Polyvascular Disease with and without Diabetes and the risk of Cardiovascular and Limb Events: Observations from EUCLID

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CPC

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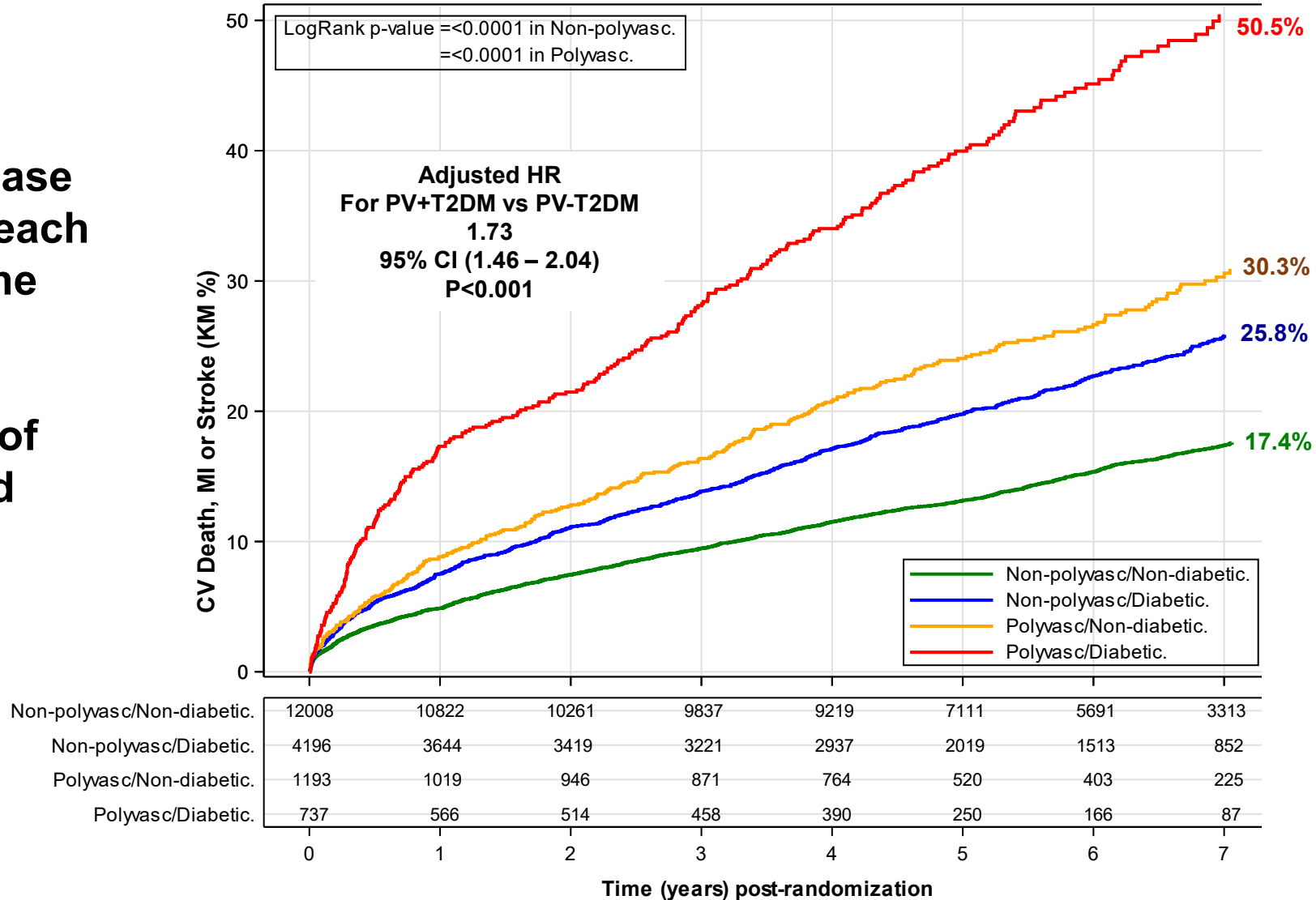
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Disclosures

