Dual Pathway Inhibition in CAD and PAD

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Agenda

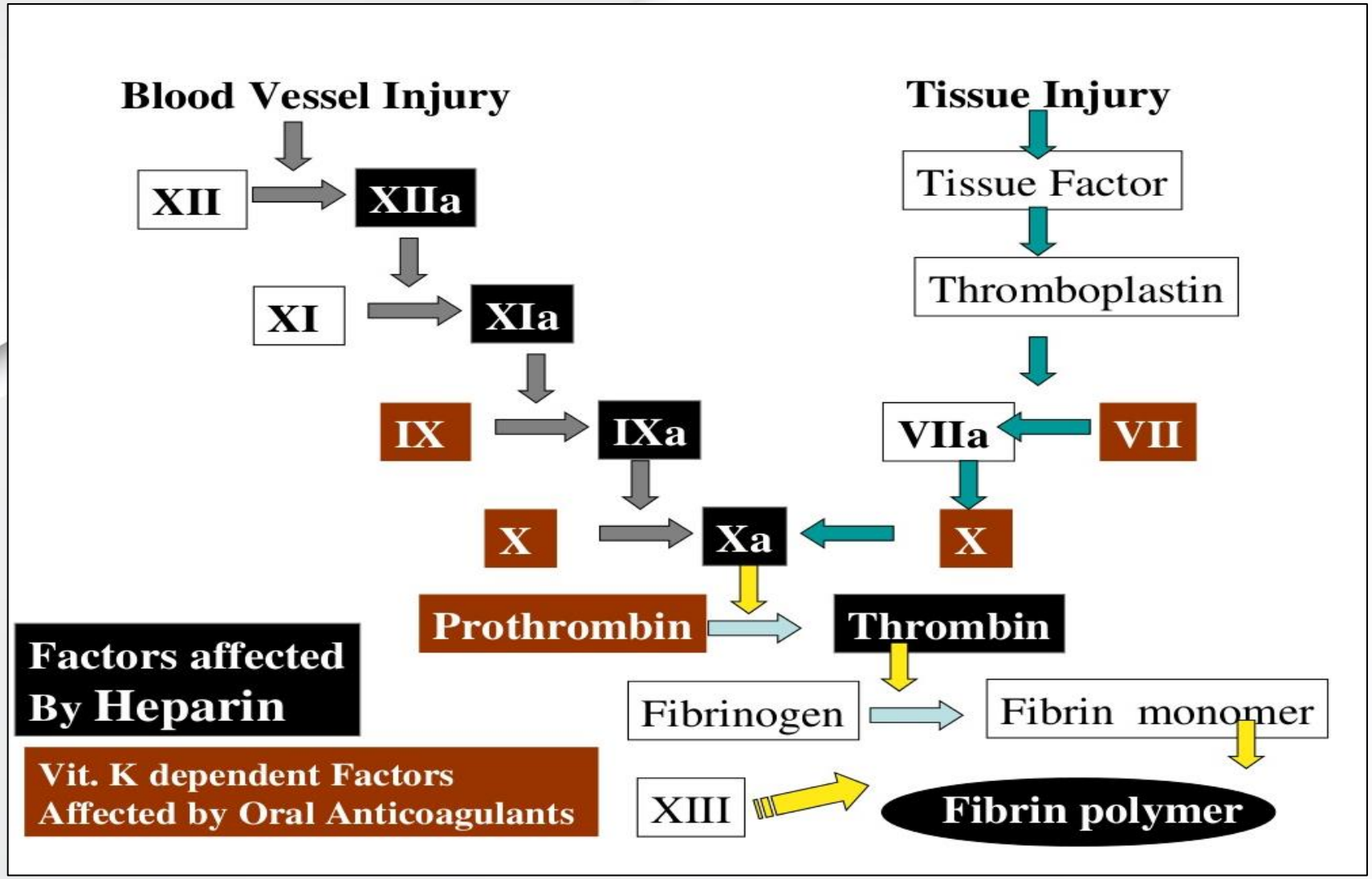
- Introduction
- Coagulation Cascade
  - Rivaroxaban
- Antithrombotic therapy in CAD and PAD
  - Goals
- Single antiplatelet therapy (SAPT)
- Dual Antiplatelet Therapy (DAPT)
- Dual Pathway Inhibition

Introduction

- **Vitamin K antagonists** (VKAs) are the mainstay of management of thromboembolic events for >5decades

