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

Connie N. Hess, Manesh R. Patel, Rupert M. Bauersachs, Sonia S. Anand, E. Sebastian Debus, Mark R. Nehler, Robert W. Yeh, Eric A. Secemsky, Joshua A. Beckman, Laura Mauri, Nicholas Govsyeyev, Warren H. Capell, Taylor T. Brackin, Scott D. Berkowitz, Lloyd P. Haskell, William R. Hiatt, Marc P. Bonaca on behalf of the VOYAGER PAD Investigators

TCT Connect 2020
Late-Breaking Clinical Trials and Science
18 October 2020

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	**Company**
Grant/Research Support to CPC Clinical Research	Bayer, Janssen, Amgen, Merck
Grant/Research Support to CPC Clinical Research	Pan-Industry Consortium (Medtronic, Boston Scientific, Cook, Philips, Bard, Surmodics, TriReme) to support statistical analyses at CPC

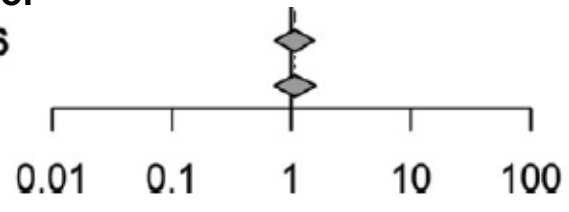
Background

- 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

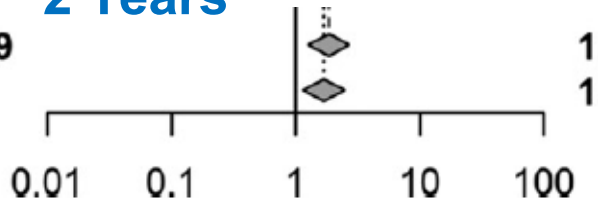
1 Year

	PTX	Control			
Fixed effect model	2506	1926	1.06 [0.73; 1.55]	100.0%	--
Random effects model			1.08 [0.72; 1.61]	--	100.0%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.98					
	Deaths: 58	45			



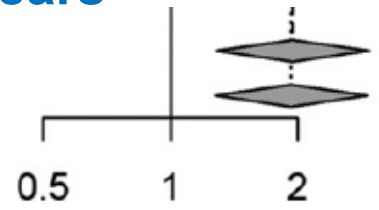
2 Years

Fixed effect model	1397	919	1.84 [1.27; 2.68]	100.0%	--
Random effects model			1.68 [1.15; 2.47]	--	100.0%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.80					
	Deaths: 101	35			



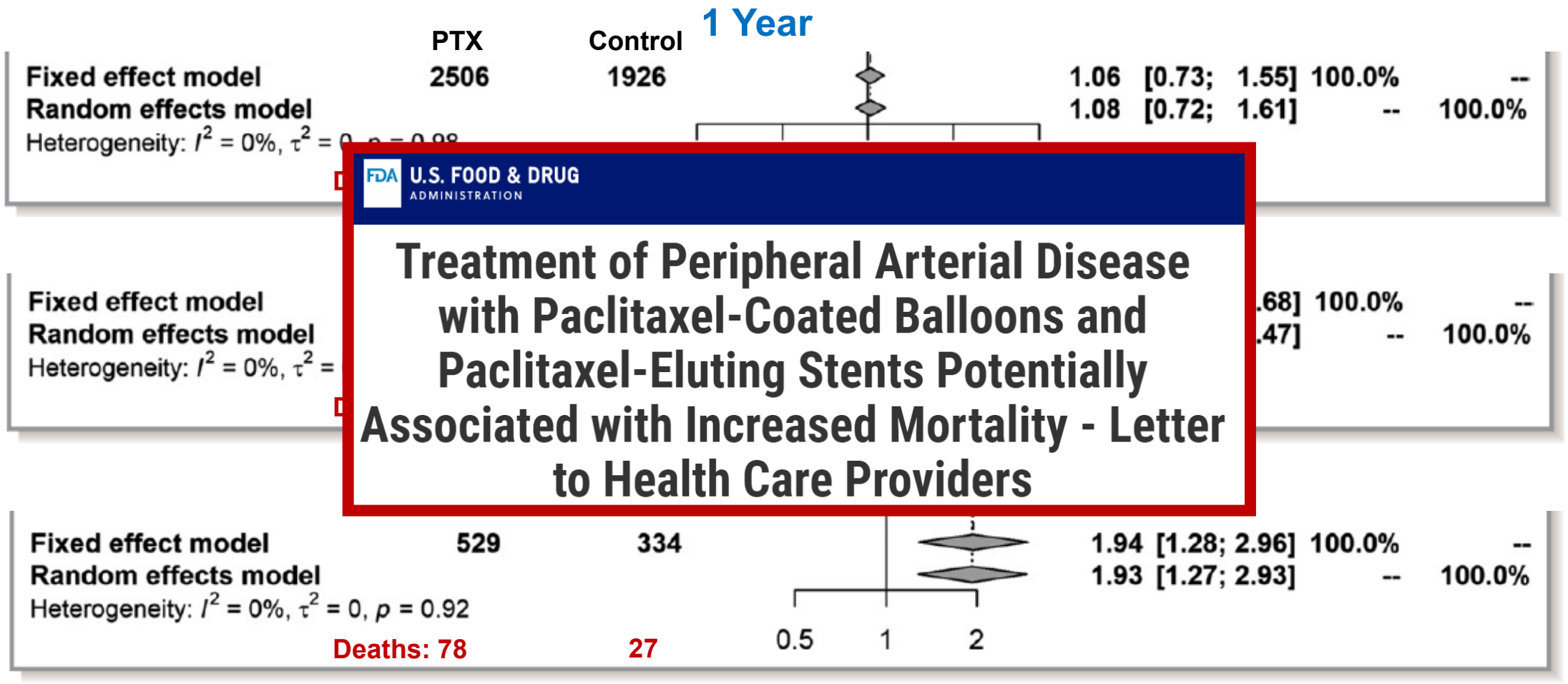
4-5 Years

Fixed effect model	529	334	1.94 [1.28; 2.96]	100.0%	--
Random effects model			1.93 [1.27; 2.93]	--	100.0%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.92					
	Deaths: 78	27			



