

The Importance of Optimal Medical Care for the Patient with Lower Extremity Disease

John R. Laird
Professor of Medicine
Medical Director of the Vascular Center
UC Davis Medical Center

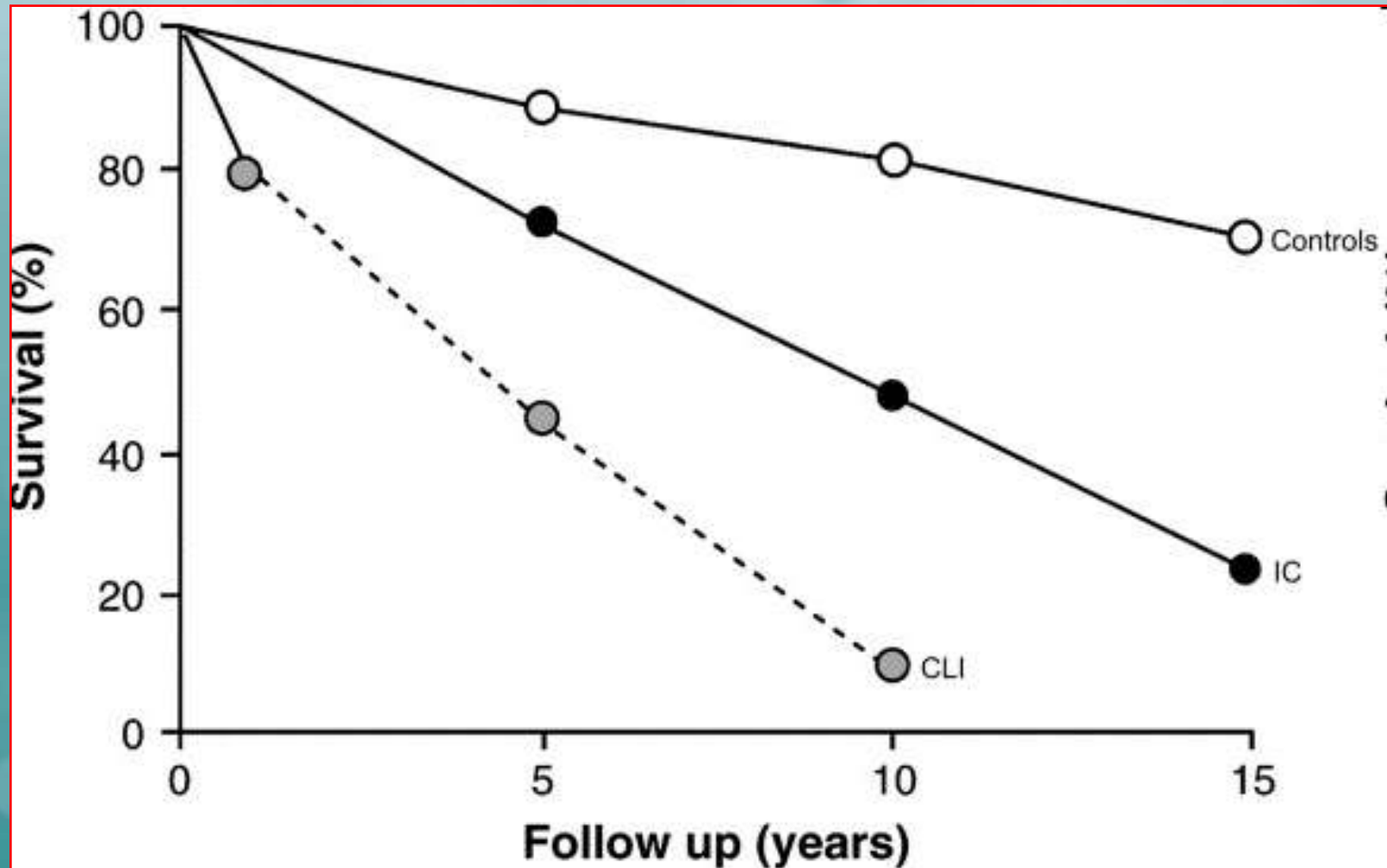
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- Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

- | <u>Affiliation/Financial Relationship</u> | <u>Company</u> |
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| ■ Consulting Fees/Honoraria | Boston Scientific, Medtronic, Abbott, Covidien, Bard Peripheral Vascular, Volcano |
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PAD Mortality: TASC II Summary of Data



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

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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 studies³ 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).

