The Role of Combination Antiplatelet and Anticoagulation Therapy in Diabetes and Cardiovascular Disease: COMPASS Diabetes

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BWH BRIGHAM AND WOMEN'S HOSPITAL
| Heart & Vascular Center |

HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

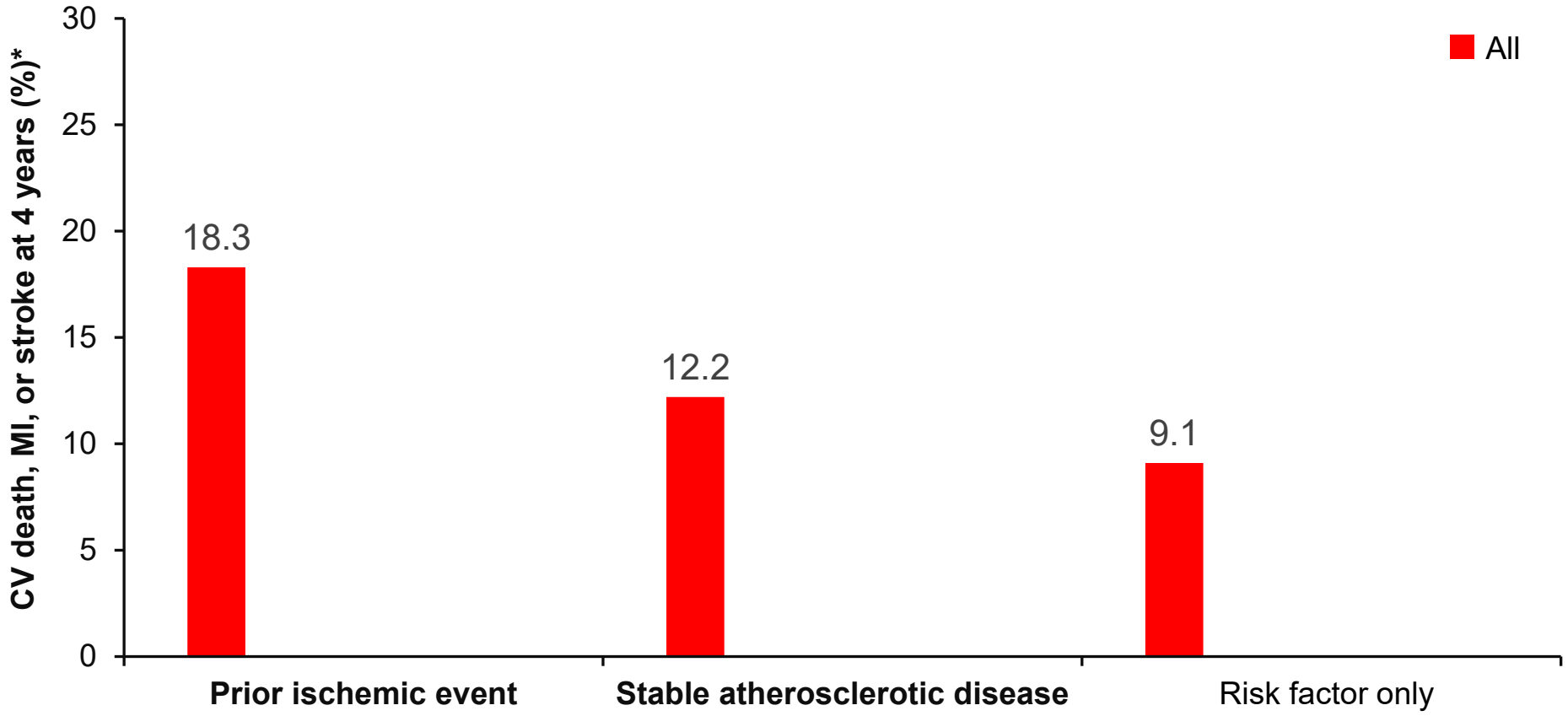
Disclosures

Dr. Deepak L. Bhatt discloses the following relationships - Advisory Board: Cardax, Cereno Scientific, Elsevier Practice Update Cardiology, Medscape Cardiology, PhaseBio, PLx Pharma, Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care, TobeSoft; Chair: American Heart Association Quality Oversight Committee; Data Monitoring Committees: Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Cleveland Clinic (including for the ExCEED trial, funded by Edwards), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo), Population Health Research Institute; **Honoraria**: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org; Vice-Chair, ACC Accreditation Committee), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim; AEGIS-II executive committee funded by CSL Behring), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees, including for the PRONOUNCE trial, funded by Ferring Pharmaceuticals), HMP Global (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), Medtelligence/ReachMD (CME steering committees), MJH Life Sciences, **Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and USA national co-leader, funded by Bayer)**, Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees); Other: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); **Research Funding**: Abbott, Afimmune, Amarin, Amgen, AstraZeneca, **Bayer**, Boehringer Ingelheim, Bristol-Myers Squibb, Cardax, Chiesi, CSL Behring, Eisai, Ethicon, Ferring Pharmaceuticals, Forest Laboratories, Fractyl, Idorsia, Ironwood, Ischemix, Lexicon, Lilly, Medtronic, Pfizer, PhaseBio, PLx Pharma, Regeneron, Roche, Sanofi Aventis, Synaptic, The Medicines Company; Royalties: Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald's Heart Disease); Site Co-Investigator: Biotronik, Boston Scientific, CSI, St. Jude Medical (now Abbott), Svelte; Trustee: American College of Cardiology; Unfunded Research: FlowCo, Merck, Novo Nordisk, Takeda.

This presentation may discuss off label and investigational uses of drugs.

COMPASS was funded by Bayer.

