Antithrombotic Therapies in Stable PAD, and Post-Revascularization

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Disclosures

Consulting and speaking for Pfizer, J&J, A.Z., NNI, and BSC

No financial conflict related to this talk

Information: evidence-based

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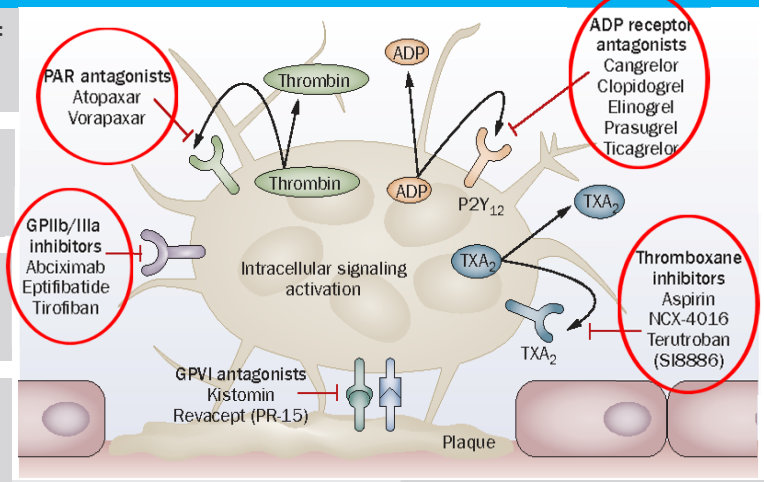
Learning Objectives

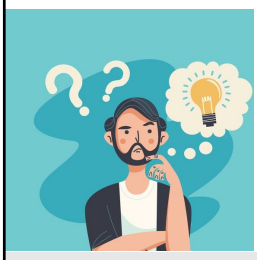
- PAD: a major under-represented health problem with worse outcome than CAD and CVD!
- Antithrombotic therapy options in chronic symptomatic PAD
- Antithrombotic therapy options following endovascular and open revascularization
- Current guidelines and evidence-based recommendations
- Summary

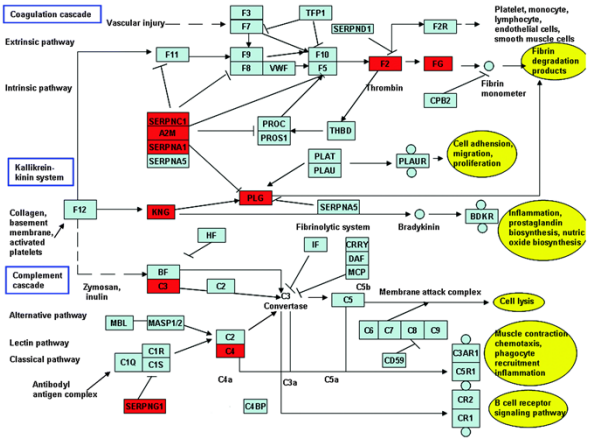
Antiplatelet Therapies with Different Targets

- **Aspirin (NSAID and sulfinpyrazone):**
  - PLT aggregation
- **The platelet P2Y12 inhibitors:**
  - PLT activation and aggregation
- **Vorapaxar, PAR 1 antagonist:**
  - PLT aggregation
- **Glycoprotein IIb/IIIa inhibitors:**
  - PLT aggregation



Coagulation Cascade





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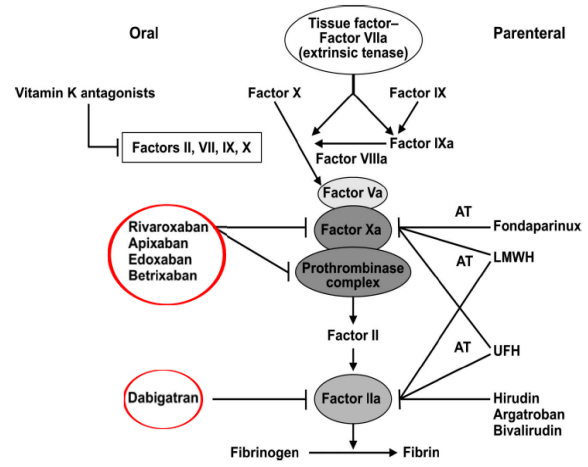
Anticoagulation Therapies with Different Targets



Ther Drug Monit. 2010 Dec;32(6):673-9

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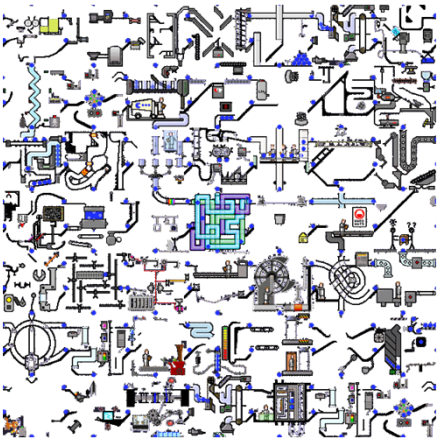
Decision Making is Very Complicated



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PAD a Major Atherosclerotic Disease

- Globally, over 236 million people with PAD , 200 million in 2010.
- PAD: 3rd. most common ASO after CAD and CVD.
- A significant cause of morbidity, mortality, and disability.
- Compared with CAD and CVD, evidence for optimal antithrombotic therapies in patients with PAD is lacking.
- PAD: Atherosclerotic stenosis, atherothrombosis, or thromboembolism

Skeik N et al. *Angiology*, in press

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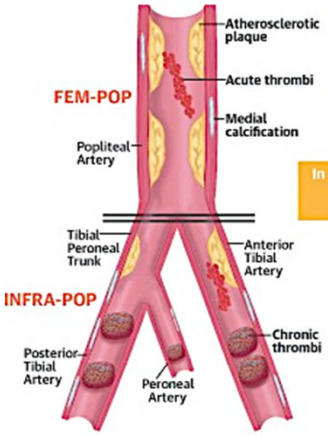
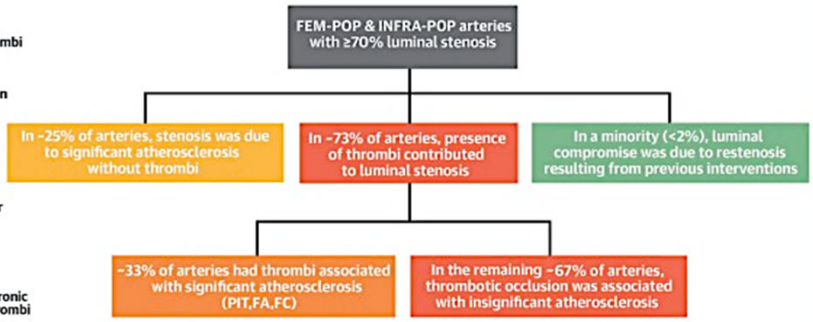
PAD Pathophysiology





Narula, N et al. *J Am Coll Cardiol.* 2018;72(18):2152-63.

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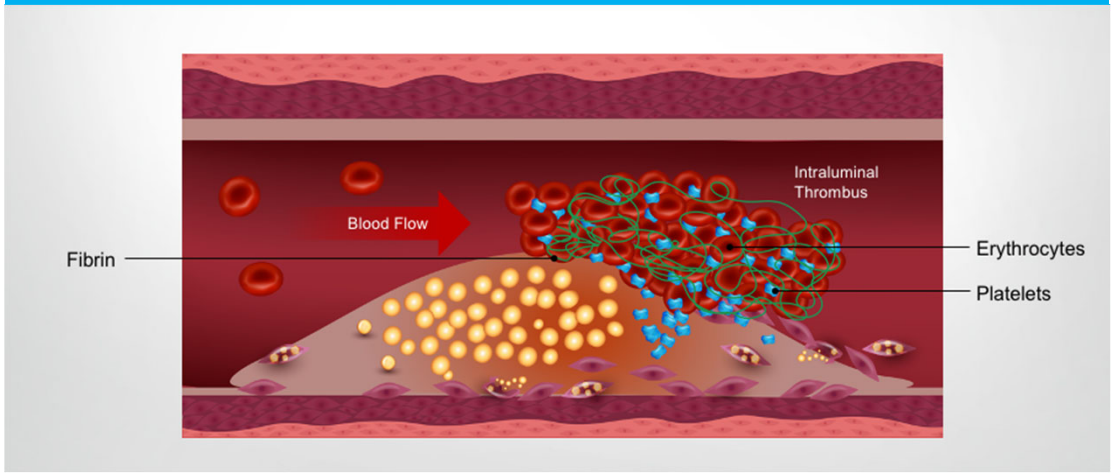
Atherosclerosis → Atherothrombosis



Vanuraju S et al. *Clinical Nuclear Cardiology: State of Art and Future Directions.* 4th ed. Philadelphia, PA: Mosby. Inc., an Affiliate of Elsevier Inc, 2010.

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Multinational Reduction of Atherothrombosis for Continued Health *(REACH) Registry*

- Large, global observational registry
- N: ~ 68,000
- Patents: CAD, PAD, CVD or ≥3 atherothrombotic risk
- Aim: prevalence, risk factors, and clinical consequences of ASO.

- Findings:
- 40% of PAD patients experienced MI, stroke, vascular death, or hospitalization over 3 years which was considerably higher than in those with coronary (30%) or cerebrovascular disease (28%).

Bhatt DL, et al. *JAMA*. 2006.295:180-189.

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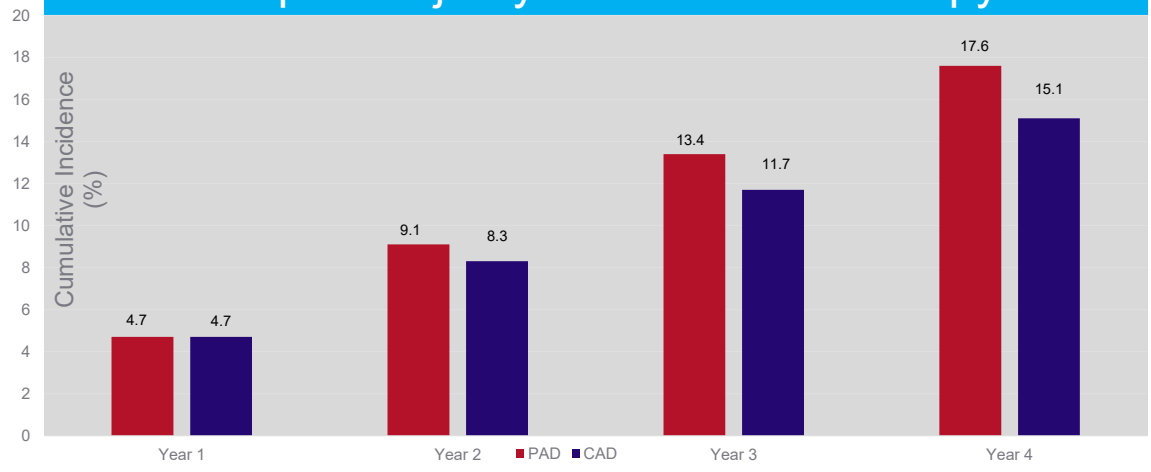
Major CV Event Rates Despite Majority on Standard Therapy



Abtan. J, et al. *Clin Card*. 2017;40:710-718

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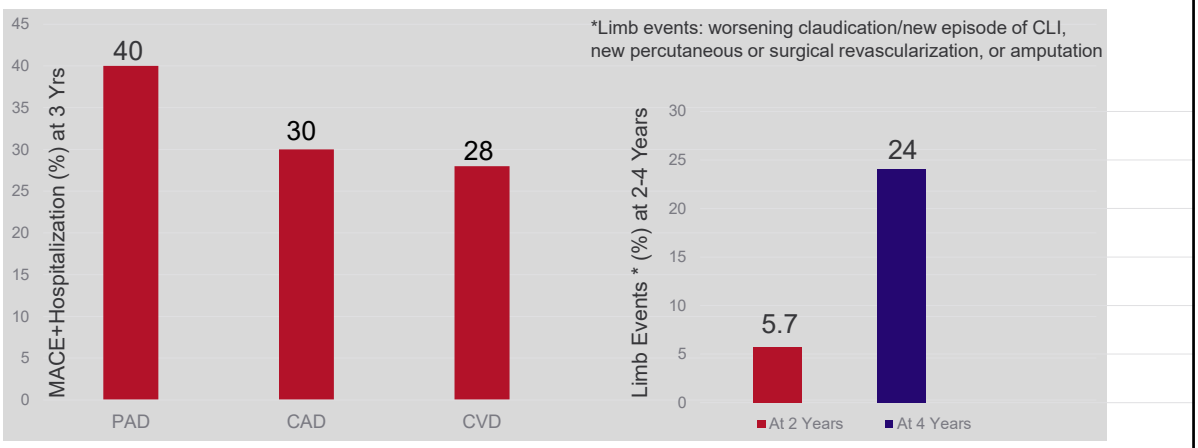
MACE and Hospitalization in PAD, CAD and CVD at 3 Years
Limb Events in PAD at 2 and 4 Years
Despite Standard Therapy



Bhatt DL, et al. *JAMA*. 2006.295:180-189.

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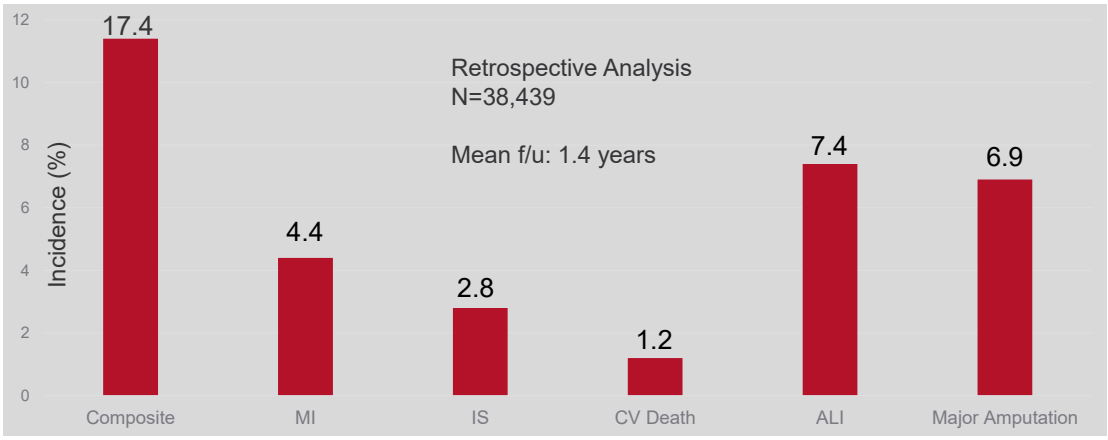
Major Atherothrombotic Vascular Events
Post-Revascularization and *Despite Standard Therapy*



Desai U et al. *Ann Vasc Surg*. 2021;S0890-5096 (21) 0025-9.

