OPTIMAL MEDICAL THERAPY FOR THE CLI PATIENT: DOES IT MAKE A DIFFERENCE?

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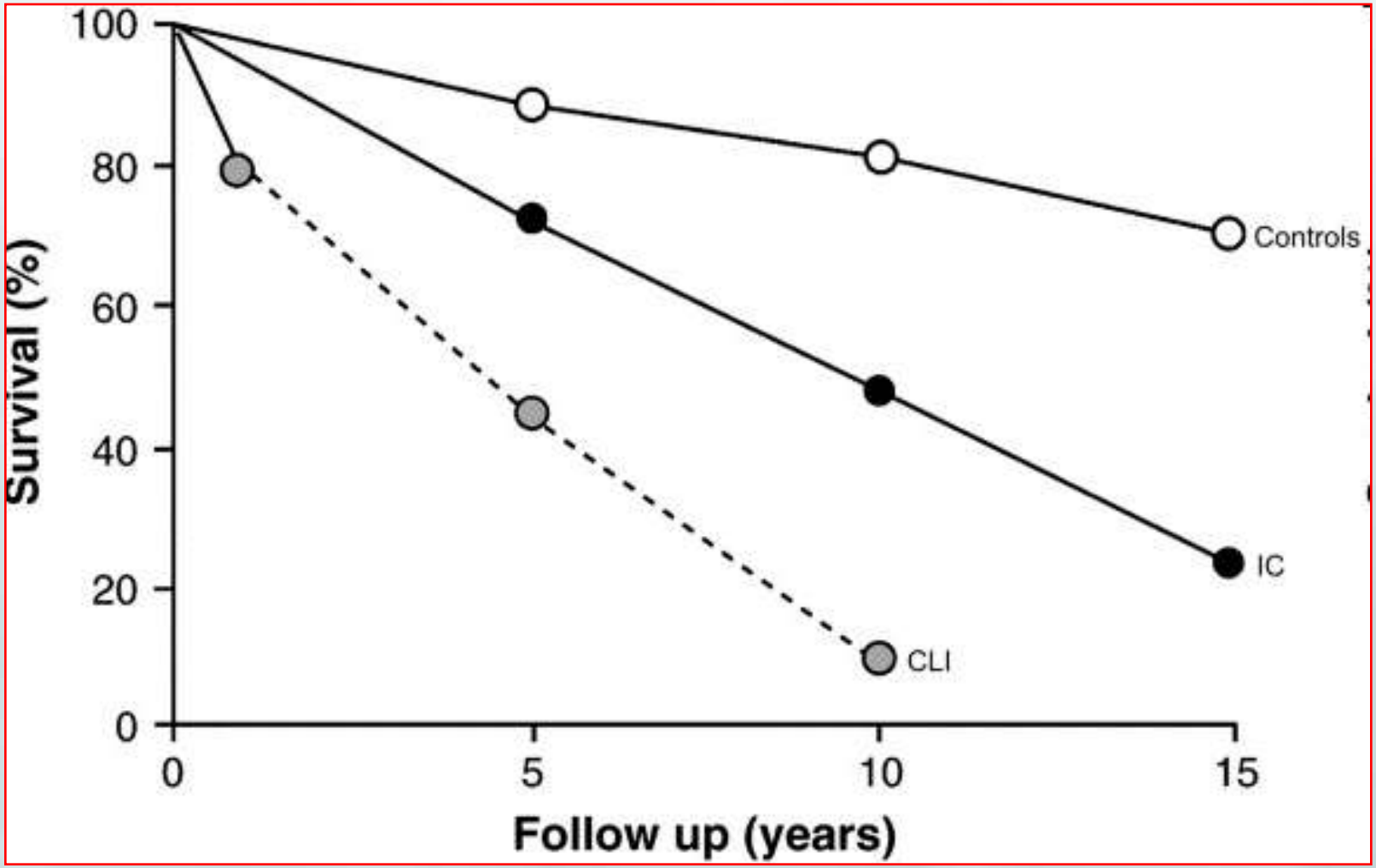
Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship	Company
▪ Grant/Research Support	▪ WL Gore, Medtronic
▪ Consulting Fees/Honoraria	▪ Abbott Vascular, Bard Peripheral Vascular, Boston Scientific, Cordis, Medtronic

The Clinical Imperative!



Norgren, L. J Vasc Surg 2007; 45(suppl 1): S5A.

Prognosis for CLI Patients

- Within 3 months of presentation:
  - death in 9%
  - MI in 1%
  - stroke in 1%
  - amputation in 12%
  - persistent CLI in 18%
- 1-year mortality: 21.0%
- 2-year mortality: 31.6%

Norgren, L. J Vasc Surg 2007; 45(suppl 1): S5A.

Two-Year Life Expectancy in Patients With Critical Limb Ischemia

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ABSTRACT

OBJECTIVES This study sought to estimate the 2-year life expectancy (2YLE) (estimated survival rate >50% at 2 years) in patients with critical limb ischemia (CLI) using the risk score based on predictors of all-cause mortality within 2 years.

Two Year Mortality 41%,nearly half due to Cardiovascular causes!

RESULTS Within 2 years, 412 patients (41%) died, and a cardiovascular cause accounted for 47% of deaths. On multivariate analysis, the independent prognostic factors were age 65 to 79 years (odds ratio [OR]: 1.9), 80 years of age or older (OR: 3.7), body mass index (BMI) 18.0 to 19.9 kg/m^2 (OR: 1.5), BMI <18.0 kg/m^2 (OR: 2.9), nonambulatory status (OR: 2.4), hemodialysis (OR: 2.1), cerebrovascular disease (OR: 1.6), left ventricular ejection fraction (LVEF) of 40% to 49% (OR: 1.8), LVEF <40% (OR: 2.6), Rutherford class 5 (OR: 1.9), and Rutherford class 6 (OR: 3.4). The 2-year survival rate in each risk score was calculated based on each OR (full score: 15 points). After that, 2YLE was estimated based on the survival rate in each risk score, the probability of a 2YLE of ≥8 points indicated a <50% probability of 2-year survival.