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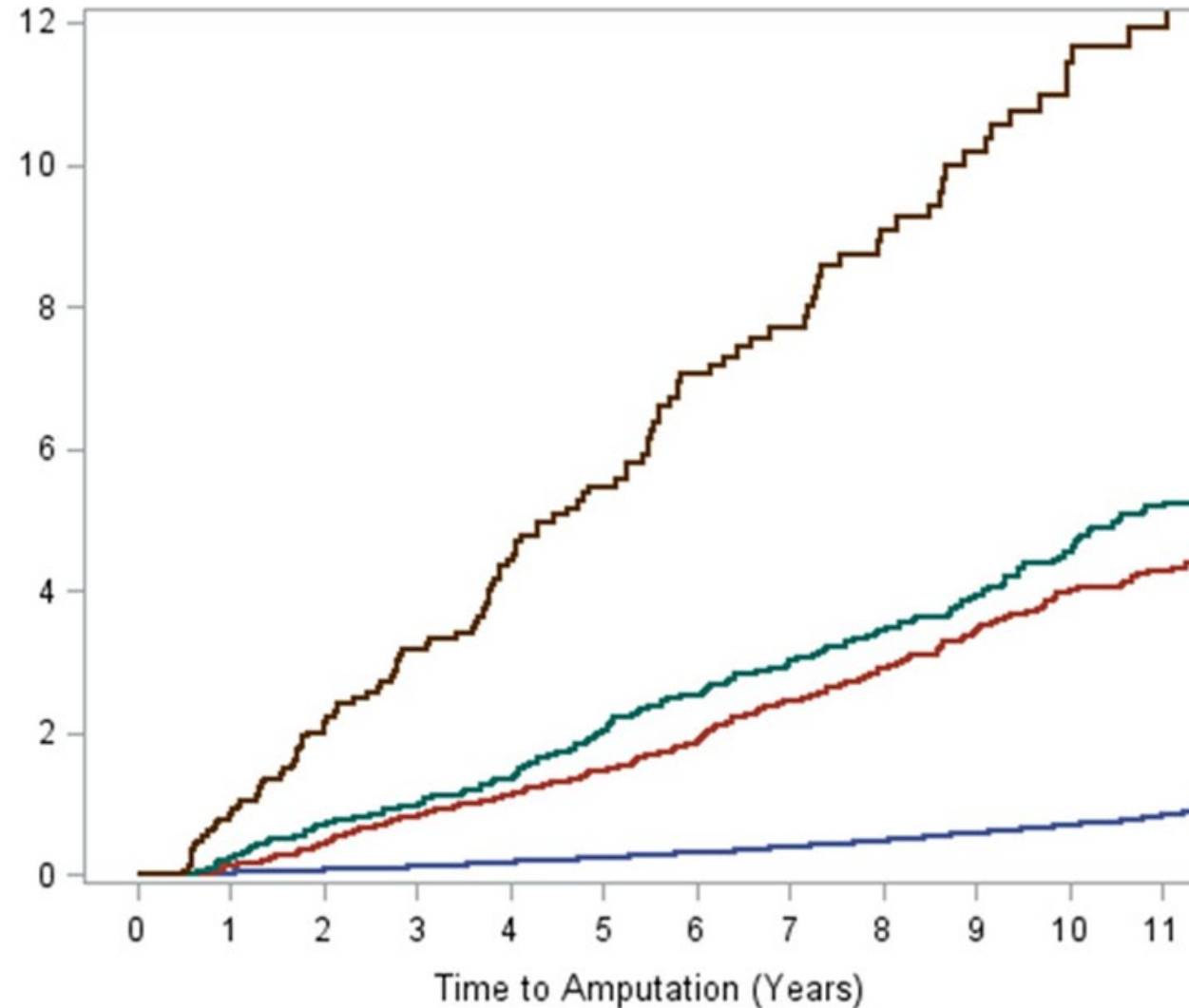
Background

In ACS Patients:

- polyvascular disease and diabetes are each associated with the risk of MACE

- The combination of both is associated with further heightened risk

LogRank p-value =<0.0001 in Non-polyvasc.
=<0.0001 in Polyvasc.

Adjusted HR
For PV+T2DM vs PV-T2DM
1.73
95% CI (1.46 – 2.04)
P<0.001

CV Death, MI or Stroke (KM %)

Legend:
- Non-polyvasc/Non-diabetic.
- Non-polyvasc/Diabetic.
- Polyvasc/Non-diabetic.
- Polyvasc/Diabetic.

50.5%
30.3%
25.8%
17.4%

	0	1	2	3	4	5	6	7
Non-polyvasc/Non-diabetic.	12008	10822	10261	9837	9219	7111	5691	3313
Non-polyvasc/Diabetic.	4196	3644	3419	3221	2937	2019	1513	852
Polyvasc/Non-diabetic.	1193	1019	946	871	764	520	403	225
Polyvasc/Diabetic.	737	566	514	458	390	250	166	87

Time (years) post-randomization

Bonaca MP…Braunwald E. et al. Lancet Diabetes and Endocrinology 2018

Background

- PAD and microvascular disease are each associated with the risk of amputation

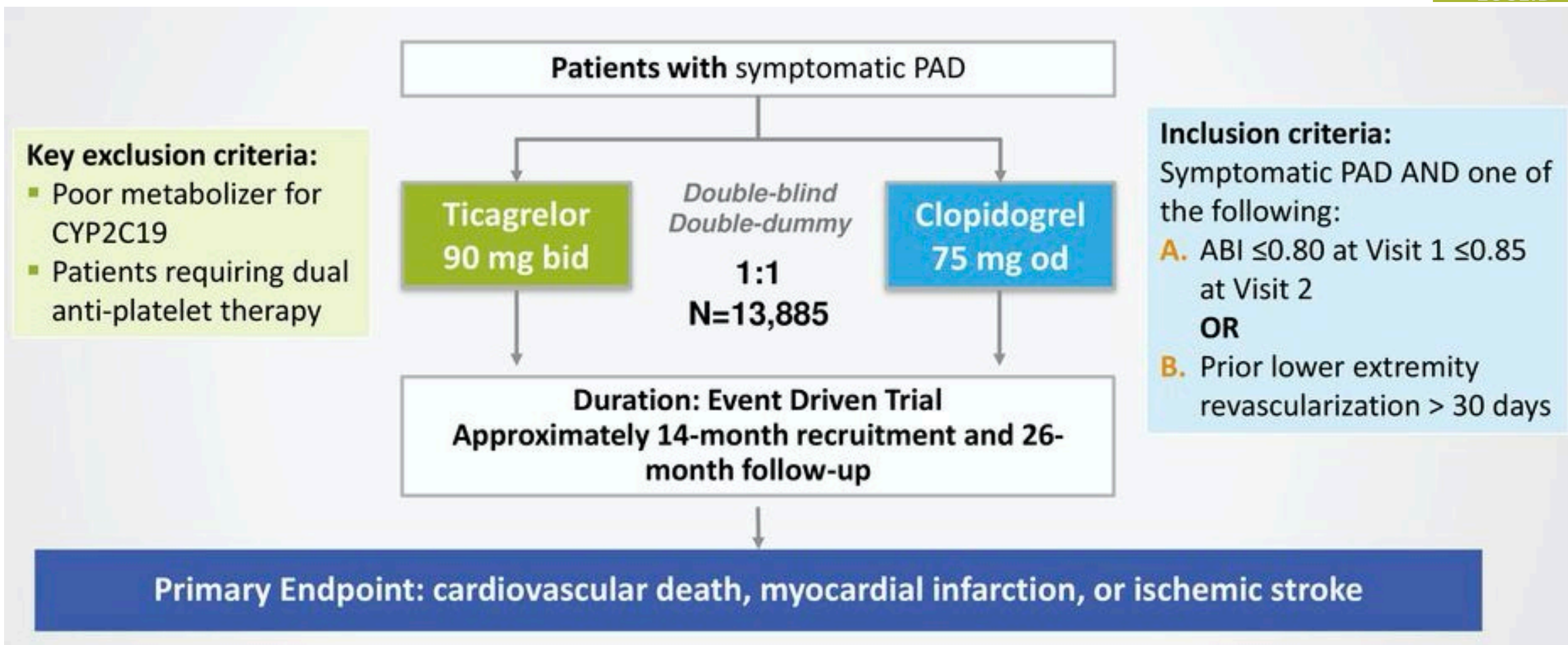- The combination of both is associated with further heightened risk

