Efficacy and Safety of Dual Antiplatelet Therapy after Peripheral Artery Revascularization: Insights from VOYAGER PAD

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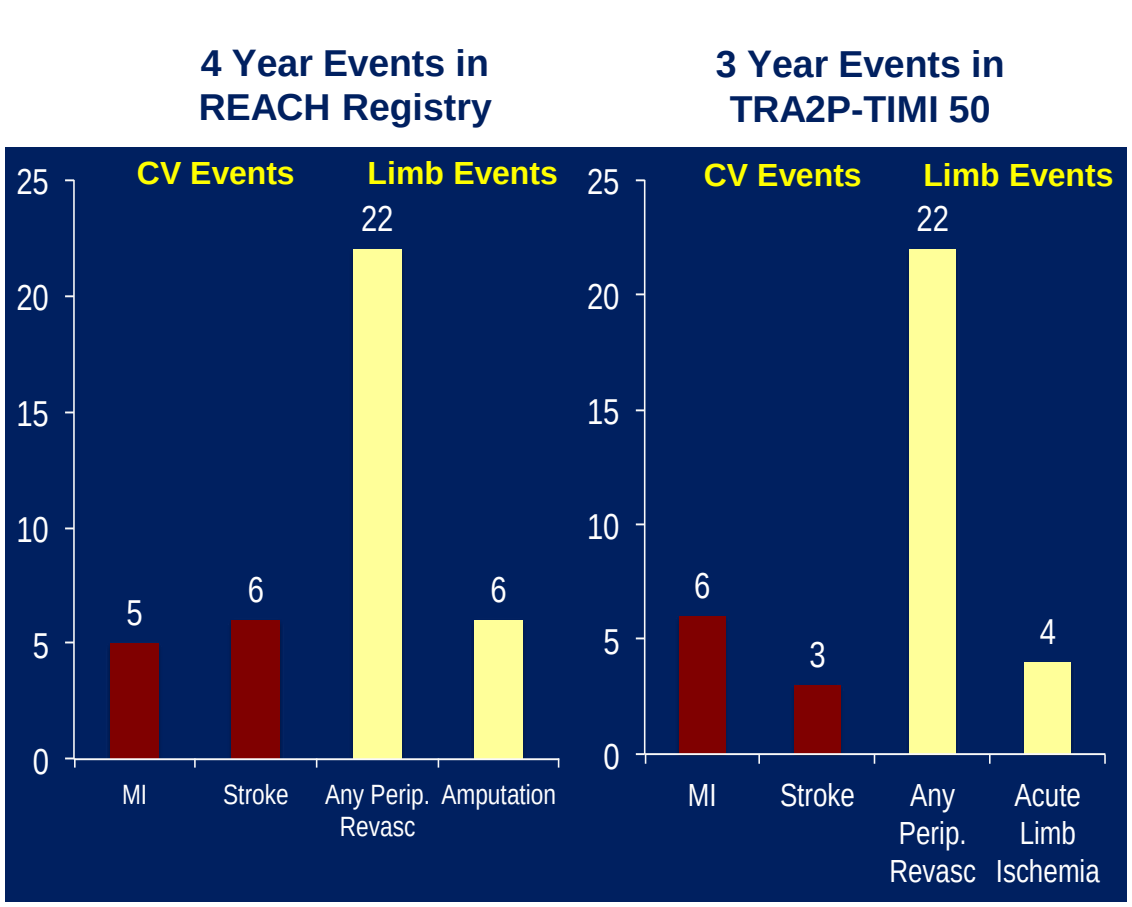
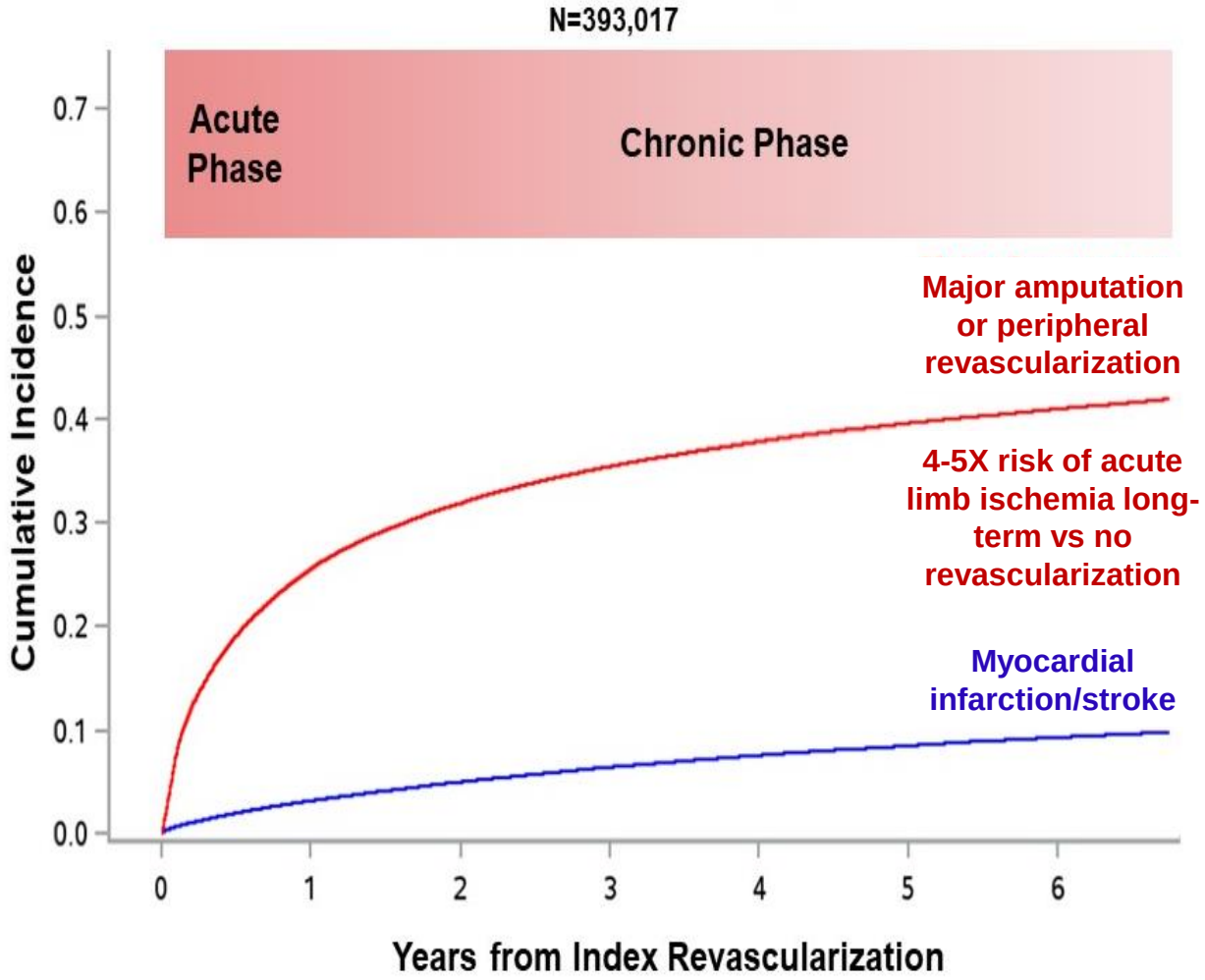
Cardiovascular and Limb Ischemic Risk in PAD