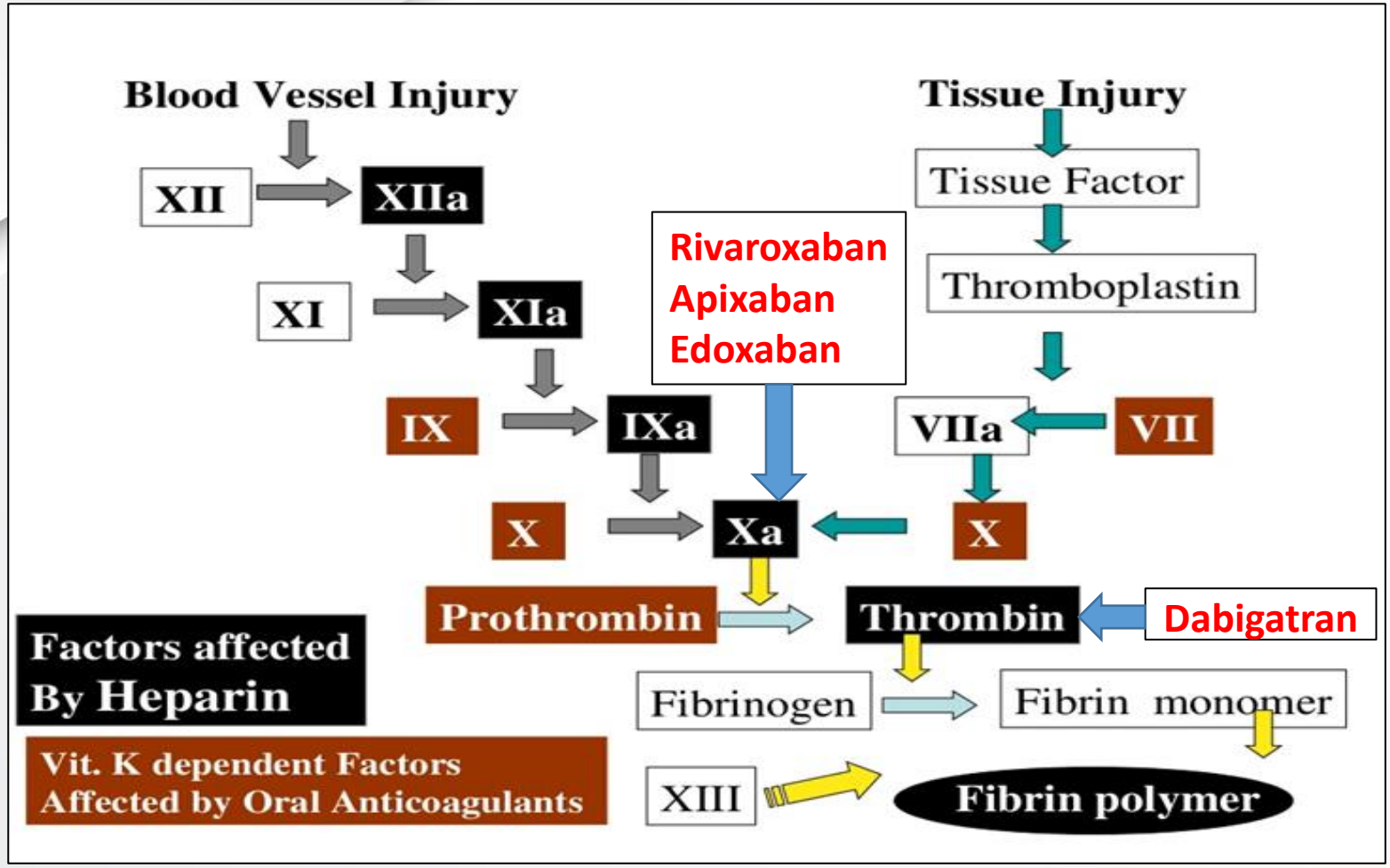
- **Limitations**:
  - Common drug or food interactions
  - Regular monitoring to adjust doses
  - Inter personal variation in response

Coagulation Cascade



What is Rivaroxaban?

Coagulation Cascade



Advantages of Direct oral anticoagulants(DOACs)

Advantage	Clinical Implications
Rapid onset of action	No need for bridging
Predictable anticoagulant effect	No need for routine coagulation monitoring
Specific coagulation enzyme target	Low risk of off-target adverse effects
Low potential for food interactions	No dietary precautions
Low potential for drug interactions	Few drug restrictions

Rivaroxaban (Axabin®)

- Factor Xa inhibitor
- Predictable therapeutic effect
  - Not affected by age, sex, body weight
  - Fixed dose
- Rapid onset
  - Peak plasma level at 2-3 hours
  - No need of overlap with heparin
- Half-life 7-14 hours

Indications and Dosage

- **Nonvalvular Atrial Fibrillation**: 15 or 20 mg, once daily
- **Treatment of DVT and/or PE**: 15 mg twice daily then 20 mg once daily
- **Prevention of DVT and/or PE** : 10 mg once daily
- **Prophylaxis of DVT Following Hip or Knee Replacement Surgery**: 10 mg once daily
- **Prophylaxis of VTE in Acutely Ill Medical Patients** : 10 mg once daily,
- **CAD or PAD: 2.5 mg twice daily in combination with aspirin (75-100 mg) once daily , FDA Approval: 2018**

