



# **Efficacy and Safety of Rivaroxaban in Patients with PAD Undergoing Lower Extremity Revascularization for Critical Limb Ischemia**

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Late Breaking Science  
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# Disclosures

- **VOYAGER PAD funded through a grant from Bayer to CPC Clinical Research**
- **Other research grants to CPC Clinical Research from Arca, Amgen, AstraZeneca, Bayer, Janssen, Merck, Novo Nordisk**

# Background

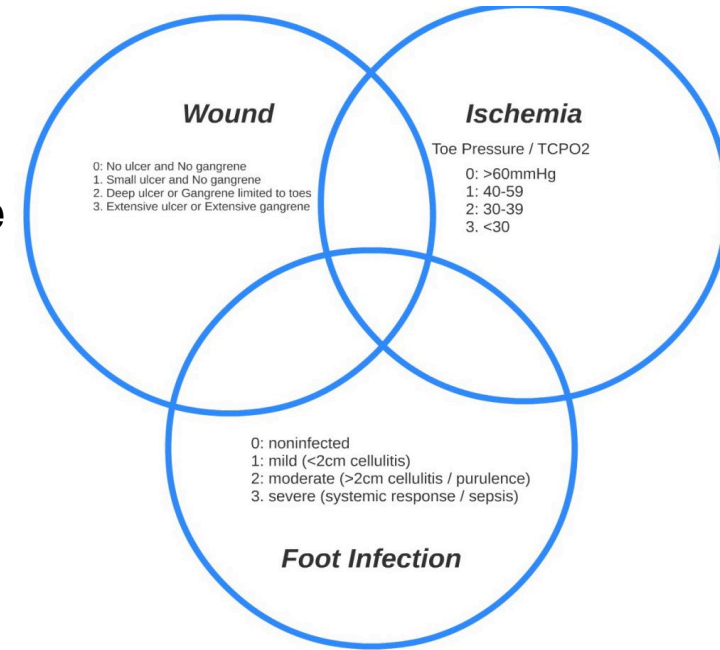


**Critical Limb Ischemia (CLI) represents the most severe manifestation of late stage peripheral artery disease**

**Traditionally defined by rest pain or tissue loss with evidence of ischemia, the most recent definition of *Chronic Limb Threatening Ischemia (CLTI)* and *WIFI* recognize its multifactorial nature including infection and wound characteristics**

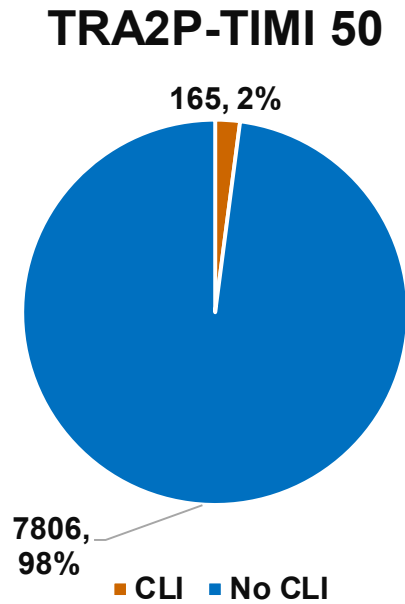
**Revascularization is recommended (Class I) to prevent/minimize tissue loss**

**Outcomes after CLI are poor with high risk of ischemic complications, amputation and mortality**

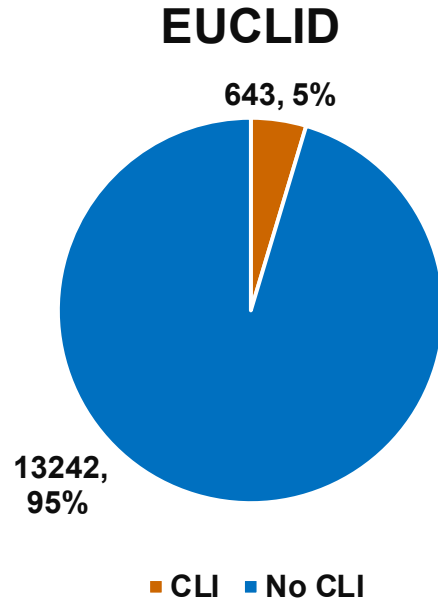


***Optimal adjunctive medical therapy to improve outcomes in CLI/CLTI patients undergoing intervention has not been defined***

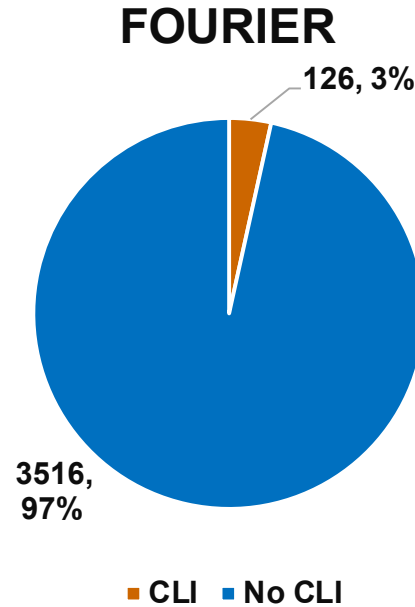
# Selected Cardiovascular Trials Enrolling Patients with PAD



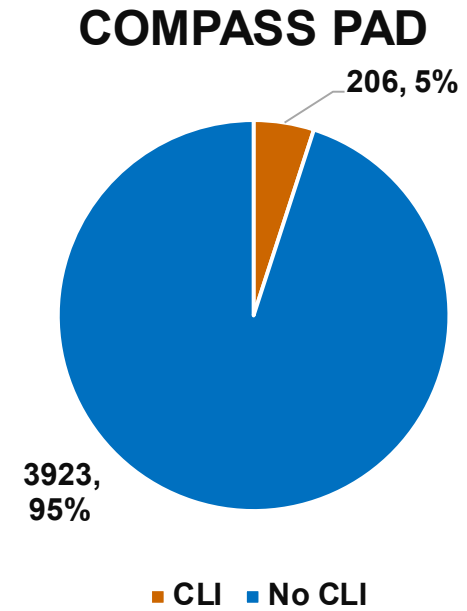
Bonaca et al. AHA 2018



Norgren et al. EJVS 2017



Bonaca et al. Circ 2018

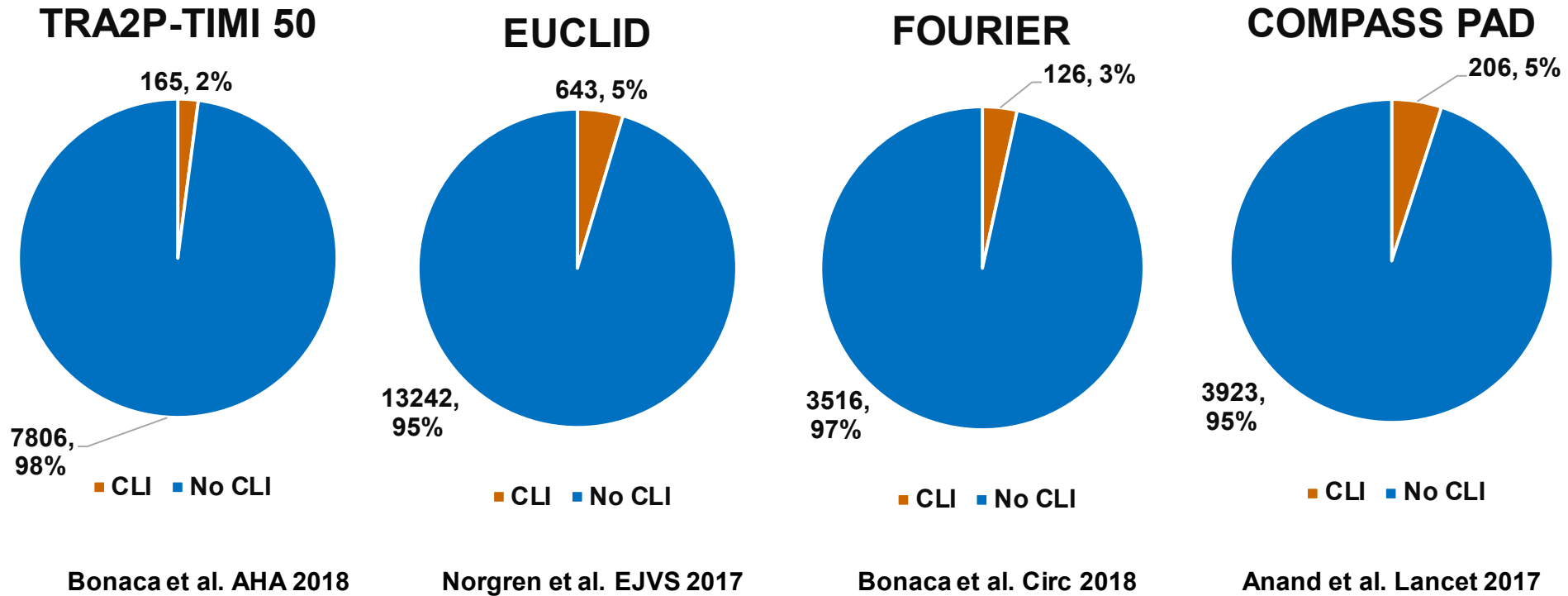


Anand et al. Lancet 2017

**Medical Therapy Trials including PAD patients generally:**

- In stable/chronic setting
- Therefore, few patients with CLI

# Selected Cardiovascular Trials Enrolling Patients with PAD



**Total = 1,140**

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- In stable/chronic setting
- Therefore, few patients with CLI

# VOYAGER PAD Design

NCT02504216

6,564 Patients with Symptomatic Lower Extremity PAD\* Undergoing Peripheral Revascularization

ASA 100 daily for all Patients  
Clopidogrel at Investigator's Discretion

Randomized 1:1 Double Blind

Rivaroxaban 2.5 mg  
twice daily

Stratified by  
Revascularization Approach  
(Surgical or Endovascular  
with and without clopidogrel)

