Primary and Secondary Prevention of CVD – Current Standard of Care

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BRIGHAM AND
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| Heart & Vascular Center |

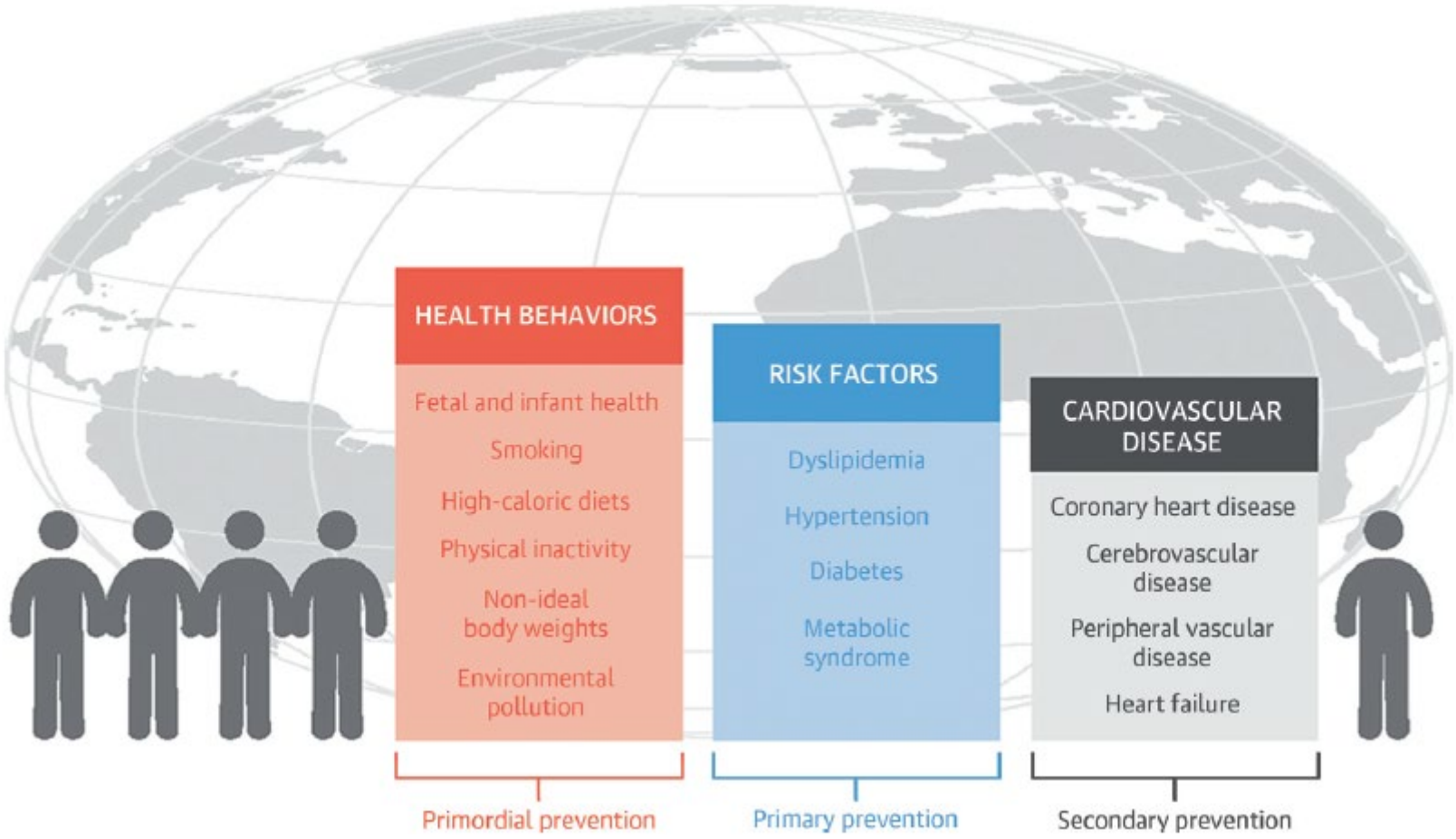
HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Disclosures

Dr. Deepak L. Bhatt discloses the following relationships - Advisory Board: Cardax, Cereno Scientific, Elsevier Practice Update Cardiology, LevelEx, 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 include off-label and/or investigational uses of drugs.

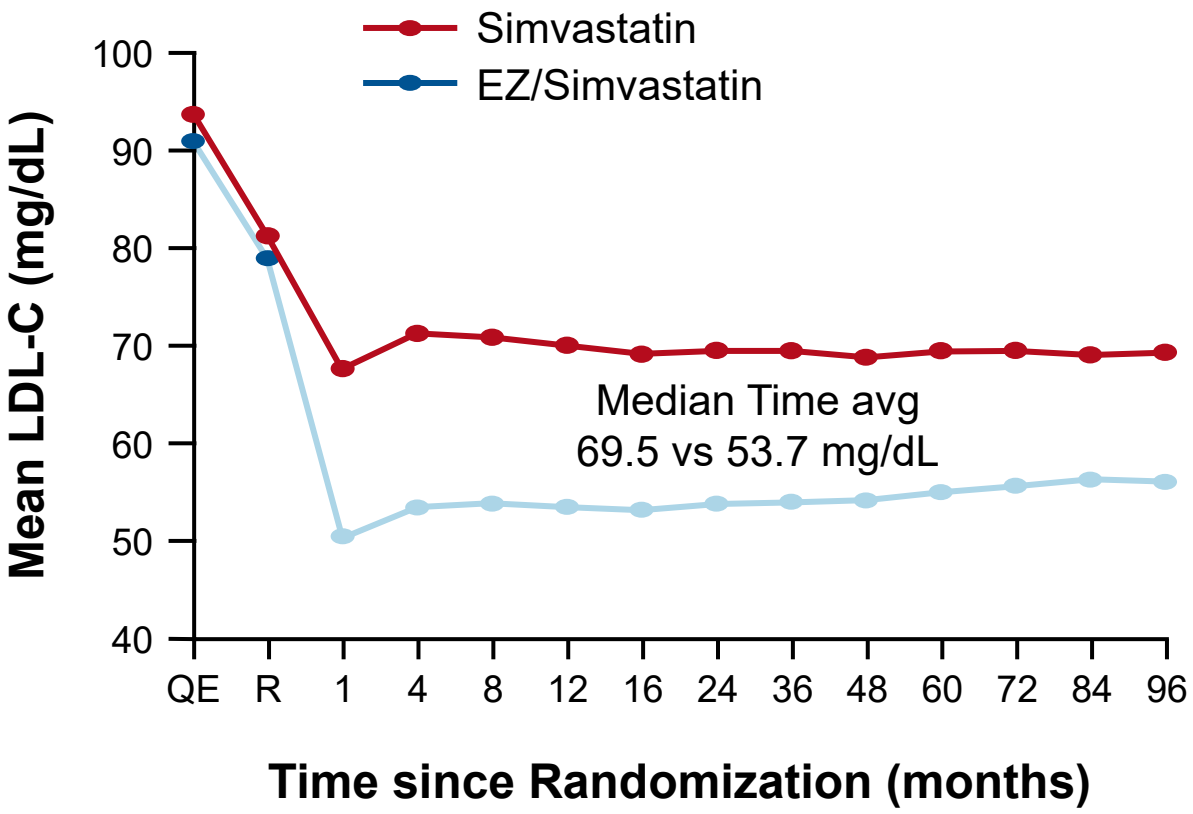
Primordial, Primary, Secondary Prevention

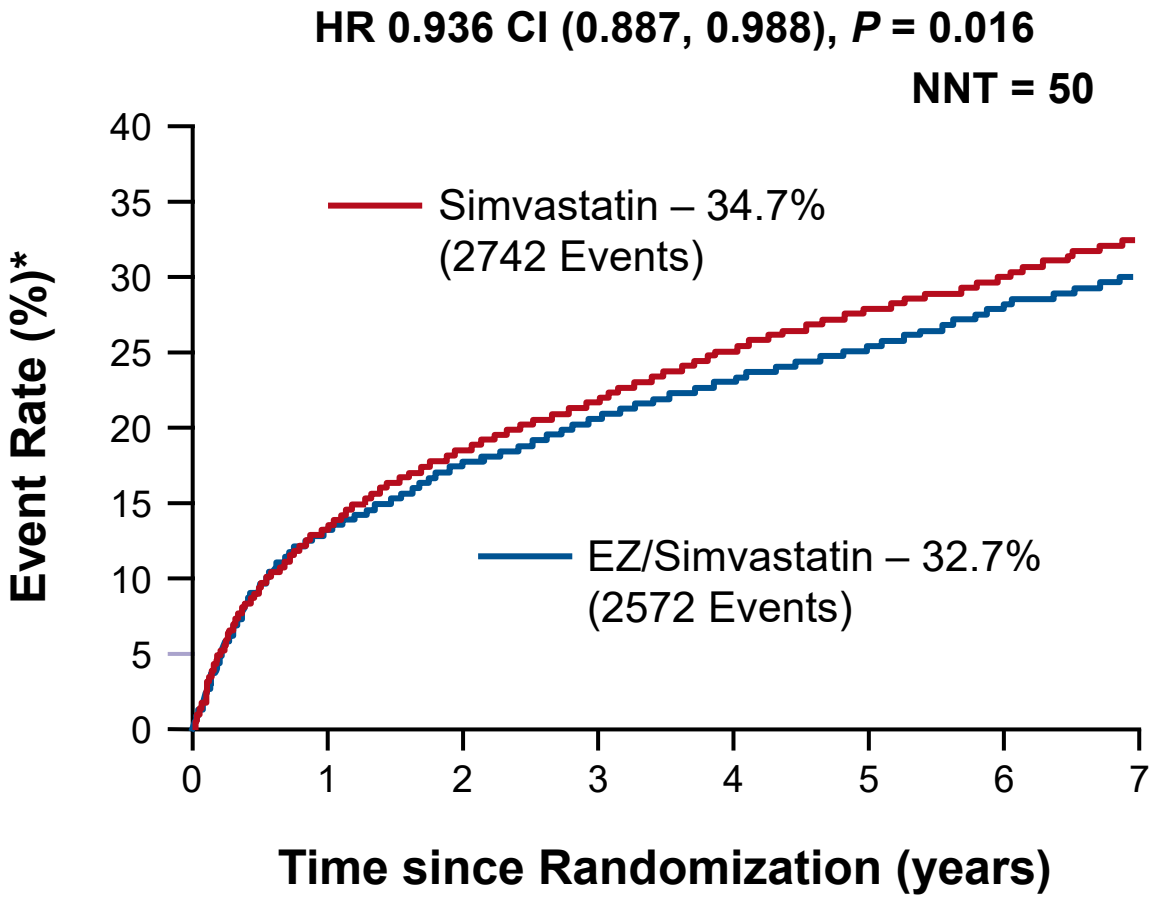


Vaduganathan M, Venkataramini AS, Bhatt DL. *JACC.* 2015.

IMPROVE-IT: Primary Results

18,144 ACS patients randomized to simvastatin alone or ezetimibe (EZ)/simvastatin, 6-year median follow up

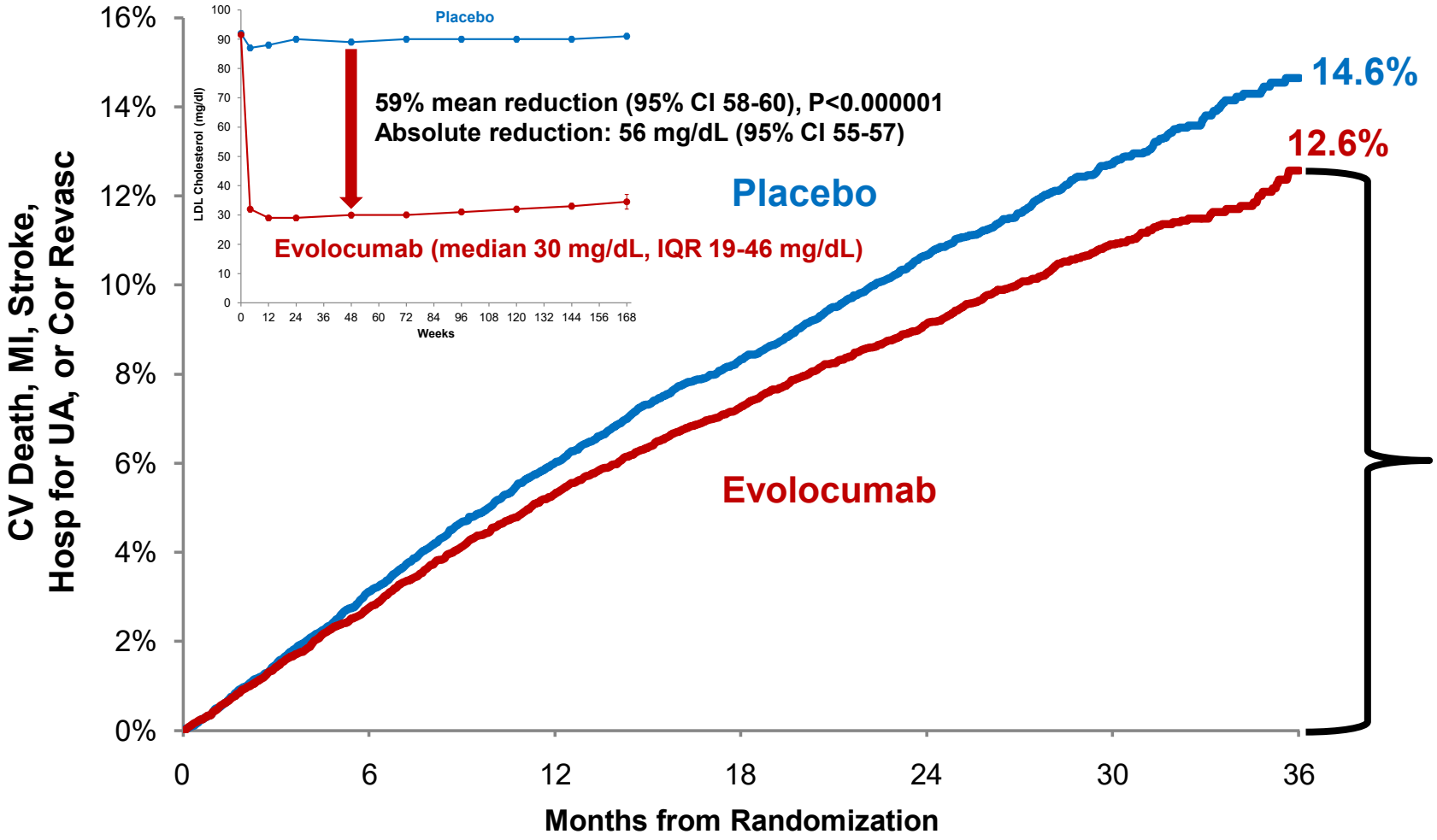




*Primary endpoint (cardiovascular death, MI, UA, coronary revascularization, or stroke).