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Reducing the Risk of Stroke, MI, Death

- Smoking cessation
- Antiplatelet therapy
- Statins
- ACE inhibitors
- HTN control
- DM management

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

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

Ehrin J. Armstrong, MD, MSc, MAS;* Debbie C. Chen, BA;* Gregory G. Westin, AB; Satinder Singh, MD; Caroline E. McCoach, MD, PhD; Heejung Bang, PhD; Khung-Keong Yeo, MBBS; David Anderson, BA; Ezra A. Amsterdam, MD; John R. Laird, MD

Background—Current guidelines recommend that patients with peripheral arterial disease (PAD) cease smoking and be treated with aspirin, statin medications, and angiotensin-converting enzyme (ACE) inhibitors. The combined effects of multiple guideline-recommended therapies in patients with symptomatic PAD have not been well characterized.

Methods and Results—We analyzed a comprehensive database of all patients with claudication or critical limb ischemia (CLI) who 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 abstinence 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

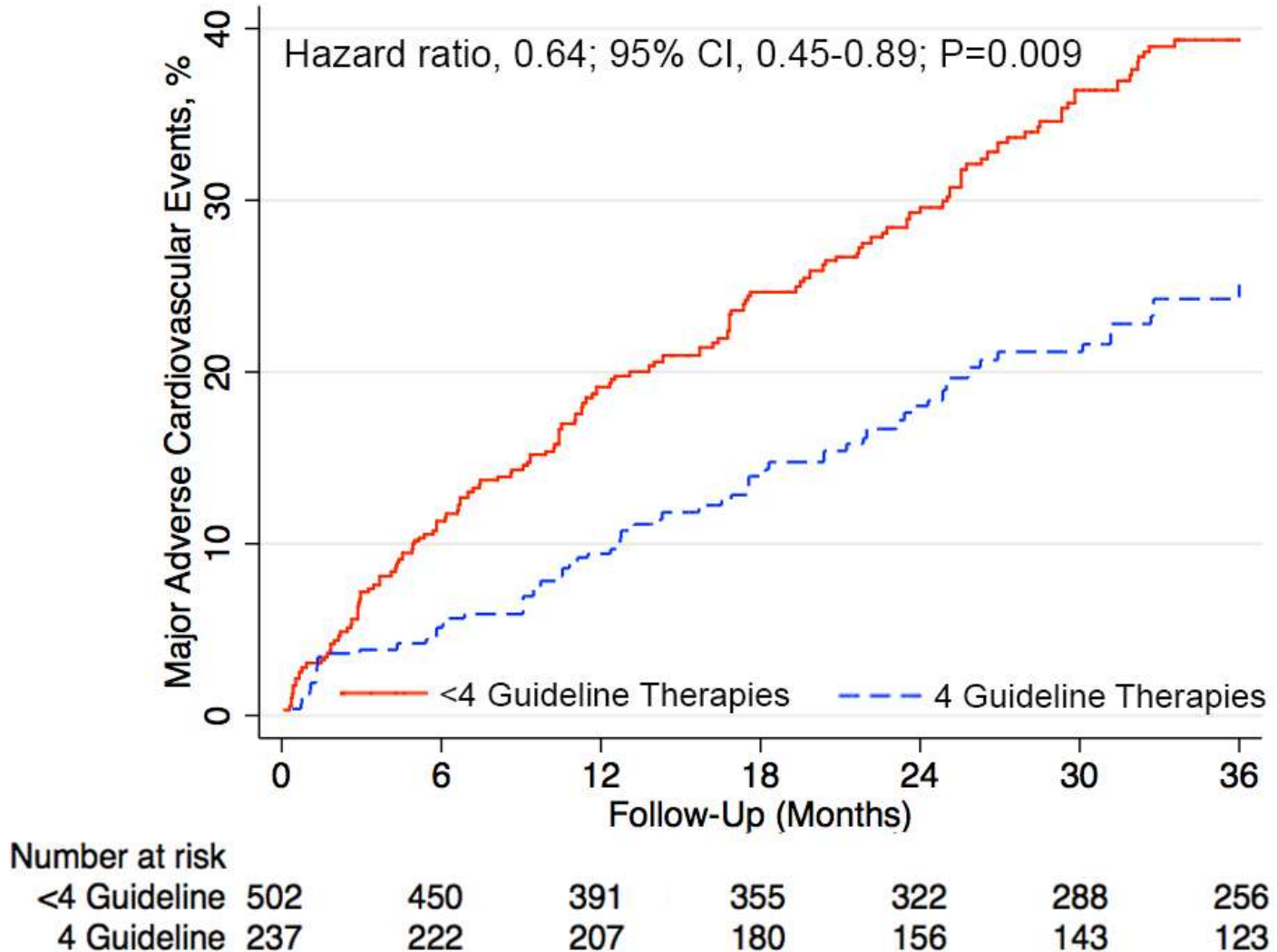
Study Design and Methods

- 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

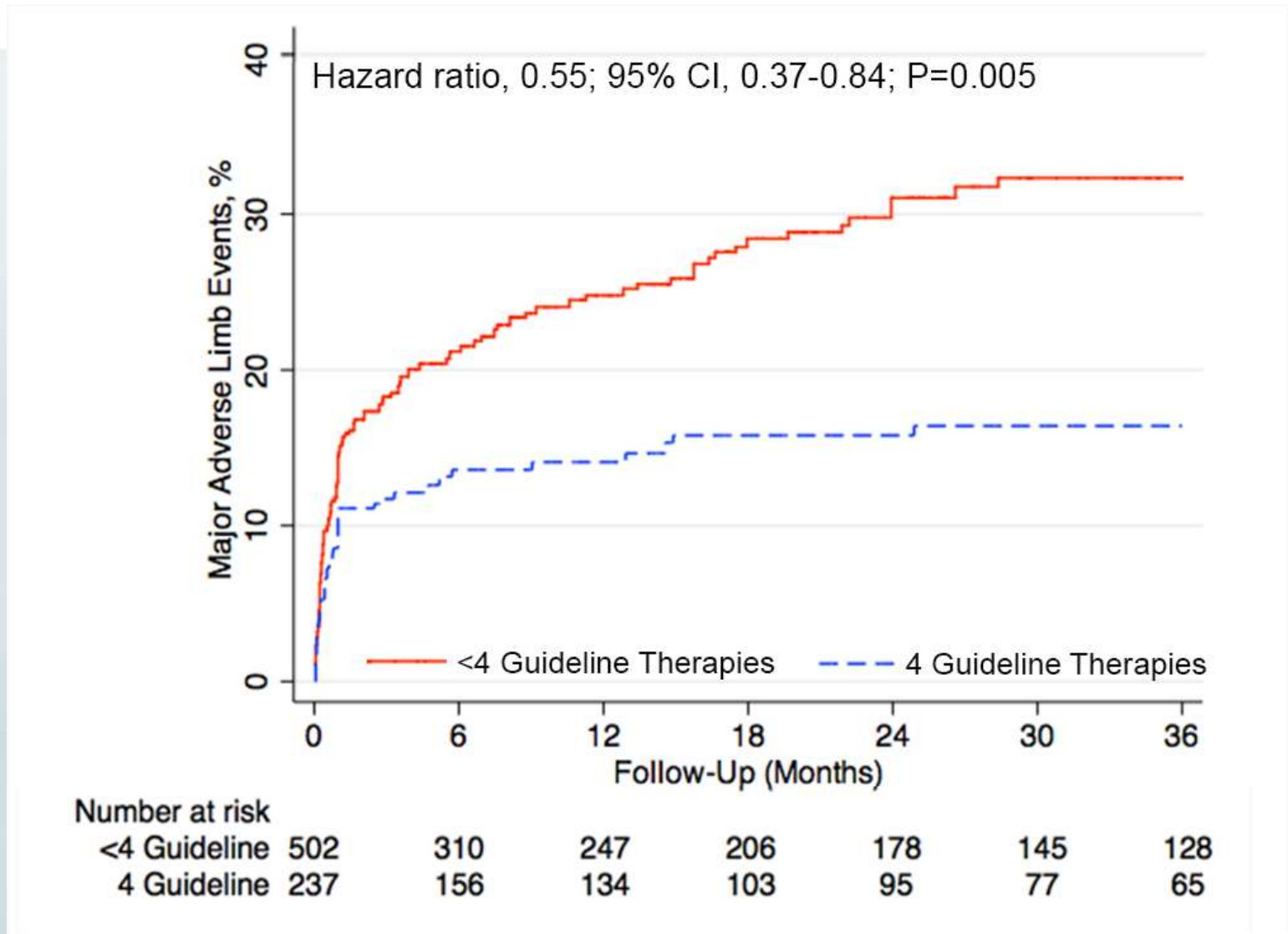
Definitions

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

36% reduction in MACE



45% reduction in MALE



Smoking Cessation Our Number One Priority!



Smoking and PAD

- Smoking is the single most important risk factor for the development and progression of PAD
- Among patients with PAD, 80% report being a current or past smoker
- Risk of PAD among smokers is 3 to 6 times higher than among nonsmokers
- PAD patients who achieve abstinence have far higher survival rates than those who do not

The Many Downsides of Smoking!