CONCLUSIONS The independent prognostic factors for the 2YLE were age, BMI, nonambulatory status, hemodialysis, cerebrovascular disease, LVEF, and tissue loss. A 2YLE score of ≥8 points indicated a <50% probability of 2-year survival. This score seemed to be helpful for identifying CLI patients with a poor prognosis. (J Am Coll Cardiol Intv 2014;7:1444–9) © 2014 by the American College of Cardiology Foundation.

Medical Treatment of Peripheral Arterial Disease

Graeme J. Hankey, MD
Paul E. Norman, DS

Context Peripheral arterial disease (PAD) affects approximately 20% of adults older than 55 years and is a powerful predictor of myocardial infarction, stroke, and death

Conclusion The substantial and increasing burden of PAD, and its local and systemic complications, can be reduced by lifestyle modification (smoking cessation, exercise) and medical therapies (nicotine replacement therapy, bupropion, antihypertensive drugs, statins, and antiplatelet drugs).

JAMA. 2006;295:547-553 www.jama.com

ally caused by atherosclerosis.[1,2]

The most widely accepted, objective definition of PAD is a resting ankle-brachial index (ABI) of less than 0.90 (ie, the ratio of the ankle systolic blood pressure [as measured by Doppler ultrasound] and the higher of the 2 brachial systolic pressures is less than 0.90).[1,2] An ABI of less than 0.90 is up to 95% sensitive in detecting angiogram-positive disease.[1] A cutoff of less than 0.95 has been used in some epidemiologic studies[3] but may overesti-

major coronary and cerebrovascular events.

Evidence Synthesis Symptoms of leg claudication, walking distance, and quality of life can be improved by smoking cessation (physician advice, nicotine replacement therapy, and bupropion), a structured exercise program, statin drugs, cilostazol, and angiotensin-converting enzyme inhibitors. The risk of major coronary and cerebrovascular events can be reduced through lowering blood pressure with angiotensin-converting enzyme inhibitors and other antihypertensive drugs, use of statin drugs, antiplatelet therapy with aspirin or clopidogrel, and probably by stopping smoking.

Conclusion The substantial and increasing burden of PAD, and its local and systemic complications, can be reduced by lifestyle modification (smoking cessation, exercise) and medical therapies (nicotine replacement therapy, bupropion, antihypertensive drugs, statins, and antiplatelet drugs).

JAMA. 2006;295:547-553 www.jama.com

ACC/AHA Guideline-Recommended Therapies for PAD

- Class I
  - Aspirin
  - Statin medications
  - Smoking Cessation
- Class IIa
  - ACE inhibitors

Does Adherence to the Guidelines Make a Difference?

Insights from the UCD-PAD Registry

ORIGINAL RESEARCH

Adherence to Guideline-Recommended Therapy Is Associated With Decreased Major Adverse Cardiovascular Events and Major Adverse Limb Events Among Patients With Peripheral Arterial Disease

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56% of Patients Had CLI

underwent diagnostic or interventional lower-extremity angiography between June 1, 2006 and May 1, 2013 at a multidisciplinary vascular center. Baseline demographics, clinical data, and long-term outcomes were obtained. Inverse probability of treatment propensity weighting was used to determine the 3-year risk of major adverse cardiovascular or cerebrovascular events (MACE; myocardial infarction, stroke, or death) and major adverse limb events (MALE; major amputation, thrombolysis, or surgical bypass). Among 739 patients with PAD, 325 (44%) had claudication and 414 (56%) had CLI. Guideline-recommended therapies at baseline included use of aspirin in 651 (88%), statin medications in 496 (67%), ACE inhibitors in 445 (60%), and smoking abstention in 528 (71%) patients. A total of 237 (32%) patients met all four guideline-recommended therapies. After adjustment for baseline covariates, patients adhering to all four guideline-recommended therapies had decreased MACE (hazard ratio [HR], 0.64; 95% CI, 0.45 to 0.89; P=0.009), MALE (HR, 0.55; 95% CI, 0.37 to 0.83; P=0.005), and mortality (HR, 0.56; 95% CI, 0.38 to 0.82; P=0.003), compared to patients receiving less than four of the recommended therapies.

Conclusions—In patients with claudication or CLI, combination treatment with four guideline-recommended therapies is associated with significant reductions in MACE, MALE, and mortality. (***J Am Heart Assoc.* 2014;3:e000697 doi: 10.1161/JAHA.113.000697**)

Key Words: atherosclerosis • claudication • peripheral vascular disease • prevention • statins

Adherence to Guideline Recommended Therapy Study Design and Methods

- Retrospective study utilizing the PAD-UCD Registry
- Comparison of outcomes for patients receiving all 4 guideline recommended therapies with those receiving less than 4 guideline recommended therapies