Antithrombotic therapy in CAD and PAD

The goals on Antithrombotic therapy in CAD and PAD

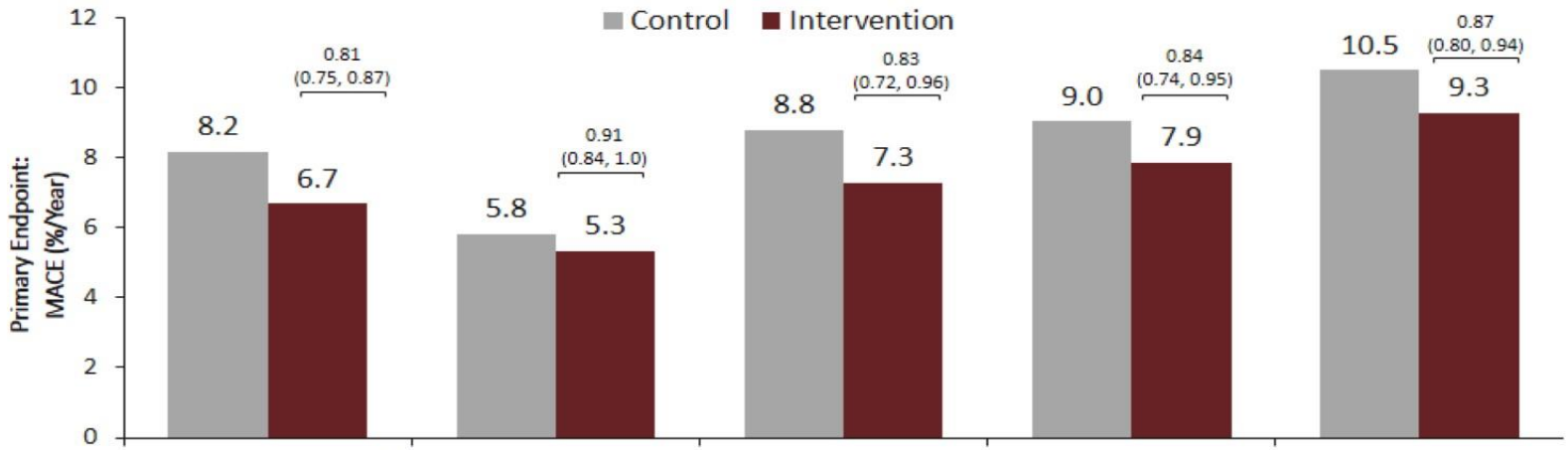
- **Reducing the risk of Major Adverse Cardiovascular Events (↓MACE)**
  - ✓ **(Composite of MI, stroke, cardiovascular death)**
- **Reduce Major Advance Limb Evens (↓MALE)**
  - ✓ **(Composite of acute limb ischemia, chronic limb ischemia, and amputation)**

Antithrombotic therapy in patients with CCS and PAD

- **Aspirin as single antiplatelet therapy (SAPT)**
  - Standard of care for chronic atherosclerotic disease

- Despite current antithrombotic therapies in patients with chronic atherosclerotic disease **(SAPT, DAPT)**
  - **The risk of MACE (MI, Stroke, cardiovascular death) at 1 year 3%- 5%**
  - **Event rates are even higher in real-world practice**

Patients With Chronic CAD or PAD Remain at Risk for Vascular Events Despite Current Optimal Medical Therapy



	ATT Collaboration[a]	CAPRIE[b]	CHARISMA[c]	PEGASUS[d]	TRA2P-TIMI 50[e]
	Control vs Aspirin	Aspirin vs Clopidogrel	Placebo + Aspirin ‖ Clopidogrel + Aspirin	Placebo + Aspirin ‖ Ticagrelor* + Aspirin	Vorapaxar + Aspirin ‖ Placebo + Aspirin ± Thienopyridine
% Use of key therapies in intervention arm					
ACEI/ARB	*Meta-analysis of 16 trials*	*Not reported*	*Up to 85.3*	*79.9*	*73.5*
Statin/ lipid-lowering		*Not reported*	*77.1 to 89.3*	*92.4*	*91.0*

*Ticagrelor 90 mg.

a. ATT Collaboration. *Lancet*. 2009;373:1849-1860; b. CAPRIE Steering Committee. *Lancet*. 1996;348:1329-1339; c. Bhatt DL, et al. *J Am Coll Cardiol*. 2007;49:1982-1988; d. Bonaca MP, et al. *N Engl J Med*. 2015;372:1791-1800; e. Morrow DA, et al. *N Engl J Med*. 2012;366:1404-1413.

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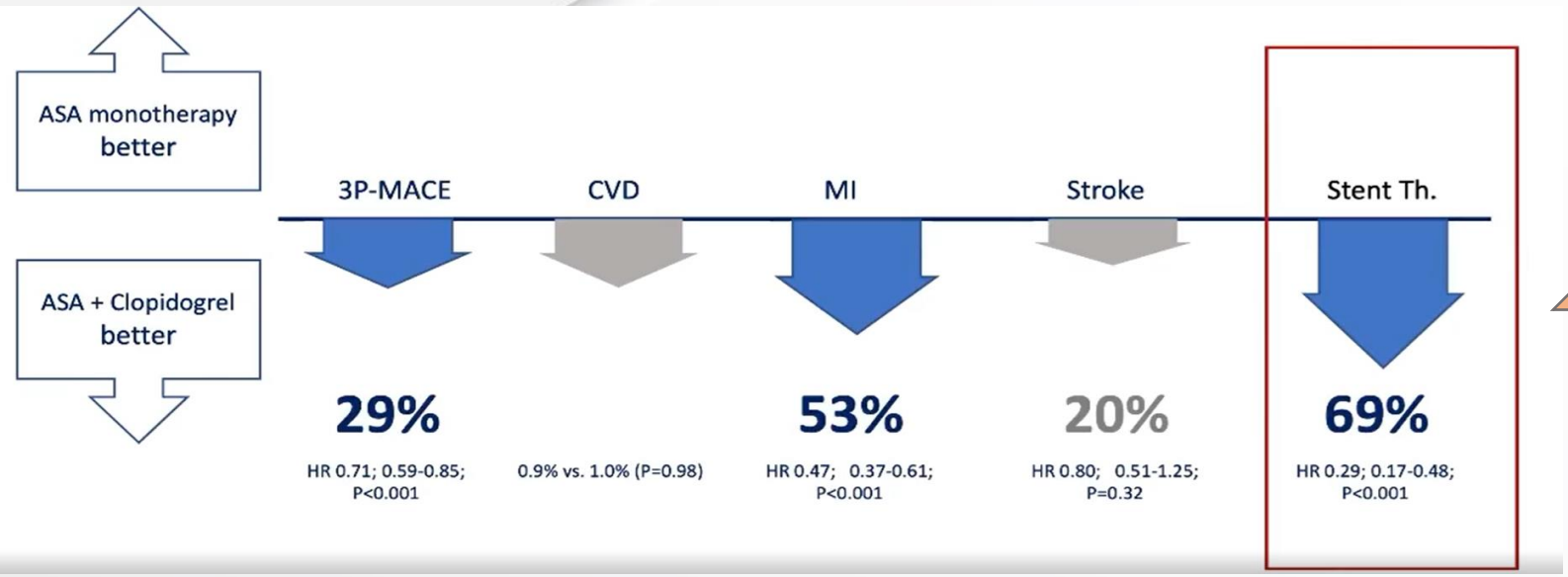
Twelve or 30 Months of Dual Antiplatelet Therapy after Drug-Eluting Stents