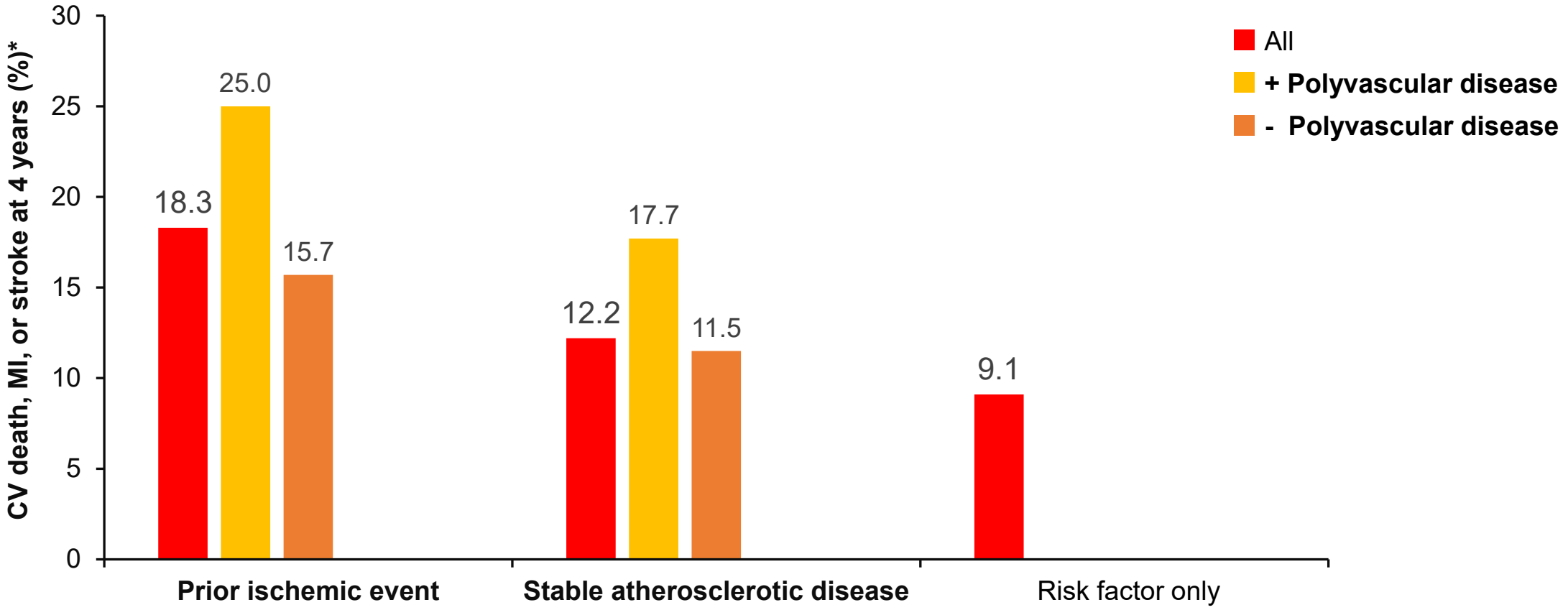
Impact of Prior Ischemic Events or Stable Atherosclerosis on CV Events at 4 Years



*All event rates adjusted for age and sex.

Bhatt DL, Eagle KA, Ohman EM, et al., and Steg PG. *JAMA* 2010; 304:1350-1357.

Impact of Polyvascular Disease on CV Events at 4 years



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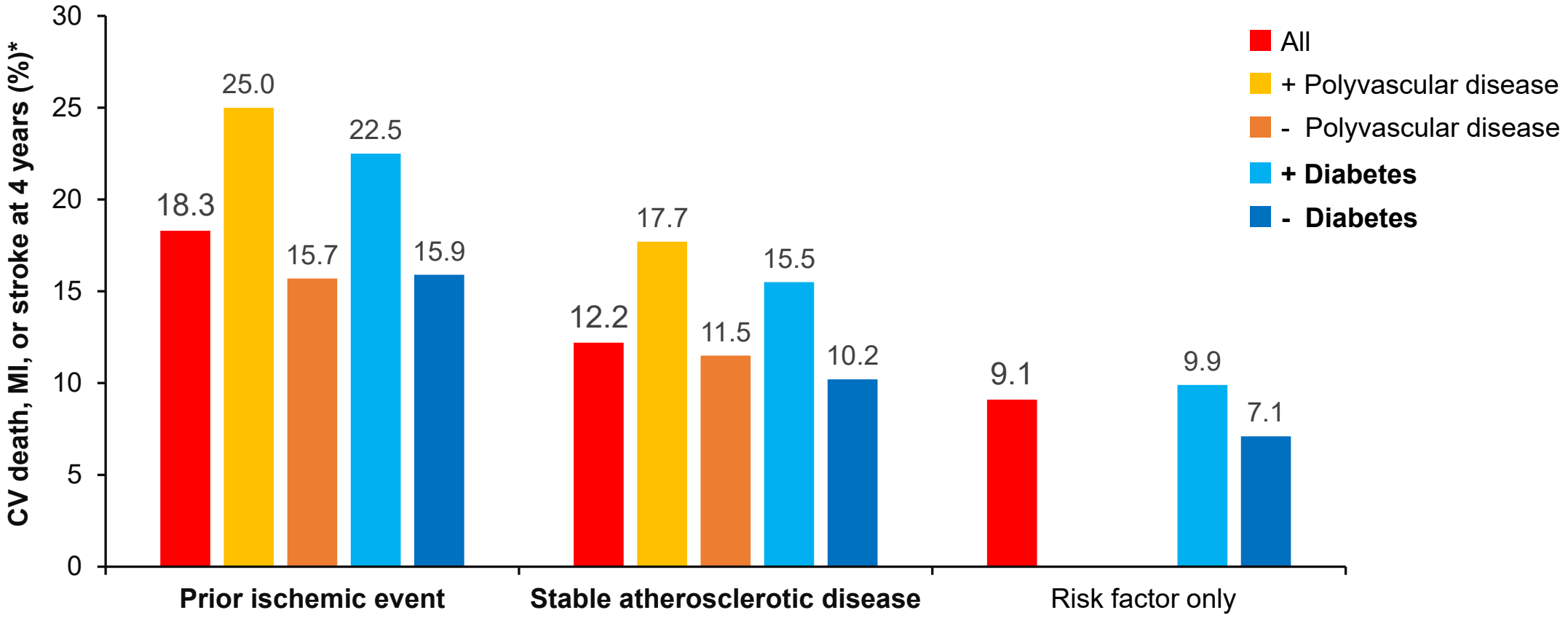
Impact of Diabetes on CV Events at 4 years



