

Long-term Safety of Drug-Coated Devices for Peripheral Artery Revascularization: Insights from VOYAGER-PAD

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Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship

Grant/Research Support to CPC Clinical Research

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Company

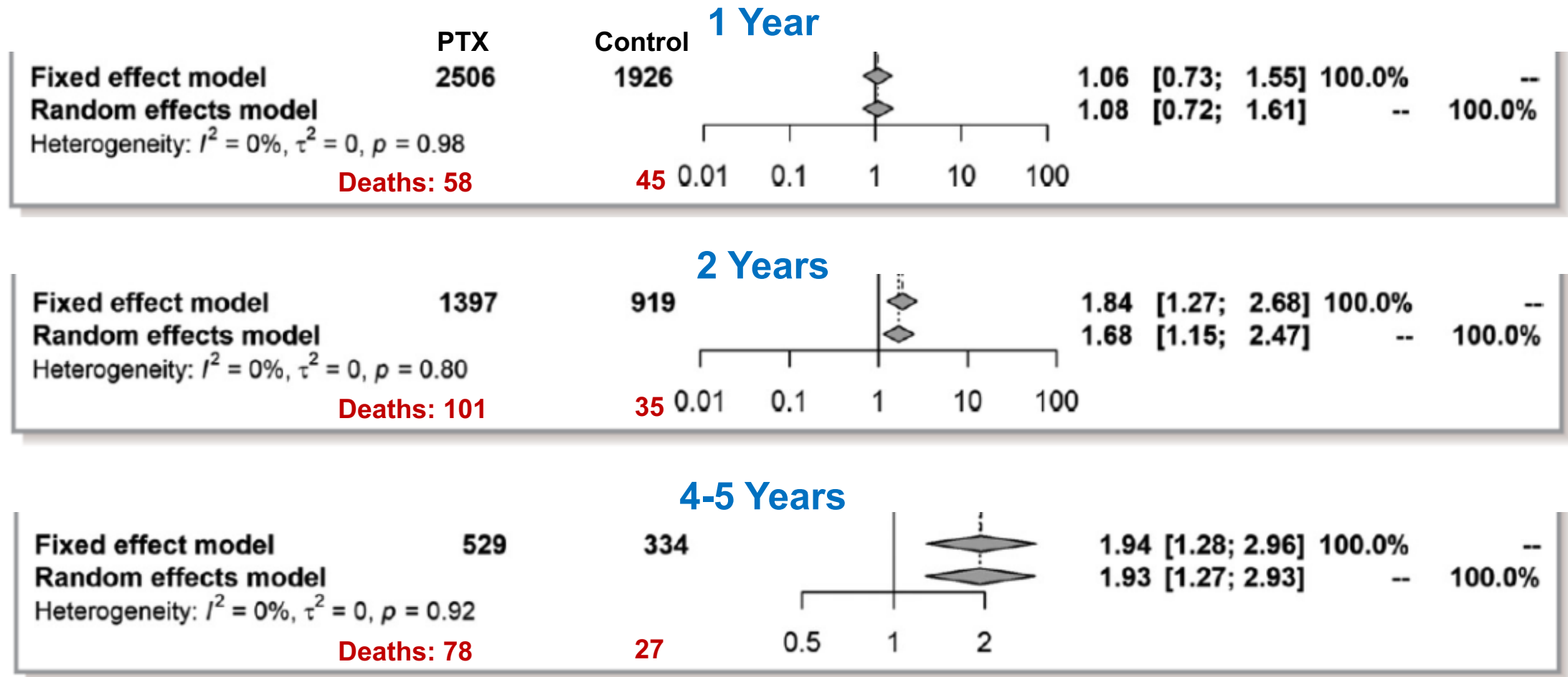
Bayer, Janssen, Amgen, Merck

Pan-Industry Consortium (Medtronic, Boston Scientific, Cook, Philips, Bard, Surmodics, TriReme) to support statistical analyses at CPC

Background

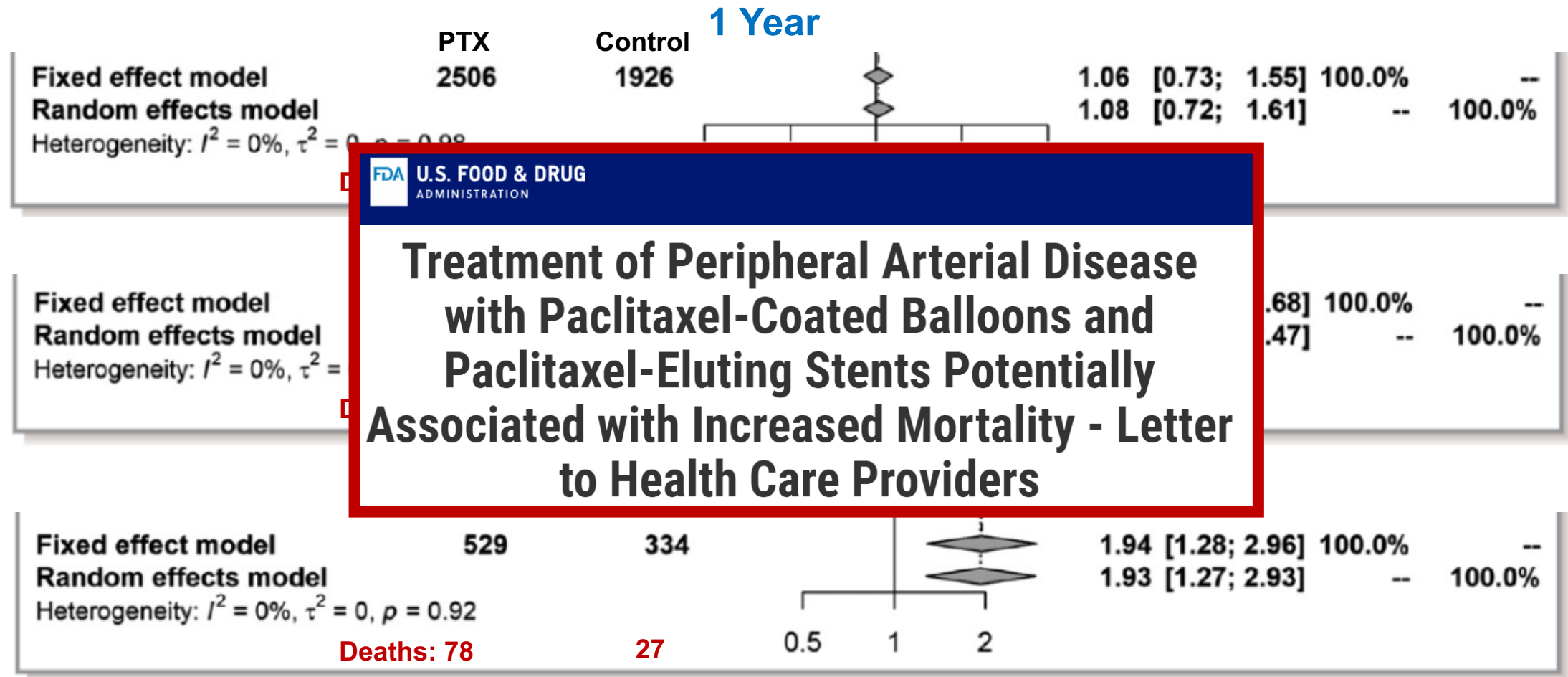
- **Endovascular revascularization is indicated for improvement of symptoms and limb salvage in symptomatic peripheral artery disease (PAD)**
- **Success of endovascular revascularization is limited by restenosis**
- **Paclitaxel drug-coated devices (DCD) were designed to attenuate restenosis and improve patency**