Risk in Chronic PAD



Risk after Peripheral Revascularization



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Kumbhani et al. EHJ 2014
Bonaca et al. Circulation 2013

Hess CN, et al. Circulation 2019
Hess CN, et al. J Am Coll Cardiol 2020

Dual vs. Single Antiplatelet Therapy after Lower Extremity Revascularization (LER)

Trial	Efficacy	Result	Safety	Result	Limitations
CASPAR *851 Patients after surgical bypass*	Graft occlusion or revascularization, amputation, death	HR 0.98 (95% CI 0.78-1.23), p=NS	Severe/moderate GUSTO bleeding	HR 2.84 (95% CI 1.32-6.08), p=0.007	Surgical bypass only
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MIRROR *80 patients after endovascular revascularization*	Target lesion revascularization	6 months: 5% vs 20%, p=0.04 12 months: 25% vs 32%, p=0.35	Bleeding events	6 months: 2.5% vs 5%, p=0.56	Small study, minimal number of events

- **No Class I recommendation for DAPT in PAD with neutral data after bypass and for chronic PAD**
- **Question remains after endovascular revascularization with data extrapolated from percutaneous coronary intervention literature & DAPT in device trial protocols**

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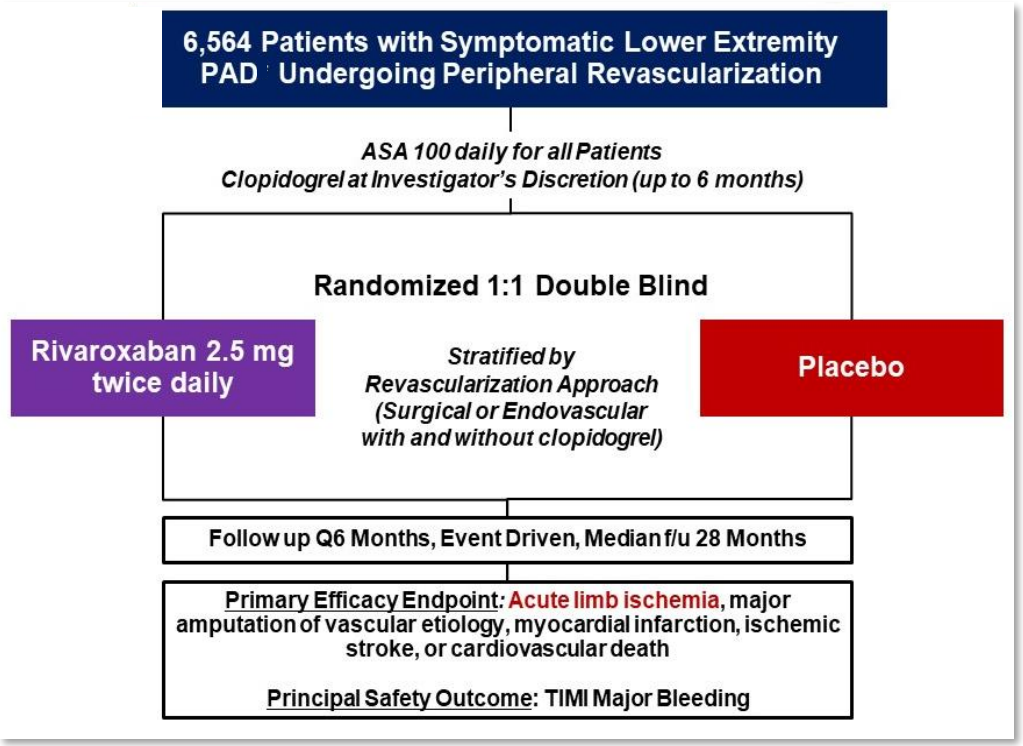
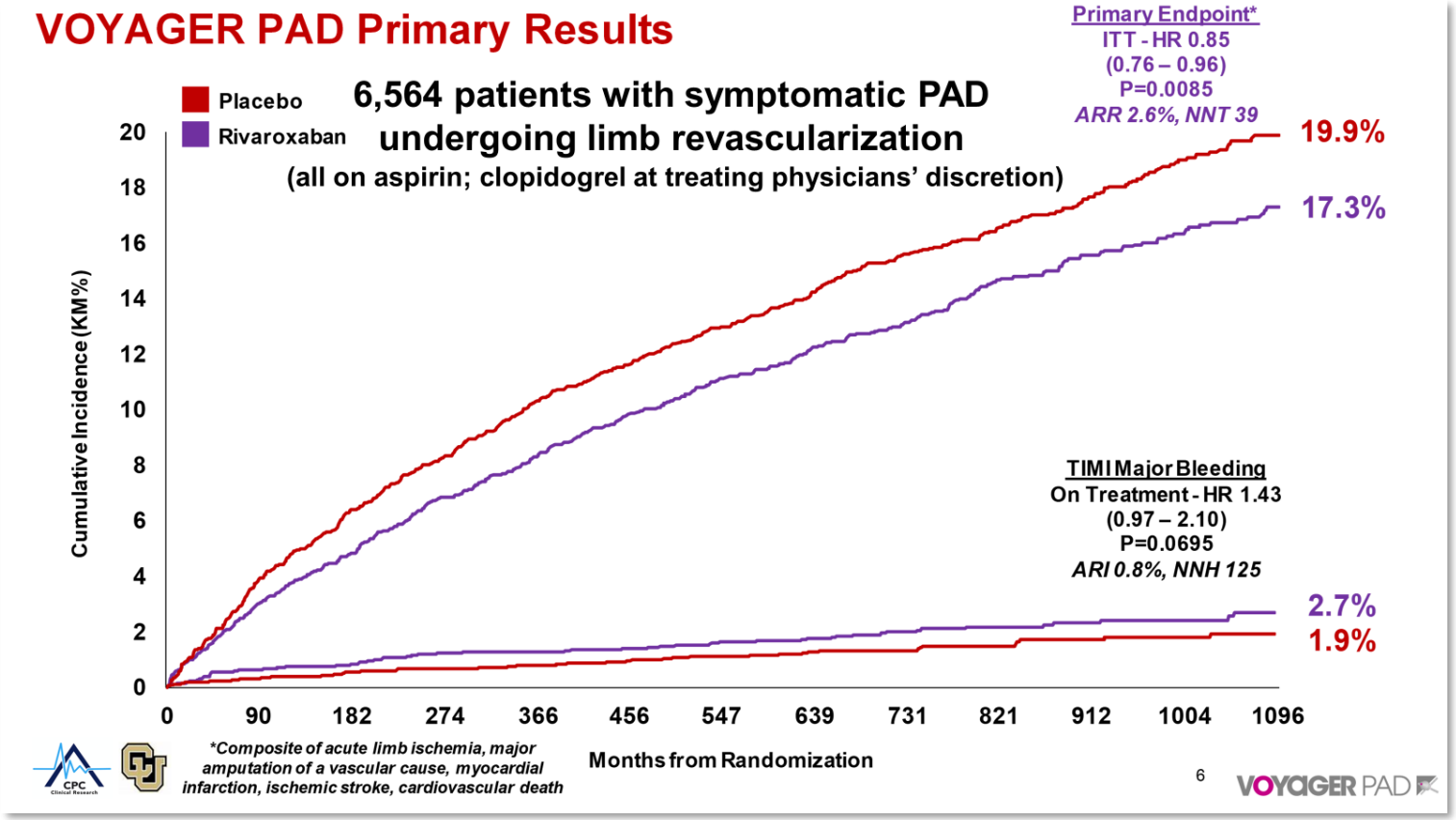
Strobl FF, et al. J Endovasc Ther 2013;20:699-706

Gerhard-Herman MD, et al. Circulation. 2017;135:e726–e779
Aboyans V, et al. Eur Heart J. 2018;39:763-816
Alonso-Coello P, et al. Chest 2012;141:e669s-e690s