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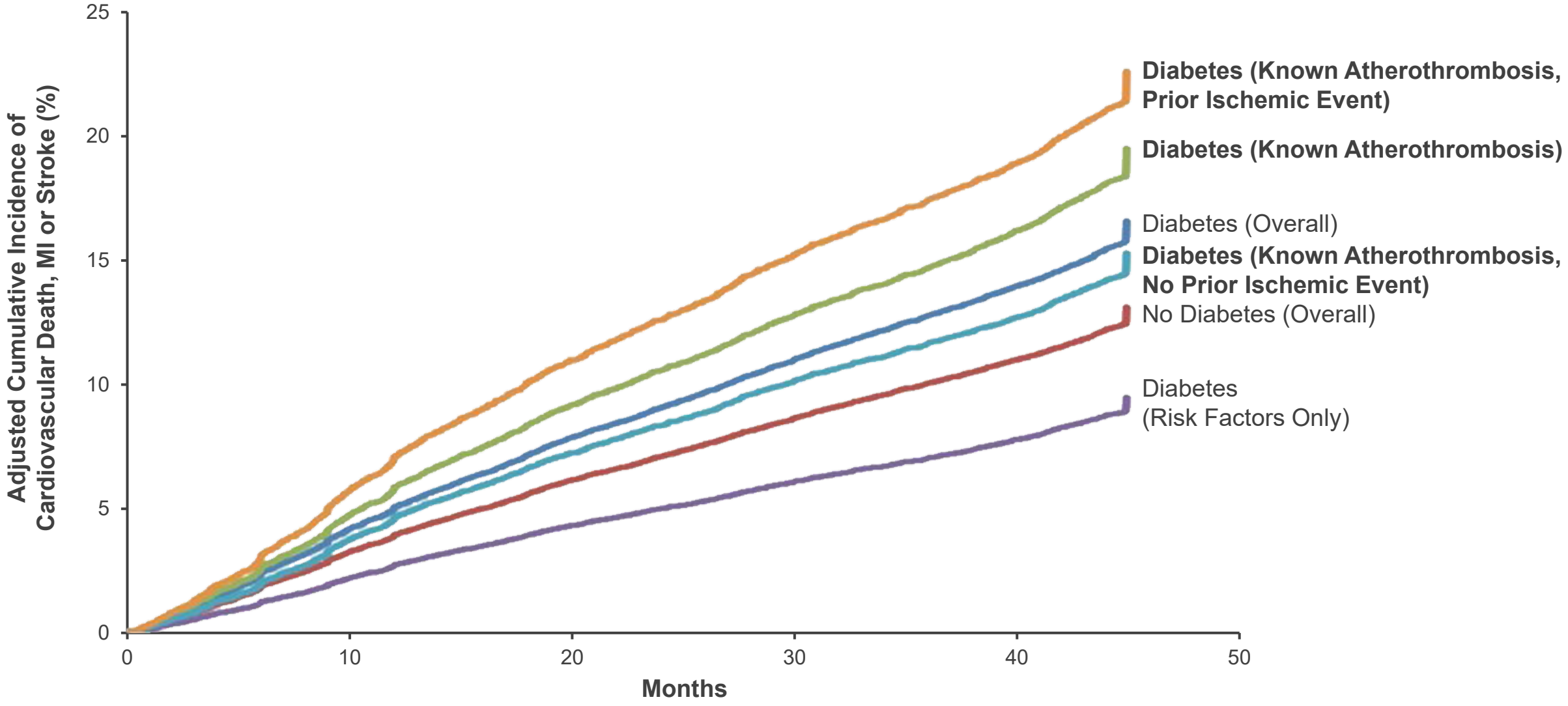
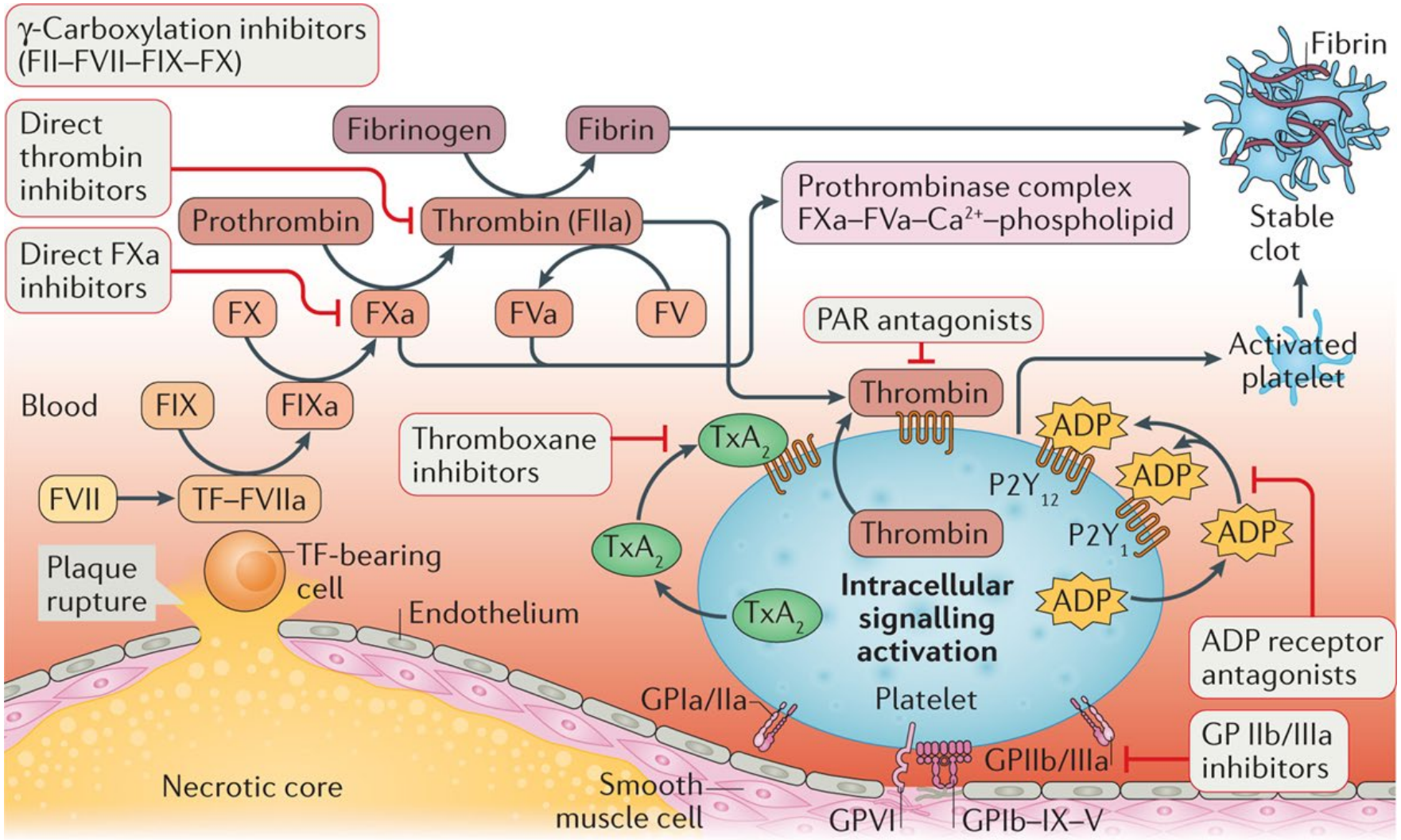
REACH - Diabetes