Long-term Mortality Associated with DCD Use



Pivotal trials with ~14-38% missing data at 5 years

Long-term Mortality Associated with DCD Use



Pivotal trials with ~14-38% missing data at 5 years

Additional studies have provided mixed results

Increased mortality

No increased mortality

Katsanos K et al. J Am Heart Assoc 2018
(Rocha-Singh KJ et al. Circulation 2020)
Others...

Dake MD et al. Cardiovasc Intervent Radiol 2019
Gray WA et al. Circulation 2019
Freisinger E et al. Eur Heart J 2019
Ouriel K et al. JACC Cardiovasc Interv 2019
Secemsky EA et al. J Am Coll Cardiol 2019
Secemsky EA et al. JAMA Cardiol 2019
Schneider PA et al. J Am Coll Cardiol 2019
Schneider PA et al. Catheter Cardiovasc Interv 2020
Others...

Limitations

RCTs

Limited sample size
Variable follow up
Variable outcome ascertainment
No standardized adjudication of death

Meta-analyses

Mostly study-level
Heterogeneity of population/design
Variable follow up
Variable outcome ascertainment
No standardized adjudication of death

Observational analyses

Non-randomized
Limited baseline characterization
Heterogenous population
Variable follow-up
Outcomes not adjudicated

VOYAGER PAD

Trial Design

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)
and Use of Clopidogrel

Placebo

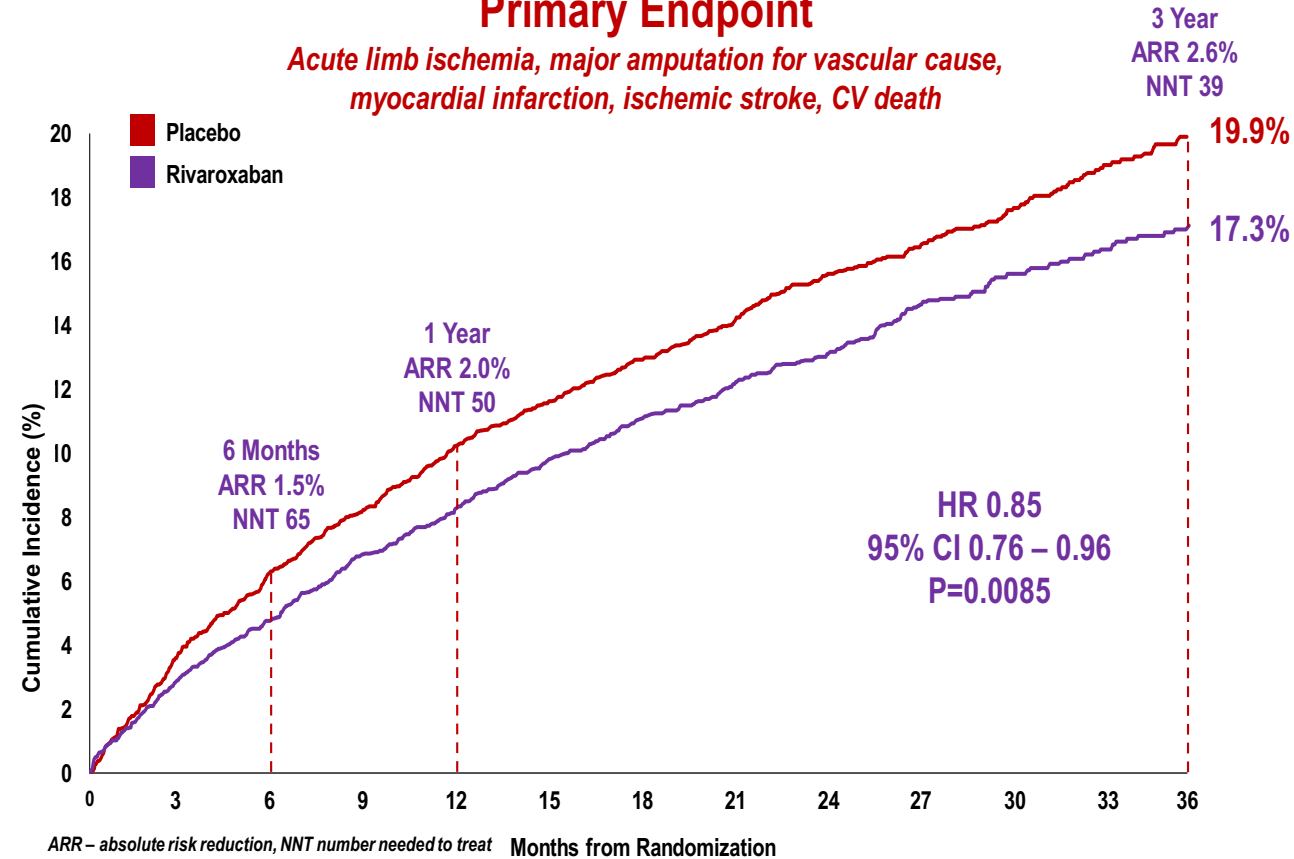
Follow up Q6 Months, Event Driven, Median f/u 28 Months