Smoking Cessation

- Combination therapy most effective
 - Behavior change
 - Support group/cessation class
 - Medications
 - 20%-25% abstinence at 1 year
 - Dose-related response
 - Brief interventions double chance of success
 - Intensive intervention 3-4 times increased

Smoking Cessation for PAD Patients

- 687 outpatient smokers with lower extremity PAD
 - 232 met eligibility requirements
 - 124 smokers (53% of eligible) enrolled
- Randomly assigned to intensive intervention group or minimal intervention
 - Physician advice, smoking cessation counseling, stop smoking medication aides

Smoking Cessation for PAD Patients

- Intensive Care Group:
 - Median number of counseling sessions: 8.5
 - Percentage using any medication: 87%
- Minimal Care Group:
 - Percentage using any medication: 67%
- Abstinence at 6-month follow-up:
 - Intensive Care: 21.3%
 - Minimal Care: 6.8%

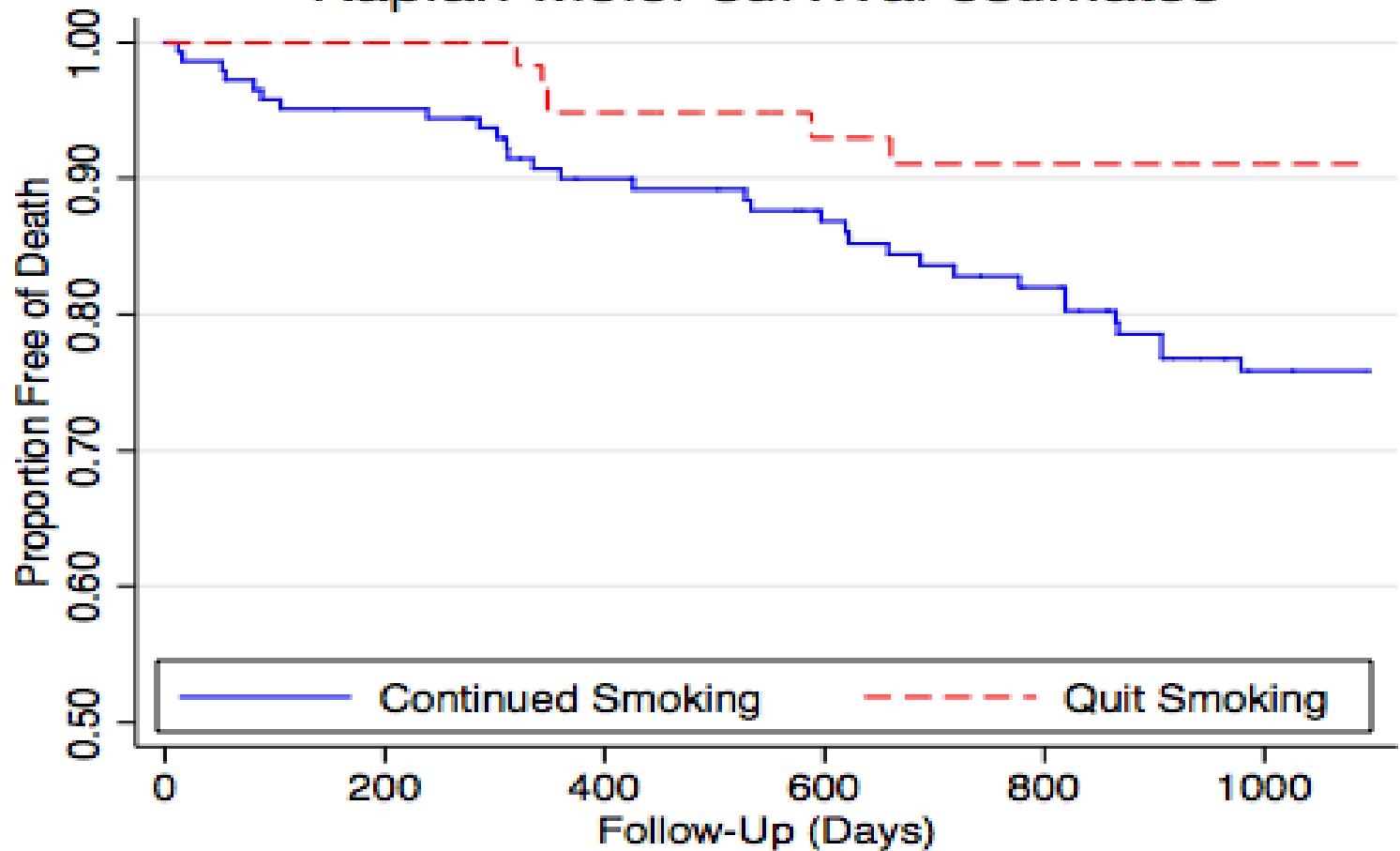
Does quitting smoking really make a difference?