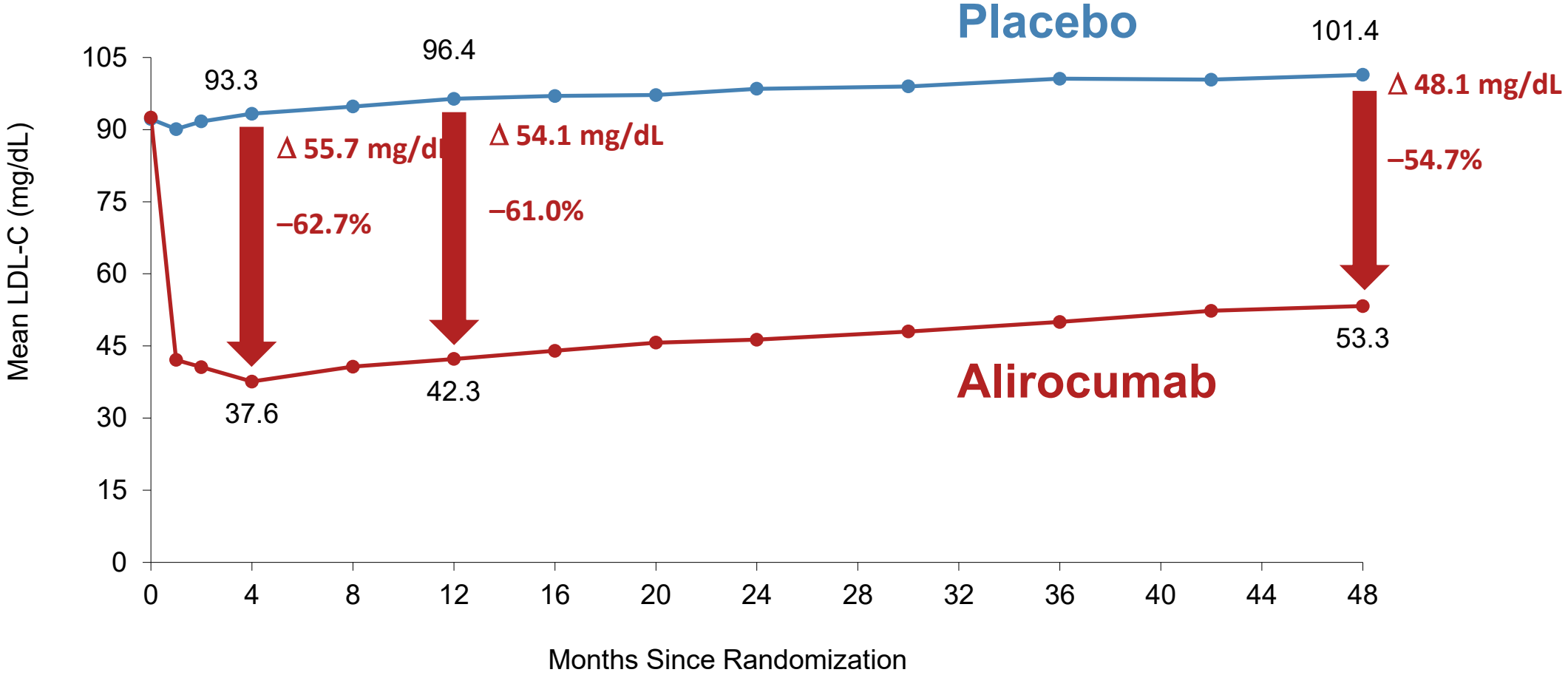
Cannon CP, Blazing MA, Giugliano RP, et al…. Braunwald E, Califf RM. *N Engl J Med.* 2015;372(25):2387–2397.

FOURIER



Sabatine MS et al. *N Engl J Med*. 2017;376:1713-22.

ODYSSEY OUTCOMES: LDL-C On-Treatment Analysis

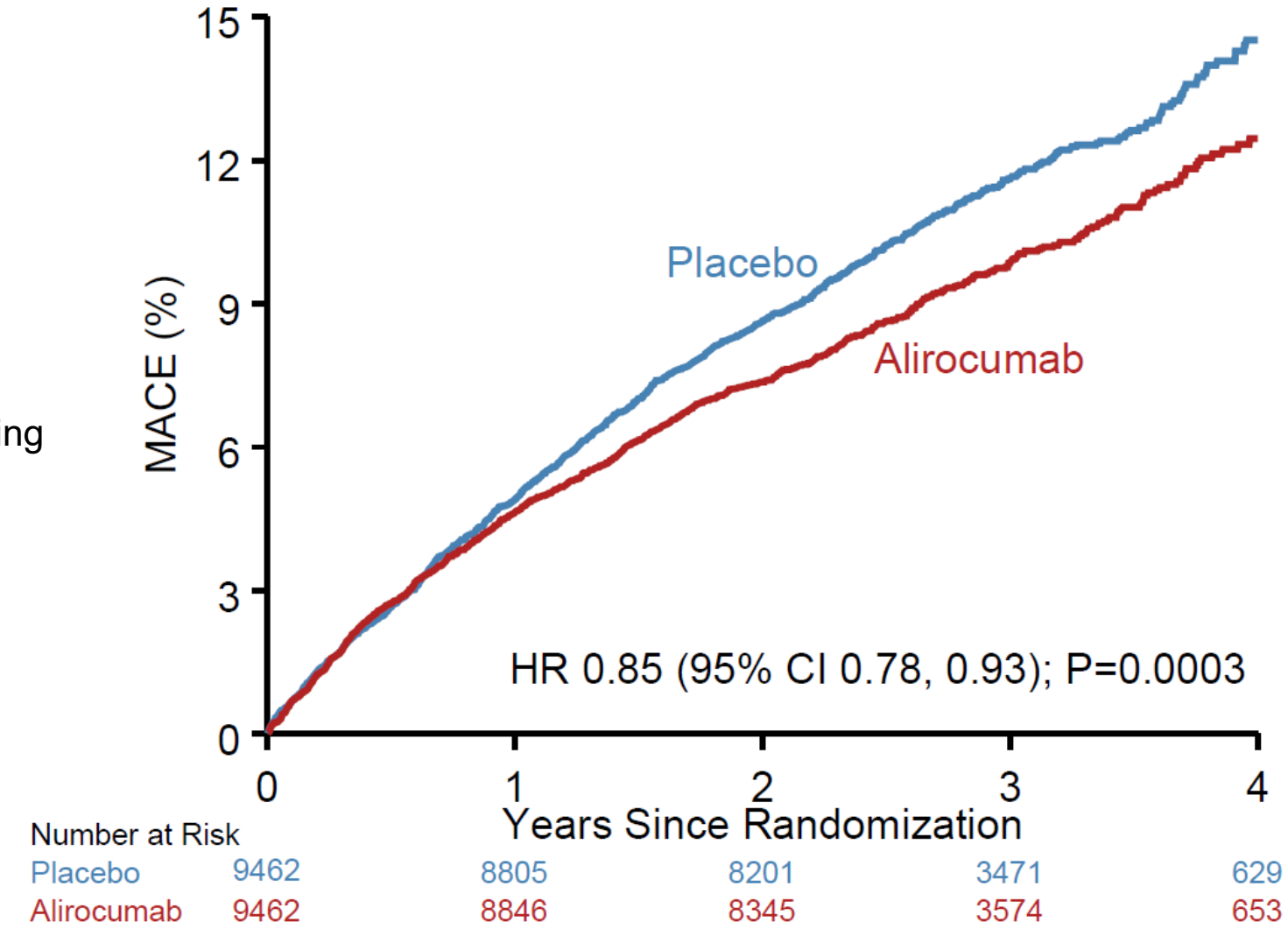


Excludes LDL-C values after premature treatment discontinuation or blinded switch to placebo. Approximately 75% of months of active treatment were at the 75 mg dose.

Schwartz GG, Steg PG, et al. *NEJM* Nov 7, 2018 doi: 10.1056/NEJMoa1801174. Steg PG, ACC 2018, Orlando, FL.

Primary Efficacy Endpoint: MACE

MACE: CHD death, non-fatal MI, ischemic stroke, or unstable angina requiring hospitalization

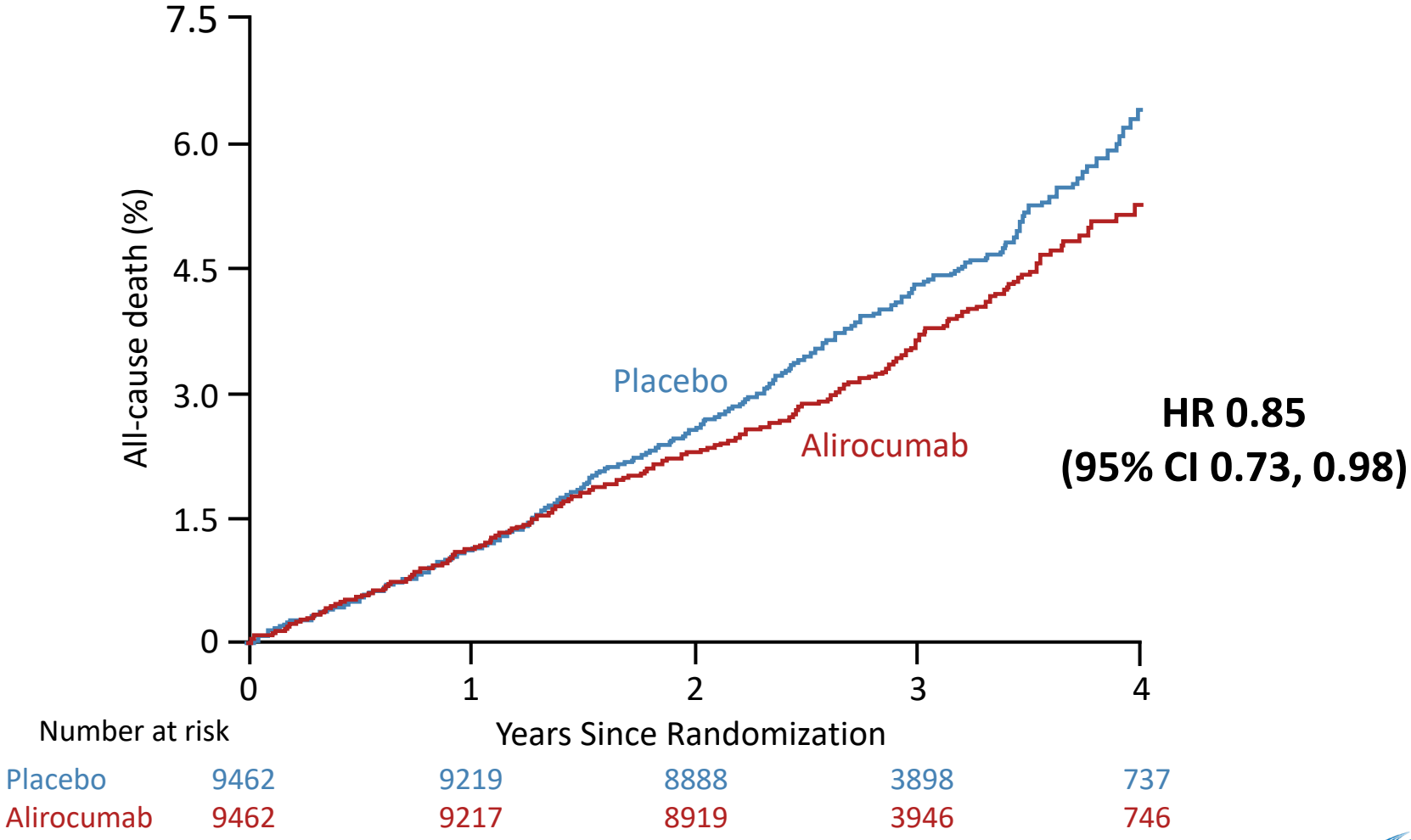


NNT 49 for 4 years

Schwartz GG, Steg PG, et al. *NEJM* 2018 doi: 10.1056/NEJMoa1801174. Steg PG, ACC 2018, Orlando, FL.

ODYSSEY OUTCOMES

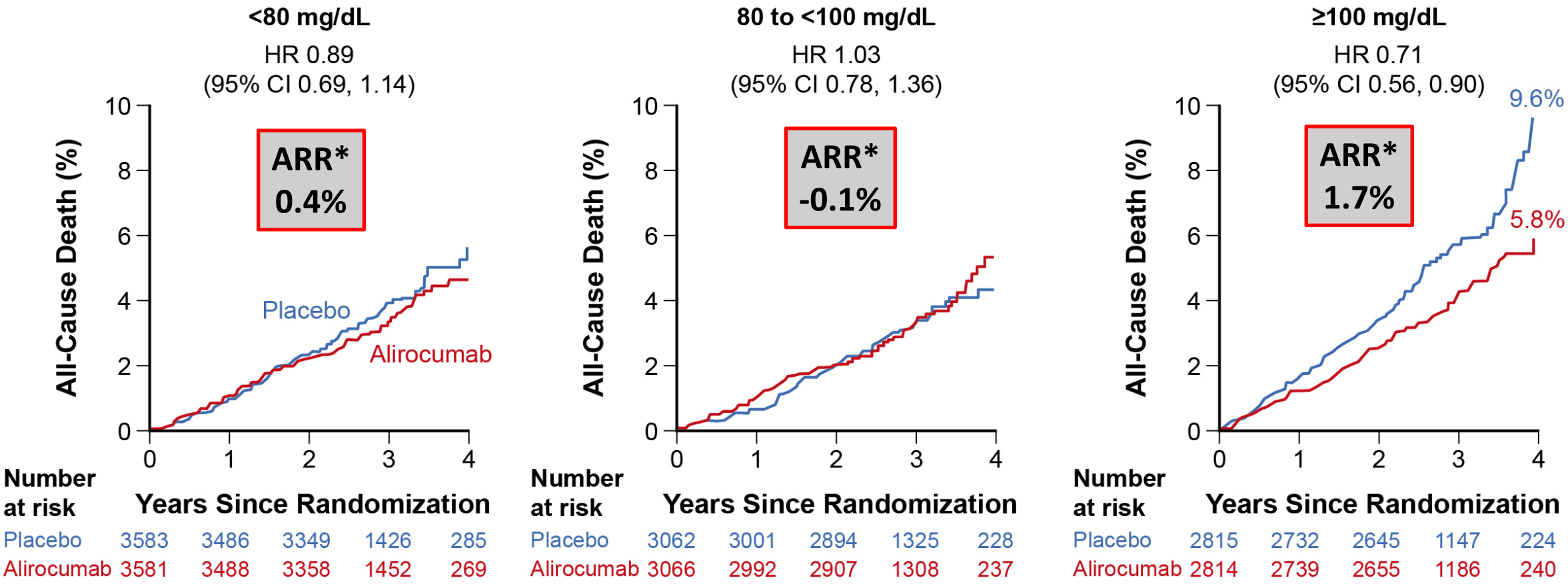
All-cause Death



Schwartz GG, Steg PG, et al. *NEJM* 2018 doi: 10.1056/NEJMoa1801174. Steg PG, ACC 2018, Orlando, FL.

ODYSSEY OUTCOMES

All-cause Death in 3 Predefined Categories of Baseline LDL-C

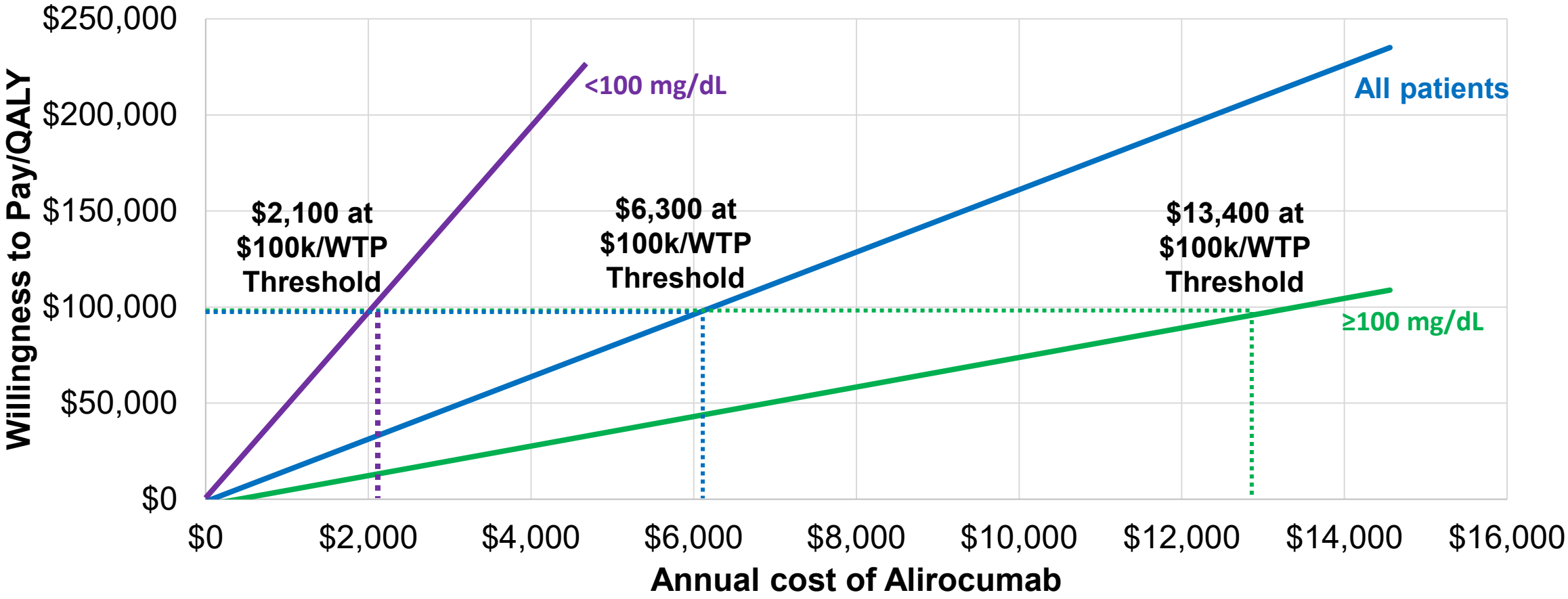


*Absolute risk reduction: Interaction P=0.005
Post hoc analysis

Steg PG, Szarek M, Bhatt DL, et al., *Circulation* 2019.