Placebo

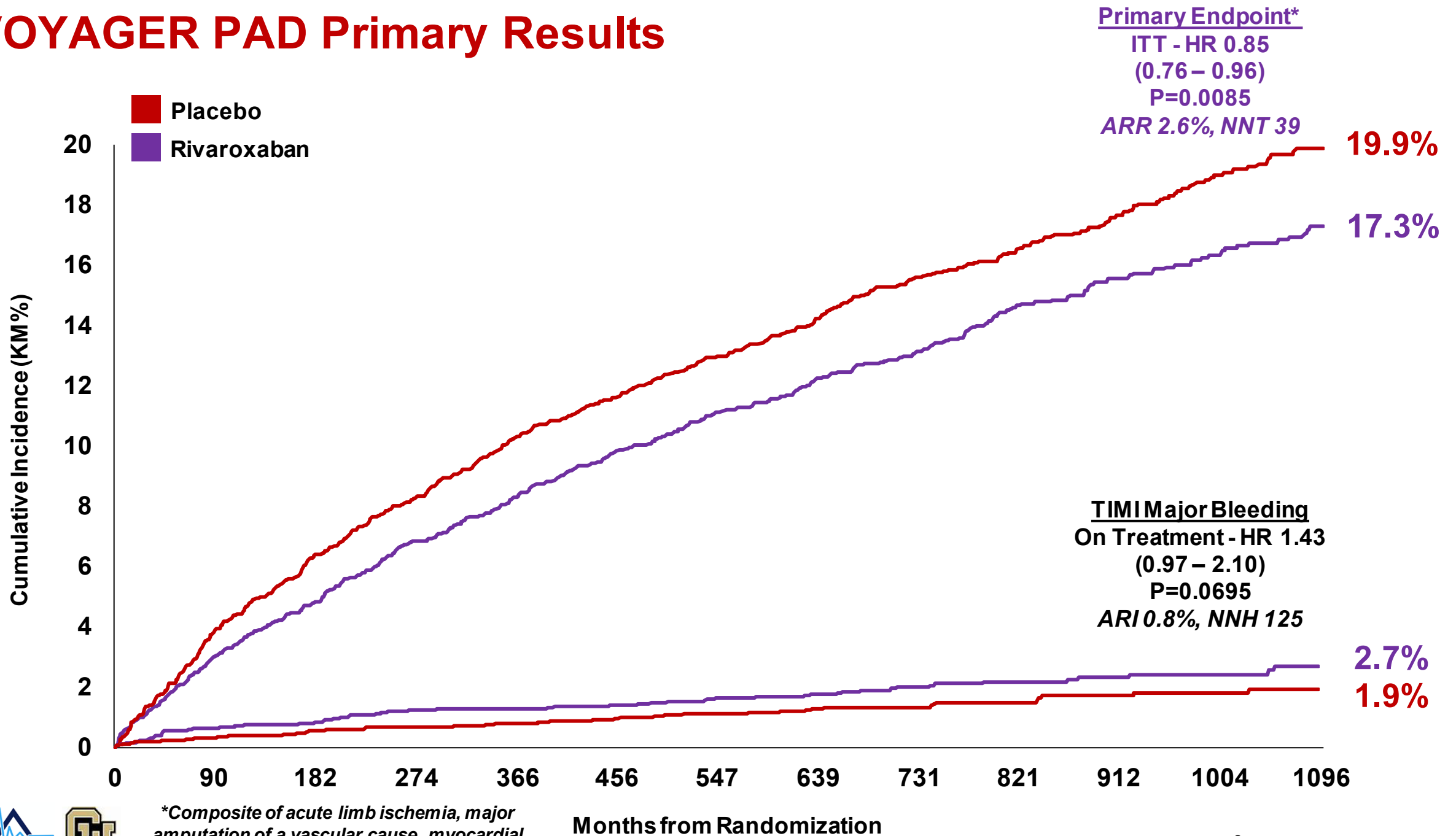
Follow up Q6 Months, Event Driven, Median f/u 28 Months

**Primary Efficacy Endpoint:** Acute limb ischemia, major amputation of vascular etiology, myocardial infarction, ischemic stroke or cardiovascular death

**Principal Safety Outcome:** TIMI Major Bleeding

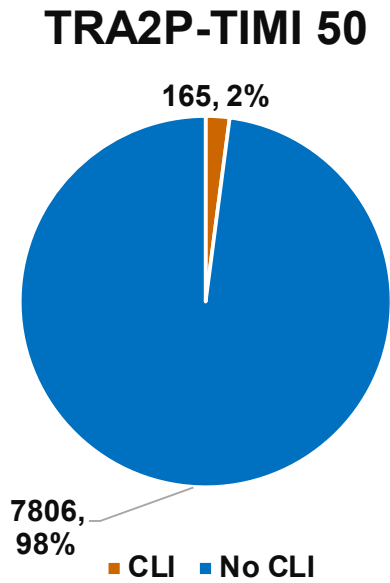
\*PAD defined as:  
**- Ischemic symptoms**  
(functional limitation, rest pain or ischemic ulceration) **AND**  
**- Imaging evidence of occlusion** **AND**  
**- Abnormal ABI/TBI**

# VOYAGER PAD Primary Results

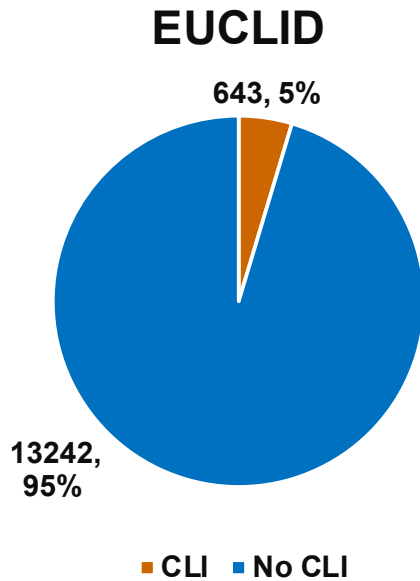


\*Composite of acute limb ischemia, major amputation of a vascular cause, myocardial infarction, ischemic stroke, cardiovascular death

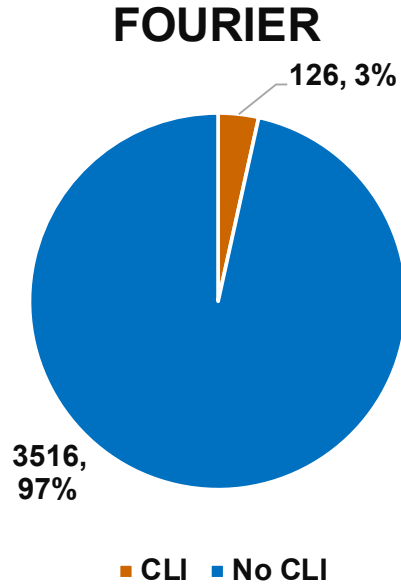
# Trials with PAD Subgroups



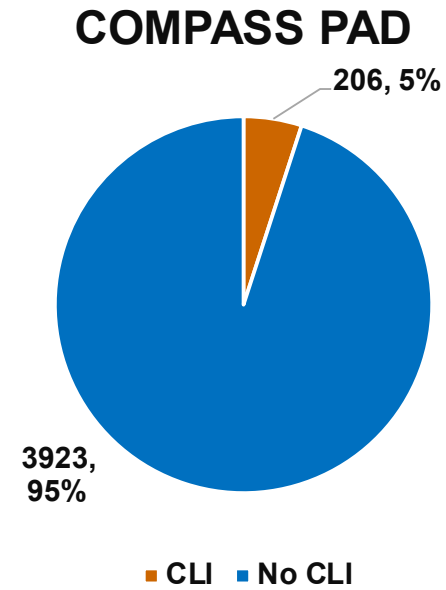
Bonaca et al. AHA 2018



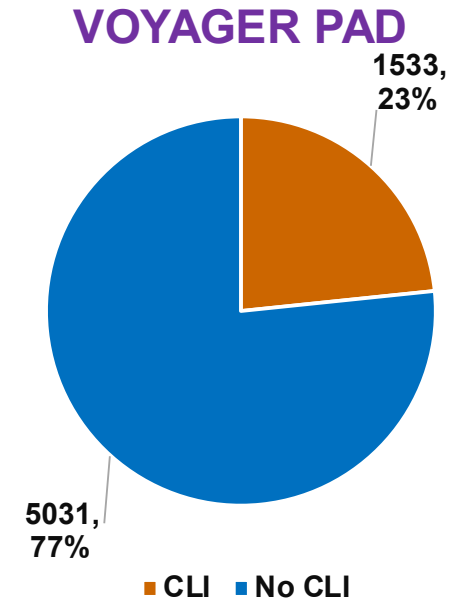
Norgren et al. EJVS 2017



Bonaca et al. Circ 2018



Anand et al. Lancet 2017



Bonaca et al. NEJM 2020

**Total = 1,140**

**VOYAGER PAD Patients  
with CLI at Baseline =  
1,533**



# Objectives

## Objectives

- To evaluate the risk profile of patients undergoing lower extremity revascularization (LER) based on CLI vs no CLI at randomization
- To evaluate whether the efficacy and safety of rivaroxaban 2.5 mg twice daily with aspirin vs. aspirin alone is consistent in those with and without CLI at randomization:
  - *Primary efficacy endpoint and principal safety outcome*
  - *Key secondary outcome of **unplanned index limb revascularization** due to the high risk of recurrent procedures in this population*
  - *Prespecified net clinical outcome including the **primary outcome, ICH, fatal bleeding and all cause mortality** due to the high mortality rate in this population*

# Objectives and Methods

## Methods

- Patients assigned Rutherford (2-3 claudication, 4-6 CLI) classification at the time of qualifying revascularization by trained vascular investigators
- Efficacy :
  - Primary composite (ITT) of acute limb ischemia, major amputation of a vascular etiology, myocardial infarction, ischemic stroke or CV death
  - Secondary outcome for efficacy of unplanned index limb revascularization
- Safety
  - Principal safety outcome (on-treatment) of TIMI major bleeding
  - Secondary outcome for safety of ISTH major bleeding
- Prespecified net outcome (safety) including irreversible harm bleeding events (ICH or fatal bleeding) and all-cause mortality
- Outcomes adjudicated by a blinded CEC
- COX model used to test for effect modification on the basis of CLI

# Baseline Characteristics

Characteristics at Randomization	CLI N=1533 %	Claudication (no CLI) N=5031 %
Age, Yrs Median	67	67
Female	29	25
Caucasian	79	81
Diabetes Mellitus	47	38
Current Smoking	30	36
COPD	10	11
eGFR < 60 ml/min/1.73m <sup>2</sup>	23	19
Coronary Artery Disease	29	32
Prior MI	8	12
Known Carotid Stenosis	7	9
Statin	81	80
ACEi or ARB	60	64