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Management Challenges

- Secondary prevention with antithrombotic therapy has been shown to reduce MACCE.
- Most evidence is from studies involving CAD patients.
- PAD is under-represented..
- Patients with PAD are often undertreated with antithrombotic agents.
- Effective/safe strategies to reduce MACCE and MALE risk in pts with PAD is critical.

Skeik N, et al. Angiology in press.

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Aspirin in Stable PAD
The Critical Leg Ischemia Prevention Study *(CLIPS) study*

- N: 366 patients with PAD and claudication
- Study Design: randomized aspirin vs placebo
- Study Duration: ~ 2 years
- Outcome: MACCE and CLI
- Results: significant reduction of MACCE and CLI with aspirin
  - (6.5% *vs* 15.5%; HR: 0.42 [95% CI: 0.21 to 0.82]).

J Intern Med. 2007;261(3):276–284.

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Aspirin in Stable PAD
The Critical Leg Ischemia Prevention Study *(CLIPS) Study*

Table 2a Aspirin versus nonaspirin: outcomes

	Aspirin (n = 185)	Nonaspirin (n = 181)	P-value[a]	HR (95% CI)
Stroke nonfatal plus fatal	2+2	6+1	0.33	0.54 (0.16–1.85)
Myocardial infarction nonfatal plus fatal	0+2	9+2	0.03	0.18 (0.04–0.83)
Pulmonary embolus nonfatal plus fatal	1+0	1+1	0.57	0.50 (0.05–5.54)
Vascular death	5	4	0.78	1.21 (0.32–4.52)
Nonvascular death[b]	2	0	0.99	–
Vascular event	7	20	0.02	0.35 (0.15–0.82)
Vascular event or critical limb ischaemia	12	28	0.01	0.42 (0.21–0.83)
Bleeding	4	0	0.99	–

–, Statistics could not be calculated because of the lack of events in the second group. [a]Aspirin versus nonaspirin groups P = 0.074 (chi-quadro = 3.18). [b]Both nonvascular deaths were from cancer.

J Intern Med. 2007;261(3):276–284.

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Aspirin for the Prevention of Cardiovascular Events in Patients With PAD: *A Meta-analysis* of Randomized Trials

- 18 trials, 16 included symptomatic PAD
- N: 5,269 patients with PAD
- Study Drugs: Aspirin with and without dipyridamole vs placebo
- Results: non-significant decrease in MACCE
- (8.9% for aspirin ± dipyridamole vs 11.0% for placebo; RR: 0.88 [95% CI: 0.76 to 1.04]).

JAMA. 2009;301(18):1909–1919

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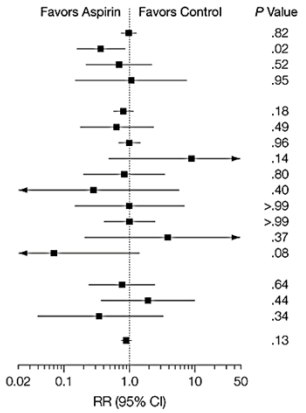
Aspirin for the Prevention of Cardiovascular Events in Patients With PAD: A *Meta-analysis* of Randomized Trials

Source	No. of Cardiovascular Events/ Total No. of Patients: Aspirin	Control	Weight, %	RR (95% CI)[a]	*P* Value
Belch et al,[9] 2008	105/638	108/638	41.3	0.97 (0.76-1.24)	.82
Catalono et al,[21] 2007	7/185	19/181	3.5	0.36 (0.16-0.84)	.02
BMFT-II,[14] 1998	5/170	7/164	2.0	0.69 (0.22-2.13)	.52
Study group on pharmacological treatment after PTA,[20] 1994	2/108	2/115	0.7	1.06 (0.15-7.43)	.95
McCollum et al,[32] 1991	53/286	61/263	23.1	0.80 (0.58-1.11)	.18
Heiss et al,[28] 1990	5/132	4/67	1.5	0.63 (0.18-2.29)	.49
Colwell et al,[22] 1989	36/110	40/121	18.3	0.99 (0.68-1.43)	.96
Donaldson et al,[23] 1985	4/33	0/32	0.3	8.74 (0.49-155.97)	.14
Hess et al,[30] 1985	5/160	3/80	1.3	0.83 (0.20-3.40)	.80
Goldman and McCollum,[25] 1984	0/22	2/31	0.3	0.28 (0.01-5.53)	.40
Kohler et al,[31] 1984	2/50	2/50	0.7	1.00 (0.15-6.82)	>.99
Schoop and Levy,[33,34] 1984	14/200	7/100	3.2	1.00 (0.42-2.40)	>.99
Green et al,[26] 1982	3/32	0/17	0.3	3.82 (0.21-69.88)	.37
Harjola et al,[27] 1981	0/200	3/100	0.3	0.07 (0.00-1.38)	.08
Ehresmann et al,[24] 1977	0/215	0/213	0.0		
Hess and Keil-Kuri,[29] 1975	5/92	6/84	1.9	0.76 (0.24-2.40)	.64
Hess and Keil-Kuri,[29] 1975	4/42	2/40	0.9	1.90 (0.37-9.83)	.44
Zekert,[35] 1975	1/148	3/150	0.5	0.34 (0.04-3.21)	.34
Total	251/2823	269/2446		0.88 (0.76-1.04)	.13



JAMA. 2009;301(18):1909–1919

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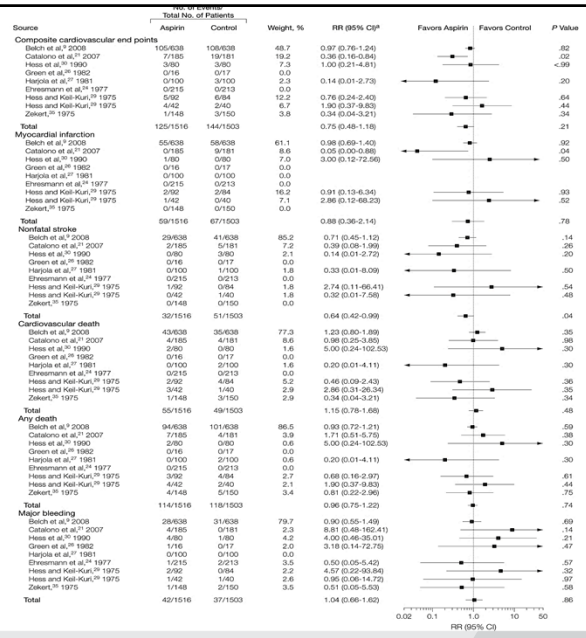
Aspirin Monotherapy



JAMA. 2009;301(18):1909–1919

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Monotherapy with P2Y12 Inhibitors in Chronic PAD
CAPRIE Trial

- N: 19,185 patients with ASO (ischemic stroke, MI, sympt PAD)
- Study Design: Randomized aspirin (325mg) vs clopidogrel
- Study Duration: 1.91 years

- Outcome: composite MACCE
- Significant reduction with clopidogrel (5.3% *vs* 5.8%)RR: 0.91 [95% CI: 0.84 to 0.997].

- Post-hoc analysis including 6,452 patients with PAD:
- More risk reduction with clopidogrel (3.7%) vs ASA (4.9%), RR: 0.76 [95% CI: 0.64 to 0.91].

Vasc Med. 1998;3(3):257-60.

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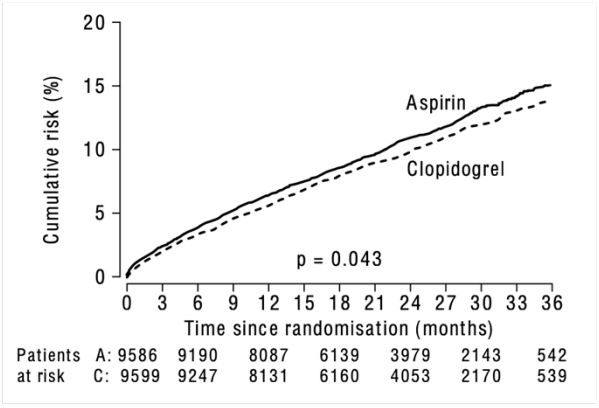
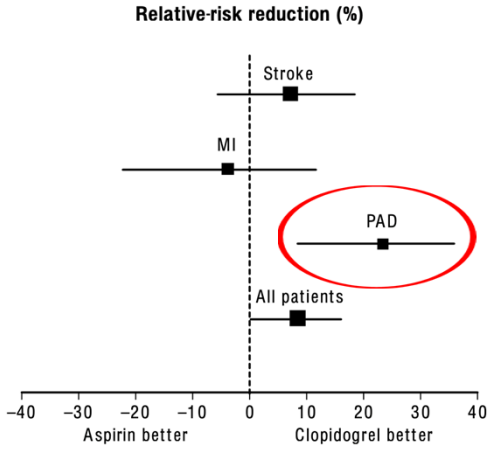
Monotherapy with P2Y12 Inhibitors in Chronic PAD
CAPRIE Trial





Vasc Med. 1998;3(3):257-60.

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Examining Use of Ticagrelor in Peripheral Artery Disease *(EUCLID) trial*

- N: 13,885 with PAD
- Study design: Clopidogrel vs ticagrelor
- Follow up: 2.5 years

- Primary Outcome: MACCE:
- No difference: (10.8 *vs* 10.6%; HR: 1.02 [95% CI: 0.92 to 1.13]).

- ALI, limb revascularization, and major bleeding
- Similar

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

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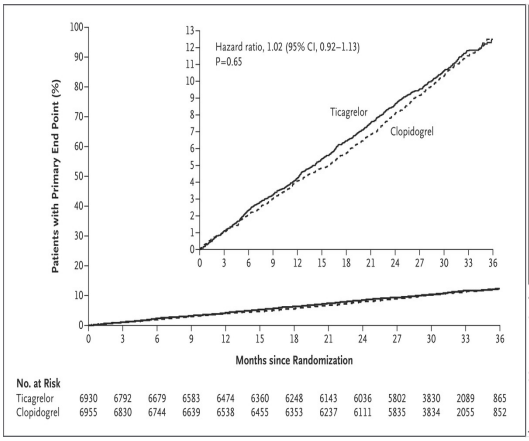
Examining Use of Ticagrelor in Peripheral Artery Disease *(EUCLID) trial*



Outcome	Ticagrelor (N=6910)	Clopidogrel (N=6932)	Hazard Ratio (95% CI)	P Value
	no. (%)			
Primary safety outcome: TIMI major bleeding	113 (1.6)	109 (1.6)	1.10 (0.84–1.43)	0.49
Intracranial bleeding	34 (0.5)	34 (0.5)	1.06 (0.66–1.70)	0.82
Fatal bleeding	10 (0.1)	20 (0.3)	0.53 (0.25–1.13)	0.10
TIMI minor bleeding	84 (1.2)	67 (1.0)	1.32 (0.96–1.83)	0.09
Adverse events leading to discontinuation†	1063 (15.4)	766 (11.1)		
Dyspnea	330 (4.8)	52 (0.8)		<0.001
Any bleeding‡	168 (2.4)	112 (1.6)		<0.001

* TIMI denotes Thrombolysis in Myocardial Infarction.
† A total of 30.1% of patients in the ticagrelor group and 25.9% in the clopidogrel group prematurely discontinued the assigned study drug during follow-up. Included in this group were patients who discontinued the study drug because of adverse events, those in whom the primary end point occurred, and those who died.
‡ This category includes adverse events leading to the permanent discontinuation of a study drug because of a bleeding event that was documented by the investigator on a case-report form; these events included unadjudicated minimal bleeding.

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

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Single Antiplatelet Therapy/Stable PAD : Summary

Ample evidence to use single antiplatelet therapy

Good evidence to support clopidogrel over aspirin

No difference in outcome between clopidogrel and ticagrelor

Skeik N et al. *Angiology*, in press

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Dual Antiplatelet Therapy in Stable PAD
Clopidogrel+ASA vs ASA alone *CHARISMA Trial*

- N: 15,603 pts with established cardiovascular disease or multiple ASO risk factors
- Study design: ASA+clopidogrel vs ASA alone
- Follow up: 2.5 years

- Primary Outcome: MACCE, no difference
- Entire group: (6.8% for ASA+clopidogrel *vs* 7.3% for ASA; RR: 0.93 [95% CI: 0.83 to 1.05])
- PAD subgroup: (7.6% for ASA+clopidogrel *vs* 8.9% for ASA; HR: 0.85 [95% CI: 0.66 to 1.08]).

- Risk of moderate bleed: almost 2 folds in ASA+clopidogrel *vs* ASA

N Engl J Med 2006; 354:1706-1717

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Dual Antiplatelet Therapy/ Stable PAD
Clopidogrel+ASA vs ASA alone *CHARISMA Trial*

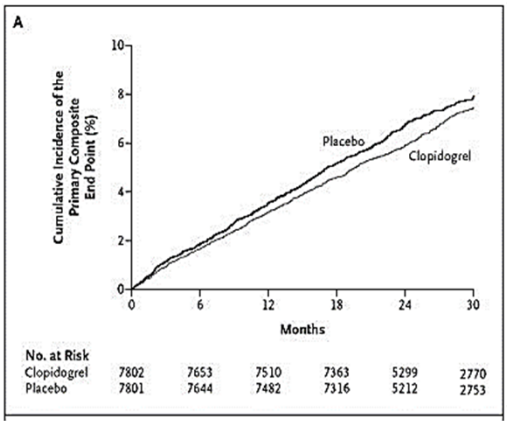

Table 4. Composite and Individual Primary and Secondary End Points.