VOYAGER PAD





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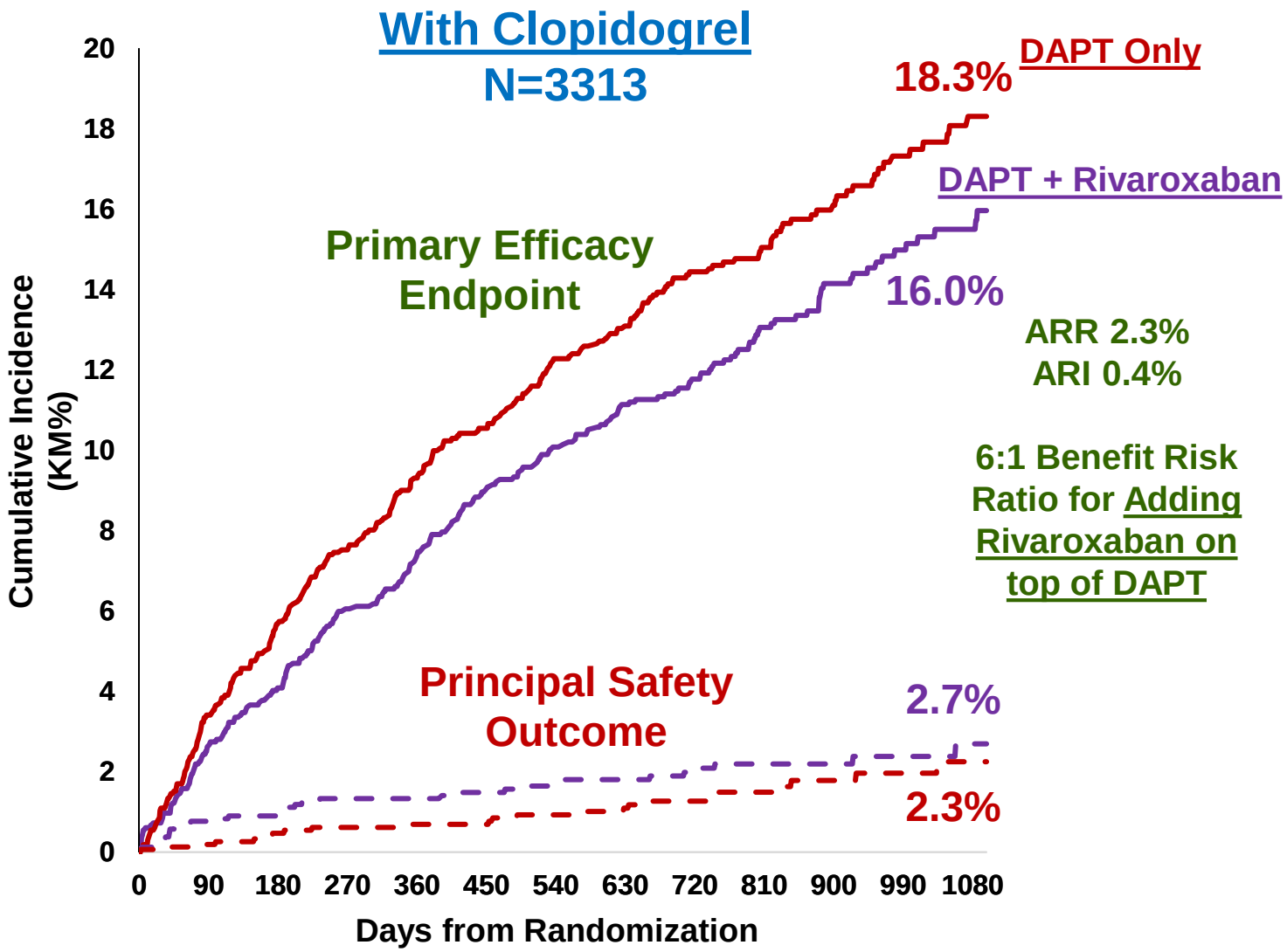
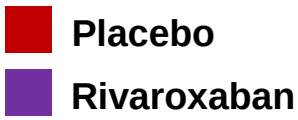
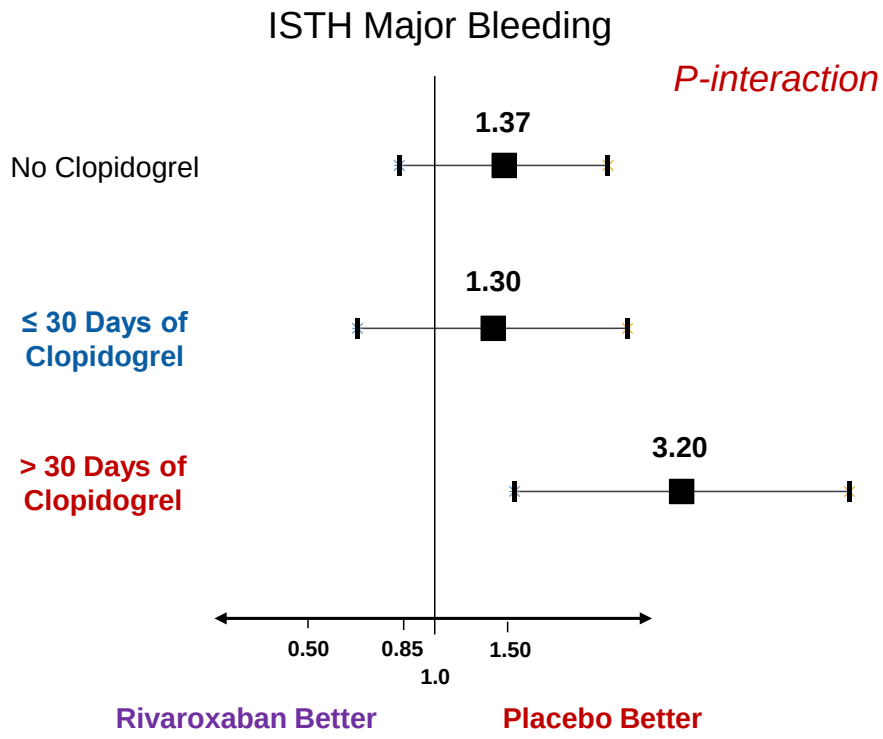
Bonaca MP, et al. NEJM 2020