CLI = Rutherford 4-6, No CLI = Rutherford 2-3/Claudication

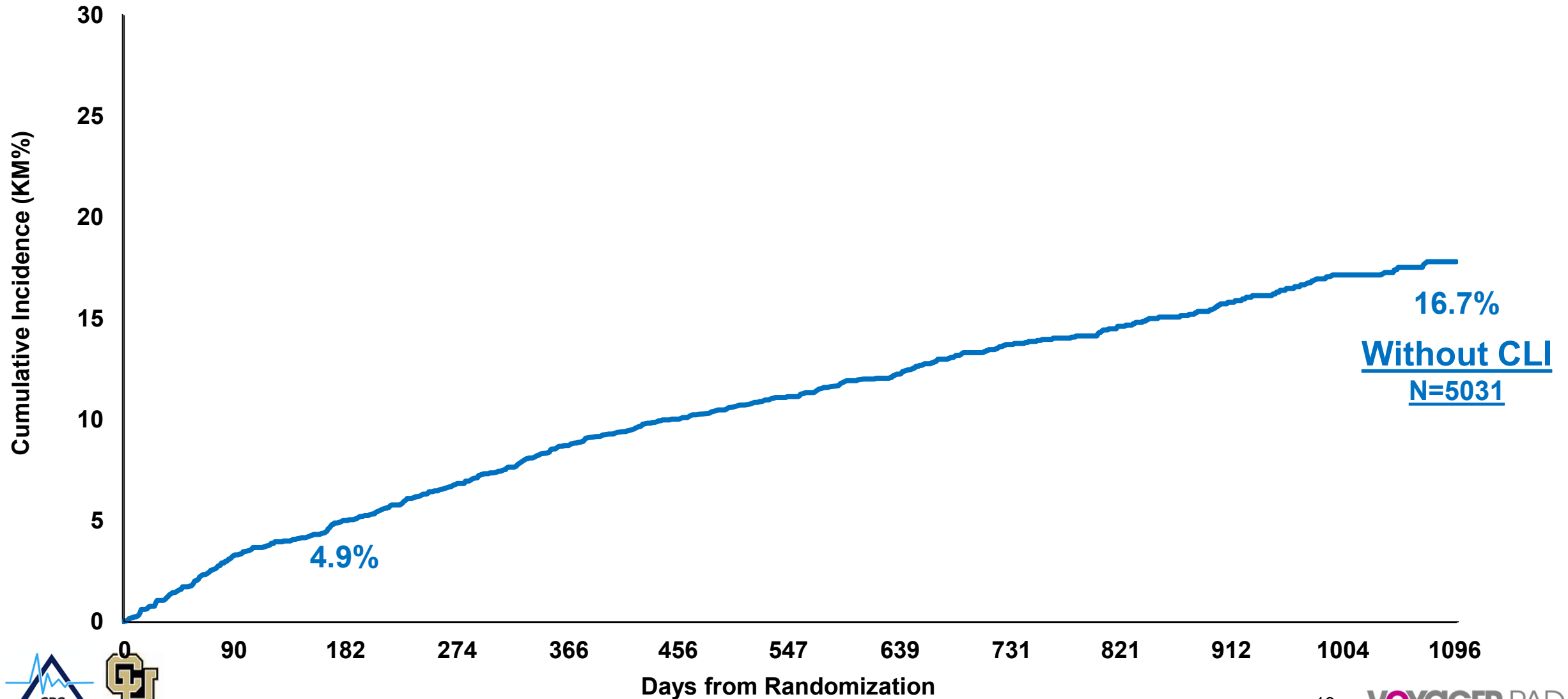
# PAD & Procedural Characteristics

Characteristics at Randomization	CLI N=1533 %	Claudication (no CLI) N=5031 %
<i>Prior Peripheral Artery Disease History</i>		
History of Claudication	82	99
History of Revascularization	27	38
History of Amputation	15	3
Ankle Brachial Index, Median (IQR)	0.46 (0.32 – 0.60)	0.58 (0.45 – 0.69)
<i>Type of Revascularization</i>		
Surgical	44	30
Endovascular or Hybrid	56	70
Days from Procedure to Rando, Median (IQR)	6 (3 – 8)	4 (2 – 7)
<i>Target Lesion Length</i>		
Short (< 5cm)	17	24
Intermediate (5cm to < 15cm)	38	40
Long (≥ 15cm)	43	32

CLI = Rutherford 4-6, No CLI = Rutherford 2-3/Claudication

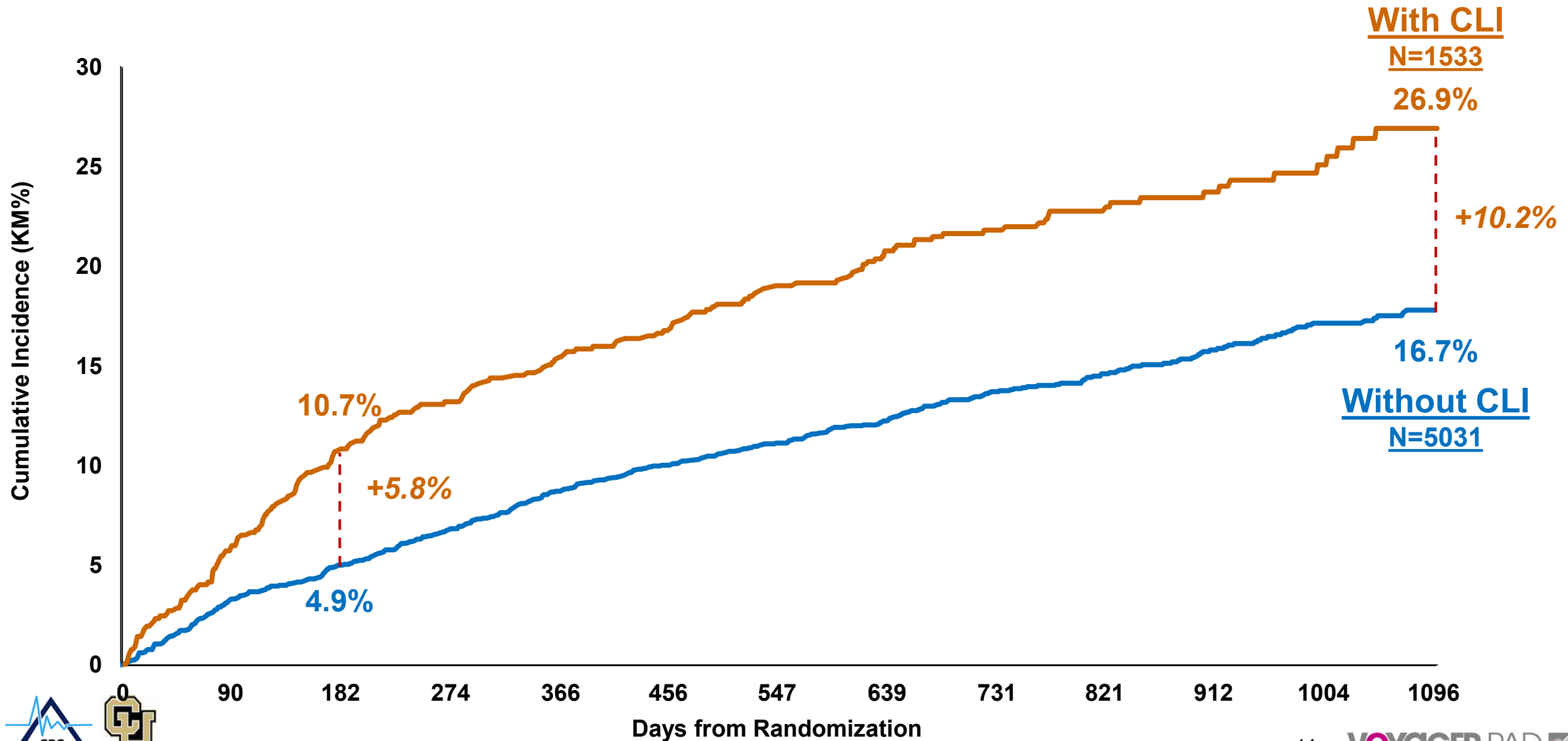
# Primary Endpoint in Placebo Arm with and without CLI at Randomization