Beckman JA et al. Circulation 2019

Objectives

1. Does the observation that polyvascular disease and diabetes are each associated with <u>MACE</u> risk and the combination with further heightened risk extend to patients with lower extremity peripheral artery disease (PAD)?

2. Do polyvascular disease and diabetes also predict the risk of major adverse limb events, including:

    - *Acute limb ischemia*
    - *Major amputation*

Methods – EUCLID Design

Patients with symptomatic PAD

Double-blind Double-dummy

Ticagrelor 90 mg bid

Clopidogrel 75 mg od

1:1
N=13,885

Key exclusion criteria:
- Poor metabolizer for CYP2C19
- Patients requiring dual anti-platelet therapy

Inclusion criteria:
Symptomatic PAD AND one of the following:
A. ABI ≤0.80 at Visit 1 ≤0.85 at Visit 2
   OR
B. Prior lower extremity revascularization > 30 days

Duration: Event Driven Trial
Approximately 14-month recruitment and 26-month follow-up

Primary Endpoint: cardiovascular death, myocardial infarction, or ischemic stroke

Hiatt…Patel et al. NEJM 2016

Methods

PAD defined as:

1. Previous revascularization of lower limbs for symptomatic disease at least 30 days before randomization OR

2. Hemodynamic evidence of PAD (ABI of < 0.80 at screening)

Polyvascular disease (PVD) defined as:

- Number of disease vascular beds (e.g. coronary or cerebrovascular) in addition to PAD (1=PAD only)

Diabetes (DM) defined as a reported history of diabetes at randomization
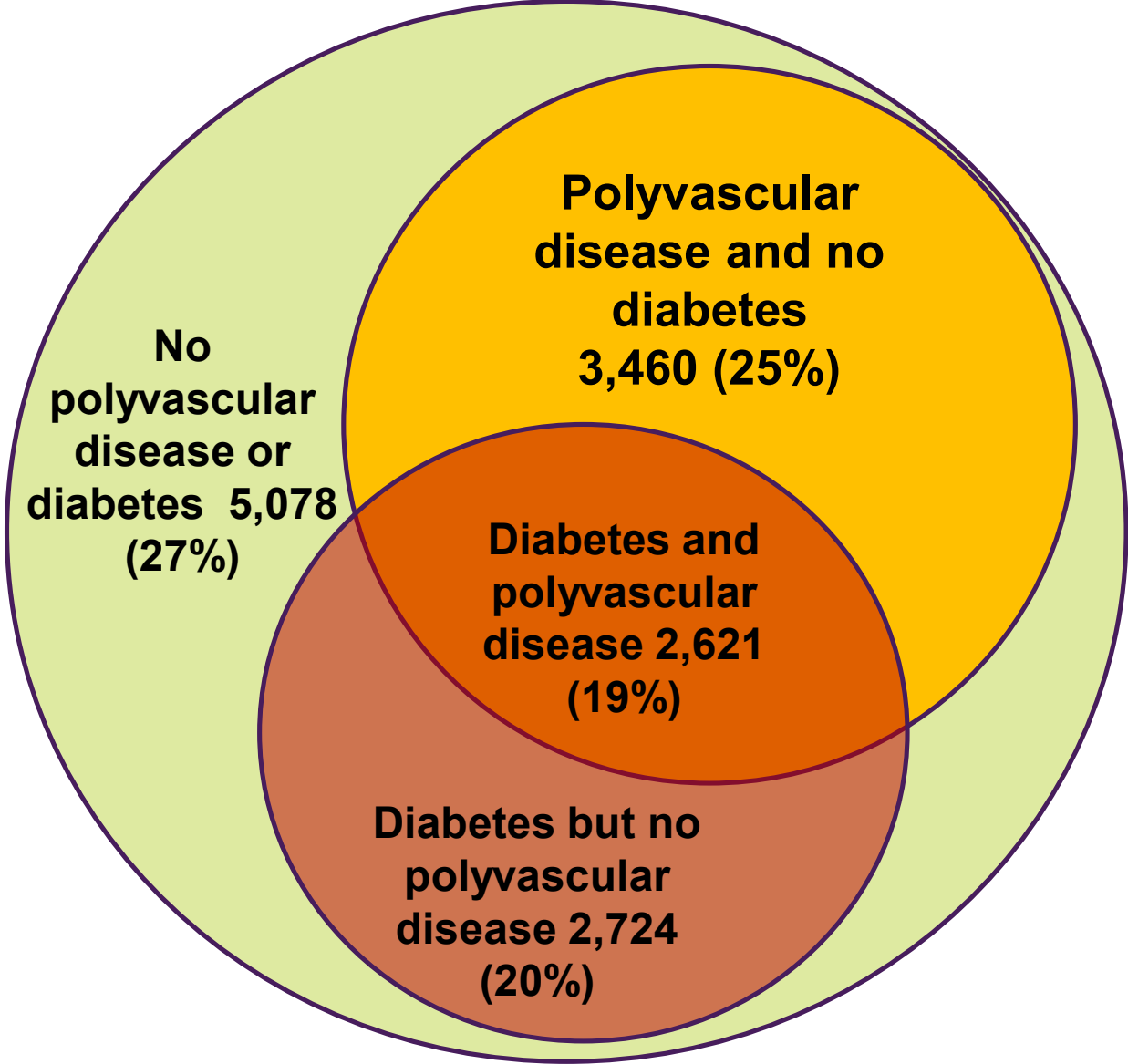
Endpoint Definitions

