# Rivaroxaban Reduces Major Cardiovascular And Limb Events In Patients With The High-risk Triad Of Chronic Kidney Disease, Peripheral Artery Disease And Recent Lower Extremity Revascularization: Insights From VOYAGER PAD

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# Disclosures

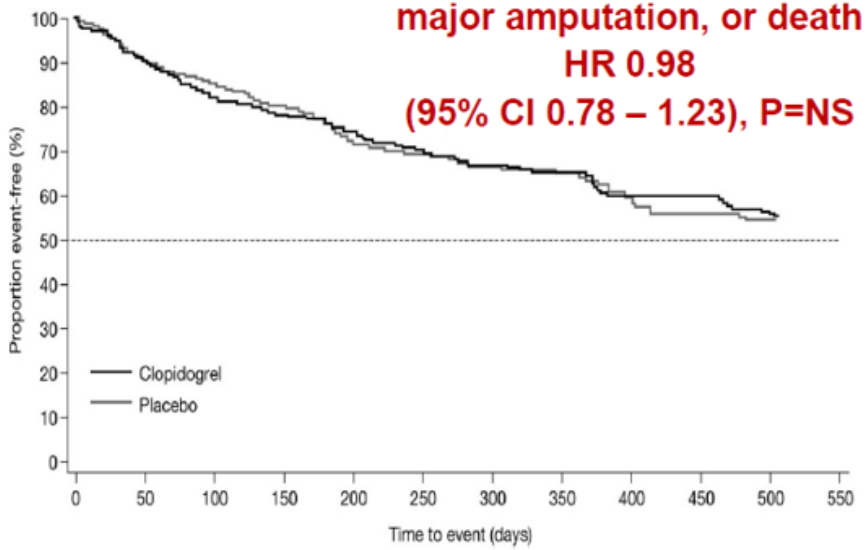
VOYAGER was funded by Bayer and Janssen

CPC Clinical Research receives research grants from Alnylam, Amgen, Arca, AstraZeneca, Bayer, CellResearch, Eidos, Janssen, NovoNordisk, Osiris, Terumo

# Background

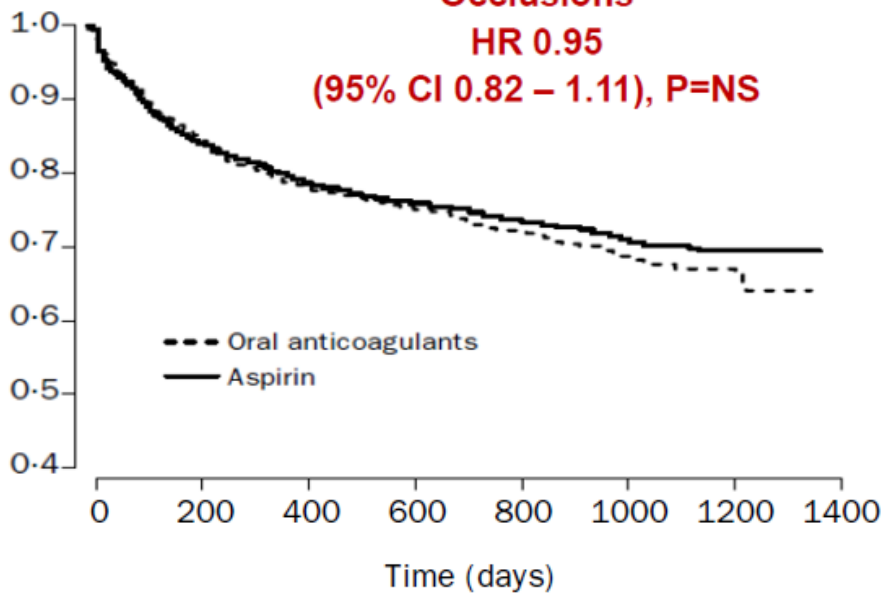
Despite high risk, prior to VOYAGER PAD no anti-thrombotic strategy had demonstrated efficacy for reducing major adverse limb and CV events after peripheral intervention for ischemia