Varying the Cost of Alirocumab

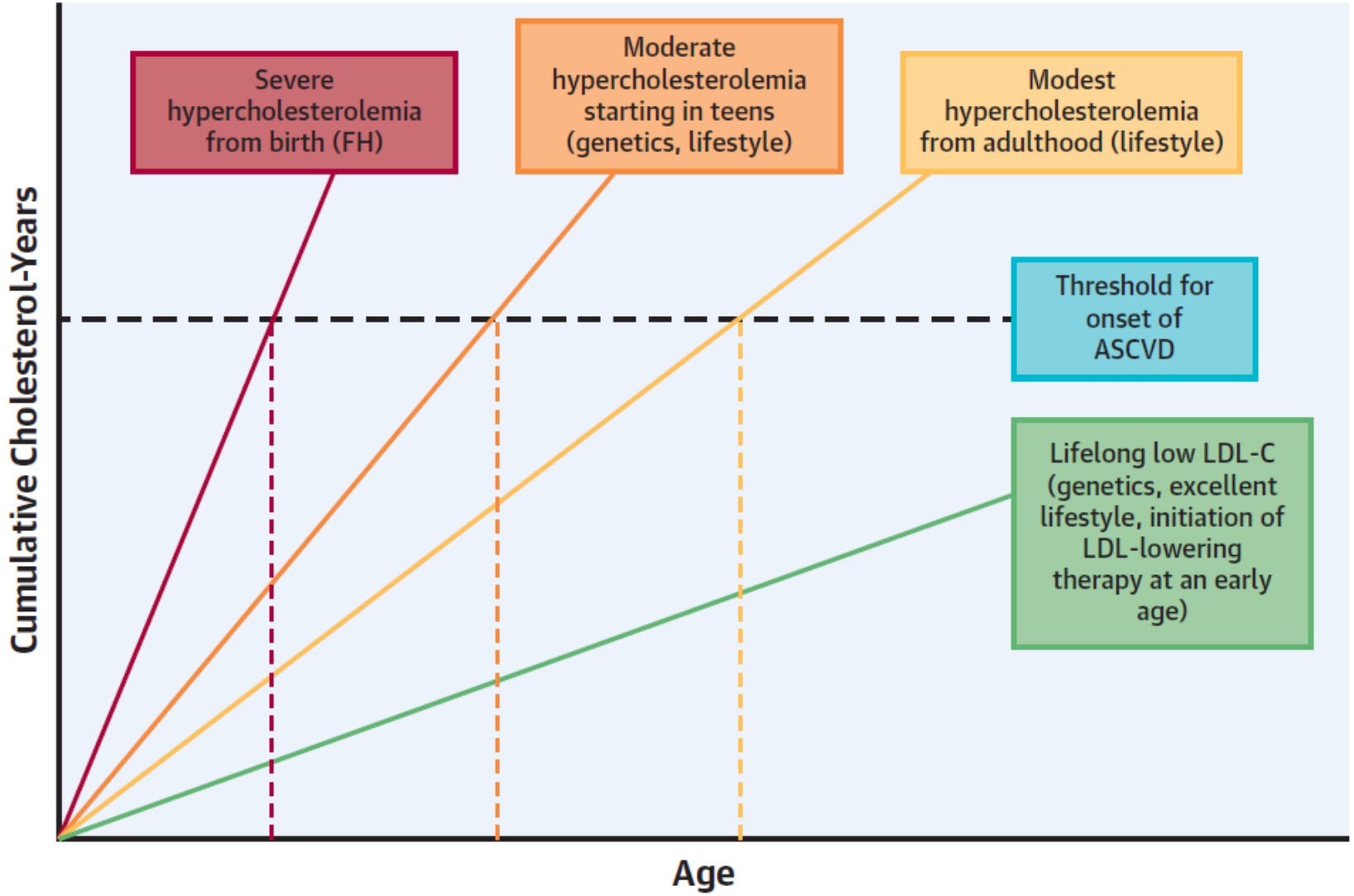
At any level of willingness to pay, cost-effectiveness is lesser in patients with baseline LDL-C values <100 mg/dL relative to the overall ITT population



Bhatt DL, Briggs AH, Reed SD, et al., Steg PG. *JACC.* 2020; 75:2297–308.

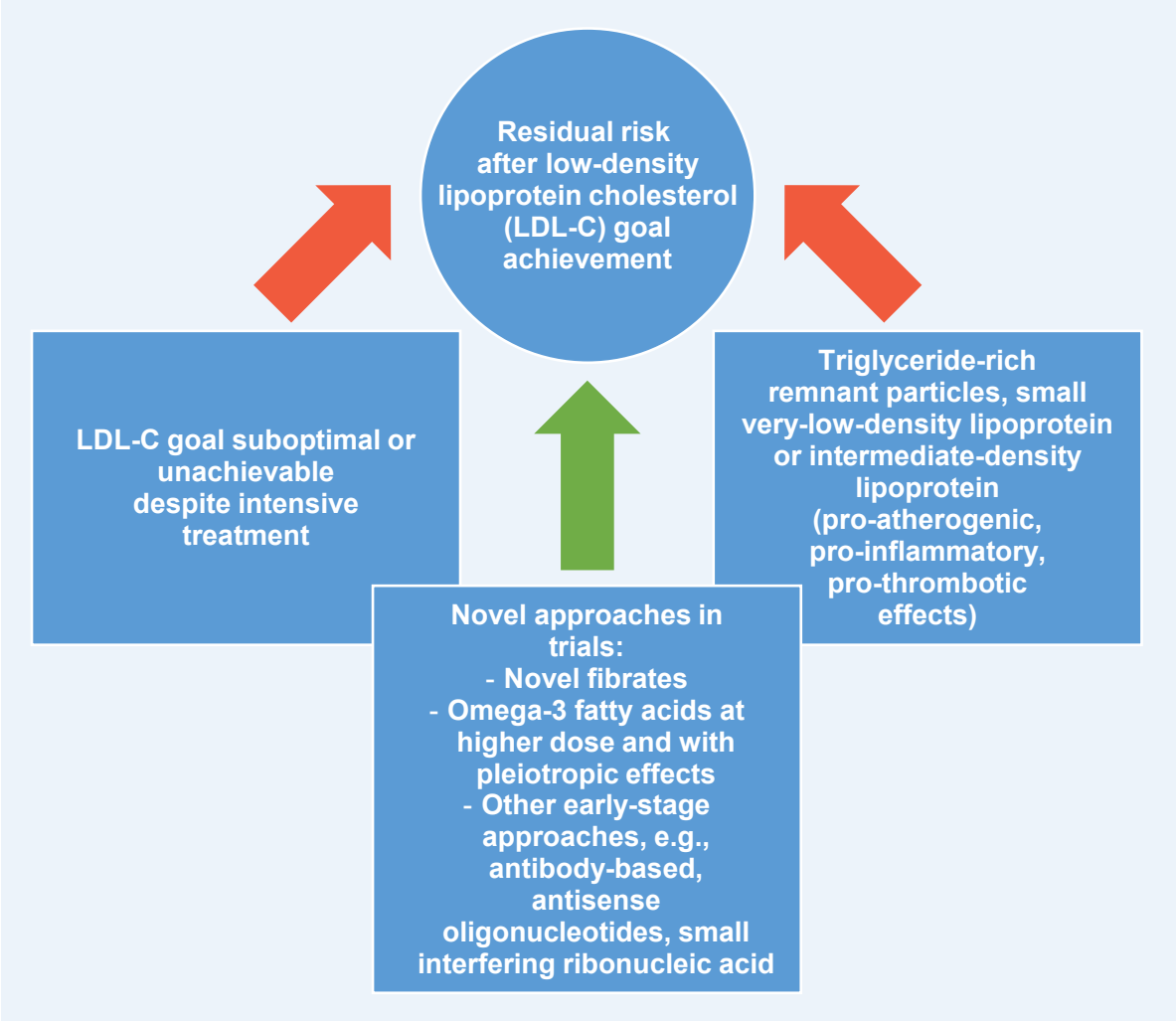
ODYSSEY OUTCOMES

“Cholesterol-Years” for CV Risk Prediction and Treatment



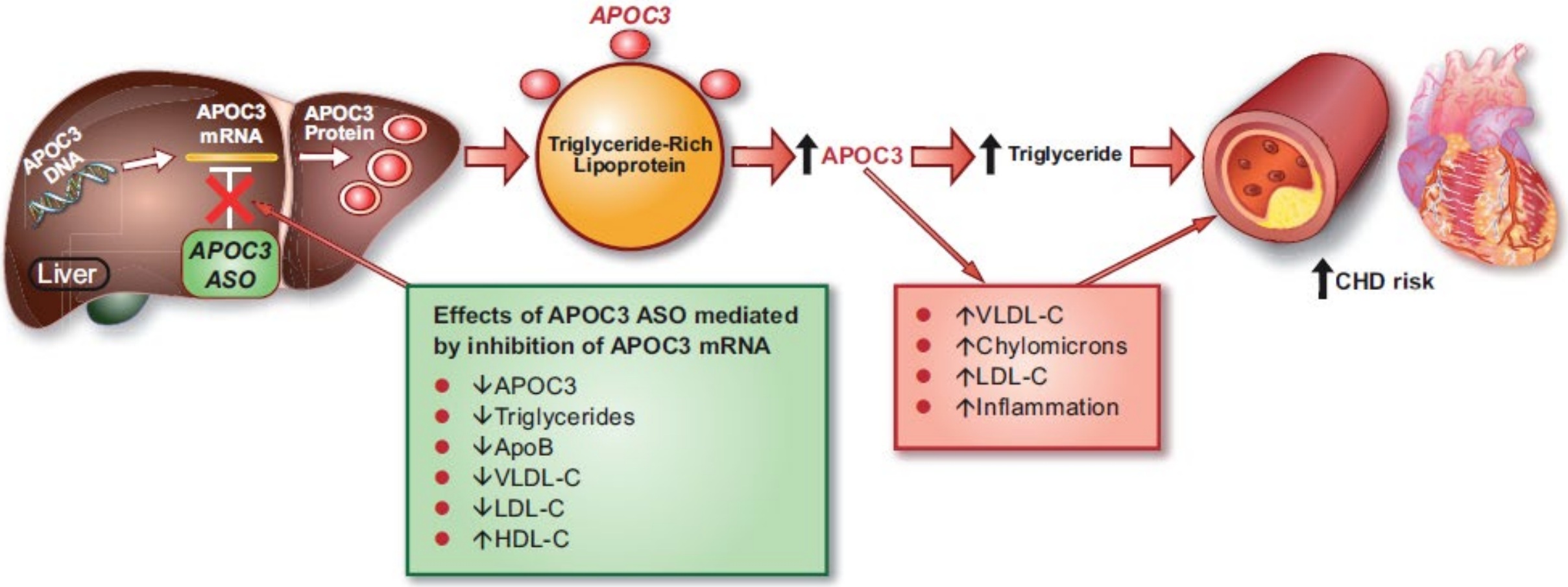
Shapiro MD, Bhatt DL. *JACC.* 2020.

Promising Therapies for Hypertriglyceridemia



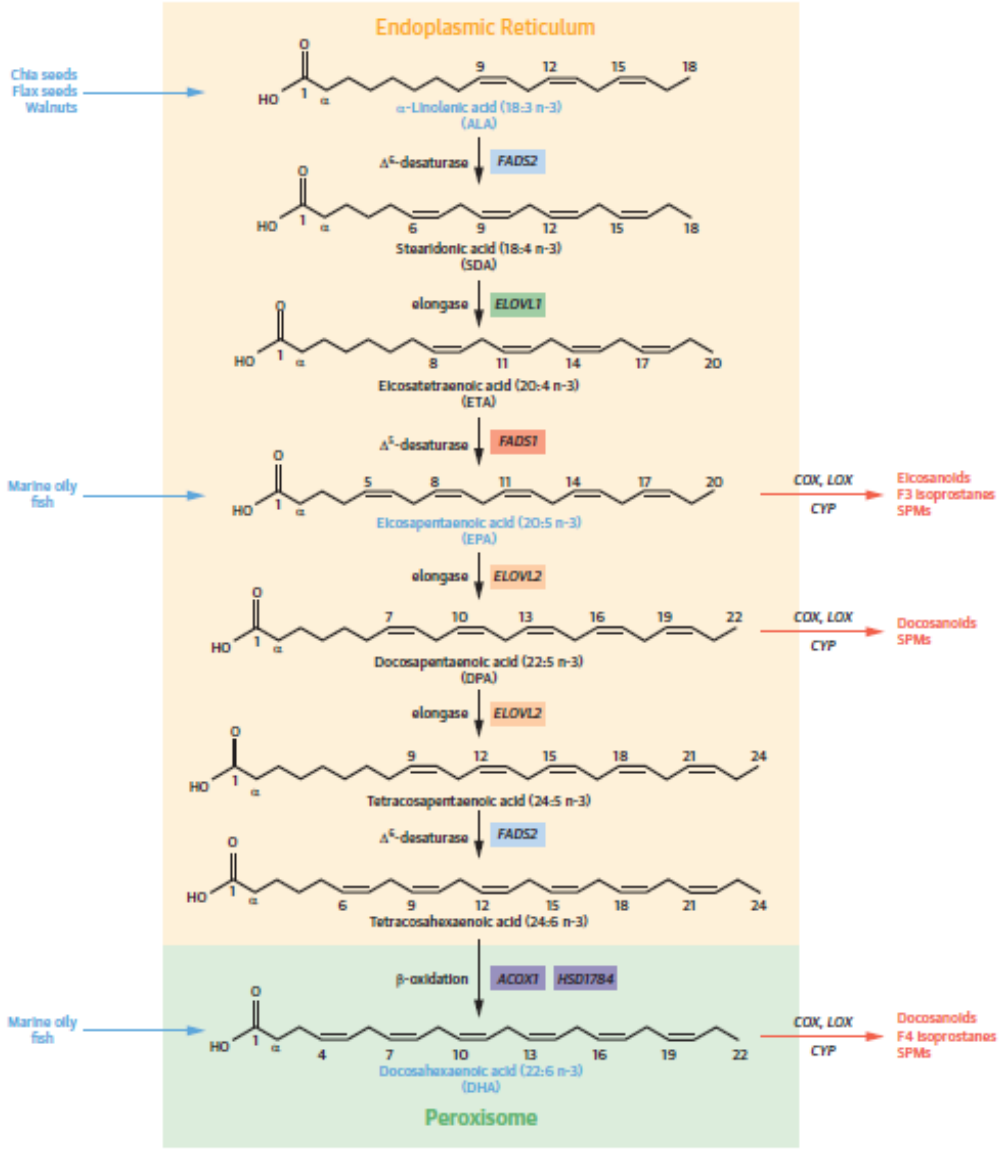
Ganda OP, Bhatt DL, Mason RP, Miller M, Boden WE. *J Am Coll Cardiol*. 2018;72:330-343.