MACE = composite of CV death, MI, Ischemic Stroke

MALE = composite of ALI and Major Amputation

Methods

- KM event rates for each subgroup and endpoint

- Cox proportional hazards model used to assess relationship between PVD x DM and clinical outcomes (MACE, MALE, and each of their component pieces) with referent the absence of both PAD and DM

- Proportional hazards assumption assessed using weighted Schoenfeld residuals

- Risk for factor and outcome adjusted for baseline differences including age, weight, sex, region, ABI, GFR, statin use, ARB use, tobacco use

Results - Population

No polyvascular disease or diabetes 5,078 (27%)

Polyvascular disease and no diabetes 3,460 (25%)

Diabetes and polyvascular disease 2,621 (19%)

Diabetes but no polyvascular disease 2,724 (20%)

Results - Population

Characteristic	-PVD -DM	+PVD -DM	-PVD +DM	+PVD +DM	P-value
Median Age (y)	65	67	66	67	<0.001
Female (%)	29	24	32	26	<0.001
HTN (%)	65	85	81	90	<0.001
HLD (%)	65	85	72	88	<0.001
Tobacco Use (%)	37	34	25	22	<0.001
Prior amp (%)	1.8	1.4	4.5	3	<0.001
Previous Periph Revasc (%)	58	60	48	59	NA
CAD (%)	-	63	-	71	NA
MI (%)	-	40	-	43	NA
Stroke (%)	-	18	-	21	NA
Cilostazol Use (%)	15	12	18	16	<0.001
Statin (%)	65	83	66	84	<0.001