Laura Mauri, M.D., Dean J. Kereiakes, M.D., Robert W. Yeh, M.D., Priscilla Driscoll-Shempp, M.B.A., Donald E. Cutlip, M.D., P. Gabriel Steg, M.D., Sharon-Lise T. Normand, Ph.D., Eugene Braunwald, M.D., Stephen D. Wiviott, M.D., David J. Cohen, M.D., David R. Holmes, Jr., M.D., Mitchell W. Krucoff, M.D., James Hermiller, M.D., Harold L. Dauerman, M.D., Daniel I. Simon, M.D., David E. Kandzari, M.D., Kirk N. Garratt, M.D., David P. Lee, M.D., Thomas K. Pow, M.D., Peter Ver Lee, M.D., Michael J. Rinaldi, M.D., and Joseph M. Massaro, Ph.D., for the DAPT Study Investigators*

DAPT study (extended)



- **100% post PCI (1 year of DAPT):**
  - **you can't extrapolate the results of this study to patients without PCI**
- **No significant reduction in cardiovascular death** and **stroke**
- **No MALE outcomes**

Laura Mauri, n engl j med 371;23, december 4, 2014

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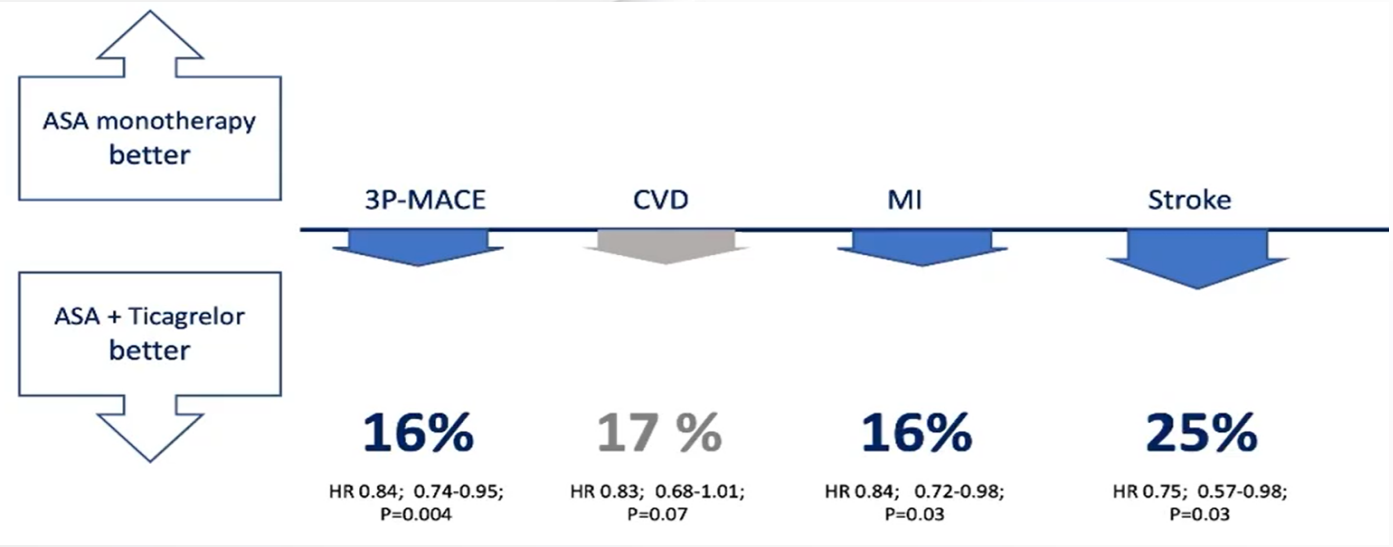
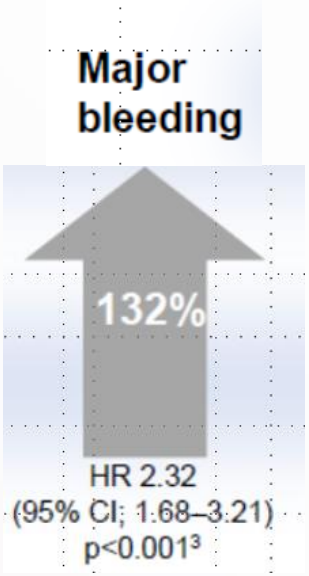
Long-Term Use of Ticagrelor in Patients with Prior Myocardial Infarction

