Antithrombotic Therapy For Peripheral Arterial Disease (PAD)

Daria Zavgorodnyaya, PharmD

PGY2 Internal Medicine Pharmacy Resident

Ascension Texas

ASCENSION

Technician objectives

- Explain complications of PAD
- Compare risk and benefit of antithrombotic therapy in PAD
- Examine antithrombotic therapy options for patients with PAD

Pharmacist objectives

- Compare risk and benefit of antithrombotic therapy in PAD
- Examine the evidence behind ACCP and ACC/AHA guidelines
- Evaluate the emerging evidence on the use of anticoagulation therapy in PAD
- Design optimal antithrombotic pharmacotherapy regimen for patients with PAD

Outline

- Epidemiology/pathophysiology
- Antithrombotic therapy in stable disease
- Antithrombotic therapy after revascularization

Epidemiology

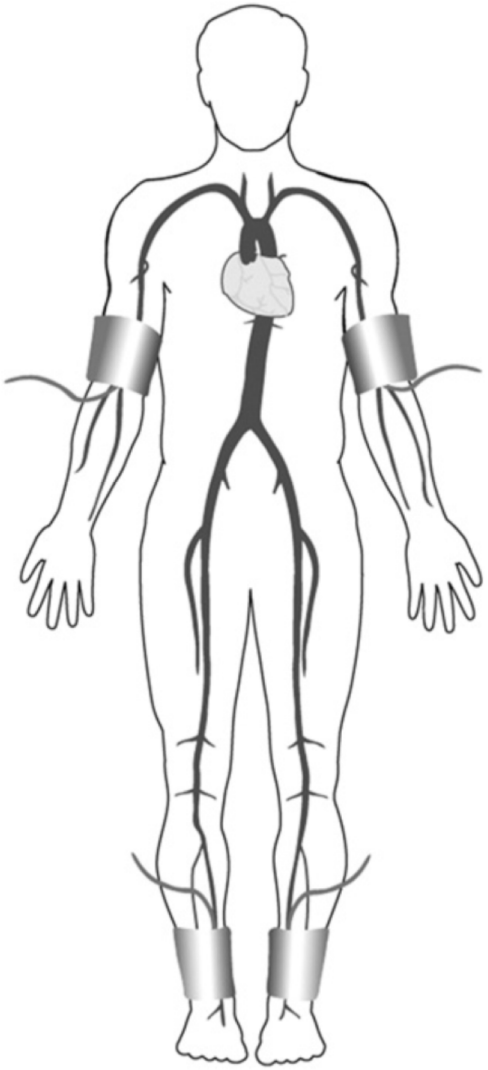
- PAD: chronic occlusive disease of the noncardiac non-intracranial arteries
  - Atherosclerosis
  - Inflammatory disorders
  - Non-inflammatory arteriopathies
- Risk factors: age, smoking, hypertension, dyslipidemia, atherosclerotic disease in another vascular bed
- 2-3-fold cardiovascular (CV) mortality
- Usually undertreated as compared to coronary artery disease (CAD) and cerebrovascular disease (CVD) populations

Kullo IJ, et al. *N Engl J Med.* 2016;374:862-871.
Conte MS. In: *Rutherford's Vascular Surgery and Endovascular Therapy.* 9th ed. 2019:1368-1376.
Sigvant B, et al. *Eur J Vasc Endovasc Surg*. 2016;51:395-403.

Diagnosis

- Ankle-brachial index (ABI) $\leq$0.9
- Diminished pulses
- Arterial bruits
- Decreased capillary refill
- Pallor on elevation
- Trophic changes

Measurement of the ABI



ASCENSION

Kullo IJ, et al. *N Engl J Med.* 2016;374:862-871.
Norgen L, et al. *J Vasc Surg.* 2007;45:S5A-S67A.

Clinical presentation

- Asymptomatic disease
- Atypical leg symptoms: pain while sitting or standing, discomfort with exercise
- Classic intermittent claudication (IC): reproducible leg pain brought on by exercise and relieved by rest
- Critical limb ischemia (CLI): pain at rest or tissue necrosis
- Acute limb ischemia (ALI): acute severe limb-threatening hypoperfusion

Conte MS. In: *Rutherford's Vascular Surgery and Endovascular Therapy.* 9th ed. 2019:1368-1376.
Gerhard-Herman MD, et al. *J Am Coll Cardiol*. 2017;69:1465-1508.

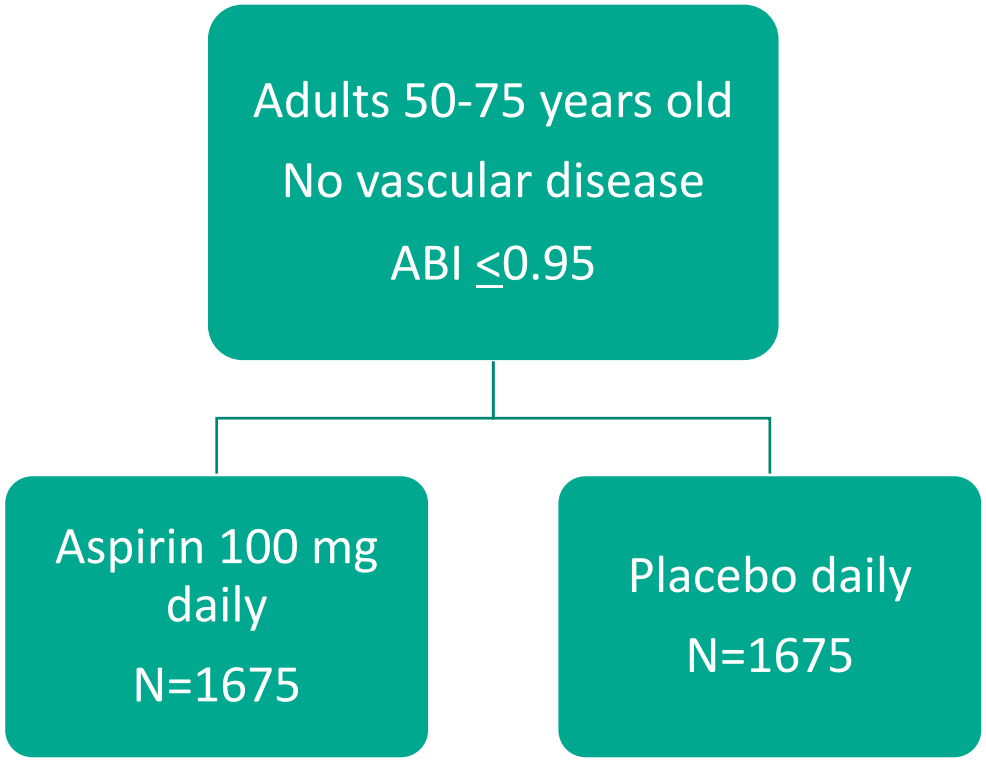
Management of stable disease

- Goals of care:
  - Reduce CV risk
    - Major adverse cardiac events (MACE): myocardial infarction (MI), stroke, CV death
  - Improve functional capacity
    - Major adverse limb events (MALE): amputation, limb ischemia
- Best medical therapy
  - Manage comorbid conditions (hypertension, smoking, glycemic control)
  - Statin
  - Antithrombotic therapy

Hess CN, et al. *JAMA*. 2018;319:2329-2330
Gerhard-Herman MD, et al. *J Am Coll Cardiol*. 2017;69:1465-1508.

Antithrombotic therapy for asymptomatic stable disease

Fowkes, et al

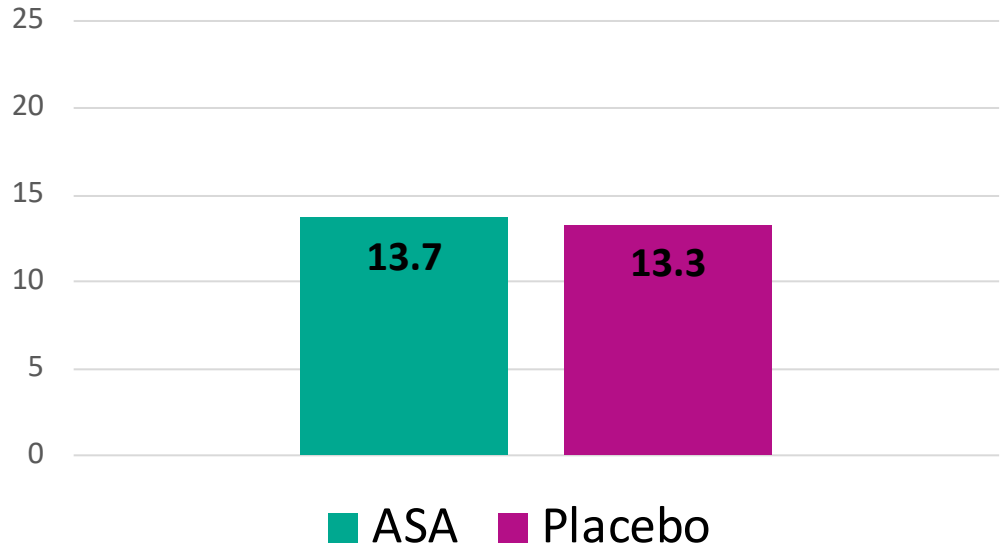


- Randomized, double-blind trial
- Primary outcome: coronary event, stroke or revascularization
- Mean age: ~62 years
- Mean ABI: 0.86
- Smokers: ~33%
- Statin use: ~4%
- Mean follow up: 8.2 years

Fowkes FGR, et al. *JAMA*. 2010;303:841-848.

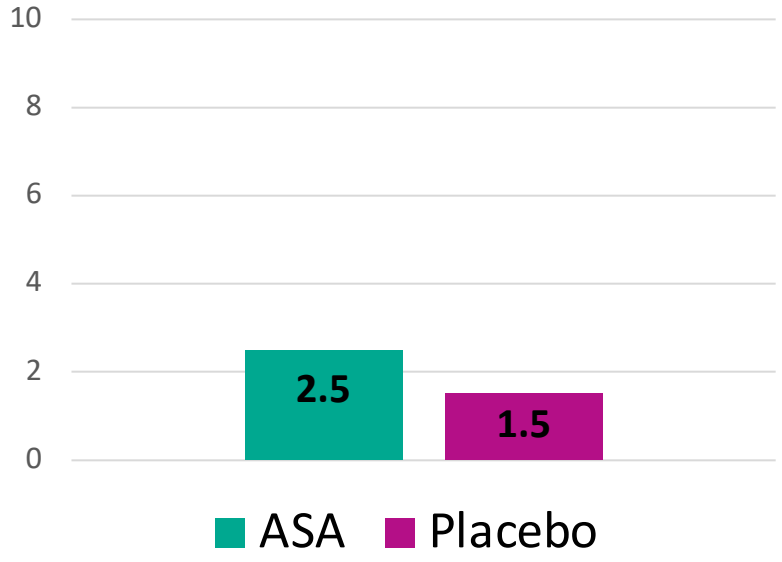
Fowkes, et al

Primary outcome: coronary event, stroke or revascularization (events per 1000 person-years)



HR 1.03; 95% CI, 0.84-1.27

Major hemorrhage (events per 1000 person-years)



HR 1.71; 95% CI, 0.99-2.97

Fowkes FGR, et al. *JAMA*. 2010;303:841-848.

Guideline recommendations

ACC/AHA 2016

In asymptomatic patients with ABI ≤0.9 antiplatelet therapy is reasonable to reduce the risk of stroke, MI or vascular death (IIa-expert opinion)

In asymptomatic patients with ABI 0.91-0.99, the usefulness of antiplatelet therapy to reduce the risk of MI, stroke or vascular death is uncertain (IIbB)

ACCP 2012

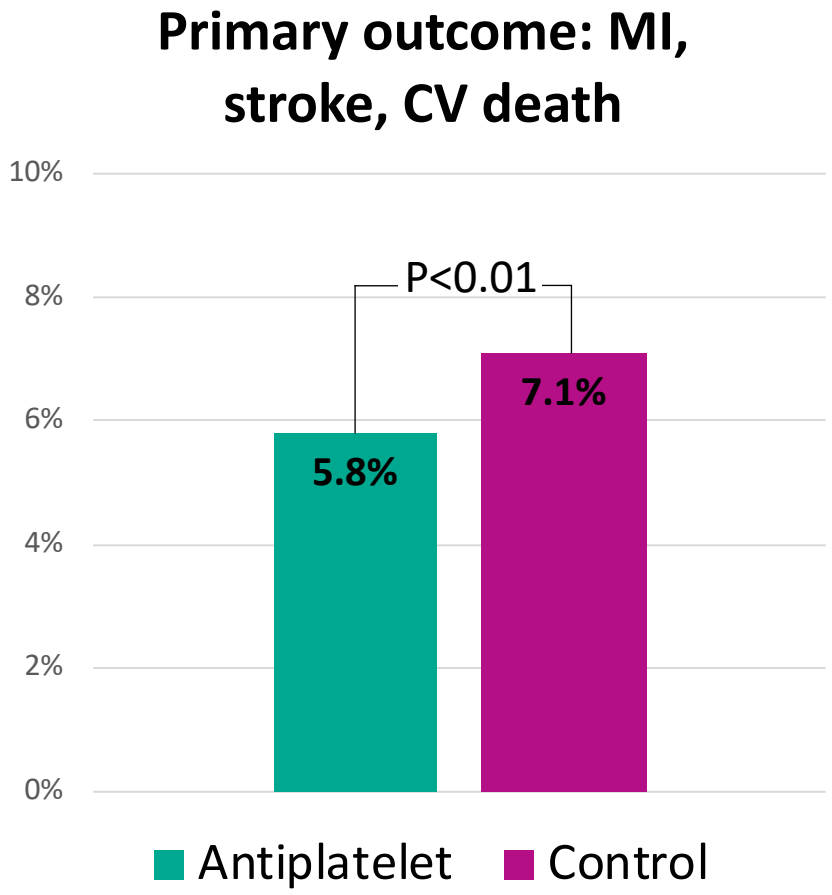
For persons with asymptomatic PAD, we suggest aspirin 75-100 mg daily over no aspirin therapy (2B)

Gerhard-Herman MD, et al. *J Am Coll Cardiol*. 2017;69:1465-1508.
Alonso-Coello P, et al. *CHEST.* 2012;141:e669S-e690S.

Antithrombotic therapy for symptomatic stable disease

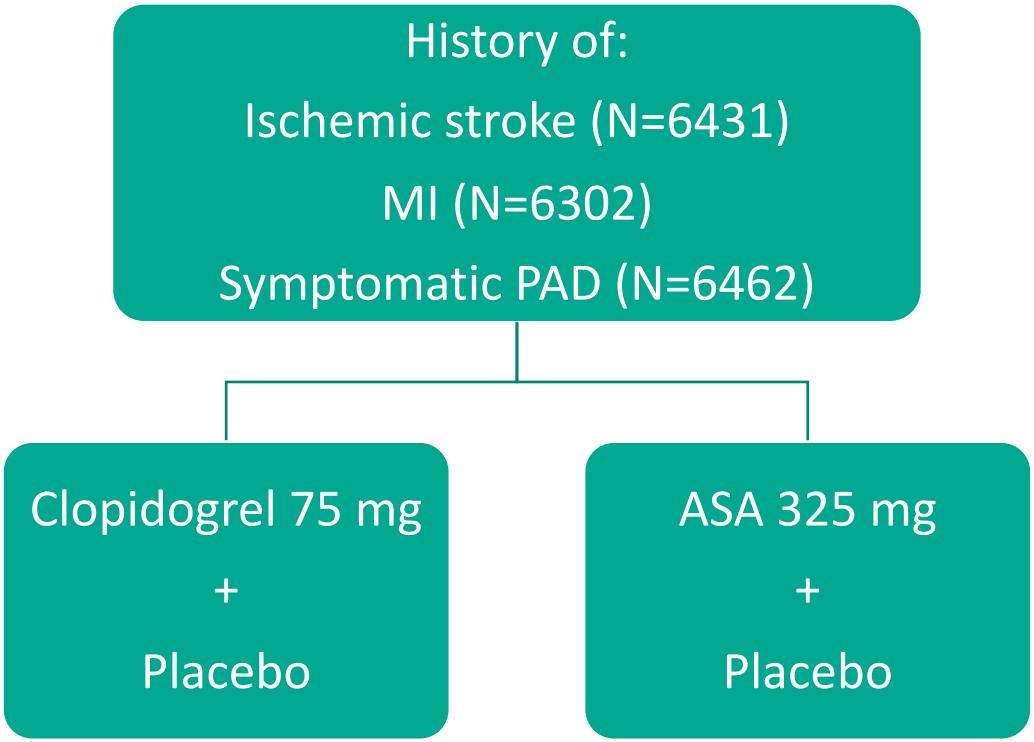
Antiplatelet therapy: Antithrombotic trialist collaboration

- Meta analysis of RCTs
- Patients at high risk of annual events:
  - Previous occlusive disease
  - Predisposing condition
- PAD cohort, N=9214, 42 trials
  - IC, N=6263
  - Revascularization, N=3443
- Majority of trials published before 1990
- Picotamide vs placebo group, N=2304
- ASA monotherapy vs placebo, 4 trials



Antithrombotic Trialists' Collaboration. *BMJ*. 2002;324:71-86.
Brass EP, et al. *Circulation.* 2017;136:785-786.

Antiplatelet therapy: CAPRIE trial

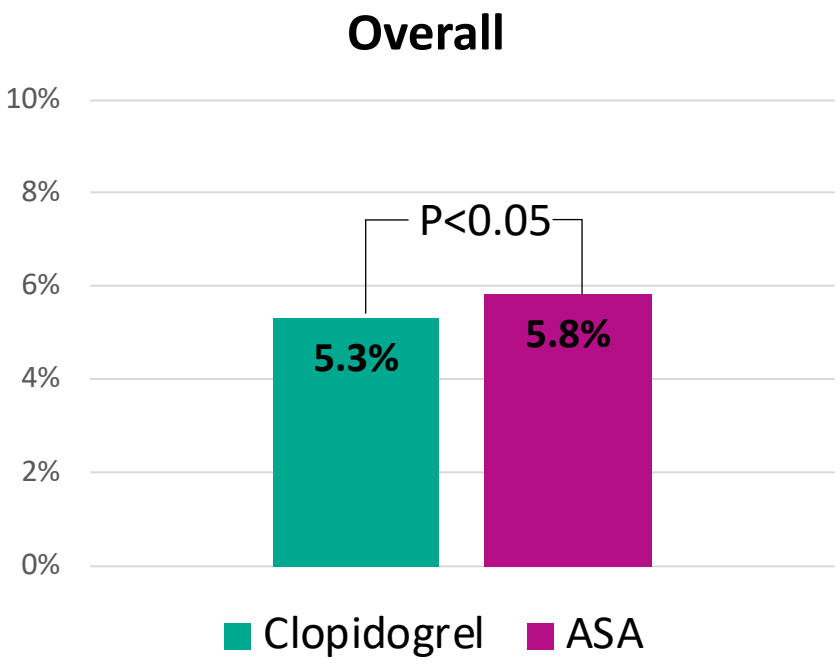


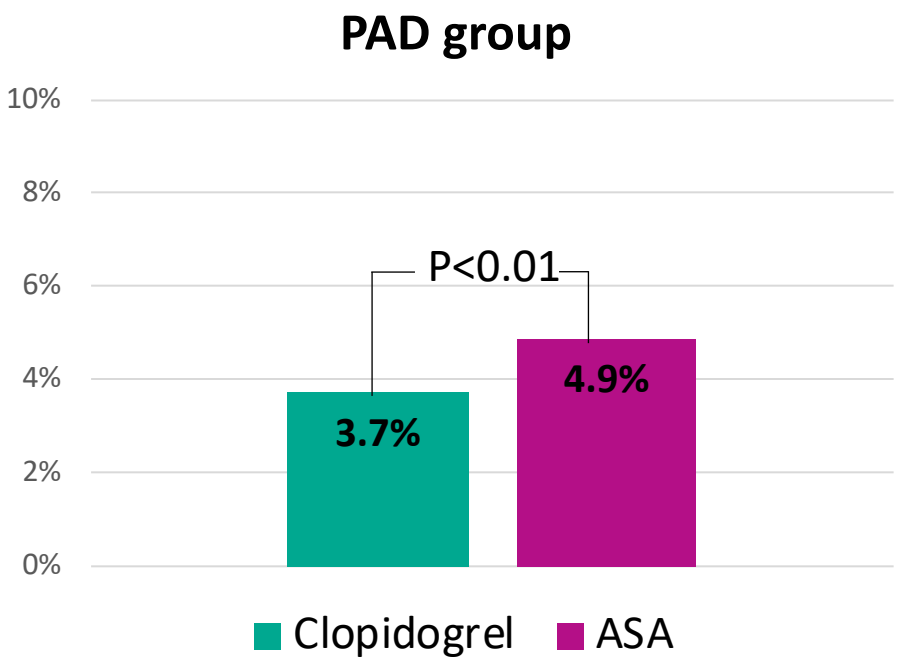
- Randomized, double blind, multi-national trial
- Mean age: 62.5 years
- Current smoker: ~30%
- ABI not reported
- Statin use not reported

CAPIRE Steering Committee. *Lancet.* 1996;348:1329-1339.