Smoking Cessation

UCD PAD Registry

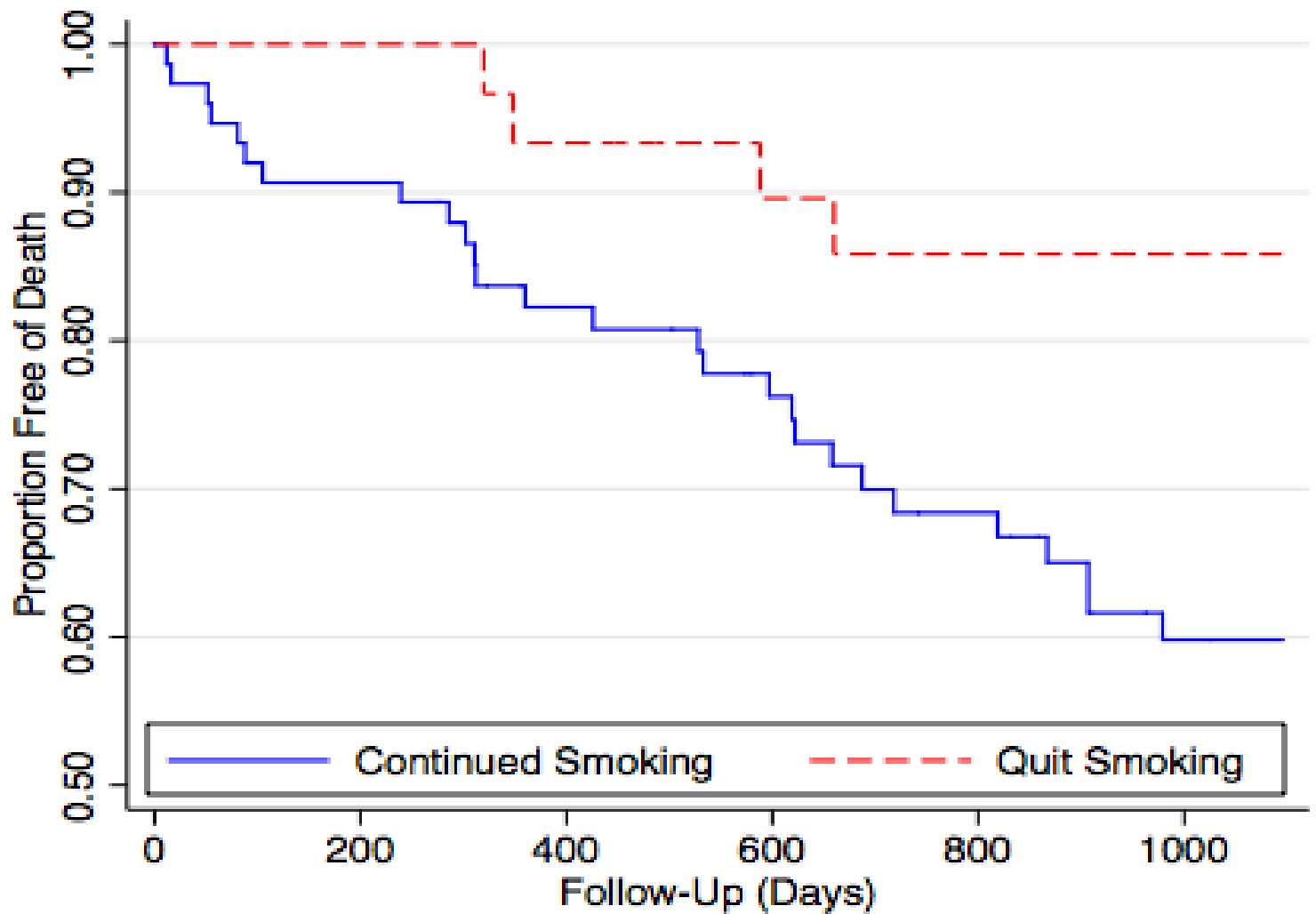
- Among 739 patients with claudication or CLI, 204 (28%) remained active smokers at the time of LE angiography.
- Mean number of cigs/day 16, mean pack-years 40
- In subsequent year, 61 (30%) patients successfully quit smoking.