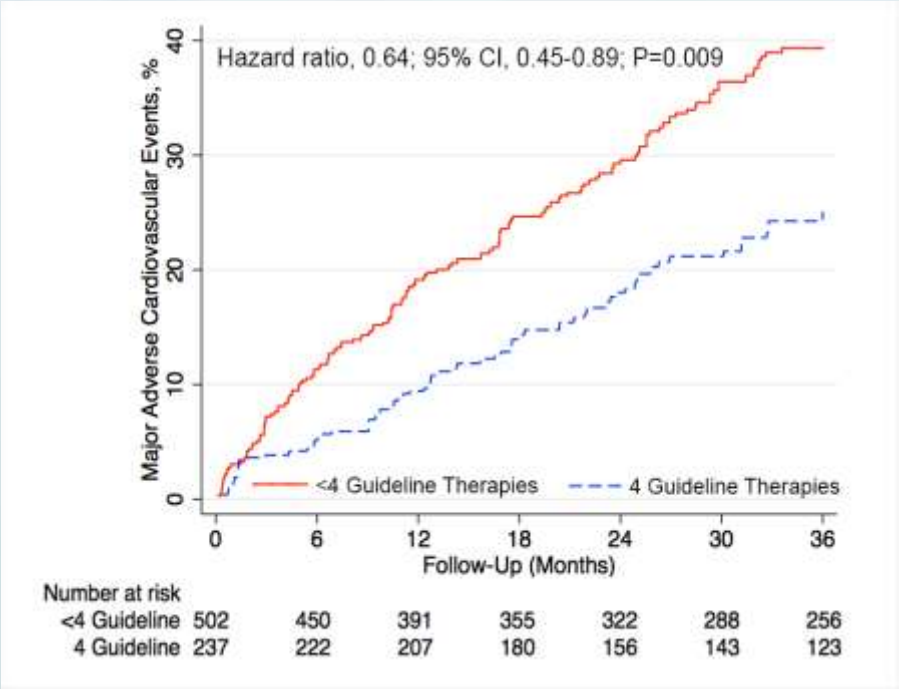
Definitions

- MACE- Major adverse cardiovascular or cerebrovascular event (myocardial infarction, stroke, death)
- MALE- Major adverse limb event (lower extremity amputation or surgical bypass)