Antiplatelet therapy: CAPRIE trial

Primary outcome: MI, stroke, CV death (events per year)





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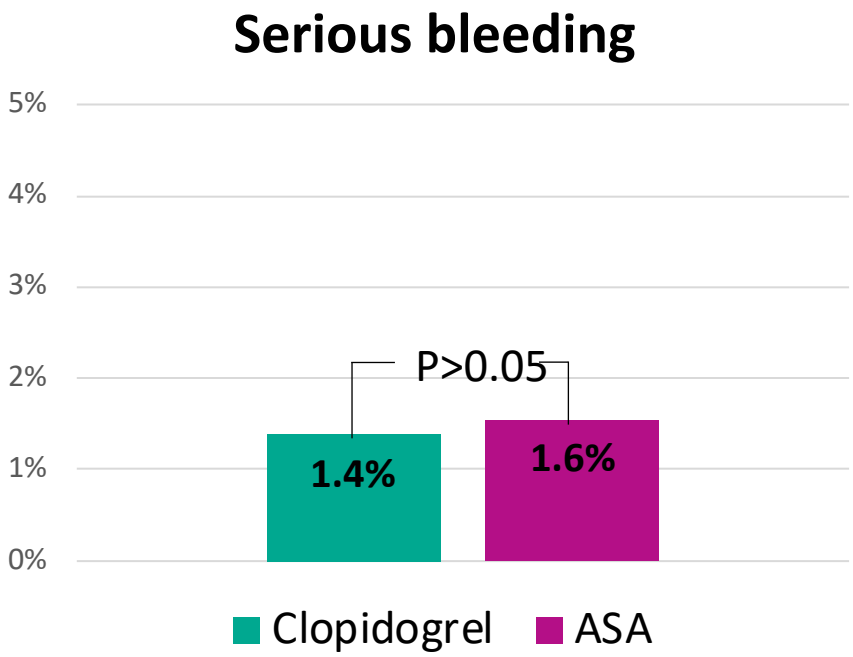
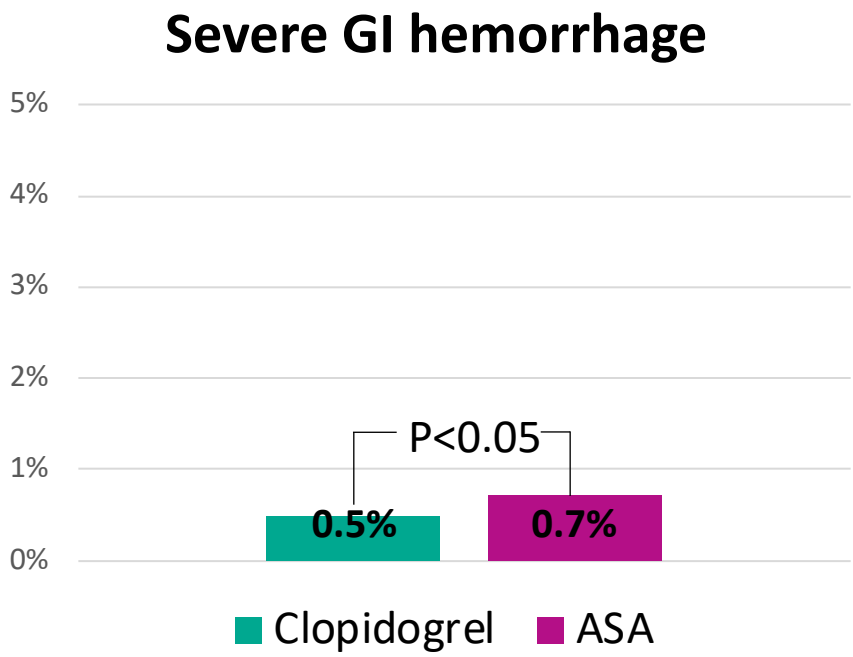
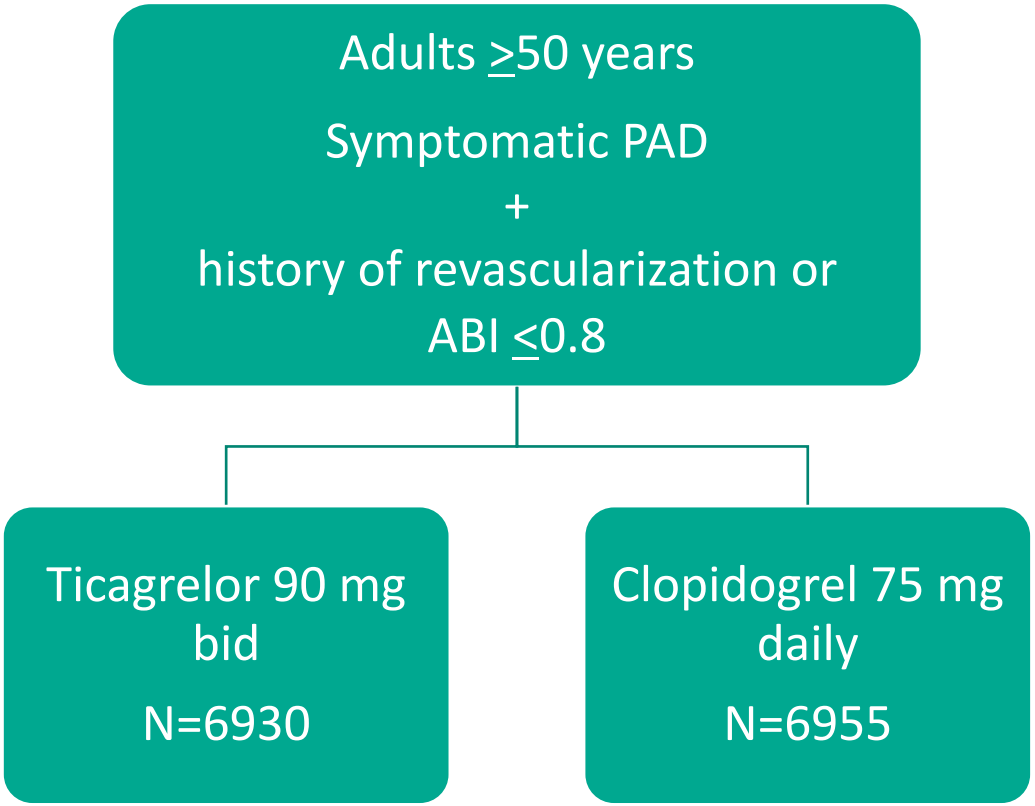
Antiplatelet therapy: CAPRIE trial





CAPIRE Steering Committee. *Lancet.* 1996;348:1329-1339.

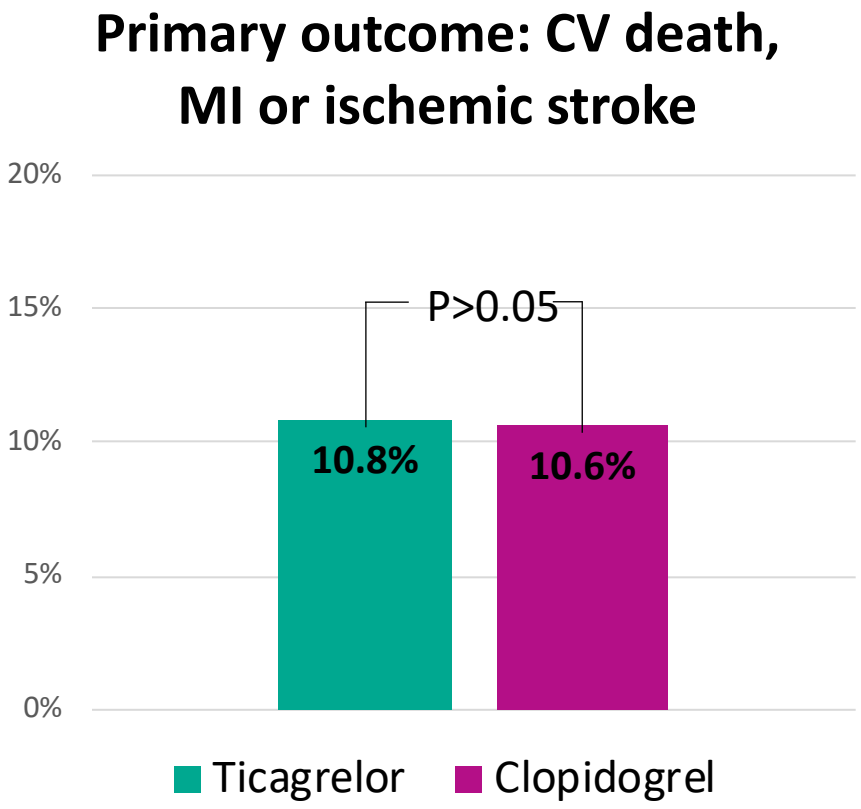
Antiplatelet therapy: EUCLID

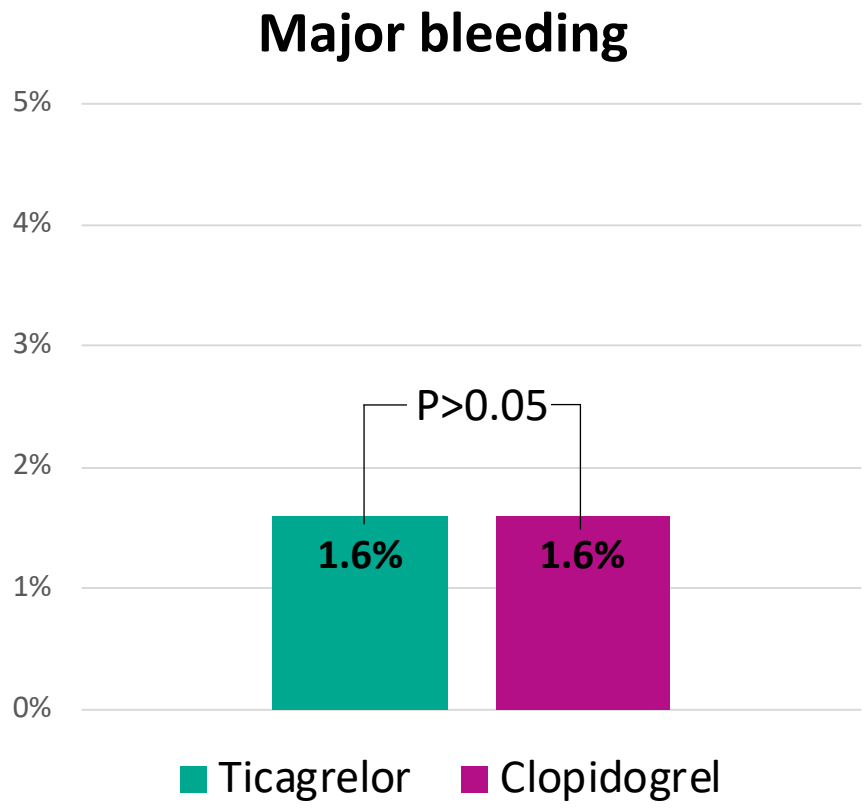


- Randomized, double-blind
- Enrollment criteria:
  - Low ABI 43%
  - Revascularization: 57%
- Median age: 66 years
- CAD/MI: 47%
- Current smoker: 31%
- Statin use: ~73%

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

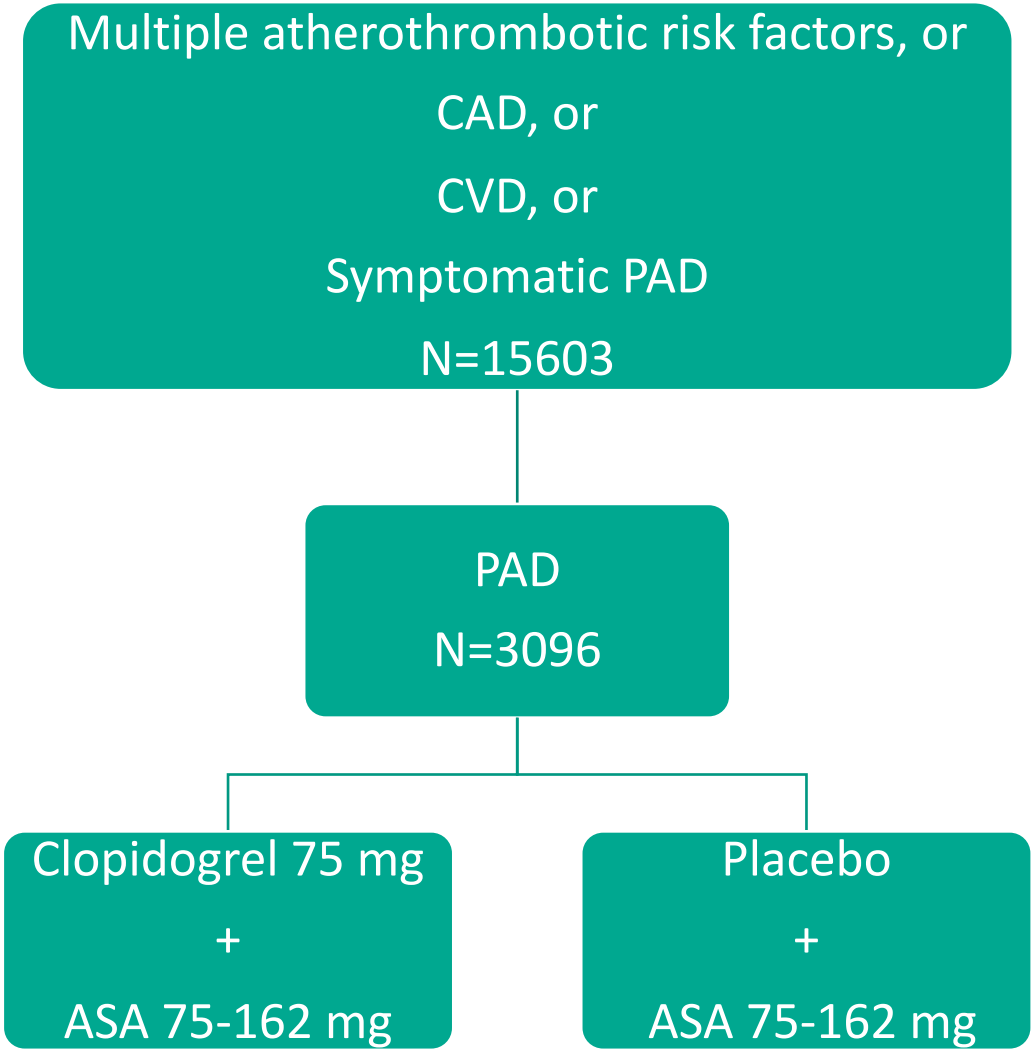
Antiplatelet therapy: EUCLID





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

DAPT: CHARISMA trial

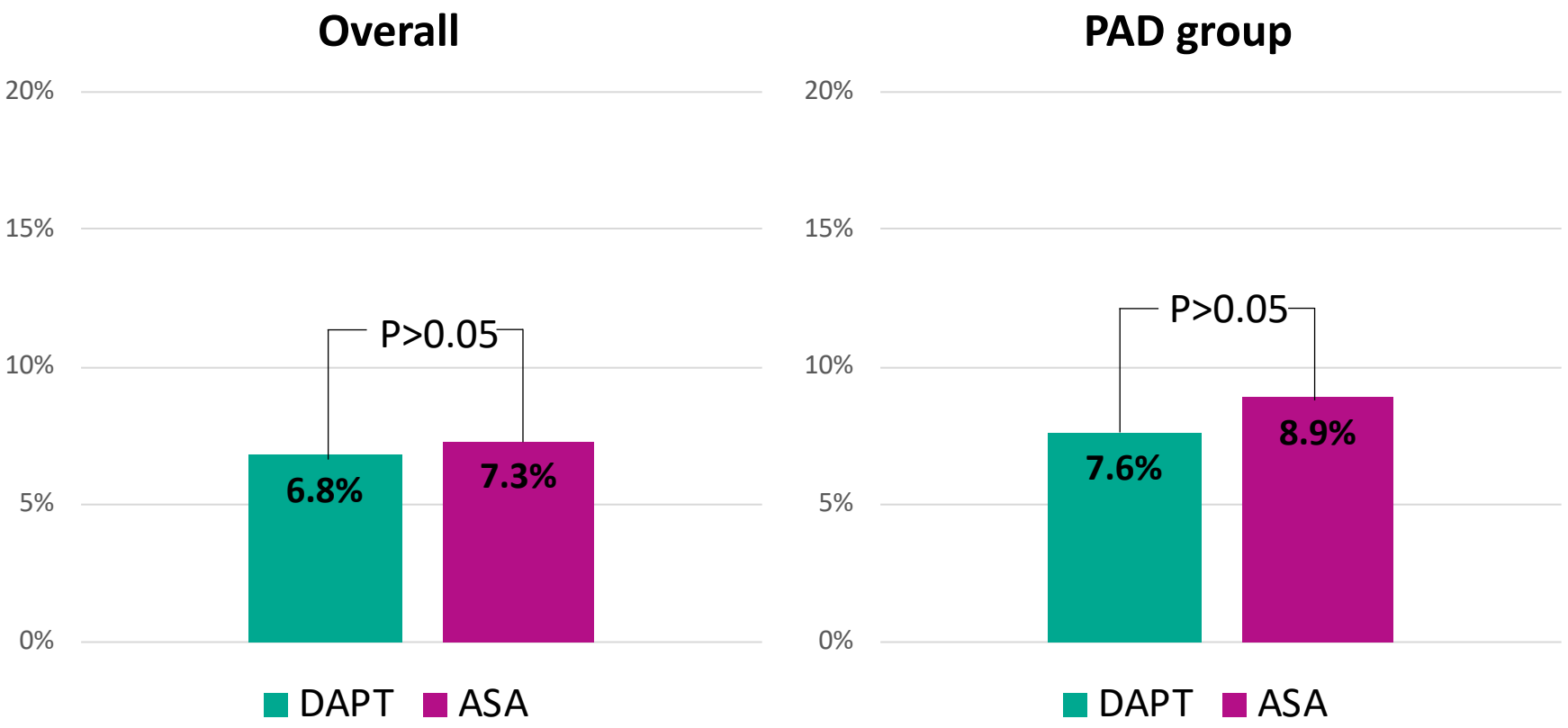


- Post-hoc analysis of randomized double-blind trial
- Mean age: 66 years
- Asymptomatic PAD: 8.4%
- Lower extremity revascularization: 50%
- Current smoker: 32%
- History of MI: 25%
- Statin use: 73%

Cacoub PP, et al. *Eur Heart Jd*. 2009; 30:1706-192-201.