Benefits of Rivaroxaban Consistent Regardless of DAPT





Question no longer DAPT vs DPI but how long to continue DAPT & can stopping clopidogrel earlier reduce bleeding risk



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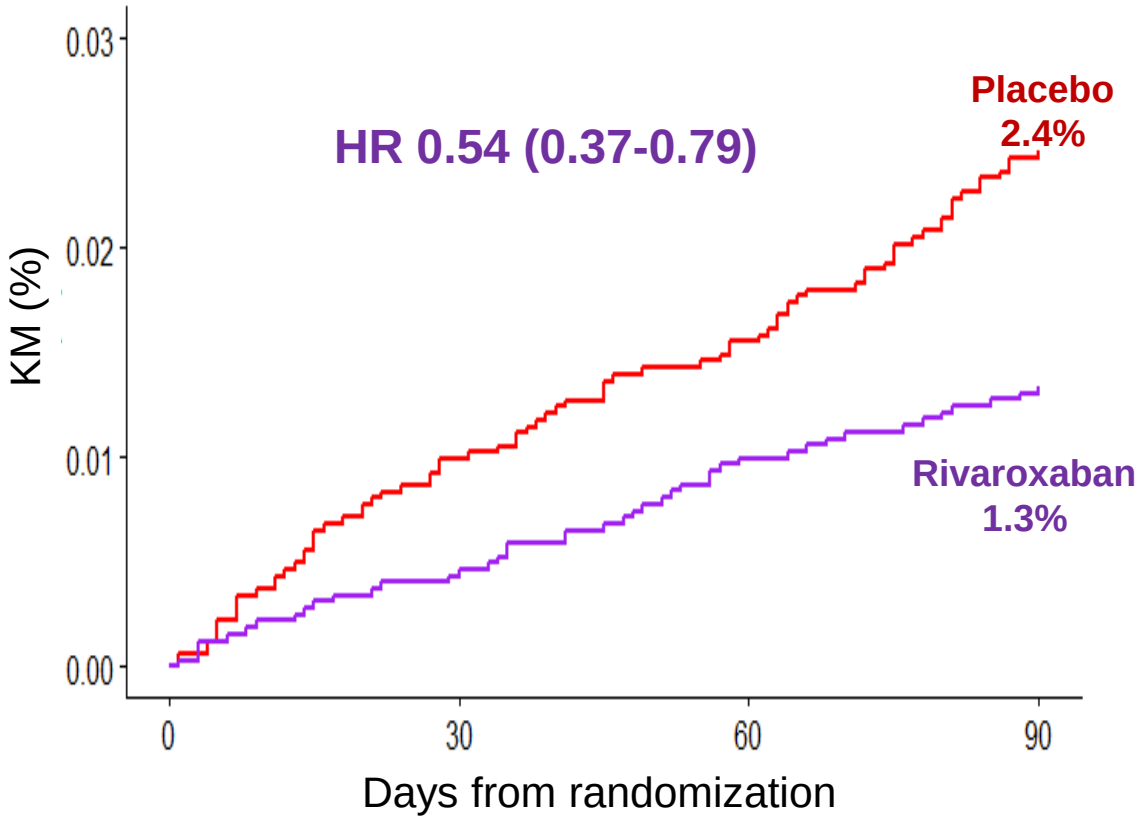
Hiatt WR et al. Circulation 2020