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

Long-term Mortality Associated with DCD Use



FDA U.S. FOOD & DRUG ADMINISTRATION

Treatment of Peripheral Arterial Disease with Paclitaxel-Coated Balloons and Paclitaxel-Eluting Stents Potentially Associated with Increased Mortality - Letter to Health Care Providers

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

An affiliate of:

CPC Clinical Research

Katsanos K, et al. JAHA 2018

Additional studies have provided mixed results

Increased mortality

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

No increased mortality

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

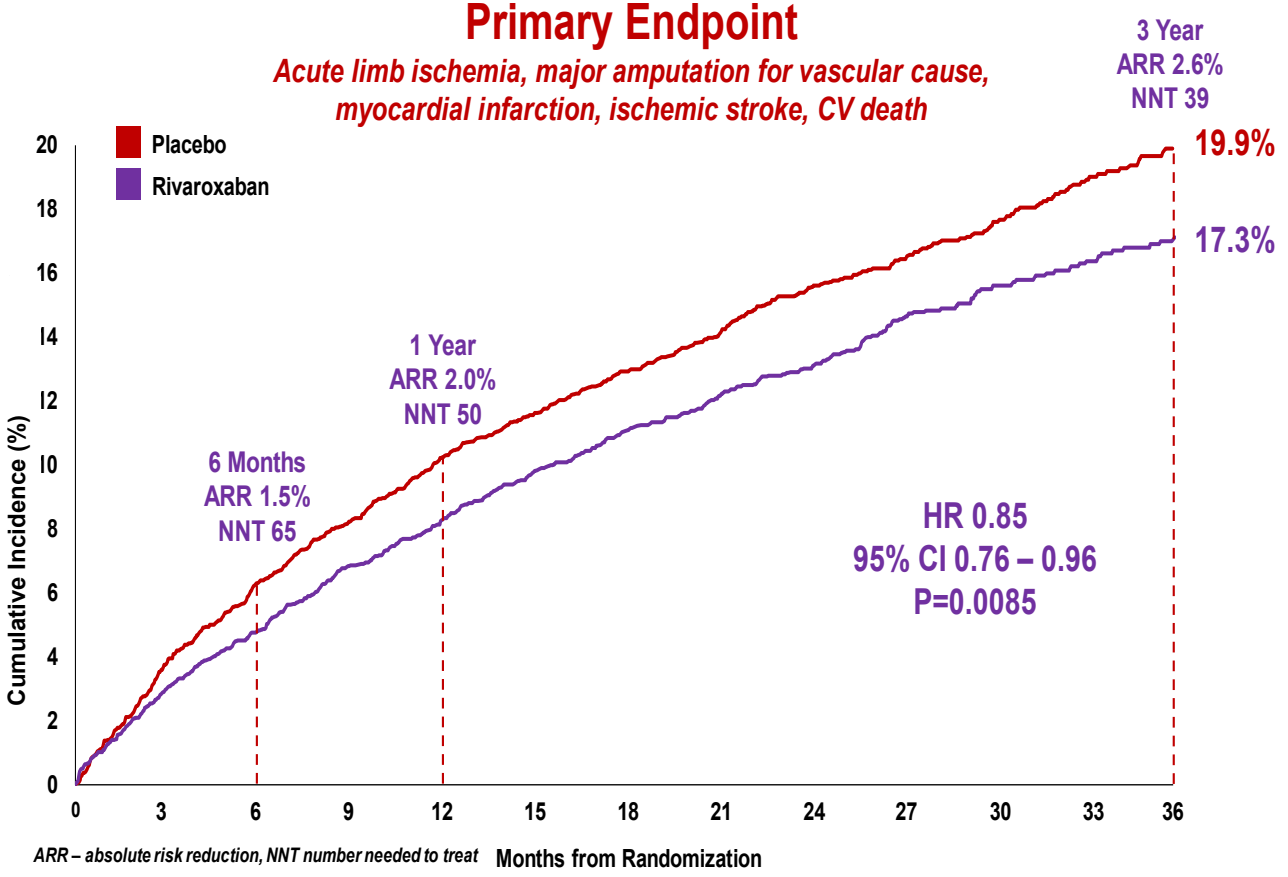
Follow up Q6 Months, Event Driven, Median f/u 28 Months