DAPT: CHARISMA trial

Primary outcome: MI, stroke, CV death



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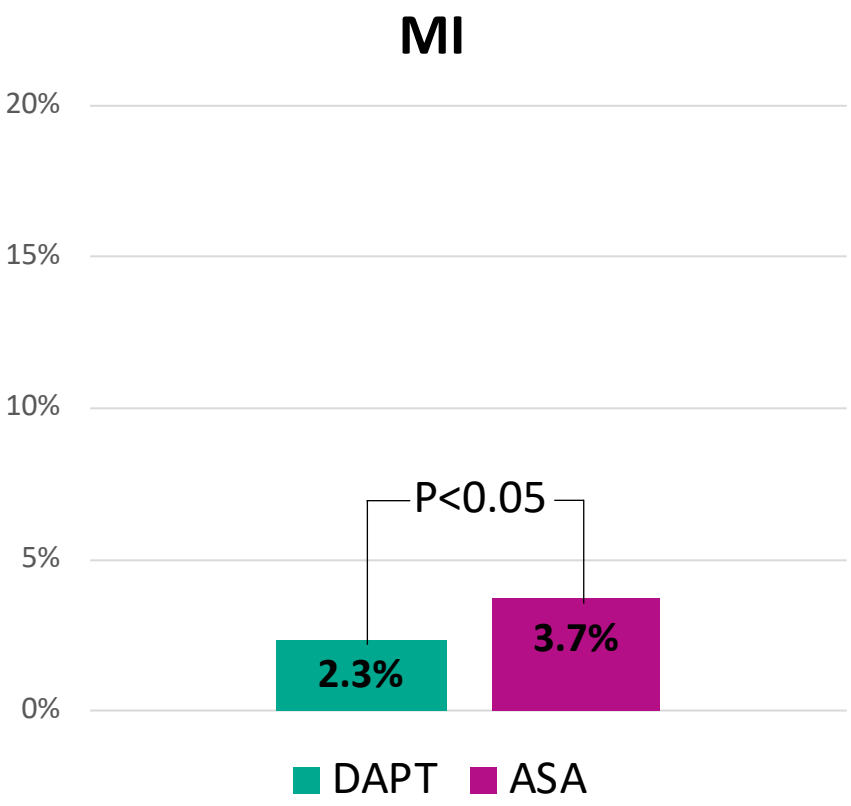
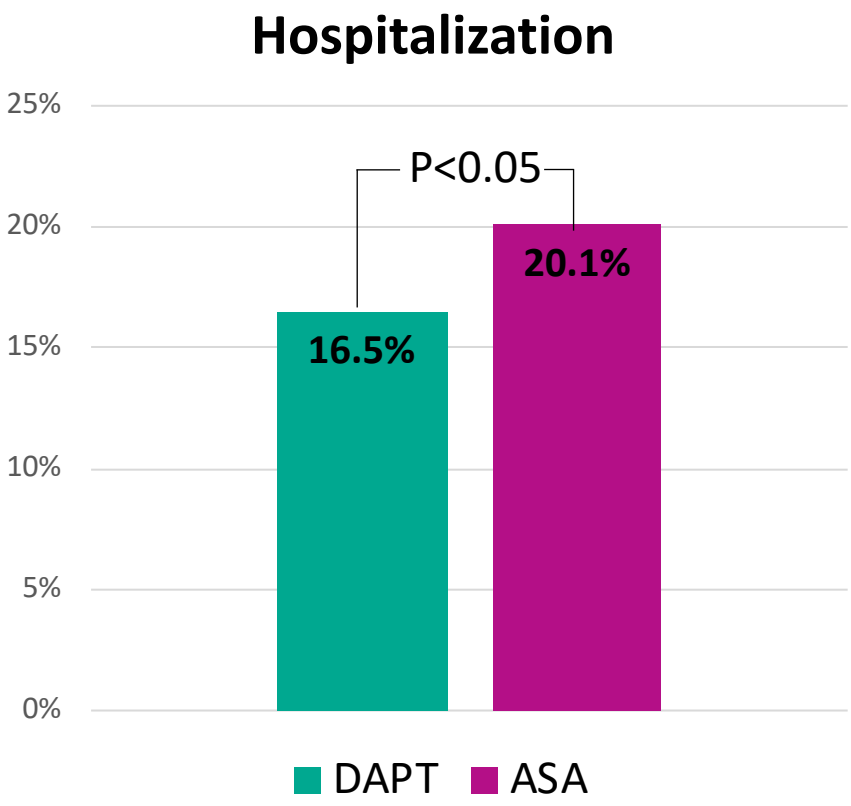
DAPT: CHARISMA trial





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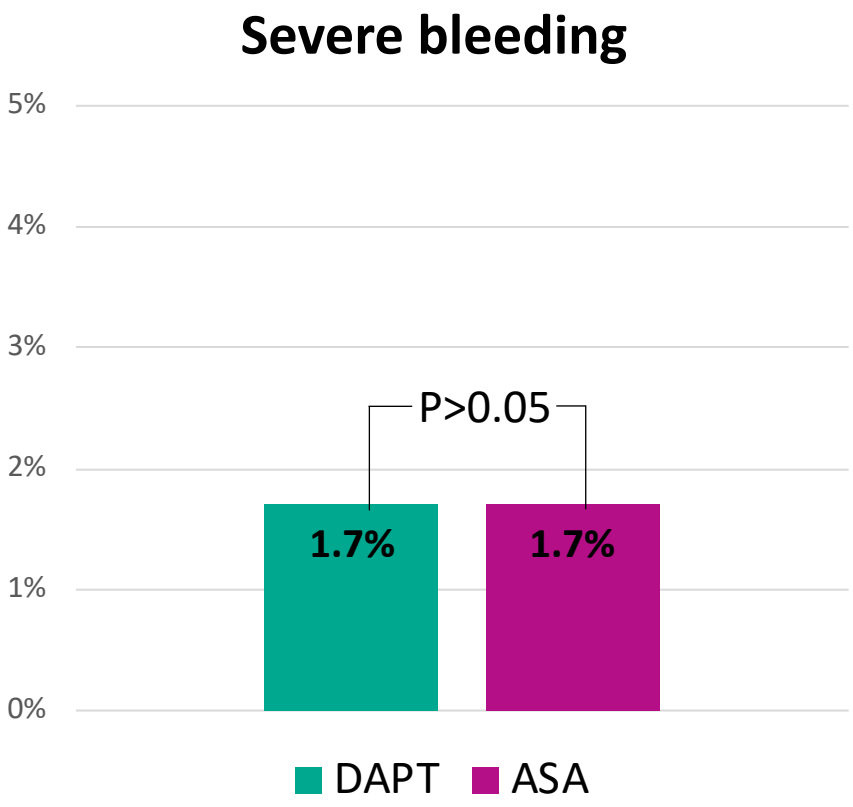
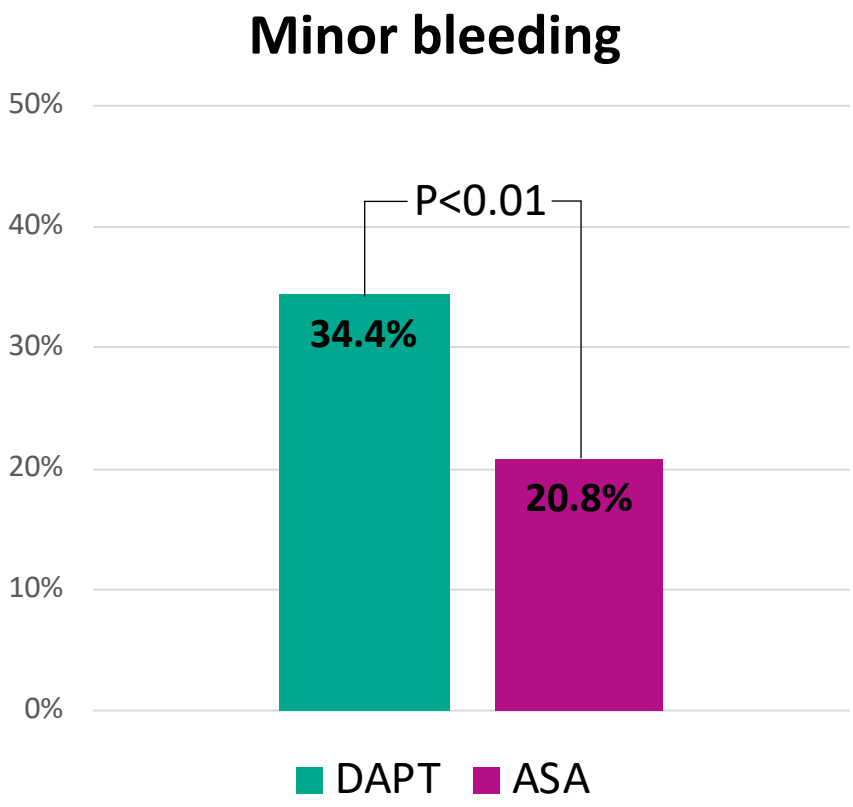
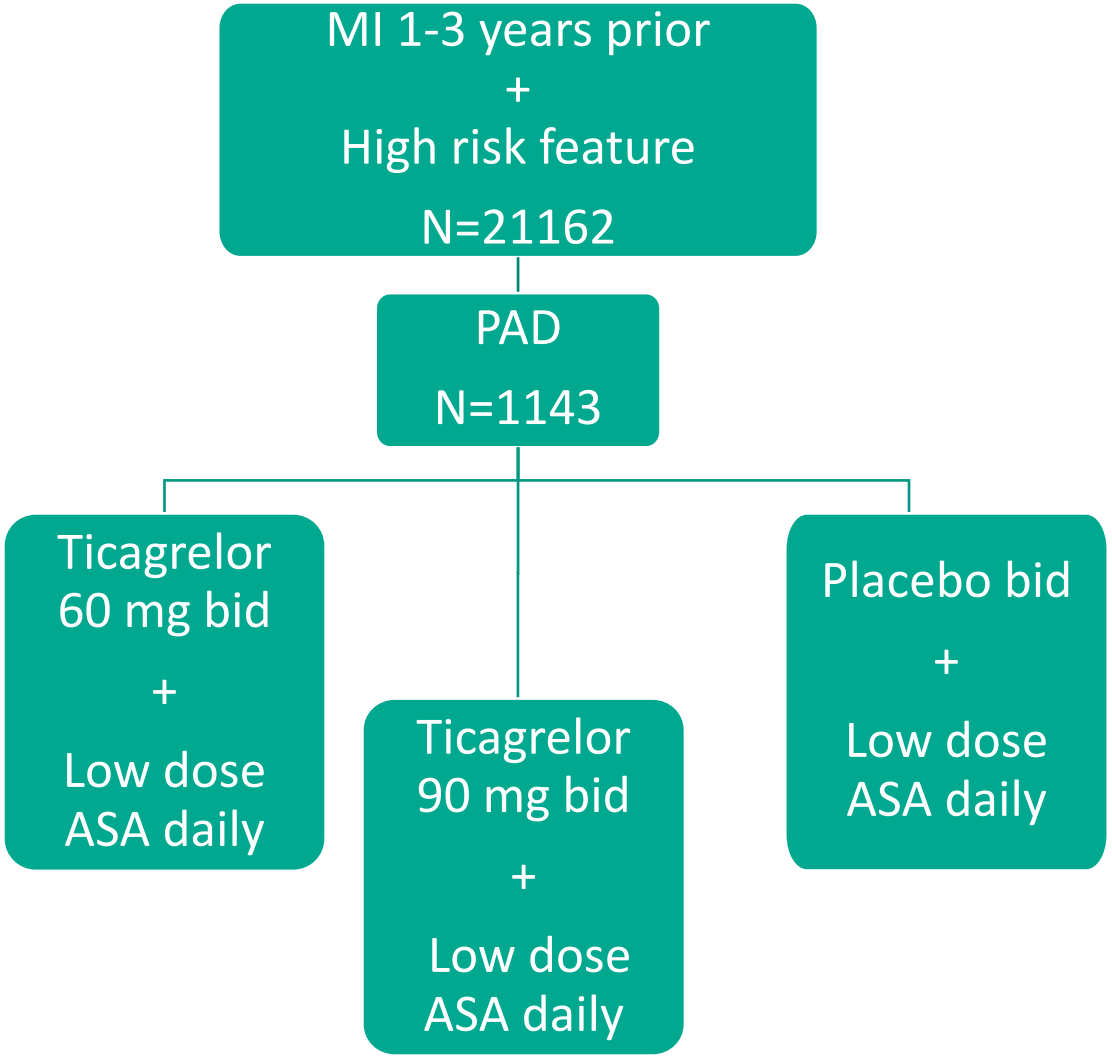
DAPT: CHARISMA trial





Cacoub PP, et al. *Eur Heart Jd*. 2009; 30:1706-192-201.

DAPT: PEGASUS TIMI

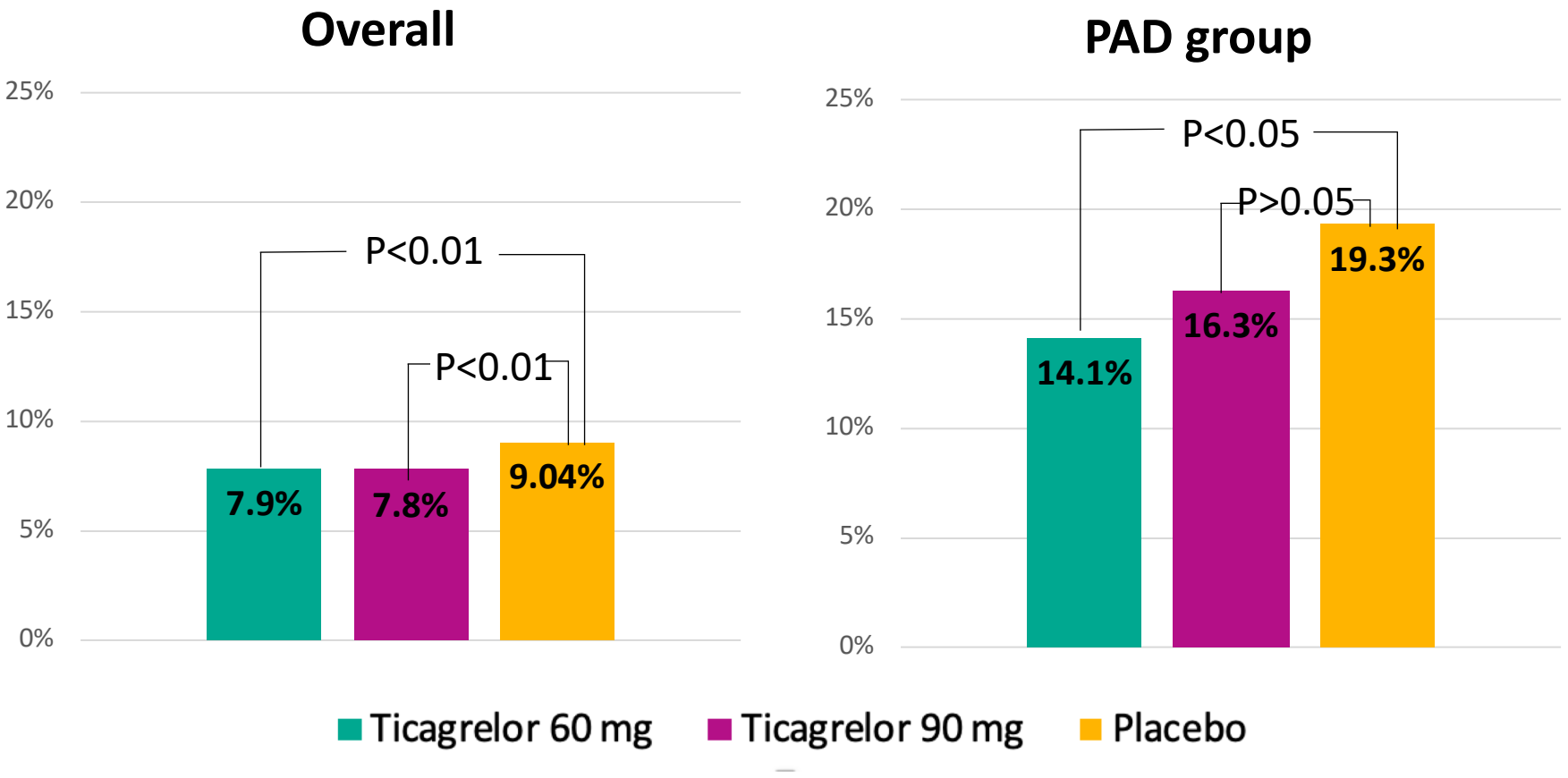


- Sub-analysis of randomized, double-blind trial
- Multi-vessel CAD: 64.4%
- History of PCI: 75.5%
- ABI ≤0.9: 19%
- Peripheral revascularizations: 34%
- Claudication: 65%
- Statin use: 93%

Bonaca MP, et al. *J Am Coll Cardiol*. 2016;67:2719-2728.

DAPT: PEGASUS TIMI

Primary outcome: MI, stroke, CV death



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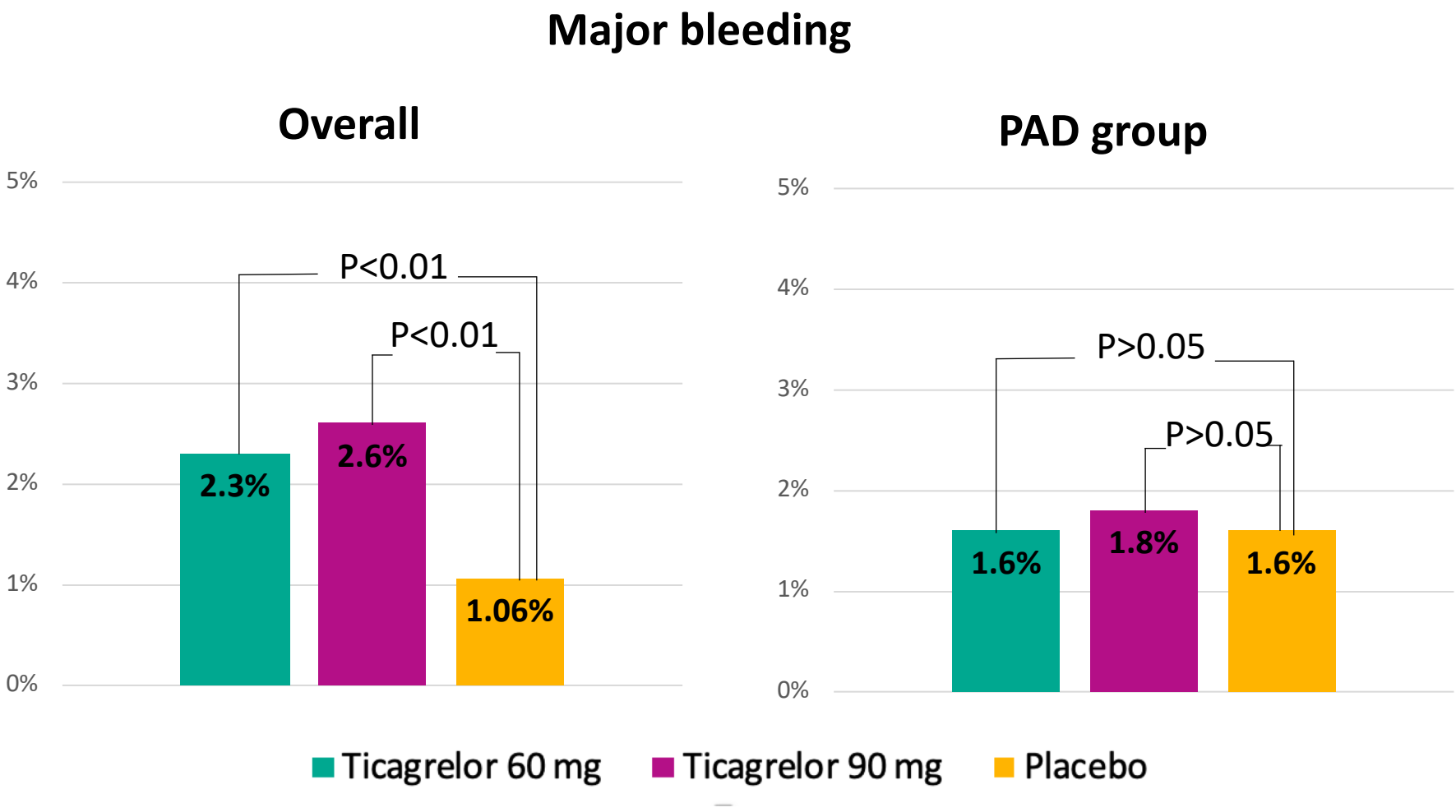
DAPT: PEGASUS TIMI