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

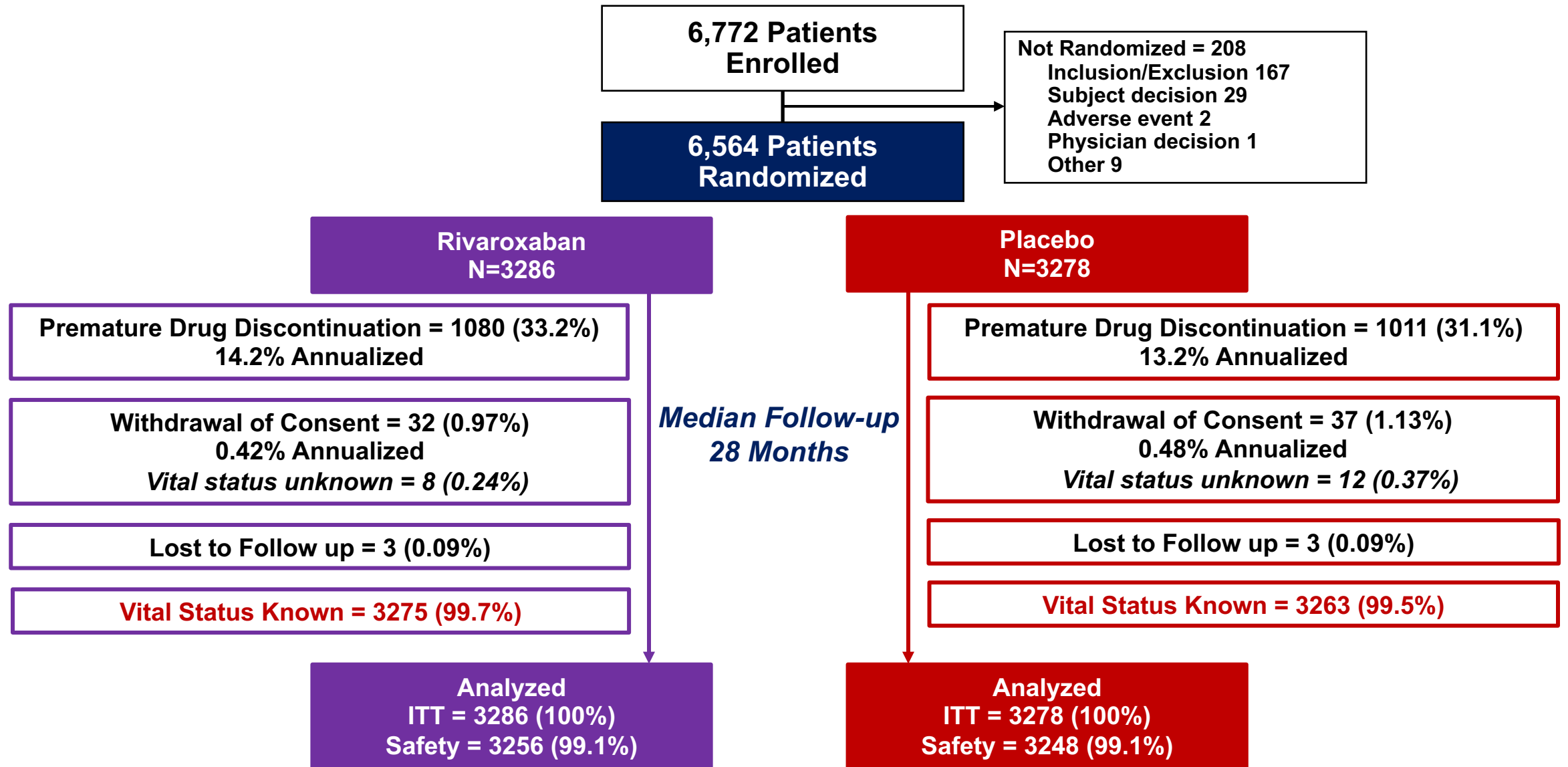
Principal Safety Endpoint: TIMI Major Bleeding

Primary Endpoint

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



VOYAGER PAD - Disposition



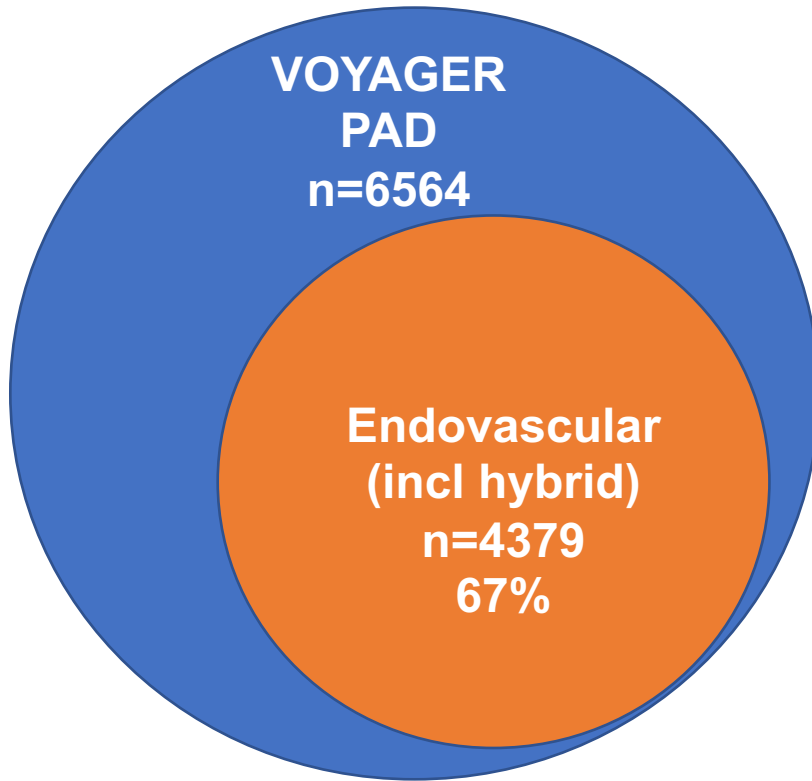
Objectives

In VOYAGER PAD patients undergoing endovascular lower extremity revascularization for symptomatic PAD:

- To assess whether use of paclitaxel drug-coated devices versus non drug-coated devices is associated with all-cause mortality**
- To evaluate whether the effect of rivaroxaban 2.5 mg twice daily plus low dose aspirin versus low dose aspirin alone on the primary efficacy endpoint is consistent with versus without DCD use**

Methods

Study Population



Analyses performed at CPC Clinical Research

Outcomes

- Prospectively ascertained and independently adjudicated
- All-cause mortality for DCD vs. no DCD
- VOYAGER PAD primary endpoint (acute limb ischemia, major amputation of vascular etiology, myocardial infarction, ischemic stroke, or cardiovascular death) for Rivaroxaban vs. Placebo