End Point	Clopidogrel plus Aspirin (N=7802)	Placebo plus Aspirin (N=7801)	Relative Risk (95% CI)*	P Value
	no. (%)			
Efficacy end points				
Primary efficacy end point	534 (6.8)	573 (7.3)	0.93 (0.83–1.05)	0.22
Death from any cause	371 (4.8)	374 (4.8)	0.99 (0.86–1.14)	0.90
Death from cardiovascular causes	238 (3.1)	229 (2.9)	1.04 (0.87–1.25)	0.68
Myocardial infarction (nonfatal)	146 (1.9)	155 (2.0)	0.94 (0.75–1.18)	0.59
Ischemic stroke (nonfatal)	132 (1.7)	163 (2.1)	0.81 (0.64–1.02)	0.07
Stroke (nonfatal)	150 (1.9)	189 (2.4)	0.79 (0.64–0.98)	0.03
Secondary efficacy end point†	1301 (16.7)	1395 (17.9)	0.92 (0.86–0.995)	0.04
Hospitalization for unstable angina, transient ischemic attack, or revascularization	866 (11.1)	957 (12.3)	0.90 (0.82–0.98)	0.02
Safety end points				
Severe bleeding	130 (1.7)	104 (1.3)	1.25 (0.97–1.61)	0.09
Fatal bleeding	26 (0.3)	17 (0.2)	1.53 (0.83–2.82)	0.17
Primary intracranial hemorrhage	26 (0.3)	27 (0.3)	0.96 (0.56–1.65)	0.89
Moderate bleeding	164 (2.1)	101 (1.3)	1.62 (1.27–2.08)	<0.001

* CI denotes confidence interval.
† The secondary efficacy end point was the first occurrence of myocardial infarction, stroke, death from cardiovascular causes, or hospitalization for unstable angina, a transient ischemic attack, or a revascularization procedure (coronary, cerebral, or peripheral).

N Engl J Med 2006; 354:1706-1717

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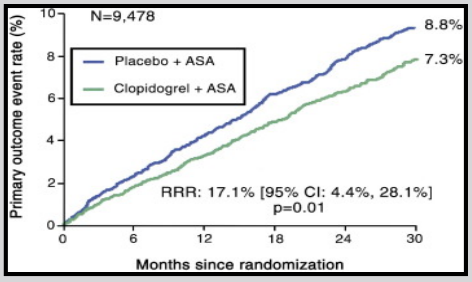
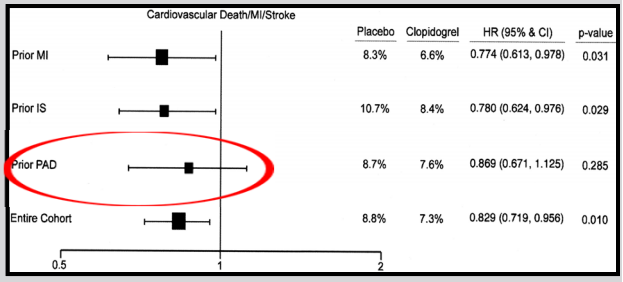
Subanalysis in High Risk Patients
CHARISMA Trial

- N: 9,478 with high risk: history of Stroke, MI or PAD





- MACCE: Lower in DAPT (7.3%) *vs* ASA (8.8%); (p=0.01).
- Not in patients with PAD.

J Am Coll Cardiol. 2007;49(19):1982–1988.

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The Platelet Inhibition and Patient Outcome
PLATO Trial

- N: 18,624 pts with ACS
- Study design: ticagrelor+ASA *vs* clopidogrel+ ASA
- Follow up: 1 year

- Primary Outcome: MACCE
- Entire group: Significantly lower with ticagrelor+ASA
- (9.8 vs 11.7%, respectively; HR: 0.84 [95% CI: 0.77 to 0.92])

- Primary Safety Outcome: major bleed
- Similar (11.6% for ticagrelor and 11.2% for clopidogrel; P=0.43)

N Engl J Med 2009; 361:1045-1057

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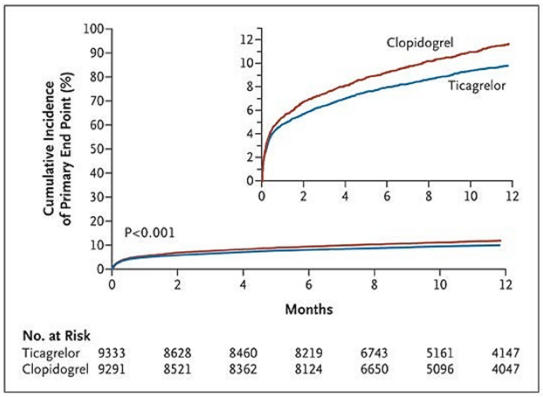
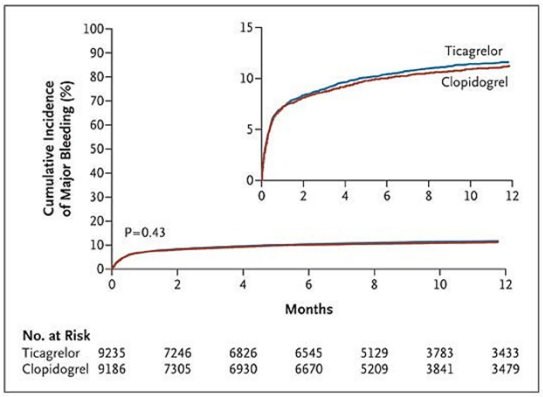
The Platelet Inhibition and Patient Outcome
PLATO Trial





N Engl J Med 2009; 361:1045-1057

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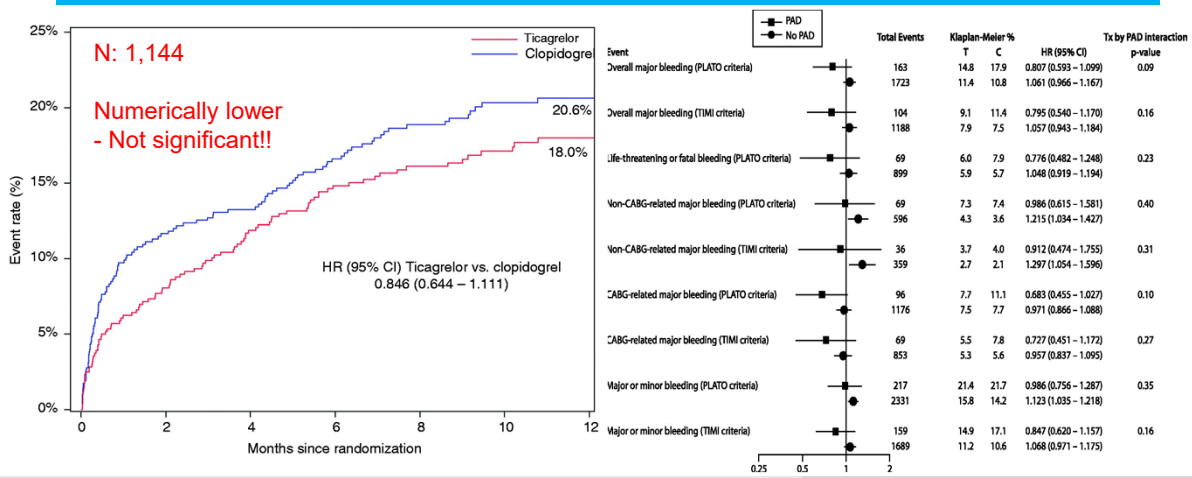
The Platelet Inhibition and Patient Outcome
PAD Sub-group PLATO Trial



Eur J Prev Cardiol. 2015;22(6):734–742.

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The *PEGASUS-TIMI 54* Trial

- N: 21,162 pts with previous MI 1-3 years
- Study design: ticagrelor 90 or 60 mg+ASA *vs* ASA
- Follow up: 1 year

- Primary Outcome: MACCE
- Entire group: Significantly lower with ticagrelor (90 and 60mg+ASA)
- (0.85 [95% CI: 0.75 to 0.96]) and (0.84 [95% CI: 0.74 to 0.95])

- Primary Safety Outcome: TIMI major bleed
- Higher: (2.60% with 90 mg and 2.30% with 60 mg) than with ASA (1.06%) (P<0.001)

N Engl J Med 2015; 372:1791-1800

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The *PEGASUS-TIMI 54* Trial

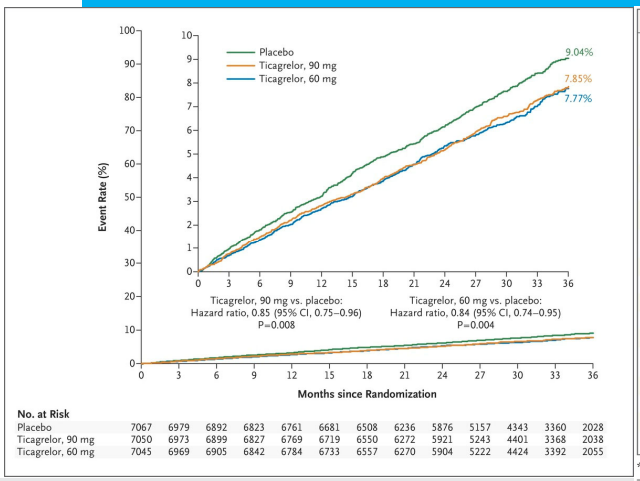

Table 3. Safety End Points as 3-Year Kaplan–Meier Estimates.*

End Point	Ticagrelor, 90 mg (N=6988)	Ticagrelor, 60 mg (N=6958)	Placebo (N=6996)	Ticagrelor, 90 mg vs. Placebo		Ticagrelor, 60 mg vs. Placebo	
				Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
	number (percent)						
Bleeding							
TIMI major bleeding	127 (2.60)	115 (2.30)	54 (1.06)	2.69 (1.96–3.70)	<0.001	2.32 (1.68–3.21)	<0.001
TIMI minor bleeding	66 (1.31)	55 (1.18)	18 (0.36)	4.15 (2.47–7.00)	<0.001	3.31 (1.94–5.63)	<0.001
Bleeding requiring transfusion	122 (2.43)	105 (2.09)	37 (0.72)	3.75 (2.59–5.42)	<0.001	3.08 (2.12–4.48)	<0.001
Bleeding leading to study-drug discontinuation	453 (7.81)	354 (6.15)	86 (1.50)	5.79 (4.60–7.29)	<0.001	4.40 (3.48–5.57)	<0.001
Fatal bleeding or nonfatal intracranial hemorrhage	32 (0.63)	33 (0.71)	30 (0.60)	1.22 (0.74–2.01)	0.43	1.20 (0.73–1.97)	0.47
Intracranial hemorrhage	29 (0.56)	28 (0.61)	23 (0.47)	1.44 (0.83–2.49)	0.19	1.33 (0.77–2.31)	0.31
Hemorrhagic stroke	4 (0.07)	8 (0.19)	9 (0.19)	0.51 (0.16–1.64)	0.26	0.97 (0.37–2.51)	0.94
Fatal bleeding	6 (0.11)	11 (0.25)	12 (0.26)	0.58 (0.22–1.54)	0.27	1.00 (0.44–2.27)	1.00
Other adverse event							
Dyspnea	1205 (18.93)	987 (15.84)	383 (6.38)	3.55 (3.16–3.98)	<0.001	2.81 (2.50–3.17)	<0.001
Event leading to study-drug discontinuation	430 (6.50)	297 (4.55)	51 (0.79)	8.89 (6.65–11.88)	<0.001	6.06 (4.50–8.15)	<0.001
Serious adverse event	22 (0.41)	23 (0.45)	9 (0.15)	2.68 (1.24–5.83)	0.01	2.70 (1.25–5.84)	0.01
Renal event	166 (3.30)	173 (3.43)	161 (2.89)	1.17 (0.94–1.46)	0.15	1.17 (0.94–1.45)	0.15
Bradyarrhythmia	107 (2.04)	121 (2.32)	106 (1.98)	1.15 (0.88–1.50)	0.31	1.24 (0.96–1.61)	0.10
Gout	115 (2.28)	101 (1.97)	74 (1.51)	1.77 (1.32–2.37)	<0.001	1.48 (1.10–2.00)	0.01

* TIMI denotes Thrombolysis in Myocardial Infarction.

N Engl J Med 2015; 372:1791-1800

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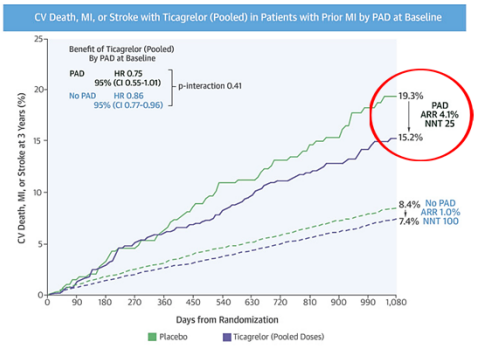
The PEGASUS-TIMI 54 Trial
PAD Subgroup

CENTRAL ILLUSTRATION: Ticagrelor in Patients With PAD and Prior MI: 3-Year Results



Bonaca, M.P. et al. J Am Coll Cardiol. 2016;67(23):2719-28.

TABLE 2 Efficacy and Safety of Ticagrelor in Patients With PAD

	Placebo n, %	Ticagrelor 60 mg n, %	Ticagrelor 90 mg n, %	Ticagrelor 60 mg HR (95% CI) p Value	Ticagrelor 90 mg HR (95% CI) p Value
Efficacy outcomes, N	404	368	371		
CV death, MI, stroke	71, 19.3	47, 14.1	54, 16.3	0.69 (0.47–0.99) p = 0.045	0.81 (0.57–1.15) p = 0.24
CV death	34, 9.6	15, 4.2	26, 7.9	0.47 (0.25–0.86) p = 0.014	0.83 (0.50–1.38) p = 0.46
All-cause mortality	51, 14.0	25, 8.2	41, 11.7	0.52 (0.32–0.84) p = 0.0074	0.88 (0.58–1.32) p = 0.53
Stroke	17, 4.0	8, 2.9	10, 3.1	0.49 (0.21–1.14) p = 0.097	0.63 (0.29–1.38) p = 0.25
Ischemic stroke	16, 3.7	8, 2.9	7, 2.0	0.52 (0.22–1.22) p = 0.13	0.47 (0.19–1.14) p = 0.095
Safety outcomes, N	399	363	368		
TIMI major	4, 1.6	4, 1.6	5, 1.8	1.18 (0.29–4.70) p = 0.82	1.46 (0.39–5.43) p = 0.57
TIMI major or minor	6, 2.2	7, 3.2	8, 3.1	1.36 (0.46–4.05) p = 0.58	1.57 (0.54–4.53) p = 0.40
ICH or fatal bleeding	3, 1.3	0, –	1, 0.4	–	0.39 (0.04–3.75) p = 0.42

Values are n, 3-year Kaplan-Meier (%), unless otherwise indicated.
CI = confidence interval; CV = cardiovascular; HR = hazard ratio; ICH = intracranial hemorrhage; MI = myocardial infarction; TIMI = Thrombosis in Myocardial Infarction.