**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**



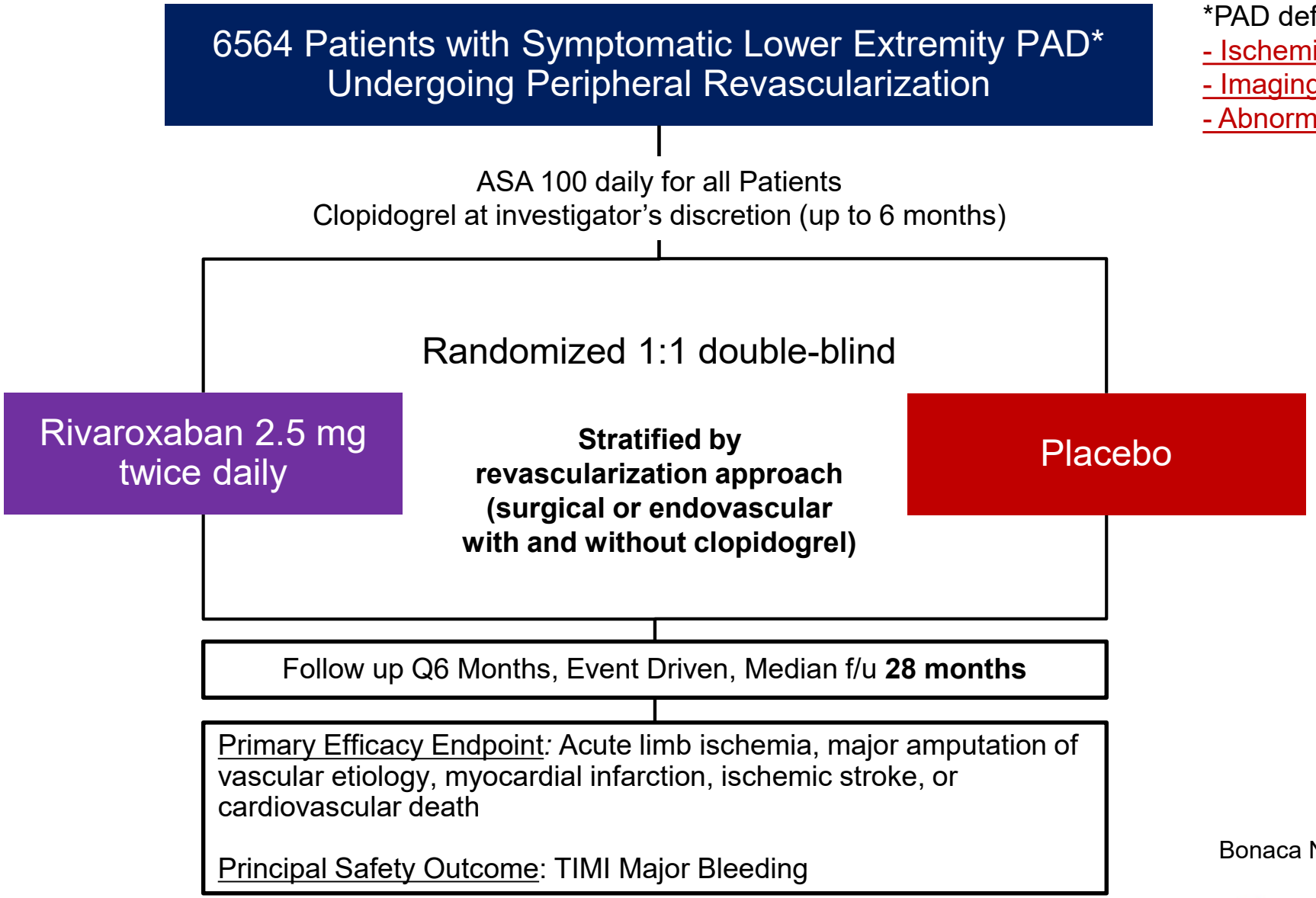

**Full Intensity Oral anticoagulation**
**Increased risk of Hemorrhagic Stroke**
**HR 3.48 (1.14 – 10.60)**



Belch et al. J Vasc Surg 2010, Dutch Bypass Oral anticoagulants or Aspirin (BOA) Study Group. Lancet 2000