Cavender MA, Steg PG, Smith SC, et al, Bhatt DL. *Circulation* 2015.

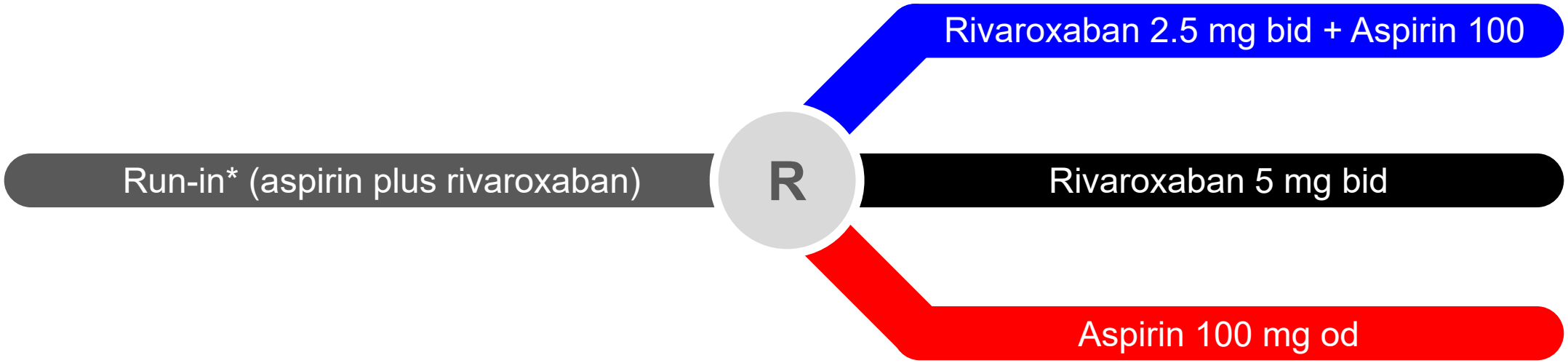
Dual Pathway Inhibition: Antiplatelet plus Anticoagulant



Bhatt DL. *Nat. Rev. Cardiol.* doi:10.1038/nrcardio.2017.212. 2018.