Targeting RNA to Lower Triglycerides:
Long Strides from Short Molecules



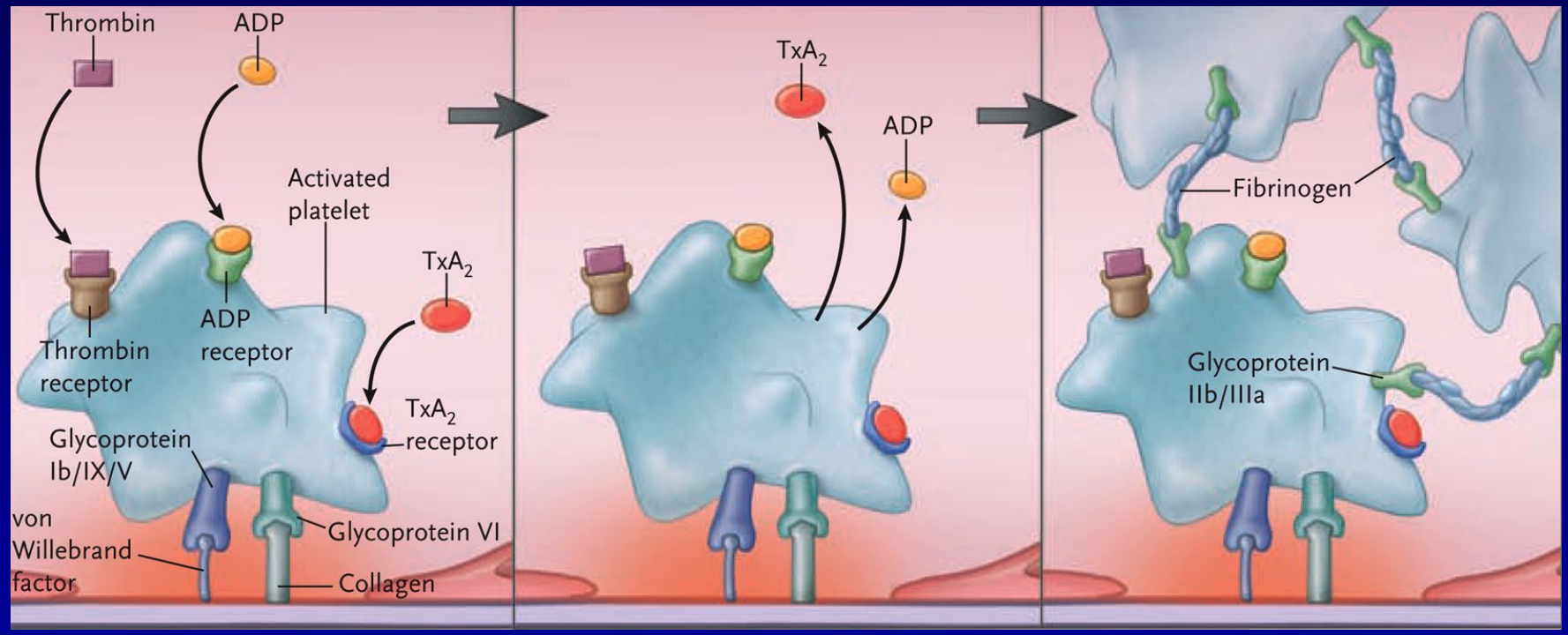
Qamar A, Libby P, Bhatt DL. Targeting RNA to lower triglycerides: long strides from short molecules. *Eur Heart J*. 2019; 40(33):2797-2800.

A Revolution in Omega-3 Fatty Acid Research



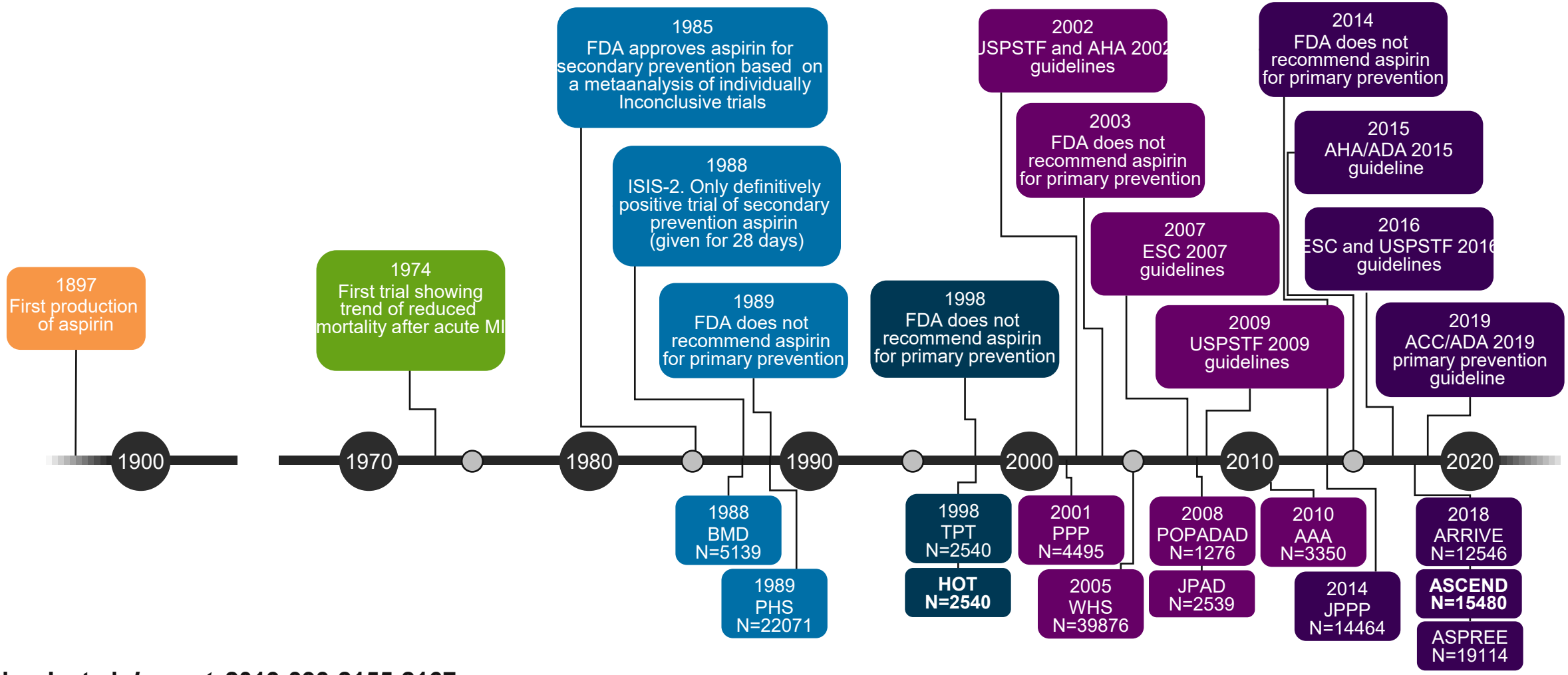
Bhatt DL, Budoff MJ, Mason RP. *JACC.* 2020.

Role of Platelet Activation and Aggregation



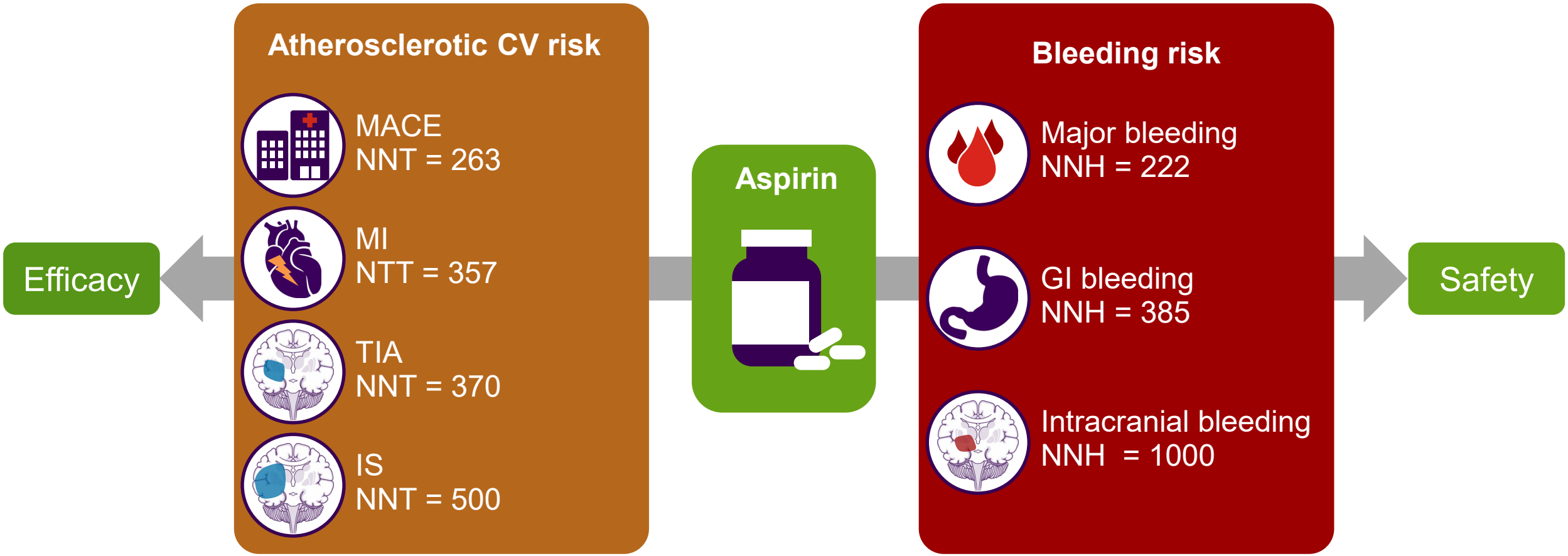
Bhatt DL. N Engl J Med 2007;357:2078-81.

The Rise and Fall of Aspirin in Primary Prevention



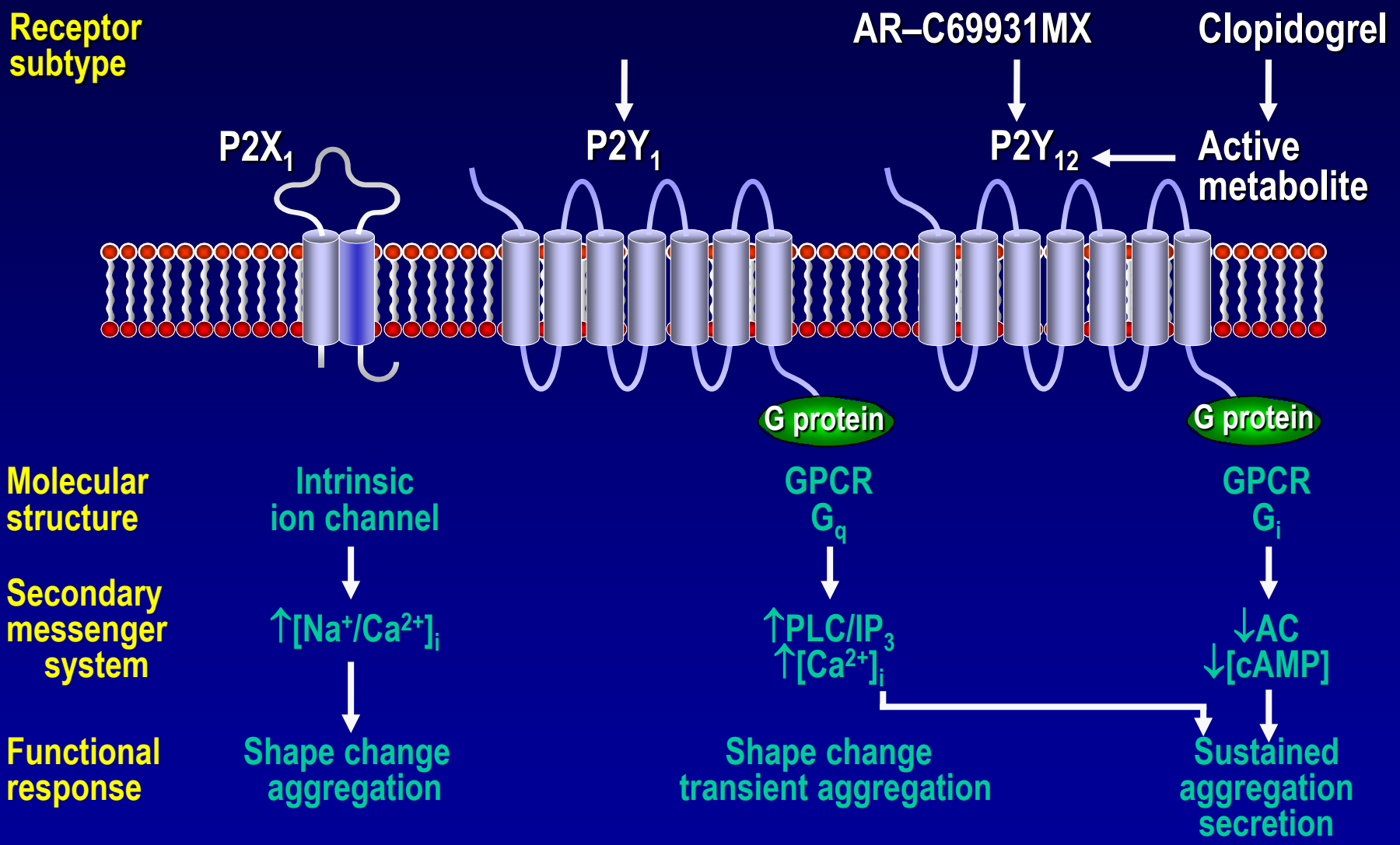
Raber I, et al. *Lancet*. 2019;393:2155-2167

Aspirin for Primary Prevention of CV Events



Abdelaziz HK, et al. *J Am Coll Cardiol*. 2019;73:2915-2929.

ADP Receptors



Bhatt DL et al. *Nat Rev Drug Discov*. 2003;2:15-28.

The NEW ENGLAND JOURNAL of MEDICINE

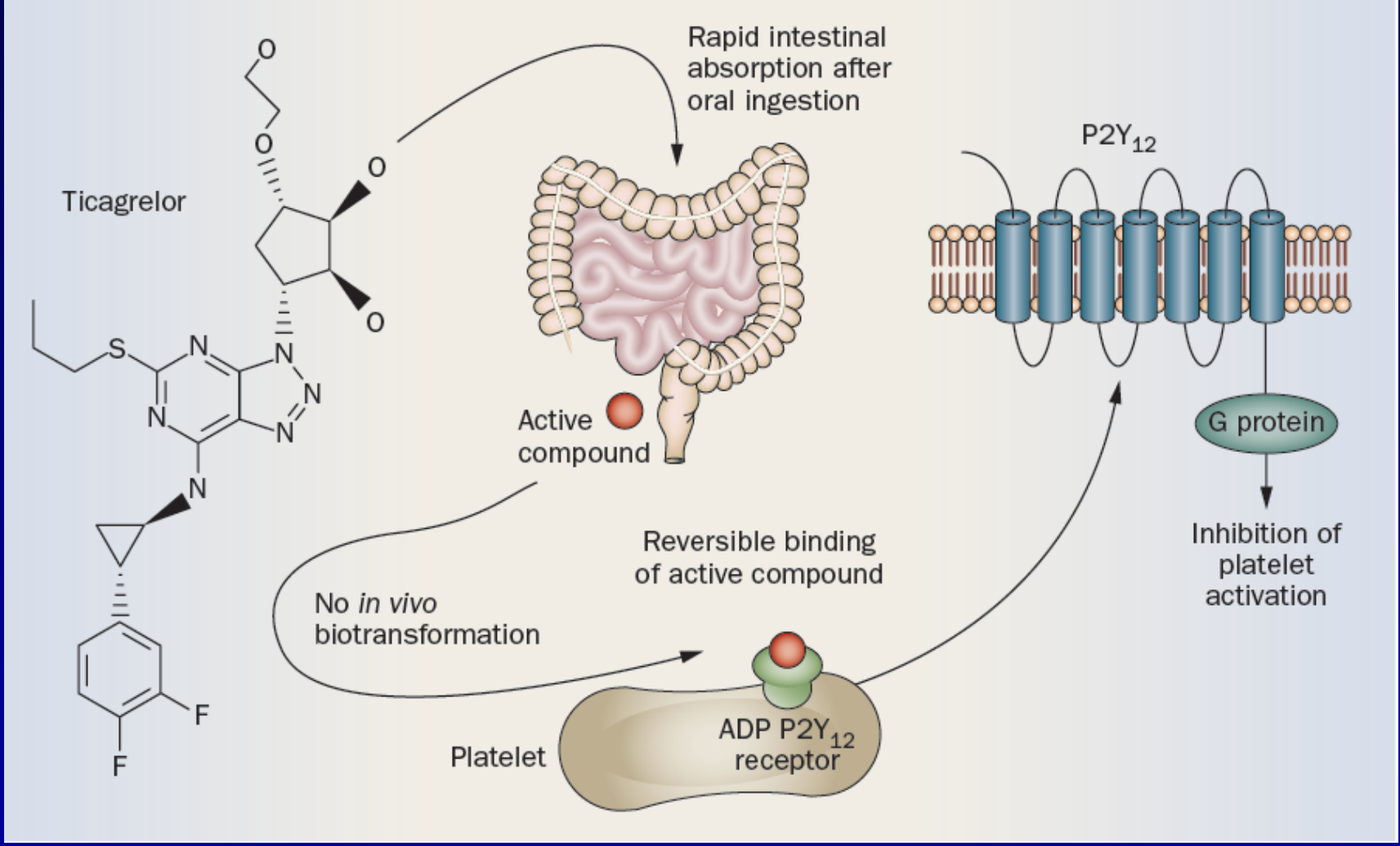
EDITORIALS

Intensifying Platelet Inhibition — Navigating between Scylla and Charybdis

Deepak L. Bhatt, M.D.