J Am Coll Cardiol. 2016;67(23):2719–2728.

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Dual Antiplatelet Therapy/Stable PAD : Summary

Some evidence to support DAPT over SAP

More bleeding!!

May reserve for pts with high thrombotic and low bleeding risk

Skeik N et al. *Angiology*, in press

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Protease-Activated Receptor 1 Antagonist in Stable PAD
TRA2°P-TIMI 50 trial

- N: 26,449 pts with previous MI, ischemic stroke or PAD
- Study design: vorapaxar *vs* placebo as add on therapy to other antiplatelet therapy
- Follow up: 3 years

- Primary Outcome: MACCE
- Entire group: Significantly lower with vorapaxar
- (9.3 *vs* 10.5%; HR: 0.87 [95% CI: 0.80 to 0.94; P=0.001])

- Primary Safety Outcome: moderate or severe bleeding
- Higher with vorapaxar: 4.2 vs 2.5% (HR, 1.66; 95% CI, 1.43 to 1.93; P<0.001)
- Higher ICH …

N Engl J Med 2012; 366:1404-1413

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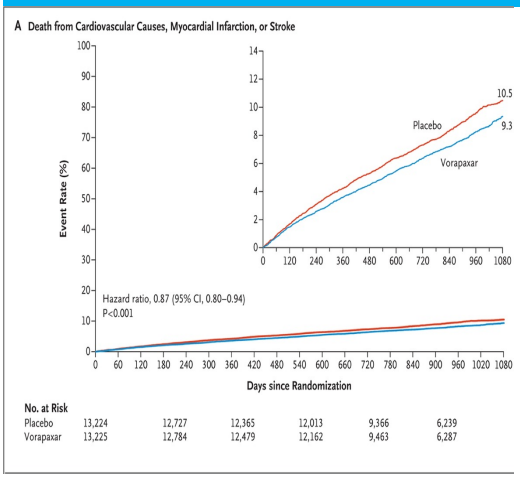
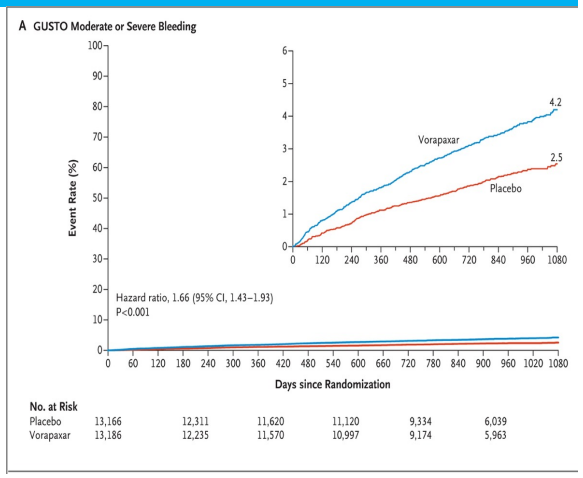
Protease-Activated Receptor 1 Antagonist
TRA2°P-TIMI 50 trial





N Engl J Med 2012; 366:1404-1413

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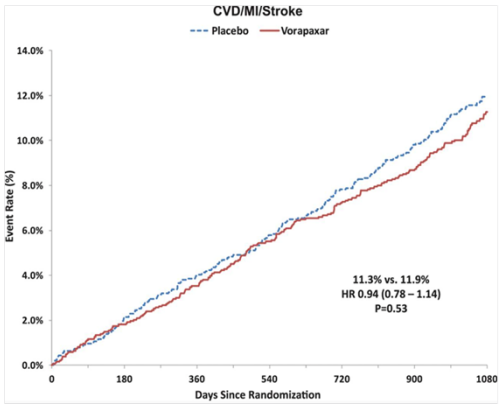
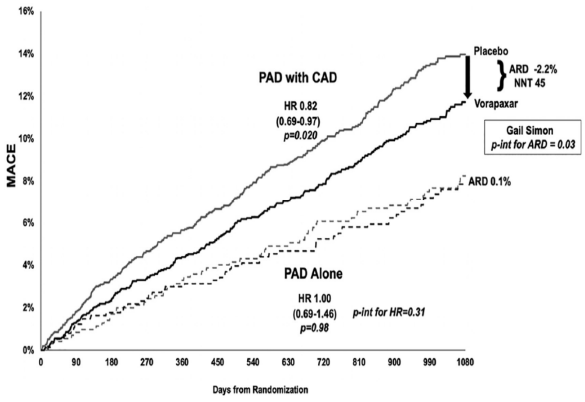
Subanalyses in Patients with PAD
TRA2°P-TIMI 50 trial





Circulation. 2013;127(14):1522–1529
Vasc Med. 2020;25(2):124-132

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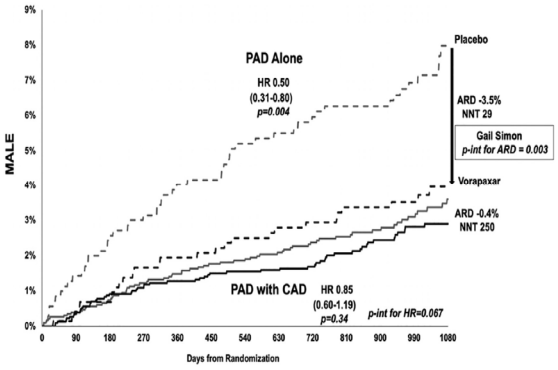
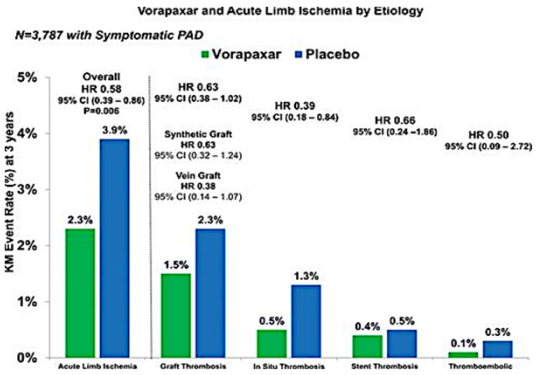
Subanalyses in Patients with PAD
TRA2°P-TIMI 50 trial

Moderate or severe bleeding: 1.5 times higher in the overall trial and in the PAD subgroups, but fatal bleeding was similar.





Circulation. 2013;127(14):1522–1529
Vasc Med. 2020;25(2):124-132.

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Anticoagulation Therapy in Stable PAD
The Warfarin Antiplatelet Vascular Evaluation: *WAVE Trial*

- N: 2,161 pts with symptomatic PAD
- Study design: warfarin+ASA *vs* ASA alone
- Follow up: 3 years

- Primary Outcome: MACCE
- No difference: (12.2 vs 13.3; RR: 0.92 [95% CI: 0.73 to 1.16])

- Safety Outcome: Life-threatening bleeding: was increased!
- Increased: (4.0 vs 1.2%; RR: 3.41 [95% CI: 1.84 to 6.35]).

N Engl J Med 2007;357:217-27.

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Anticoagulation Therapy/Stable PAD
The Warfarin Antiplatelet Vascular Evaluation: *WAVE Trial*

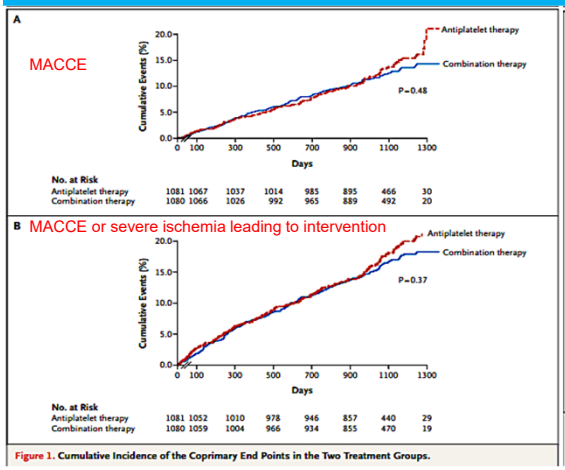

Figure 1. Cumulative Incidence of the Coprimary End Points in the Two Treatment Groups.

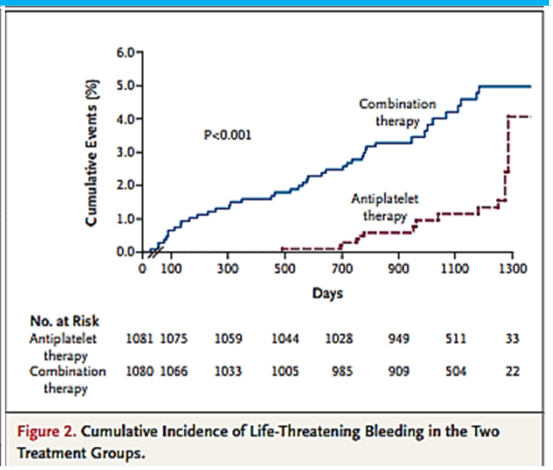

Figure 2. Cumulative Incidence of Life-Threatening Bleeding in the Two Treatment Groups.

N Engl J Med 2007;357:217-27.

Rivaroxaban 2.5 mg BID and ASA: *COMPASS Trial*

- N: 27,395 pts with stable CAD +/- PAD (27% had PAD)
- Study design: Rivaroxaban 2.5 mg BID+ASA *vs* rivaroxaban 5 mg bid *vs* ASA alone
- Follow up: 23 months, *stopped early due to benefit*

- Primary Outcome: MACCE
- Significant reduction: (4.1 vs 5.4%, respectively; HR: 0.76 [95% CI: 0.66 to 0.86]).

- Safety Outcome: Major bleeding
- Increased: (3.1 vs 1.9% for aspirin; HR: 1.61 [95% CI: 1.12 to 2.31])

N Engl J Med 2017; 377:1319-1330

Rivaroxaban 2.5 mg BID and ASA: *COMPASS Trial*

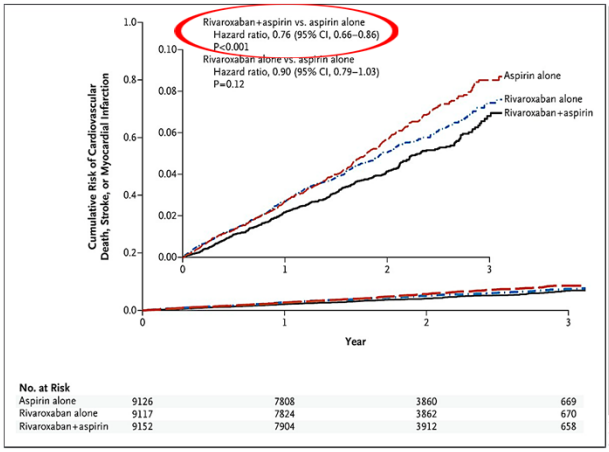

Table 3. Bleeding Events and Net Clinical Benefit.*

Outcome	Rivaroxaban plus Aspirin (N=9152)	Rivaroxaban Alone (N=9117)	Aspirin Alone (N=9126)	Rivaroxaban plus Aspirin vs. Aspirin Alone		Rivaroxaban Alone vs. Aspirin Alone	
				Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
	number (percent)						
Major and minor bleeding							
Major bleeding	288 (3.1)	255 (2.8)	170 (1.9)	1.70 (1.40–2.05)	<0.001	1.51 (1.25–1.84)	<0.001
Fatal bleeding†	15 (0.2)	14 (0.2)	10 (0.1)	1.49 (0.67–3.33)	0.32	1.40 (0.62–3.15)	0.41
Nonfatal symptomatic ICH†	21 (0.2)	32 (0.4)	19 (0.2)	1.10 (0.59–2.04)	0.77	1.69 (0.96–2.98)	0.07
Nonfatal, non-ICH, symptomatic bleeding into critical organ†	42 (0.5)	45 (0.5)	29 (0.3)	1.43 (0.89–2.29)	0.14	1.57 (0.98–2.50)	0.06
Other major bleeding†	210 (2.3)	164 (1.8)	112 (1.2)	1.88 (1.49–2.36)	<0.001	1.47 (1.16–1.87)	0.001
Fatal bleeding or symptomatic ICH	36 (0.4)	46 (0.5)	29 (0.3)	1.23 (0.76–2.01)	0.40	1.59 (1.00–2.53)	0.05
Fatal bleeding or symptomatic bleeding into critical organ	78 (0.9)	91 (1.0)	58 (0.6)	1.34 (0.95–1.88)	0.09	1.58 (1.13–2.19)	0.006
Major bleeding according to ISTH criteria	206 (2.3)	175 (1.9)	116 (1.3)	1.78 (1.41–2.23)	<0.001	1.52 (1.20–1.92)	<0.001
Transfusion within 48 hr after bleeding	87 (1.0)	66 (0.7)	44 (0.5)	1.97 (1.37–2.83)	<0.001	1.50 (1.03–2.20)	0.03
Minor bleeding	838 (9.2)	741 (8.1)	503 (5.5)	1.70 (1.52–1.90)	<0.001	1.50 (1.34–1.68)	<0.001
Site of major bleeding							
Gastrointestinal	140 (1.5)	91 (1.0)	65 (0.7)	2.15 (1.60–2.89)	<0.001	1.40 (1.02–1.93)	0.04
Intracranial	28 (0.3)	43 (0.5)	24 (0.3)	1.16 (0.67–2.00)	0.60	1.80 (1.09–2.96)	0.02
Skin or injection site	28 (0.3)	28 (0.3)	12 (0.1)	2.31 (1.18–4.54)	0.01	2.34 (1.19–4.60)	0.01
Urinary	13 (0.1)	30 (0.3)	21 (0.2)	0.61 (0.31–1.23)	0.16	1.43 (0.82–2.50)	0.20
Net-clinical-benefit outcome: CV death, stroke, myocardial infarction, fatal bleeding, or symptomatic bleeding into critical organ	431 (4.7)	504 (5.5)	534 (5.9)	0.80 (0.70–0.91)	<0.001	0.94 (0.84–1.07)	0.36

* ICH denotes intracranial hemorrhage, and ISTH International Society on Thrombosis and Haemostasis.
† If a participant had more than one event of major bleeding, only the most serious bleeding event was counted in these analyses.