# Trial design

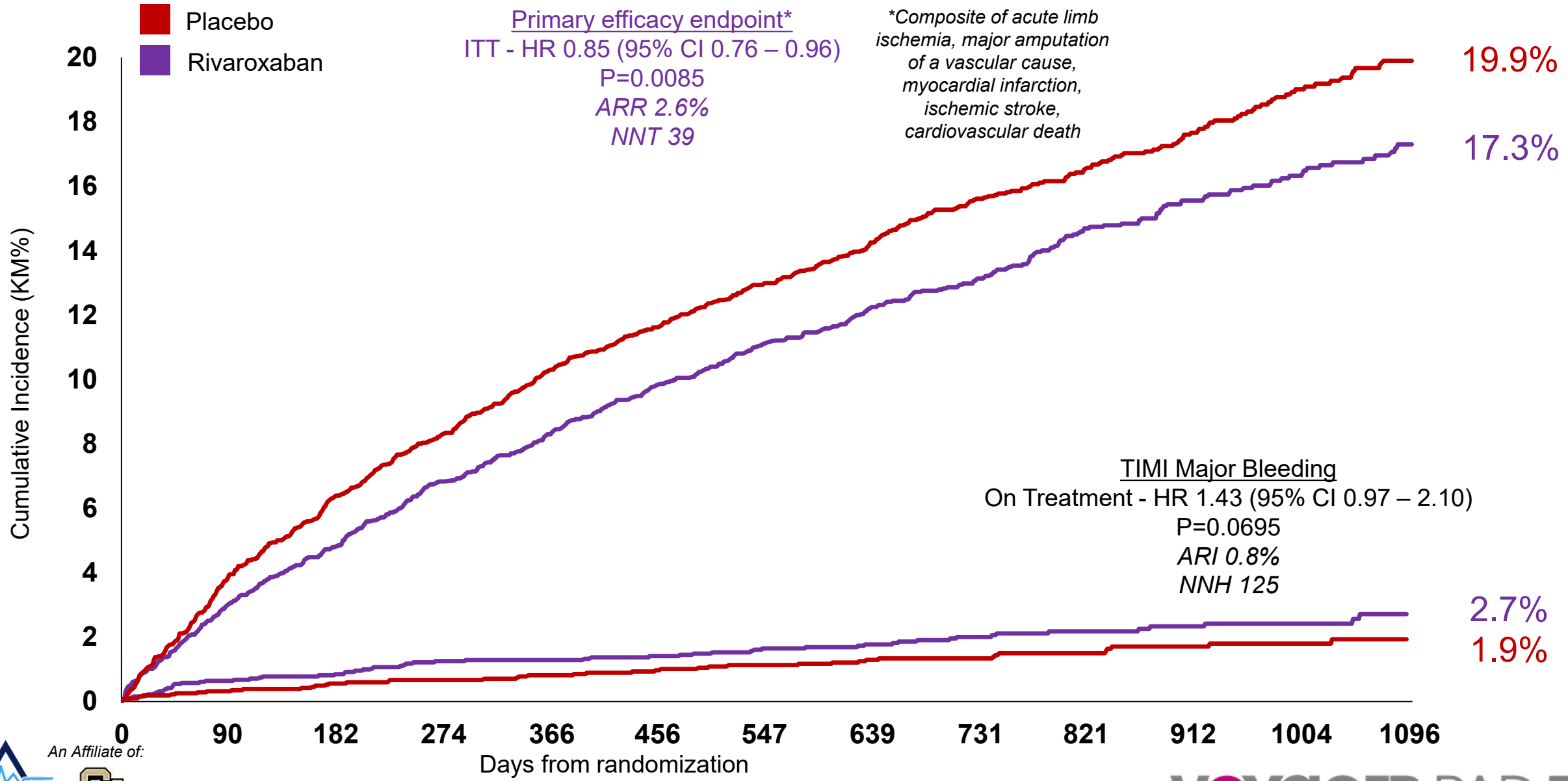
NCT02504216




*PAD defined as:
- Ischemic symptoms AND
- Imaging evidence of PAD AND
- Abnormal ABI/TBI

Bonaca NEJM 2020;382:1994

# VOYAGER PAD Primary Results






Bonaca NEJM 2020;382:1994

# Patients with CKD in VOYAGER PAD

## eGFR exclusion criterion

Any condition requiring dialysis or renal replacement therapy, or eGFR <15 mL/min/ 1.73m$^2$

If eGFR <30 prior to revascularization procedure, it must remain >15 at 72h after the procedure

# Rivaroxaban in patients with renal impairment

**Xarelto® USPI**

The relationship between systemic exposure and pharmacodynamic activity of rivaroxaban was altered in subjects with renal impairment relative to healthy control subjects *[see Use in Specific Populations (8.6)]*.

**Table 10: Percentage Increase in Rivaroxaban PK and PD Measures in Subjects with Renal Impairment Relative to Healthy Subjects from Clinical Pharmacology Studies**

| Measure | Parameter | Creatinine Clearance (mL/min) | | | | |
|---|---|---|---|---|---|---|
| | | 50-79 | 30-49 | 15-29 | ESRD (on dialysis)* | ESRD (post-dialysis)* |
| Exposure | AUC | 44 | 52 | 64 | 47 | 56 |
| FXa Inhibition | AUEC | 50 | 86 | 100 | 49 | 33 |
| PT Prolongation | AUEC | 33 | 116 | 144 | 112 | 158 |

**Separate stand-alone study.*

PT = Prothrombin time; FXa = Coagulation factor Xa; AUC = Area under the plasma concentration-time curve; AUEC = Area under the effect-time curve