Marc P. Bonaca, M.D., M.P.H., Deepak L. Bhatt, M.D., M.P.H., Marc Cohen, M.D., Philippe Gabriel Steg, M.D., Robert F. Storey, M.D., Eva C. Jensen, M.D., Ph.D., Giulia Magnani, M.D., Sameer Bansilal, M.D., M. Polly Fish, B.A., Kyungah Im, Ph.D., Olof Bengtsson, Ph.Lic., Ton Oude Ophuis, M.D., Ph.D., Andrzej Budaj, M.D., Ph.D., Pierre Theroux, M.D., Mikhail Ruda, M.D., Christian Hamm, M.D., Shinya Goto, M.D., Jindrich Spinar, M.D., José Carlos Nicolau, M.D., Ph.D., Robert G. Kiss, M.D., Ph.D., Sabina A. Murphy, M.P.H., Stephen D. Wiviott, M.D., Peter Held, M.D., Ph.D., Eugene Braunwald, M.D., and Marc S. Sabatine, M.D., M.P.H., for the PEGASUS-TIMI 54 Steering Committee and Investigators*

PEGASUS STUDY





- **100% prior MI (1-3 years post)**
- **NO reduction in cardiovascular death**
- **The most major bleeding**

PEGASUS STUDY

TABLE 3 Limb Vascular Efficacy With Ticagrelor

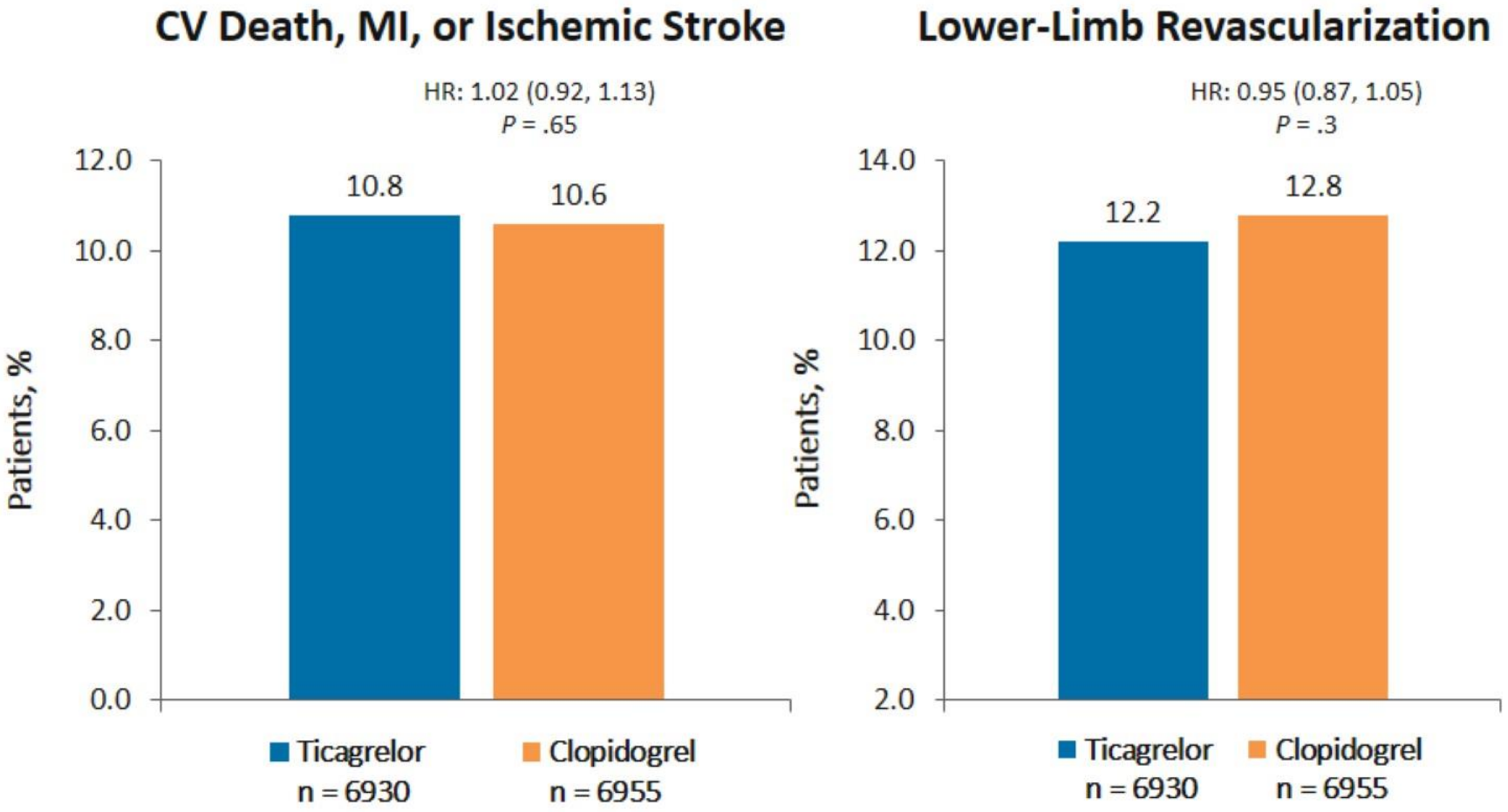
	Placebo (n = 7,067) n, %	Ticagrelor 60 mg (n = 7,045) n, %	Ticagrelor 90 mg (n = 7,050) n, %	Ticagrelor 60 mg HR (95% CI) p Value	Ticagrelor 90 mg HR (95% CI) p Value
Acute limb ischemia or peripheral revascularization for ischemia	47, 0.71	38, 0.60	23, 0.32	0.81 (0.53-1.24) p = 0.33	0.49 (0.30-0.81) p = 0.005
Acute limb ischemia	9, 0.13	6, 0.11	4, 0.06	0.67 (0.24-1.87)	0.45 (0.14-1.45)
Peripheral revascularization for ischemia	46, 0.70	37, 0.59	21, 0.29	0.80 (0.52-1.24)	0.46 (0.27-0.76)
Peripheral revascularization	60, 0.94	46, 0.74	38, 0.55	0.77 (0.52-1.13)	0.63 (0.42-0.95)

Values are n, 3-year Kaplan-Meier (%), unless otherwise indicated.