N Engl J Med 2017; 377:1319-1330

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Rivaroxaban 2.5 mg BID and ASA: *COMPASS Trial*
PAD Subgroup (N: 7470)

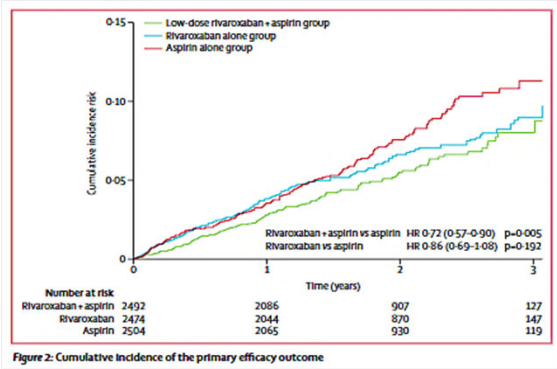

Figure 2: Cumulative incidence of the primary efficacy outcome

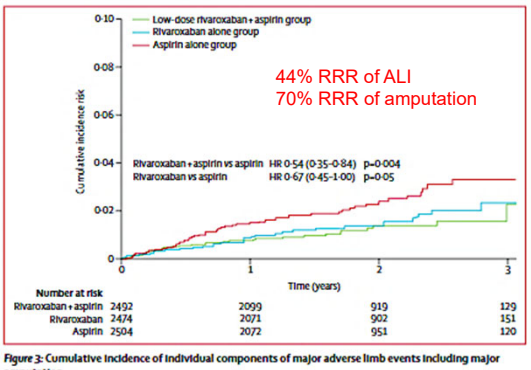

Figure 3: Cumulative incidence of individual components of major adverse limb events including major amputation

Lancet. 2018;391(10117):219-229.

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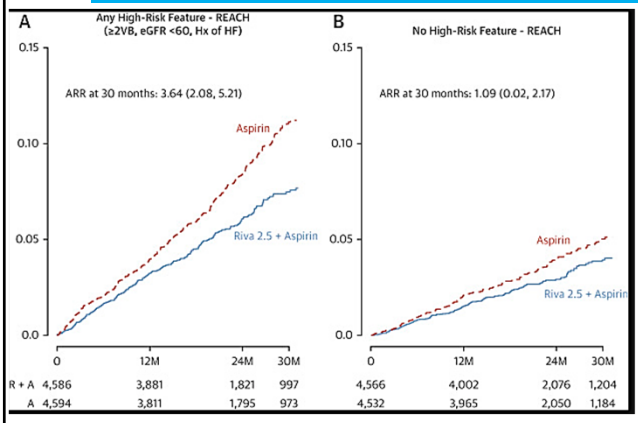
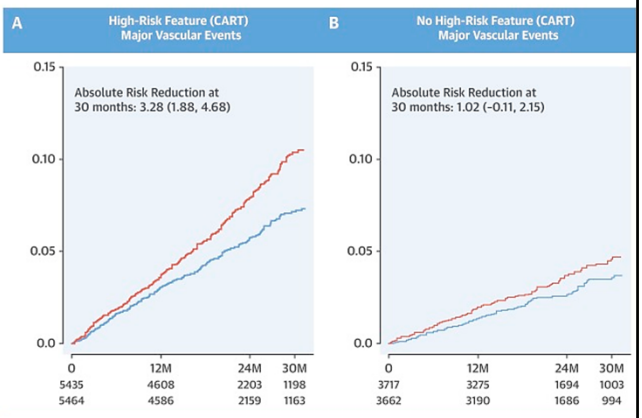
Rivaroxaban 2.5 mg BID and ASA: *COMPASS Trial*
Post-hoc Analysis-Risk Stratification (REACH and CART Scores)



REACH Risk Factors: Poly-vascular, eGFR<60, HF



CART Risk Factors: Poly-vascular, HF, DM

https://doi.org/10.1016/j.jacc.2019.02.079

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Anticoagulation Therapy/Stable PAD : Summary

No strong evidence to support anticoagulation with warfarin

Rivaroxaban 2.5 mg BID+ASA (75-100mg) should be considered in high risk patients (polyvascular, DM, CHF, CKD,) and low risk for bleeding

Vorapaxar may be considered as an alternative based on risk/benefit

Skeik N et al. *Angiology*, in press

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Singe Antiplatelet Therapy Following Open Revascularization
The Antithrombotic Trialists Collaboration: *ATC Meta-analysis*

- Study design: meta-analysis of 287 studies
- Comparisons of antiplatelet therapy versus control: 135,000 pts
- Comparisons of different antiplatelet regimens:7,000 pts
- Follow up: ~ 2 years

- N: 2,497 undergoing bypass grafting
- Primary Outcome: MACCE
- Insignificantly reduced: by 22% by antiplatelet agents (ASA or other agents)

BMJ 2002;324:71

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Singe Antiplatelet Therapy Following Open Revascularization
The Antithrombotic Trialists Collaboration: *ATC Meta-analysis*

	No of trial with data	No (%) of vascular events: Allocated antiplatelet	Adjusted control	Observed Expected	Variance	Odds ratio (CI) Antiplatelet control	% Odds reduction (SE)
Peripheral arterial disease:							
Intermittent claudication	26	201/3123 (6.4)	249/3140 (7.9)	-22.3	86.6		23 (9)
Peripheral grafting	12	67/1249 (5.4)	81/1248 (6.5)	-7.3	29.1		22 (16)
Peripheral angioplasty	4	12/472 (2.5)	17/474 (3.6)	-2.0	5.8		29 (35)
Subtotal	42	280/4844 (5.8)	347/4862 (7.1)	-31.6	121.5		23 (8)

BMJ 2002;324:71

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Antiplatelet Agents for Preventing Thrombosis after Peripheral Arterial Bypass Surgery: *Meta-analysis*

- Study design: meta-analysis of 16 studies with 5683 pts after bypass grafting
- Different antiplatelet regimens including single or dual
- Follow up: 1 year

- Outcome: Graft patency
- Improved with ASA +/- dipyridamole vs placebo :
- OR:0.42 [95% CI: 0.22 to 0.83]
- The benefit of ASA was mostly seen in prosthetic grafts (OR: 0.19 [95% CI: 0.10 to 0.36]) rather than vein grafts (OR: 0.60 [95% CI: 0.48 to 0.99]).

Cochrane Database Syst Rev. 2015 Feb; 2015(2): CD000535.

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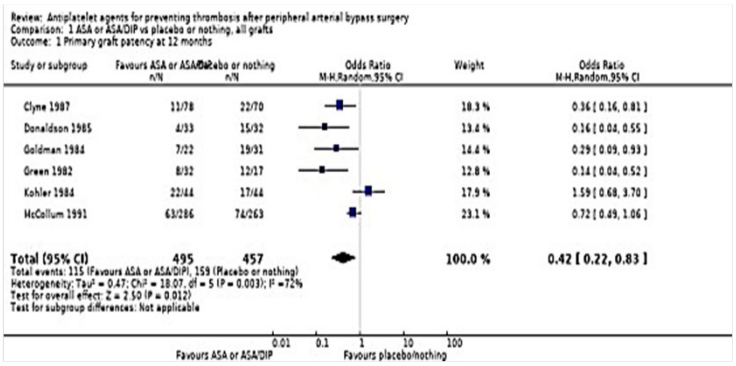
Antiplatelet Agents for Preventing Thrombosis after Peripheral Arterial Bypass Surgery: *Meta-analysis*



Cochrane Database Syst Rev. 2015 Feb; 2015(2): CD000535.

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DAPT after Peripheral Arterial Bypass Surgery: Clopidogrel and ASA in Bypass Surgery for PAD *CASPAR Trial*

- N: 851 pts undergoing *below-knee bypass grafting*
- Study design: CRT
- Study drugs: Clopidogrel+ASA *vs* ASA

- Outcome: composite rate of graft occlusion, revascularization, amputation, or death
- No difference: (35.1% for DAPT vs 35.4% for ASA; HR: 0.98 [95% CI: 0.78 to 1.23]).

- Sub-analysis in pts receiving prosthetic graft:
- Improved with DAPT: (HR: 0.65 [95% CI: 0.45 to 0.95])
- increased bleeding (16.7 vs 7.1%, respectively; p<0.001) (not severe bleeding..)

Journal of Vascular Surgery Volume 52, Issue 4, October 2010, Pages 825-833.e2

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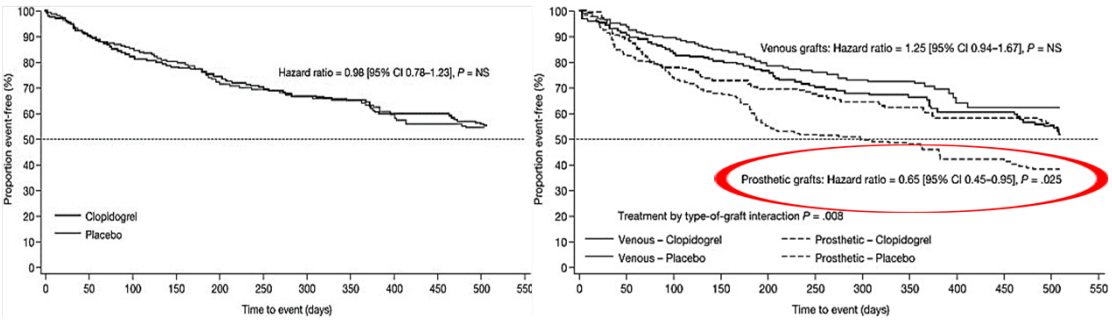
DAPT after Peripheral Arterial Bypass Surgery: Clopidogrel and ASA in Bypass Surgery for PAD *CASPAR Trial*



Primary outcome: graft occlusion/revascularization/replacement, amputation above ankle, death

Journal of Vascular Surgery Volume 52, Issue 4, October 2010, Pages 825-833.e2

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Anticoagulation after Open Revascularization: Dutch Bypass Oral anticoagulants or Aspirin *BOA Trial*

- N: 2,690 pts undergoing infrainguinal bypass
- Study design: CRT
- Study Drugs: high intensity anticoagulation with phenprocoumon or acenocoumarol (goal INR: 3.0 to 4.5) vs ASA.

- Outcome: Graft occlusion
- Similar: 13.5% for anticoagulation vs 14.2% for ASA; HR: 0.95 [95% CI: 0.82 to 1.11]

- Subgroup analyses: vein graft or prosthetic graft:
- Better vein graft patency: (HR: 0.69 [95% CI: 0.54 to 0.88])
- Worse prosthetic graft patency (HR 1.26 [95% CI: 1.03-1.55])

- Major bleeding, higher with anticoagulation (8.1 vs 4.2%, respectively; HR: 1.96 [95% CI: 1.42 to 2.71]).

Lancet. 2000(9201);355:346–351.
J Vasc Surg. 1998;28(3):446-457.

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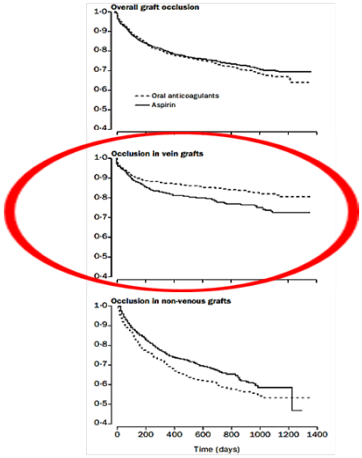
Anticoagulation after Open Revascularization: Dutch Bypass Oral anticoagulants or Aspirin *BOA Trial*



Subgroup	Oral anti-coagulants	Aspirin	Hazard ratio (95% CI)
Femoropopliteal grafts (n=2119)	233	236	0·97 (0·81–1·16)
Femorocrural/-pedal grafts (n=531)	75	86	0·95 (0·70–1·30
Vein grafts (n=156)	112	155	0·69 (0·54–0·88)
Non-venous grafts (n=1104)	196	167	1·26 (1·03–1·55)
Vein femoropopliteal grafts (n=1140)	74	97	0·69 (0·51–0·94)
Vein femorocrural/-pedal grafts (n=406)	38	58	0·73 (0·48–1·10)
Non-venus femoropopliteal grafts (n=979)	159	139	1·23 (0·98–1·55)
Non-venous femorocrural/-pedal grafts (n=125)	37	28	1·31 (0·80–2·14)

Table 5: **Subgroup analysis of occlusion**

Lancet. 2000(9201);355:346–351.
J Vasc Surg. 1998;28(3):446-457.

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Anticoagulation after Open Revascularization: Small Study with High-Risk Patients: *TP Sarac et al*

- N: 56 pts undergoing infrainguinal bypass who are high risk for graft failure
- Study design: randomized prospective trial for 3 years.
- Study Drugs: warfarin + ASA vs ASA.

- Outcome: Graft patency, limb salvage
- Improved: (74 *vs* 51% [p = 0.04] and 81 *vs* 31% [p = 0.02], respectively)

- Wound hematoma:
- Worse: (31 *vs* 4%, respectively; p=0.004).

J Vasc Surg 1998 Sep;28(3):446-57.

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Anticoagulation after Open/Endo Revascularization: *VOYAGER PAD Trial*

- N: 6,564 pts undergoing open or endo revasc
- Study design: CRT f/u for 3 years
- Study Drugs: rivaroxaban 2.5 mg bid + ASA vs ASA.