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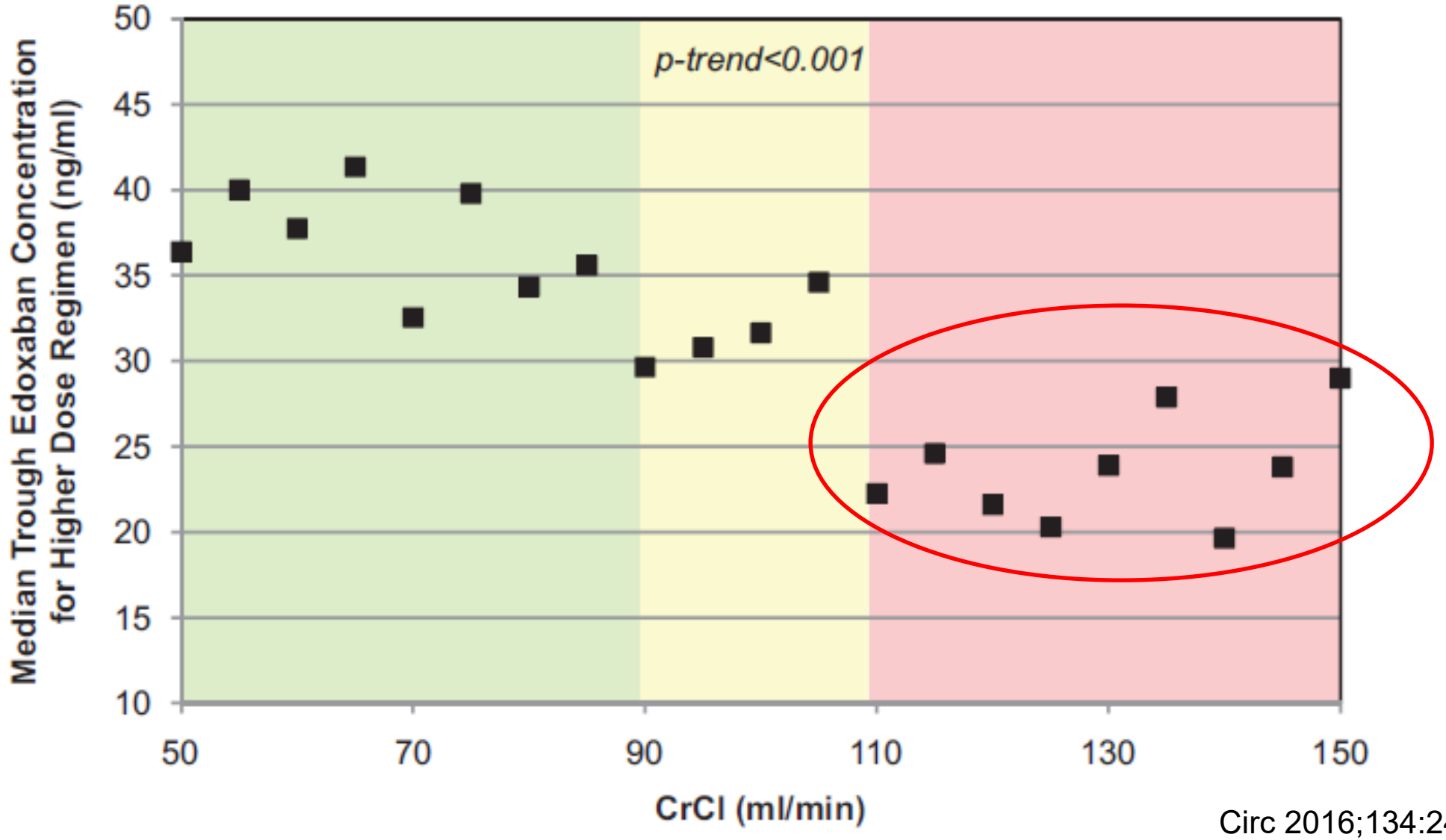
# Similarly, edoxaban exposure was inversely related to creatinine clearance

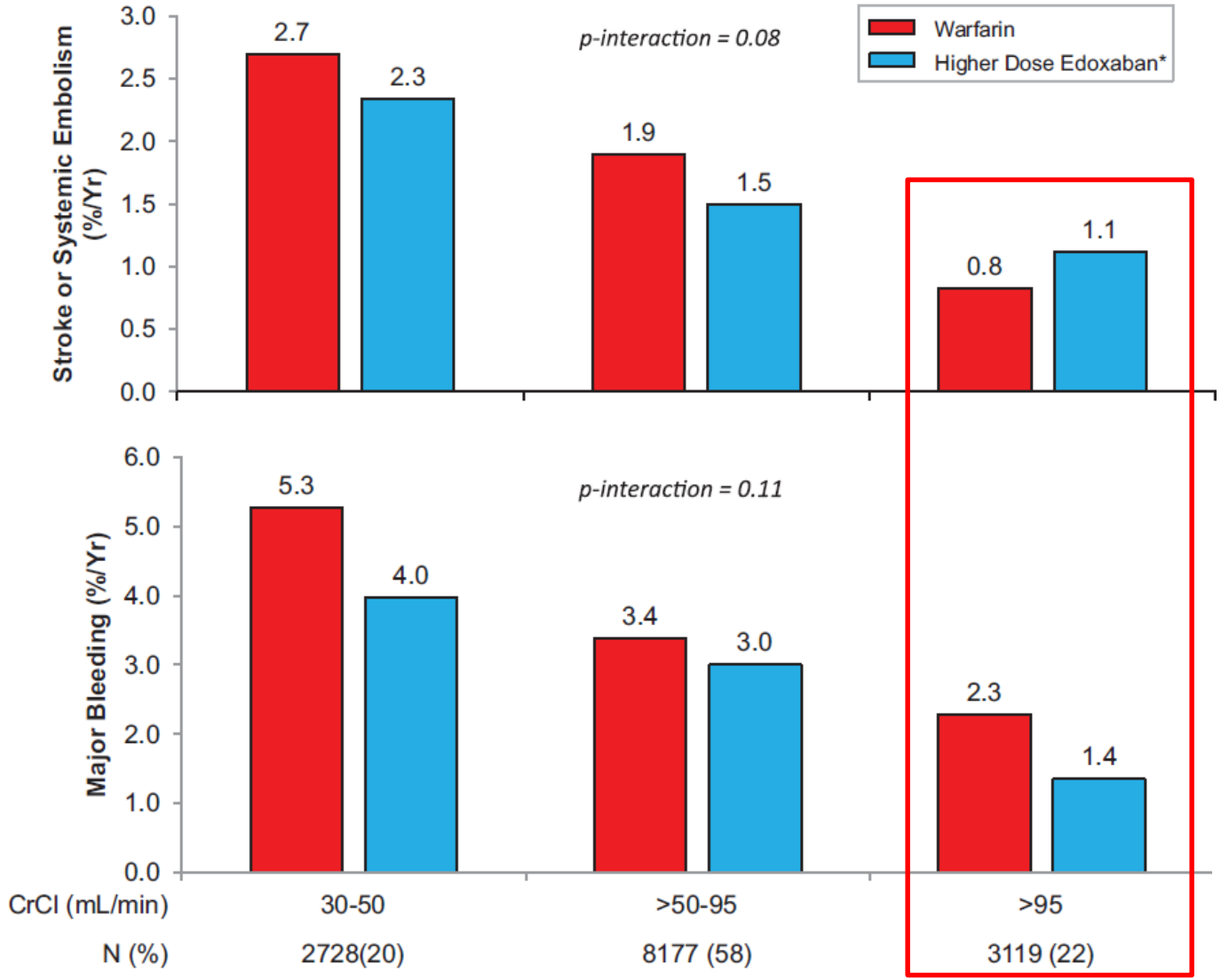
**ENGAGE AF-TIMI 48: 14071 patients with atrial fibrillation randomized to edoxaban or warfarin**