COMPASS Design

Stable CAD or PAD
27,395 participants randomized



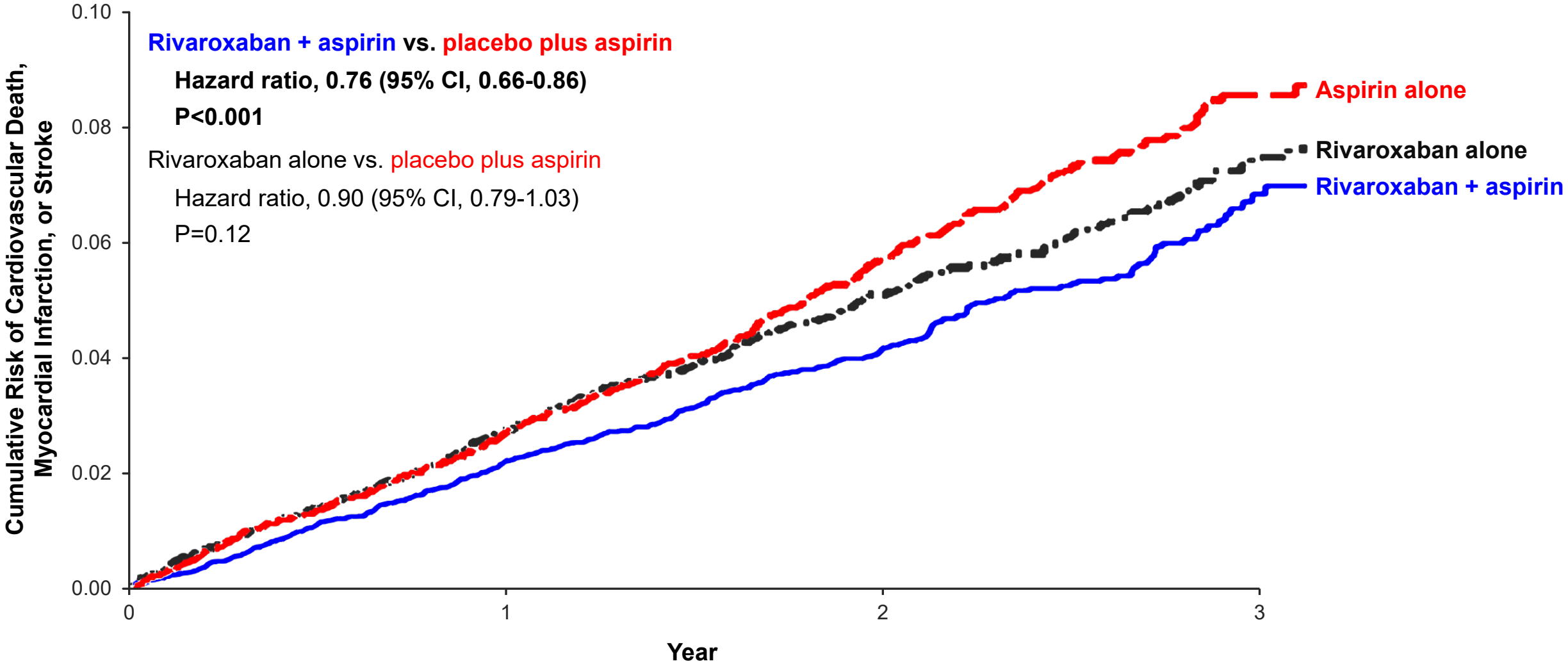
Expected mean follow up: 3-4 years

*excluding patients enrolled 4-14 days post CABG

Bosch JJ, et al. *Can J Cardiol* 2017; 33:1027-1035.

COMPASS Trial Primary outcome

Population Health Research Institute
HEALTH THROUGH KNOWLEDGE



Eikelboom JW, et al. *N Engl J Med* 2017; 377:1319-30.

COMPASS Diabetes Analysis

Effects in patients with diabetes at baseline (N=6,922) versus without diabetes (N=11,356)

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COMPASS Diabetes Analysis

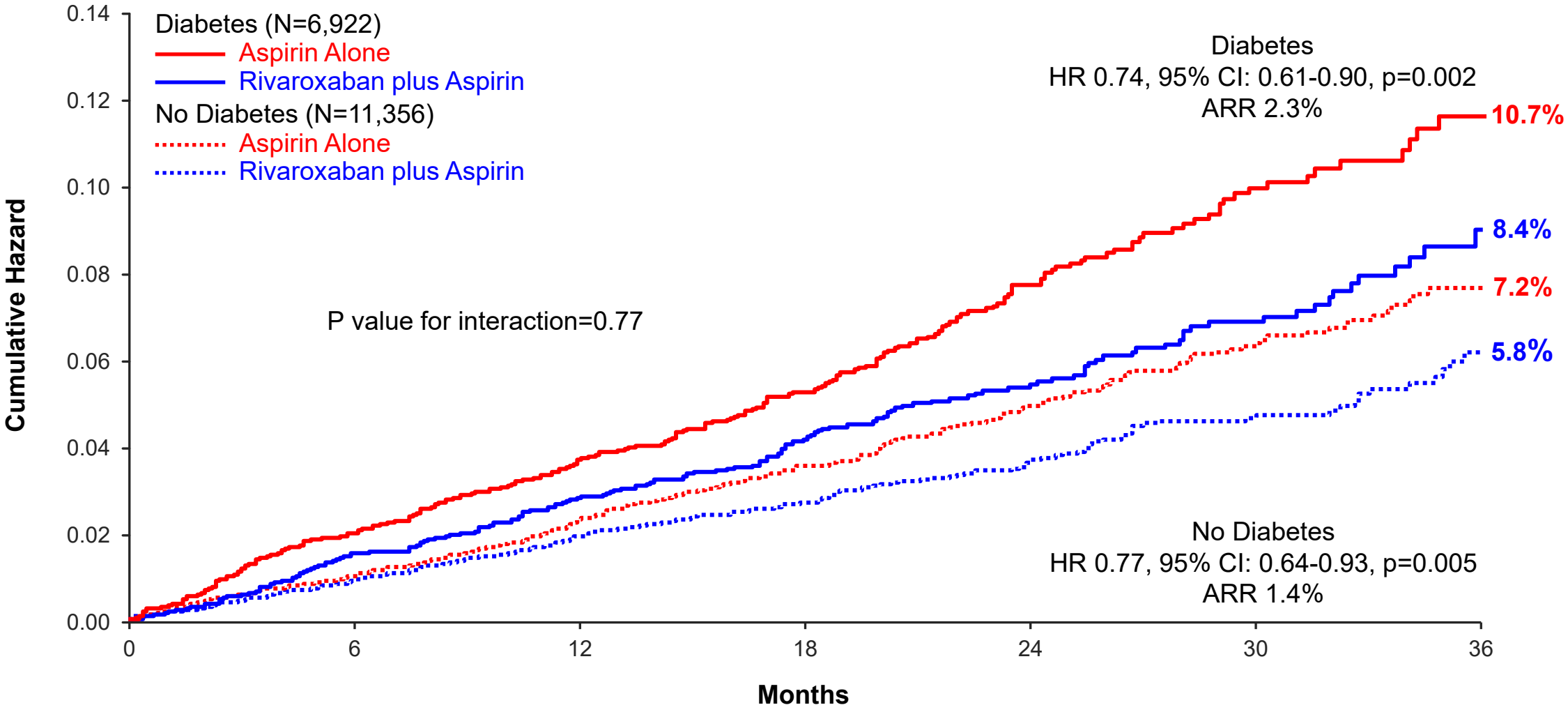
Effects in patients with diabetes at baseline (N=6,922) versus without diabetes (N=11,356)