Kaplan-Meier survival estimates



Number at risk							
Continued Smoking	143	135	118	109	98	80	
Quit Smoking	61	60	55	50	48	45	

- At three years, mortality 9% vs. 24%
 - HR 0.34, 95% CI 0.13-0.88

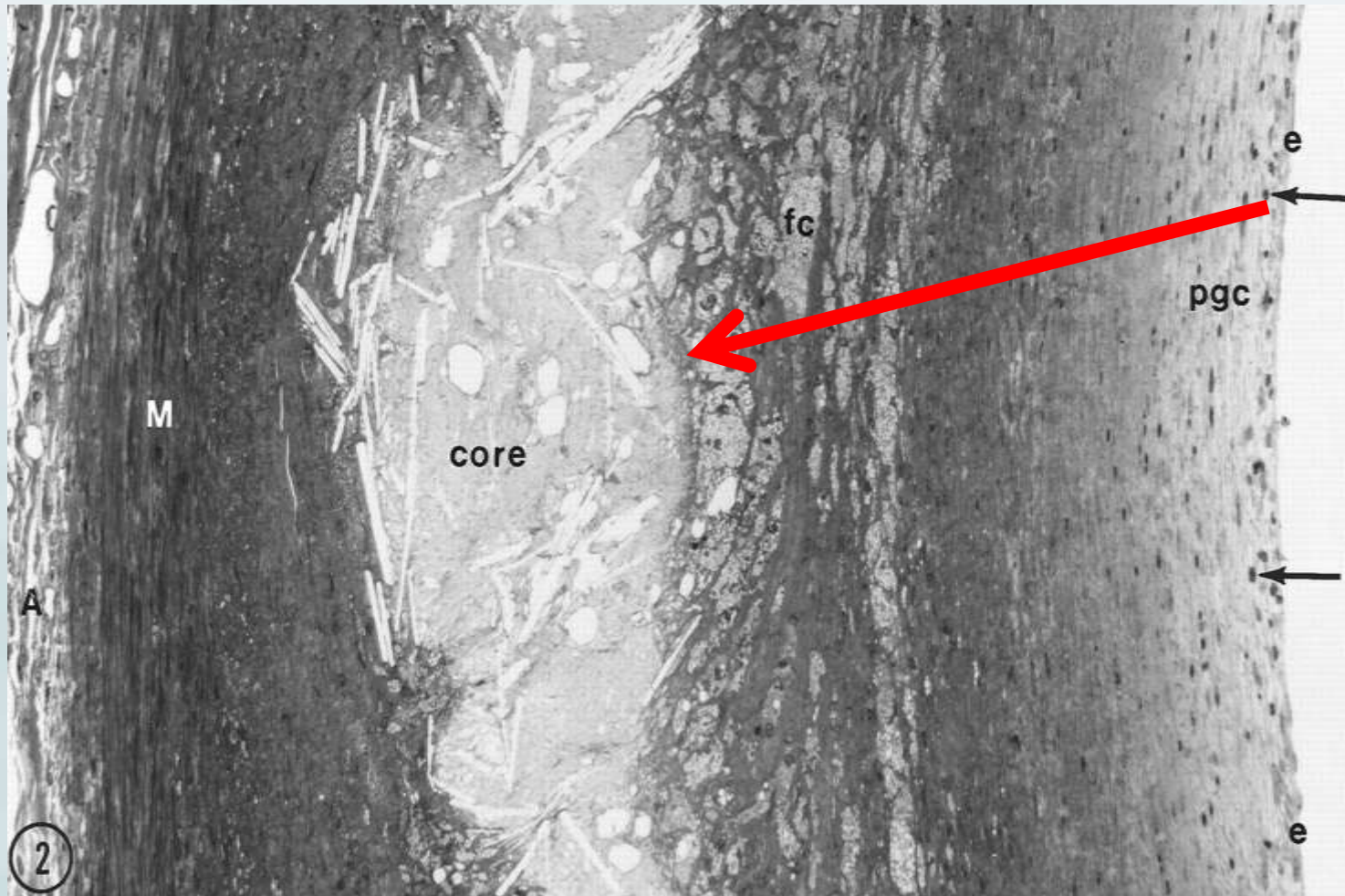


	0	200	400	600	800	1000
Continued Smoking	75	68	56	49	42	33
Quit Smoking	32	31	28	24	23	21