Abbreviations as in Table 2.

EUCLID

Ticagrelor vs Clopidogrel for PAD



Hiatt WR, et al. *N Engl J Med*. 2017;376:32-40.

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Ticagrelor in Patients with Stable Coronary Disease and Diabetes

P.G. Steg, D.L. Bhatt, T. Simon, K. Fox, S.R. Mehta, R.A. Harrington, C. Held, M. Andersson, A. Himmelmann, W. Ridderstråle, M. Leonsson-Zachrisson, Y. Liu, G. Opolski, D. Zateyshchikov, J. Ge, J.C. Nicolau, R. Corbalán, J.H. Cornel, P. Widimský, and L.A. Leiter, for the THEMIS Steering Committee and Investigators*

Table 2. Primary, Secondary, and Other Ischemic Efficacy Outcomes (Modified Intention-to-Treat Population).

Outcome	Ticagrelor (N = 9619)		Placebo (N = 9601)		Hazard Ratio (95% CI)*	P Value
Secondary efficacy outcomes						
Cardiovascular death	364 (3.8)	3.3	357 (3.7)	3.0	1.02 (0.88–1.18)	0.79
Myocardial infarction	274 (2.8)	2.6	328 (3.4)	3.3	0.84 (0.71–0.98)	
Ischemic stroke	152 (1.6)	1.5	191 (2.0)	1.8	0.80 (0.64–0.99)	
Death from any cause‡	579 (6.0)	5.1	592 (6.2)	4.9	0.98 (0.87–1.10)	

Adjudicated adverse events†						
TIMI major bleeding	206 (2.2)	0.89	100 (1.0)	0.38	2.32 (1.82–2.94)	<0.001
TIMI major or minor bleeding	285 (3.0)	1.23	129 (1.4)	0.49	2.49 (2.02–3.07)	<0.001
Intracranial hemorrhage	70 (0.7)	0.30	46 (0.5)	0.18	1.71 (1.18–2.48)	0.005
Dyspnea						
Any	2049 (21.4)	8.82	700 (7.3)	2.66	3.33 (3.06–3.63)	<0.001
Leading to discontinuation of ticagrelor or placebo	661 (6.9)	2.84	75 (0.8)	0.29	9.27 (7.30–11.77)	<0.001

- The incidence of an exploratory composite outcome of irreversible harm (death from any cause, myocardial infarction, stroke, fatal bleeding, or intracranial hemorrhage) ***was similar in the ticagrelor group and the placebo group*** ***(10.1% vs. 10.8%; hazard ratio, 0.93; 95% CI, 0.86 to 1.02).***
- for most patients with type 2 diabetes and known coronary disease who fit the THEMIS enrollment criteria, ***the addition of ticagrelor to aspirin is not recommended***