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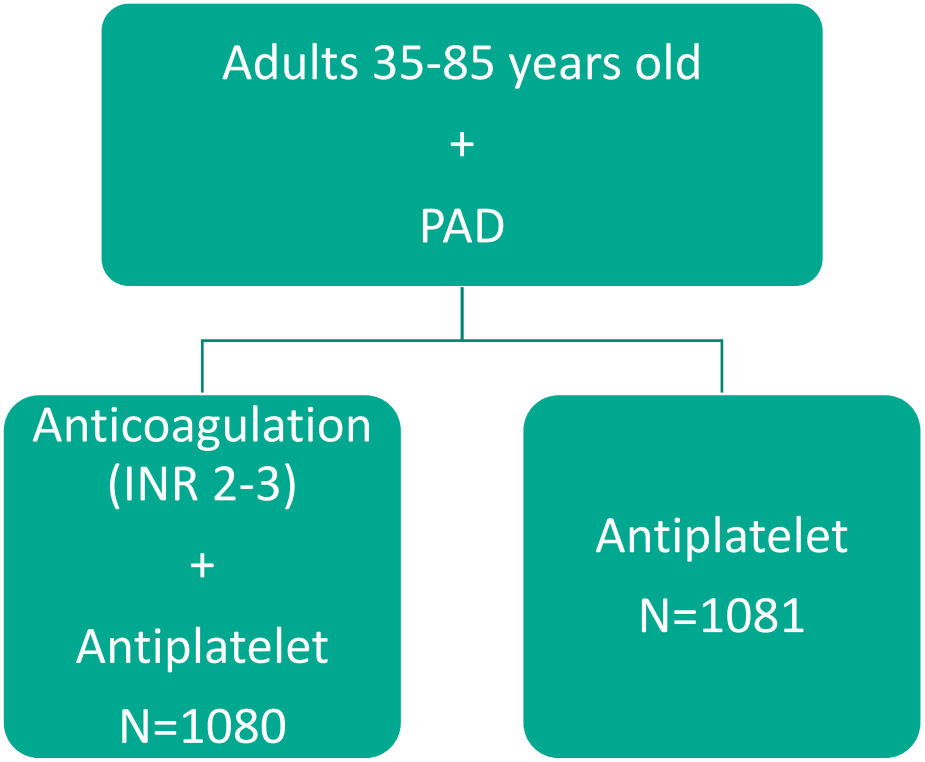
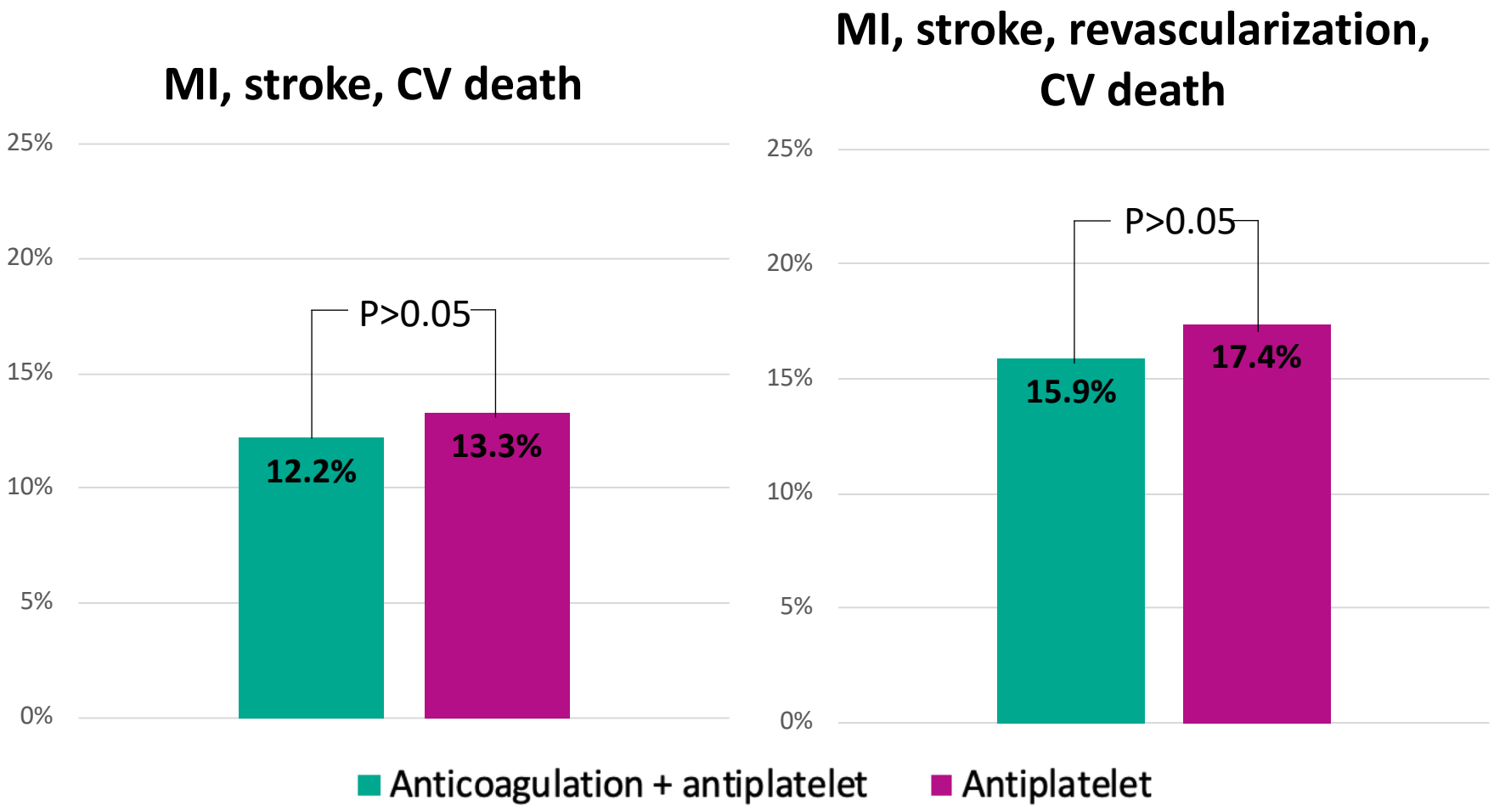
Anticoagulation: WAVE trial



- Randomized, open-label, multi-national trial
- PAD:
  - Symptomatic disease of lower extremities: ~82%
  - Carotid or subclavian atherosclerosis: history of stroke or TIA, carotid endarterectomy or stenosis >50%: ~18%
- Median age: 64 years
- Current smoker: ~29%
- Median ABI: 0.83
- CAD: ~47%
- ASA use: ~92%
- Statin use: ~44%

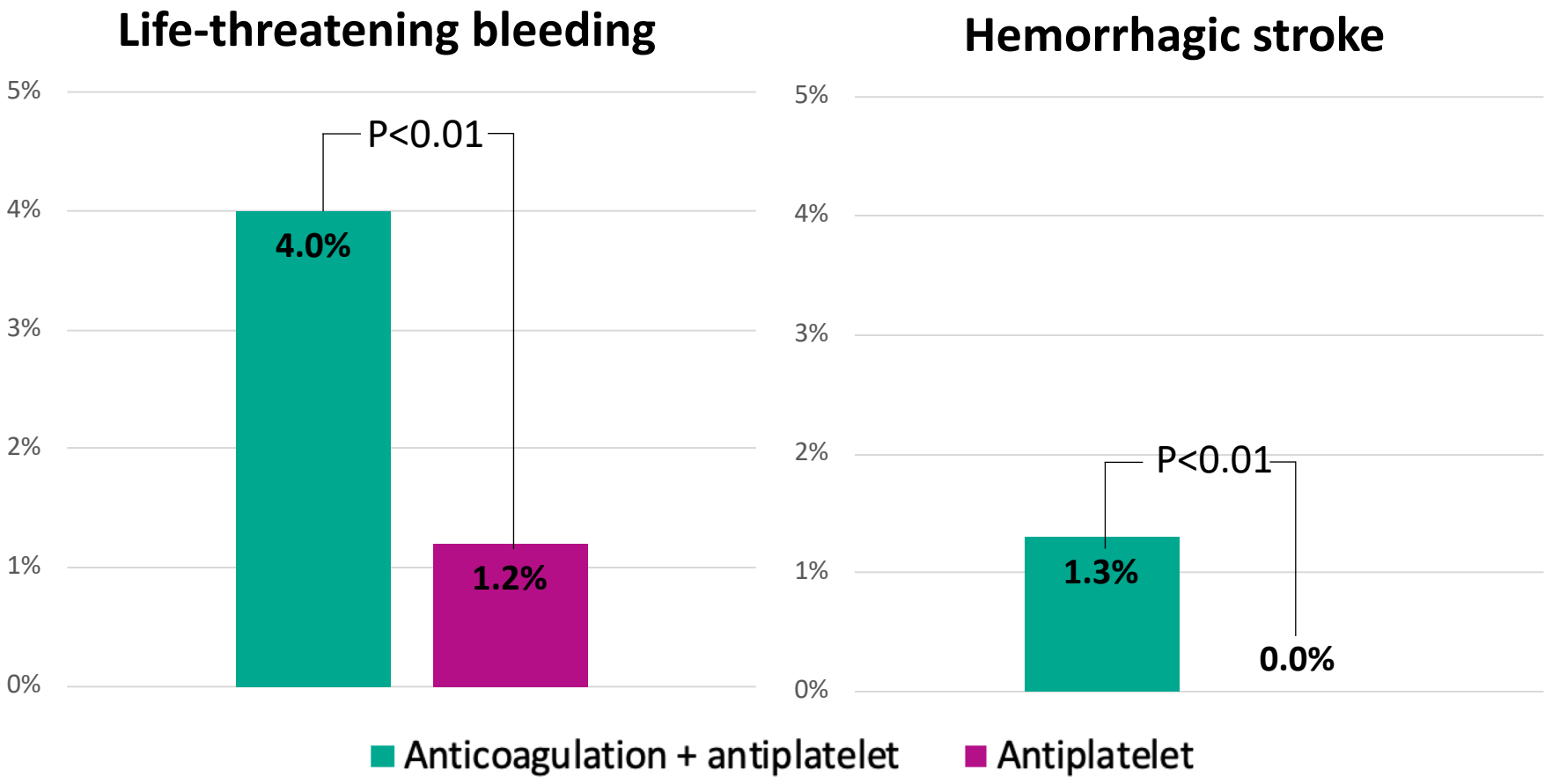
WAVE investigators. *N Engl J Med.* 2007;357:217-227.

Anticoagulation: WAVE trial



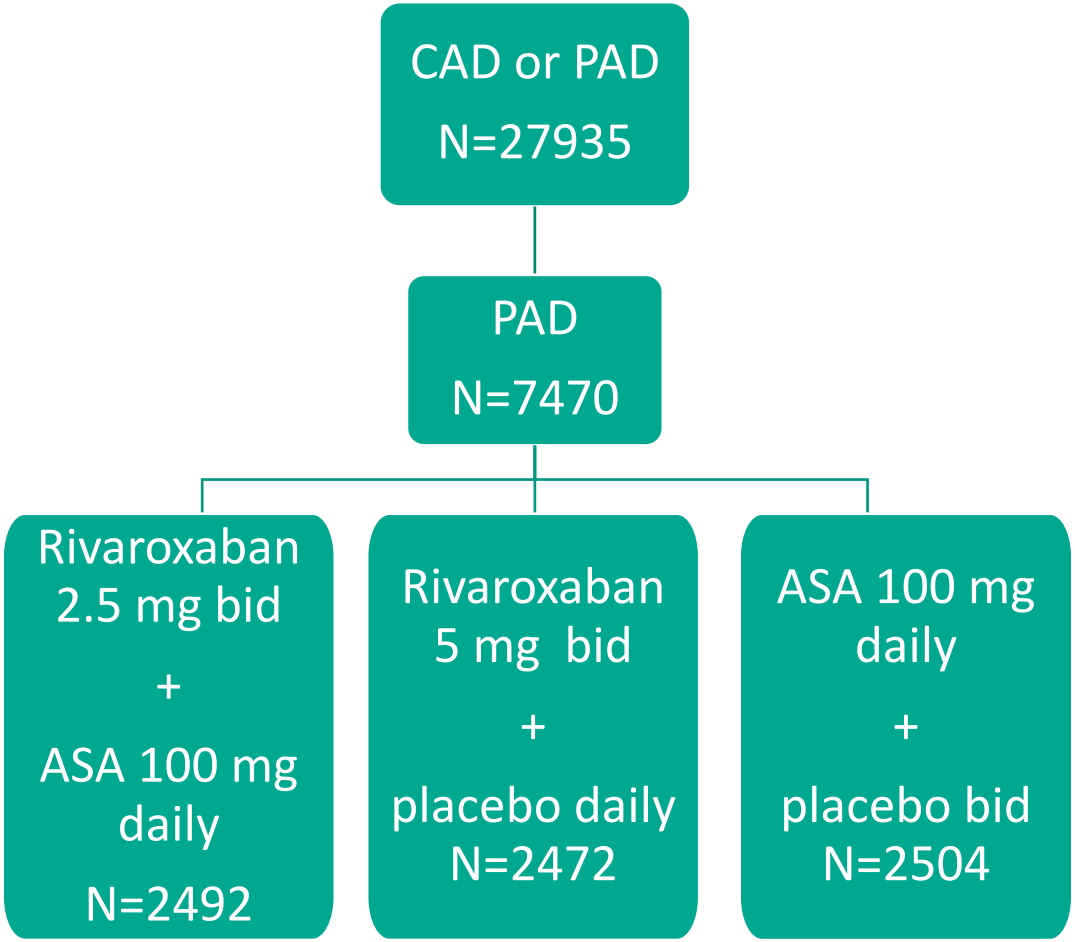
WAVE investigators. *N Engl J Med.* 2007;357:217-227.

Anticoagulation: WAVE trial



WAVE investigators. *N Engl J Med.* 2007;357:217-227.

Anticoagulation: COMPASS trial

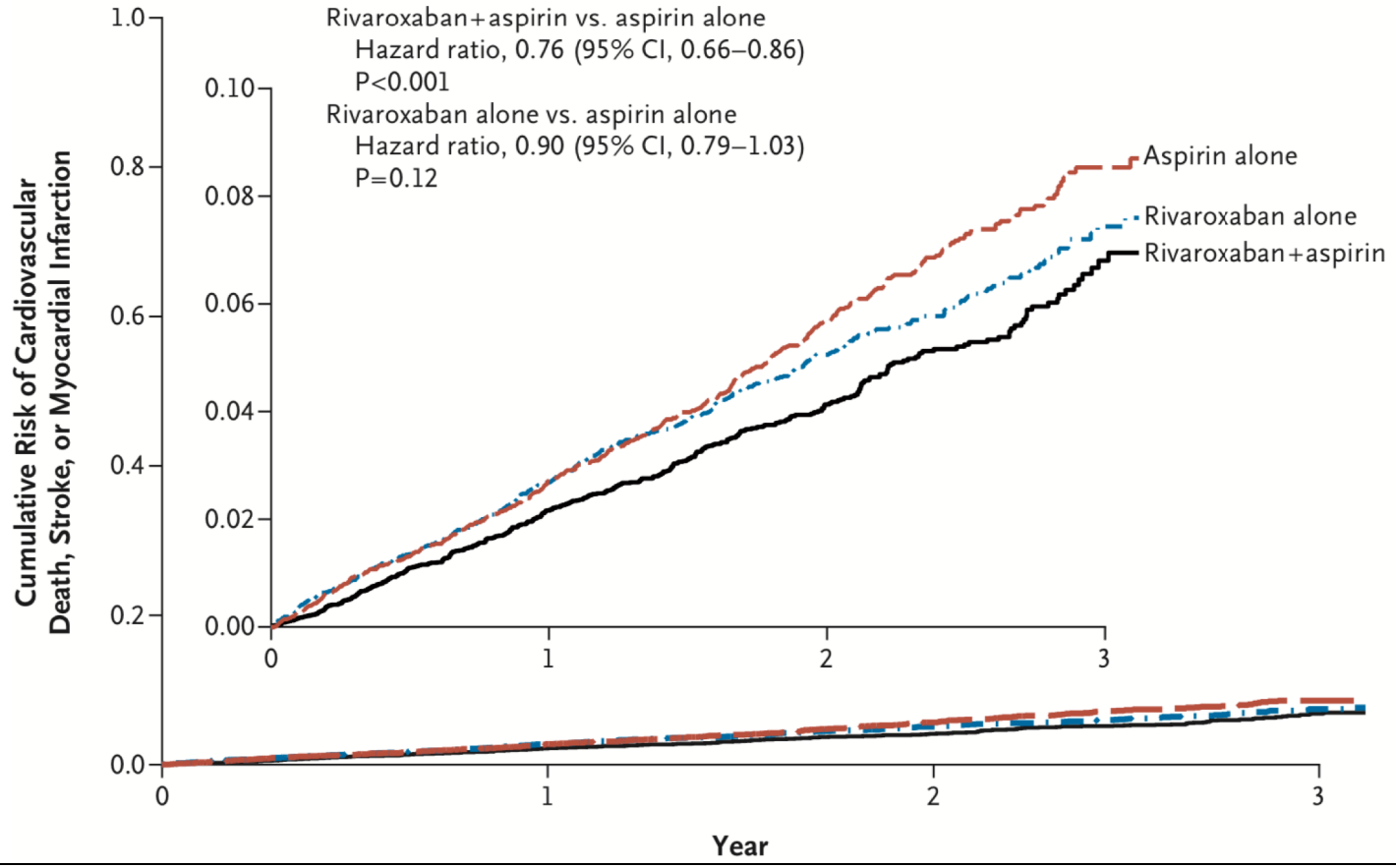


- Randomized, double-blind, multi-national
- PAD cohort inclusion:
  - Symptomatic PAD of lower extremities: 55%
  - Symptomatic PAD of carotid arteries: 26%
  - CAD + ABI $\leq$0.9: 19%
- Exclusion criteria
  - High risk of bleeding
  - EF <30%
  - CrCl <15 mL/min
- Mean age: ~68 years
- Current smoker: ~27%
- Lipid-lowering therapy: ~83%
- History of lower extremity revascularization: ~27%

Anand SS, et al. *Lancet.* 2018;391:219-229.
Eikelboom JW, et al. *N Engl J Med.* 2017;377:1319-1330.