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

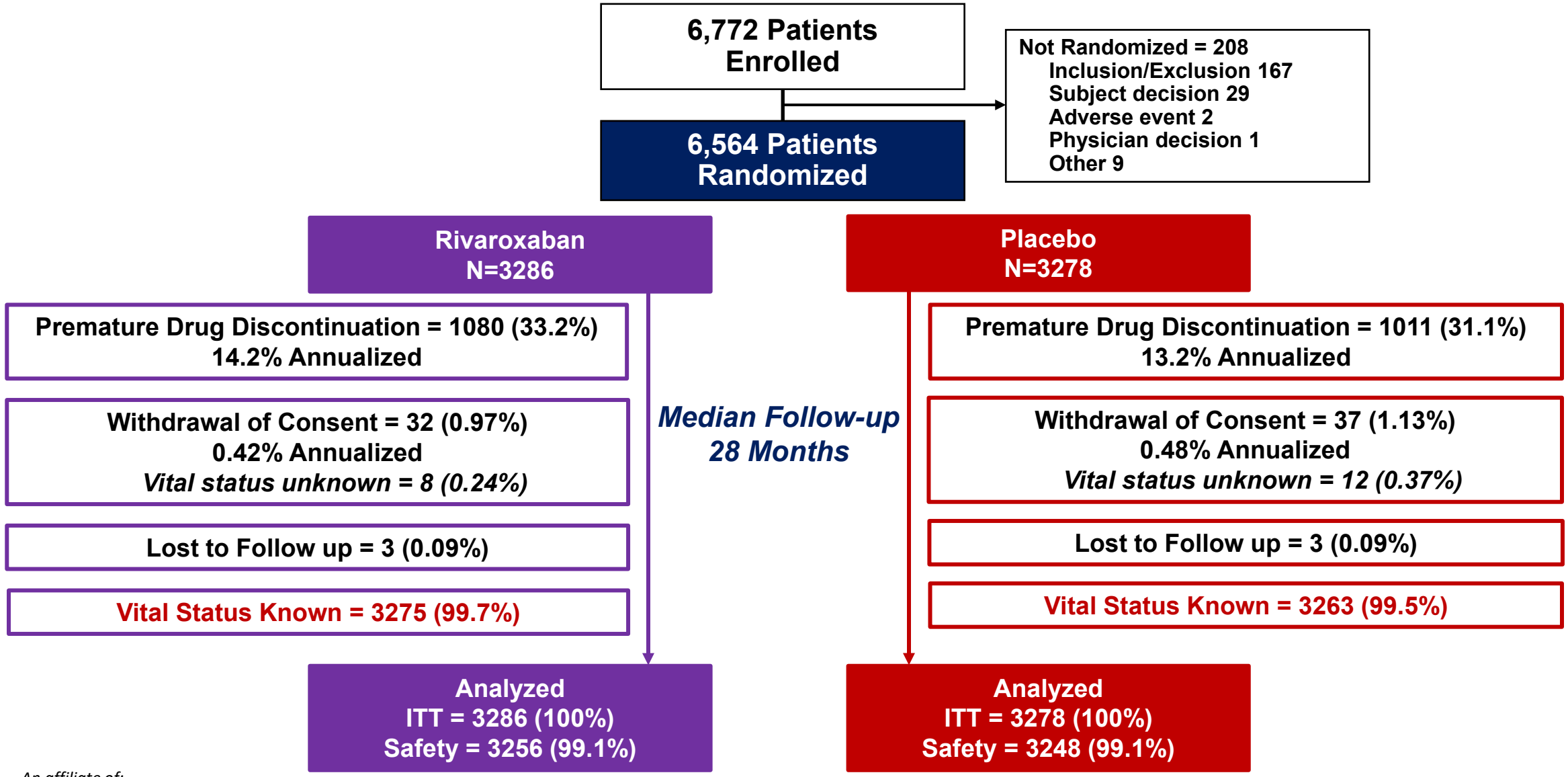


An affiliate of:

CPC Clinical Research

Bonaca MP, et al. NEJM 2020

VOYAGER PAD - Disposition



Bonaca MP, et al. NEJM 2020

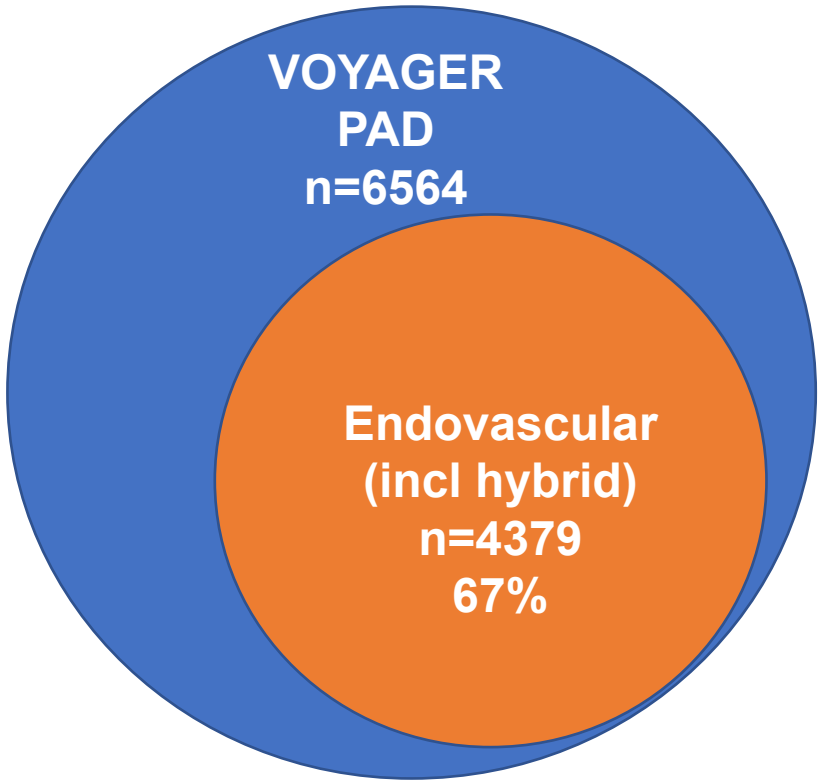
Objectives

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

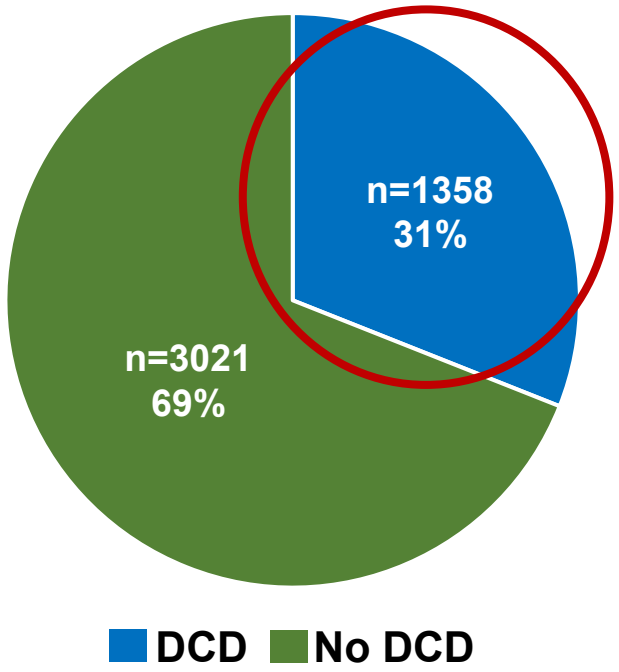
Statistical Analysis

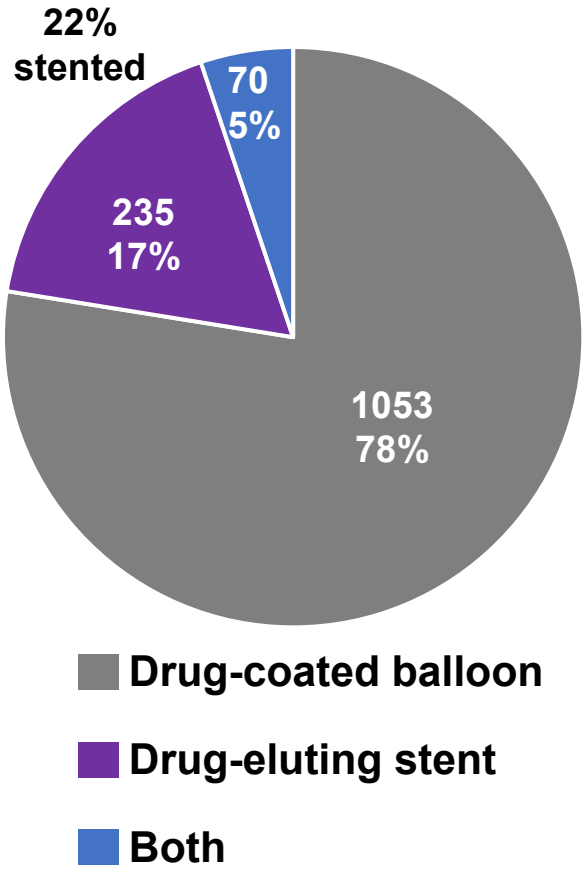
- Prespecified analysis of VOYAGER PAD
- Inverse Probability Treatment Weighting (IPTW)
- Two independent statistical teams
- Sensitivity analysis using stabilized weights
- Cox proportional hazards to assess for consistency of efficacy of rivaroxaban in those with and without DCD

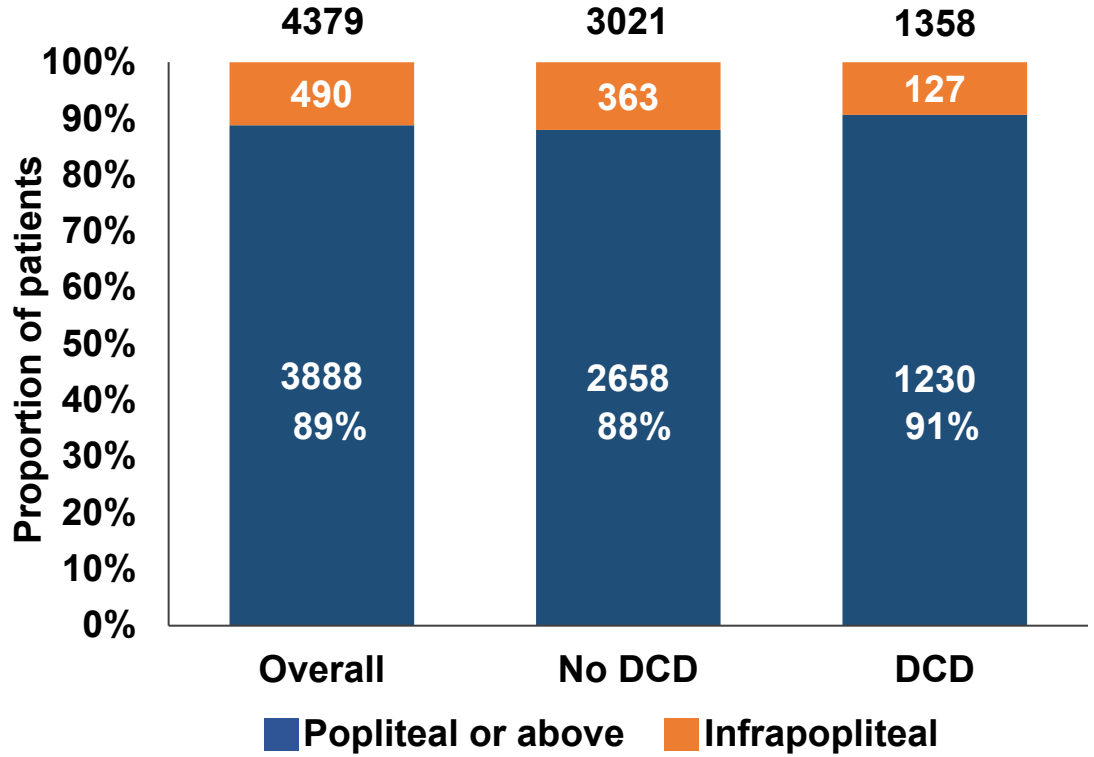
Results

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

Complete ascertainment of vital status in 99.6% of patients







An affiliate of:

CPC Clinical Research

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

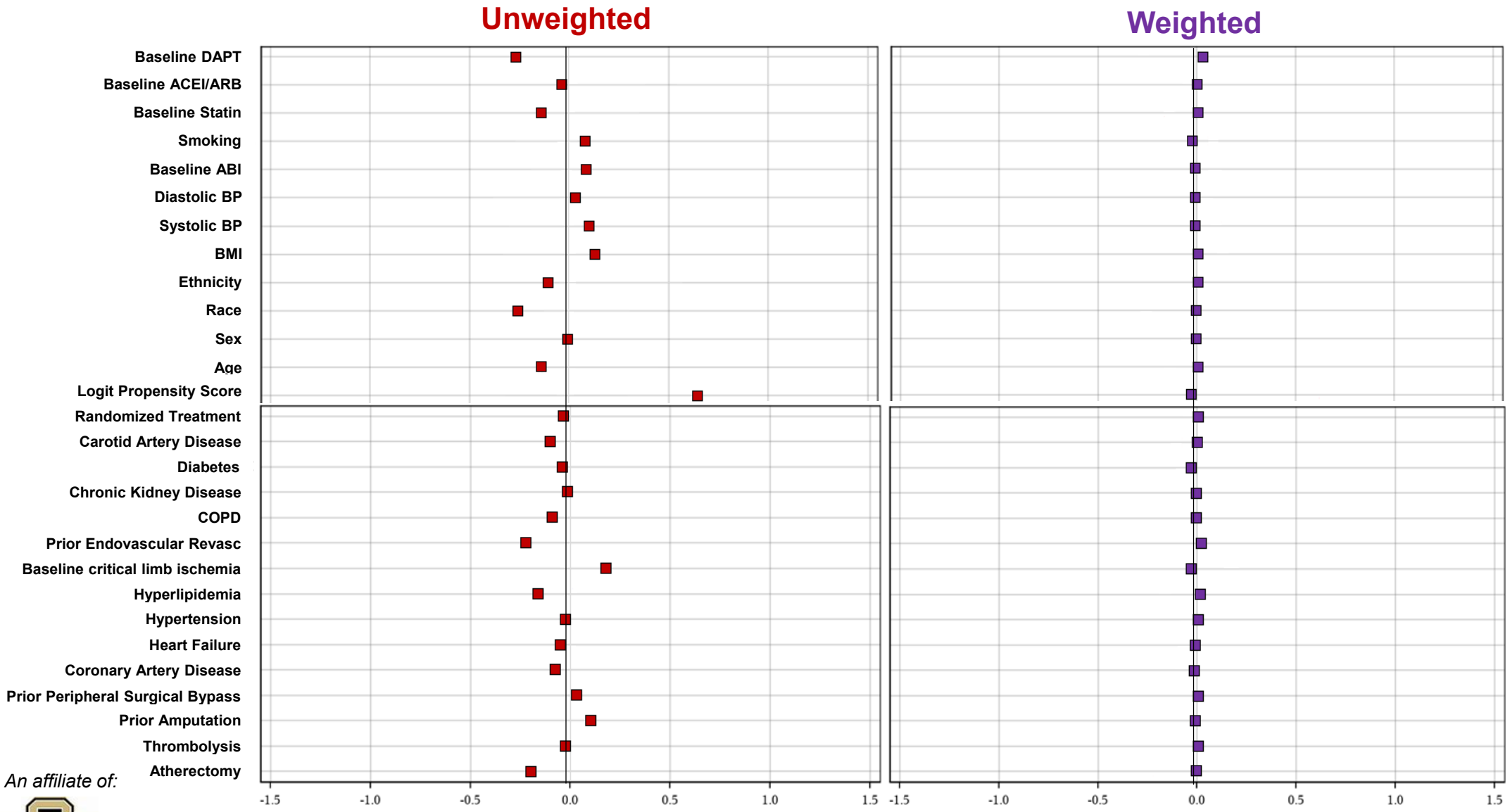
PAD & Procedural Characteristics
Propensity Model Comparisons

Characteristics at Randomization	Unweighted Model		
	Drug-coated N=1342 %	Not Drug-coated N=2974 %	Standardized Difference**
PAD History			
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
Indication for Revascularization			
Critical limb ischemia	15	22	0.18
Claudication	85	79	
Endovascular Revascularization			
Atherectomy	11	6	0.20
Thrombolysis	1	1	0.02
Target Lesion Length			
Short (<5cm)	21	28	
Intermediate (5cm to <15cm)	44	41	
Long (≥15cm)	33	28	