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



# Primary Endpoint in Placebo Arm with and without CLI at Randomization

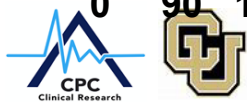
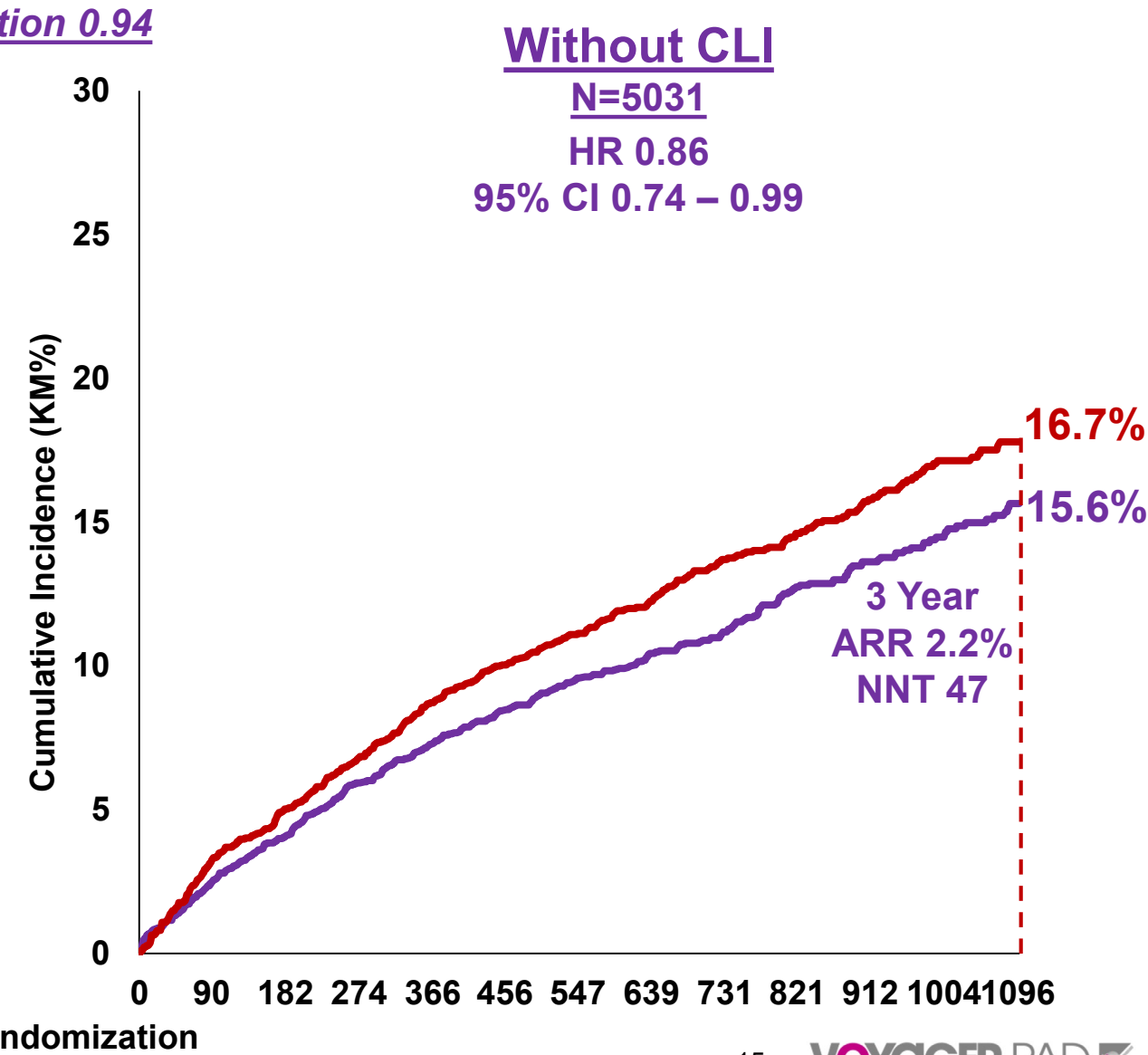
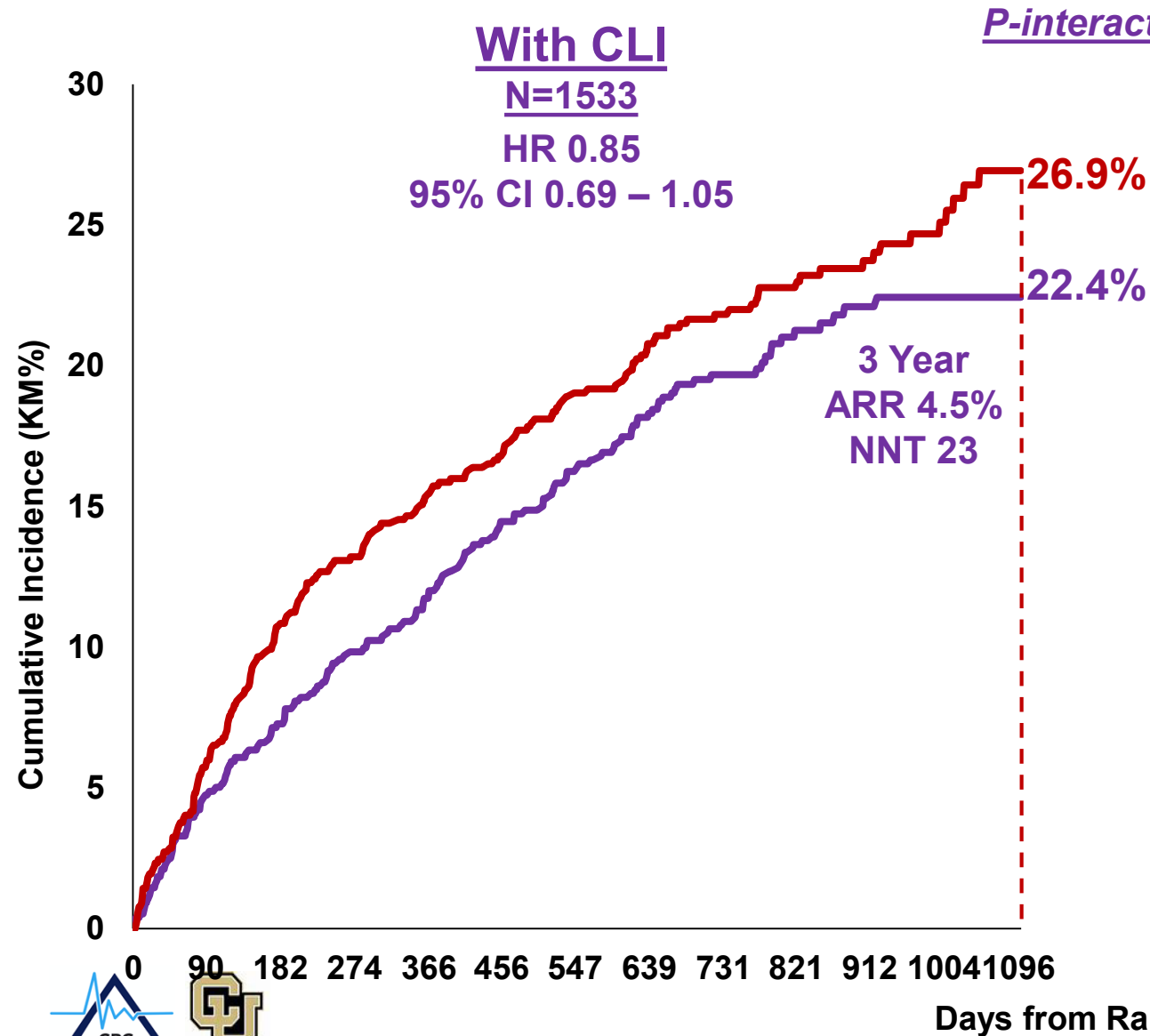
*Acute limb ischemia, major amputation for vascular cause, myocardial infarction, ischemic stroke, CV death*