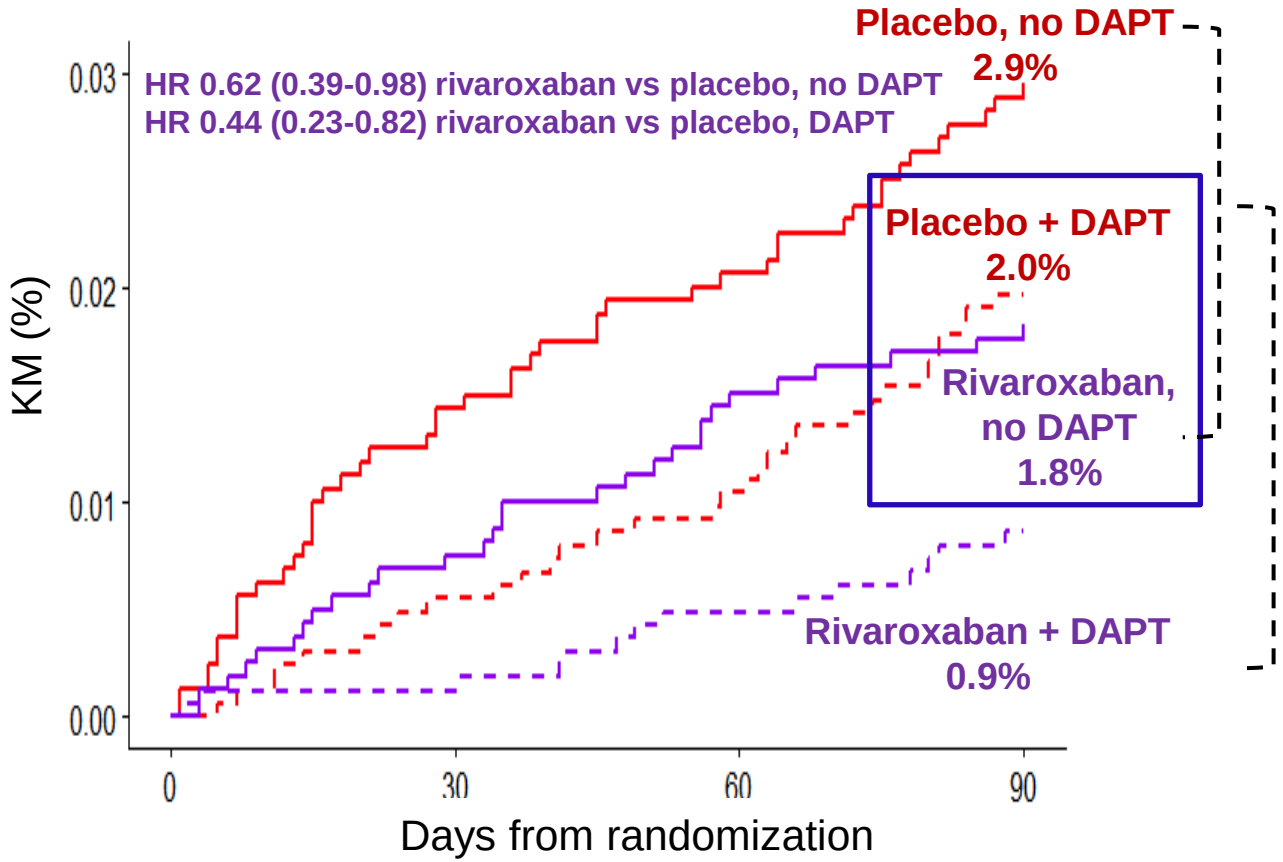
VOYAGER PAD

But…Non-Randomized Comparisons Raise Questions About Potential Benefit of DAPT

MALE at 90 Days



MALE at 90 Days



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Bonaca et al. ACC 2023; Rogers et al. Under Review

VOYAGER PAD

Baseline Characteristics

Characteristic at Randomization	Yes Clopidogrel N=3313 %	No Clopidogrel N=3234 %	P-value
Age, years (median-IQR)	67 (61-73)	67 (61-73)	0.35
Female n	28	24	<0.0001
White race	80	82	<0.0001
Hypertension	82	80	0.03
Type 2 diabetes mellitus	43	34	<0.0001
Hyperlipidemia	65	55	<0.0001
Current smoking	34	35	0.10
COPD	10	12	0.048
eGFR < 60 ml/min/1.73m^2	22	19	0.003
Coronary artery disease	34	29	<0.0001
Prior CABG	9	7	0.04
Prior coronary intervention	16	10	<0.0001
Carotid stenosis ≥ 50%	9	7	0.004

Hiatt WR et al. Circulation 2020

PAD & Procedural Characteristics

	Yes Clopidogrel N=3313 %	No Clopidogrel N=3234 %	P-value
Peripheral Artery Disease History			
Prior lower extremity revascularization	40	31	<0.0001
Prior amputation	1.2	0.8	0.13
ABI at screening, median (IQR)	0.58 (0.46-0.70)	0.52 (0.40-0.64)	< 0.0001
Indication for Revascularization			
Critical limb ischemia	20	27	<0.0001
Claudication	80	73	0.78
Type of Revascularization			
Surgical	9	58	<0.0001
Endovascular or hybrid	91	42	<0.0001

Hiatt WR et al. Circulation 2020

Objectives

- **To describe the use of clopidogrel plus aspirin after lower extremity revascularization for patients with symptomatic PAD**

- **To evaluate the efficacy and safety of clopidogrel plus aspirin versus aspirin alone in this clinical setting**