- Outcome: ALI, major amputation, MI, ischemic stroke, or CV death
- Improved: 17.3% and 19.9%, respectively (HR: 0.85 [95% CI: 0.76 to 0.96])

- TIMI- Major bleeding:
- Not different: 2.65% and 1.87%; HR,1.43; 95% CI, 0.97 to 2.10; P=0.07
- ISTH Major bleed:
- Increased: 5.94% and 4.06%; HR, 1.42; 95% CI, 1.10 to 1.84; P=0.007

N Engl J Med 2020; 382:1994-2004

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Anticoagulation after Open/Endo Revascularization: *VOYAGER PAD Trial*

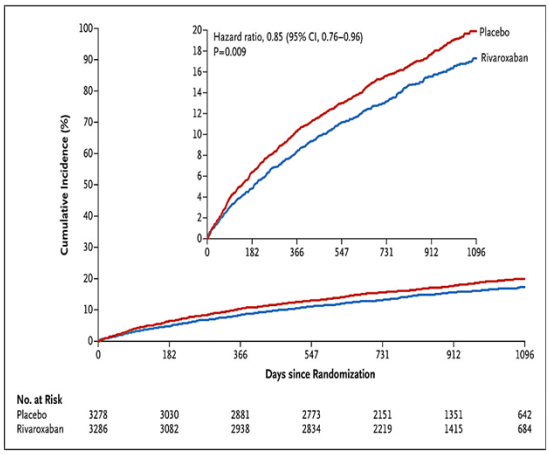

Table 3. Safety Outcomes.*

Outcome	Rivaroxaban (N=3256)		Placebo (N=3248)		Hazard Ratio (95% CI)	P Value
	Patients with Event	K–M Estimate at 3 Yr	Patients with Event	K-M Estimate at 3 Yr		
	no. (%)	%	*no. (%)*	%		
Principal safety outcome: TIMI major bleeding	62 (1.90)	2.65	44 (1.35)	1.87	1.43 (0.97–2.10)	0.07
Intracranial hemorrhage	13 (0.40)	0.60	17 (0.52)	0.90	0.78 (0.38–1.61)	
Fatal bleeding	6 (0.18)	0.21	6 (0.18)	0.21	1.02 (0.33–3.15)	
Intracranial or fatal bleeding	17 (0.52)	0.74	19 (0.58)	0.97	0.91 (0.47–1.76)	
Secondary safety outcomes						
ISTH major bleeding	140 (4.30)	5.94	100 (3.08)	4.06	1.42 (1.10–1.84)	0.007
BARC major bleeding†	93 (2.86)	3.86	73 (2.25)	2.92	1.29 (0.95–1.76)	0.10

* Safety analyses included all patients who underwent randomization and had received at least one dose of trial medication. ISTH denotes International Society on Thrombosis and Haemostasis, and TIMI Thrombolysis in Myocardial Infarction.
† Bleeding Academic Research Consortium (BARC) major bleeding is defined as grade 3b or higher.

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Anticoagulation after Open/Endo Revascularization: *VOYAGER PAD Trial*

Table 2. Primary and Secondary Efficacy Outcomes.*

Outcome	Rivaroxaban (N=3286)		Placebo (N=3278)		Hazard Ratio (95% CI)	P Value
	Patients with Event	K–M Estimate at 3 Yr	Patients with Event	K–M Estimate at 3 Yr		
	no. (%)	%	*no. (%)*	%		
Primary efficacy outcome: acute limb ischemia, major amputation for vascular causes, myocardial infarction, ischemic stroke, or death from cardiovascular causes	508 (15.5)	17.3	584 (17.8)	19.9	0.85 (0.76–0.96)	0.009
Acute limb ischemia	155 (4.7)	5.2	227 (6.9)	7.8	0.67 (0.55–0.82)	
Major amputation for vascular causes	103 (3.1)	3.4	115 (3.5)	3.9	0.89 (0.68–1.16)	
Myocardial infarction	131 (4.0)	4.6	148 (4.5)	5.2	0.88 (0.70–1.12)	
Ischemic stroke	71 (2.2)	2.7	82 (2.5)	3.0	0.87 (0.63–1.19)	
Death from cardiovascular causes	199 (6.1)	7.1	174 (5.3)	6.4	1.14 (0.93–1.40)	
Secondary efficacy outcomes						
Acute limb ischemia, major amputation for a vascular cause, myocardial infarction, ischemic stroke, or death from coronary heart disease	433 (13.2)	14.7	528 (16.1)	18.2	0.80 (0.71–0.91)	<0.001
Unplanned index-limb revascularization for recurrent limb ischemia	584 (17.8)	20.0	655 (20.0)	22.5	0.88 (0.79–0.99)	0.03
Hospitalization for coronary or peripheral event of a thrombotic nature	262 (8.0)	8.7	356 (10.9)	12.1	0.72 (0.62–0.85)	<0.001
Acute limb ischemia, major amputation for a vascular cause, myocardial infarction, ischemic stroke, or death from any cause	614 (18.7)	20.6	679 (20.7)	23.2	0.89 (0.79–0.99)	0.03
Acute limb ischemia, major amputation for a vascular cause, myocardial infarction, stroke from any cause, or death from any cause	514 (15.6)	17.5	588 (17.9)	20.1	0.86 (0.76–0.96)	0.01
Death from any cause	321 (9.8)	11.1	297 (9.1)	10.9	1.08 (0.92–1.27)	0.34
Venous thromboembolism	25 (0.8)	0.8	41 (1.3)	1.7	0.61 (0.37–1.00)	

* All efficacy outcomes were analyzed on an intention-to-treat basis. K–M denotes Kaplan–Meier.

N Engl J Med 2020; 382:1994-2004

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Antithrombotic Therapies After Open Revasc: Summary

- Some evidence to use SAP: ASA
- DAPT: may use ASA+Plavix after *prosthetic* graft if bleeding risk is not high
- Riva 2.5mg bid+ASA *should be* considered based on risk and benefit
- Warfarin may be considered after *vein* graft if bleeding risk is not high
- Warfarin+ASA may be considered after *high-risk bypass* (increased hematoma)

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Singe Antiplatelet Therapy Following Endo Revascularization
The Antithrombotic Trialists Collaboration: *ATC Meta-analysis*

- Study design: meta-analyisis of 287 studies
  - Comparisons of antiplatelet therapy versus control: 135,000 pts
  - Comparisons of different antiplatelet regimens: 7,000 pts
- Follow up: ~ 2 years

- N: 946 undergoing peripheral angioplasty
- Primary Outcome: MACCE
- Insignificant: (29% reduction) 2.5 *vs* 3.6%, respectively

BMJ 2002;324:71

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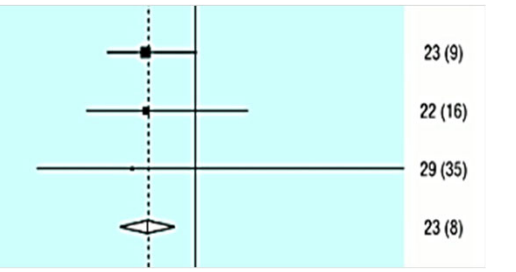
Singe Antiplatelet Therapy Following Open Revascularization
The Antithrombotic Trialists Collaboration: *ATC Meta-analysis*

	No of trial with data	No (%) of vascular events: Allocated antiplatelet	Adjusted control	Observed Expected	Variance	Odds ratio (CI) Antiplatelet control	% Odds reduction (SE)
Peripheral arterial disease:							
Intermittent claudication	26	201/3123 (6.4)	249/3140 (7.9)	-22.3	86.6		23 (9)
Peripheral grafting	12	67/1249 (5.4)	81/1248 (6.5)	-7.3	29.1		22 (16)
Peripheral angioplasty	4	12/472 (2.5)	17/474 (3.6)	-2.0	5.8		29 (35)
Subtotal	42	280/4844 (5.8)	347/4862 (7.1)	-31.6	121.5		23 (8)



BMJ 2002;324:71

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Dual Antiplatelet Therapy Following Endo Revascularization
The management of peripheral arterial interventions with mono or dual antiplatelet therapy: *MIROR Trial*

- N: 80 pts requiring peripheral angioplasty +/- stenting
- Study design: CRT with clopidogrel+ASA *vs* ASA
- Follow up: 6 and 12 months

- Primary Outcome: Target revasc
- At 6 months:
- Improved: (5 *vs* 20%; p=0.04)

- At 12 months
- Non-significant: (25 *vs* 32%; p=0.35).

European Radiology volume 22, pages 1998–2006 (2012)

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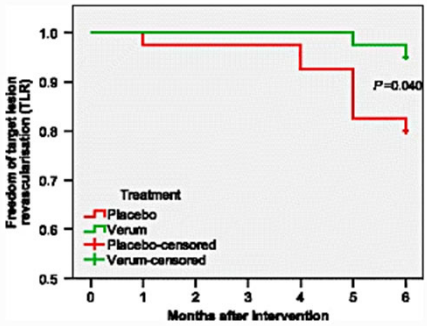
Dual Antiplatelet Therapy Following Endo Revascularization, The management of peripheral arterial interventions with mono or dual antiplatelet therapy: *MIROR Trial*



Measure	True (*n* = 40)	Placebo (*n* = 40)	*P* value
TLR in the 6 months after the intervention	5% (2/40)	20% (8/40)	0.040
Additional days in the hospital because of target lesion in the 6 months after the intervention, mean ± SD	0.13 ± 0.56	0.98 ± 2.29	0.026
Binary restenosis ≥50% 6 months after the intervention	40% (14/35)	39.4% (13/33)	1.000
Total occlusion 6 months after the intervention	8.8% (3/35)	3% (1/33)	0.615
Evaluation of restenosis			
Angiography	82.9% (29/35)	81.8% (27/33)	1.000
Sonography	17.1% (6/35)	18.2% (6/33)	
Amputation above the feet in the 6 months after the intervention	17.1% (6/35)	18.2% (6/33)	
Embolic complications during the intervention	0% (0/40)	5% (2/40)	0.494
Bleeding complications in the 6 months after the intervention	2.5% (1/40)	5% (2/40)	0.559
Cardiovascular event in the 6 months after the intervention	30% (12/40)	37.5% (15/40)	0.508
Mortality in the 6 months after the intervention	0% (0/40)	2.5% (1/40)	0.317
ABI change from baseline to follow-up, mean ± SD	0.14 ± 0.31 (33/40)	0.13 ± 0.45 (29/40)	0.960
Improvement of Rutherford category ≥1 6 months after the intervention compared with baseline	63.2% (24/38)	52.6% (20/38)	0.486

European Radiology volume 22, pages 1998–2006 (2012)

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Dual Antiplatelet Therapy Following Endo Revascularization, *A Cochrane Meta-analysis*

- N: 356 pts requiring peripheral angioplasty +/- stenting
- Study design: Meta-analysis of trials including different antithrombotic therapies following endovasc intervention
- Drugs: dipyridamole+ high dose ASA *vs* high-dose ASA alone
- Primary Outcome: Re-occlusion
- At 6 months:

- Reduced: OR: 0.40 [95% CI: 0.19 to 0.84]).

Cochrane Database Syst Rev. 2012;2012(8):CD002071.

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Dual Antiplatelet Therapy Using Cilostazol Following Endo Revascularization
RCTs

- Cilostazol+ASA better than ticlopidine+ASA for patency at 12, 24 and 36 months.[1]
- Cilostazol+ASA better than ASA for restenosis at 12 months.[2]
- Cilostazol+ASA better than ASA for reintervention at 2 years.[3]

1- *J Vasc Surg.* 2008;48(1):144-149.
2- *Circulation.* 2013;127(23):2307-2315. 3- *J Am Coll Cardiol.* 2009;53(1):48-53.

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Anticoagulation after Endo/Open Revascularization:
VOYAGER PAD Trial

- N: 6,564 pts undergoing open or edno revasc (2/3rd had endo)
- Study design: CRT f/u for 3 years
- Study Drugs: rivaroxaban 2.5 bid + ASA vs ASA.
- Outcome: ALI, major amputation, MI, ischemic stroke, or CV death
  - Improved: 17.3% and 19.9%, respectively (HR: 0.85 [95% CI: 0.76 to 0.96])
- TIMI- Major bleeding:
  - Not different: 2.65% and 1.87%; HR,1.43; 95% CI, 0.97 to 2.10; P=0.07
- ISTH Major bleed:
  - More: 5.94% and 4.06%; HR, 1.42; 95% CI, 1.10 to 1.84; P=0.007

N Engl J Med 2020; 382:1994-2004

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Anticoagulation after Endo/Open Revascularization, Baseline Characteristics: *VOYAGER PAD Trial*

Peripheral artery disease–related history	Riva+ASA	ASA
Median ankle–brachial index (IQR)	0.56 (0.42–0.67)	0.56 (0.42–0.67)
Previous amputation — no. (%)	194 (5.9)	196 (6.0)
History of claudication — no. (%)	3132 (95.3)	3137 (95.7)
History of critical limb ischemia — no. (%)	999 (30.4)	969 (29.6)
Previous peripheral revascularization — no. (%)	1181 (35.9)	1155 (35.2)
Qualifying revascularization — no. (%)		
Performed for claudication	2521 (76.7)	2504 (76.4)
Performed for critical limb ischemia§	762 (23.2)	771 (23.5)
Endovascular	2153 (65.5)	2140 (65.3)
Surgical	1133 (34.5)	1138 (34.7)
Medications — no. (%)		
Statin	2608 (79.4)	2641 (80.6)
ACE inhibitor or ARB	2096 (63.8)	2063 (62.9)
Aspirin at randomization	3256 (99.1)	3248 (99.1)
Clopidogrel at randomization	1658 (50.5)	1655 (50.5)

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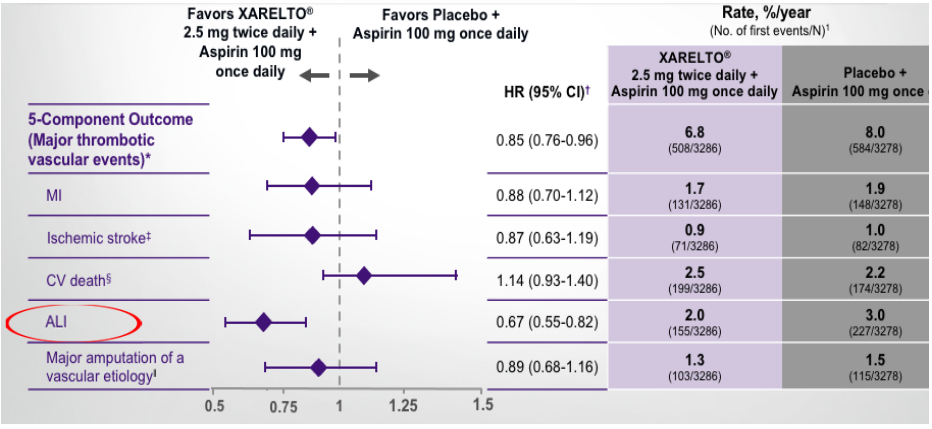
Anticoagulation after Endo/Open Revascularization: *VOYAGER PAD Trial*