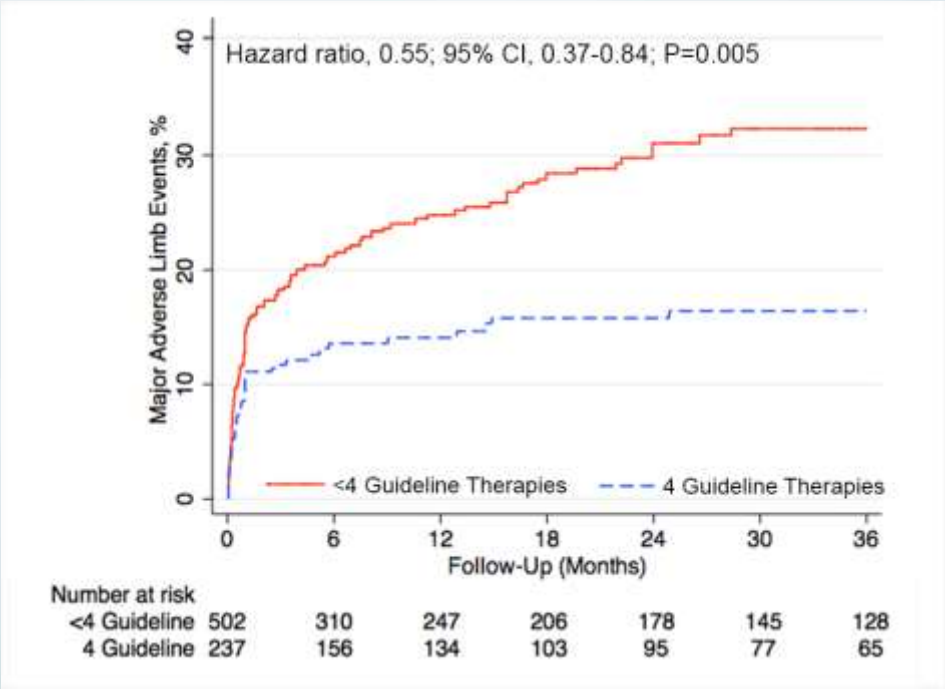
Armstrong, J Am Heart Assoc 2014

Adherence to all 4 Guidelines Based Therapies

36% reduction in MACE



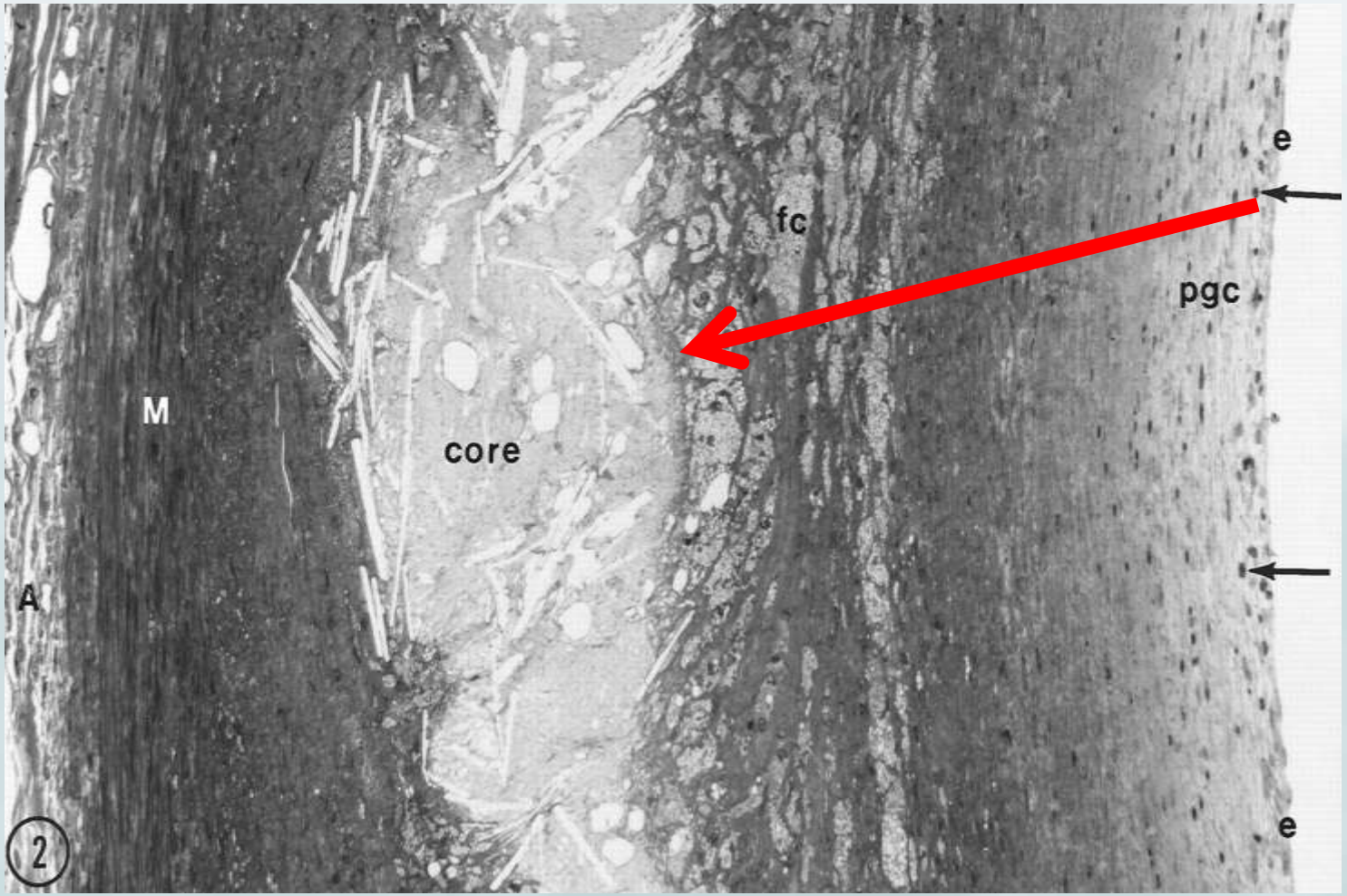
45% reduction in MALE



Armstrong, J Am Heart Assoc 2014

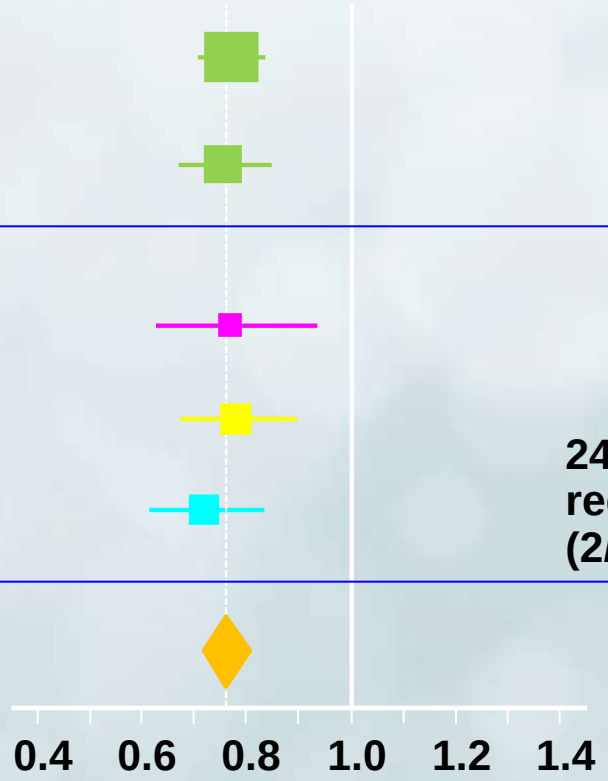
What About Statins in PAD and CLI?

Lipid Lowering and Plaque Stabilization



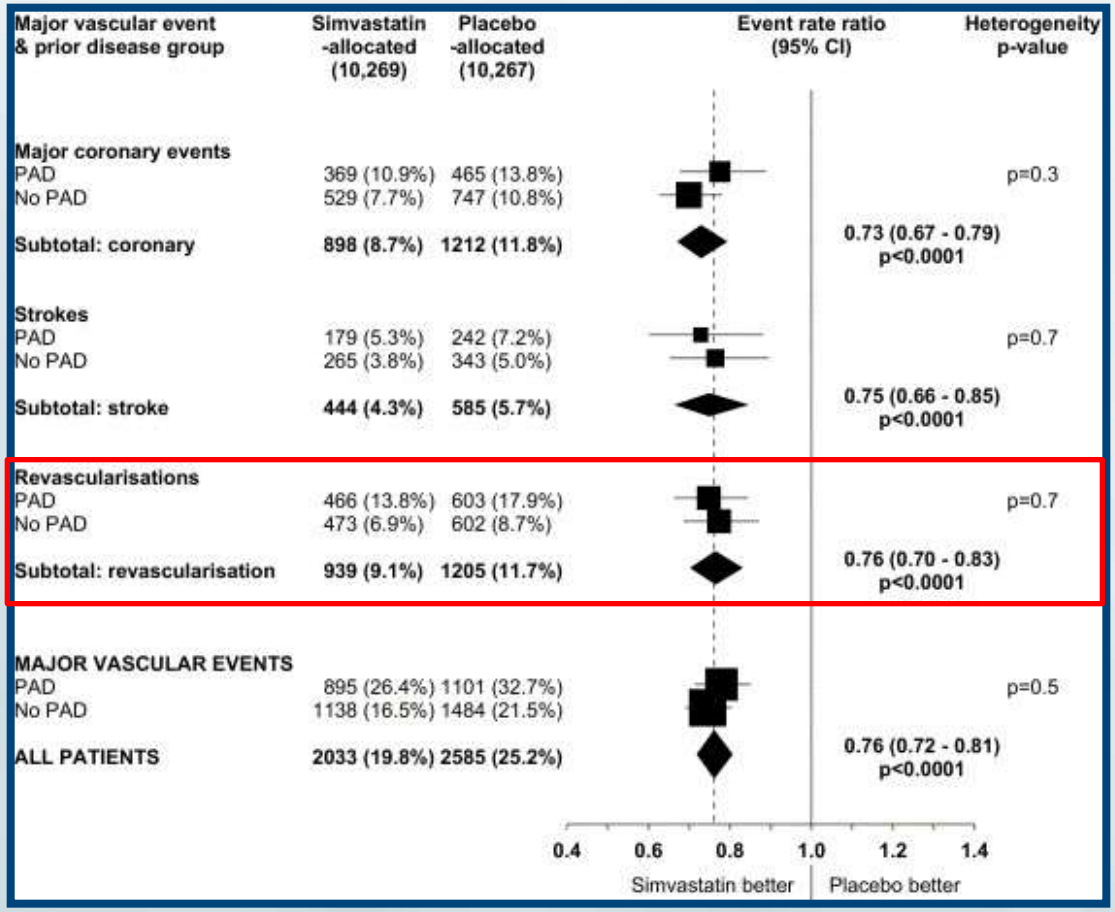
Heart Protection Study: Vascular Event by Prior Disease