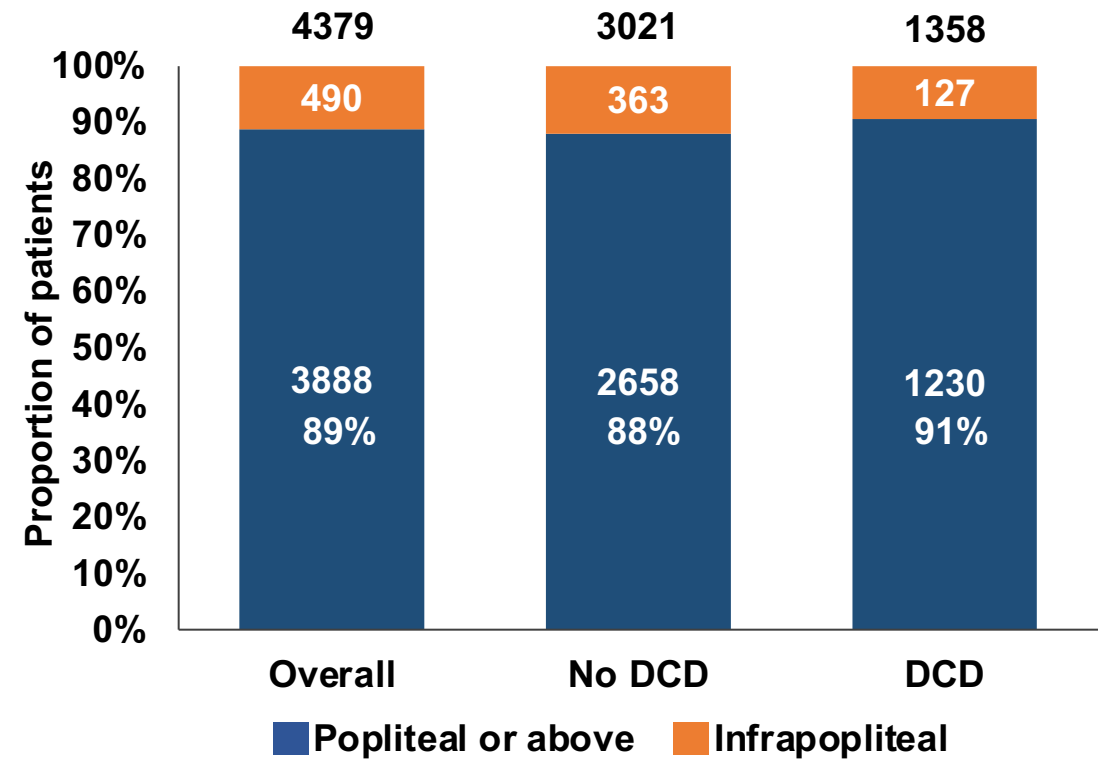
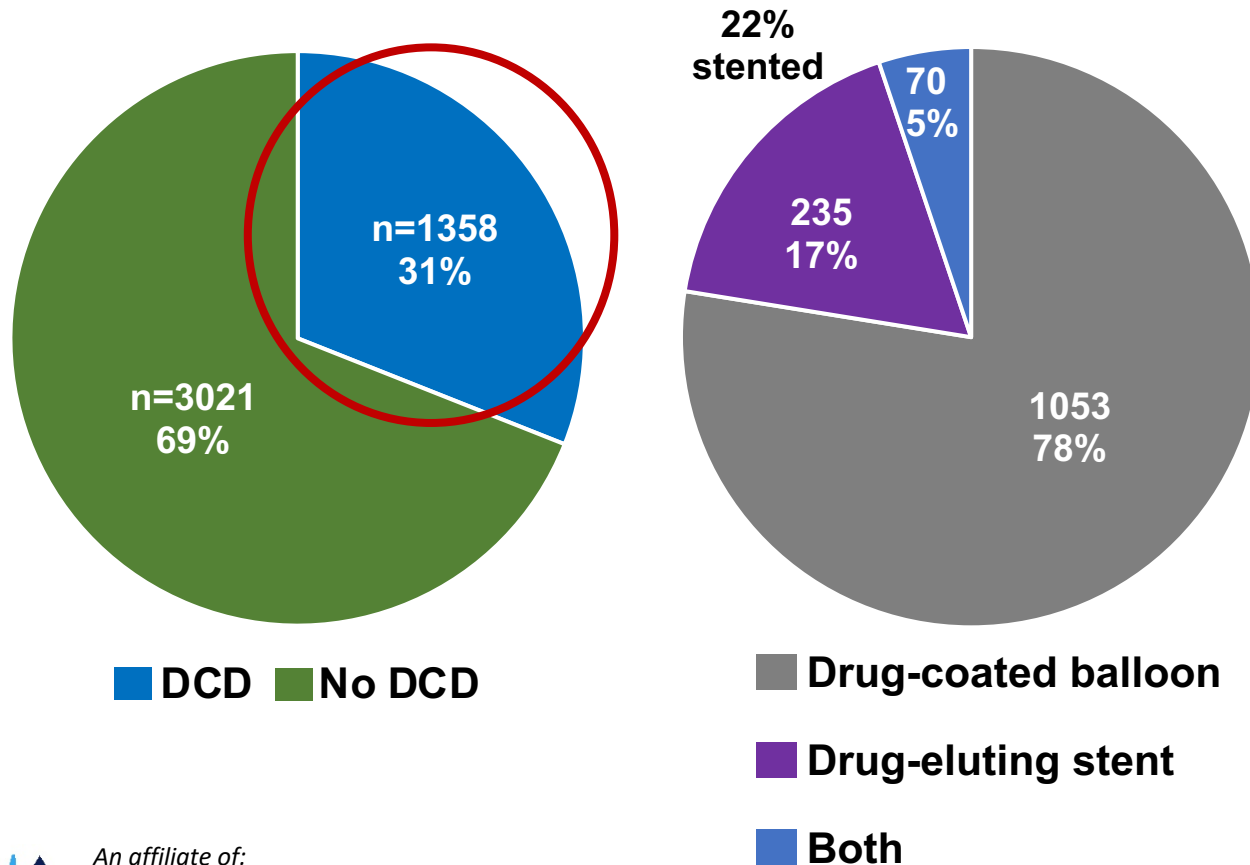
Statistical Analysis

- Prespecified analysis of VOYAGER PAD
- Inverse Probability Treatment Weighting (IPTW)
- Two independent statistical teams
- Sensitivity analysis using stabilized weights
- Cox proportional hazards to assess for consistency of efficacy of rivaroxaban in those with and without DCD

Results

Median follow-up 31 months (IQR 25 – 37)

Complete ascertainment of vital status in 99.6% of patients



Baseline Characteristics

Propensity Model Comparisons

Characteristics at Randomization	Unweighted Model*		
	Drug-coated N=1342* %	Not Drug-coated N=2974* %	Standardized Difference**
Age, Yrs Mean	67	68	0.14
Female	28	29	0.01
Caucasian	84	73	0.26
Geographic Region			
North America	19	10	
Western Europe	41	26	
Eastern Europe	24	34	
Asia Pacific	11	22	
South America	5	9	
Current/Former Smoking	80	76	0.08
Diabetes Mellitus	46	44	0.04
COPD	12	9	0.09
Chronic Kidney Disease	27	26	0.02
Coronary Artery Disease	35	32	0.07
Carotid Artery Disease	11	8	0.10
ACEI/ARB	67	65	0.04
DAPT	62	49	0.27
Statin	86	80	0.14
Rivaroxaban 2.5mg BID + Aspirin	49	51	0.04

*4,379 patients underwent endovascular revascularization; 63 patients excluded for missing baseline data (16 DCD, 47 non DCD)