Patients randomized to rivaroxaban plus aspirin (N=9,126) versus placebo plus aspirin (N=9,126)

- 1° efficacy: CV death, MI, stroke
- 2° efficacy:
  - All-cause mortality
  - CV death, MI, stroke, MALE, including amputation
- 1° safety: modified ISTH criteria - major bleeding
- Prespecified net clinical benefit: CV death, MI, stroke, fatal bleeding, symptomatic bleeding into a critical organ

Bhatt DL, Eikelboom JW, Connolly SJ, et al, Yusuf S. *Circulation*. 2020.

CV Death, Myocardial Infarction, or Stroke



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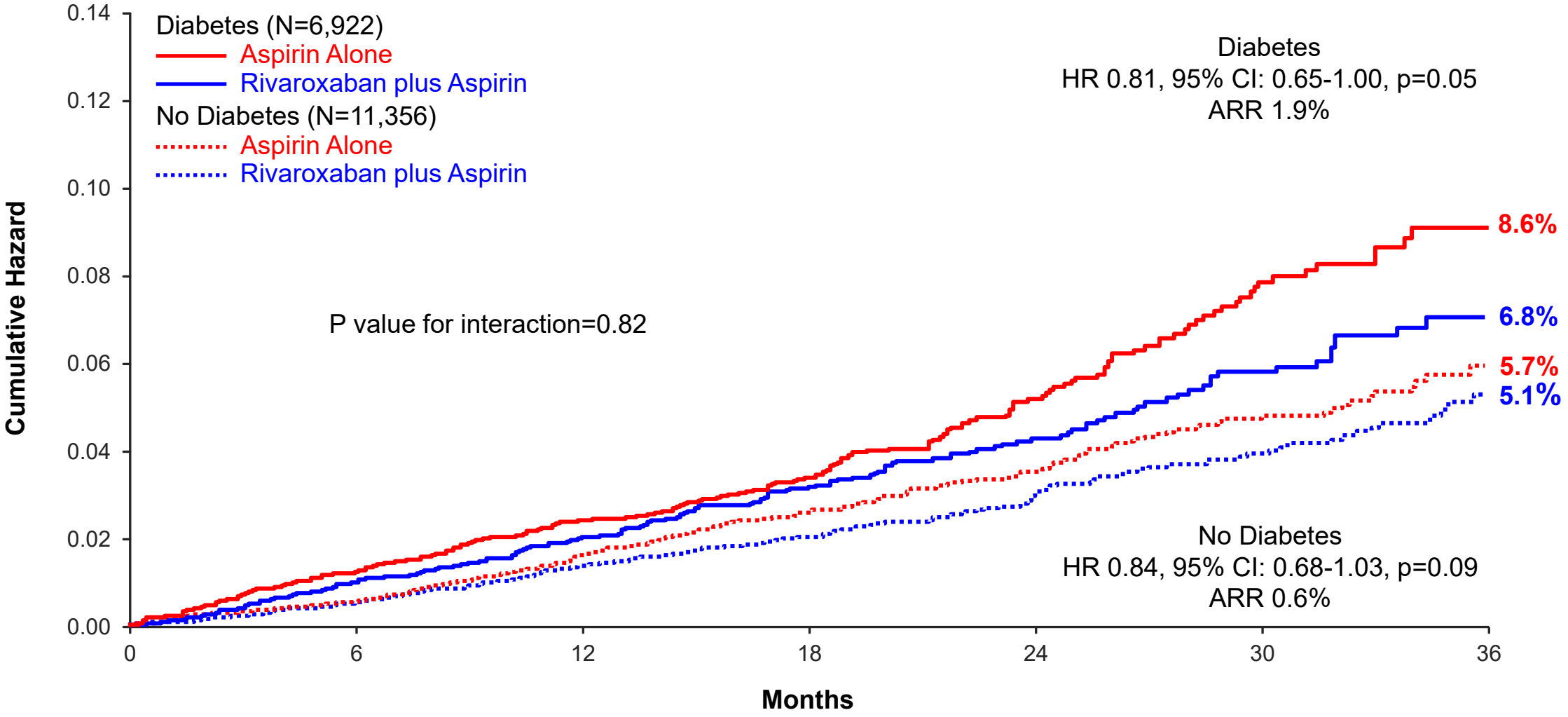
All-Cause Death