Bhatt DL. N Engl J Med 2007;357:2078-81.

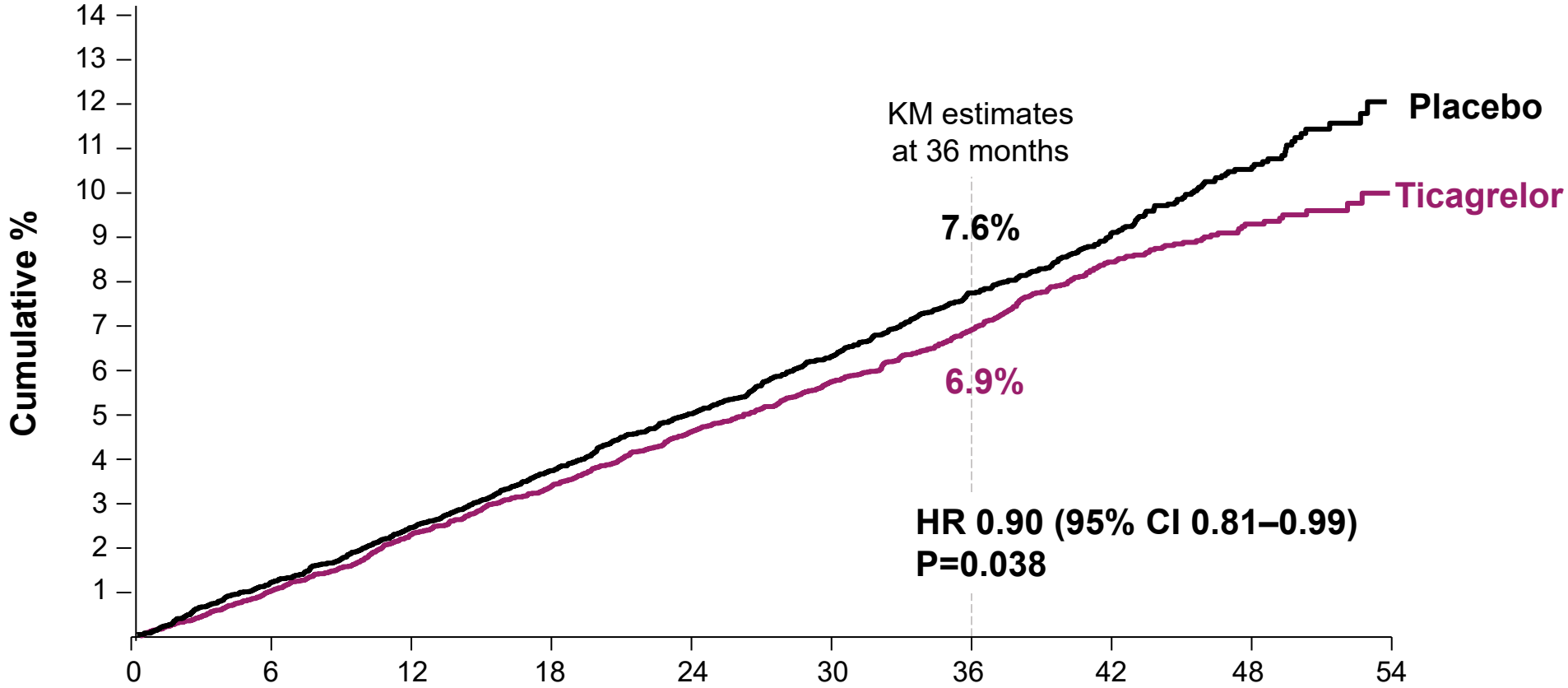
Mechanism of Action of Ticagrelor



Bhatt DL. *Nature Reviews Cardiology*. 2009;6:737-38.

Primary Composite Endpoint

Cardiovascular death/MI/stroke

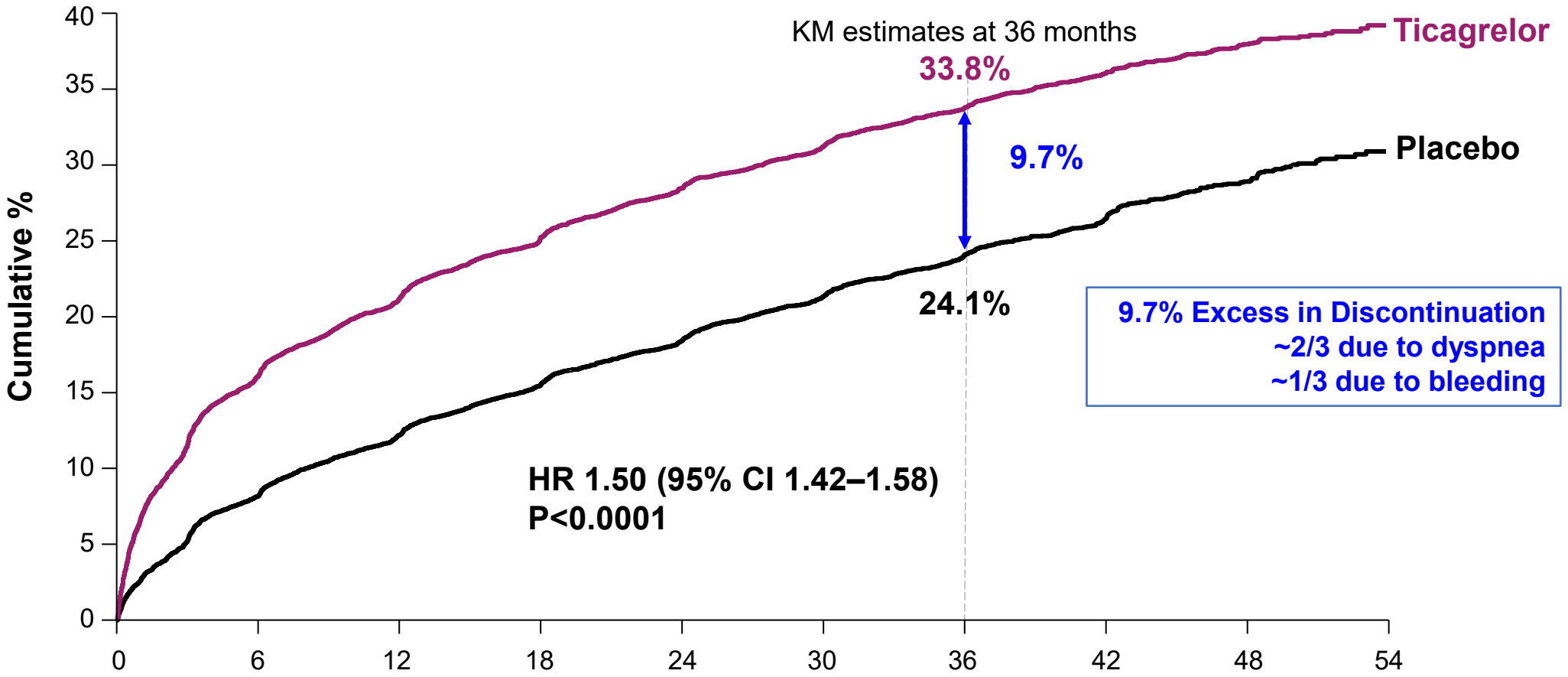


N at Risk										
Ticagrelor	9619	9416	9237	9074	8909	8692	5974	3664	1684	170
Placebo	9601	9414	9246	9076	8909	8692	5934	3682	1685	174

CI=confidence interval; HR=hazard ratio; KM=Kaplan-Meier; MI=myocardial infarction; N=number of patients

Steg PG, Bhatt DL, et al. NEJM 2019 DOI: 10.1056/NEJMoa1908077.

Permanent Treatment Discontinuation



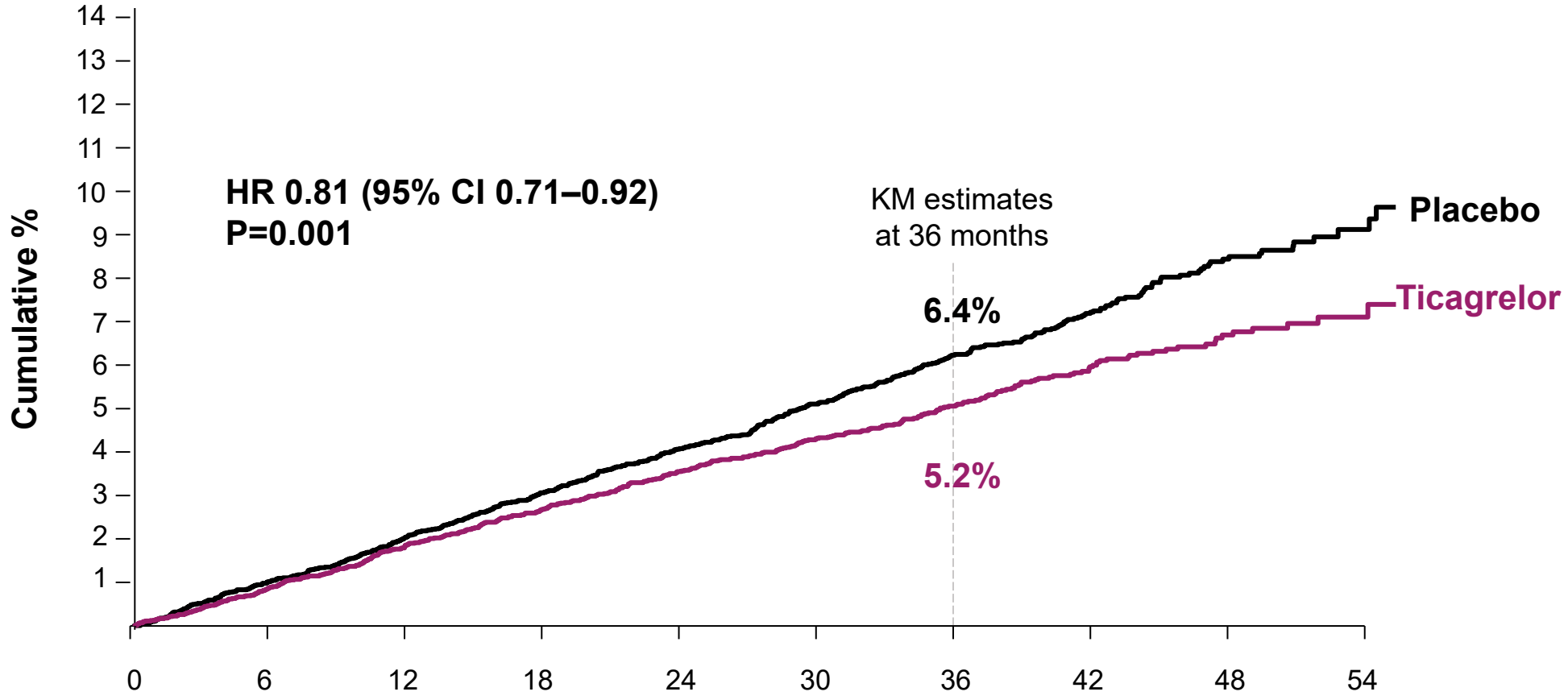
Number at risk										
Ticagrelor	9562	7904	7316	6831	6414	6029	4105	2483	1172	173
Placebo	9531	8660	8179	7772	7367	6974	4786	2959	1362	218

Discontinuation due to dyspnea 6.9% on ticagrelor vs. 0.8% on placebo (HR 9.27 [7.30-11.77] p <0.001); due to bleeding 4.9% vs 1.3% (HR 4.04 [3.32-4.92] p<0.001). CI=confidence interval; HR=hazard ratio; KM=Kaplan-Meier

Steg PG, Bhatt DL, et al. NEJM 2019 DOI: 10.1056/NEJMoa1908077.

Primary Composite Endpoint

Cardiovascular death/MI/stroke – on treatment*



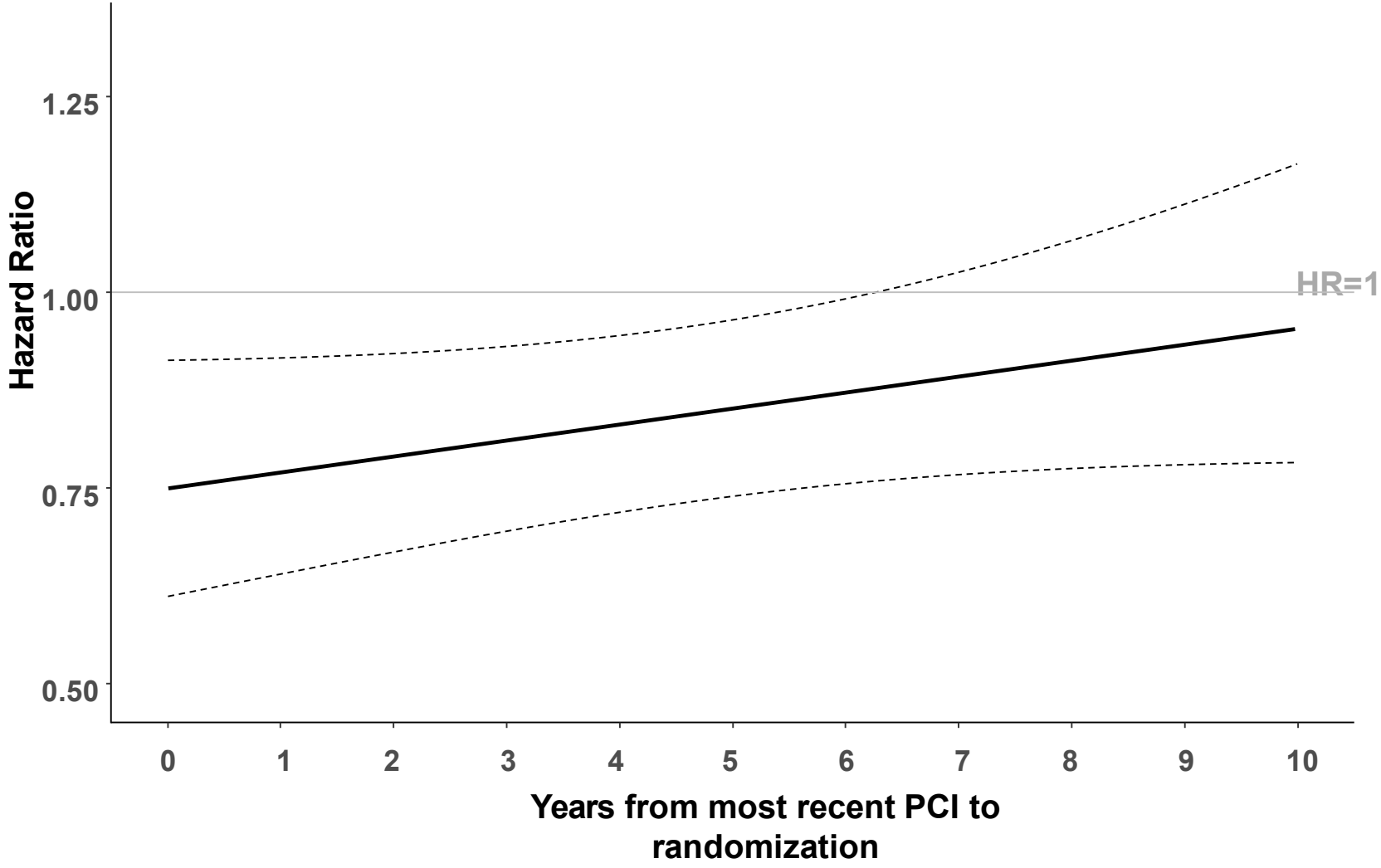
Number at Risk										
Ticagrelor	9562	7891	7291	6799	6343	5962	4040	2431	1137	168
Placebo	9531	8639	8136	7702	7373	6875	4712	2904	1333	213

*Prespecified analysis with patients censored 3 days after the last dose; CI=confidence interval; HR=hazard ratio; KM=Kaplan-Meier; MI=myocardial infarction; N=number of patients

Steg PG, Bhatt DL, et al. NEJM 2019 DOI: 10.1056/NEJMoa1908077.

