Peripheral Artery Disease (PAD) and Dual Inhibition Therapy

BOTTOM LINE

DO	DON'T	CONSIDER	CAUTION
• Do assess baseline renal function at steady state • Do define duration of DAPT and communicate about stop date if post-procedure • Do assess bleeding risk (usually done qualitatively) • Do assess thrombotic risk to estimate the potential benefits of dual pathway inhibition (aspirin + rivaroxaban) • Do educate patients about short- and long-term benefits of dual pathway inhibition	• Do not use rivaroxaban 2.5mg once daily or apixaban 2.5mg twice daily for CAD/PAD indication • Do not use rivaroxaban 2.5mg BID if patient has a need for higher dose anticoagulation (e.g., AF, VTE) or DOAC contraindication (e.g., mechanical valve replacement) • Do not use rivaroxaban 2.5mg twice daily without ASA • Do not use a loading dose of rivaroxaban at initiation	• Consider the cost of rivaroxaban to patient • Consider the impact of polypharmacy and drug-drug interaction (P-gp and CYP3A4) • Consider the intended duration of dual pathway inhibition therapy (often indefinite duration) • Consider the shortest duration of DAPT post-procedure to minimize bleeding risk if using rivaroxaban 2.5mg BID • Consider the role of gastro-protection (e.g., use of PPI)	• Be cautious when using higher doses of ASA (>100mg) • Be cautious when higher doses of anticoagulation (at therapeutic dosing) are needed for acute limb ischemia • Be cautious about combining with stronger P2Y12 inhibitors (ticagrelor or prasugrel) • Be cautious about patients who are unable/unwilling to take twice daily medications • Be cautious about patients who use other supplements that promote bleeding (e.g., turmeric) or PgP and CYP3A4 medication • Be cautious when eGFR < 15mL/min

MOST BENEFIT OF DUAL INHIBITION THERAPY WAS SEEN IN THE HIGHEST RISK PATIENTS

Key Points:

- Studies were conducted in symptomatic PAD only (asymptomatic was excluded)
- Dual pathway inhibition was studied in the clinical trials using **rivaroxaban 2.5mg twice daily and aspirin (either 81mg or 100mg) once daily**
- High risk groups with ≥1 comorbidity (high-risk features in Table 2) accrue more benefit with rivaroxaban and ASA; however low risk patients still may benefit
- VOYAGER PAD found benefit in the post-revascularization setting with dual inhibition therapy in both endovascular and surgical settings
- High risk bleeding included prior intracranial hemorrhage, prior major bleeding, need for therapeutic anticoagulation, bleeding diathesis, known GI ulcer (see bleeding risk table)
- Bleeding risk from both COMPASS and VOYAGER trials did not show increase in fatal bleeding or intracranial bleeding, and bleeding risk is front-loaded in the first year
- Therapeutic anticoagulation dosing should be considered in acute limb ischemia, otherwise dual inhibition therapy dosing is 1/4th the systemic anticoagulation dose of rivaroxaban
- Analysis from COMPASS trial showed majority of bleeding was gastrointestinal

Background

Peripheral Arterial Disease (PAD) is an atherosclerotic disease process causing partial or complete obstruction of the lower extremity peripheral arteries, leading to ischemic symptoms and damage ranging from intermittent claudication to pain at rest to tissue loss. Diagnosis can be done with imaging (e.g., CT angiography) or vascular lab (ankle-brachial index/toe-brachial index). Medical management with antithrombotic medications is a mainstay of therapy, found to reduce major adverse cardiac and limb events including amputation and need for revascularization.

Dual Inhibition Therapy: Aspirin is a COX-1 inhibitor which blocks platelet activation via TXA-2. Rivaroxaban is a factor Xa inhibitor which blocks platelet activation by inhibition of thrombin formation by the coagulation pathway. The rationale behind a dual inhibition pathway is to block two different mechanisms for platelet activation to further reduce thrombotic risk. COMPASS and VOYAGER PAD studied low dose **rivaroxaban 2.5mg twice daily with ASA (100mg)** for PAD.

Table 1

	Favors Therapy	Favors Alternative
SAPT	• Mild disease • Moderate-high bleeding risk	• Previous peripheral revascularization • Previous coronary event • Previous limb ischemia
DAPT with clopidogrel	Limited use in stable PAD; consider if concerns for high bleeding risk with concomitant high risk of cardiac events, recent ACS, or recent coronary stent. Additionally, may consider for a short period after infra-inguinal stent implantation and below-the-knee bypass with prosthetic graft.	
Aspirin and rivaroxaban 2.5 mg BID	• Previous peripheral revascularization • Previous ischemic limb events • High risk for amputation or limb ischemia • High risk for cardiovascular events • Prior carotid artery revascularization or carotid stenosis ≥ 50%	• High bleeding risk • Previous lacunar stroke • Severe heart failure (EF <30% or NYHA III/IV) • Severe renal disease (eGFR <15 mL/min) • Use of strong inducers or inhibitors of CYP3A4 or P-gp • Cost concern

Risk Stratification: A subsequent analysis of the COMPASS trial in the stable PAD group identified an increase in benefit to high-risk patients with concomitant comorbidities (Table 2). These patients had absolute risk reduction of 4.2% in both MACE and MALE at 30 months, equal to **42 events prevented per 1000** (Table 3).