** ≥0.10 considered meaningful imbalance

PAD & Procedural Characteristics

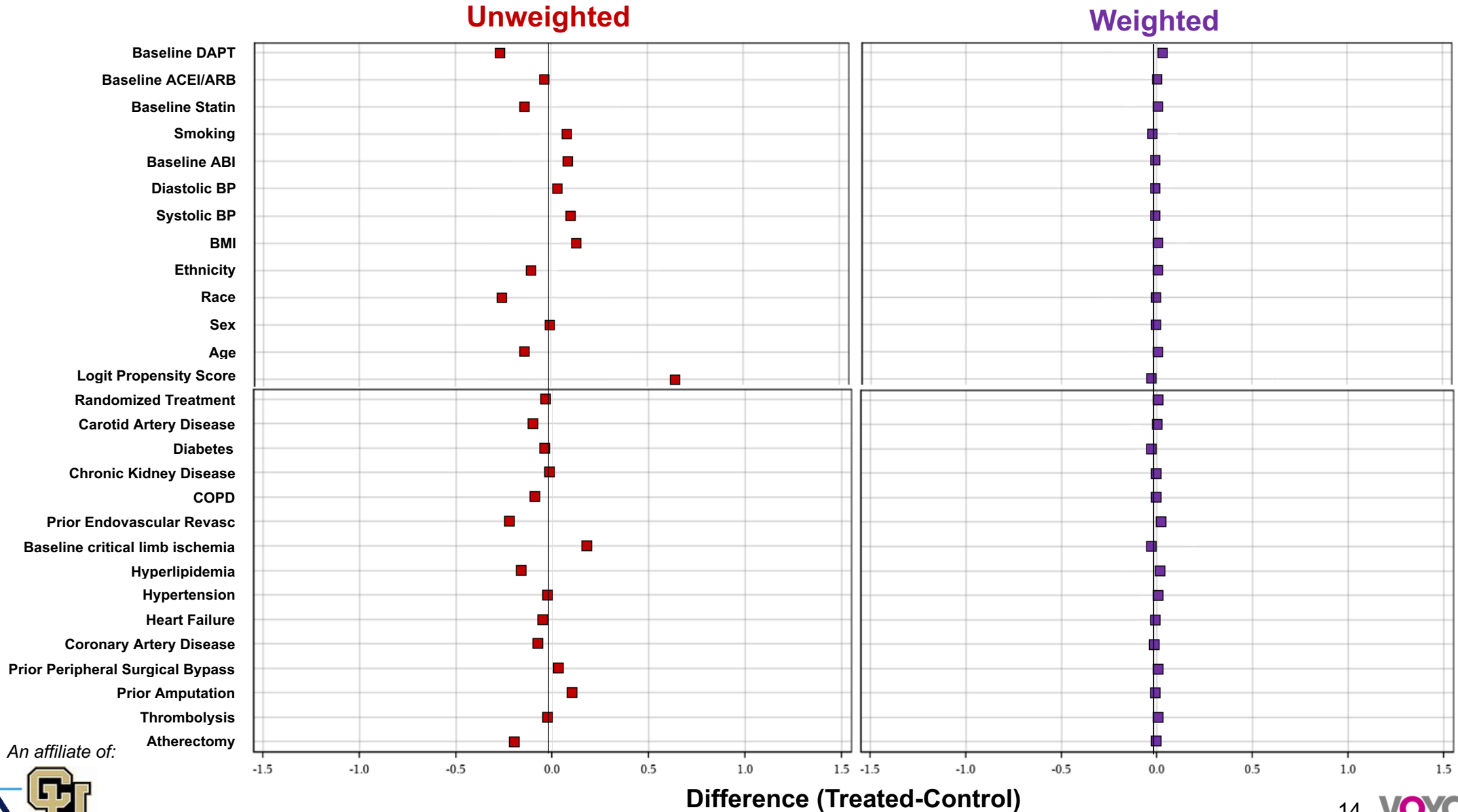
Propensity Model Comparisons

Characteristics at Randomization	Unweighted Model		
	Drug-coated N=1342 %	Not Drug-coated N=2974 %	Standardized Difference**
<i>PAD History</i>			
Prior Endovascular Revascularization	43	32	0.22
Prior Surgical Revascularization	6	7	0.03
Prior Amputation	4	7	0.10
Ankle Brachial Index, Mean (SD)	0.64 (0.22)	0.62 (0.23)	0.09
<i>Indication for Revascularization</i>			
Critical limb ischemia	15	22	0.18
Claudication	85	79	
<i>Endovascular Revascularization</i>			
Atherectomy	11	6	0.20
Thrombolysis	1	1	0.02
<i>Target Lesion Length</i>			
Short (<5cm)	21	28	
Intermediate (5cm to <15cm)	44	41	
Long (≥15cm)	33	28	