Benefit of Ticagrelor vs Placebo

as a Function of Time between PCI and randomization



Dotted lines signify 95% confidence interval; HR=hazard ratio; PCI=percutaneous coronary intervention

Bhatt DL, Steg PG, et al. *Lancet* 2019 http://dx.doi.org/10.1016/ S0140-6736(19)31887-2.

Optimal Duration of DAPT?

	≤12 months DAPT	≥12 months DAPT
Patient-related factors 	Patients with stable CAD Patients with a history of bleeding Patients with high risk of bleeding	Patients with ACS Patients with diabetes mellitus Patients with renal dysfunction Patients with CHF Patients with previous ST Patients with PAD
Anatomy-related factors 	Short lesion Single-vessel disease	Long lesion Small vessel Bifurcation lesion Complex anatomy Left-main coronary artery
Stent-related factors 	Second-generation DES	First-generation DES Long stent Multiple stents

Eisen A, Bhatt DL. Nature Reviews Cardiology 2015.

Breaking Update: US FDA Approval

Current FDA Approvals

Agent	ACS + PCI	ACS (Medical)	Prior MI	CAD (No Event)
Clopidogrel	✓	✓	✓	
Ticagrelor	✓	✓	✓	
Prasugrel	✓			

Steg PG, Bhatt DL et al. *N Engl J Med* 2019. Bhatt DL, Steg PG, et al. *Lancet* 2019.

Breaking Update: US FDA Approval

Ticagrelor approved by FDA June 1, 2020 "to reduce the risk of a first MI or stroke in patients with coronary artery disease at high risk for such events"

Agent	ACS + PCI	ACS (Medical)	Prior MI	CAD (No Event)
Clopidogrel	✓	✓	✓	
Ticagrelor	✓	✓	✓	✓
Prasugrel	✓			

Steg PG, Bhatt DL et al. *N Engl J Med* 2019. Bhatt DL, Steg PG, et al. *Lancet* 2019.

ORIGINAL RESEARCH ARTICLE

Dual Antiplatelet Therapy After Percutaneous Coronary Intervention and Drug-Eluting Stents

A Systematic Review and Network Meta-Analysis

BACKGROUND: The optimal duration of dual antiplatelet therapy (DAPT) after percutaneous coronary intervention with drug-eluting stents remains uncertain. We compared short-term (<6-month) DAPT followed by aspirin or P2Y12 inhibitor monotherapy; midterm (6-month) DAPT; 12-month DAPT; and extended-term (>12-month) DAPT after percutaneous coronary intervention with drug-eluting stents.

METHODS: Twenty-four randomized, controlled trials were selected using Medline, Embase, Cochrane library, and online databases through September 2019. The coprimary end points were myocardial infarction and major bleeding, which constituted the net clinical benefit. A frequentist network meta-analysis was conducted with a random-effects model.

RESULTS: In 79 073 patients, at a median follow-up of 18 months, extended-term DAPT was associated with a reduced risk of myocardial infarction in comparison with 12-month DAPT (absolute risk difference, –3.8 incident cases per 1000 person-years; relative risk, 0.68 [95% CI, 0.54–0.87]), midterm DAPT (absolute risk difference, –4.6 incident cases per 1000 person-years; relative risk, 0.61 [0.45–0.83]), and short-term DAPT followed by

Safi U. Khan, MD
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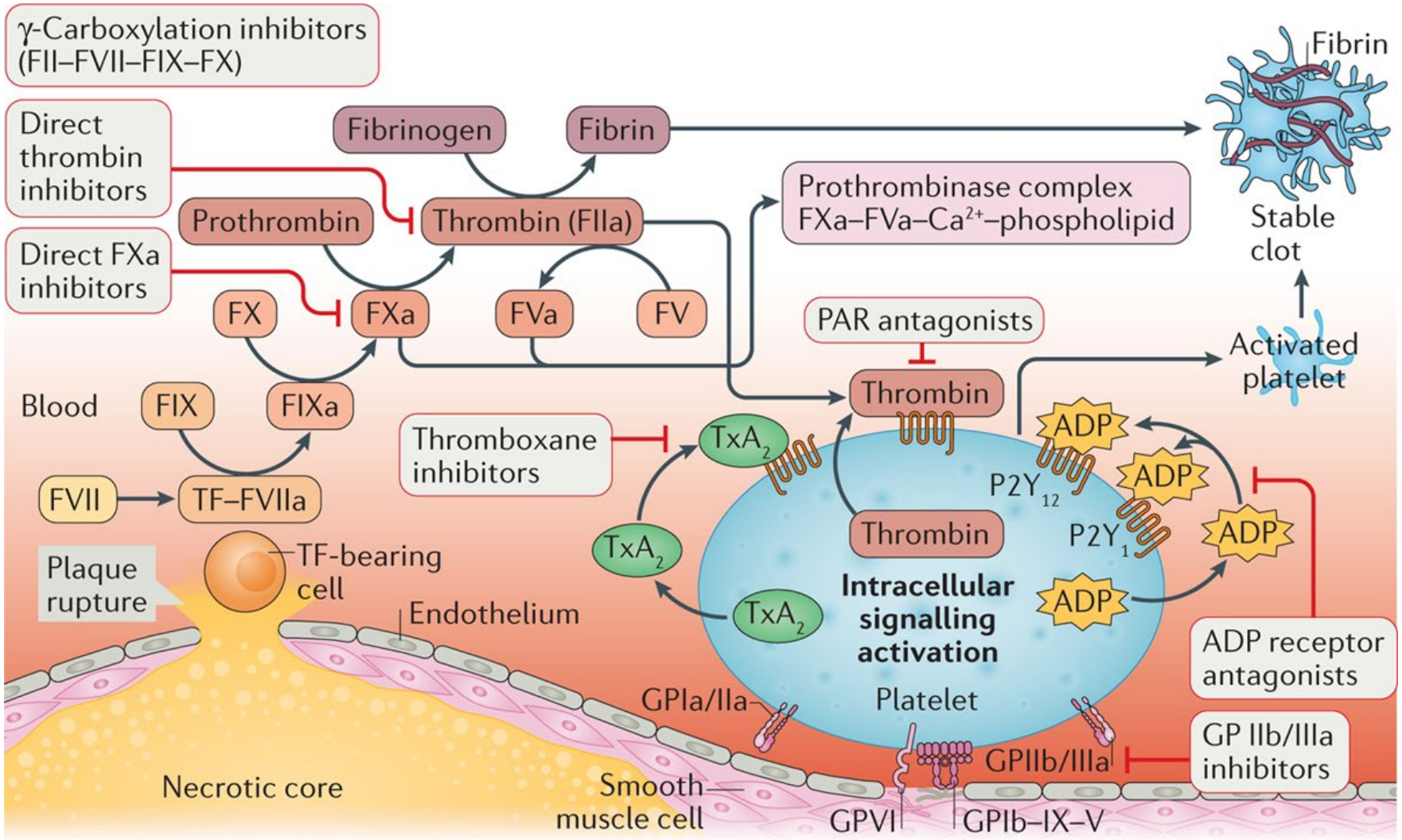
Ahmad N. Lone, MD
Muhammad Zia Khan, MD
Muhammad Shahzeb Khan, MD
Preethi Mani, MD
Samir R. Kapadia, MD
Erin D. Michos, MD, MHS
Gregg W. Stone, MD
Ankur Kalra, MD*
Deepak L. Bhatt, MD, MPH*

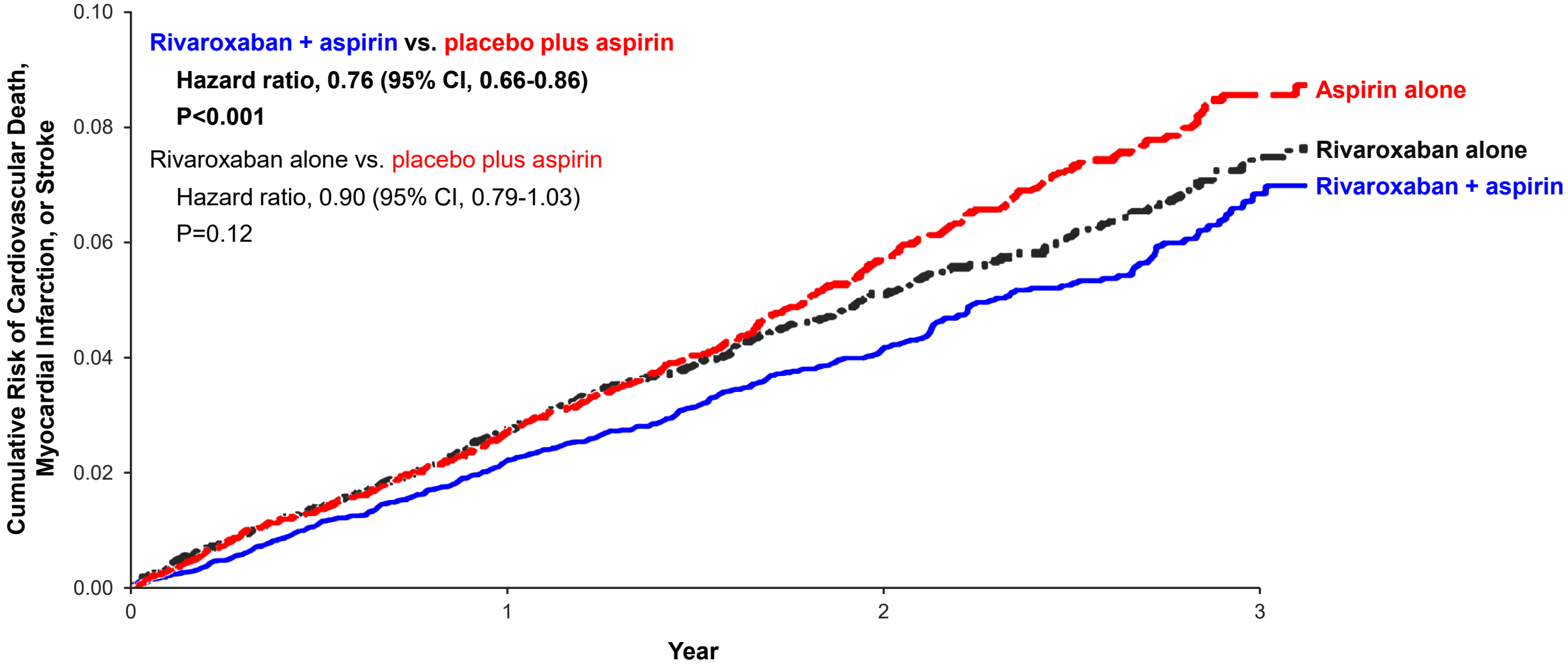
Dual Pathway Inhibition: Antiplatelet plus Anticoagulant