Dual Pathway Inhibition

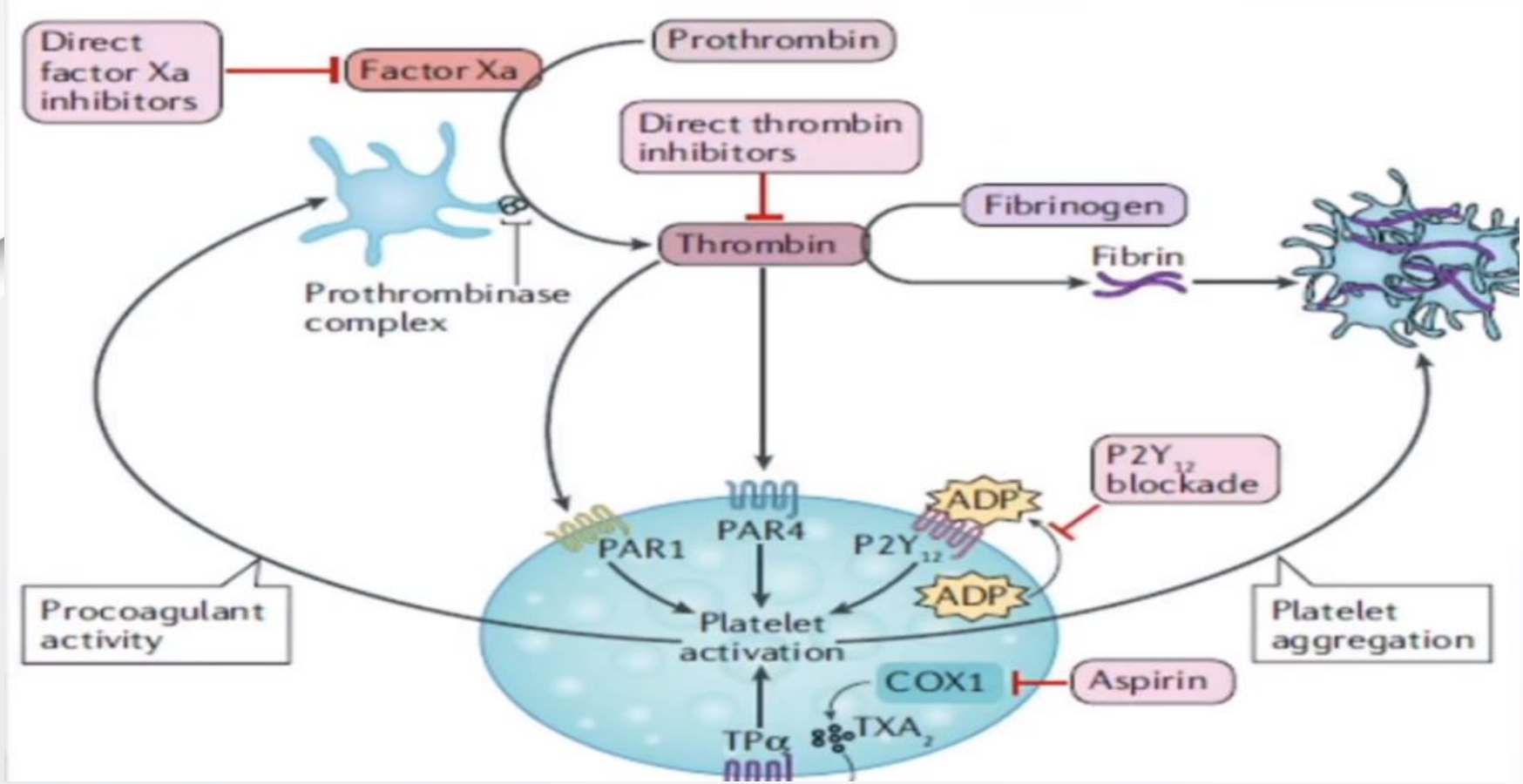
Rivaroxaban 2.5 mg BD

+

Aspirin 75-100 mg OD

in CAD and PAD

Synergy of Dual Pathway Inhibition

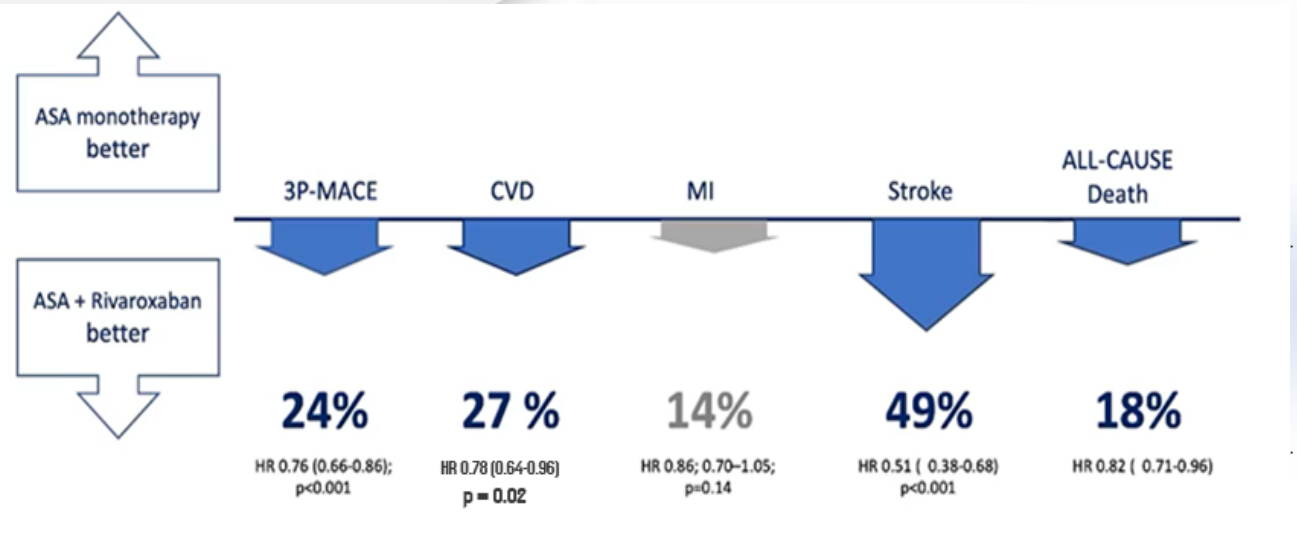


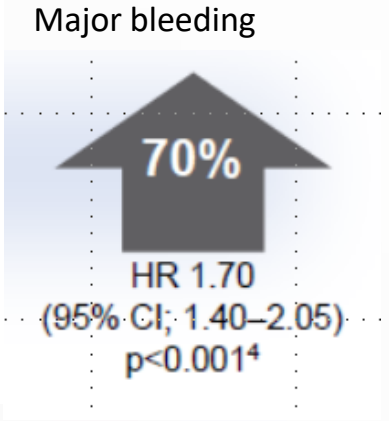
Rationale for DPI strategy

- Factor Xa and thrombin are critical for platelet activation and fibrin formation
- Factor Xa, through activation of PAR1 (proteinase activated receptor) PAR2, and thrombin, promote pro- inflammatory cytokine production, expression of cell- adhesion molecules on endothelial cells and proliferation of endothelial cells and vascular smooth muscle cells.
- Thrombin generation is increased in patients with clinical manifestations of ASCVD compared with those without

COMPASS STUDY

(Rivaroxaban 2.5 mg BD + Aspirin 75-100 mg OD)





- **Patients had chronic CAD & PAD, 38% No previous MI**
- **Significant reduction** in **cardiovascular death**
- **49% reduction** in **stroke**