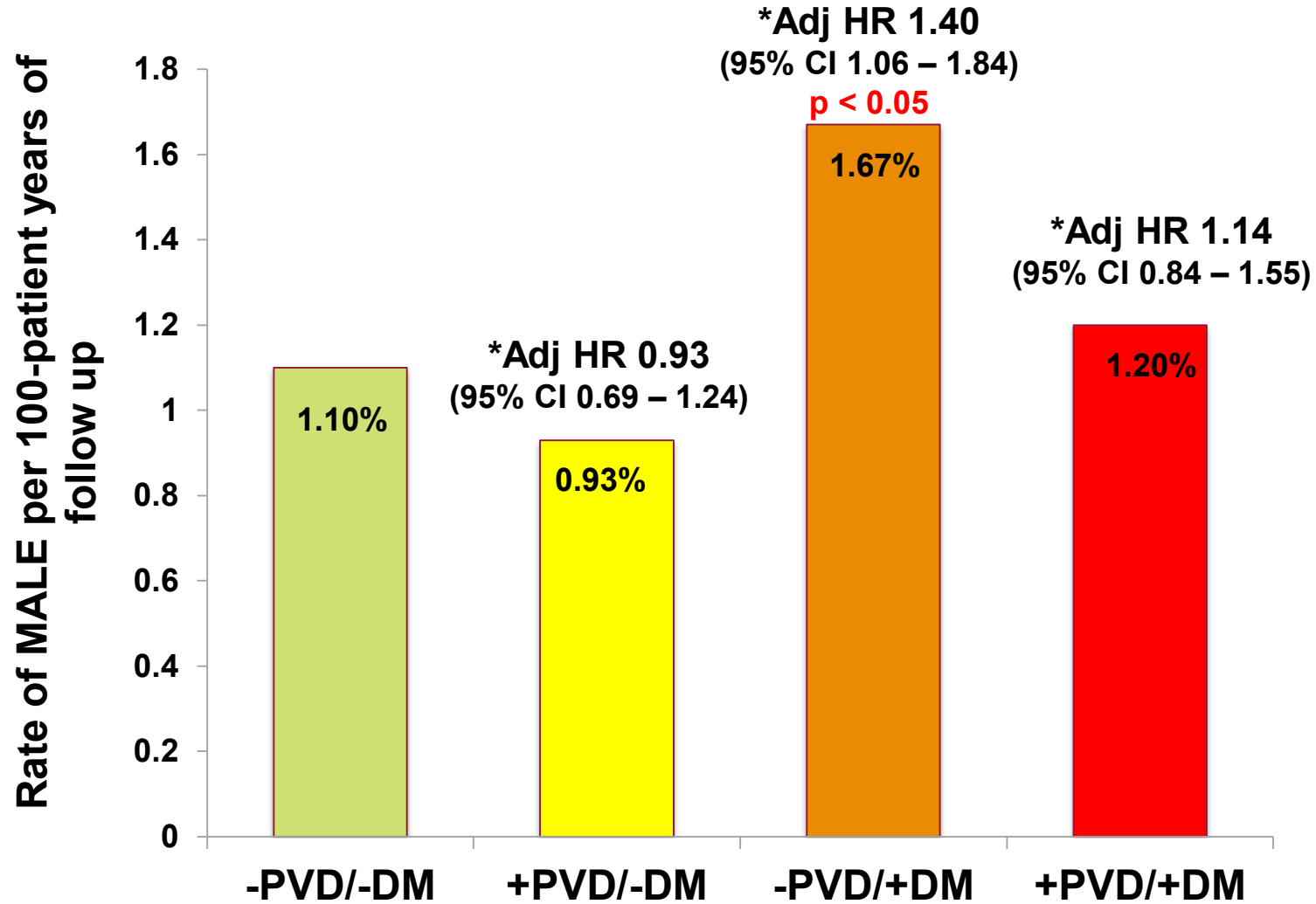# Results – Risk of Major Adverse Cardiovascular Events