Anticoagulation: COMPASS trial

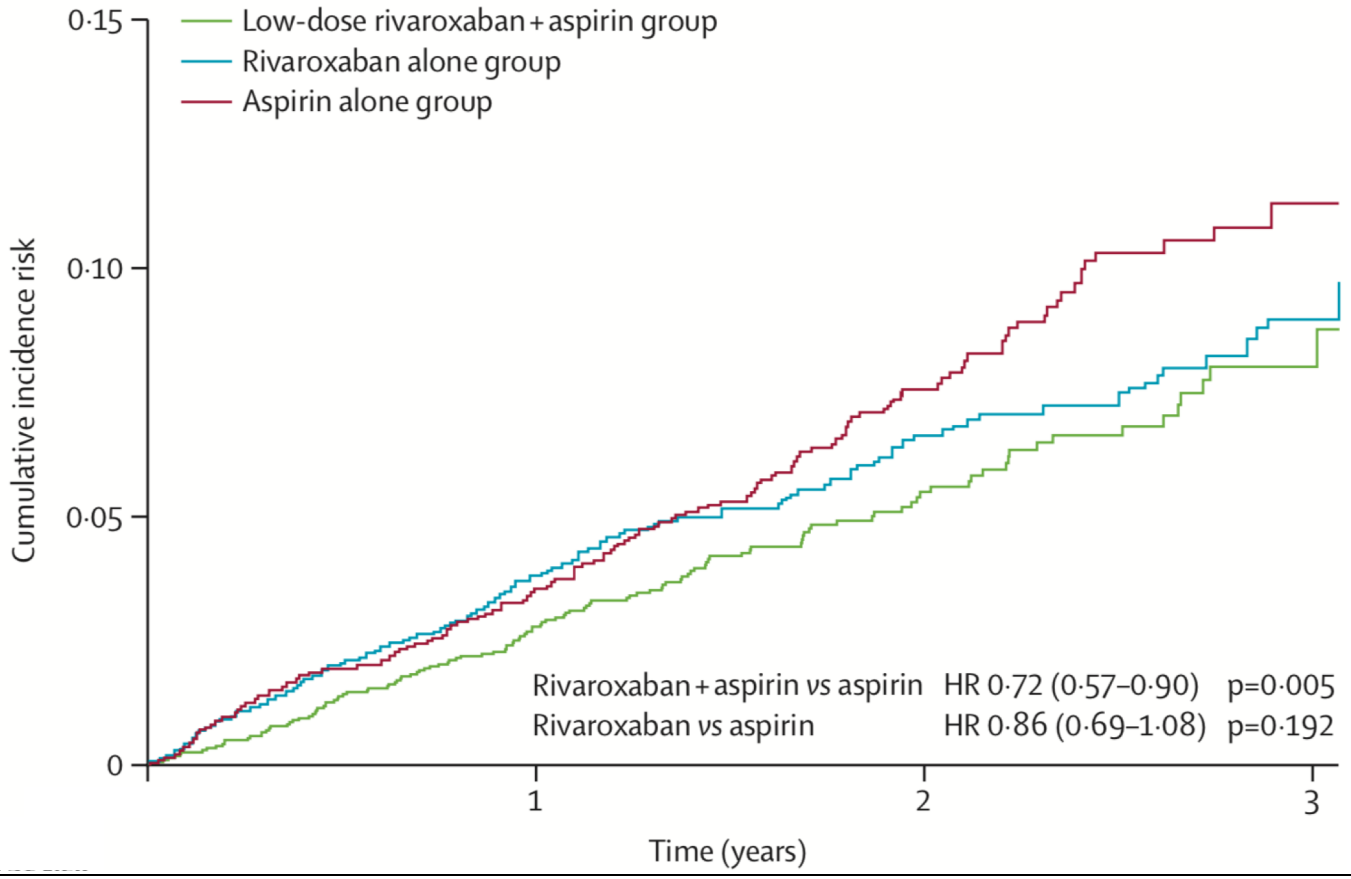
Primary outcome, overall population: CV death, stroke or MI



Eikelboom JW, et al. *N Engl J Med.* 2017;377:1319-1330.

Anticoagulation: COMPASS trial

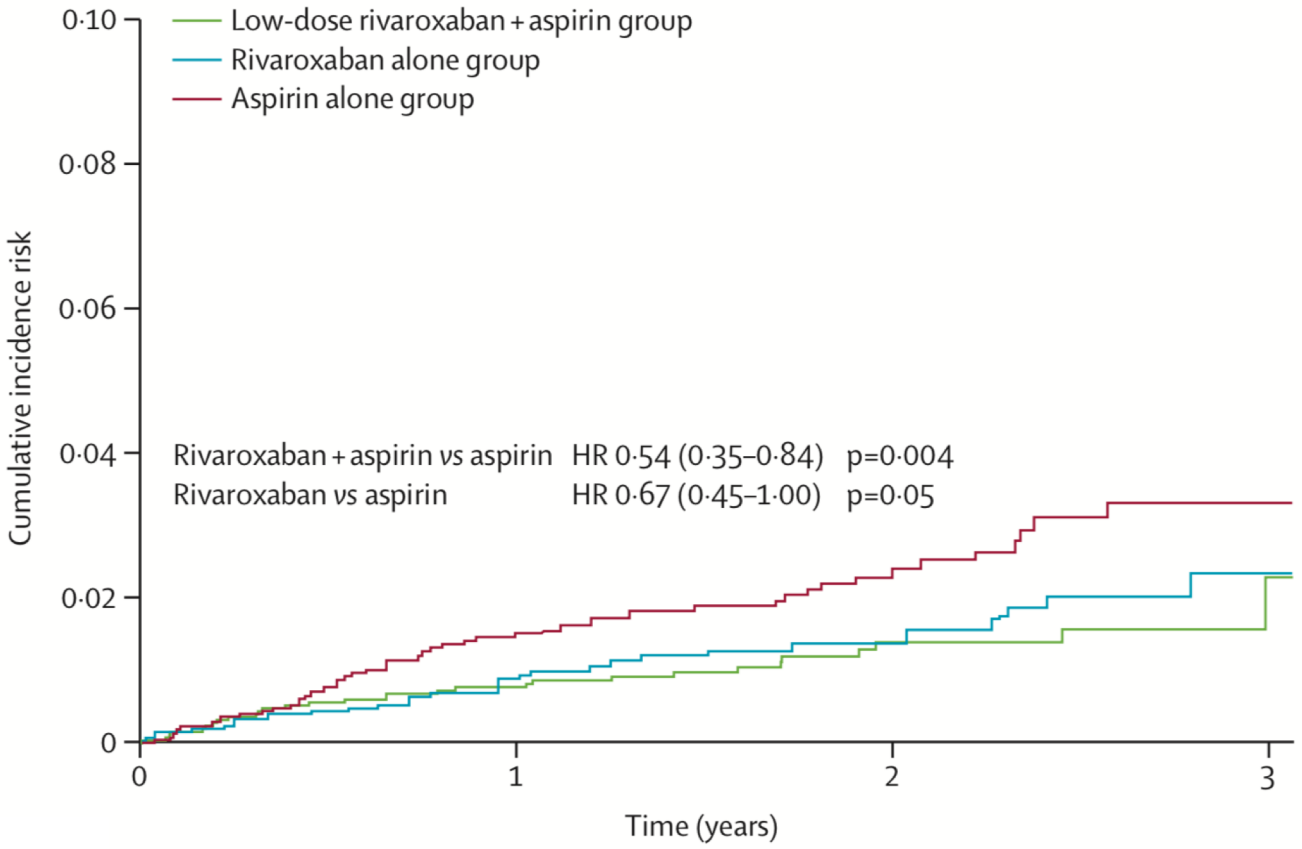
Primary outcome, PAD group: CV death, stroke or MI



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

Anticoagulation: COMPASS trial

Major adverse limb events: acute or chronic limb ischemia, amputations



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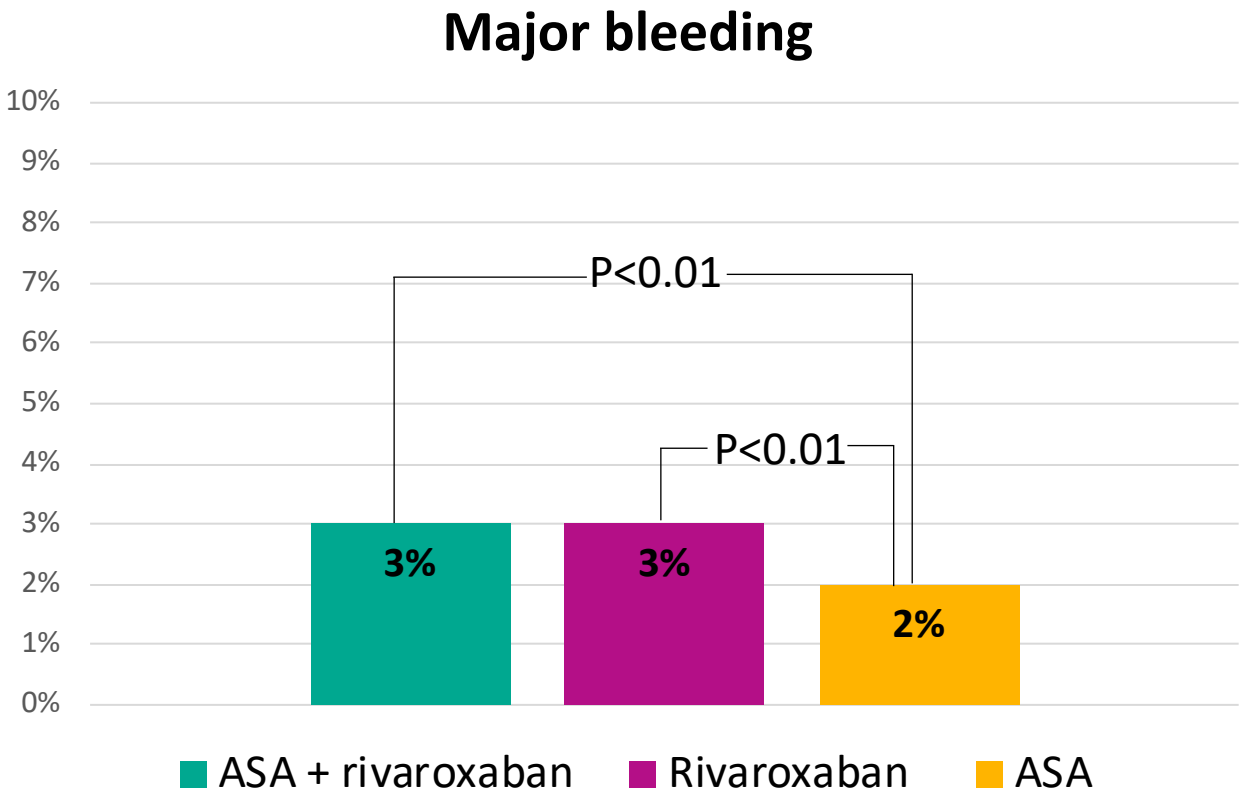
Anticoagulation: COMPASS trial



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

Guideline recommendations

ACC/AHA 2016	ACCP 2012
Antiplatelet monotherapy with ASA (75-325 mg) or clopidogrel (75 mg) to reduce MI, stroke or vascular death in patients with symptomatic PAD (IA)	For secondary prevention in symptomatic PAD we recommend antiplatelet monotherapy with ASA (75-100 mg) or clopidogrel (75 mg) long-term (1A)
Effectiveness of DAPT to reduce the risk of CV ischemic events is not well established (IIbB)	We suggest not to use DAPT with ASA + clopidogrel (2B)
Anticoagulation should not be used to reduce the risk of CV ischemic events in patients with PAD (IIIA)	We recommend not to use an antiplatelet agent with moderate-intensity warfarin(1B)

Gerhard-Herman MD, et al. *J Am Coll Cardiol*. 2017;69:1465-1508.
Alonso-Coello P, et al. *CHEST.* 2012;141:e669S-e690S.

Antithrombotic therapy after revascularization

Indications for revascularization

- Intermittent claudication (IC)
- Critical limb ischemia (CLI)
- Acute limb ischemia (ALI)

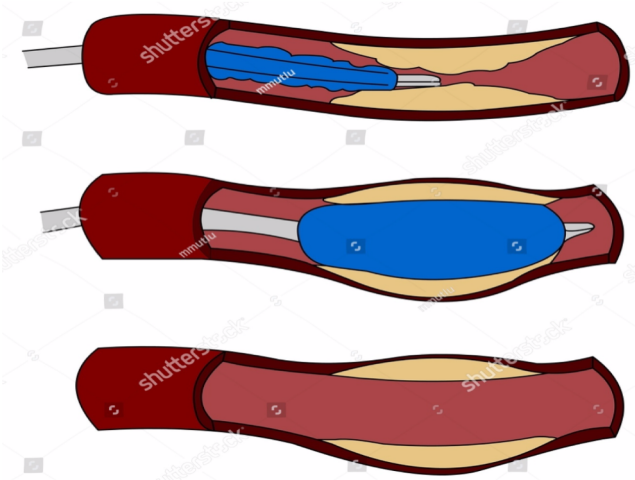
Goals of therapy after vascular interventions

- Prevent major adverse limb events (MALE):
  - Amputation
  - Reintervention
- Maintain patency
  - Primary patency: requires no intervention to maintain
  - Primary assisted patency: requires intervention to maintain
- Subjective outcomes:
  - Function
  - Quality of life

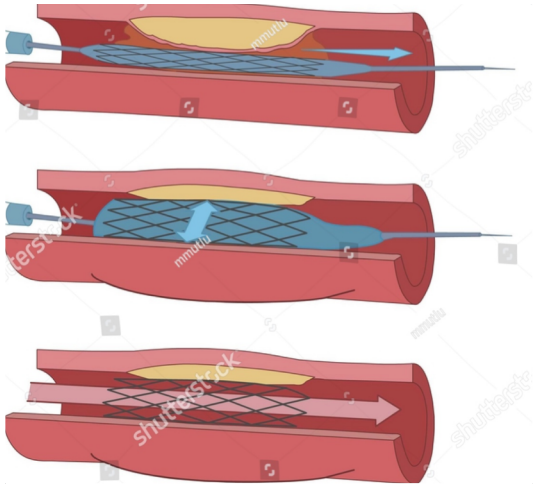
Revascularization methods:

Endovascular revascularization (EVT)

Drug-coated or bare balloon



Drug-coated or bare stent

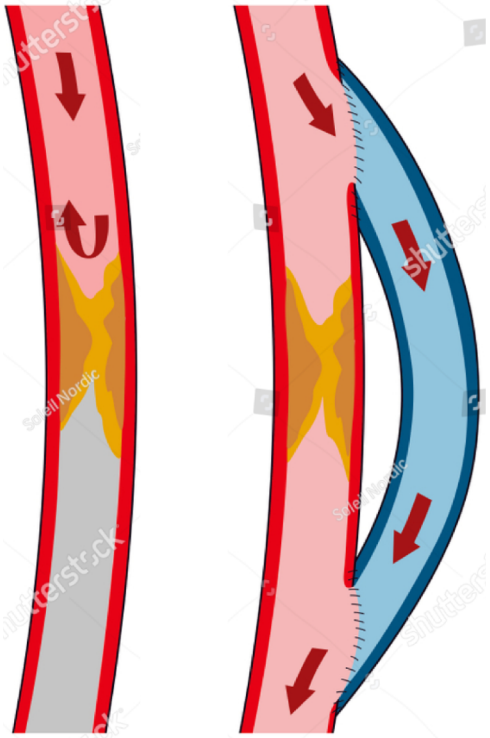


Atherectomy

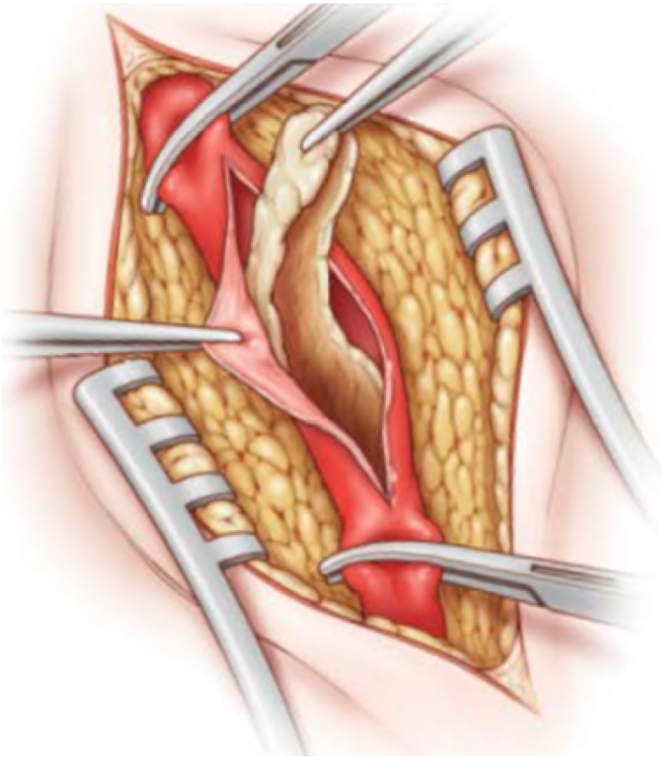
Revascularization methods:

Surgical revascularization

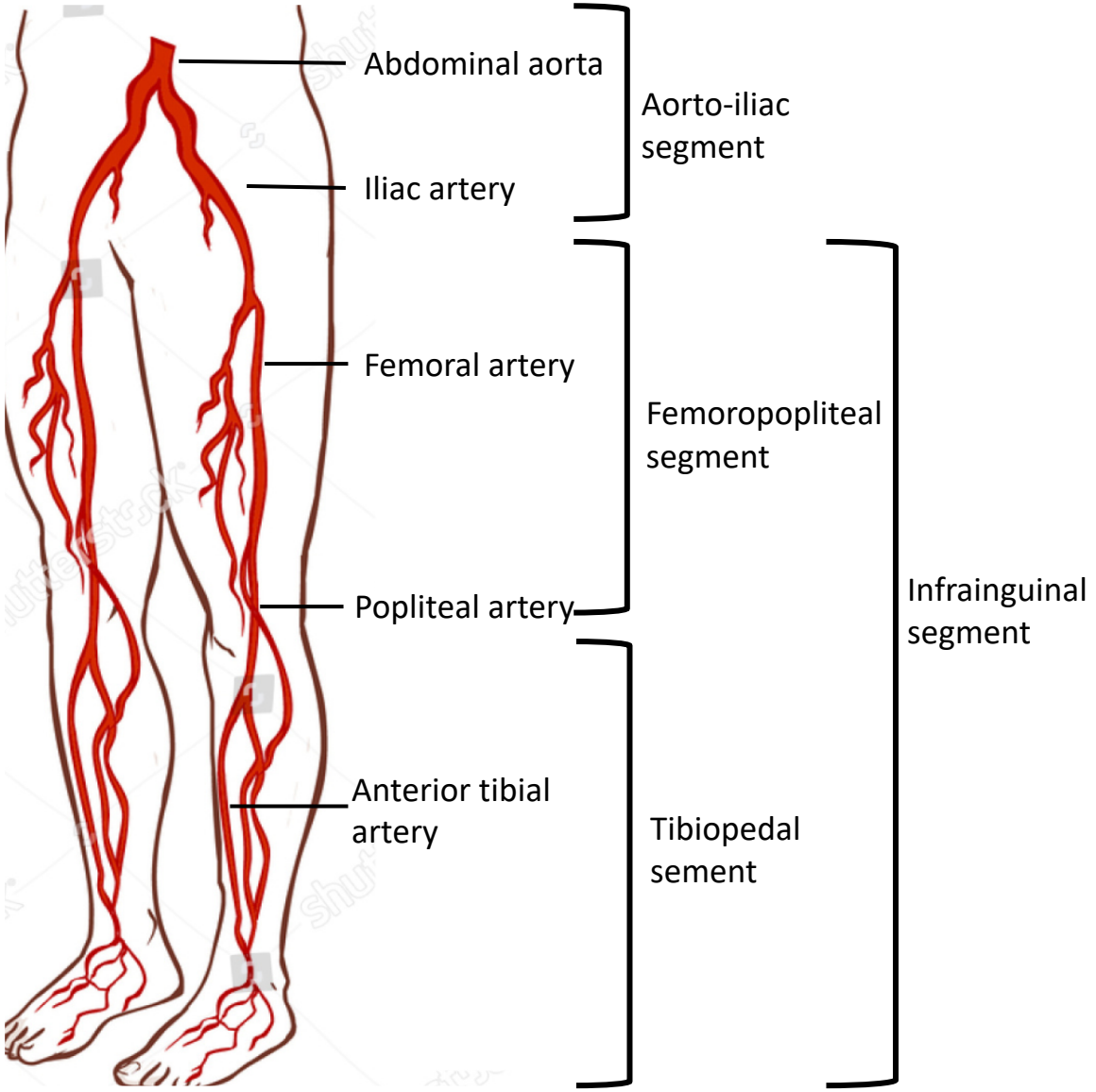
Prosthetic or venous bypass



Endarterectomy



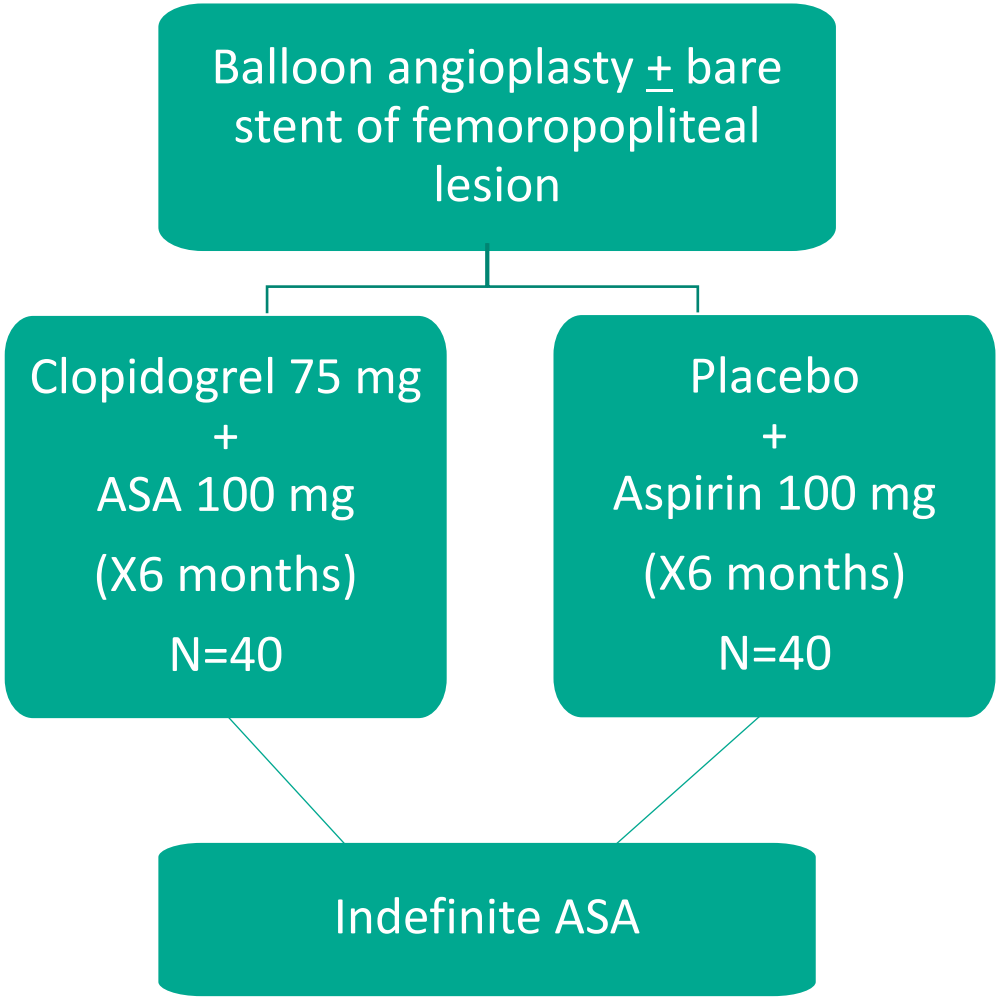
Anatomic landmarks



Predictors of poor outcomes

- No optimal medical therapy
- Below-knee (tibial) revascularization
- Presentation with CLI
- Tissue loss
- Smoking
- History of intervention of the same segment
- Bypass: non-venous material