Circ 2016;134:24-36

# Patients with normal renal function had lower edoxaban levels, more thrombotic events and less bleeding compared with warfarin

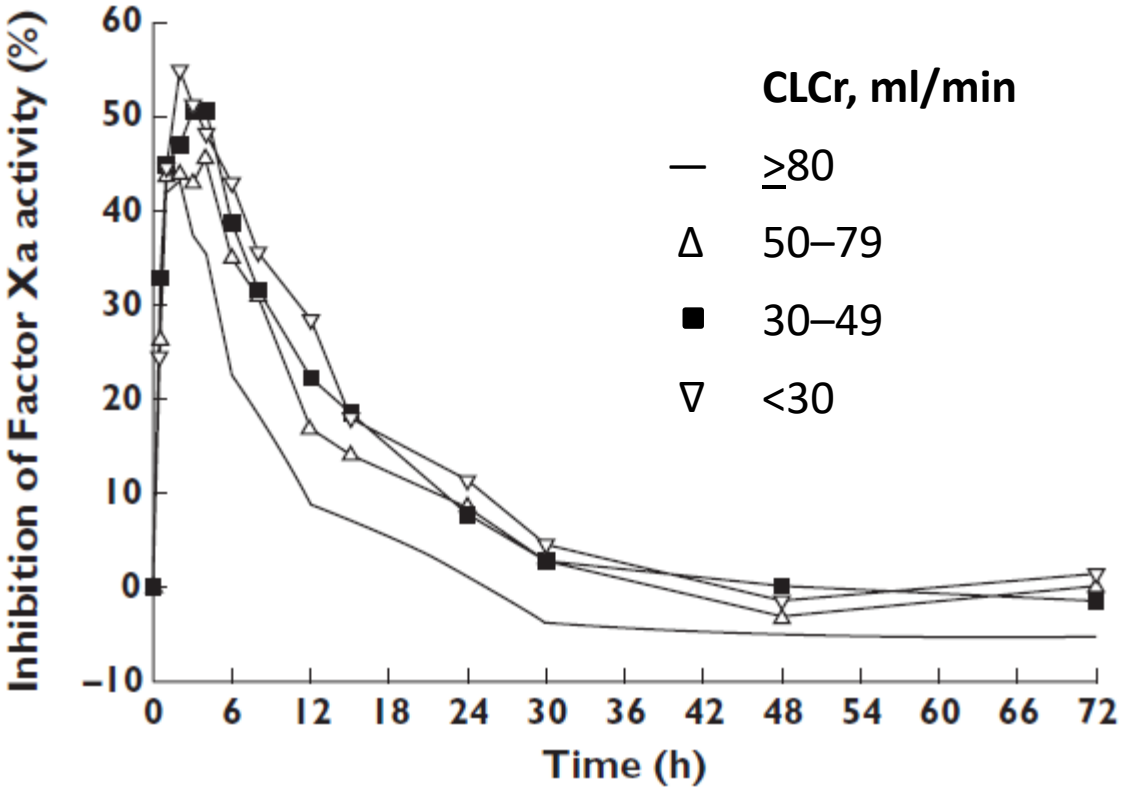





Circ 2016;134:24-36

# With rivaroxaban, greater efficacy and potentially more bleeding might be anticipated in patients with CKD due to higher exposure