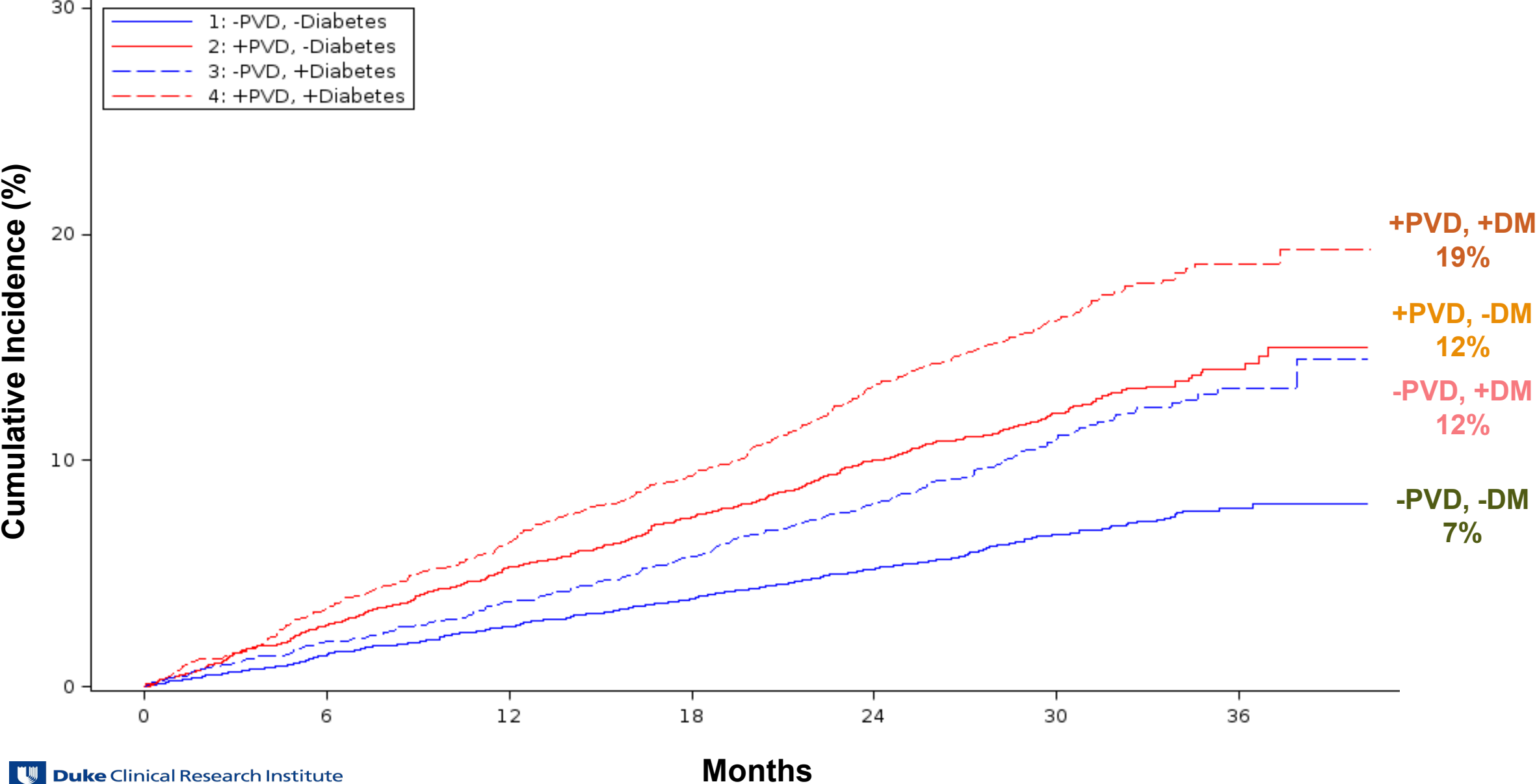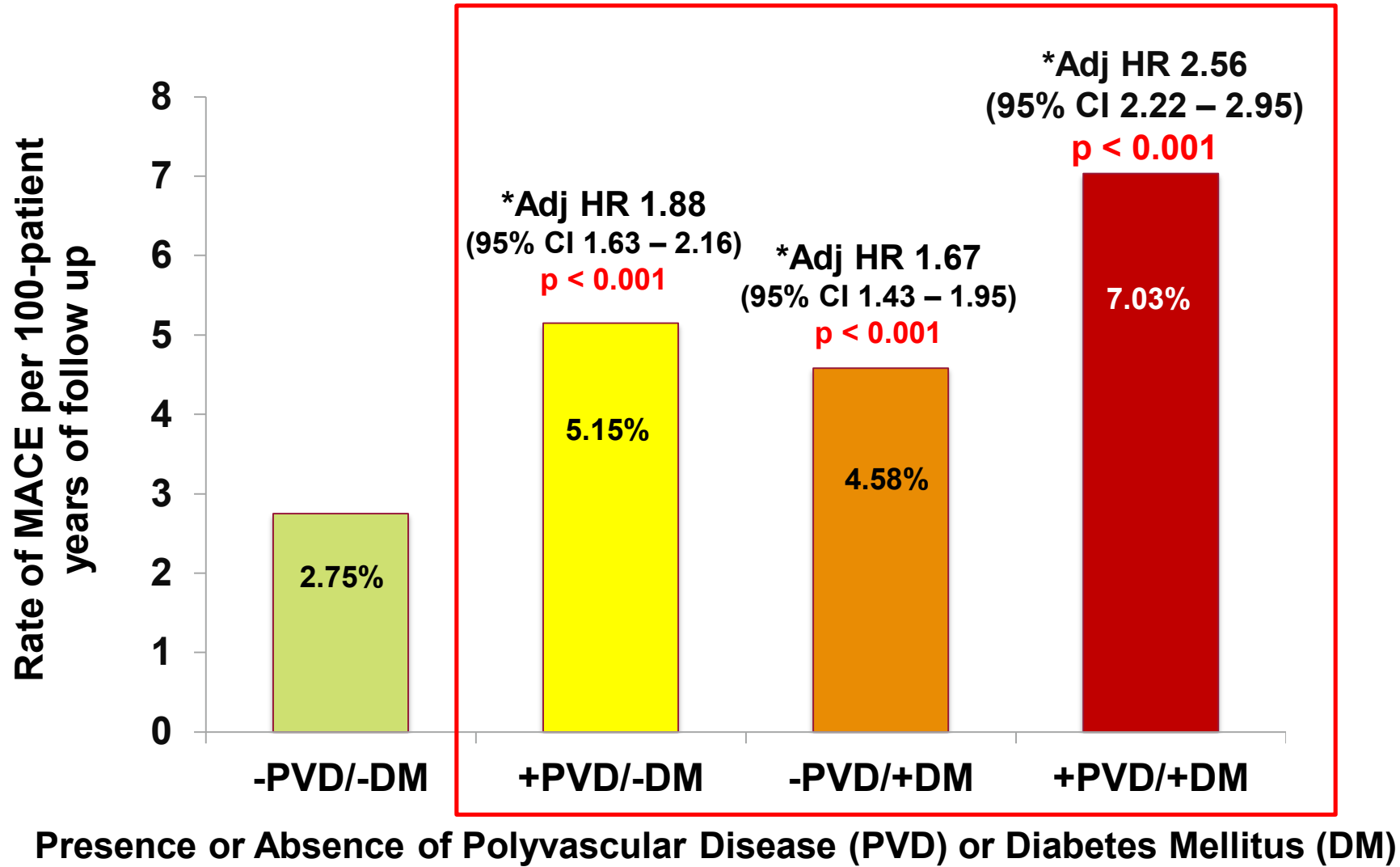
Results – Risk of Major Adverse Cardiovascular Events

