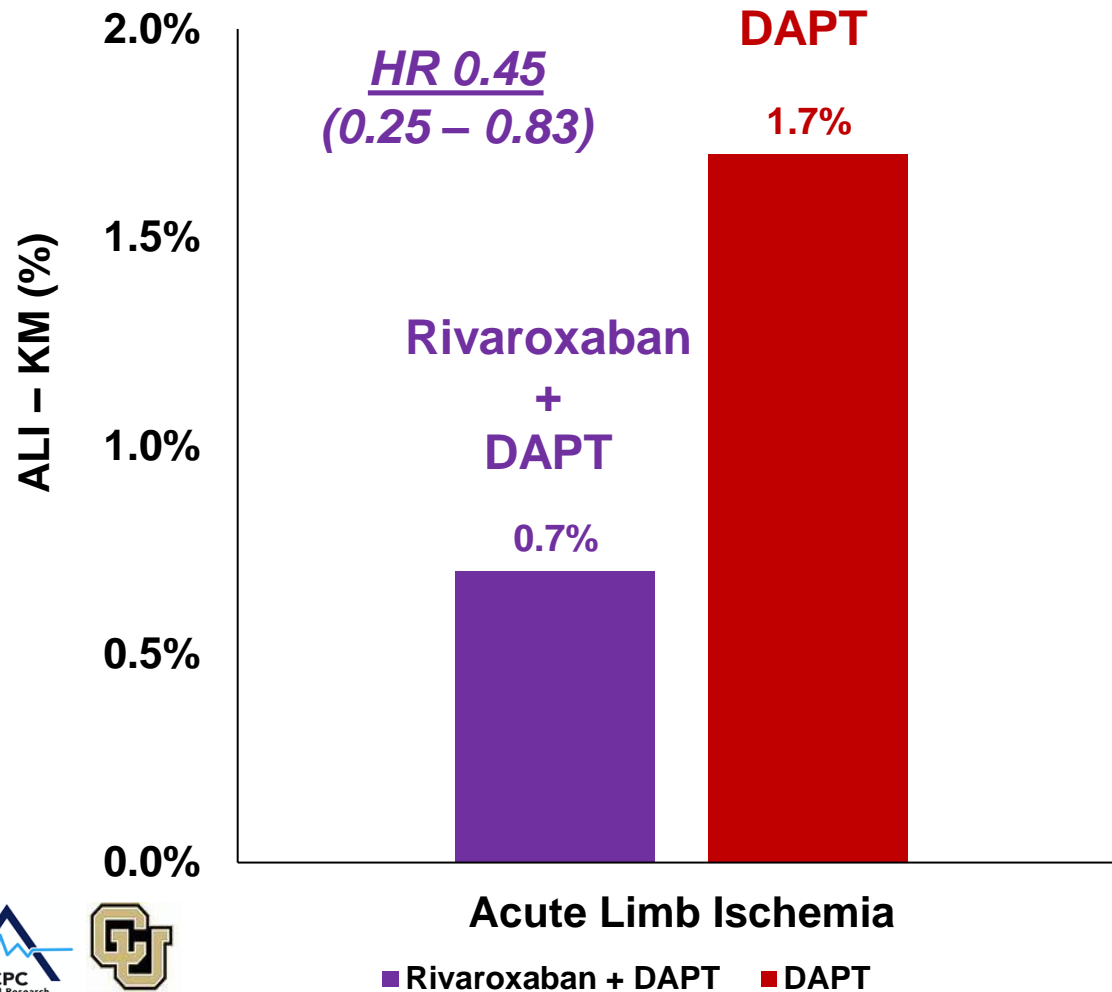


Acute Limb Ischemia or Major Amputation of a Vascular Etiology
First 90 Days

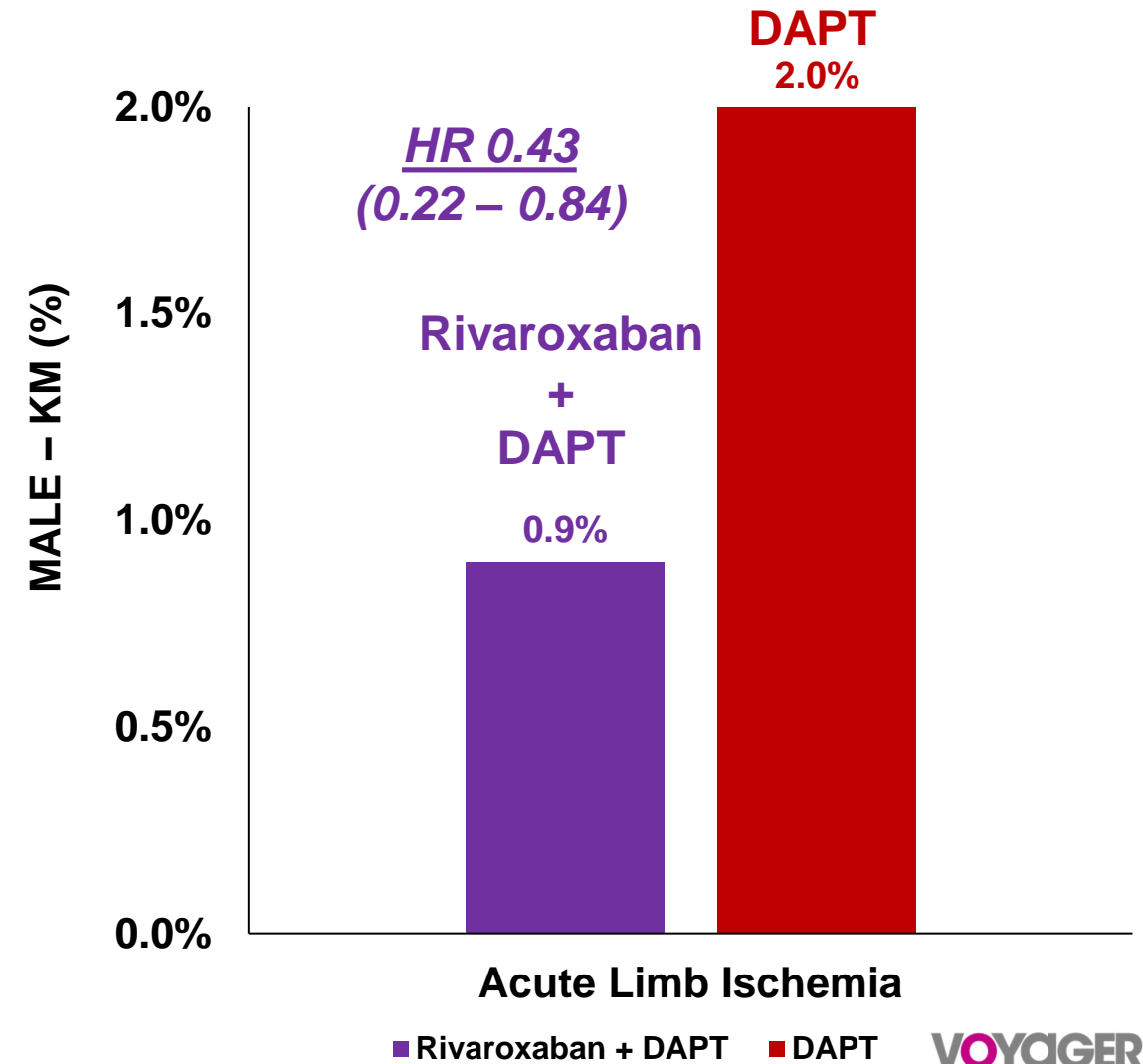


MALE and ALI in those Receiving DAPT – First 90 Days

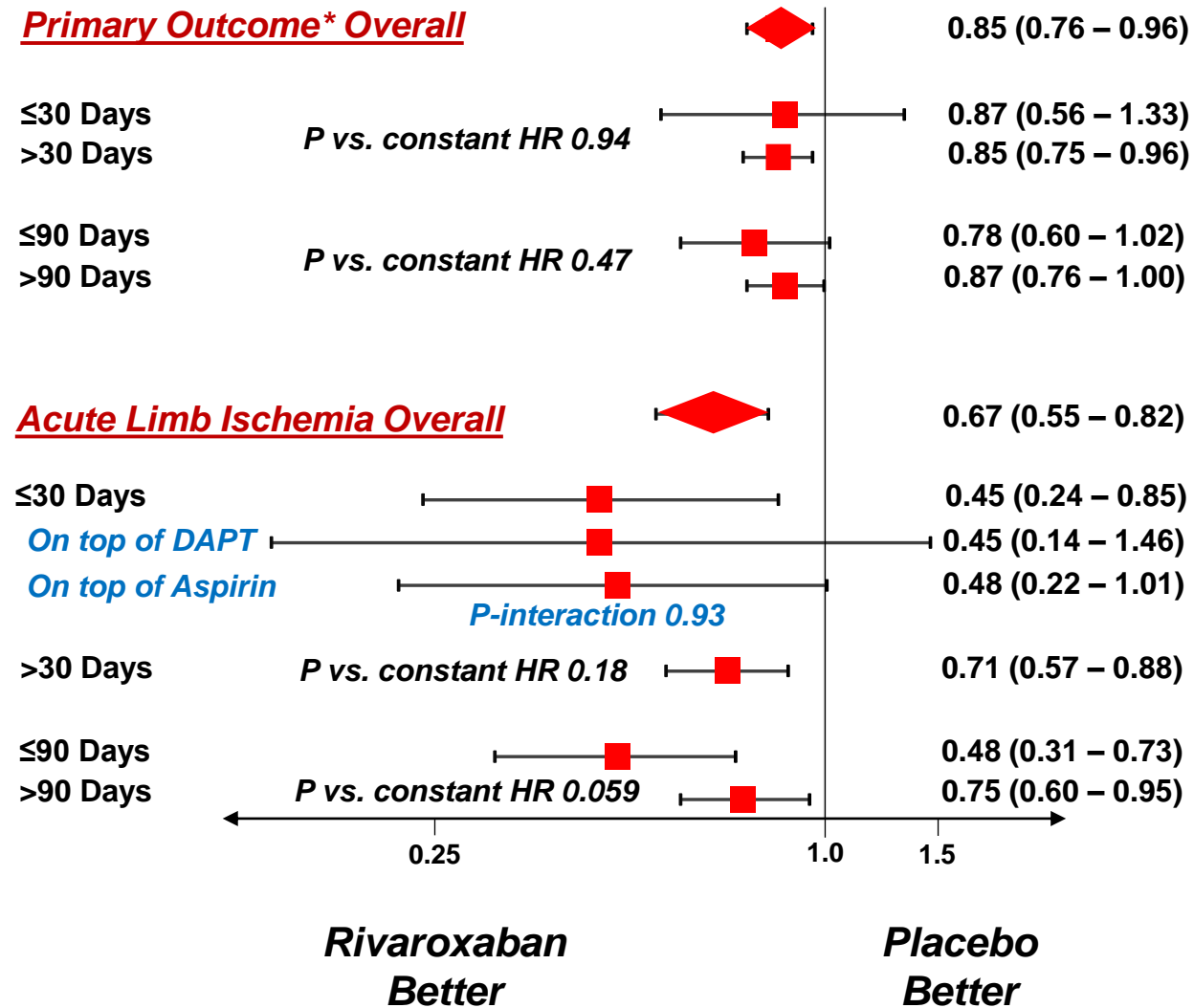
Acute Limb Ischemia
at 90 Days



Acute Limb Ischemia or Major Amputation of a Vascular Etiology
First 90 Days



Primary Outcome* and Acute Limb Ischemia Early and Late



*acute limb ischemia, major amputation of a vascular etiology, myocardial infarction, ischemic stroke, or CV death

Summary

After LER, rivaroxaban 2.5 mg twice daily added to antiplatelet therapy

- *Reduces MACE and MALE and increases bleeding but with an overall favorable benefit-risk profile*
- *This favorable benefit-risk profile is present both early and late after LER*
- *Rates of acute limb ischemia and major amputation of vascular etiology are high early LER despite DAPT (2%)*
- *Rivaroxaban reduced this risk when started within 10 days of LER (~50% within 5 days in trial) after LER by ~50%*

Conclusions

- **VOYAGER PAD and other contemporary datasets (e.g. BEST CLI) demonstrate high rates of morbid limb complications after lower extremity revascularization for symptomatic PAD**
- **Rates of acute limb ischemia and amputation are high after LER despite the use of DAPT**
- **Rivaroxaban 2.5 mg twice daily reduces irreversible harm events of the heart limb and brain:**
 - **Early after LER**
 - **When added to aspirin alone or to DAPT**
 - **In chronic PAD (including mortality & amputation benefit – COMPASS)**
- ***In eligible patients, rivaroxaban 2.5 mg twice daily should be started early after LER and continued long-term regardless of DAPT***