Baseline Feature	STATIN (10,269)	PLACEBO (10,267)
Previous MI	999 (23.5%)	1250 (29.4%)
Other CHD (not MI)	460 (18.9%)	591 (24.2%)
No prior CHD		
CVD	172 (18.7%)	212 (23.6%)
PAD n=3748	327 (24.7%)	420 (30.5%)
Diabetes	276 (13.8%)	367 (18.6%)
ALL PATIENTS	2033 (19.8%)	2585 (25.2%)



Reprinted with permission from Heart Protection Study Collaborative Group. *Lancet*. 2002;360:7-22.

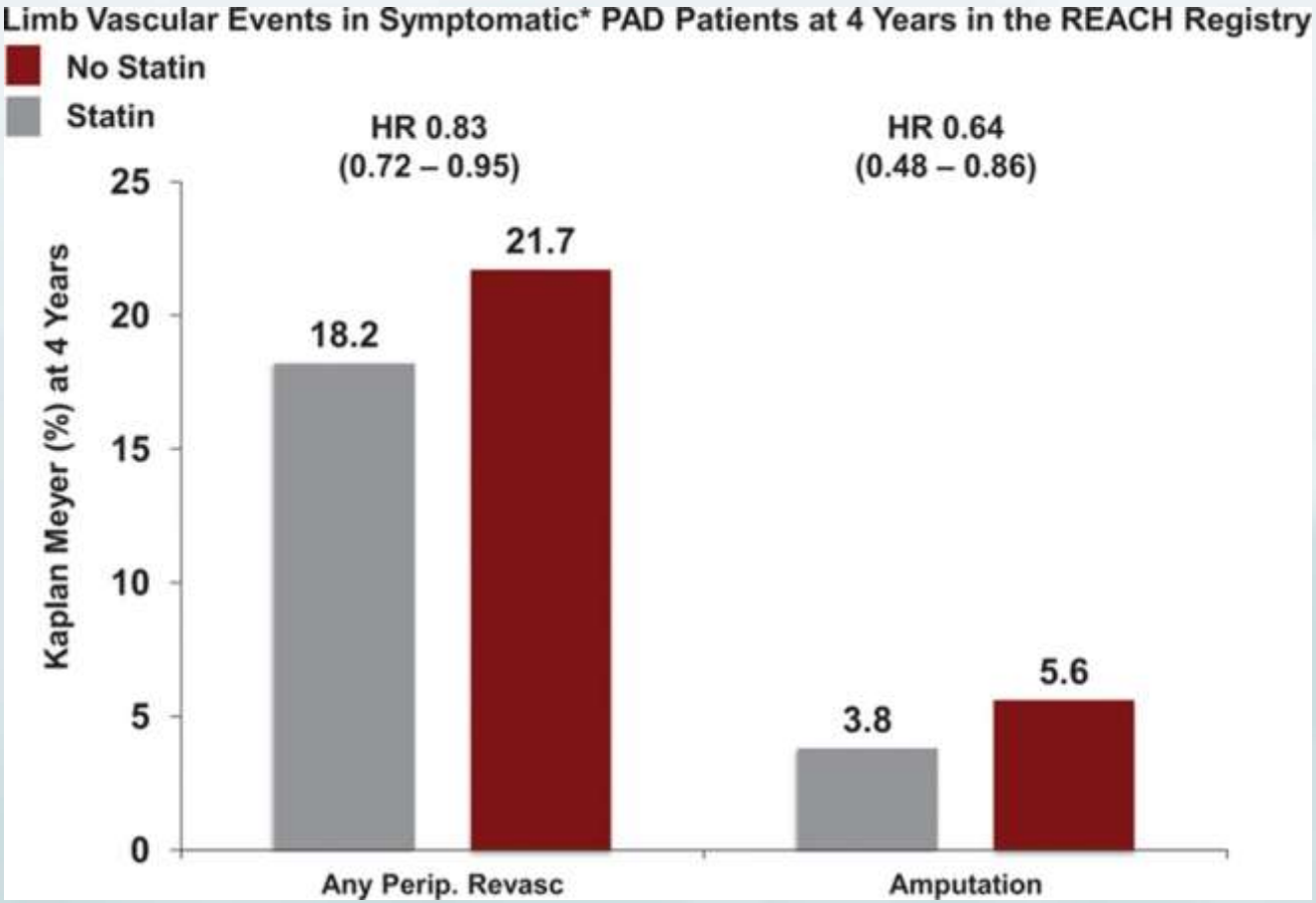
Heart Protection Study: 2007 PAD Subset Analysis



- N=4,588
- **20% reduction** in risk of noncoronary revascularization in PAD patients randomized to statin
- No effect of simvastatin on LE amputation

HPS Collaborative Group. J Vasc Surg 2007;45:645.