*Adjusted for: age, weight, sex, region, ABI, GFR, statin use, ARB use, tobacco use

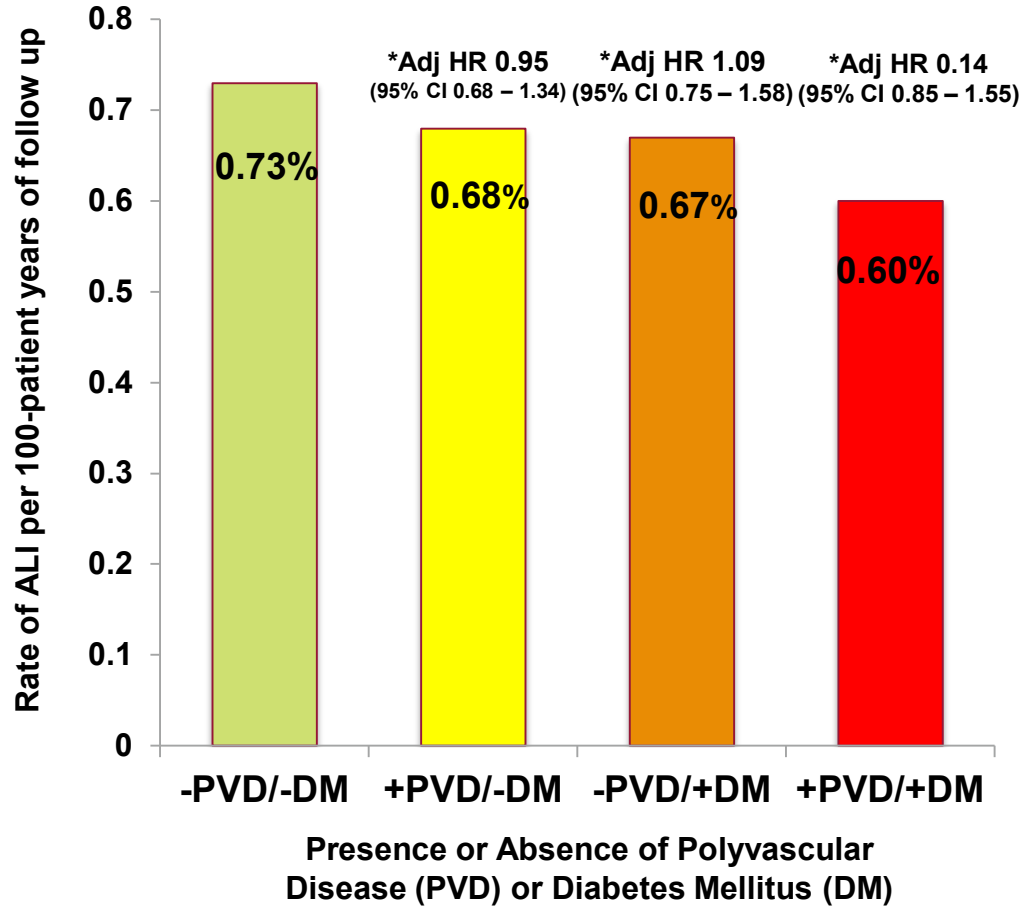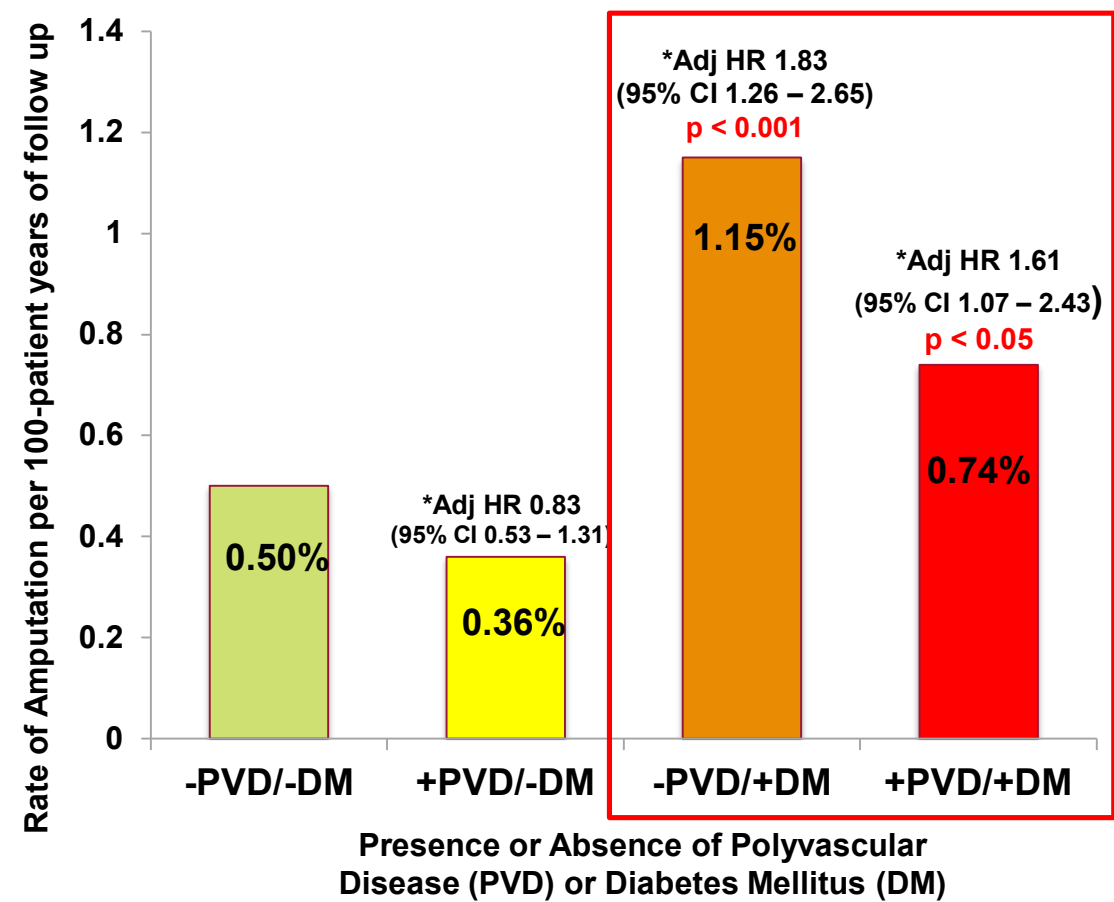# Results – Risk of Major Adverse Limb Events

Presence or Absence of Polyvascular Disease (PVD) or Diabetes Mellitus (DM)

*Adjusted for: age, weight, sex, region, ABI, GFR, statin use, ARB use, tobacco use

Results – Risk of Major Adverse Limb Events

ALI

*Adj HR 0.95 (95% CI 0.68 – 1.34)
*Adj HR 1.09 (95% CI 0.75 – 1.58)
*Adj HR 0.14 (95% CI 0.85 – 1.55)

0.73%
0.68%
0.67%
0.60%

-PVD/-DM   +PVD/-DM   -PVD/+DM   +PVD/+DM

Rate of ALI per 100-patient years of follow up

Presence or Absence of Polyvascular Disease (PVD) or Diabetes Mellitus (DM)