**Time course of factor Xa inhibition with rivaroxaban in subjects with renal impairment**






Br J Clin Pharmacol 2010;70:703–712

# Objectives

In PAD patients undergoing lower extremity revascularization (LER) for ischemic symptoms

1. To what extent were those with CKD at higher risk for major CV and limb events

2. Were the efficacy and safety of rivaroxaban in patients with CKD consistent with the overall cohort

# Methods

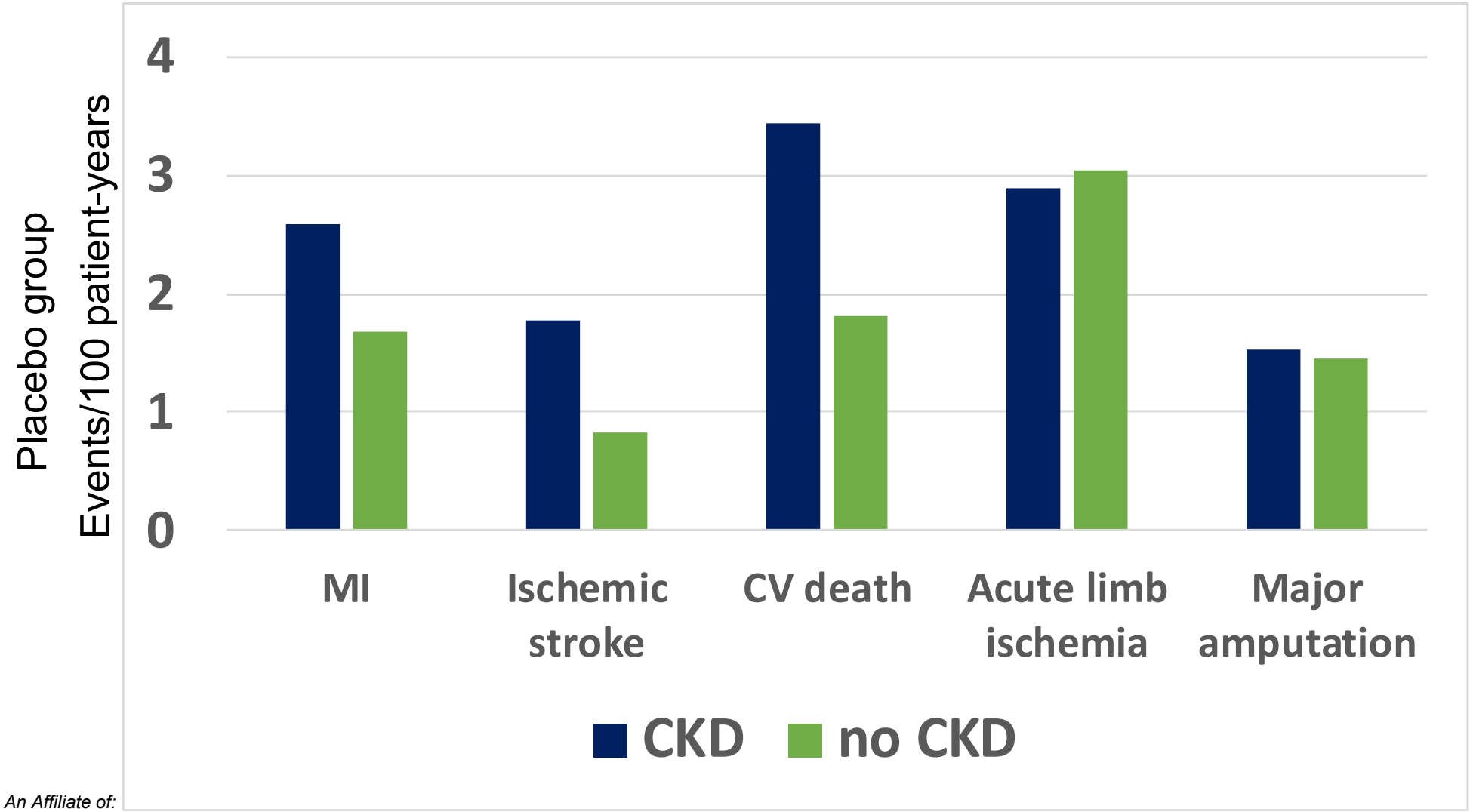
- CKD defined as baseline eGFR<60 ml/min/1.73m$^2$ (MDRD equation)
- Major CV and limb events were prospectively ascertained and independently adjudicated by a blinded committee using established definitions
- Prespecified secondary analysis of VOYAGER PAD
- Effect of rivaroxaban estimated with Cox proportional hazards model stratified according to revascularization type (surgical vs endovascular) and clopidogrel use