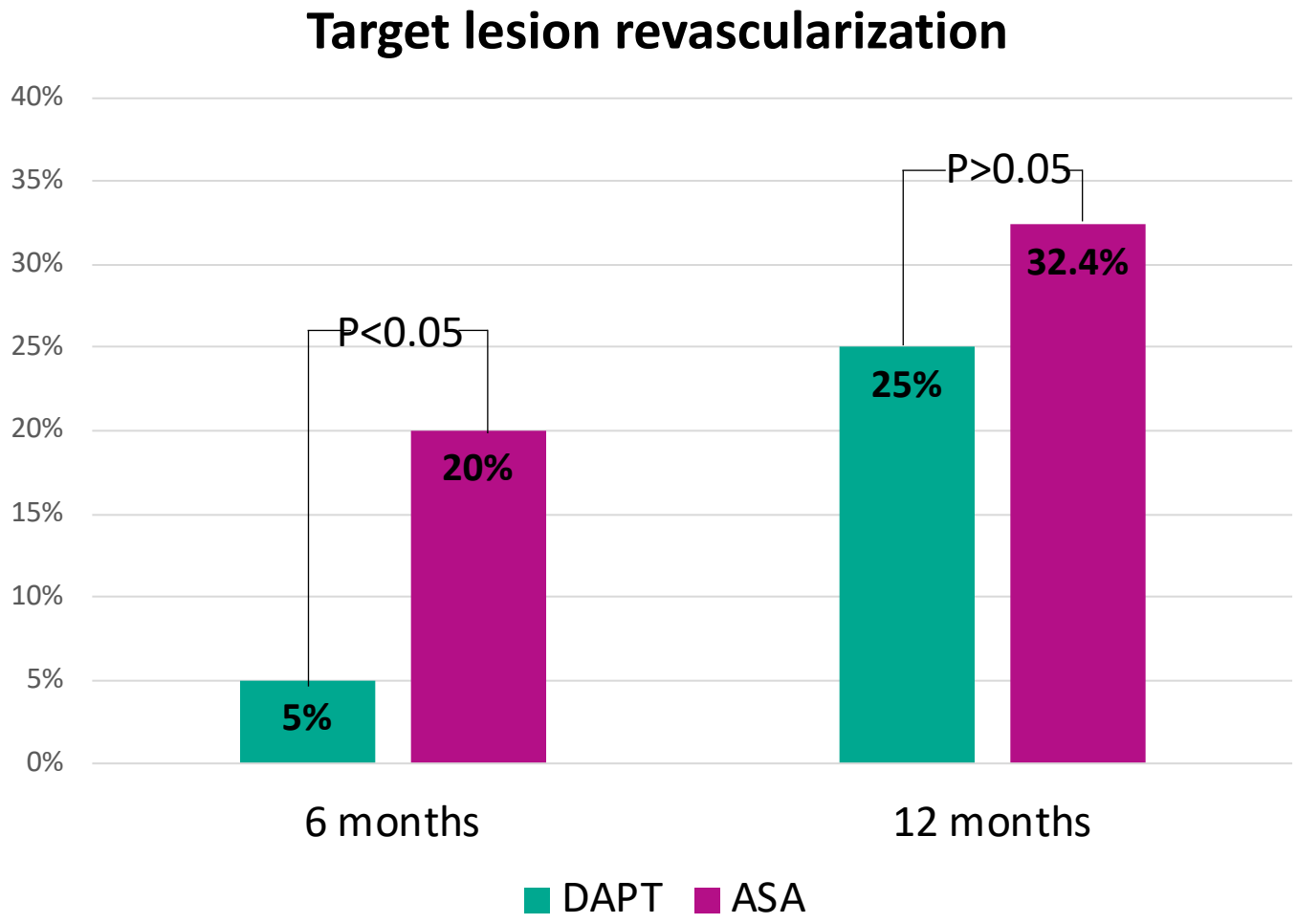
DAPT: MIRROR



- Randomized, double-blind trial
- Primary outcome: concentration of platelet activation markers
- Age: ~70 years
- Smokers: ~40%
- Received stent:
  - DAPT: 62.5%
  - ASA: 47.5%

Strobl FF. *J Endovasc Ther.* 2013;20:699-706.

DAPT: MIRROR



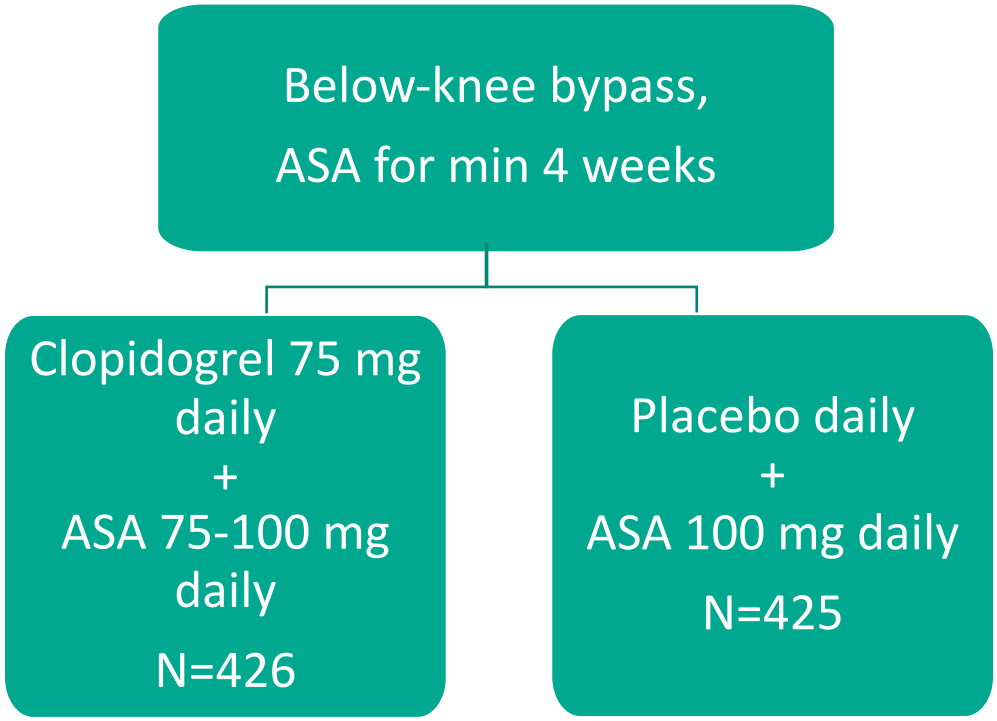
Strobl FF. *J Endovasc Ther.* 2013;20:699-706.

DAPT: MIRROR

- Considerations:
  - Less revascularization in the DAPT group at 6 months, but no difference in restenosis >50% at 6 months
  - Very small sample size → likely underpowered
    - Cannot estimate risk of bleeding
    - Cannot estimate risk or redo revascularization with angioplasty vs stent
  - More patients in the DAPT group received stent
  - No information on concomitant therapy
- Conclusion:
  - DAPT may prevent need for repeat revascularization after angioplasty ± stent, but the net risk/benefit cannot be determined from this trial due to limited sample size

Strobl FF. *J Endovasc Ther.* 2013;20:699-706.

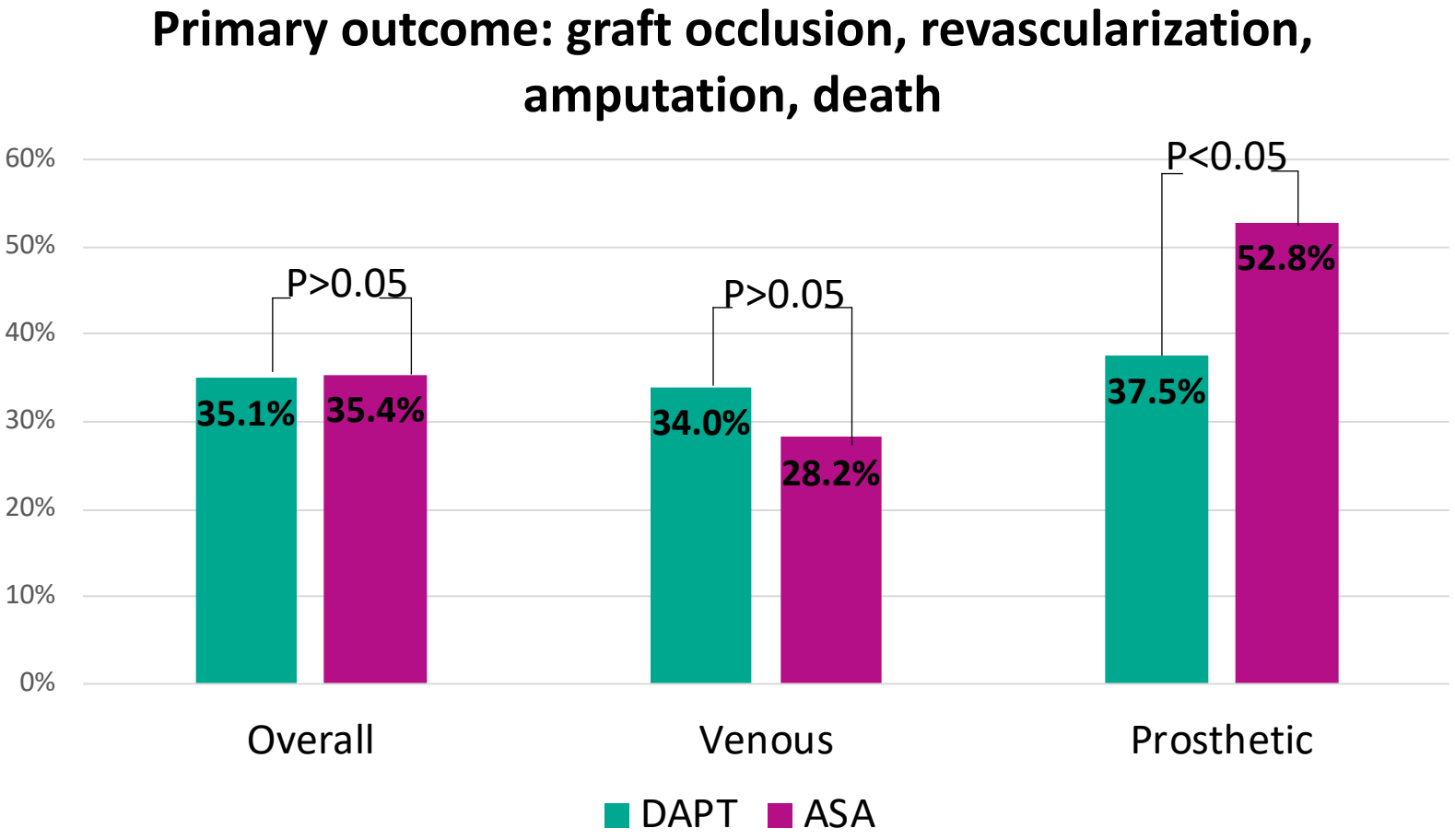
DAPT: CASPAR



- Randomized, double-blind trial
- Age: ~66 years
- Smoker: ~37%
- Ulcer/gangrene: ~40%
- Statin use: ~48%
- Venous graft: ~70%
- Follow up: 6-24 months

Belch JJF, et al. *J Vasc Surg.* 2010;52:825-833

DAPT: CASPAR



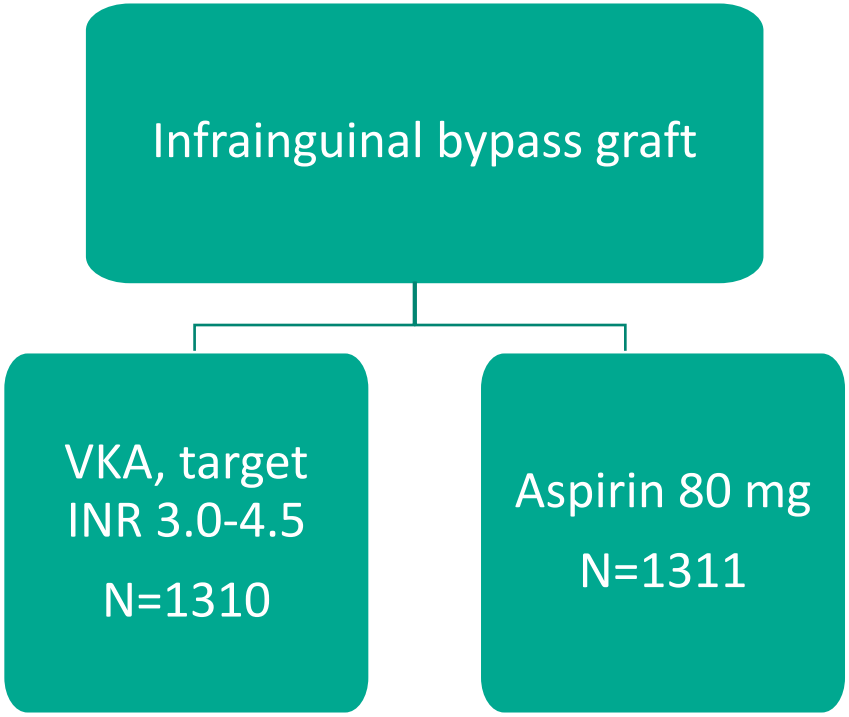
Belch JJF, et al. *J Vasc Surg.* 2010;52:825-833

DAPT: CASPAR

- Less amputations DAPT vs ASA in prosthetic group: 9.4% vs 19.2%, P<0.05
- Bleeding, DAPT vs ASA
  - All bleeding: 16.7 %vs 7.1%, P<0.01
  - Severe bleeding: 2.1% vs 1.2%, P>0.05
- Considerations:
  - High risk population
  - Well balanced groups
  - High rates of bleeding and amputations
  - Only 50% received statin at baseline
- DAPT X 12 months may be considered for patients at high risk of restenosis and amputation (below-knee prosthetic graft) who are at low risk of bleeding

Belch JJF, et al. *J Vasc Surg.* 2010;52:825-833

Anticoagulation: BOA study

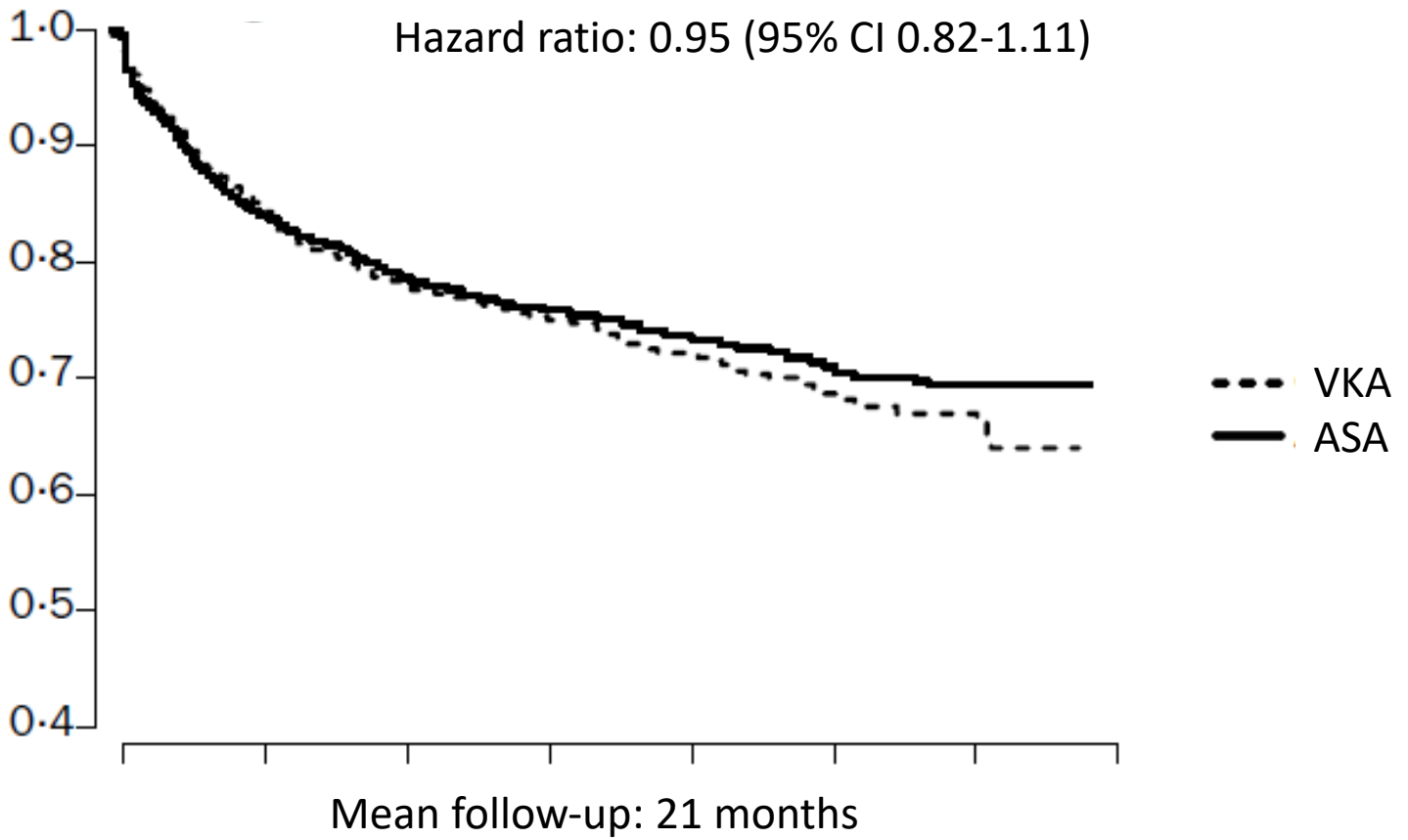


- Randomized, prospective, open-label
- Mean age: 69 years
- Indication
  - IC: 50%
  - Pain at rest: 21%
- Site of anastomosis
  - Femoropopliteal, above knee: 46%
  - Femoropopliteal, below knee: 34%
- Graft material
  - Vein: 59%
  - Prosthetic: 32%

BOA Study Group. *Lancet.* 2000;355:346-351.