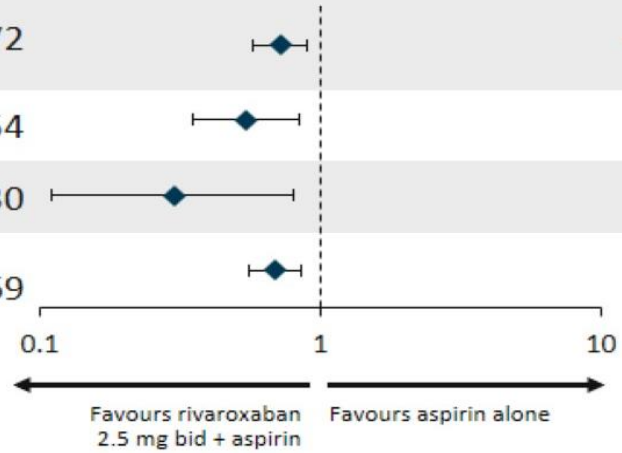
Only in COMPASS Trial:

Significant reduction in ALL- CAUSE death

COMPASS STUDY

Pre-Specified Efficacy Outcomes in the PAD Population (N=7470) MACE (Primary Outcome) and MALE

Outcome*	Rivaroxaban 2.5 mg BID + aspirin (n = 2492) %	Aspirin (n = 2504) %	HR	HR (95% CI)	*P* value
CV death, stroke, MI (MACE)	5.1	6.9	0.72		< .005
MALE	1.2	2.2	0.54		.005
Major amputation	0.2	0.7	0.30		.01
MACE, MALE or major amputation†	6.3	9.0	0.69		.0003

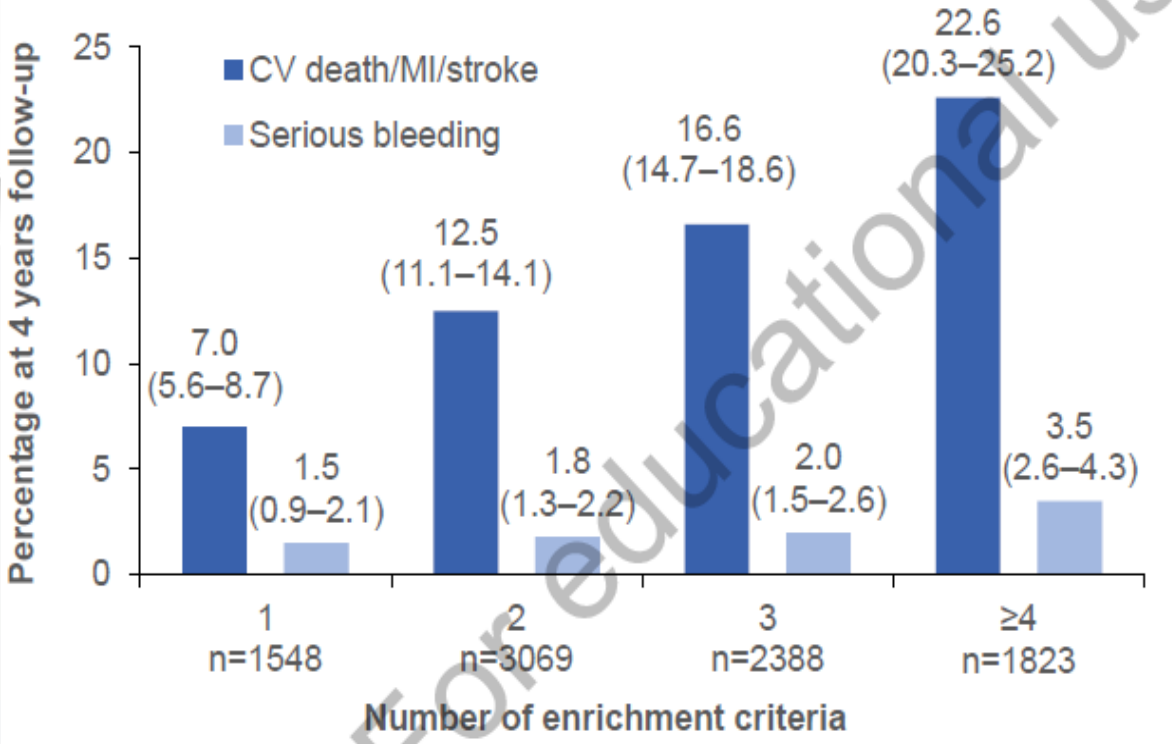


*Crude incidence over mean follow-up of 21 months; †Pre-specified composite outcome

Anand S et al, *Lancet* 2018;391:219-229.

Identifying High-Benefit Patients for Dual Pathway Inhibition

Ischaemic and bleeding outcomes in COMPASS-eligible patients in the REACH registry according to the number of enrichment criteria[1]



Enrichment criteria:

- Age >65 years old
- Smoking
- Diabetes
- Renal dysfunction
- HF
- Carotid disease
- PAD
- Prior stroke

Values show above the bars are % (95% CI)

Darmon A *et al*, *JACC* 2019;73:3281–3291

Patients Who Derive Greatest Benefit from DPI Regimen

Patients with chronic atherosclerotic coronary or peripheral artery disease and:

- ✓ Polyvascular disease
- ✓ ***Diabetes***
- ✓ Mild or moderate Chronic kidney disease
- ✓ CAD & PAD together
- ✓ Current Smoking
- ✓ Carotid disease
- ✓ Prior ischemic Stroke

THANK YOU