# Primary Endpoint

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

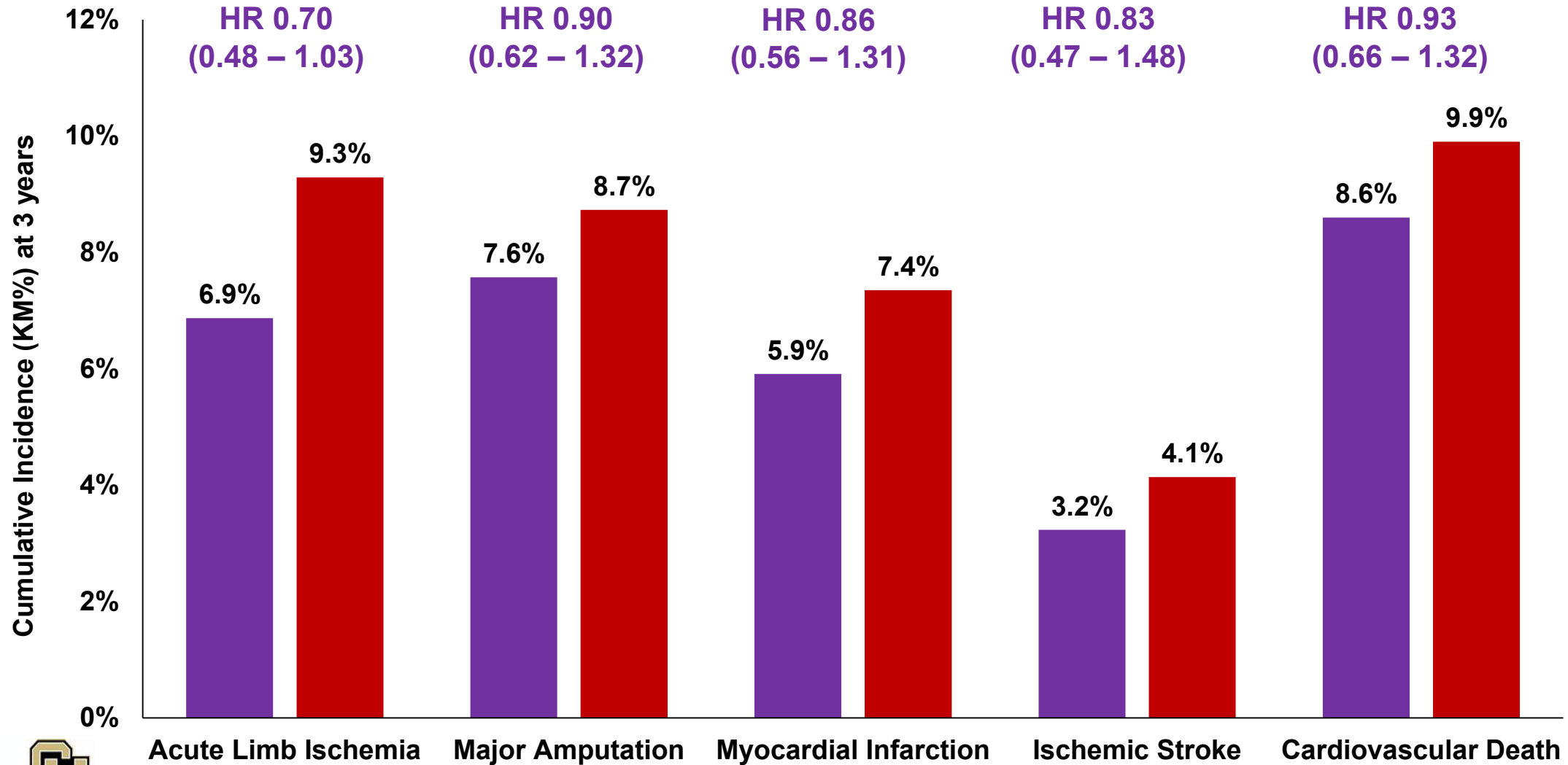
- Placebo
- Rivaroxaban



ARR – absolute risk reduction, NNT number needed to treat

# Primary Endpoint Components in Patients with CLI

■ Placebo  
■ Rivaroxaban



ARR – absolute risk reduction, NNT number needed to treat

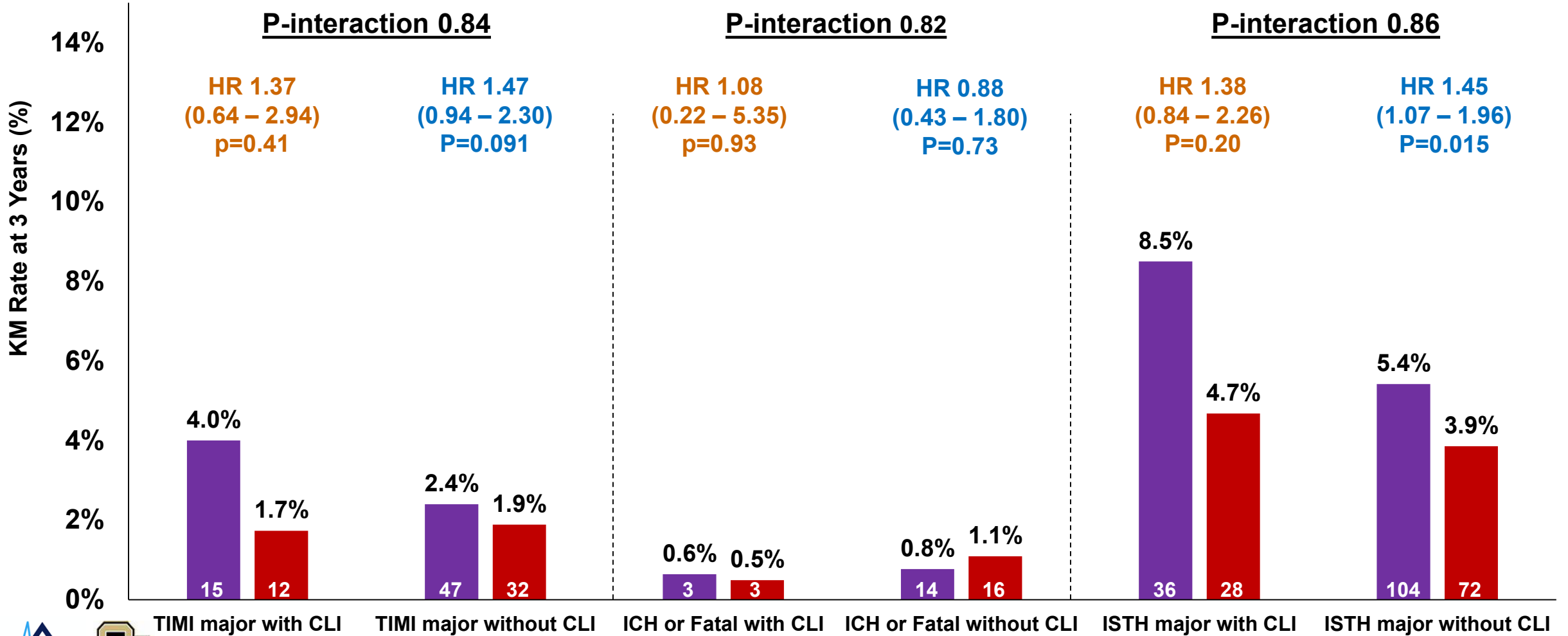


# Safety of Rivaroxaban by CLI at Randomization

■ Placebo  
■ Rivaroxaban

**With CLI**  
 N=1533

**Without CLI**  
 N=5031