** ≥0.10 considered meaningful imbalance

Inverse Probability Treatment Weighting

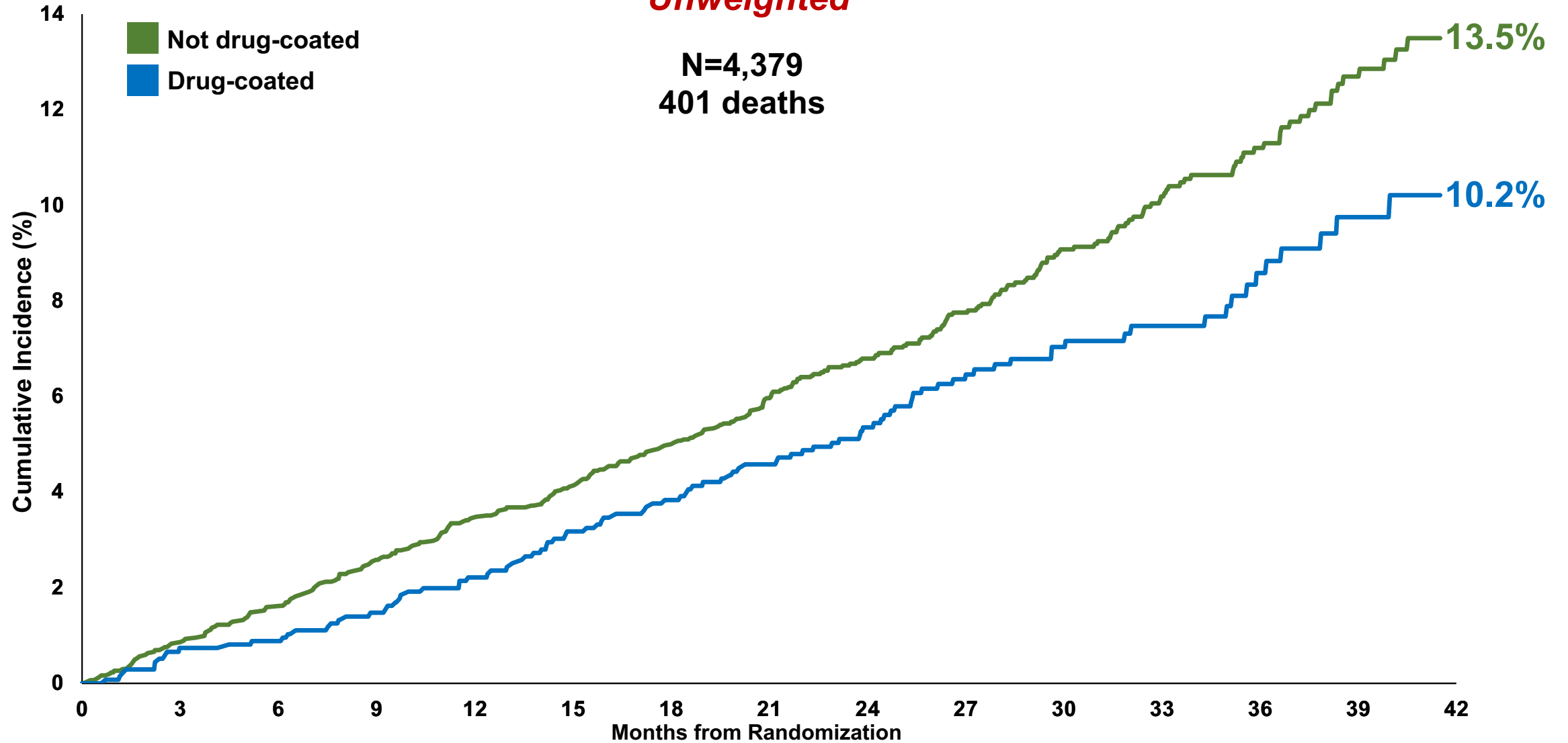
Standardized Differences



All-cause Mortality

Unweighted

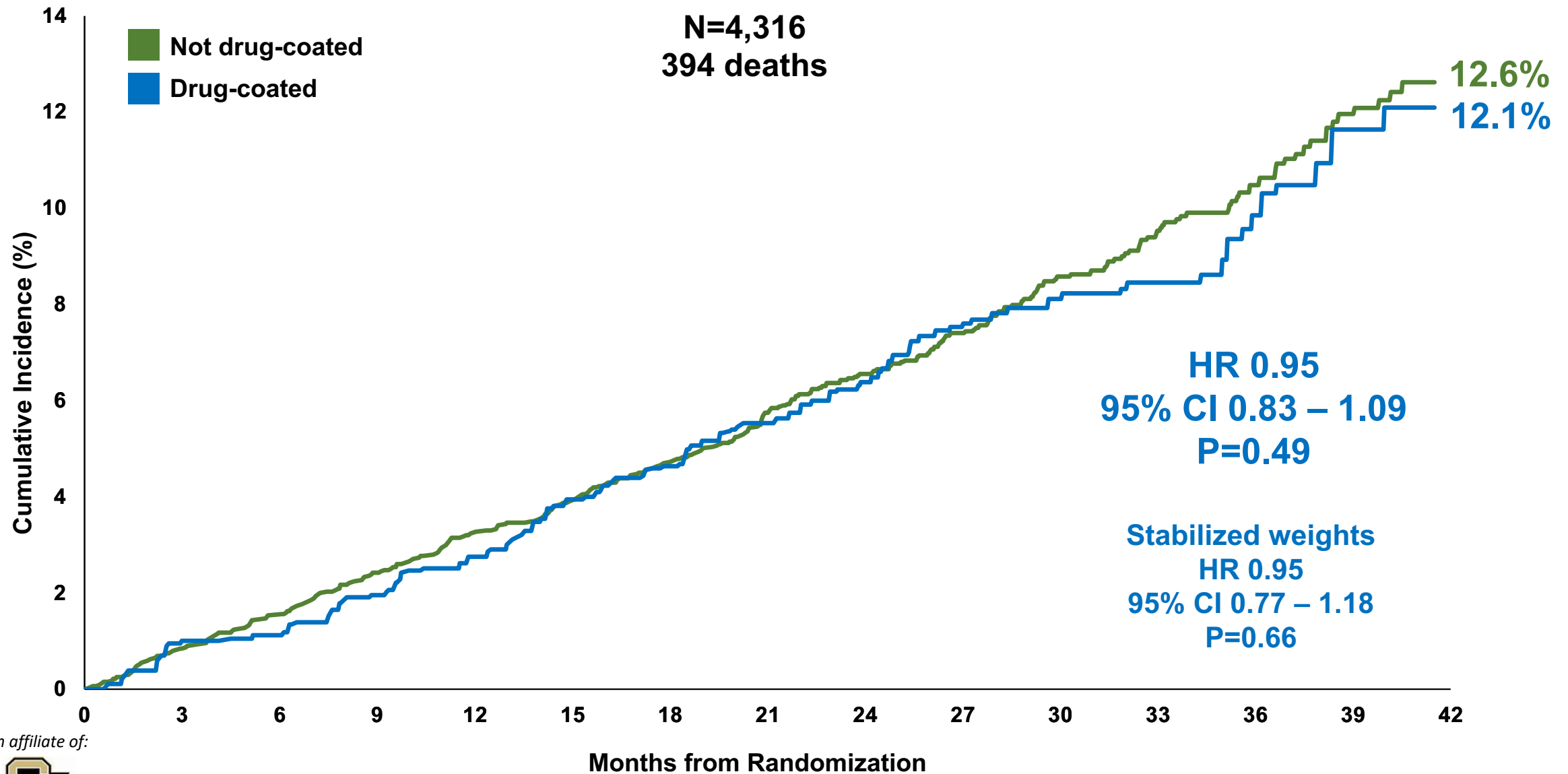
N=4,379