Capell Am Heart J 2018;199:83-91

# Baseline characteristics

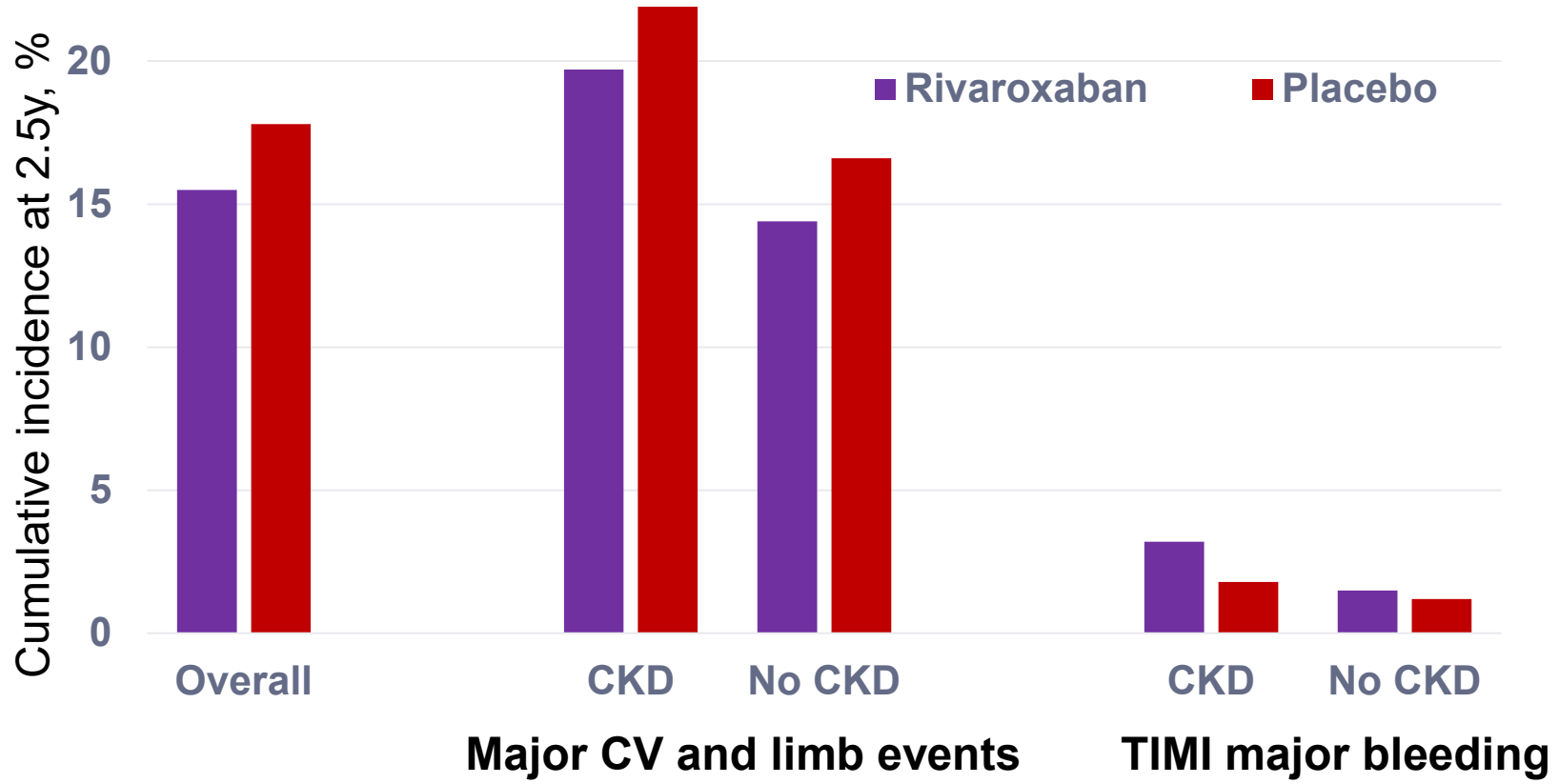
| | CKD, n=1327 | No CKD, n=4992 | p value |
|---|---|---|---|
| Age, years, mean (SD) | 72.4 (8.1) | 65.7 (8.1) | <0.0001 |
| Female, % | 38 | 23 | <0.0001 |
| Race, % | | | <0.0001 |
| White | 73 | 82 | |
| Asian | 22 | 13 | |
| Black/African-American | 3 | 2 | |
| Hypertension, % | 91 | 79 | <0.0001 |
| Diabetes mellitus, % | 53 | 37 | <0.0001 |
| Hyperlipidemia, % | 65 | 59 | <0.0001 |
| Current smoking, % | 21 | 38 | <0.0001 |
| eGFR, ml/min/1.73m$^2$, mean (SD) | 48.0 (8.7) | 86.5 (20.9) | <0.0001 |
| CKD stage 3 | 1284 | | |
| CKD stage 4 | 41 | | |
| CKD stage 5 | 2 | | |