Anticoagulation: BOA study

Primary outcome: graft occlusion

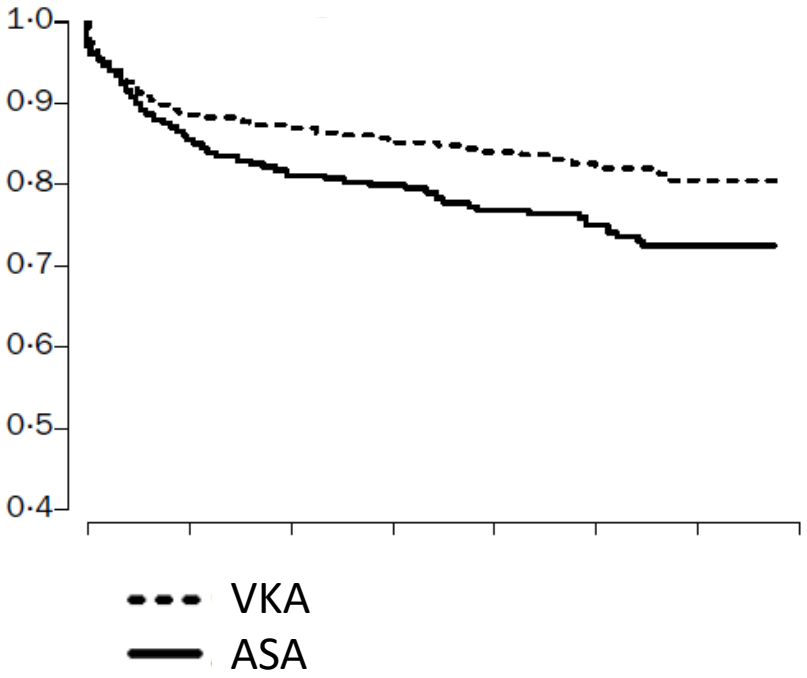


BOA Study Group. *Lancet.* 2000;355:346-351.

Anticoagulation: BOA study

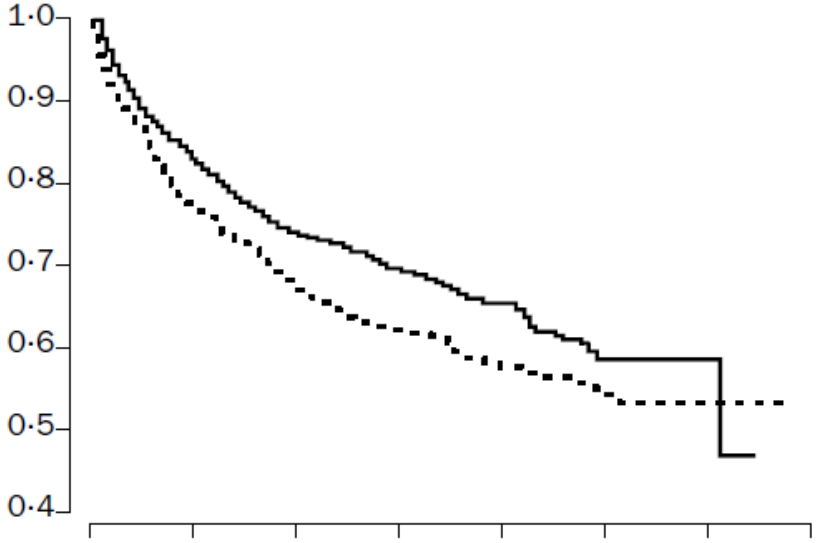
Occlusion in vein grafts

Hazard ratio: 0.64 (95% CI 0.54-0.88)



Occlusion in non-venous grafts

Hazard ratio: 1.26 (95% CI 1.03-1.55)



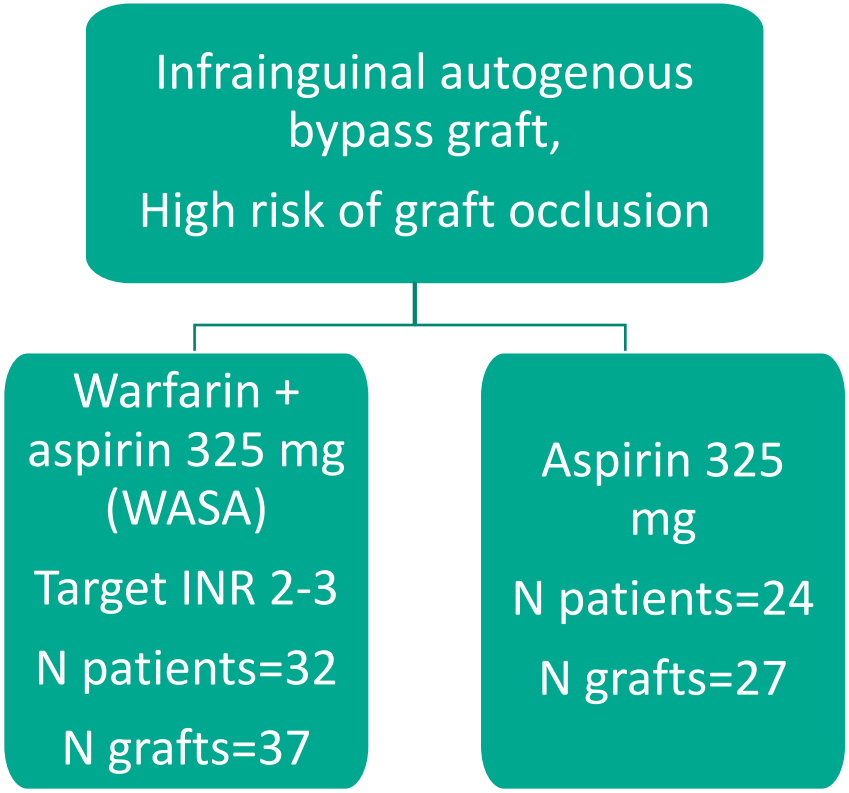
BOA Study Group. *Lancet.* 2000;355:346-351.

Anticoagulation: BOA study

- Safety, VKA vs ASA:
  - Hemorrhage hazard ratio: 1.96 (95% CI 1.42-2.71)
  - Hemorrhagic stroke hazard ratio: 3.48 (95% CI 1.14-10.6)
- Considerations:
  - High INR goal
  - Pre- and post-intervention use of statin is not described
  - Percent smokers not reported
  - Overall possibly low risk patients
- Conclusion: High intensity warfarin cannot be recommended for the prevention of graft occlusion in low-risk patients due to excessive risk of bleeding.

BOA Study Group. *Lancet.* 2000;355:346-351.

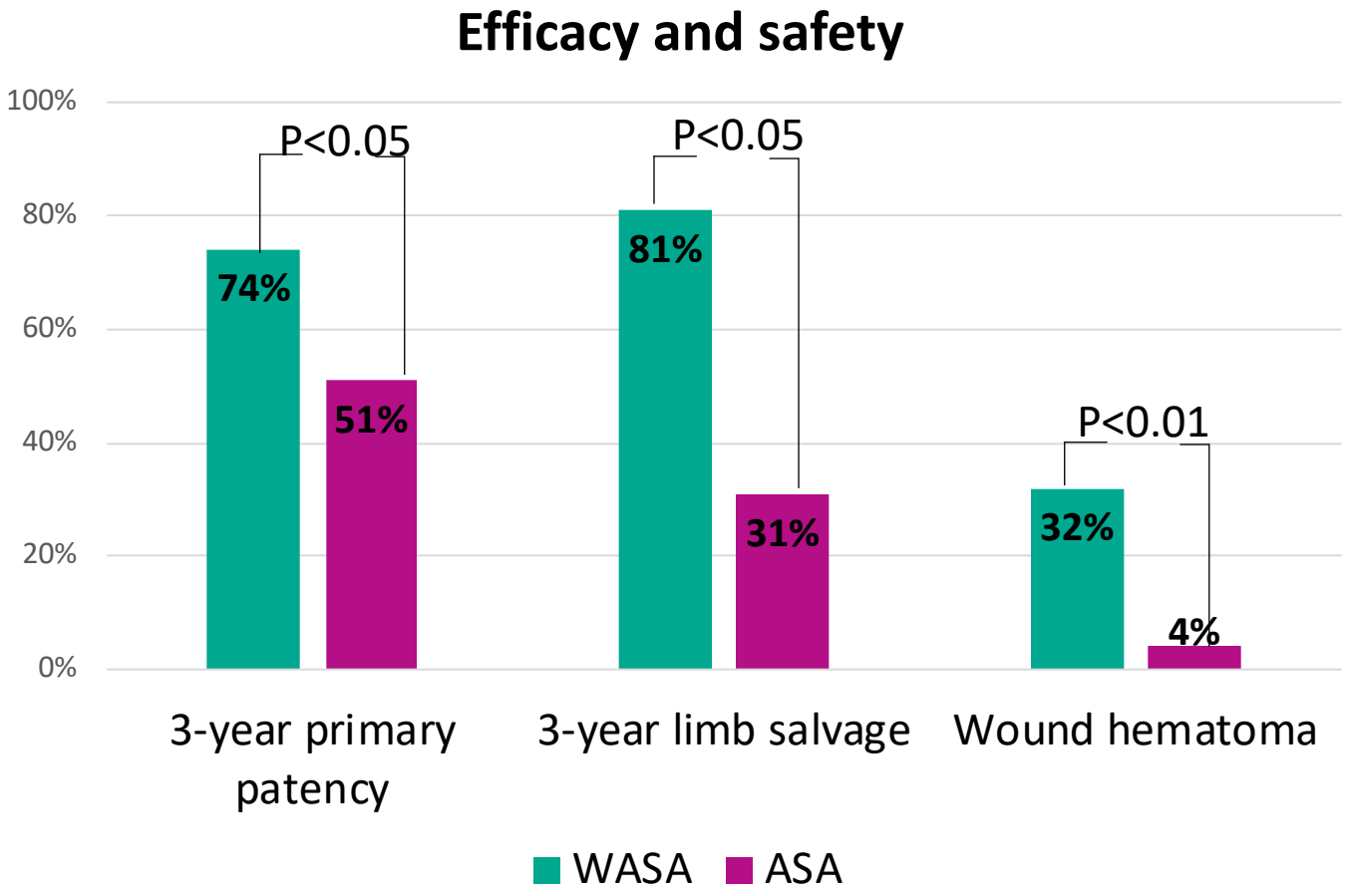
Anticoagulation+antiplatelet: Sarac, et al



- Randomized, open label
- Excluded: history of intracranial, GI or GI bleeding
- High risk of occlusion:
  - Poor venous conduit
  - Poor arterial runoff
  - Redo bypass
- Mean age: ~67 years
- Baseline characteristics, WASA vs ASA:
  - >1 inclusion criterion: 24% vs 33%
  - Smoker: 41% vs 25%
  - Below-knee target: 92% vs 74%

Sarac TP, et al. *J Vasc Surg. 1998*;28:446-457

Anticoagulation + antiplatelet: Sarac et al



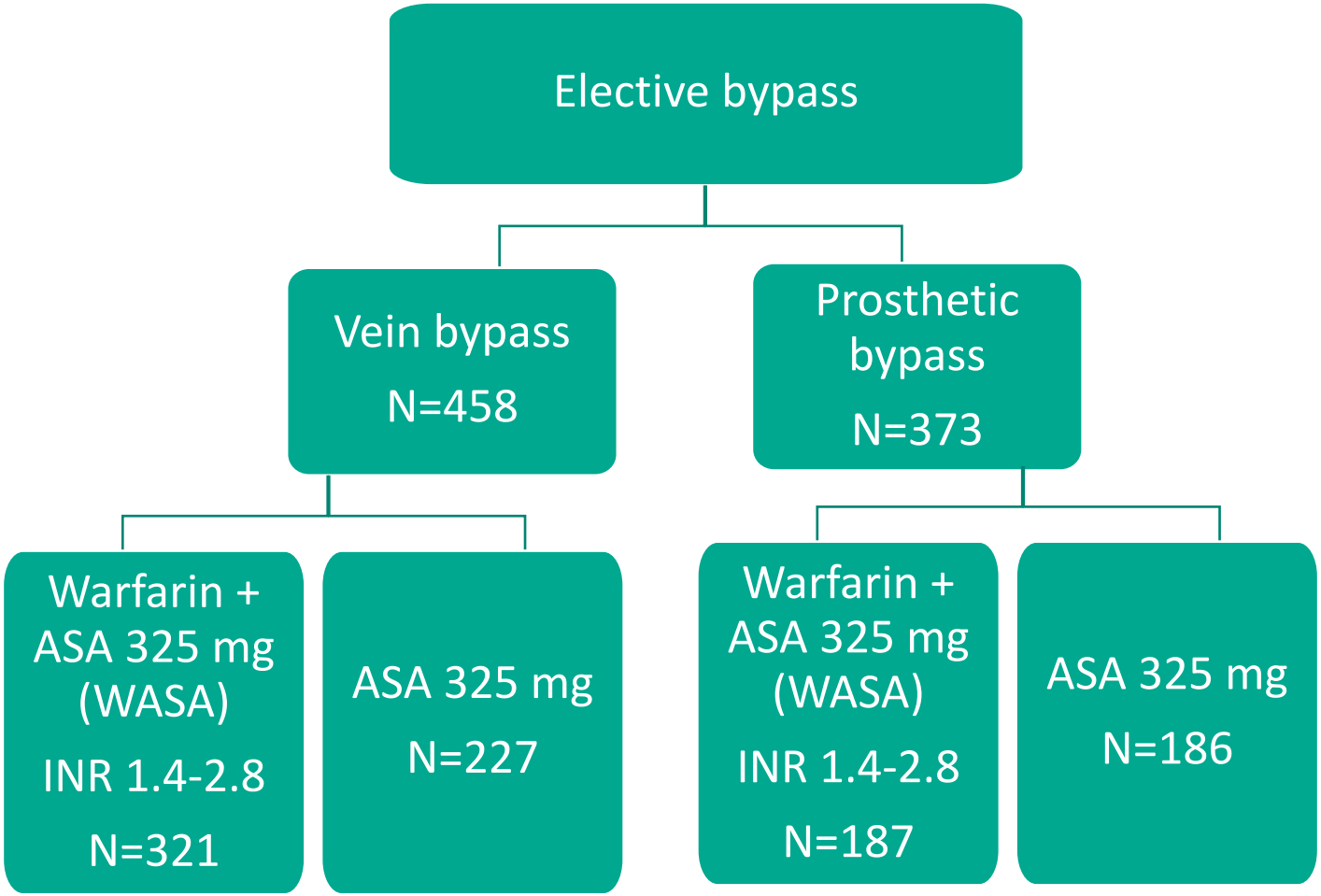
Sarac TP, et al. *J Vasc Surg. 1998*;28:446-457

Anticoagulation + antiplatelet: Sarac et al

- Considerations:
  - Patient with high risk of bleeding excluded
  - High risk population
  - High dose aspirin
  - Statin use is not reported
  - Unclear duration of therapy
  - Only pre-operative hemorrhage rates reported
  - 3 co-primary outcomes
- Conclusion: Moderate intensity warfarin in combination with aspirin 325 mg may prevent vein graft occlusion and amputation in high risk patients but cannot be recommended due to uncertain risk of bleeding

Sarac TP, et al. *J Vasc Surg. 1998*;28:446-457

Anticoagulation + antiplatelet: Johnson, et al



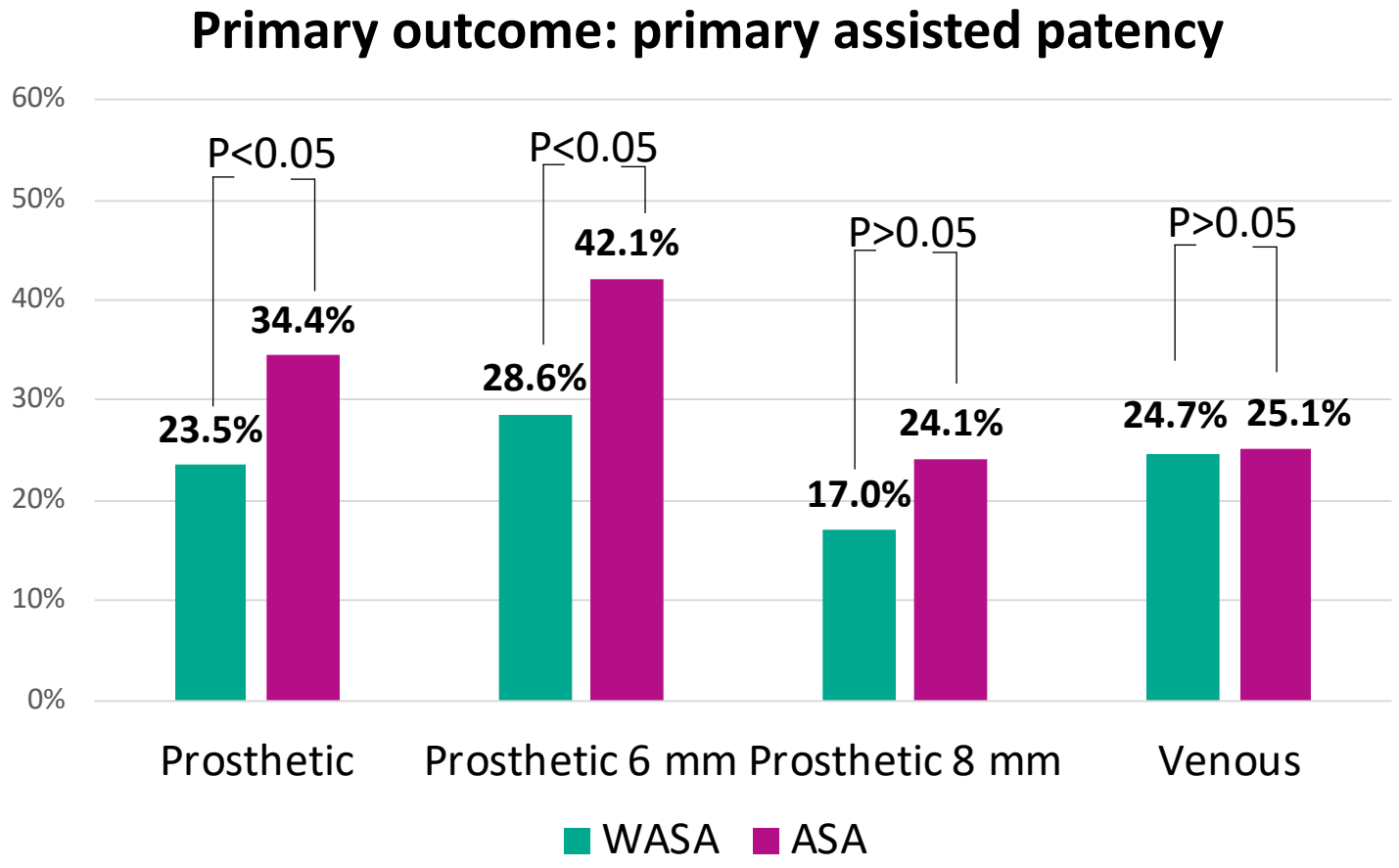
Johnson WC, et al. *J Vasc Surg. 2002*;35:413-421.

Anticoagulation + antiplatelet: Johnson, et al

- Randomized, open label
- Excluded:
  - Prior prosthetic bypass in the same location
  - High bleeding risk, CKD

Johnson WC, et al. *J Vasc Surg. 2002*;35:413-421.