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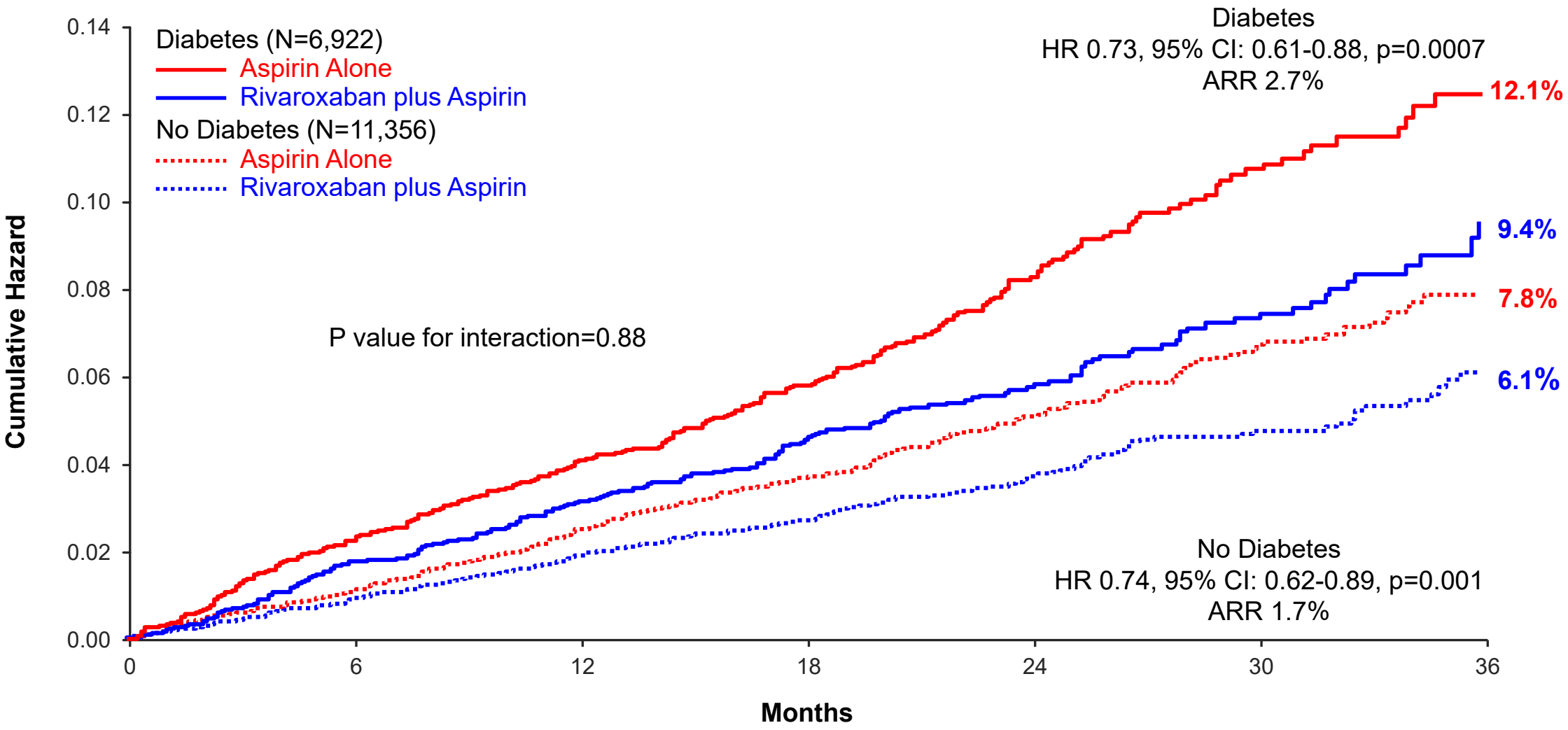
CV Death, Myocardial Infarction, Stroke, MALE, or Major Vascular Amputation



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Safety Outcomes

	Rivaroxaban plus Aspirin		Aspirin Alone				
	No. of first events/ patients (%)	Kaplan-Meier risk at 36 months	No. of first events/ patients (%)	Kaplan-Meier risk at 36 months	Hazard Ratio (95% CI)	P value	P value for interaction
Major bleeding							0.97
No diabetes at baseline	178/5704 (3.1)	4.4	105/5652 (1.9)	3.2	1.69 (1.33-2.15)	<0.0001	
Diabetes at baseline	110/3448 (3.2)	4.5	65/3474 (1.9)	3.4	1.70 (1.25-2.31)	0.0006	
Intracranial bleeding							0.44
No diabetes at baseline	17/5704 (0.3)	0.4	17/5652 (0.3)	0.7	0.99 (0.51-1.95)	0.98	
Diabetes at baseline	11/3448 (0.3)	0.4	7/3474 (0.2)	0.4	1.57 (0.61-4.05)	0.35	
Fatal bleeding							0.87
No diabetes at baseline	10/5704 (0.2)	0.4	7/5652 (0.1)	0.2	1.43 (0.55-3.77)	0.46	
Diabetes at baseline	5/3448 (0.1)	0.2	3/3474 (<0.1)	0.2	1.66 (0.40-6.93)	0.48	