	HR (95% CI)†	Rate, %/year (No. of first events/N)‡ XARELTO® 2.5 mg twice daily + Aspirin 100 mg once daily	Placebo + Aspirin 100 mg once
5-Component Outcome (Major thrombotic vascular events)*	0.85 (0.76-0.96)	6.8 (508/3286)	8.0 (584/3278)
MI	0.88 (0.70-1.12)	1.7 (131/3286)	1.9 (148/3278)
Ischemic stroke‡	0.87 (0.63-1.19)	0.9 (71/3286)	1.0 (82/3278)
CV death§	1.14 (0.93-1.40)	2.5 (199/3286)	2.2 (174/3278)
ALI	0.67 (0.55-0.82)	2.0 (155/3286)	3.0 (227/3278)
Major amputation of a vascular etiology‖	0.89 (0.68-1.16)	1.3 (103/3286)	1.5 (115/3278)

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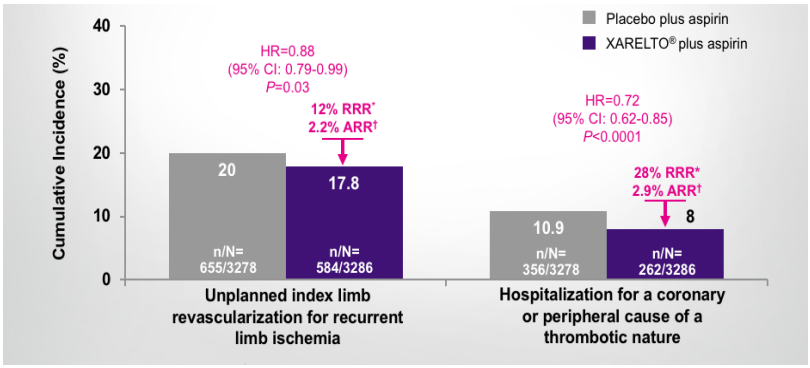
Anticoagulation after Endo/Open Revascularization: Secondary Outcomes
VOYAGER PAD Trial



N Engl J Med 2020; 382:1994-2004 (Courtesy to J&J)

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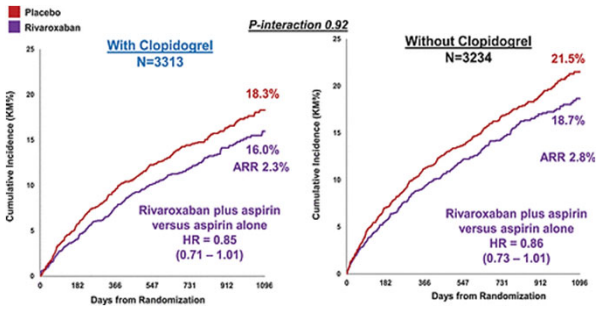
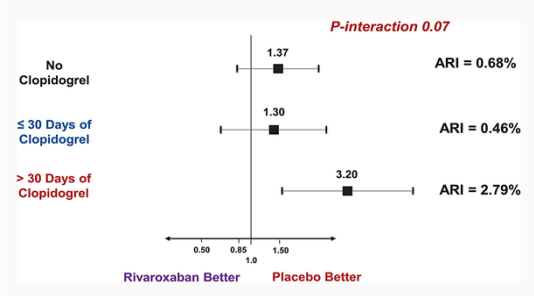
Anticoagulation after Endo/Open Revascularization, Plavix Effect?:
VOYAGER PAD Trial



Primary endpoint



ISTH Major bleeding within 365 days

Circulation. 2020;142:2219–2230 (Courtesy to J&J)

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Anticoagulation after Open Revascularization: *ePAD Trial*

- N: 203 pts undergoing femoropopliteal endo intervention
- Study design: CRT f/u for 3 and 6 months
- Study Drugs: edoxaban + ASA vs clopidogrel+ASA.

- Outcome: Restenosis or re-occlusion at 6 months.
- Not significantly different: 30.9 *vs* 34.7%; RR 0.89 [95% CI 0.59 to 1.34, p=0.643]

- TIMI- or ISTH Major bleeding:
- Not different!

J Endovasc Ther 2018 Apr;25(2):158-168.

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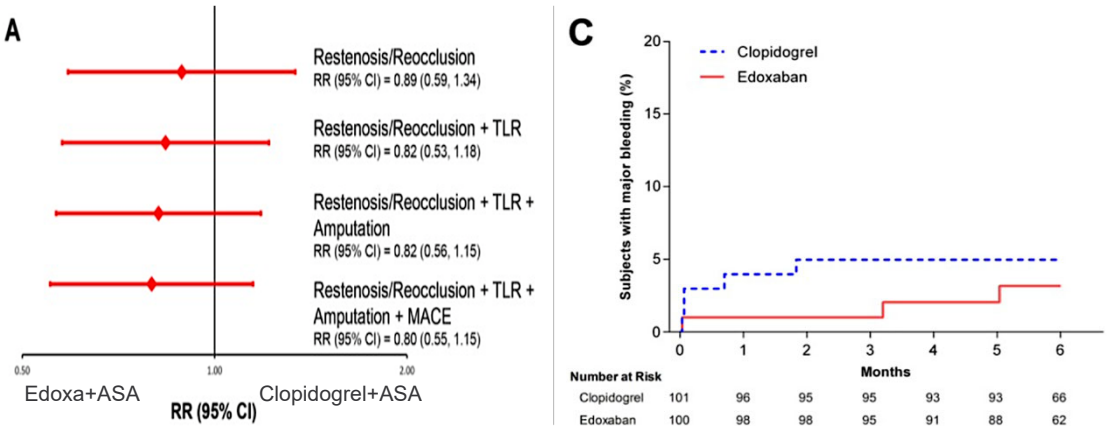
Anticoagulation after Open Revascularization: *ePAD Trial*



J Endovasc Ther 2018 Apr;25(2):158-168.

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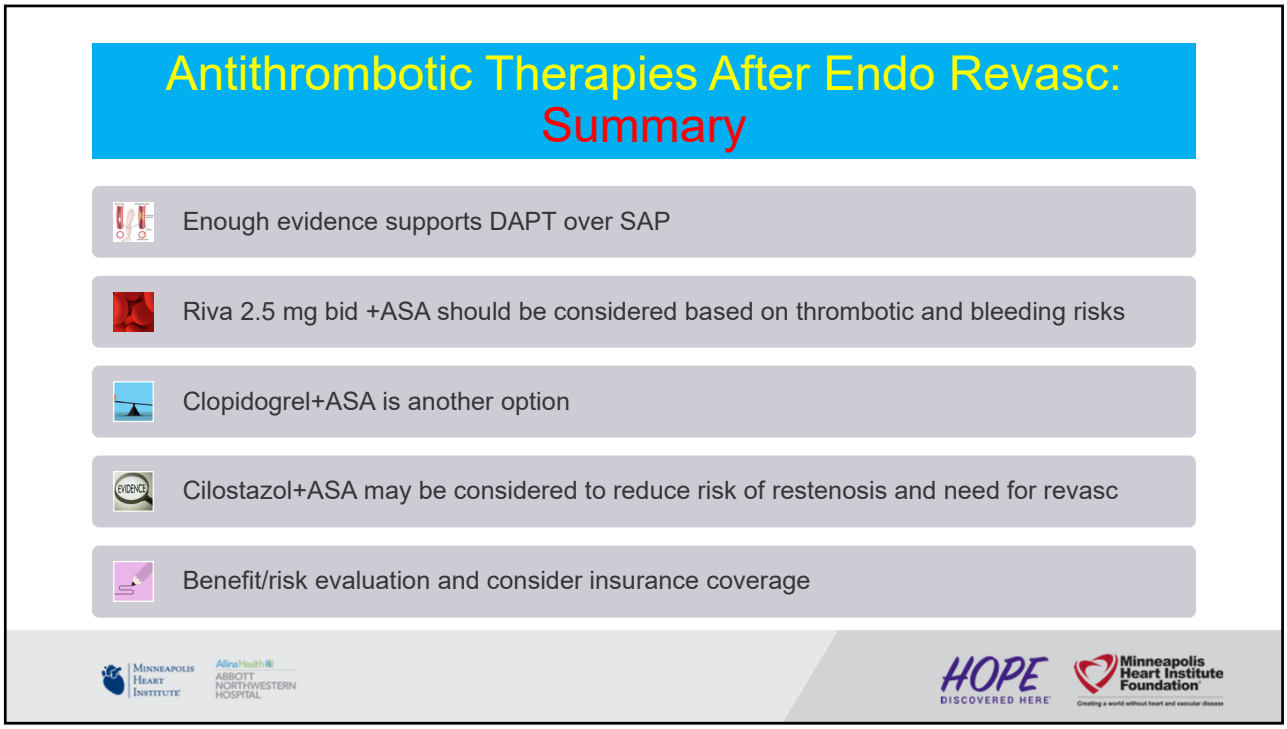

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Antithrombotic Therapies in Chronic Stable PAD

Trial / Author	Publication type	Patients (n)	Treatment arms	Incidence of MACCE	RR or HR [95% CI]
Single Antiplatelet Therapy					
CAPRIE 1996 [10]	RCT	6452*	Clopidogrel	3.7%	RR 0.76 [0.64 - 0.91]
			ASA	4.9%	
CLIPS 2007 [8]	RCT	366	ASA	6.5% †	HR 0.42 [0.21 - 0.82]
			Placebo	15.5% †	
Berger et al 2009 [9]	Meta-analysis	5269	ASA ± dipyridamole	8.9%	RR 0.88 [0.76 - 1.04]
			Placebo	11.0%	
EUCLID 2017 [11]	RCT	13885	Ticagrelor	10.8%	HR 1.02 [0.92 - 1.13]
			Clopidogrel	10.6%	
Dual Antiplatelet Therapy					
CHARISMA 2009 [13-15]	RCT	3096*	ASA + clopidogrel	7.6%	HR 0.85 [0.66 - 1.08]
			ASA	8.9%	
PLATO 2015 [16]	RCT	1144*	ASA + ticagrelor	18%	HR 0.85 [0.64 - 1.11]
			ASA + clopidogrel	20.6%	
PEGASUS-TIMI 54 2015 [18]	RCT	1143*	ASA + ticagrelor	14.1%	HR 0.69 [0.47 - 0.99]
			ASA	19.3%	
Protease-Activated Receptor 1 Antagonist					
TRA2°P-TIMI 50 2013 [22]	RCT	3787*	Vorapaxar	11.3%	HR 0.94 [0.78 - 1.14]
			Placebo	11.9%	
Anticoagulation					
WAVE 2007 [26]	RCT	2161	Warfarin or acenocoumarol + Antiplatelet	12.2%	RR 0.92 [0.73 - 1.16]
			Antiplatelet	13.3%	
COMPASS 2017 [28]	RCT	7470*	Rivaroxaban + ASA	5.1%	HR 0.72 [0.57 - 0.90]
			ASA	6.9%	

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COMPASS 2017 [28]	RCT	7470*	Rivaroxaban + ASA	5.1%	HR 0.72 [0.57 - 0.90]
			ASA	6.9%	

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Antithrombotic Therapies in Chronic Stable PAD

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			ASA	4.9%	
CLIPS 2007 [8]	RCT	366	ASA	6.5% †	HR 0.42 [0.21 - 0.82]
			Placebo	15.5% †	
Berger et al 2009 [9]	Meta-analysis	5269	ASA ± dipyridamole	8.9%	RR 0.88 [0.76 - 1.04]
			Placebo	11.0%	
EUCLID 2017 [11]	RCT	13885	Ticagrelor	10.8%	HR 1.02 [0.92 - 1.13]
			Clopidogrel	10.6%	
Dual Antiplatelet Therapy					
CHARISMA 2009 [13-15]	RCT	3096*	ASA + clopidogrel	7.6%	HR 0.85 [0.66 - 1.08]
			ASA	8.9%	
PLATO 2015 [16]	RCT	1144*	ASA + ticagrelor	18%	HR 0.85 [0.64 - 1.11]
			ASA + clopidogrel	20.6%	
PEGASUS-TIMI 54 2015 [18]	RCT	1143*	ASA + ticagrelor	14.1%	HR 0.69 [0.47 - 0.99]
			ASA	19.3%	
Protease-Activated Receptor 1 Antagonist					
TRA2°P-TIMI 50 2013 [22]	RCT	3787*	Vorapaxar	11.3%	HR 0.94 [0.78 - 1.14]
			Placebo	11.9%	
Anticoagulation					
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Antithrombotic Therapies After Open Revasc

Trial/ Author	Publication type	Patients (n)	Primary End Point	Treatment arms	Incidence	Results
Antiplatelet Therapy						
ATC 2002 [29]	Meta-analysis	2497	MACCE	Antiplatelet	10.7%	Odds reduction 22%
				Placebo	13.2%	
CASPAR 2010 [31]	RCT	851	Graft occlusion, revascularization, amputation, death	ASA + clopidogrel	35.1%	HR 0.98 [0.78 - 1.23]
				ASA	35.4%	
Bedenis et al 2015 [30]	Meta-analysis	5683	Bypass graft occlusion	ASA ± dipyridamole	23.2%	OR 0.42 [0.22 - 0.83]
				Placebo	34.8%	
Anticoagulation						
Sarac et al 1998 [33]	RCT	56	Bypass graft patency	Warfarin + ASA	74%	p = 0.04
				ASA	51%	
Dutch BOA 2000 [32]	RCT	2690	Graft occlusion	Phenprocoumon or acenocoumarol	13.5%	HR 0.95 [0.82 - 1.11]
				ASA	14.2%	
Johnson et al 2002 [35]	RCT	831	Vein bypass graft occlusion	Warfarin + ASA	24.7%	RR 1.04 [0.72 - 1.51]
				ASA	25.1%	
			Prosthetic bypass graft occlusion	Warfarin + ASA	23.5%	RR 0.62 [0.42 - 1.92]
				ASA	34.4%	
Jivegård et al 2005 [36]	RCT	284	Bypass graft patency	Dalteparin + ASA	59%	p = NS
				ASA	59%	
Monaco et al 2012 [34]	RCT	341	Bypass graft patency	Clopidogrel + warfarin	44.4%	p =0.026
				Clopidogrel + ASA	30.4%	
			Freedom from ischemia	Clopidogrel + warfarin	77.6%	p = 0.044
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VOYAGER 2020 [37]	RCT	6564*	MACCE + ALI and amputation	Rivaroxaban 2.5 mg + ASA	15.5%	HR 0.85 [0.76 - 0.96]
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Antithrombotic Therapies After Endo Revasc