Anticoagulation + antiplatelet: Johnson, et al



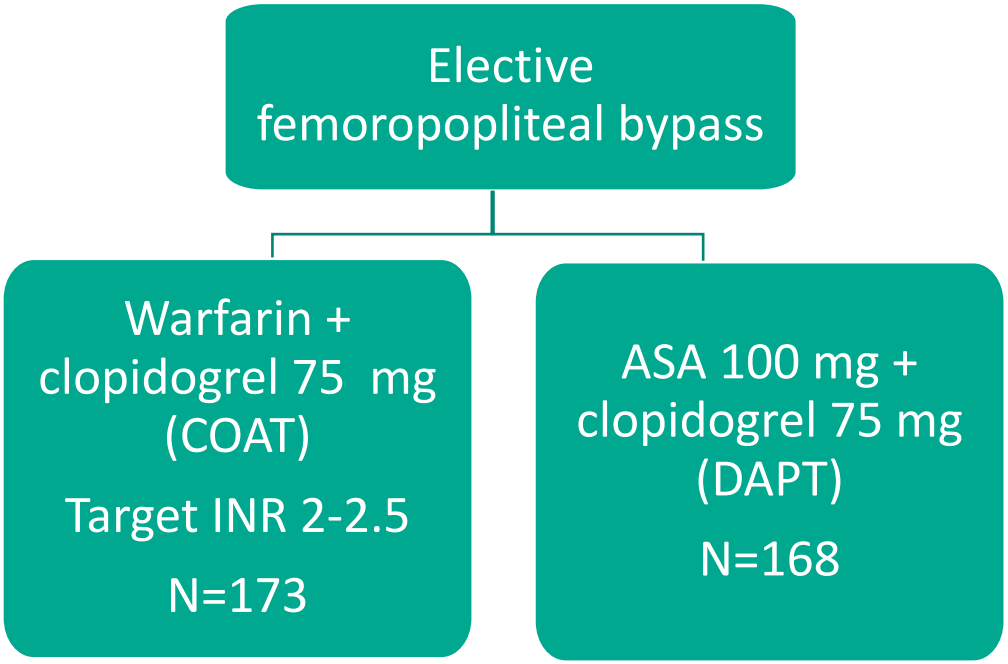
Johnson WC, et al. *J Vasc Surg. 2002*;35:413-421.

Anticoagulation + antiplatelet: Johnson, et al

- Mean follow-up 36.6 months
- Death, WAFA vs ASA: 31.8% vs 23%, P=0.01
- Major hemorrhage, WAFA vs ASA: 6.9% vs 3.6%, P=0.02
- Considerations:
  - Patients censored from primary analysis at time of death or amputation
  - Percent smokers not described
  - Rate statin users not described
  - Outcome of primary assisted patency is less valuable than primary patency
  - INR 1.4-2.8, ASA dose 325 mg
- Conclusion: Warfarin + ASA cannot be recommended after elective bypass as risk of treatment likely outweighs the risk

Johnson WC, et al. *J Vasc Surg. 2002*;35:413-421.

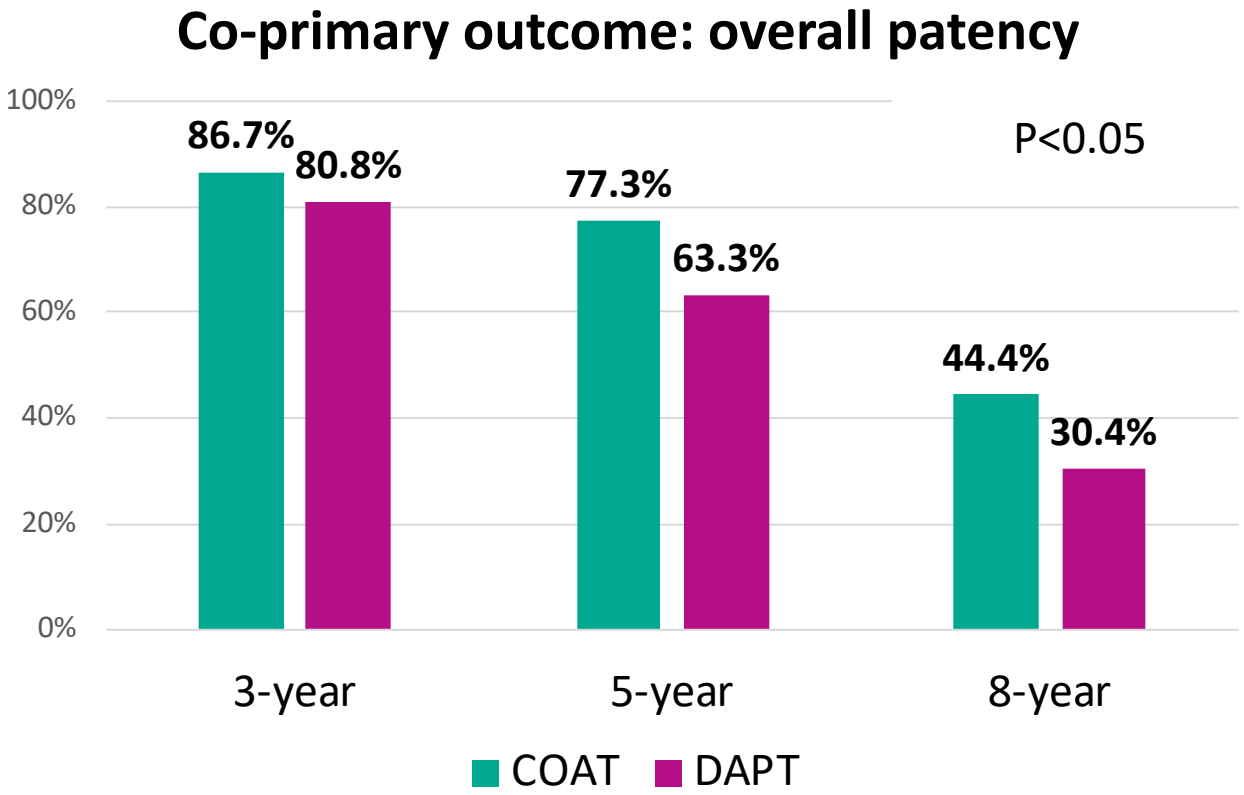
Anticoagulation + antiplatelet: Monaco



- Randomized, open-label
- Prosthetic graft for above-knee anastomosis
- Venous graft for below-knee anastomosis
- Age: ~ 67 years
- Baseline characteristics, COAT vs DAPT:
  - Smoking: 18.5% vs 26.8%
  - High risk: 23.7% vs 22%
  - Below-knee: 36.4% vs 29.7

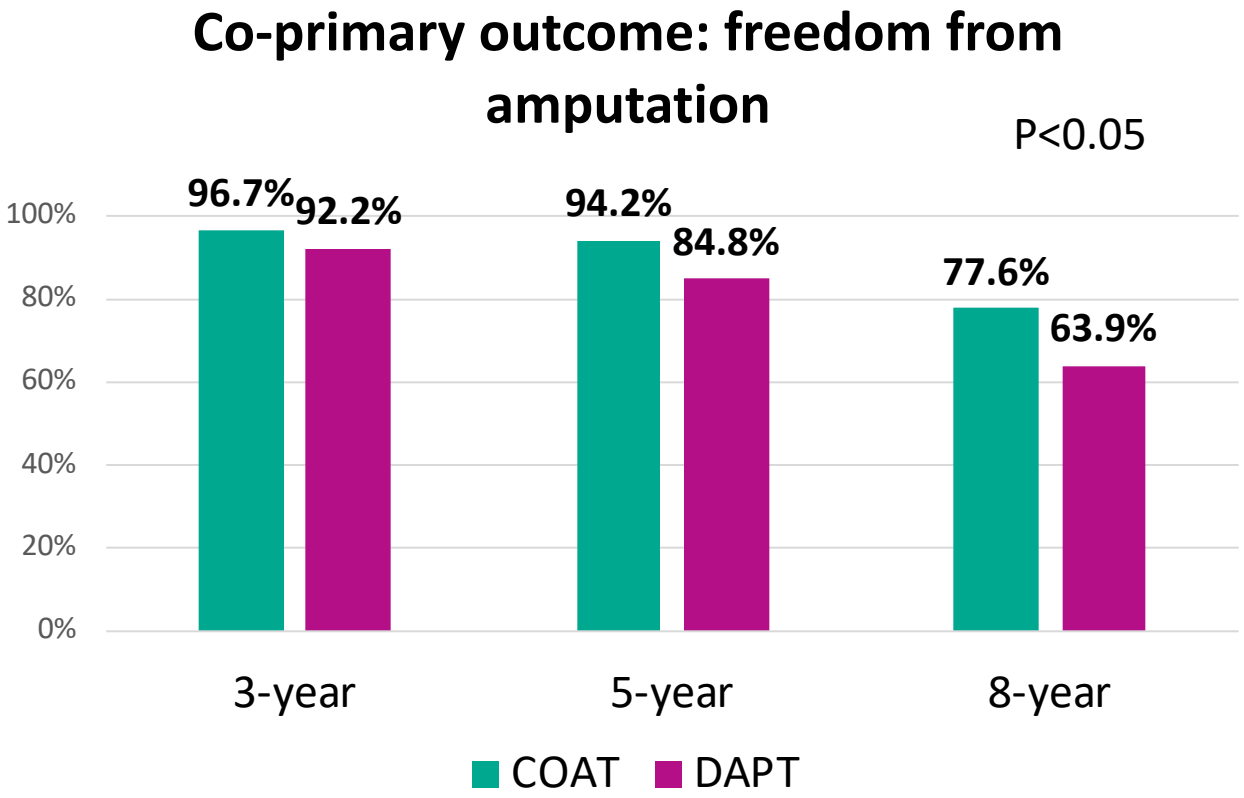
Monaco, et al. *J Vasc Surg.* 2012;56:96-105.

Anticoagulation + antiplatelet: Monaco



Monaco, et al. *J Vasc Surg.* 2012;56:96-105.

Anticoagulation + antiplatelet: Monaco



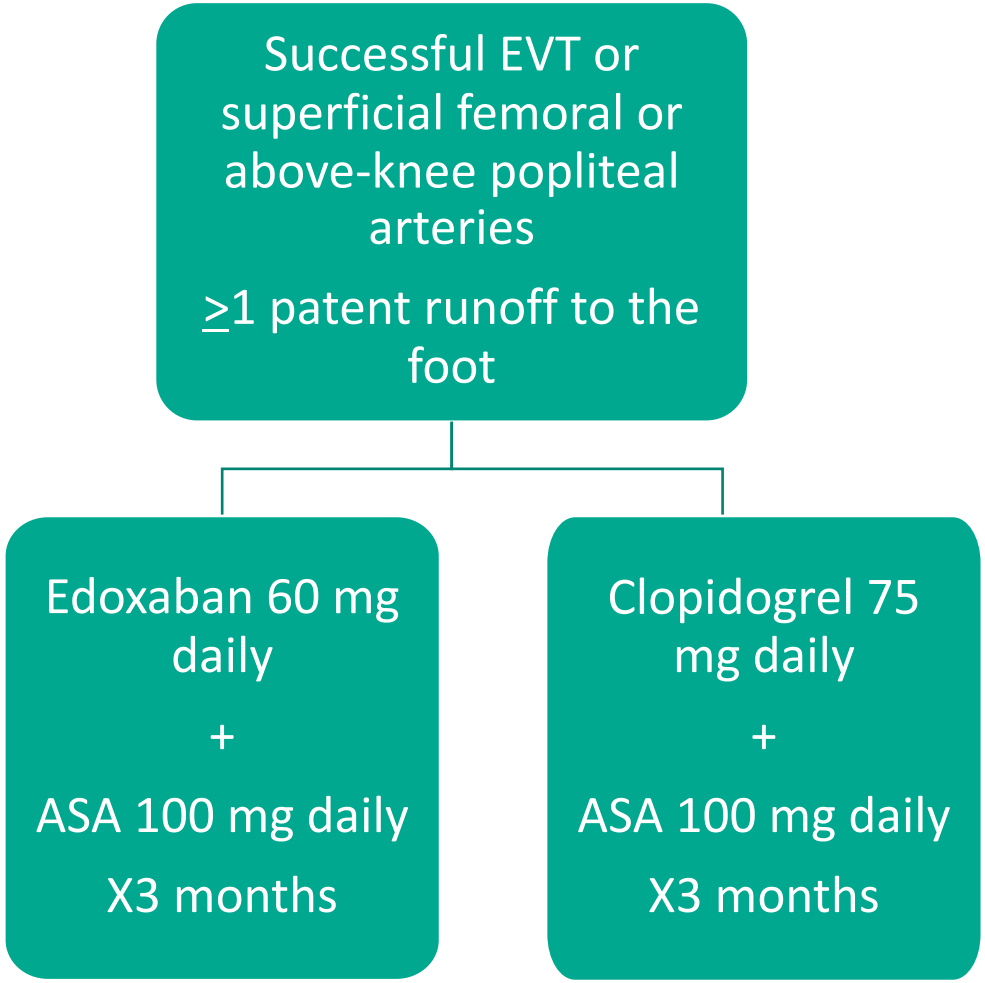
Monaco, et al. *J Vasc Surg.* 2012;56:96-105.

Anticoagulation + antiplatelet: Monaco

- Mean follow-up: 6.4 years
- Safety, COAT vs. DAPT:
  - All bleeding: 4.63% patient-year vs 2.99% patient-year, P=0.06
  - Serious bleeding: 1.78% patient-year vs 1.62% patient-year, P=0.7
- Considerations:
- Conclusion: Warfarin can be considered to prevent graft occlusion and amputation after femoropopliteal bypass if the benefit is estimated to exceed the risk (i.e. high risk of occlusion/amputation and low risk of bleeding)

Monaco, et al. *J Vasc Surg.* 2012;56:96-105.

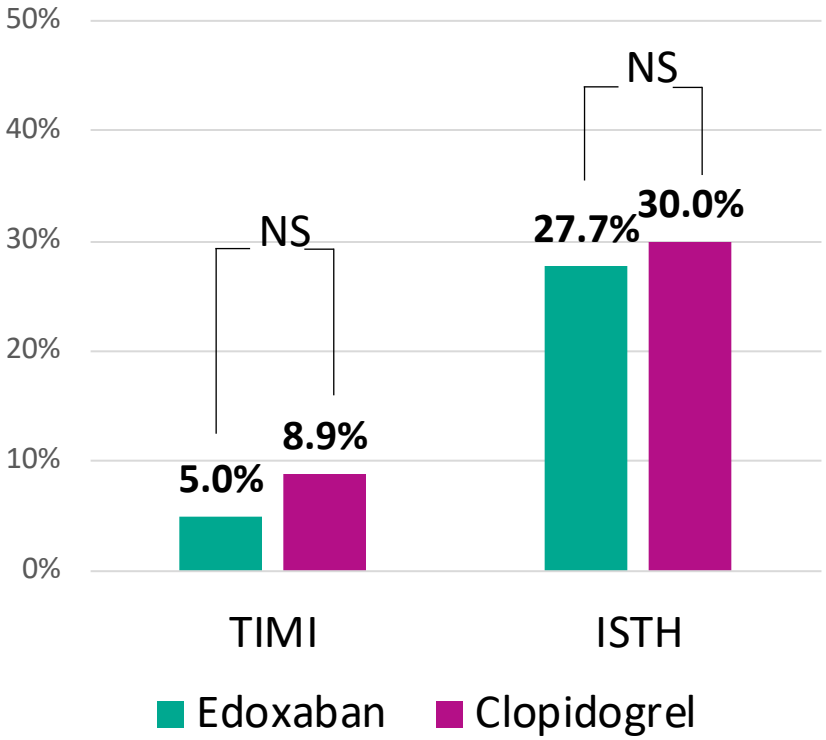
Anticoagulation + antiplatelet: ePAD

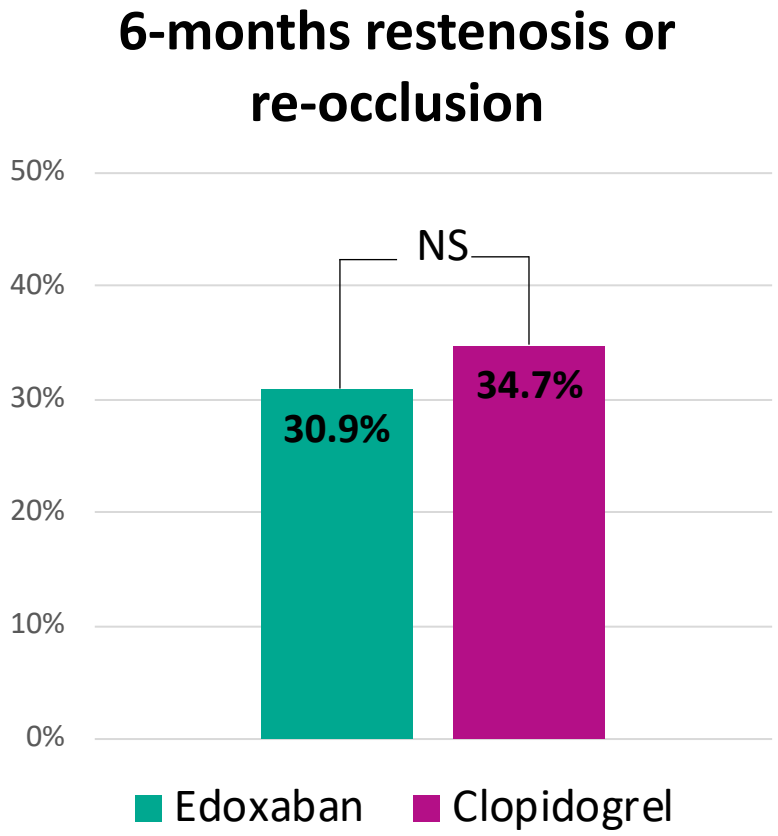


- Randomized, open-label, multi-national proof-of-concept study
- Mean age: ~67 years
- Femoral lesion: 92.2%
- Stent placement: 54%
- Current smoker: ~35%
- Statin treatment: not disclosed

Moll F, et al. *J End Ther.* 2018;25:158-168.

Anticoagulation + antiplatelet: ePAD





Moll F, et al. *J End Ther.* 2018;25:158-168.

Anticoagulation + antiplatelet: ePAD

- Considerations:
  - Comparator (DAPT) is not standard of therapy
  - Proof-of-concept design: underpowered
  - Low risk population
  - Utilization of optimal medical therapy is not disclosed
- Conclusion: edoxaban + ASA appears to be comparable to clopidogrel + ASA in terms of efficacy and safety, but adequately powered trial is needed before use of edoxaban + ASA can be considered in patients undergoing EVT of above-knee lesions

Moll F, et al. *J End Ther.* 2018;25:158-168.

Evidence for use of antithrombotic therapy after vascular intervention

- No standard-of-care therapy
- Heterogenous populations (disease location, intervention)
- Confounders: surgical technique, individual anatomy
- Change in surgical practice and materials over the past two decades
- No data on patients with iliac revascularization
- Very limited data on patients undergoing endovascular interventions
- Some benefit seen with DAPT and anticoagulation + antiplatelet after bypass procedures, but quality of evidence is low-moderate

Guideline recommendations

ACC/AHA 2016

DAPT (ASA + clopidogrel) may be reasonable to reduce the risk of CV ischemic events in symptomatic PAD after revascularization (IIb-limited data)

The usefulness of anticoagulation to improve patency after autogenous or prosthetic bypass in uncertain (IIbB)

ACCP 2012

Long-term ASA 75-100 mg/day or clopidogrel after EVT (1A)

Single antiplatelet therapy over DAPT after EVT with stenting (2C)

Single antiplatelet therapy over warfarin after bypass (1B)

DAPT after prosthetic below-knee bypass (2C)

Single antiplatelet therapy over DAPT after bypass (2B)

Gerhard-Herman MD, et al. *J Am Coll Cardiol*. 2017;69:1465-1508.
Alonso-Coello P, et al. *CHEST.* 2012;141:e669S-e690S.

Ongoing trials

- **VOYAGER PAD** (NCT02504216), finished enrolling: rivaroxaban 2.5 mg bid + ASA 100 mg qDay vs ASA 100 mg qDay after EVT
- **ASPIRE** (NCT02217501), recruiting: DAPT x12 months vs DAPT x3 months after EVT
- **LONGDAPTPAD** (NCT02798913), recruiting: DAPT x12 months vs DAPT x3 months after EVT