Effect of Statin Treatment on *Limb Vascular Events*



Bonaca M, and Creager M. Circulation Research. 2015;116:1579-1598

Multiple Benefits of Statins in PAD

Other benefits:

- Shown to improve claudication in single-center and 1 multicenter study[1]
- May slow rate of functional decline among patients with PAD[2]
- Use associated with improved patency of infrainguinal bypass grafts[3]

1 Mohler E, et al. Circulation. 2003;108:1481.

2 Giri J, et al. J Am Coll Cardiol. 2006;47:998.

3 Abbruzzese TA, et al. J Vasc Surg. 2004;39:1178.

Statins are independently associated with reduced mortality in patients undergoing infrainguinal bypass graft surgery for critical limb ischemia

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Objective: Evidence suggesting a beneficial effect of cardioprotective medications in patients with lower extremity atherosclerosis derives largely from secondary prevention studies of heterogeneous populations. Patients with critical

Statin Use Associated with significant survival advantage at 1 year: 86% vs. 81%, p=0.03

taking antiplatelet drugs. Perioperative major adverse cardiovascular events (7.8%) and early mortality (2.7%) were not measurably affected by the use of any drug class. Statin use was associated with a significant survival advantage at 1 year of 86% vs 81% (hazard ratio [HR], 0.71; 95% confidence interval [CI], 0.52-0.98; $P = .03$) by analysis of both unweighted and propensity score-weighted data. Use of β-blockers and antiplatelet drugs had no appreciable impact on survival. None of the drug classes were associated with graft patency measures at 1 year. Significant predictors of 1-year mortality by Cox regression modeling were statin use (HR, 0.67; 95% CI, 0.51-0.90; $P = .001$), age >75 (HR, 2.1; 95% CI, 1.60-2.82; $P = .001$), coronary artery disease (HR, 1.5; 95% CI, 1.15-2.01; $P = .001$), chronic kidney disease stages 4 (HR, 2.0; 95% CI, 1.17-3.55; $P = .001$) and 5 (HR, 3.4; 95% CI, 2.39-4.73; $P < .001$), and tissue loss (HR, 1.9; 95% CI, 1.23-2.80; $P = .003$).

Conclusions: Statin use is associated with improved survival in CLI patients 1 year after surgical revascularization. Further studies are indicated to determine optimal dosing in this population and to definitively address the question of relationship to graft patency. These data add to the growing literature supporting statin use in patients with advanced peripheral arterial disease. (J Vasc Surg 2008;47:774-81.)

From the Peripheral Vascular Surgery Society

Statin therapy is associated with superior clinical outcomes after endovascular treatment of critical limb ischemia

Statin use associated with higher primary patency, limb salvage and overall survival

were created according to whether they were receiving statin therapy at the time of intervention. Demographics, lesion morphology, overall mortality, primary and secondary patency, and limb salvage were compared between these groups. Analysis was performed using multivariate regression and Kaplan-Meier analysis.

Results: Between 2004 and 2009, 646 patients, 319 receiving statin therapy and 327 without, underwent an endovascular intervention for CLI. The statin group had significantly higher rates of diabetes mellitus, coronary artery disease, congestive heart failure, previous myocardial infarction, and coronary artery bypass grafting ($P < .05$). The two groups had similar lesion length, location, lesion type, TransAtlantic Inter-Society Consensus (TASC) classification, and primary procedure. At 24 months, the statin-treated group had higher rates of primary patency (43% vs 33%; $P = .007$), secondary patency (66% vs 51%; $P = .001$), limb salvage (83% vs 62%; $P = .001$), and overall survival (77% vs 62%; $P = .038$). Statin therapy was also independently associated with improved limb salvage by multivariate regression analysis (hazard ratio, 2.55; $P < .001$).

Conclusions: Patients who were receiving statin therapy when they underwent interventions to treat CLI had significantly improved overall survival, primary and secondary patency, and limb salvage rates. Our findings suggest that statins should be part of the periprocedural treatment regimen and support further investigation into the beneficial effects of statins in patients undergoing endovascular treatment of CLI. (J Vasc Surg 2012;55:371-80.)

Association Between Statin Medications and Mortality, Major Adverse Cardiovascular Event, and Amputation-Free Survival Rates in Patients With Critical Limb Ischemia

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Sacramento and Davis, California

Objectives The aim of this study was to determine the associations between statin use and major adverse cardiovascular and cerebrovascular events (MACCE) and amputation-free survival in critical limb ischemia (CLI) patients.

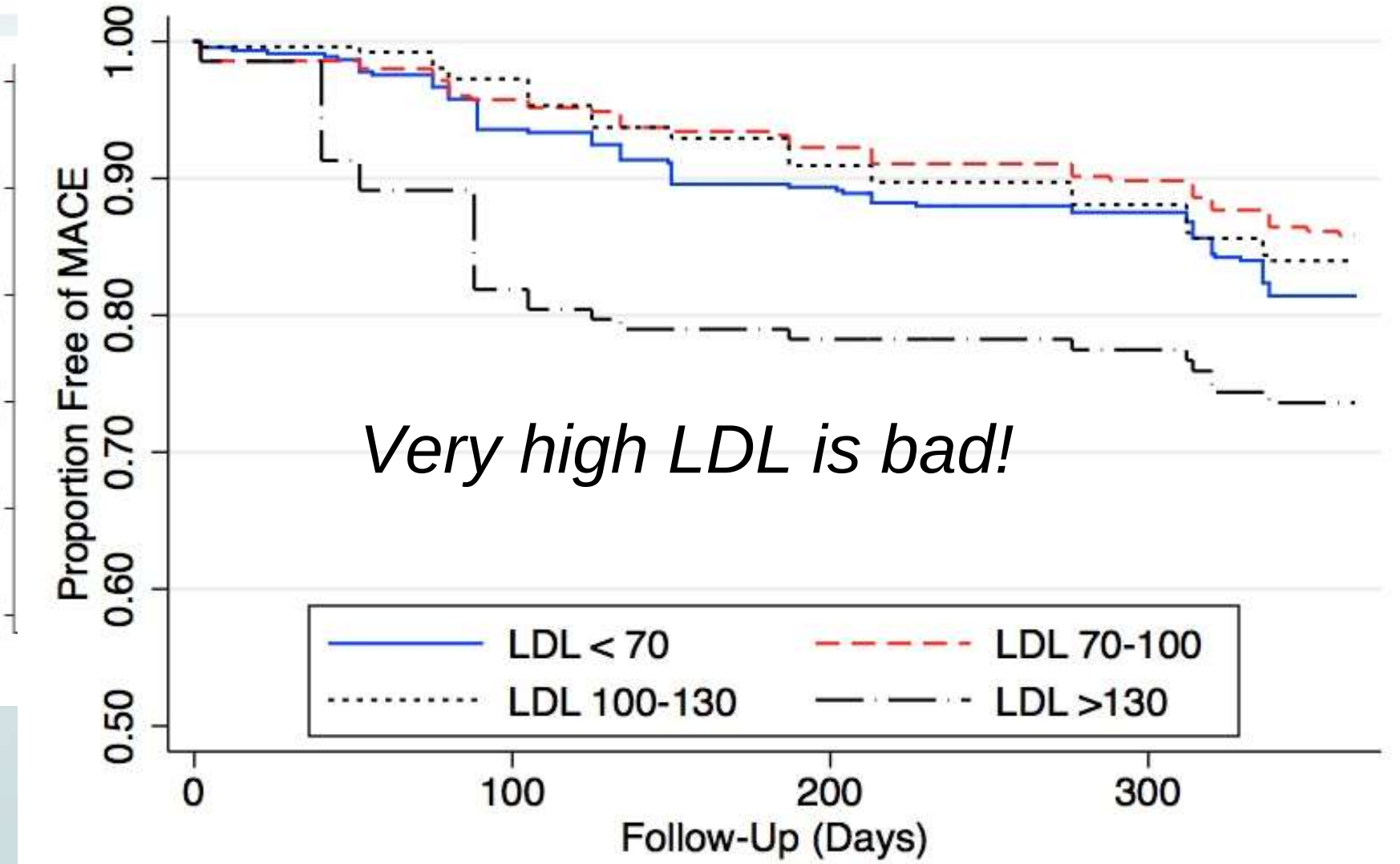
Background CLI is an advanced form of peripheral arterial disease associated with nonhealing arterial ulcers and high rates of MACCE and major amputation. Although statin medications are recommended for secondary prevention in peripheral arterial disease, their effectiveness in CLI is uncertain.