Table 2

High-Risk Comorbidities	High-Risk Limb Presentation
Renal dysfunction- eGFR <60mL/min	Previous amputation
Heart Failure	Previous revascularization
Diabetes	Rest Pain
≥ 2 vascular beds affected	Necrosis or gangrene of limb

ASSESS BLEEDING RISK

- Need for DAPT, other non-aspirin antiplatelet therapy, or OAC therapy
- History of hemorrhagic stroke
- History of significant bleeding
- GI ulceration
- Malignant neoplasms at risk of bleeding
- Esophageal varices
- Vascular aneurysms
- Coagulopathies or bleeding disorders
- Prior intracranial hemorrhage or major bleeding

References: **1.** Aboyans V, Ricco JB, Bartelink MEL, et al. Eur Heart J. 2018 Mar 1;39(9):763-816. PMID: 28886620. **2.** Anand SS, Bosch J, Eikelboom JW, et al. Lancet. 2018 Jan 20;391(10117):219-229. PMID: 29132880. **3.** Anand SS, Eikelboom JW, Dyal L, et al. J Am Coll Cardiol. 2019 Jul 2;73(25):3271-3280. PMID: 31248548. **4.** Bhatt DL, Eikelboom JW, Connolly SJ, et al. 2020 Jun 9;141(23):1841-1854. PMID: 32223318; PMCID: PMC7314494. **5.** Bonaca MP, Bauersachs RM, Anand SS, et al. N Engl J Med. 2020 May 21;382(21):1994-2004. PMID: 32222135. **6.** Gerhard-Herman MD, Gornik HL, Barrett C, et al. Vasc Med. 2017 Jun;22(3):NP1-NP43. PMID: 28494710. **7.** Kaplovitch E, Eikelboom JW, Dyal L, et al. JAMA Cardiol. 2020 Sep 30;e204390. PMID: 32997098; PMCID: PMC7527938.

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	AHA/ACC PAD Guidelines (2016)		ESC PAD Guidelines (2017)	
SAPT	Antiplatelet therapy with ASA alone or clopidogrel alone is recommended to reduce MI, stroke, and vascular death in patients with symptomatic PAD	I-A	Long term single antiplatelet therapy is recommended for symptomatic PAD patients	I-A
			Long term single antiplatelet therapy is recommended in all patients who have undergone revascularization	I-C
DAPT	Dual antiplatelet therapy may be reasonable to reduce risk of limb-related events in patients with symptomatic PAD after lower extremity revascularization	IIb-C-LD	DAPT with aspirin and clopidogrel for at least 1 month should be considered after infra-inguinal stent implantation	IIa-C
			DAPT may be considered in below-the-knee bypass with prosthetic graft	IIb-B
OAC +/- SAPT	The usefulness of anticoagulation to improve patency after lower extremity autologous vein or prosthetic bypass is uncertain	IIb-B-R	Vitamin K antagonists may be considered after autologous vein infra-inguinal bypass	IIb-B
			After endovascular revascularization, ASA or clopidogrel should be considered in addition to OAC for at least 1 month if bleeding risk is low compared with risk of stent/graft occlusion	IIa-C
	Anticoagulation should not be used to reduce the risk of cardiovascular ischemic events in patients with PAD	III HARM-A	After endovascular revascularization, OAC alone should be considered if the bleeding risk is high compared with risk of stent/graft occlusion	IIa-C
			In patients with PAD who have an indication for OAC, OAC alone should be considered	IIa-B

COMPASS (PAD Subgroup Analysis, 2017): Included patients with PAD defined as aortofemoral bypass, limb bypass, PTA revascularization of iliac or infra-inguinal arteries, limb or foot amputation, intermittent claudication plus either ABI<0.9 OR PAD stenosis ≥50% on duplex/angio, or finally, carotid revascularization or carotid stenosis >50% on duplex/angio. Rivaroxaban 2.5mg BID with ASA was superior to ASA alone with reductions in MACE by 28% and MALE by 46%; however, major bleeding increased, along with GI-related bleeding. The net risk-benefit analysis was still favorable.