# Major CV events, but not limb events, were more frequent among patients with CKD

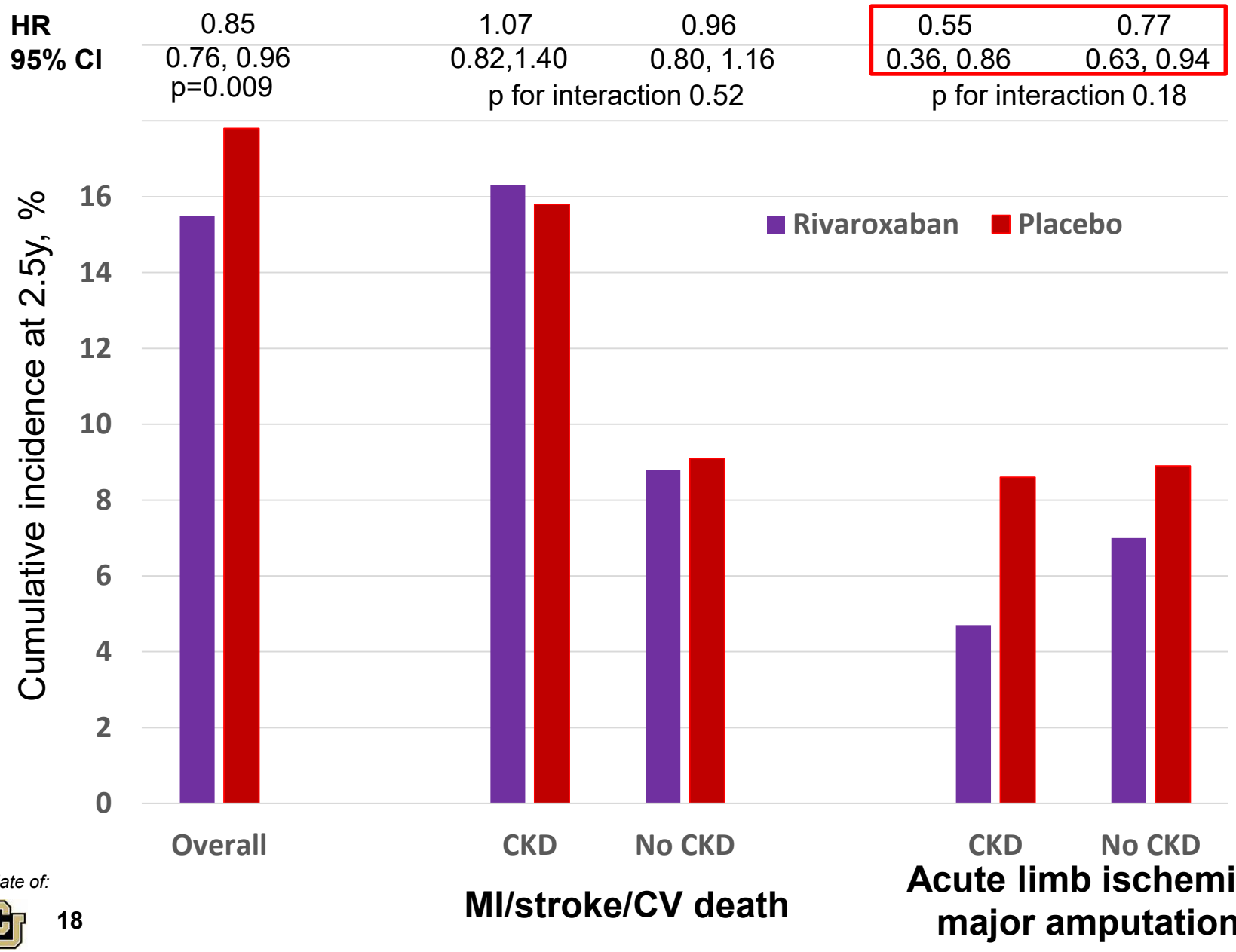


# Primary efficacy and safety endpoints by CKD category

| | | | | | |
|---|---|---|---|---|---|
| HR | 0.85 | 0.90 | 0.85 | 1.86 | 1.27 |
| 95% CI | 0.76, 0.96 | (0.71, 1.15) | (0.73, 0.97) | (0.92, 3.79) | (0.79, 2.05) |
| | p=0.009 | p for interaction 0.62 | | p for interaction 0.37 | |



# Major CV and limb events by CKD category



# Summary

- Patients with PAD, recent lower extremity revascularization and CKD (mostly stage 3) had a higher rate of major CV events than patients without CKD
- Rivaroxaban reduced the composite primary endpoint of major CV and limb events with no heterogeneity by CKD category
- Rivaroxaban reduced major limb events (acute limb ischemia and major amputation) among patients with or without CKD
- TIMI major bleeding showed no heterogeneity by CKD category

# Conclusion

In PAD patients undergoing lower extremity revascularization (LER) for ischemic symptoms

- Patients with CKD were at higher risk for major CV events (MI/stroke/CV death), but were not at higher risk for limb events (acute limb ischemia/major amputation)

- Efficacy and safety of rivaroxaban in patients with CKD were consistent with the overall cohort