Methods We reviewed 380 CLI patients who underwent diagnostic angiography or therapeutic endovascular intervention from 2006 through 2012. Propensity scores and inverse probability of treatment weighting were used to adjust for baseline differences between patients taking and not taking statins.

Results Statins were prescribed for 246 (65%) patients. The mean serum low-density lipoprotein (LDL) level was lower in patients prescribed statins (75 ± 28 mg/dl vs. 96 ± 40 mg/dl, $p < 0.001$). Patients prescribed statins had more baseline comorbidities including diabetes, coronary artery disease, and hypertension, as well as more extensive lower extremity disease (all p values <0.05). After propensity weighting, statin therapy was associated with lower 1-year rates of MACCE (stroke, myocardial infarction, or death; hazard ratio [HR]: 0.53; 95% confidence interval [CI]: 0.28 to 0.99), mortality (HR: 0.49, 95% CI: 0.24 to 0.97), and major amputation or death (HR: 0.53, 95% CI: 0.35 to 0.98). Statin use was also associated with improved lesion patency among patients undergoing infrapopliteal angioplasty. Patients with LDL levels >130 mg/dl had increased HRs of MACCE and mortality compared with patients with lower levels of LDL.

Conclusions Statins are associated with lower rates of mortality and MACCE and increased amputation-free survival in CLI patients. (J Am Coll Cardiol 2014;63:682–90)

Decreased Hazard of MACE in Statin Group



Westin, et al. J Am Coll Cardiol 2014

SHOULD CLI PATIENTS BE TREATED WITH DUAL ANTIPLATELET THERAPY?

2011 PAD Guideline Focused Update Recommendations for Antiplatelet and Antithrombotic Drugs (MODIFIED)

- Antiplatelet therapy for symptomatic PAD to *reduce CV complications* (I-A)
- ASA (75-325 mg) daily for symptomatic PAD to *reduce CV complications* (I-B)
- Clopidogrel (75 mg daily) as an alternative to ASA for symptomatic PAD to *reduce CV complications* (I-B)

Rooke, et al. Circ. 2011;124:2020.

CHARISMA Trial Subgroup

	Patients with PAD		HR (95% CI)[a]	*P*-value
	Clopidogrel plus aspirin ($n = 1545$)	Placebo plus aspirin ($n = 1551$)		
Efficacy endpoints				
Primary endpoint	117 (7.6)	138 (8.9)	0.85 (0.66–1.08)	0.183
Death from any cause	104 (6.7)	117 (7.5)	0.89 (0.68–1.16)	0.387
Death from cardiovascular causes	65 (4.2)	71 (4.6)	0.92 (0.65–1.28)	0.613
Myocardial infarction[b]	36 (2.3)	57 (3.7)	0.63 (0.42–0.96)	0.028
Ischaemic stroke[b]	32 (2.1)	39 (2.5)	0.82 (0.52–1.32)	0.416
Stroke[b]	36 (2.3)	46 (3.0)	0.79 (0.51–1.21)	0.275
Hospitalization[c]	255 (16.5)	331 (20.1)	0.81 (0.68–0.95)	0.011

- Among patients with PAD, dual antiplatelet therapy possibly associated with reduced myocardial infarction.

- Event rates are much lower for patients with stable PAD on optimal medical therapy.

Cacoub, Eur Heart J 2008

Association of dual-antiplatelet therapy with reduced major adverse cardiovascular events in patients with symptomatic peripheral arterial disease

Ehrin J. Armstrong, MD, MS,[a] David R. Anderson, MD,[b] Khung-Keong Yeo, MBBS,[b] Gagan D. Singh, MD,[b] Heejung Bang, PhD,[c] Ezra A. Amsterdam, MD,[b] Julie A. Freischlag, MD,[d] and John R. Laird, MD,[b] *Denver, Colo; and Sacramento, Calif*

Objective: This study was conducted to determine whether there is additive benefit of dual-antiplatelet therapy (DAPT) with aspirin (acetylsalicylic acid [ASA]) and clopidogrel compared with ASA monotherapy among patients with symptomatic peripheral arterial disease.