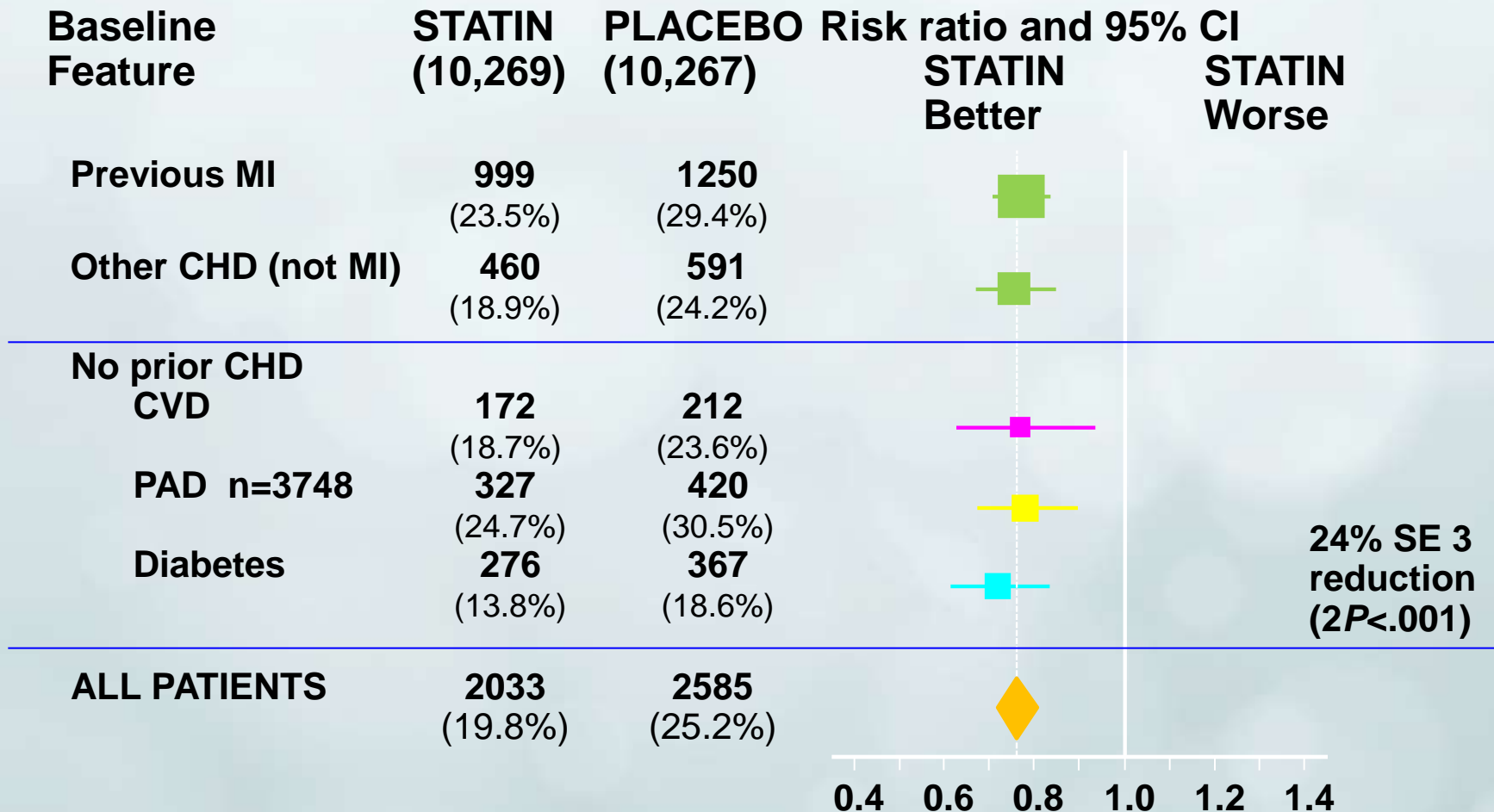
- Dramatic difference in survival for patients with critical limb ischemia

Our Number Two Priority!

Lipid Lowering and Plaque Stabilization



Heart Protection Study: Vascular Event by Prior Disease



Background

- Study of 646 patients with CLI undergoing endovascular treatment.
- Only 49% of patients were prescribed a statin.
- At 24 months, statin use was associated with improved primary patency (43% vs. 33%), secondary patency (66% vs. 51%), limb salvage (83% vs. 62%), and survival (77% vs. 62%).