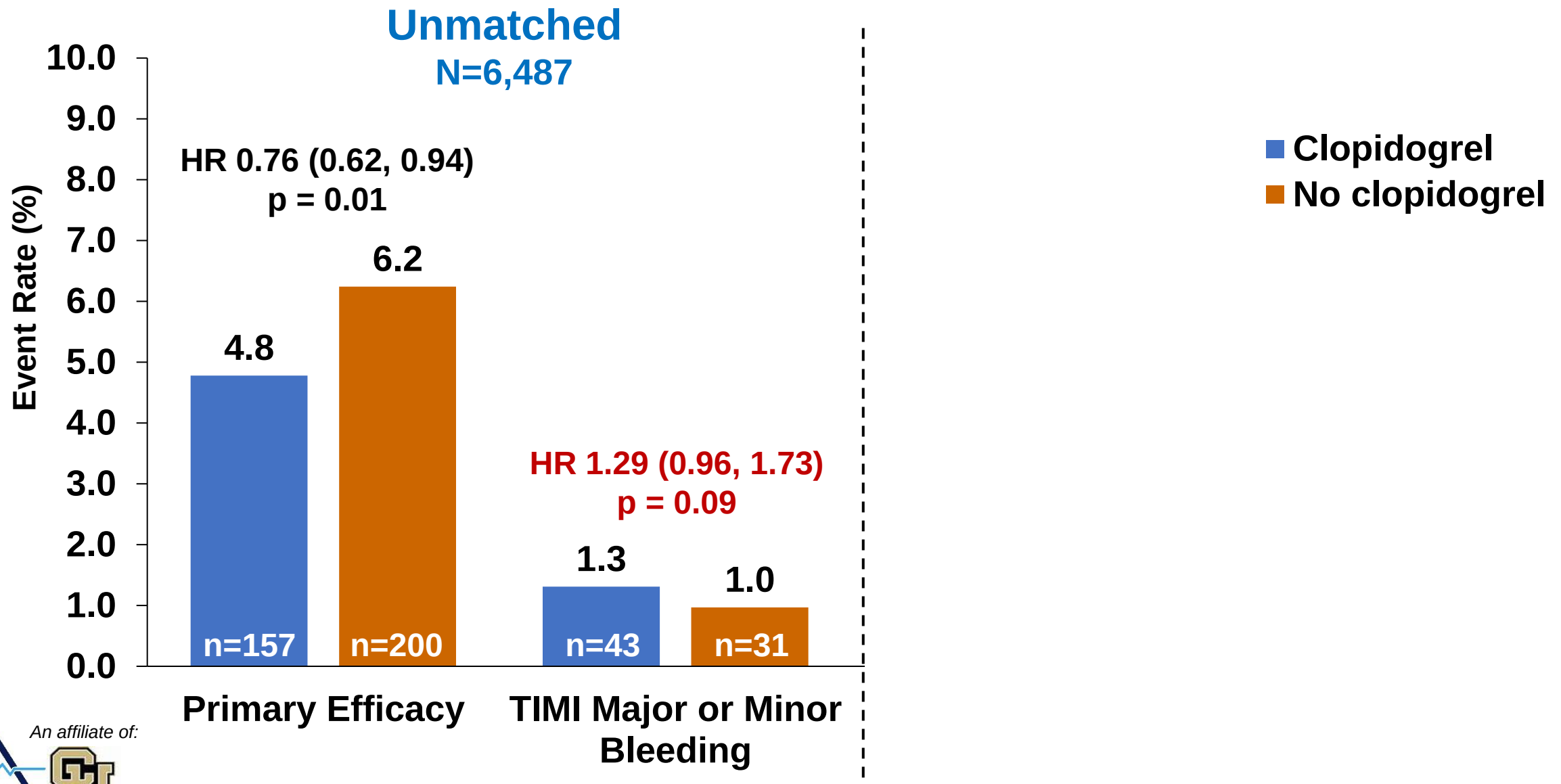
Methods

- Patients categorized according to actual clopidogrel use at randomization
- Efficacy assessed using primary composite endpoint of acute limb ischemia, major amputation of vascular etiology, myocardial infarction, ischemic stroke, or cardiovascular death
  - Unplanned index limb revascularization prespecified as secondary endpoint
- Safety assessed using TIMI major/minor bleeding
- 180-day outcomes examined
- Propensity score matching used to balance baseline characteristics
- Relationship between outcomes and baseline clopidogrel evaluated with Cox proportional hazards regression