Methods: This was an observational cohort analysis that included 629 patients with claudication or critical limb ischemia. The prevalence of patients taking ASA monotherapy vs DAPT was assessed monthly for up to 3 years. A propensity model was constructed to adjust for baseline demographic characteristics and to assess the effect of DAPT on major adverse cardiovascular events (MACEs) and major adverse limb events.

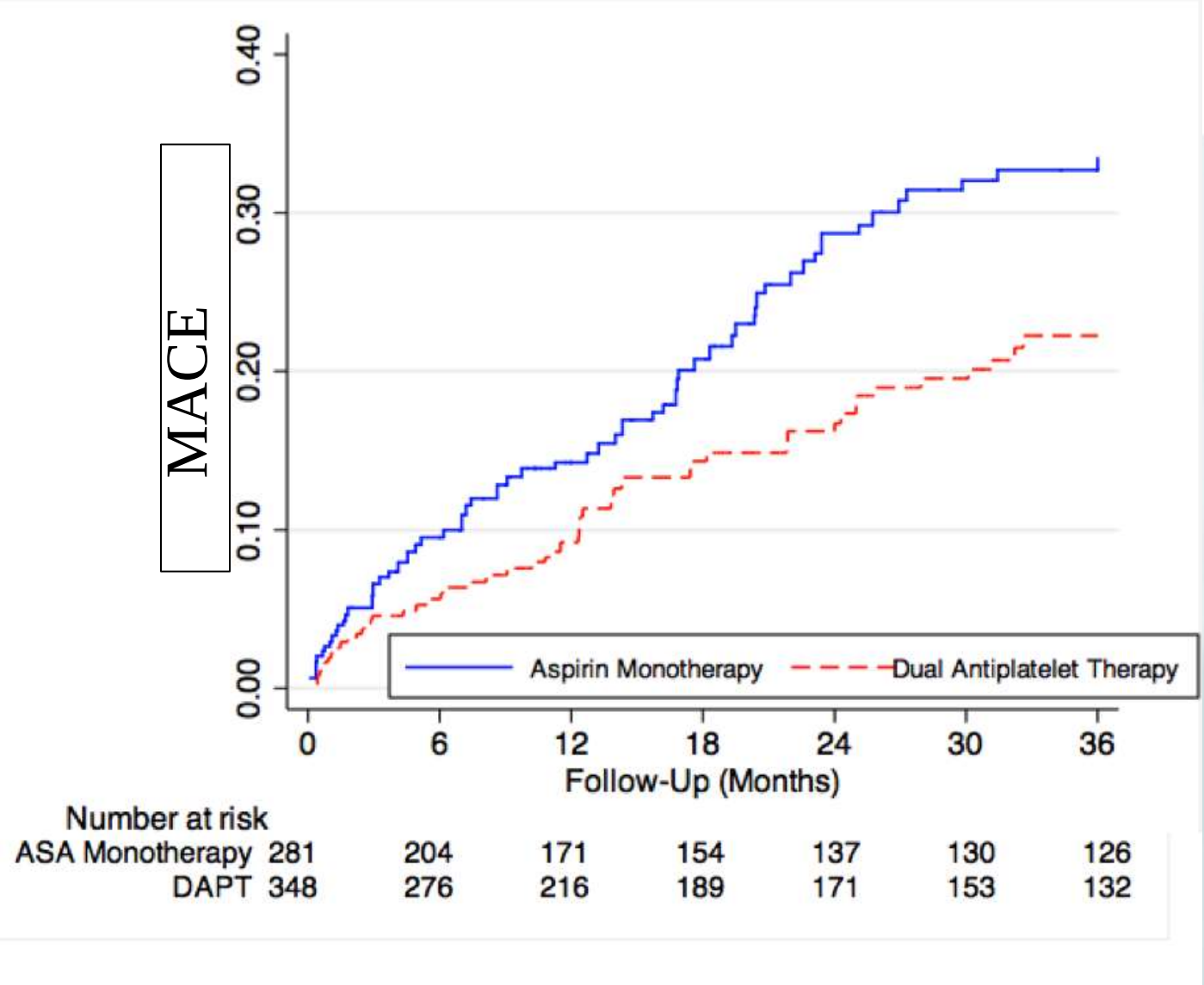
Results: At baseline, 348 patients were taking DAPT and 281 were taking ASA monotherapy. During 3 years of follow-up, 50 events (20%) occurred in the DAPT group vs 59 (29%) in the ASA monotherapy group. After propensity weighting, DAPT use was associated with a decreased risk of MACEs (adjusted hazard ratio [HR], 0.65; 95% confidence interval [CI], 0.44-0.96) and overall mortality (adjusted HR, 0.55; 95% CI, 0.35-0.89). No association was found between DAPT use and the risk of major amputation (adjusted HR, 0.69; 95% CI, 0.37-1.29). In a subgroup of 94 patients who underwent point-of-care platelet function testing, 21% had decreased response to ASA and 55% had a decreased response to clopidogrel. No association was found between a reduced response to ASA or clopidogrel and adverse events at 1 year.

Conclusions: DAPT may be associated with reduced rates of MACEs and death among patients with symptomatic peripheral arterial disease. (J Vasc Surg 2015;62:157-65.)

Dual Antiplatelet Therapy in Symptomatic PAD

- 629 patients with claudication or critical limb ischemia who underwent lower extremity angiography.
  - ASA + clopidogrel: 348 patients
  - ASA monotherapy: 281 patients
  - Patients taking coumadin excluded
- ASA and clopidogrel use assessed monthly post-procedure.
  - Time-varying Cox regression model

Armstrong, et al. ACC 2014



Adjusted HR 0.65 (95% CI 0.44-0.96)

Armstrong, et al. JVS 2015;62:157-65

Summary

- Appropriate medical care in patients with lower extremity disease is critically important to reduce the risk of major adverse cardiovascular events
- Adherence to guidelines based therapy does make a difference!
- CLI patients are an extremely high risk group (41% 2-year mortality) and may benefit the most from aggressive medical intervention