** ≥0.10 considered meaningful imbalance

Inverse Probability Treatment Weighting

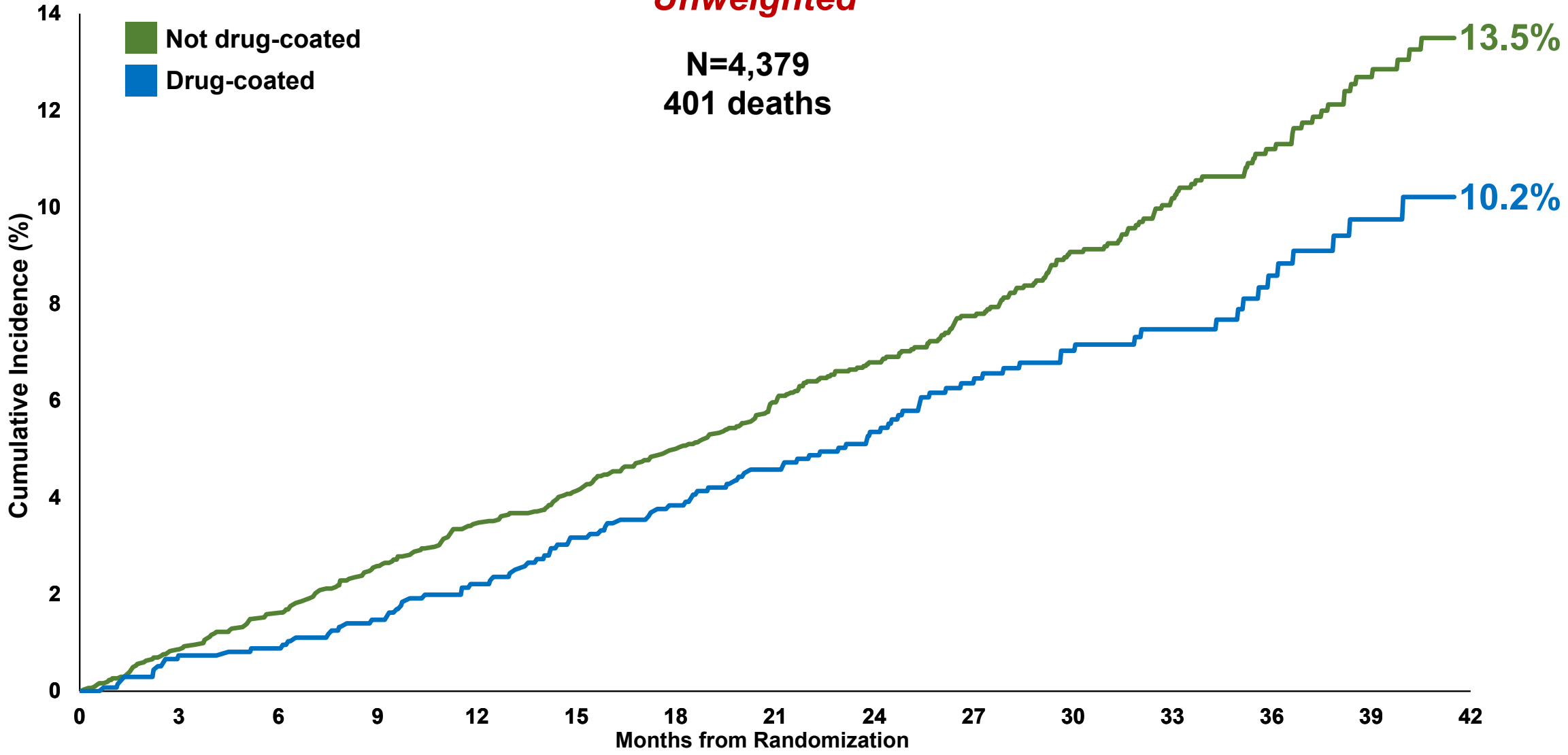
Standardized Differences



An affiliate of:

All-cause Mortality

Unweighted



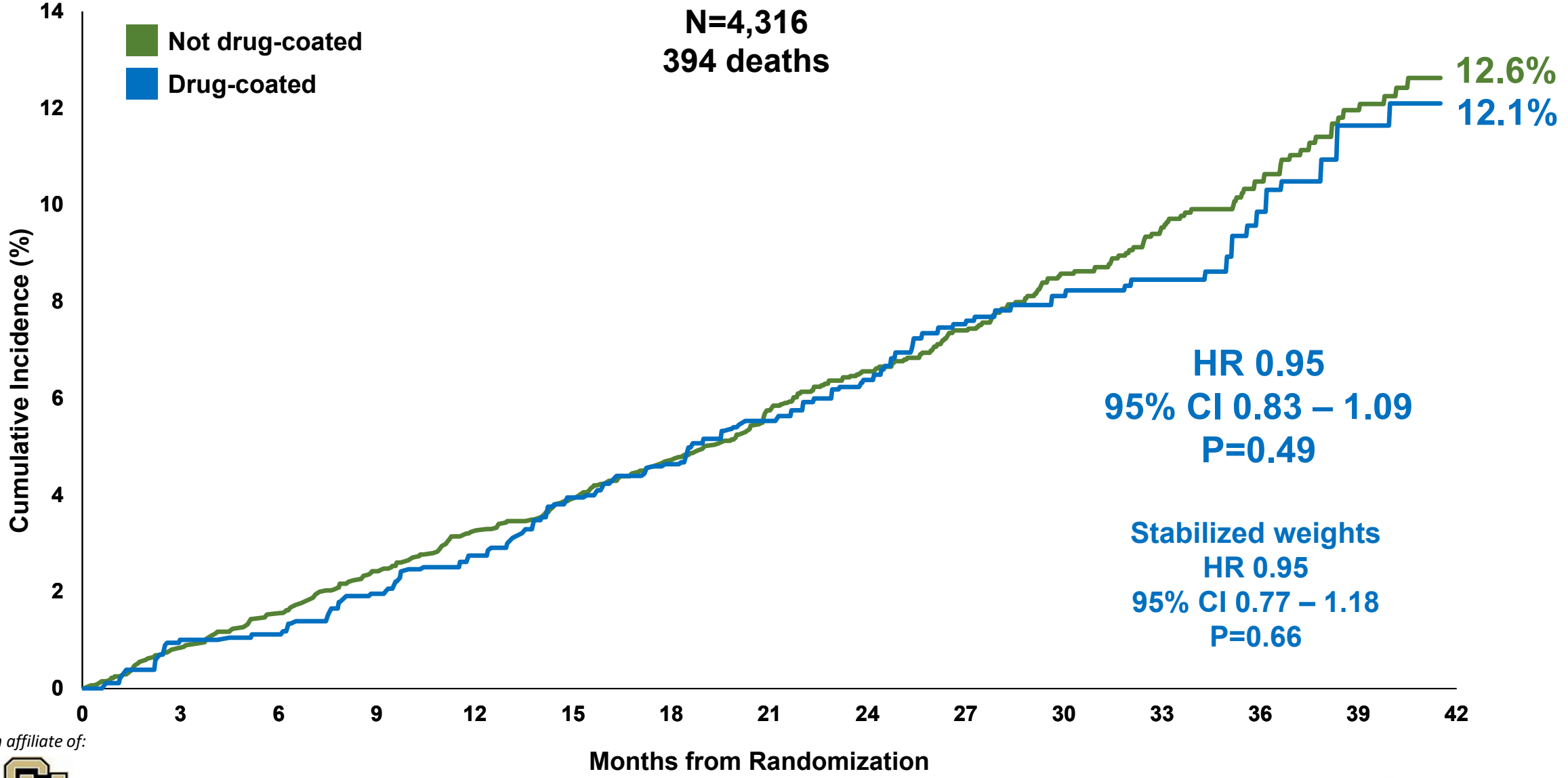
# at risk DCD	1358	1347	1344	1336	1325	1313	1301	1290	1127	923	728	536	373	243	104
# at risk no DCD	3021	2992	2970	2938	2911	2891	2864	2829	2491	2023	1639	1253	882	544	220