VOYAGER-PAD (2020): Included patients with symptomatic PAD (ischemic symptoms with imaging evidence) who underwent successful revascularization of lower extremity for ischemia. The primary composite MALE and MACE endpoint was reduced by 15% in the rivaroxaban plus ASA group versus ASA alone. No difference was observed in the primary safety outcome of TIMI major bleeding.

Summary of COMPASS Clinical Trial

Background: This study compared rivaroxaban 2.5mg BID plus ASA 100mg vs ASA alone in stable symptomatic PAD disease.

- Symptomatic PAD was defined as intermittent claudication plus imaging evidence, aortofemoral bypass, limb bypass, PCTA revascularization, limb or foot amputation
- Population: 66% of patients had CAD, 44% had DM, and 6-7% had history of stroke
- Excluded: need for DAPT, need for other non-ASA therapy, high risk of bleeding, need for oral anticoagulant therapy, severe HF (EF <30%), eGFR <15mL/min, patients on strong CYP3A4 inducer/inhibitor medications

Outcome	Riva 2.5mg BID + ASA (n=2492)	ASA alone (n=2504)	HR (P-value)
CV death, stroke, non-fatal MI	5% (126)	7% (174)	HR 0.72 (p=0.005)
CV death, stroke, MI & MALE	6% (155)	9% (222)	HR 0.69 (p<0.001)
MALE	1% (30)	2% (56)	HR 0.54 (p=0.005)
The low dose rivaroxaban group revealed lower rates of composite outcomes of MACE and MALE.			
Major bleeding	3% (77)	2% (48)	HR 1.61 (p=0.008)

Bleeding risk: No difference was observed regarding fatal bleeding, non-fatal symptomatic intracranial hemorrhage, or symptomatic bleeding into a critical organ. The primary outcome of major bleeding was statistically higher in the rivaroxaban group and was mostly driven by bleeding leading to hospitalization. Majority of bleeding was gastrointestinal.

Summary of VOYAGER PAD Clinical Trial

Background: This study compared rivaroxaban 2.5mg BID plus ASA 100mg vs ASA alone in symptomatic PAD disease undergoing revascularization.

- 32% of patients had CAD, 40% had DM, 9% had known carotid stenosis
- Interventions included endovascular (65%) and surgical (35%)
- Exclusion: revascularization for asymptomatic disease, recent revascularization within 10d, ALI w/n 2wk, ACS w/n 30d, current major tissue loss, need for stronger antiplatelet or AC, need for longer term DAPT >6mo, high risk of bleeding

Outcome	Riva 2.5mg BID + ASA (n=3286)	ASA alone (n=3278)	HR (P-value)
ALI, major amputation, MI, ischemic stroke, CV death	17.3%	19.9%	HR 0.85 (p=0.009)
Acute Limb Ischemia	5.2%	7.8%	HR 0.67 (0.55-0.82)
ALI, major amputation, MI, ischemic stroke, coronary death	14.7%	18.2%	HR 0.8 (p<0.001)
Unplanned index-limb revascularization for recurrent ischemia	20%	22.5%	HR 0.88 (p=0.03)
Hospitalization for coronary or peripheral thrombotic event	8.7%	12.1%	HR 0.72 (p<0.001)
The low dose rivaroxaban arm revealed lower rates of composite MACE/MALE and ALI. There were also lower limb-related rates of unplanned index-limb revascularization and hospitalization for coronary/peripheral thrombotic event. These benefits were observed regardless of baseline clopidogrel use.			
TIMI Major bleeding	2.65%	1.87%	HR 1.43 (p=0.07)
ISTH Major bleeding	5.94%	4.06%	HR 1.42 (p=0.007)

Bleeding risk: There was no difference in TIMI major bleeding, including intracranial bleeding or fatal bleeding between groups. There was a higher rate of ISTH major bleeding.

Table 3

Sub-Analysis of Lower Extremity PAD from COMPASS, Absolute Risk Change with Rivaroxaban + ASA vs ASA at 30 Months

MACE or MALE if high risk feature	ARR 4.2%
MACE or MALE if no high risk feature	ARR 1%
Major bleeding if high risk feature	ARI 2%
Major bleeding if no high risk feature	ARI 0.8%

Abbreviations:

ABI- ankle-brachial index
AC- anticoagulation
ACS- acute coronary syndrome
AF- atrial fibrillation
ALI- acute limb ischemia
ARR- absolute risk reduction
ARI- absolute risk increase
CAD- coronary artery disease
DAPT- dual antiplatelet therapy
DM- diabetes mellitus
DOAC- direct oral anticoagulant
HF- heart failure
MACE- major adverse cardiac event
MALE- major adverse limb event
OAC- oral anticoagulant
PAD- peripheral arterial disease
PTA- percutaneous transluminal angioplasty
SAPT- single antiplatelet therapy
VTE- venous thromboembolism

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