Results

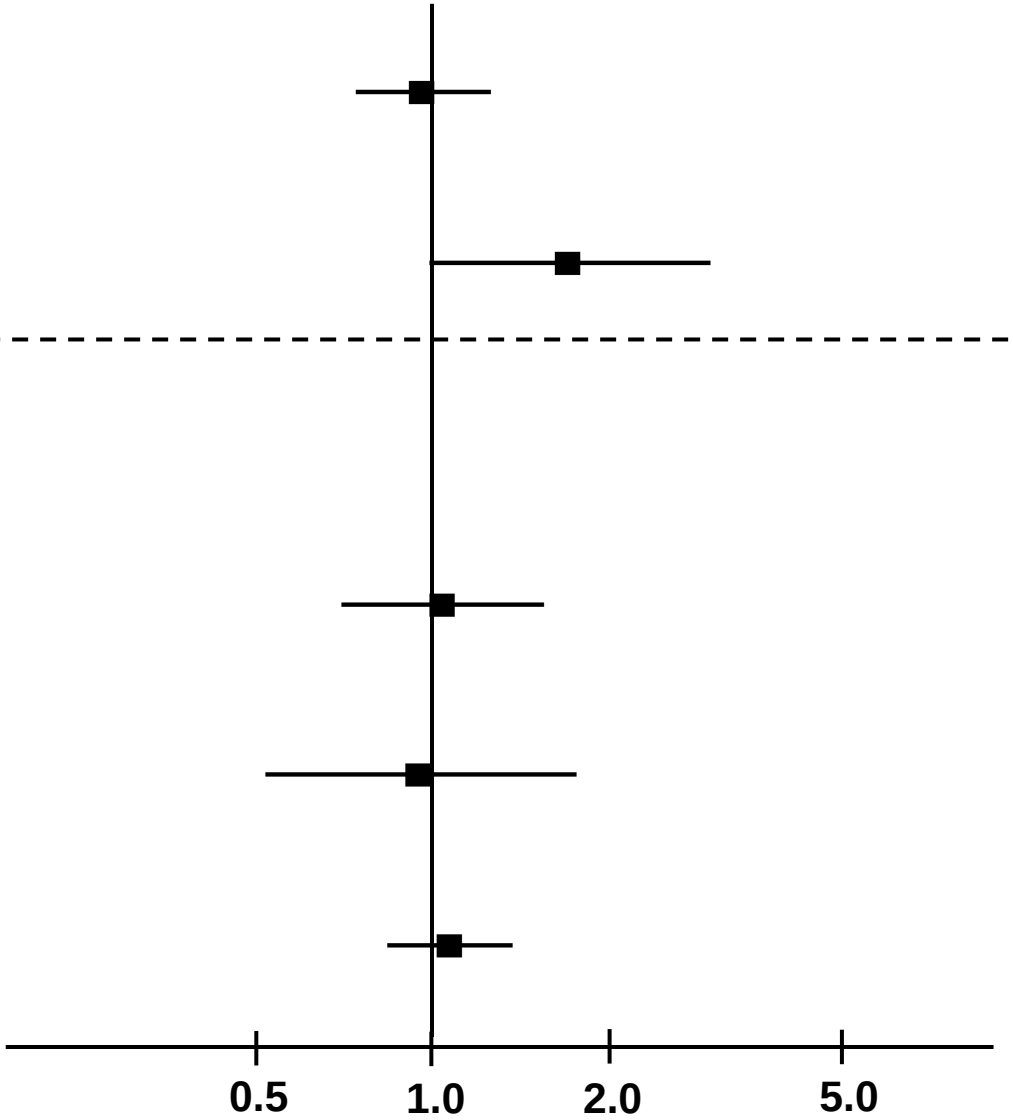
- 6,564 randomized patients (median follow up 28 months)
- Data regarding clopidogrel use at baseline available for 6,547 patients
- 50.6% (n=3313) were treated with clopidogrel
- Median duration of clopidogrel treatment was 29 days (IQR 29-49.5 in rivaroxaban group; 26-50 days in placebo group)
- 2312 pts treated with clopidogrel could be matched (4624 propensity-score matched patients)
  - Rivaroxaban and placebo balanced between clopidogrel and no clopidogrel groups

DAPT vs. SAPT and 180-Day Outcomes



Additional 180-Day Outcomes with DAPT vs. SAPT

180-Day Outcome*	HR (95% CI)	p-value
Primary Efficacy Composite	0.96 (0.74-1.26)	0.78
TIMI Major/Minor Bleeding	1.71 (0.99-2.98)	0.056
Other Selected Outcomes*		
Acute Limb Ischemia	1.04 (0.70-1.55)	0.84
Major Amputation	0.95 (0.52-1.76)	0.87
Unplanned Index Limb Revascularization	1.07 (0.84-1.37)	0.58



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Results after PS matching

VOYAGER PAD DAPT Findings in Context

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VOYAGER PAD *6564 Patients* *4624 in DAPT analysis >90% endo*	ALI, major amputation of vascular etiology, MI, stroke, CV death	HR 0.96 (95% CI 0.74- 1.26), p=0.78	TIMI major/minor bleeding	HR 1.71 (95% CI 0.99-2.98), p=0.056	Clopidogrel use not randomized

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Summary

- **In VOYAGER PAD, clopidogrel was used in half of patients (N=3313) undergoing LER for symptomatic PAD**
- **Use of DAPT did not modify the benefit/risk of rivaroxaban overall; however, prolonged DAPT use was associated with more bleeding**
- **Propensity score-adjusted analysis of DAPT vs. no DAPT**
  - **No associated pattern for lower risk of MACE or MALE with DAPT**
  - **~70% increase in TIMI major/minor bleeding with DAPT**

Conclusions

- **DAPT use after LER is based on data extrapolated from coronary intervention (e.g. stent thrombosis prevention); in coronary field, there is a movement to shorten DAPT to reduce bleeding risk**
- **VOYAGER PAD data do not demonstrate lower rates of limb outcomes with DAPT; outcomes are similar to those of prior RCT**
- **Clear increase in bleeding risk for DAPT with HRs ranging from 1.7 to 2.8**
- **In context of favorable benefit/risk of rivaroxaban + aspirin early and late after LER and no convincing benefit seen for DAPT (but increased bleeding risk)**
  - **Early initiation of aspirin plus rivaroxaban after LER (as studied in VOYAGER PAD) should be considered**
  - **Bleeding liability of DAPT should be carefully weighed (in absence of benefit)**
  - **DAPT exposure should be limited…if utilized at all**

Thank you!