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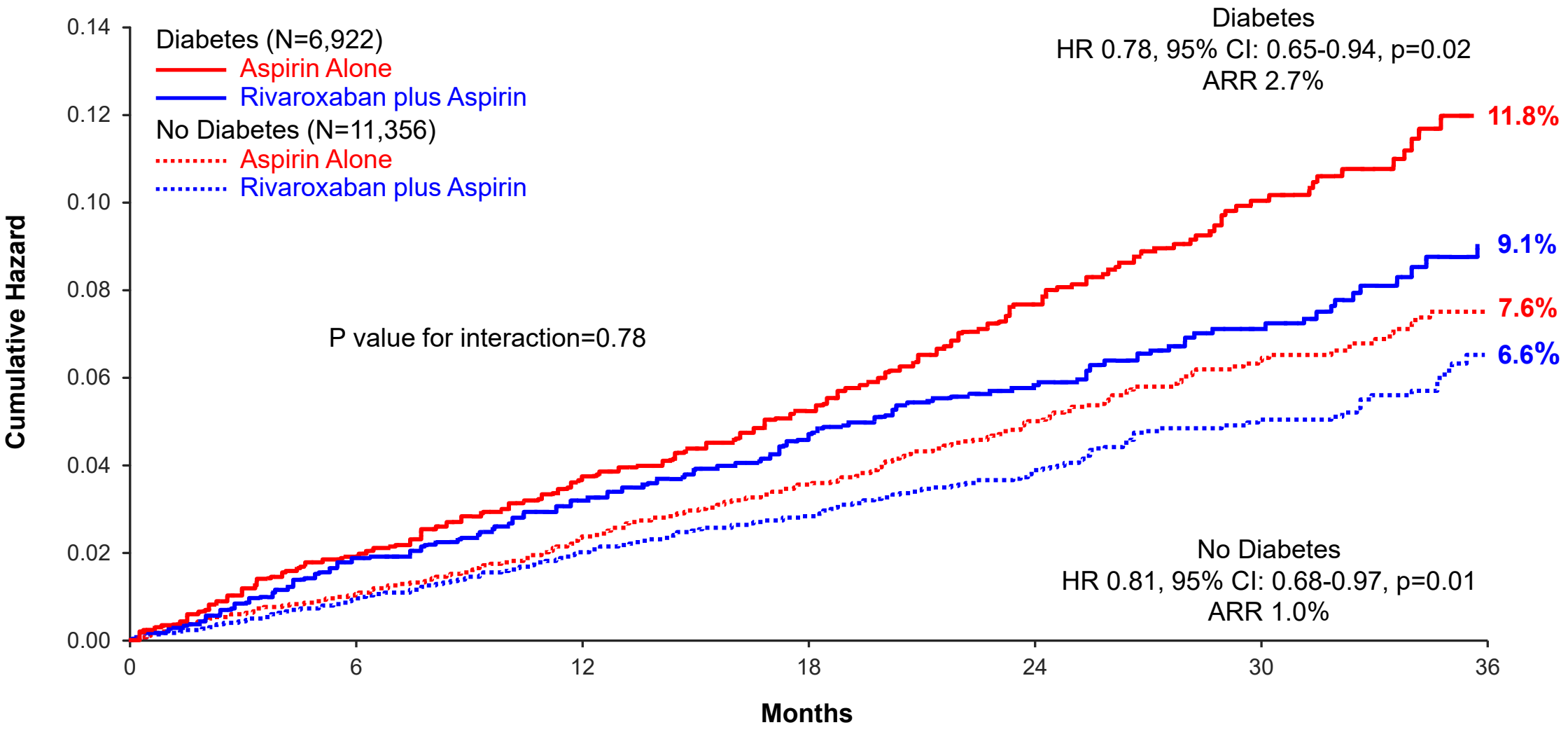
CV Death, MI, Stroke, Fatal Bleeding, or Symptomatic Bleeding into Critical Organ



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Benefits in Diabetes +/- Prior Ischemic Events or Revascularization: CV Death/MI/Stroke

	Rivaroxaban plus Aspirin		Aspirin Alone				
	No. of first events/ patients (%)	Kaplan-Meier risk at 36 months	No. of first events/ patients (%)	Kaplan-Meier risk at 36 months	Hazard Ratio (95% CI)	P value	P value for interaction
Prior ischemic events							0.85
No	42/937 (4.5)	8.8	57/981 (5.8)	10.1	0.76 (0.51-1.14)	0.18	
Yes	137/2511 (5.5)	8.3	182/2493 (7.3)	11.0	0.73 (0.59-0.91)	0.006	
Prior revasc							0.87
No	58/978 (5.9)	10.0	85/1068 (8.0)	12.8	0.73 (0.52-1.02)	0.06	
Yes	121 / 2470 (4.9)	7.9	154/2406 (6.4)	9.9	0.75 (0.59-0.95)	0.02	
Prior ischemic events, revasc							0.88
No	18/416 (4.3)	11.0	26/435 (6.0)	12.3	0.71 (0.39-1.30)	0.27	
Yes	161/3032 (5.3)	8.3	213/3039 (7.0)	10.6	0.74 (0.61-0.91)	0.004	

Bhatt DL, Eikelboom JW, Connolly SJ, et al, Yusuf S. *Circulation*. 2020.

Limitations

Diabetes subgroup not specifically powered for efficacy or safety

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Early stopping of the trial further limits the power of subgroup analysis

- Though the independent DSMB felt the trial needed to be stopped due to overwhelming efficacy, including a reduction in all-cause mortality

Bhatt DL, Eikelboom JW, Connolly SJ, et al, Yusuf S. *Circulation*. 2020.

Conclusions

Low-dose rivaroxaban + aspirin reduced major CV events in stable atherosclerosis, irrespective of the presence or absence of diabetes, though absolute risk reductions were numerically larger with diabetes, including for all-cause mortality.

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The net clinical benefit when examining irreversible outcomes appeared numerically greater in those with diabetes.

Use of dual pathway inhibition with low-dose rivaroxaban + aspirin is particularly attractive in high-risk patients, such as those with diabetes.

Bhatt DL, Eikelboom JW, Connolly SJ, et al, Yusuf S. *Circulation*. 2020.

Circulation

Circulation. 2020; [published online ahead of print]. DOI: 10.1161/CIRCULATIONAHA.119.044586

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American Heart Association.

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Thank You!

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