An affiliate of:

CPC Clinical Research

All-cause Mortality

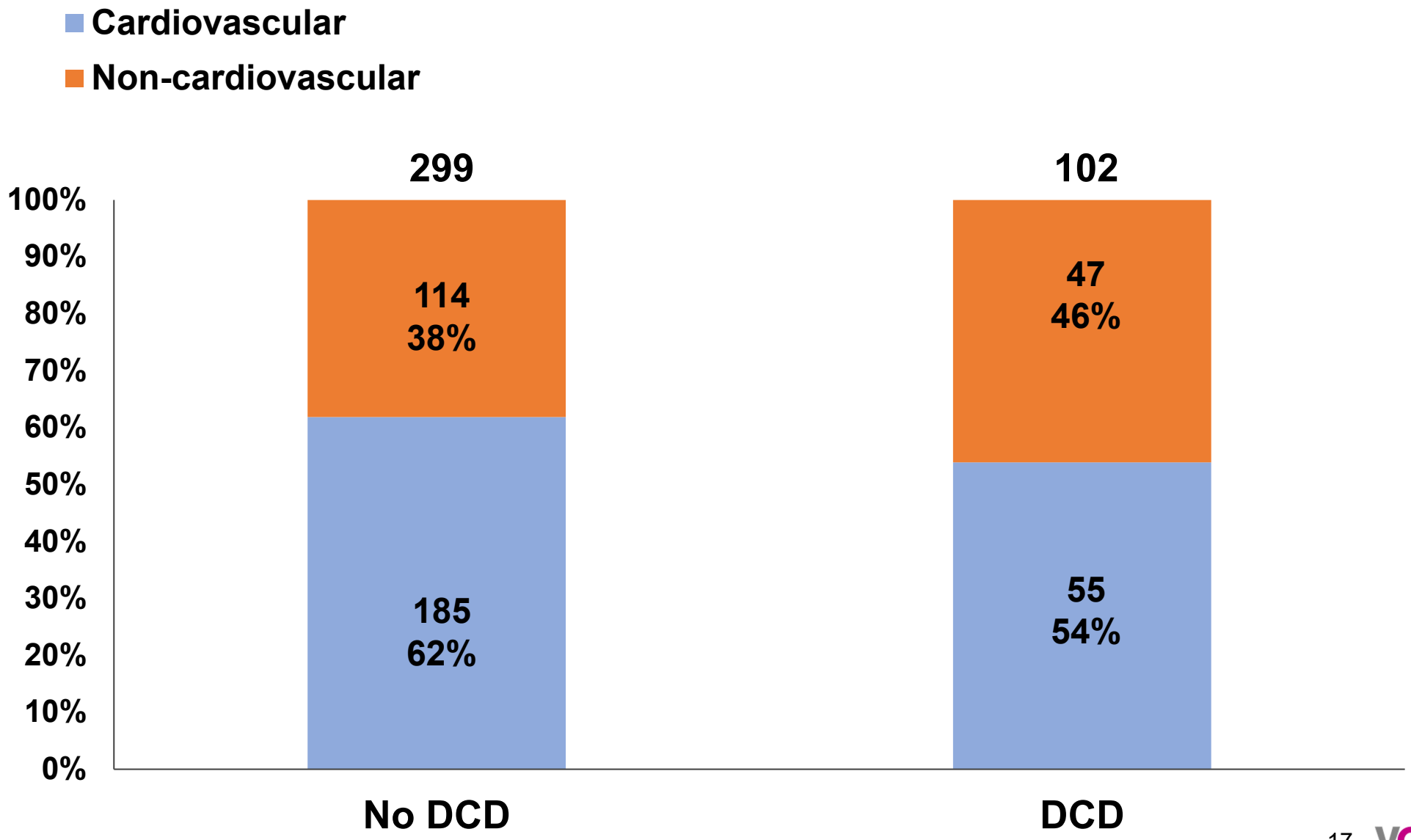
Weighted



An affiliate of:

CPC Clinical Research

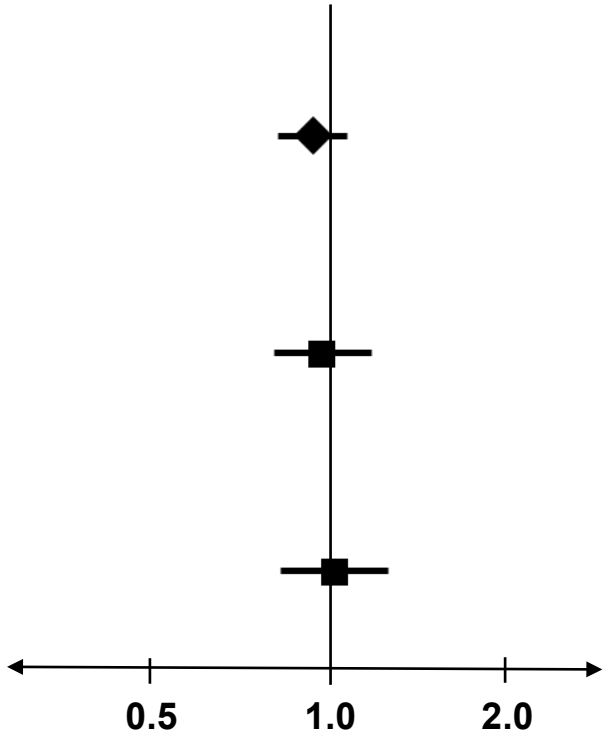
Causes of Mortality



Mortality and DCD Use by Device Type

Weighted Hazard

Device Type	DCD n/N (%)	No DCD n/N (%)	HR (95% CI)
Overall	102/1342 (7.6)	292/2974 (9.8)	0.95 (0.83, 1.09)
DCB vs. PTA	61/820 (7.4)	144/1479 (9.7)	0.99 (0.82, 1.20)
DES vs. BMS	19/231 (8.2)	148/1495 (9.9)	1.04 (0.84, 1.28)