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

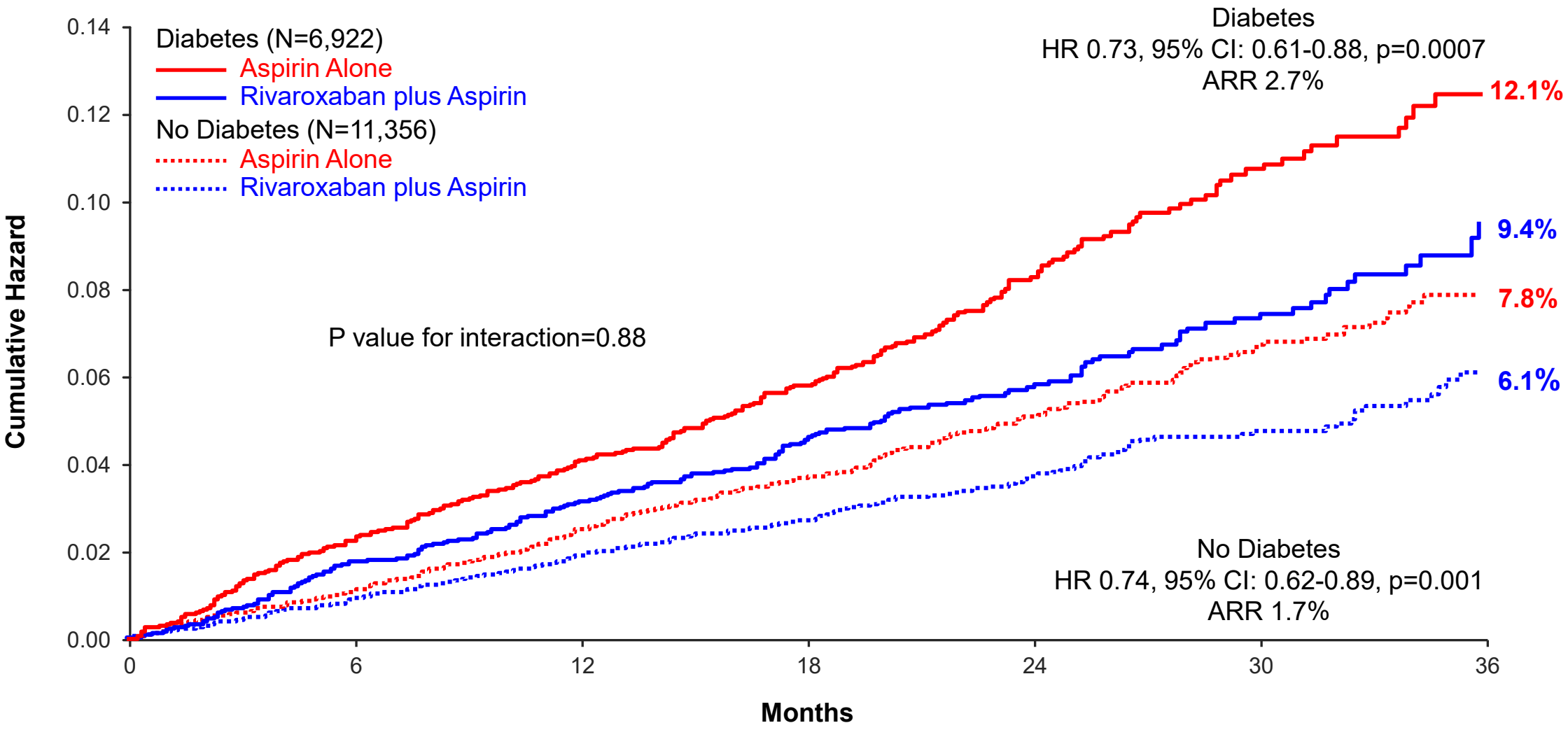
COMPASS Trial Primary outcome

Population Health Research Institute
HEALTH THROUGH KNOWLEDGE



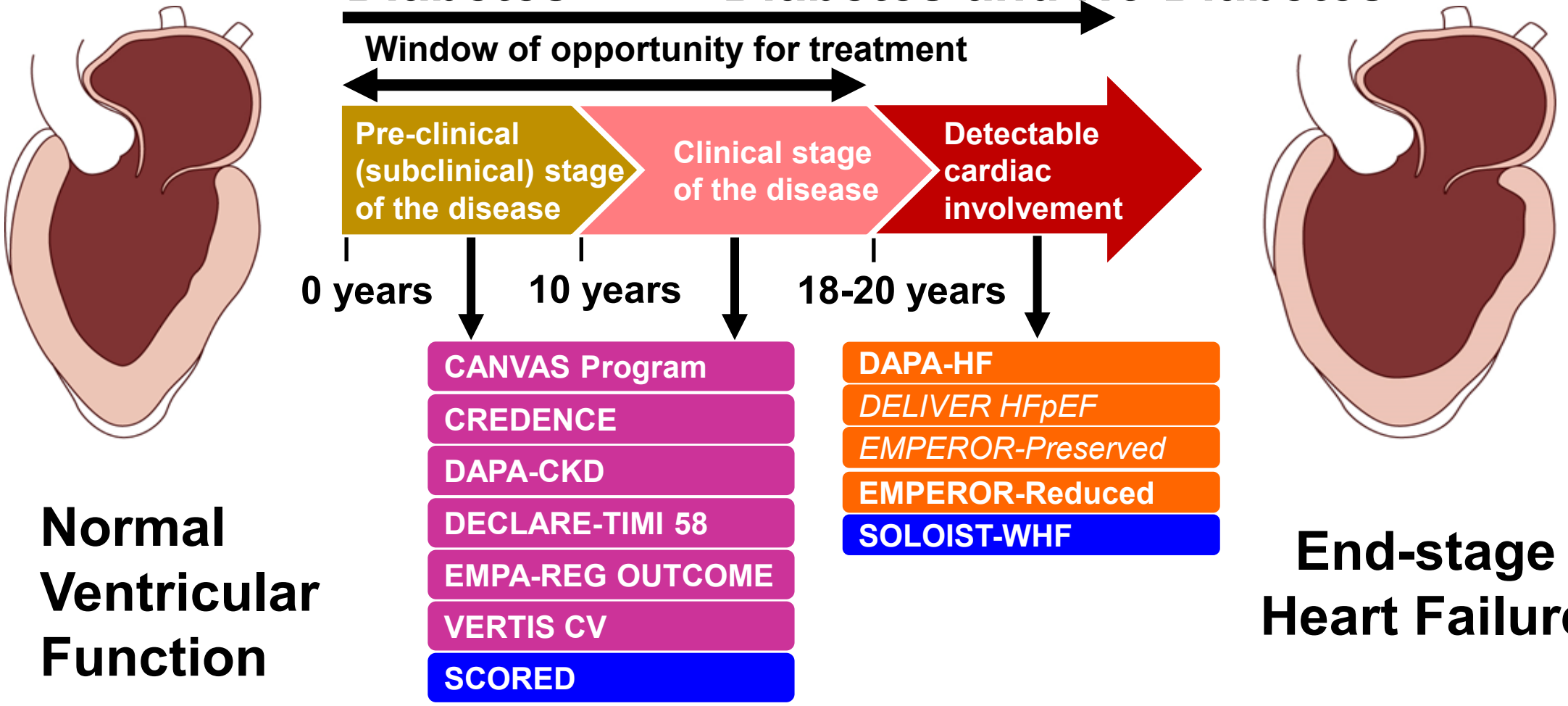
Eikelboom JW, et al. *N Engl J Med* 2017; 377:1319-30.

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



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

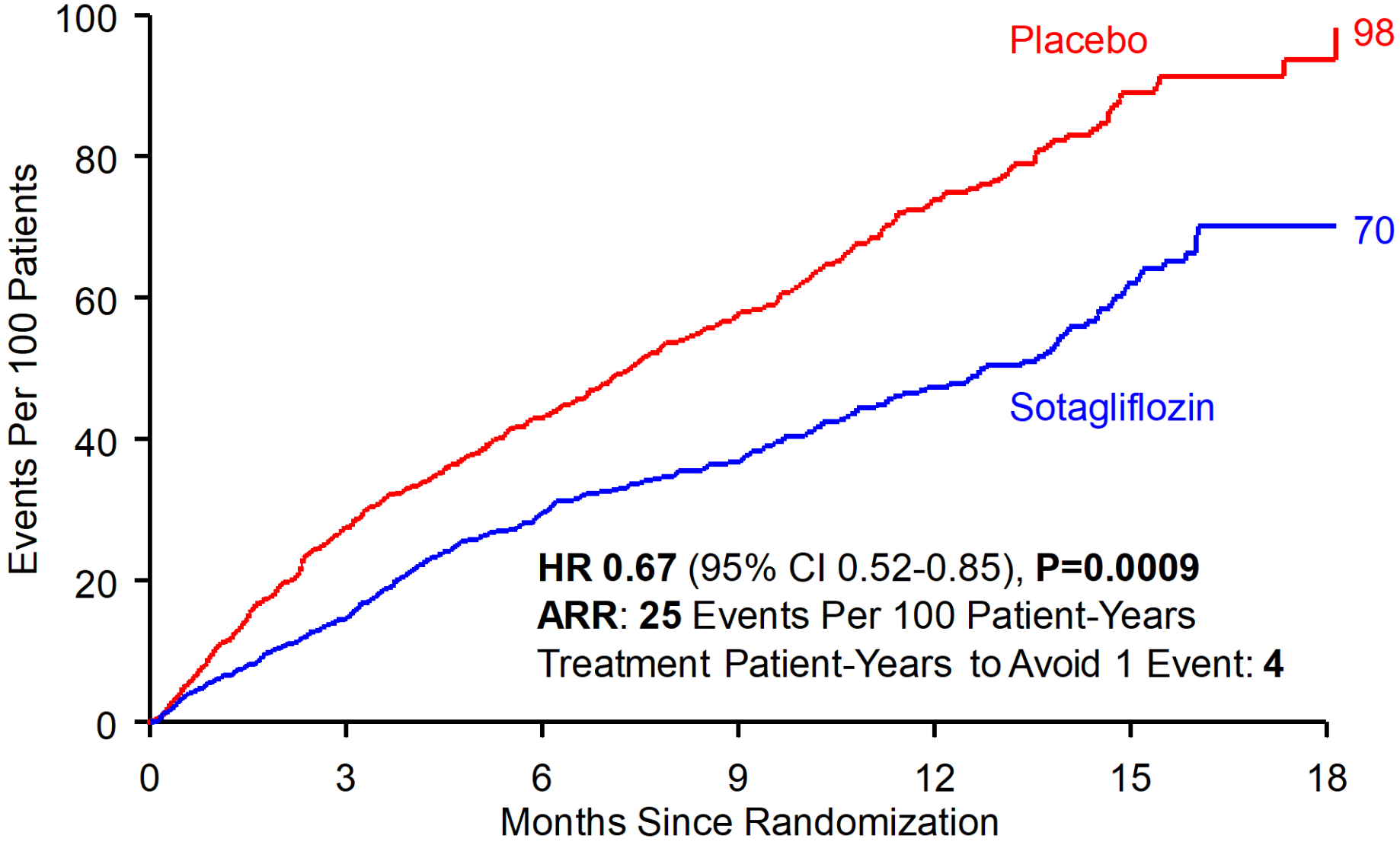
The Evolution of SGLT2i in HF Management



Adapted from Bhatt DL, Verma S, Braunwald E. *Cell Metabolism*. 2019;30:847-849.

Primary Efficacy: Total CV Death, HHF, and Urgent HF Visit

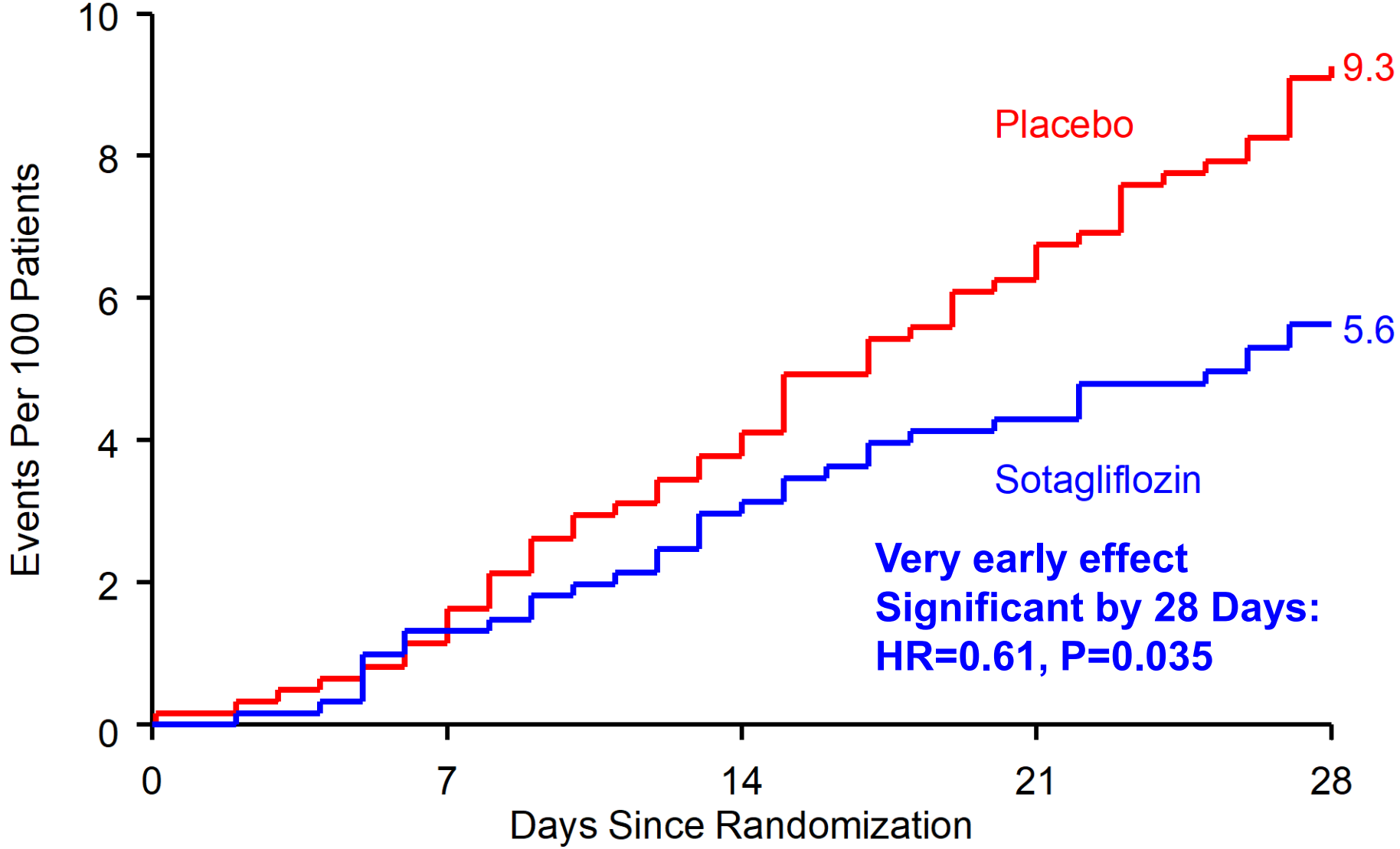
SOLOIST



Bhatt DL, Szarek M, Steg PG, et al., and Pitt B. *N Engl J Med.* 2020. Bhatt DL. AHA 2020, virtual.

Primary Efficacy: Total CV Death, HHF, and Urgent HF Visit – Significant by 28 Days

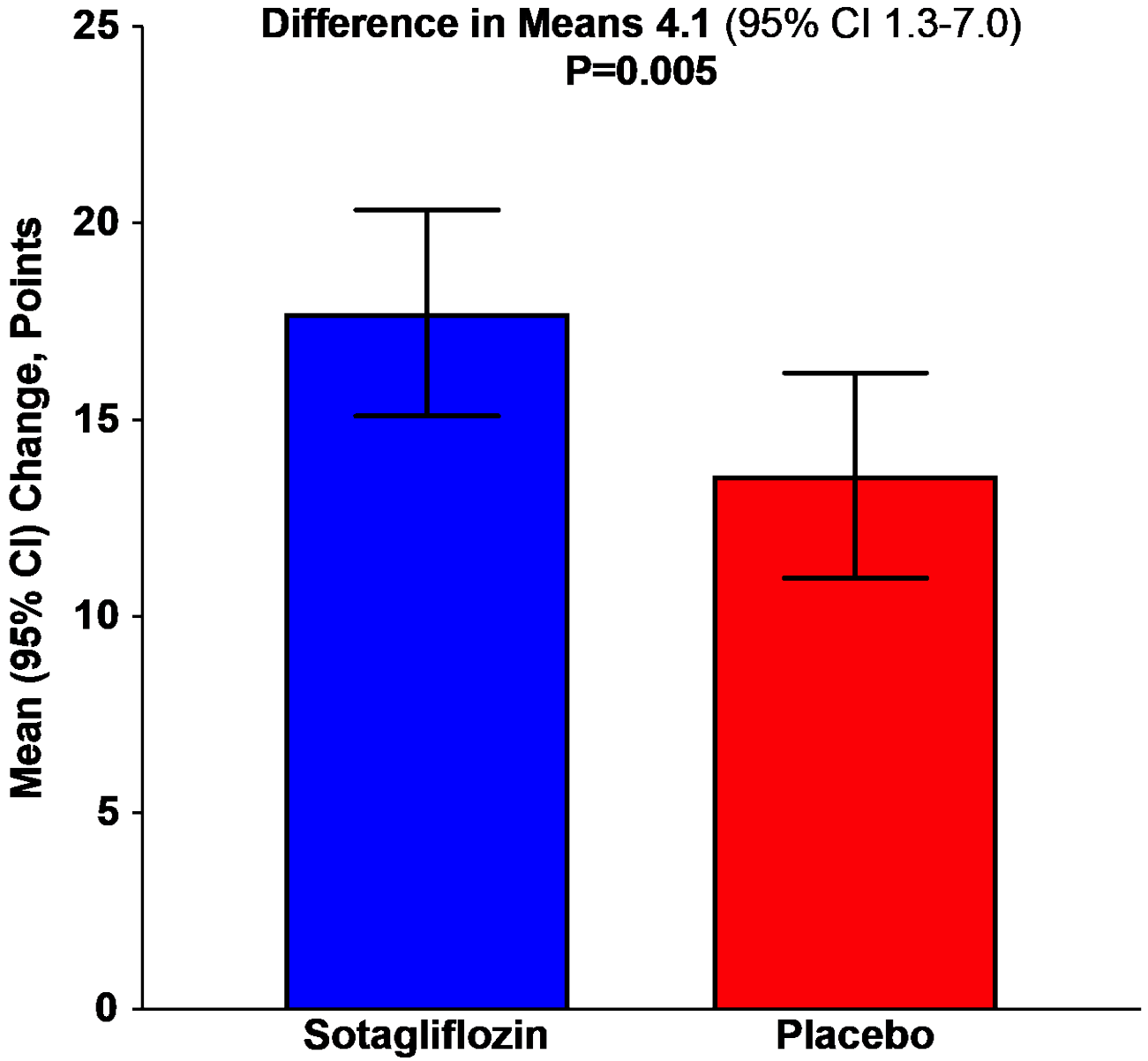
SOLOIST



Bhatt DL, Szarek M, Steg PG, et al., and Pitt B. *N Engl J Med.* 2020. Bhatt DL. AHA 2020, virtual.