Major Amputation

*Adj HR 1.83 (95% CI 1.26 – 2.65) p < 0.001
*Adj HR 1.61 (95% CI 1.07 – 2.43) p < 0.05
*Adj HR 0.83 (95% CI 0.53 – 1.31)

0.50%
0.36%
1.15%
0.74%

-PVD/-DM   +PVD/-DM   -PVD/+DM   +PVD/+DM

Rate of Amputation per 100-patient years of follow up

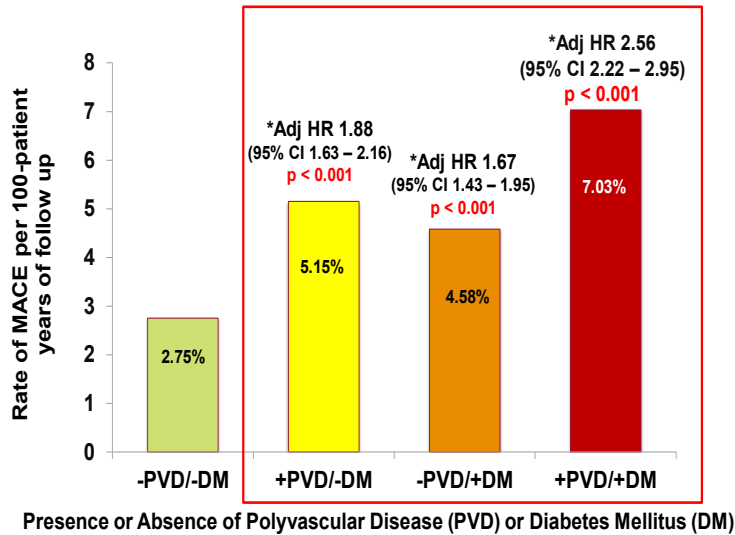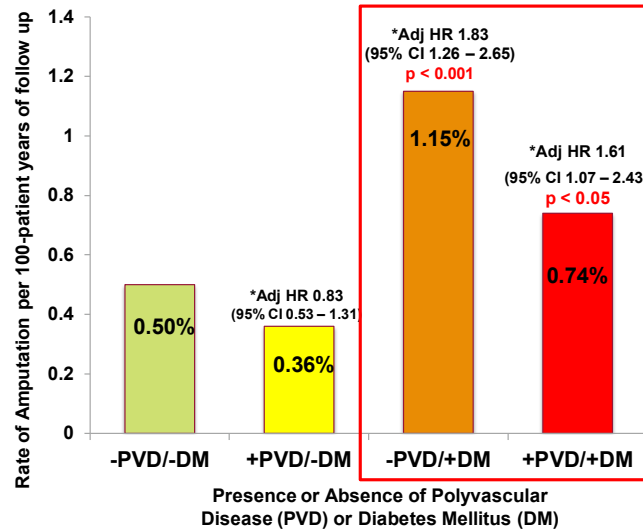Presence or Absence of Polyvascular Disease (PVD) or Diabetes Mellitus (DM)

*Adjusted for: age, weight, sex, region, ABI, GFR, statin use, ARB use, tobacco use
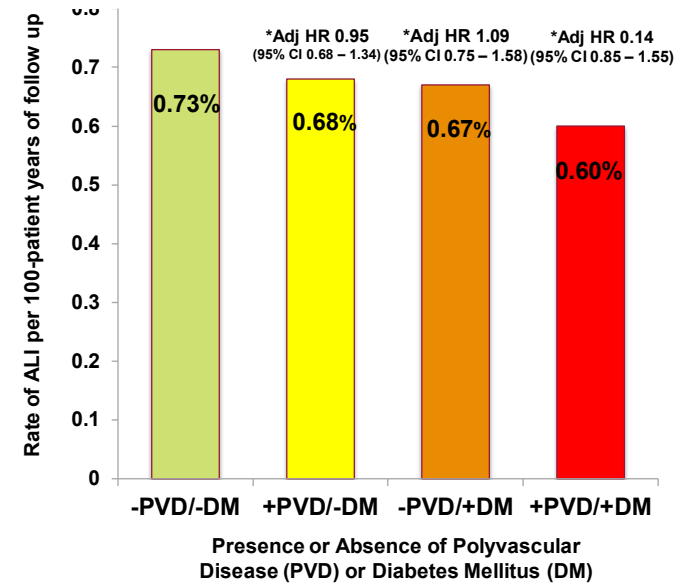
Results – Summary

Both polyvascular disease and diabetes independently associated with **MACE**

Diabetes but not polyvascular disease independently associated with **Amputation**

Neither polyvascular disease or diabetes independently associated with **Acute limb ischemia**

The predictors of MACE and limb outcomes may differ and the predictors of limb outcomes may depend on the type and underlying biology

Summary

- **The risk relationship for diabetes, polyvascular disease and the combination for MACE extends to patients with lower extremity PAD**

- **The relationship of these factors MALE risk is different overall and by type of event:**

  - **Acute limb ischemia, a thrombotic complication, is not associated with concomitant coronary or cerebrovascular disease or diabetes**

  - **Amputation, of multifactorial etiology including infection and microvascular disease, is driven by concomitant diabetes**

Conclusion

- Risk factors for cardiovascular and limb events may differ based on the underlying etiology of the events

- Polyvascular disease and diabetes are potent and independent predictors of major adverse cardiovascular events

- Diabetes is an independent predictor of amputation

- Acute limb ischemia, a severe thrombotic event, does not appear to be driven by polyvascular disease or diabetes and additional investigation to enable risk stratification for this outcome is needed