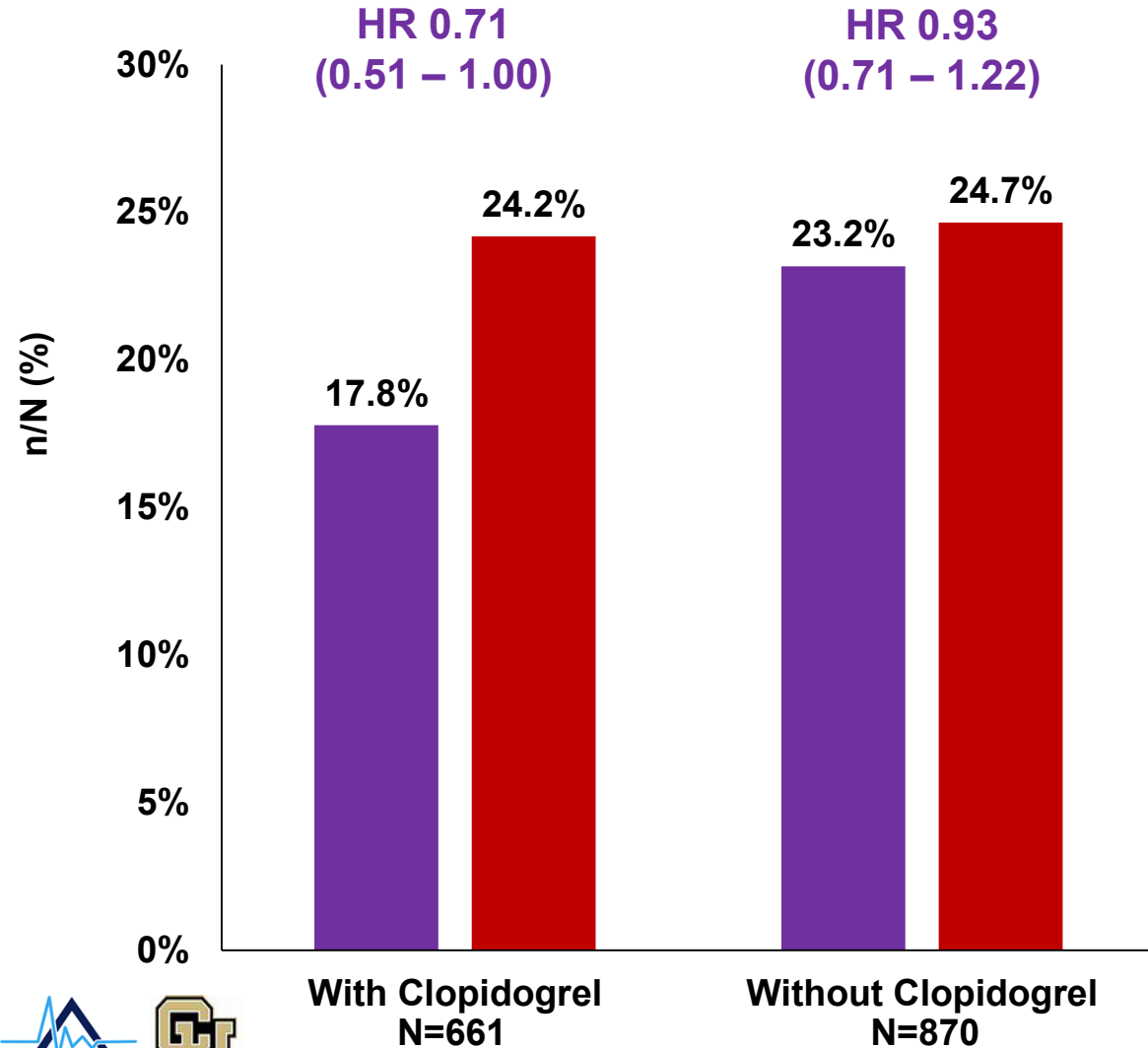


# Primary Endpoint CLI Patients by Concomitant Clopidogrel Use

■ Placebo  
■ Rivaroxaban

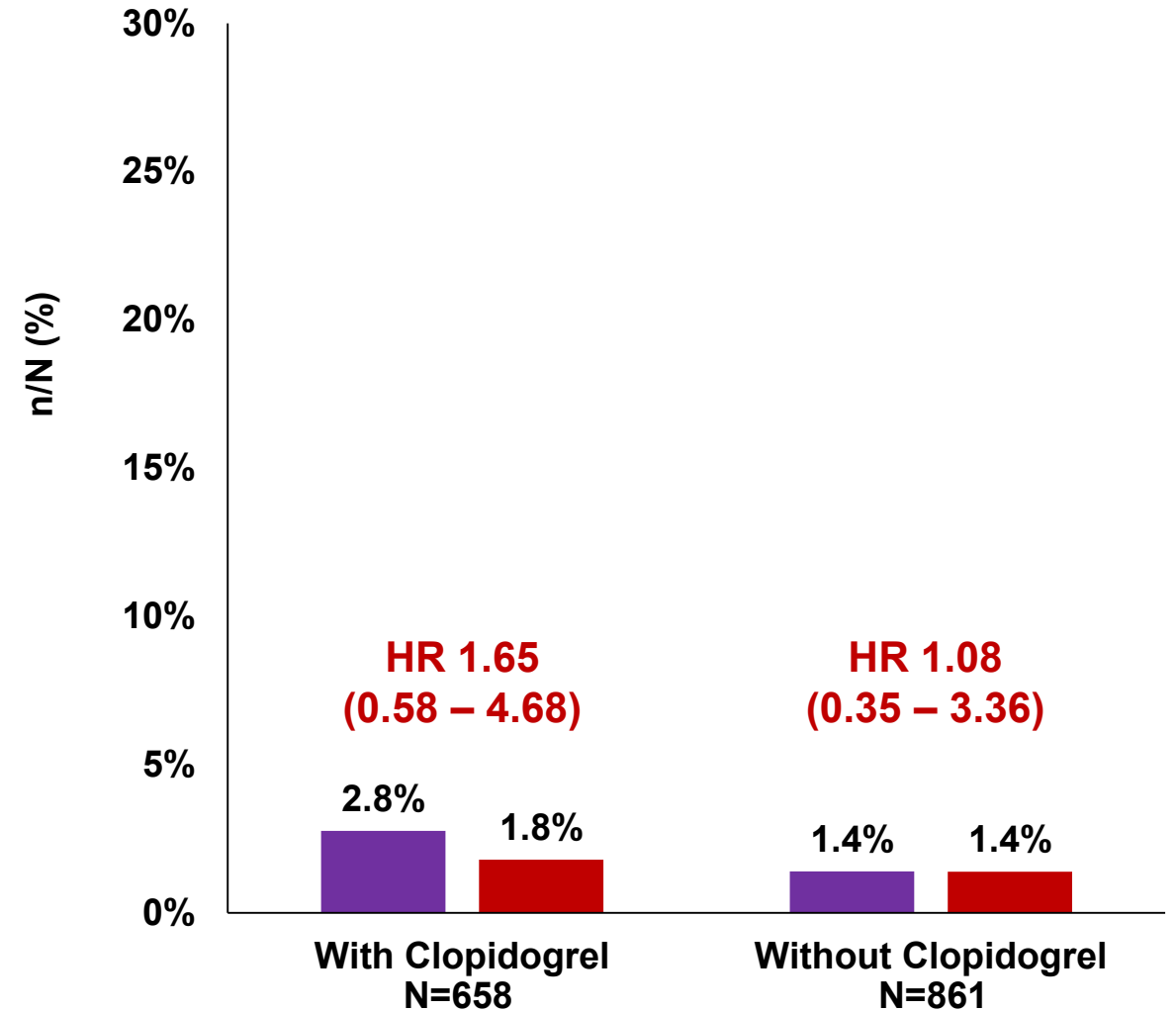
## Primary Endpoint

*P-interaction 0.21*



## TIMI major bleeding

*P-interaction 0.53*

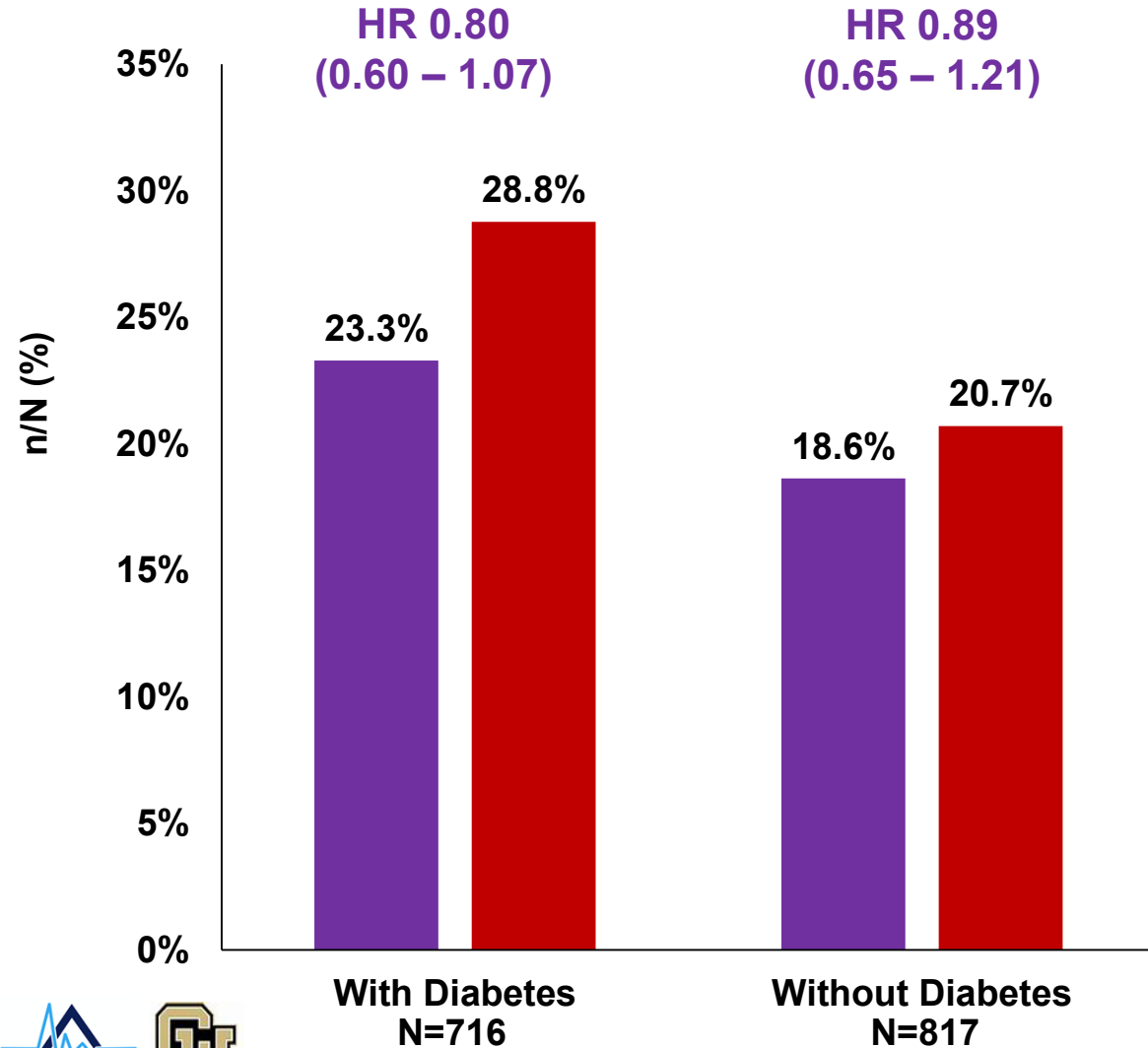


# Primary Endpoint in CLI Patients by Concomitant Diabetes Mellitus

■ Placebo  
■ Rivaroxaban

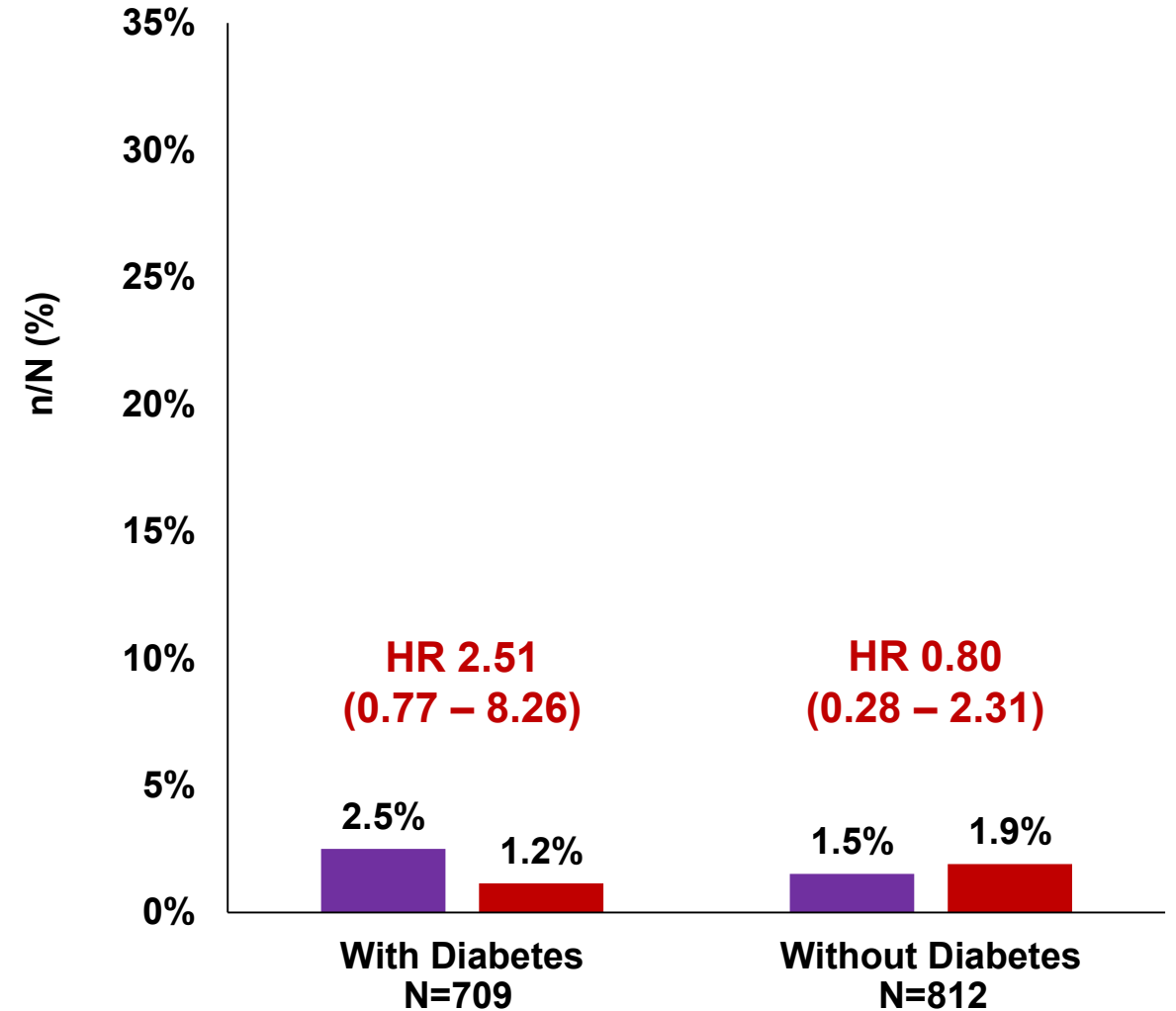
## Primary Endpoint

*P-interaction 0.62*



## TIMI major bleeding

*P-interaction 0.16*