Improvement in KCCQ-12 to Month 4

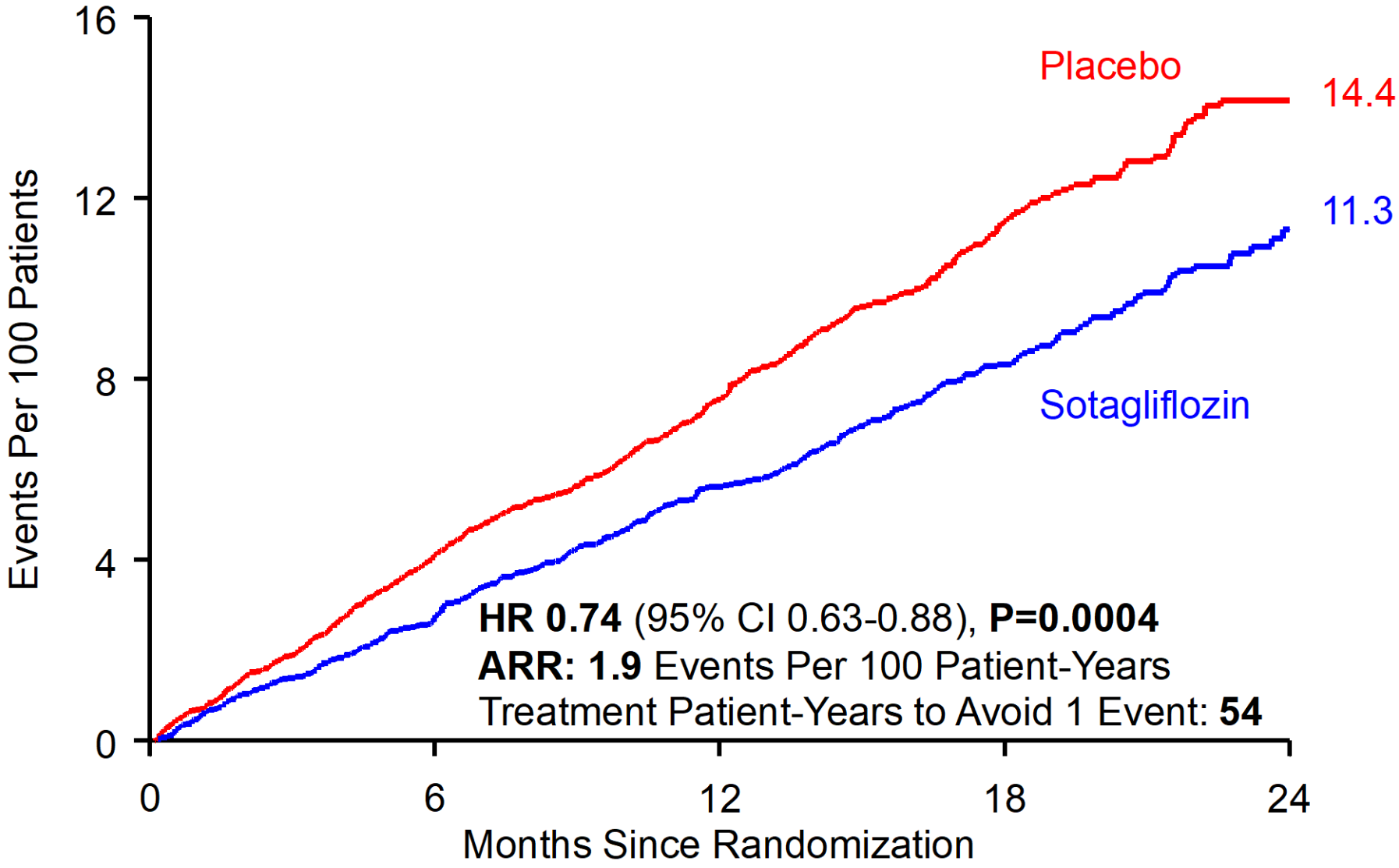
SOLOIST



Bhatt DL, Szarek M, Steg PG, et al., and Pitt B. *N Engl J Med.* 2020. Bhatt DL. AHA 2020, virtual.

Primary Efficacy: Total CV Death, HHF, and Urgent HF Visit

SCORED



Bhatt DL, Szarek M, Pitt B, et al., and Steg PG. *N Engl J Med.* 2020. Bhatt DL. AHA 2020, virtual.

Primary Efficacy: Total CV Death, HHF, and Urgent HF Visit – Significant by 95 Days

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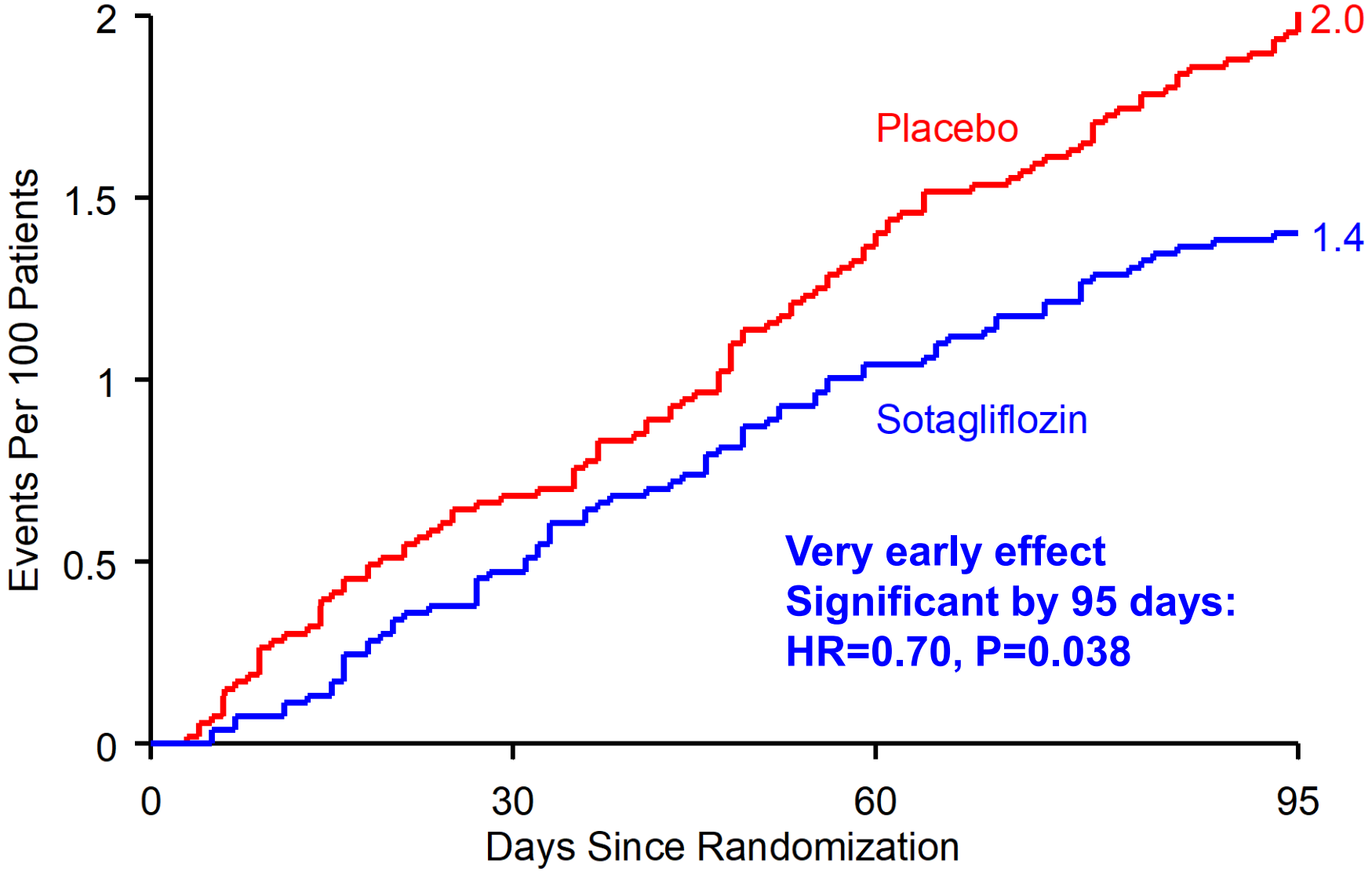

Bhatt DL, Szarek M, Pitt B, et al., and Steg PG. *N Engl J Med.* 2020. Bhatt DL. AHA 2020, virtual.

Total CV Death, Non-Fatal MI, or Non-Fatal Stroke

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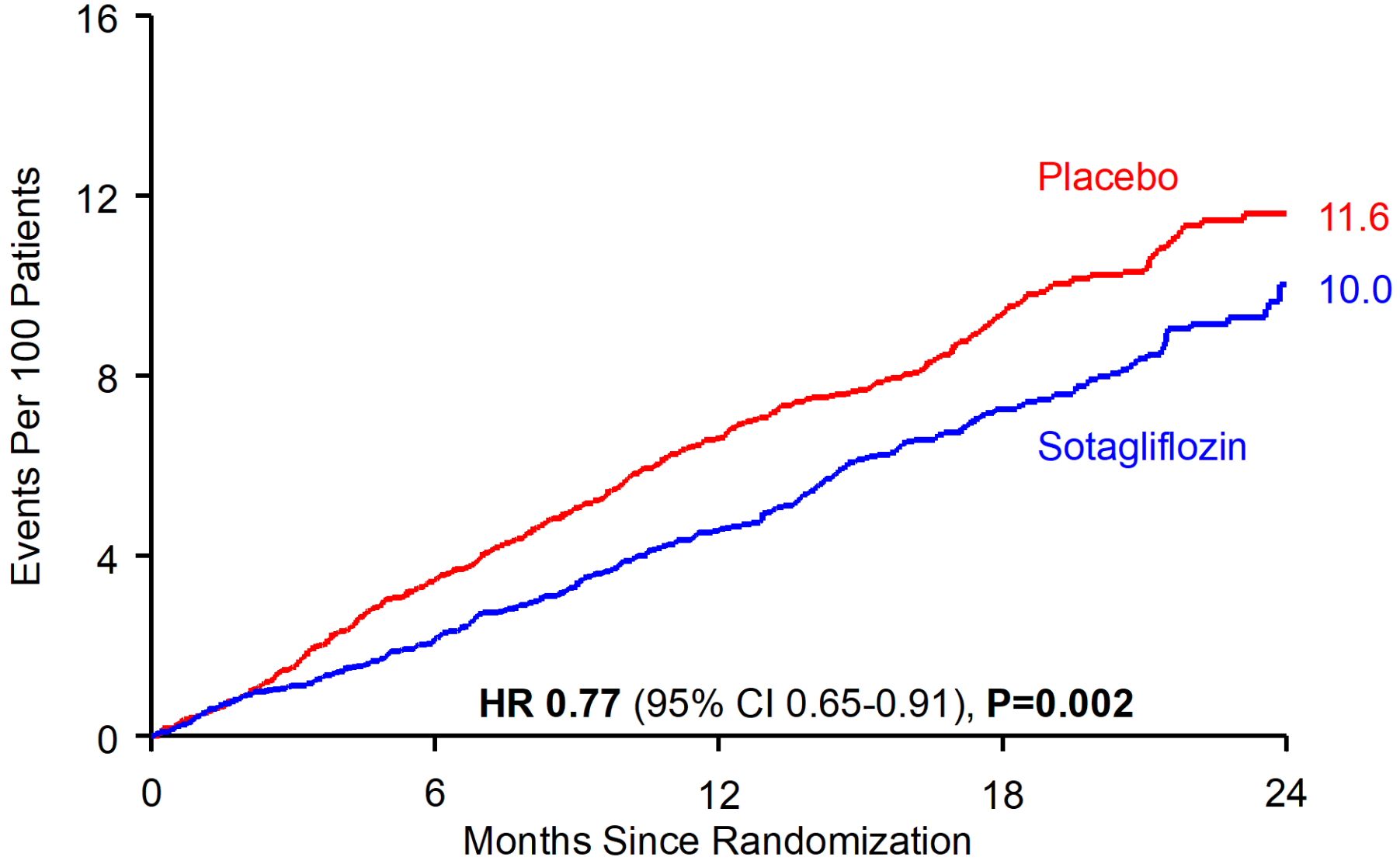


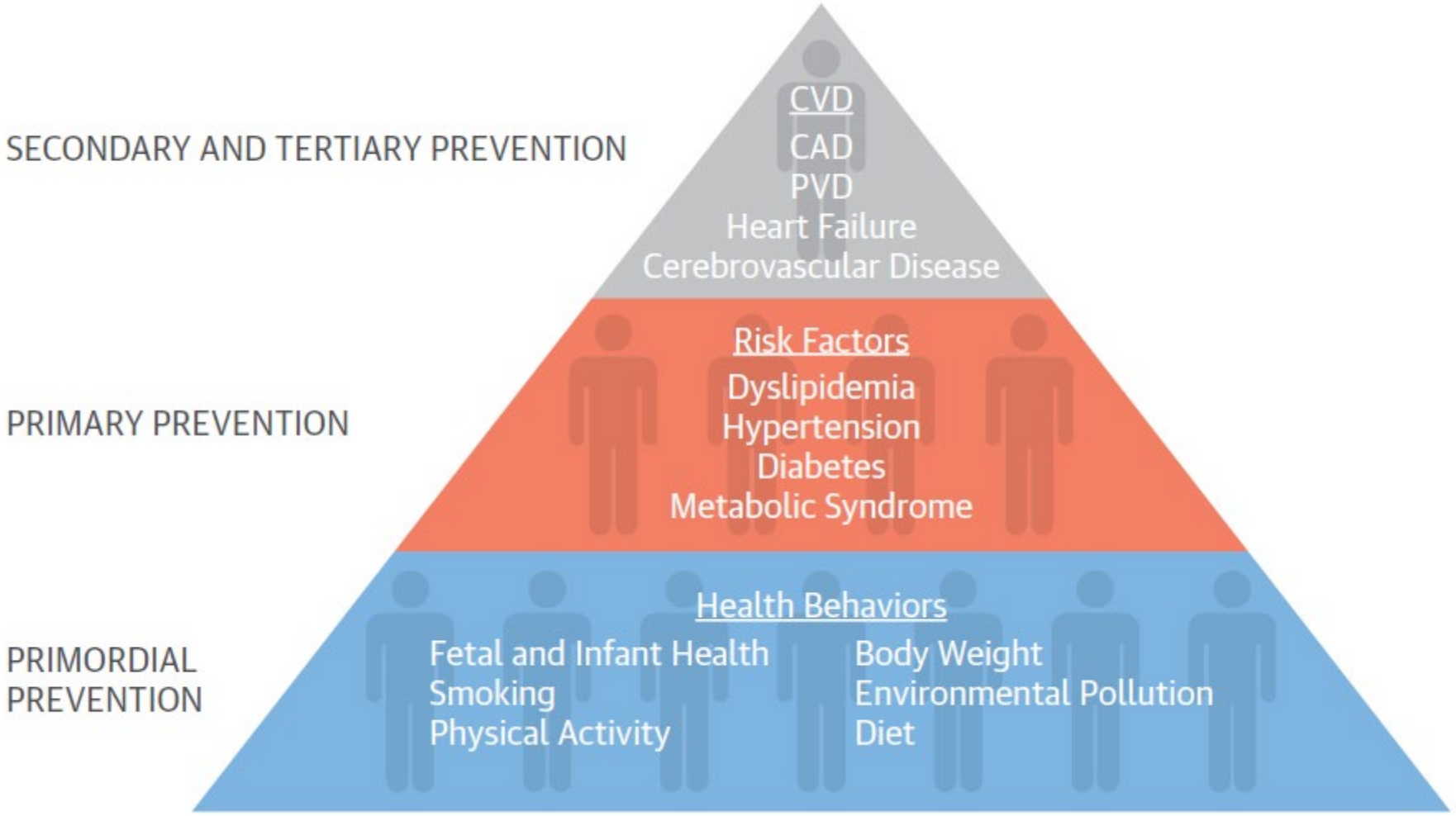
Bhatt DL, Szarek M, Pitt B, et al., and Steg PG. *N Engl J Med.* 2020. Bhatt DL. AHA 2020, virtual.

Redefining Residual Risk in the Current Era

Biological Issue	Residual Cholesterol Risk	Residual Inflammatory Risk	Residual Thrombotic Risk	Residual Triglyceride Risk	Residual Lp(a) Risk	Residual Diabetes Risk
						
Critical Biomarker	LDL-C ≥100 mg/dL	hsCRP ≥2mg/L	No simple biomarker	TG ≥150mg/dL	Lp(a) ≥50mg/dL	HbA1c Fasting glucose
Potential Intervention	Targeted LDL/Apo B Reduction	Targeted Inflammation Reduction	Targeted Antithrombotic Reduction	Targeted Triglyceride Reduction	Targeted Lp(a) Reduction	SGLT2 Inhibitors GLP-1 Agonists
Randomized Trial Evidence	IMPROVE-IT FOURIER SPIRE ODYSSEY	CANTOS COLCOT *LoDoCo2* *OASIS-9*	PEGASUS COMPASS THEMIS	REDUCE-IT *PROMINENT*	Planned	EMPA-REG CANVAS DECLARE CREDENCE LEADER SUSTAIN-6 REWIND

Lawler PR, Libby P, Bhatt DL, Godoy LC, Luscher TF, Bonow RO, VermaS, Ridker PM. *European Heart Journal* 2020.

Pyramid of Risk



Hong KN, Fuster V, Rosenson RS, Rosendorff C, Bhatt DL. *JACC* 2017;70:2171-2185.

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Thank You!

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