401 deaths



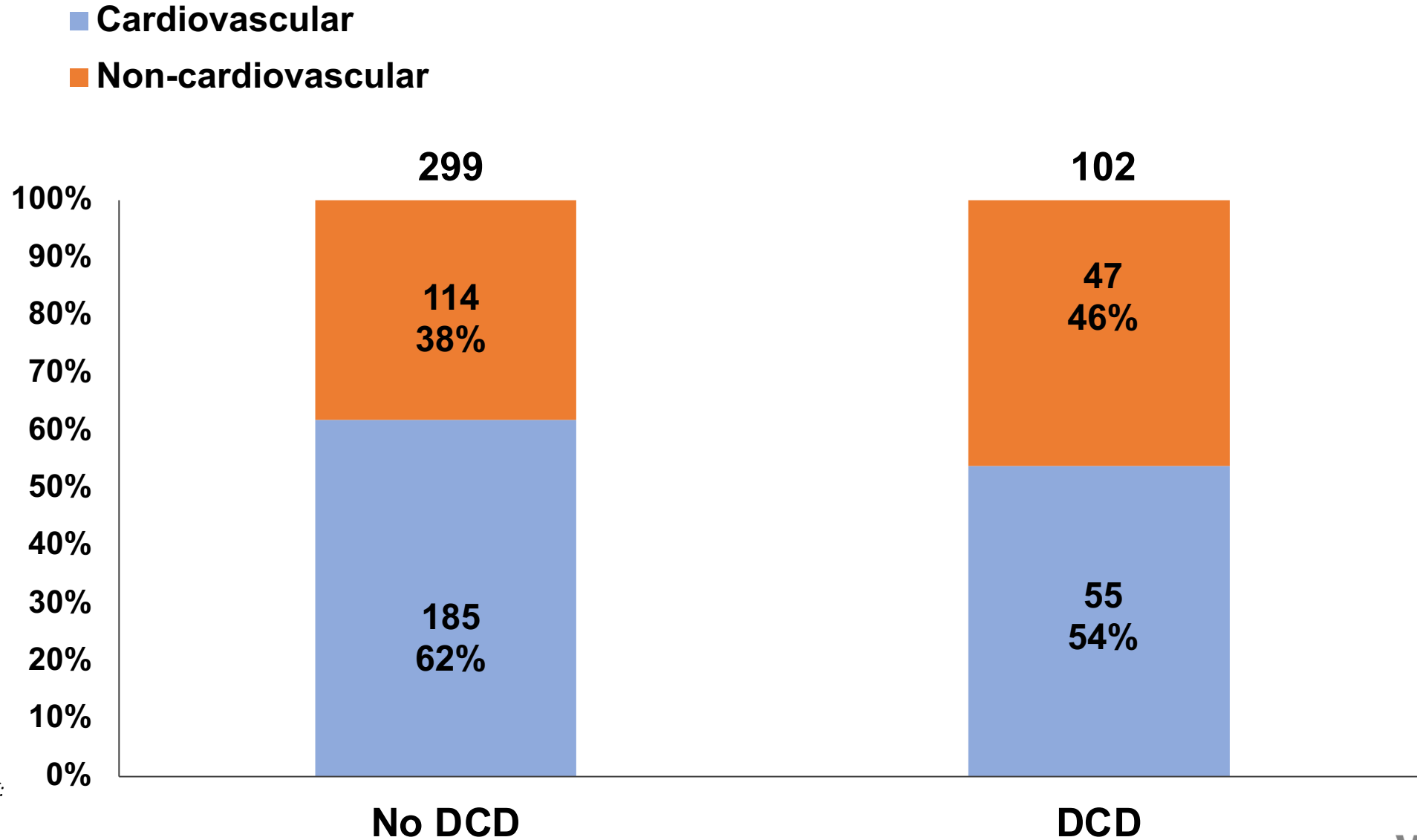
# at risk DCD	1358	1347	1344	1336	1325	1313	1301	1290	1127	923	728	536	373	243	104
# at risk no DCD	3021	2992	2970	2938	2911	2891	2864	2829	2491	2023	1639	1253	882	544	220