An affiliate of:

DCB = drug-coated balloon
PTA = percutaneous transluminal angioplasty

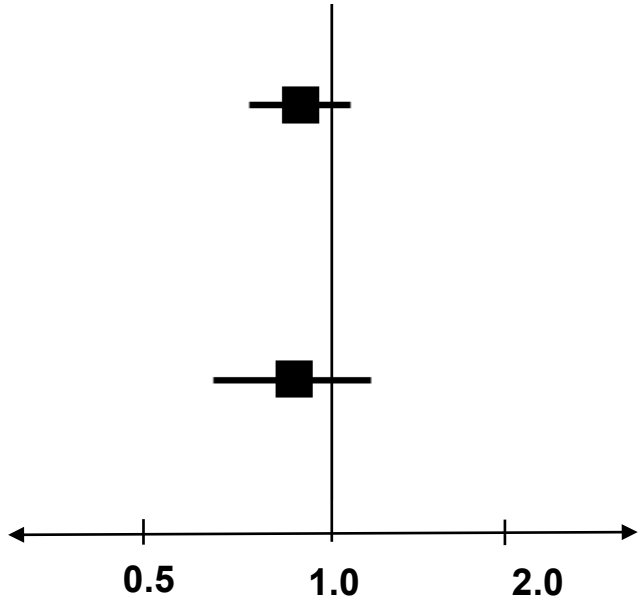
DES = drug-eluting stent
BMS = bare metal stent

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

Characteristic	Rivaroxaban n/N (%)	Placebo n/N (%)	Absolute Difference (%)	HR (95% CI)	P-interaction
No DCD use	221/1536 (14.4)	238/1485 (16.0)	1.6	0.89 (0.74, 1.07)	0.88
DCD use	88/666 (13.2)	104/692 (15.0)	1.8	0.87 (0.65, 1.15)	



An affiliate of:

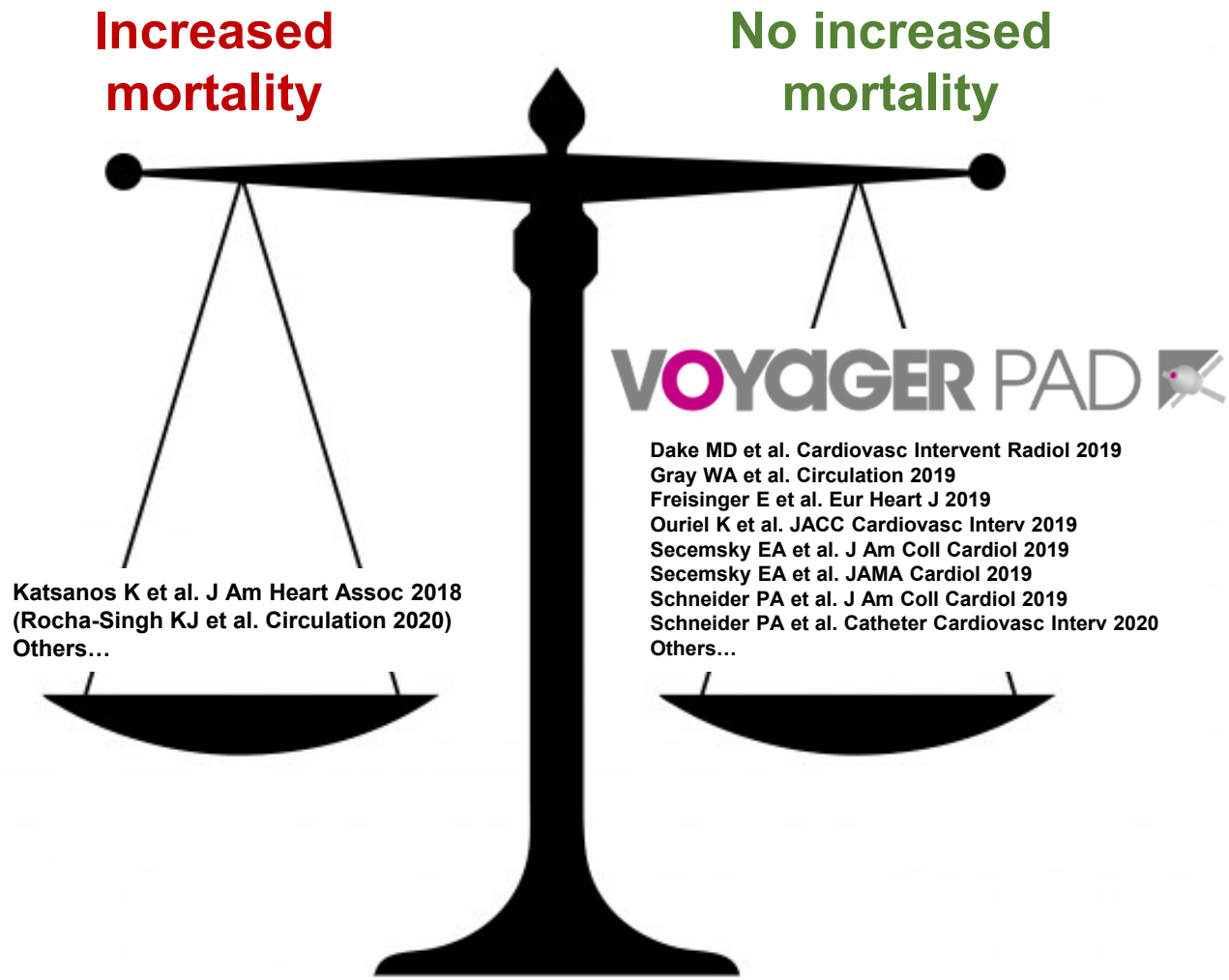
Summary

- 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

- 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