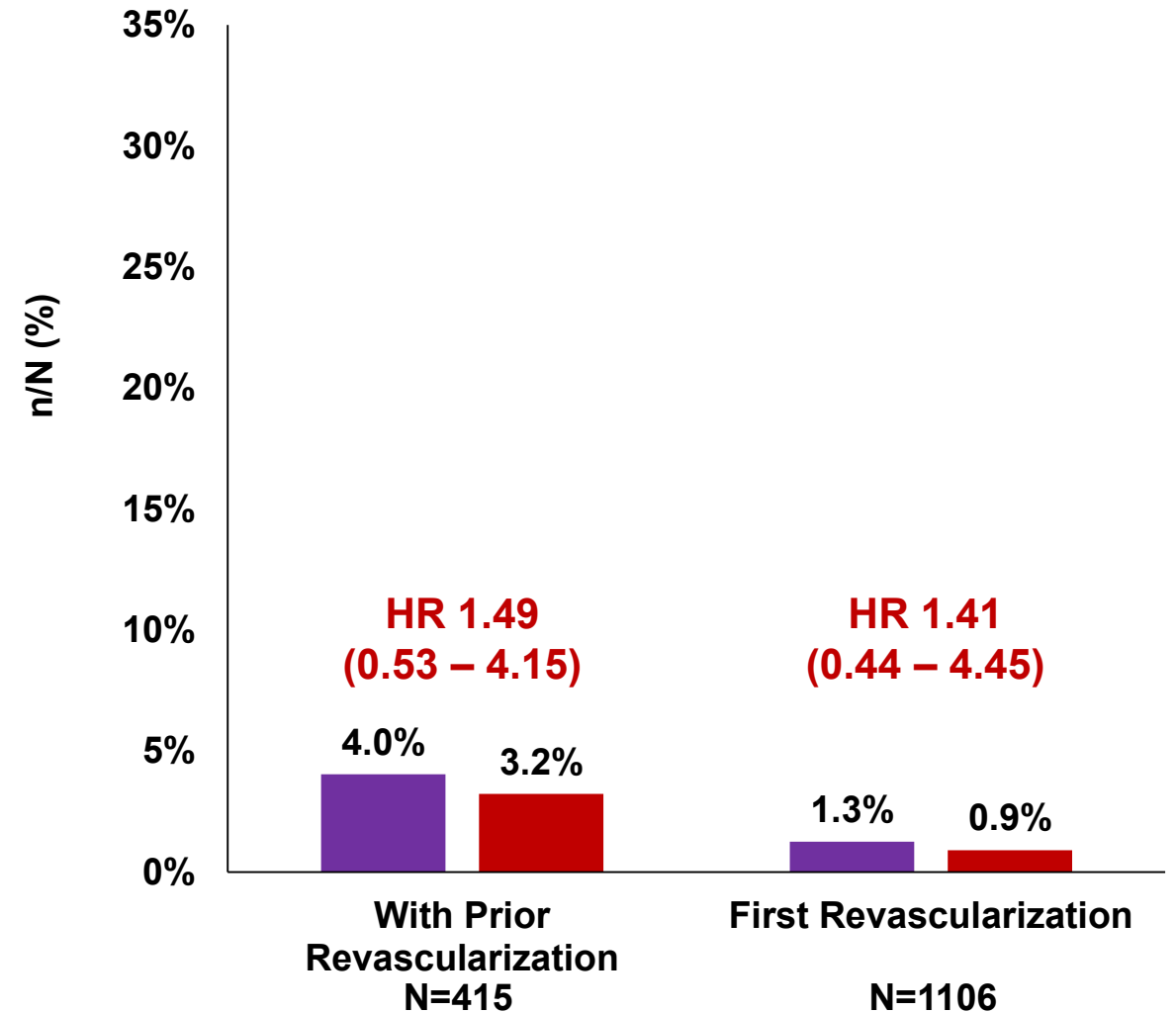
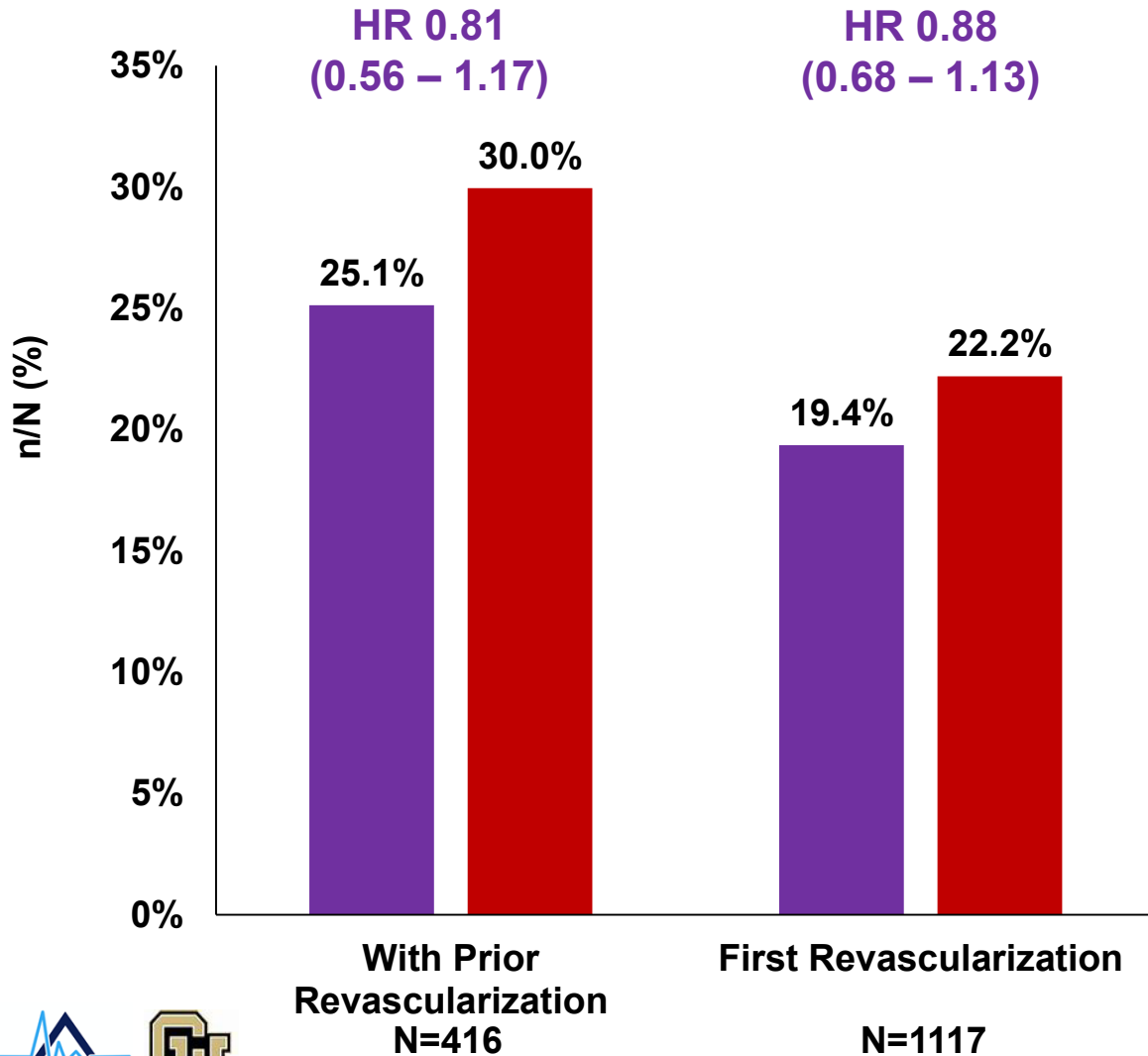


# Primary Endpoint CLI Patients by Prior Limb Revascularization

■ Placebo  
■ Rivaroxaban

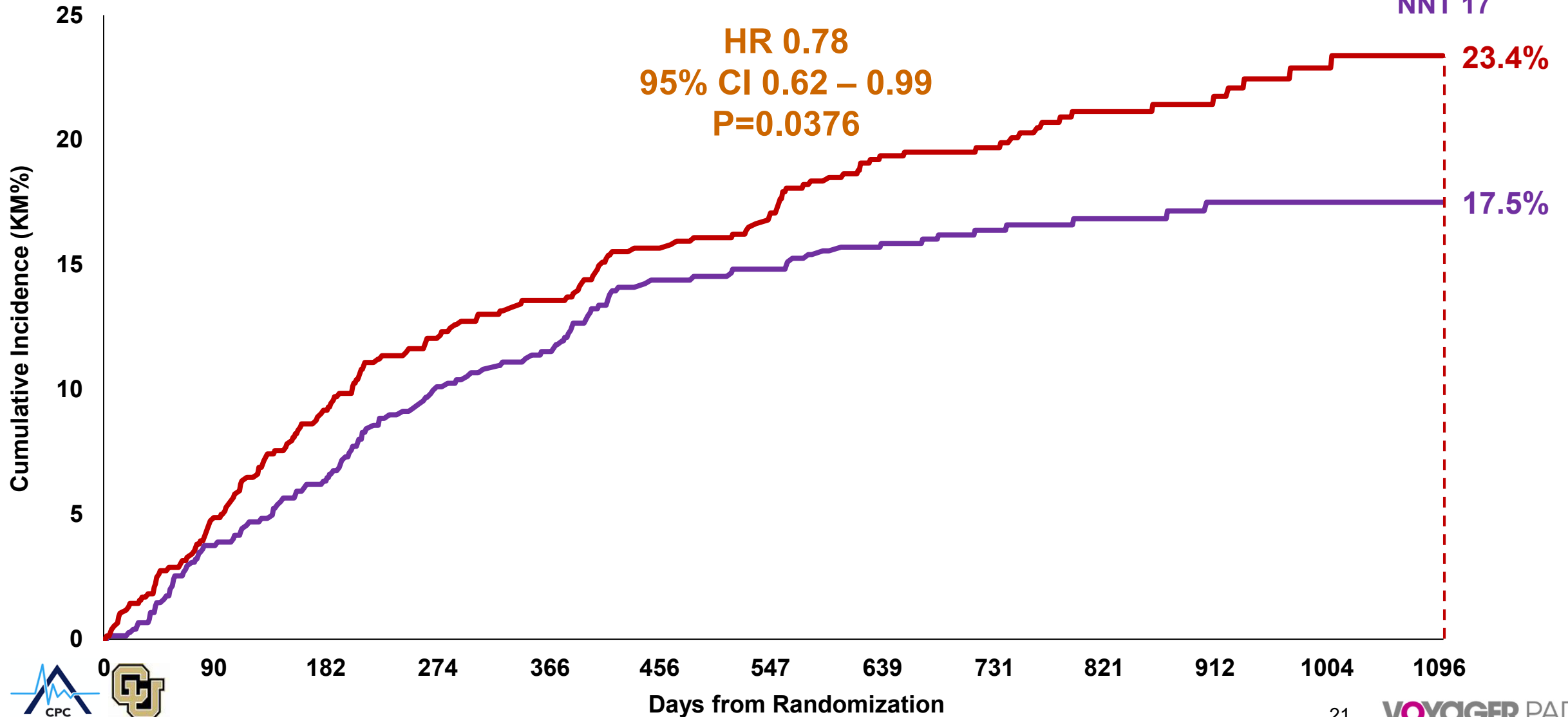
**Primary Endpoint**  
*P-interaction 0.73*

**TIMI major bleeding**  
*P-interaction 0.90*



# Unplanned Index Limb Revascularization

■ Placebo  
■ Rivaroxaban



ARR – absolute risk reduction, NNT number needed to treat

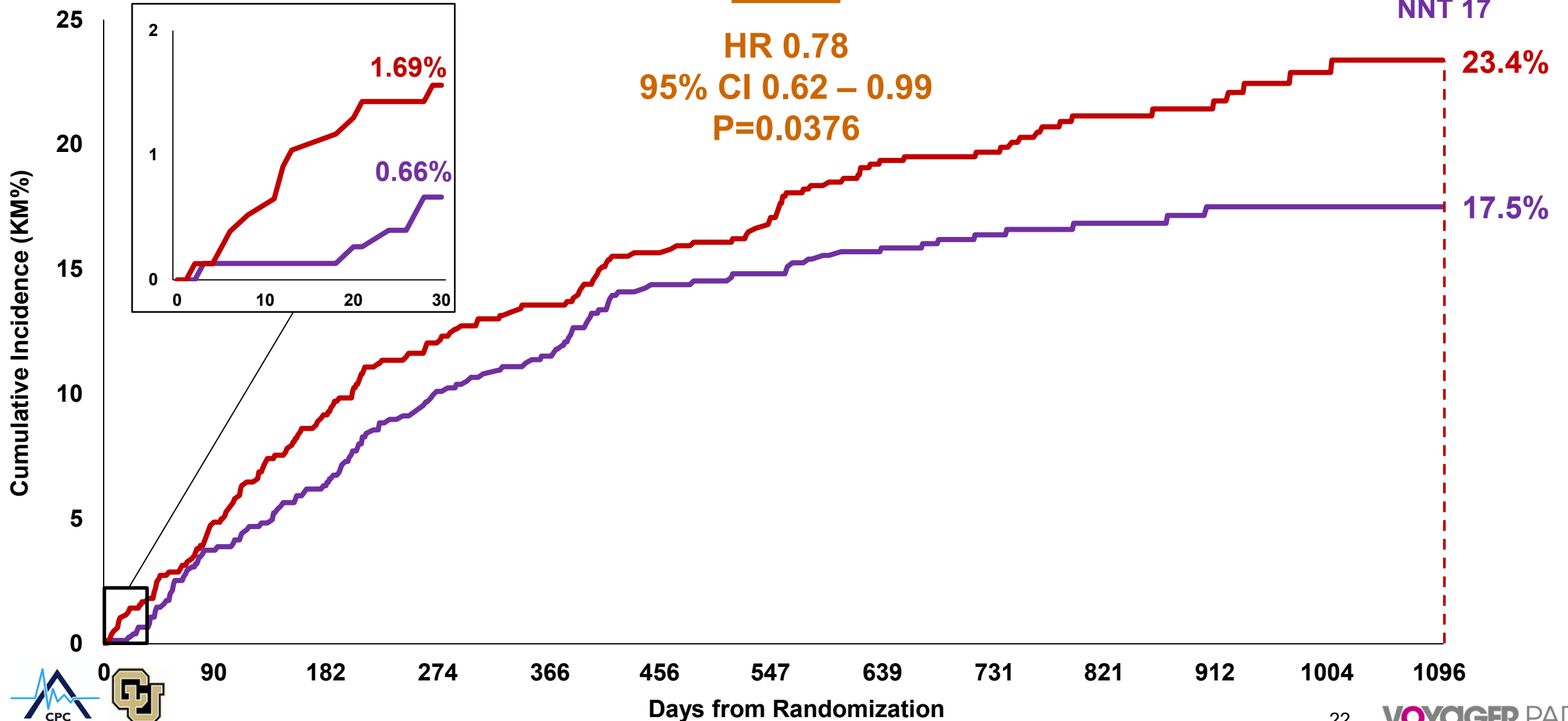
# Unplanned Index Limb Revascularization