All-cause Mortality

Weighted

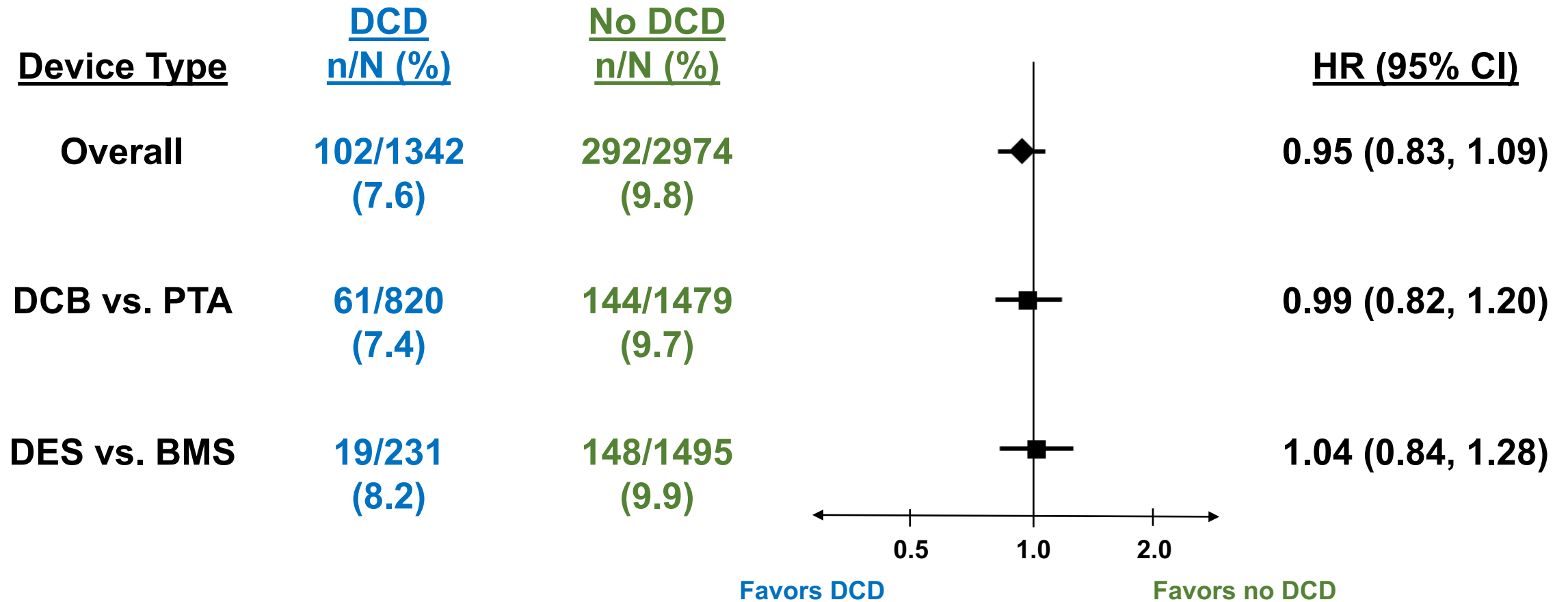


Causes of Mortality



Mortality and DCD Use by Device Type

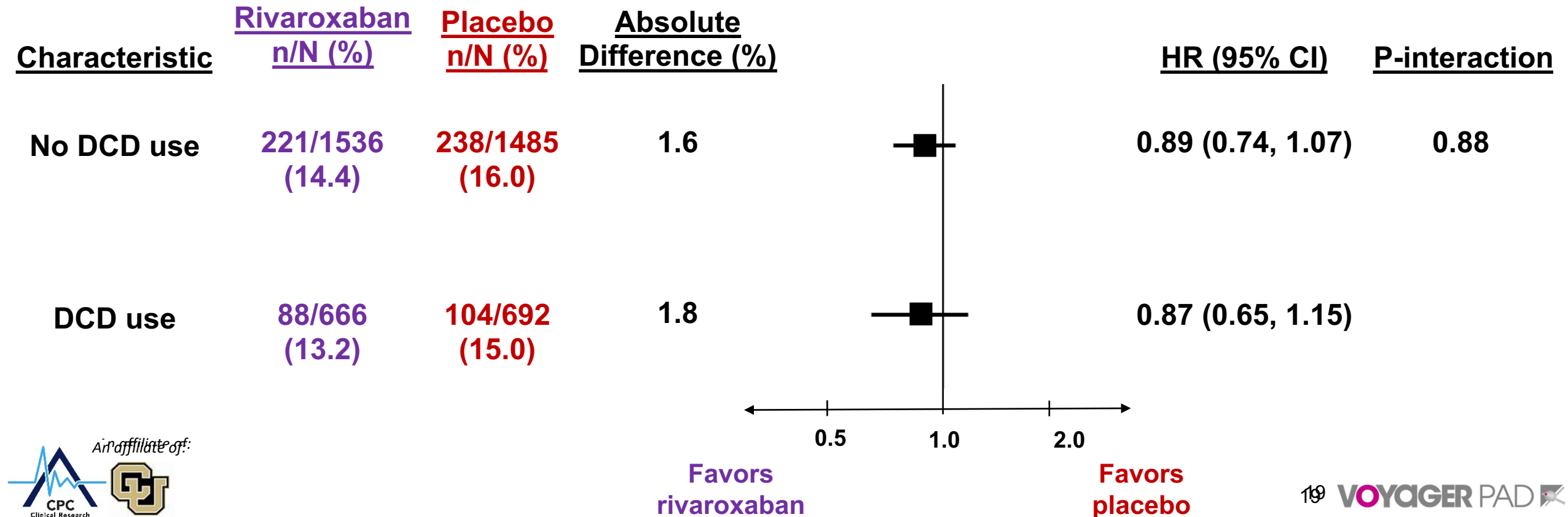
Weighted Hazard



Effect of Rivaroxaban According to DCD Use

Acute limb ischemia, major amputation of vascular etiology, myocardial infarction, ischemic stroke, or cardiovascular death

**Overall HR 0.85 for Rivaroxaban vs. Placebo
(95% CI 0.76 – 0.96), p=0.0085**



Summary

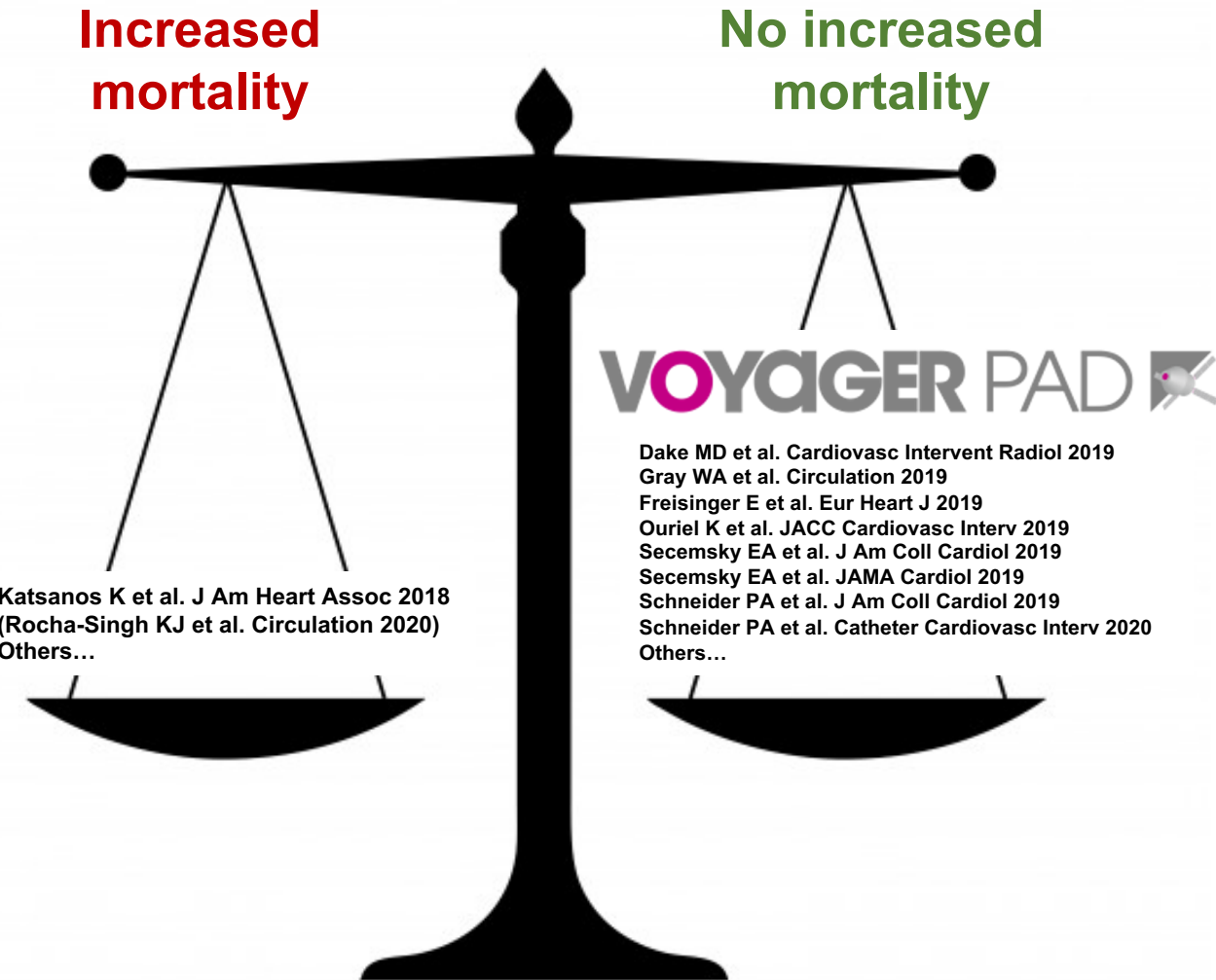
- Among >4300 VOYAGER PAD patients undergoing endovascular revascularization with 99.6% ascertainment of mortality
- IPTW successfully adjusted for known confounders and showed *no mortality risk or benefit associated with DCD*, including in subgroups by device type
- The benefit of **rivaroxaban 2.5 mg twice daily with aspirin** versus **aspirin alone** on reducing ischemic limb and cardiovascular outcomes after revascularization for symptomatic PAD is consistent regardless of DCD use

Conclusions

VOYAGER PAD

- Large sample size
- Well characterized cohort
- 99.6% ascertainment of vital status with ~400 deaths in this sub-analysis
- Long-term follow-up
- Adjudicated outcomes

No association of mortality with paclitaxel DCD



Thank You