Trial / Author	Publication type	Patients (n)	Primary End Point	Treatment arms	Incidence	Results
Antiplatelet Therapy						
ATC 2002 [29]	Meta-analysis	946	MACCE	Antiplatelet	2.5%	Odds reduction 29%
				Placebo	3.6%	
Iida et al 2008 [41]	RCT	127	Patency	Cilostazol + ASA	73%	OR 0.32 [0.13 - 0.76]
				Ticlopidine + ASA	51%	
Soga et al 2009 [43]	RCT	78	Freedom from reintervention	Cilostazol + ASA	84.6%	p = 0.04
				ASA	62.2%	
Robertson et al 2012 [38]	Meta-analysis	365	Target vessel occlusion	ASA + dipyridamole	*	OR 0.40 † [0.19 - 0.84]
				Placebo	*	
MIRROR 2012 [39,40]	RCT	80	Reintervention at 6 months	Clopidogrel + ASA	5%	p = 0.04
				ASA	20%	
			Reintervention at 1 year	Clopidogrel + ASA	25%	p = 0.35
				ASA	32%	
STOP-IC 2013 [43]	RCT	200	Restenosis	Cilostazol + ASA	20%	OR 0.26 [0.13 - 0.53]
				ASA	49%	
Anticoagulation						
VOYAGER 2020 [37]	RCT	6564‡	MACCE + ALI and amputation	Rivaroxaban 2.5 mg + ASA	15.5%	HR 0.85 [0.76 - 0.96]
				ASA	17.8%	

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Societal Guidelines

- AHA/ACC and ESC: all symptomatic PAD pts should be on antiplatelet therapy (Grade 1 Level A).
  - Clopidogrel may be preferred.
- ESC, ADA and SVS: consider riva 2.5 mg bid+ASA in chronic PAD to reduce MALE and MACCE.
- SVS and ESC: Consider DAPT after prosthetic bypass
  - SVS: in infrainguinal, ESC: in below knee.
- ESC: consider VKA after infra-inguinal bypass with autologous conduit (2B).
- SVS and ESC: Recommend at least 1 month of DAPT post-endovasc
  - SVS: recommends extending to 6 months in pts with repeated revasc provided low bleeding risk (2C).
- AHA/ACC: DAPT: reasonable after revasc to reduce limb loss but reduction of MACCE no well-established (2C, 2B)

J Am Coll Cardiol. 2017;69(11):1465-1508.
Eur Heart J. 2018;39(9):763–816.
J Vasc Surg. 2019;69(6)supp:3S-125S.

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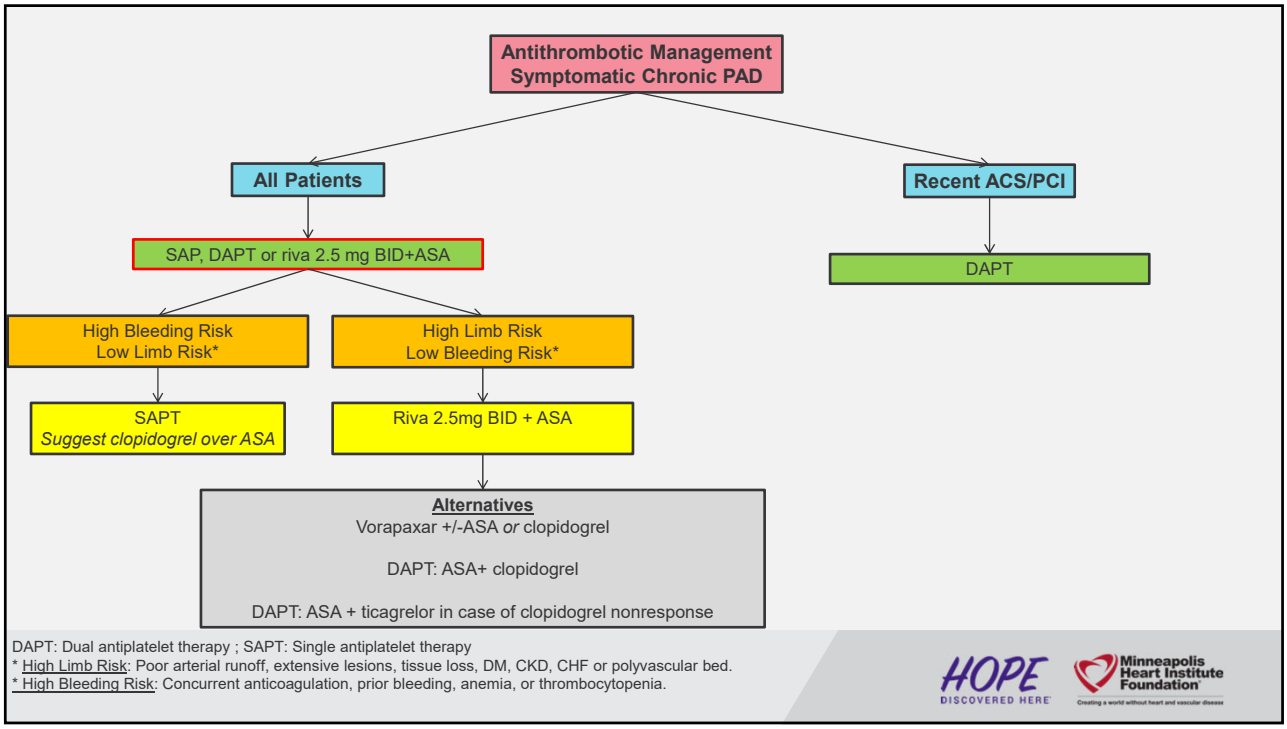

DAPT: Dual antiplatelet therapy ; SAPT: Single antiplatelet therapy
* High Limb Risk: Poor arterial runoff, extensive lesions, tissue loss, DM, CKD, CHF or polyvascular bed.
* High Bleeding Risk: Concurrent anticoagulation, prior bleeding, anemia, or thrombocytopenia.

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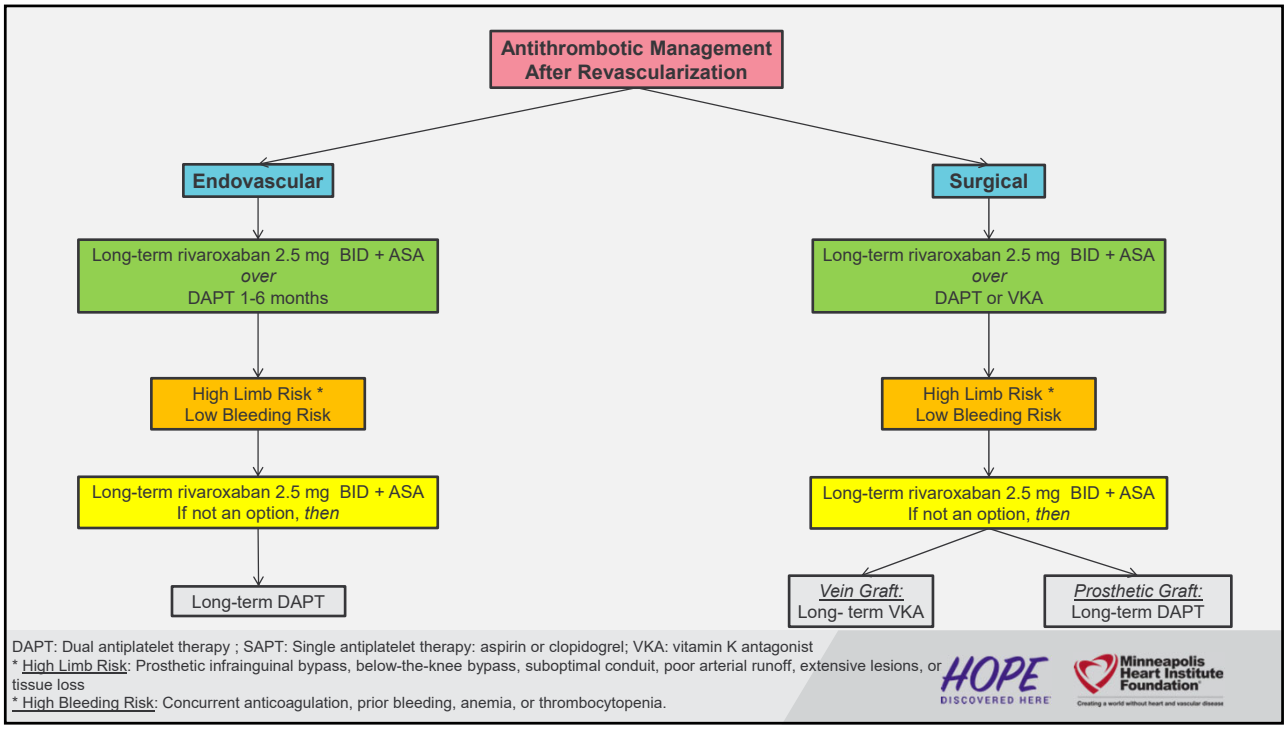
Antithrombotic Management After Revascularization
Endovascular
Surgical
Long-term rivaroxaban 2.5 mg BID + ASA over DAPT 1-6 months
Long-term rivaroxaban 2.5 mg BID + ASA over DAPT or VKA
High Limb Risk * Low Bleeding Risk
High Limb Risk * Low Bleeding Risk
Long-term rivaroxaban 2.5 mg BID + ASA If not an option, then
Long-term rivaroxaban 2.5 mg BID + ASA If not an option, then
Long-term DAPT
Vein Graft: Long- term VKA
Prosthetic Graft: Long-term DAPT
DAPT: Dual antiplatelet therapy ; SAPT: Single antiplatelet therapy: aspirin or clopidogrel; VKA: vitamin K antagonist
* High Limb Risk: Prosthetic infrainguinal bypass, below-the-knee bypass, suboptimal conduit, poor arterial runoff, extensive lesions, or tissue loss
* High Bleeding Risk: Concurrent anticoagulation, prior bleeding, anemia, or thrombocytopenia.
HOPE DISCOVERED HERE
Minneapolis Heart Institute Foundation

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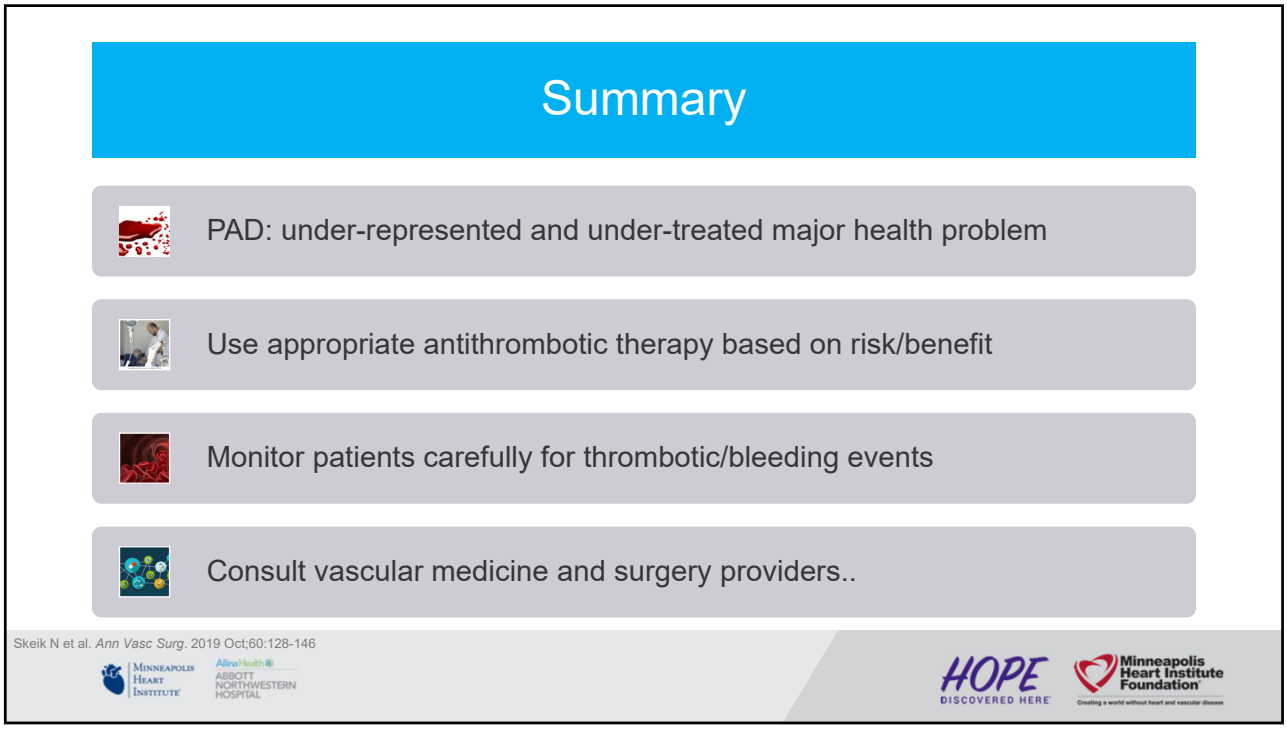
Summary
PAD: under-represented and under-treated major health problem
Use appropriate antithrombotic therapy based on risk/benefit
Monitor patients carefully for thrombotic/bleeding events
Consult vascular medicine and surgery providers..
Skeik N et al. Ann Vasc Surg. 2019 Oct;60:128-146
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