- Placebo
- Rivaroxaban

**With CLI**  
N=1533

3 Year  
ARR 5.9%  
NNT 17

30 Day ARR=1.02%



# Net Clinical Benefit

*Acute limb ischemia, major amputation of a vascular etiology, myocardial infarction, ischemic stroke, all cause mortality, ICH or fatal bleeding*

■ Placebo  
■ Rivaroxaban

*P-interaction 0.77*

With CLI

N=1,521\*

HR 0.78

95% CI 0.61 – 1.00

p=0.0457

3 Year  
ARR 5.7%

24.9%

19.2%

NNT 18

Without CLI

N=4,983\*

HR 0.74

95% CI 0.63 – 0.88

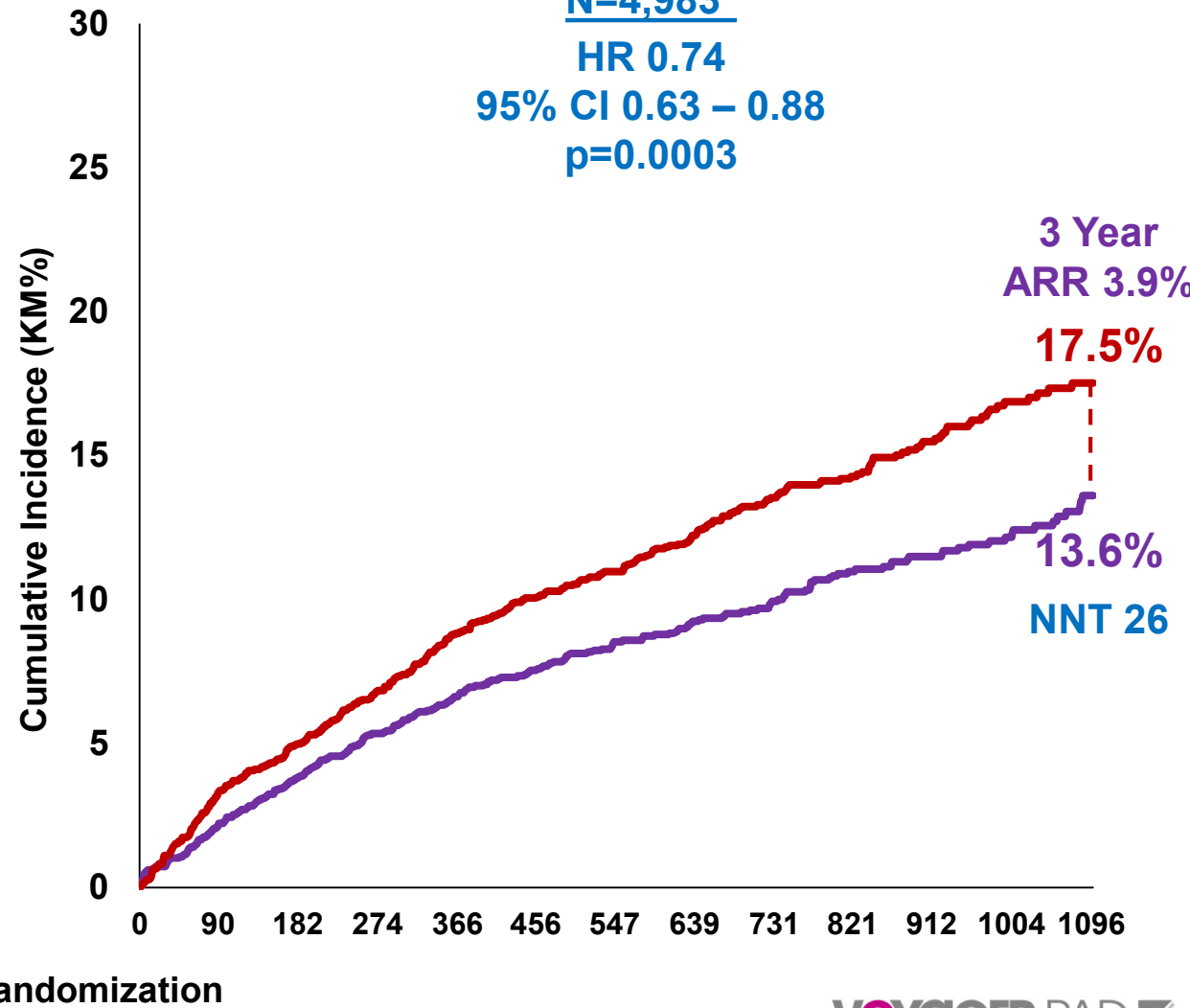
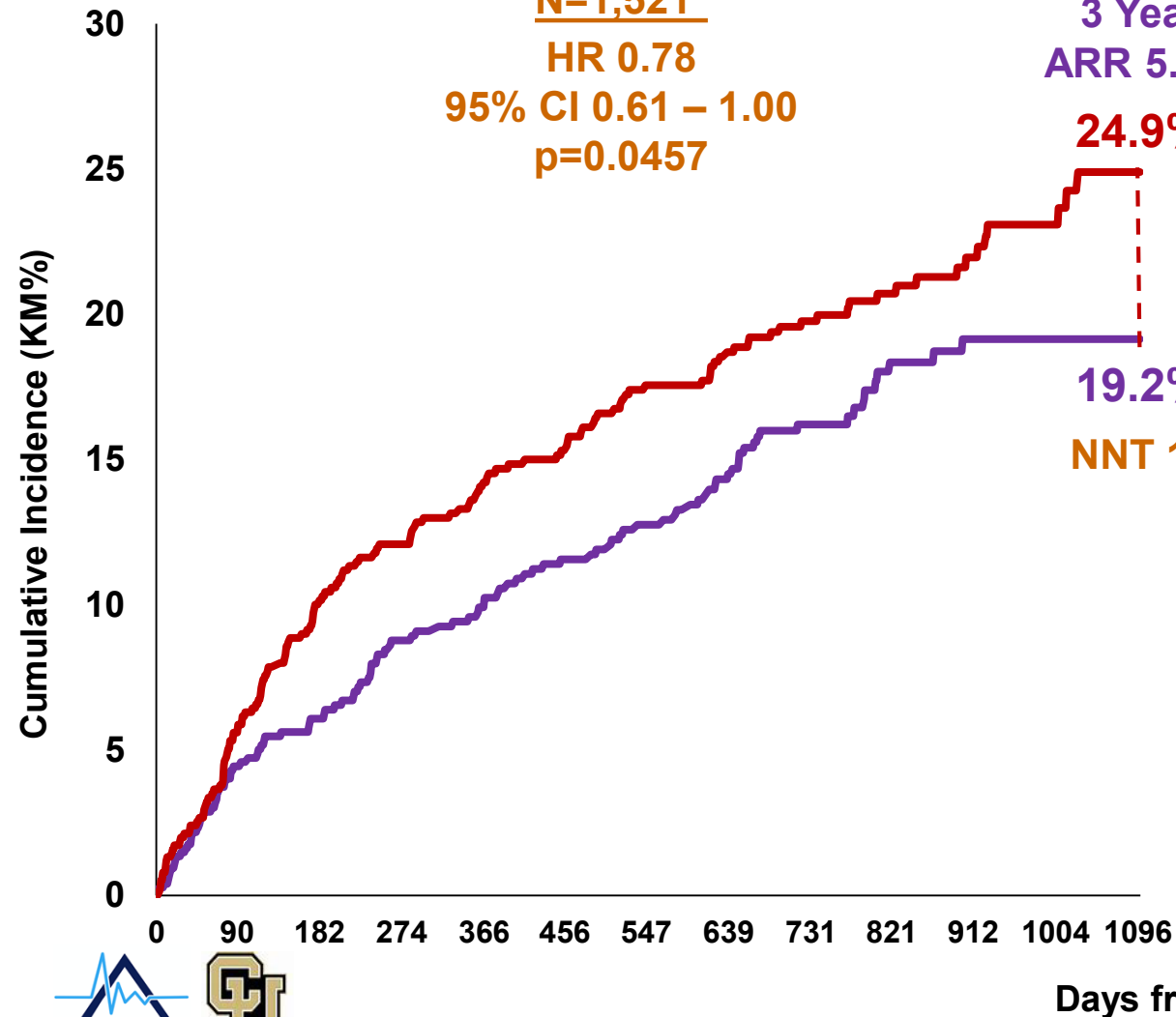
p=0.0003

3 Year  
ARR 3.9%

17.5%

13.6%

NNT 26



\*Safety Population, On-Treatment Scope

# Summary

- In VOYAGER PAD, patients with PAD presenting for LER for CLI were at very high risk of irreversible harm events of the heart, limb and brain with:
  - ~1 in 10 having a first event within 6 months of intervention
  - > 1 in 4 having a first event within 3 years of intervention
- Rivaroxaban 2.5 mg twice daily with aspirin versus aspirin alone significantly reduces this risk with benefits apparent early and continued over time and with consistency in those with and without CLI
- The benefits of rivaroxaban 2.5 mg twice daily with aspirin versus aspirin alone extend to reductions in the need for unplanned index limb revascularization with benefits apparent at 1 month after LER



# Conclusions

- **Patients with CLI (now CLTI), one of the most severe manifestations of PAD, represent an extreme risk population characterized by high rates of recurrent procedures and adverse events of the limb, heart and brain**
- **Lower extremity revascularization is recommended in CLI to minimize/prevent tissue loss; however, the risk of complications appears particularly high in the post intervention setting**
- **Despite this extreme risk profile, there are few adjunctive medical therapies that have demonstrated benefit in CLI patients overall and particularly after intervention**
- ***Rivaroxaban 2.5 mg twice daily with aspirin should be considered as adjunctive therapy after LER for CLI to reduce adverse events of the heart, limb and brain as well as the need for repeat revascularizations***