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

Gregory G. Westin, AB, MAS,* Ehrin J. Armstrong, MD, MSc, MAS,† Heejung Bang, PhD,‡ Khung-Keong Yeo, MBBS,† David Anderson, BA,* David L. Dawson, MD,§ William C. Pevec, MD,§ Ezra A. Amsterdam, MD,† John R. Laird, MD†

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) © 2014 by the American College of Cardiology Foundation

UC Davis Experience

- UC Davis Peripheral Arterial Disease Registry:
 - All patients with CLI with peripheral angiography from July 2006 to May 2012
 - Demographics, clinical data, and follow-up from electronic medical records
 - Full angiographic review performed

Methods: Predictors and Outcomes

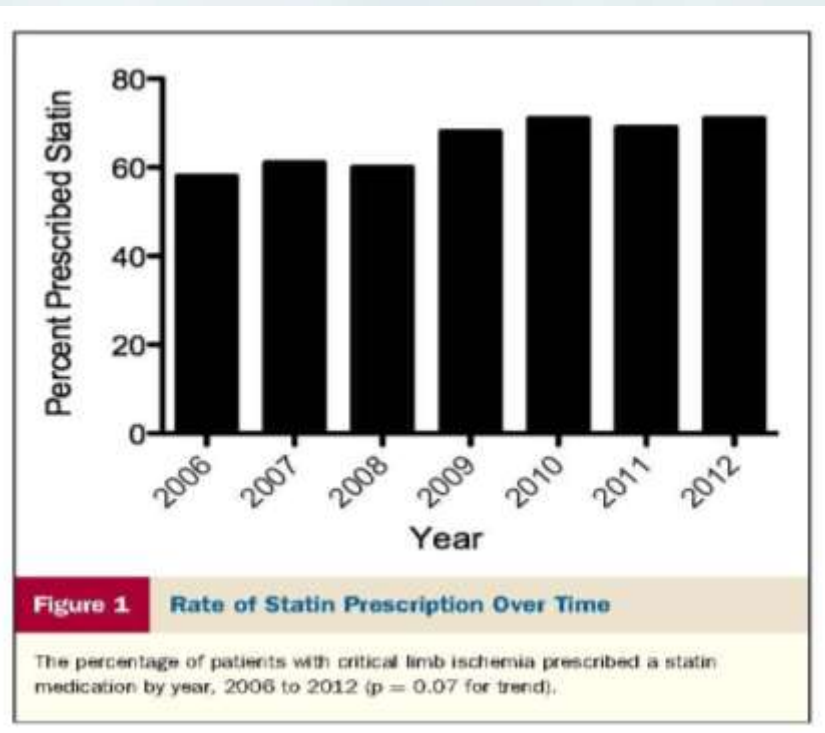
- Predictors
 - Statin use at baseline
 - LDL at baseline

- Primary outcome: MACCE at 1 year

- Secondary outcomes
 - Mortality at 1 year
 - Major amputation at 1 year

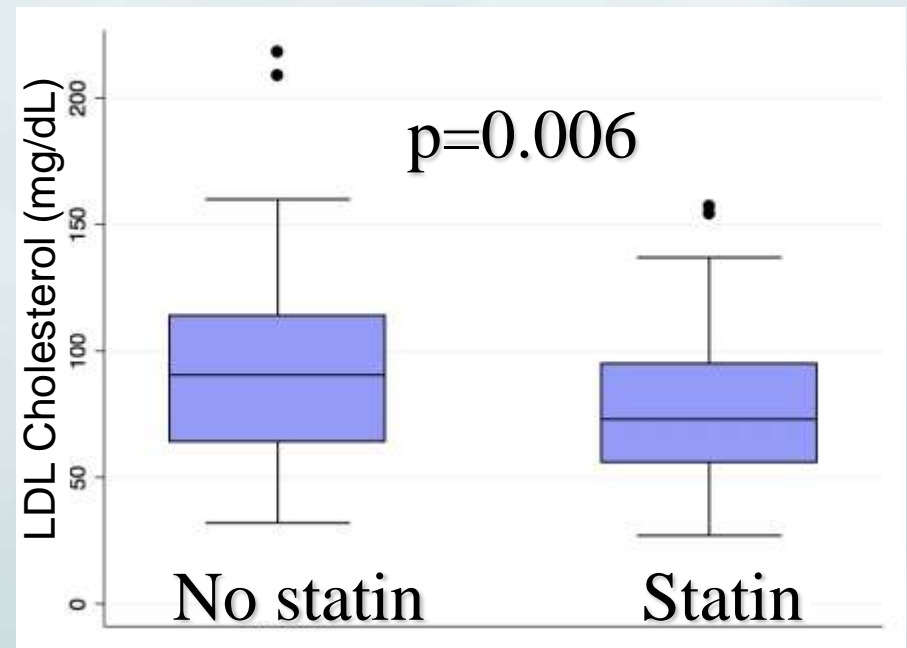
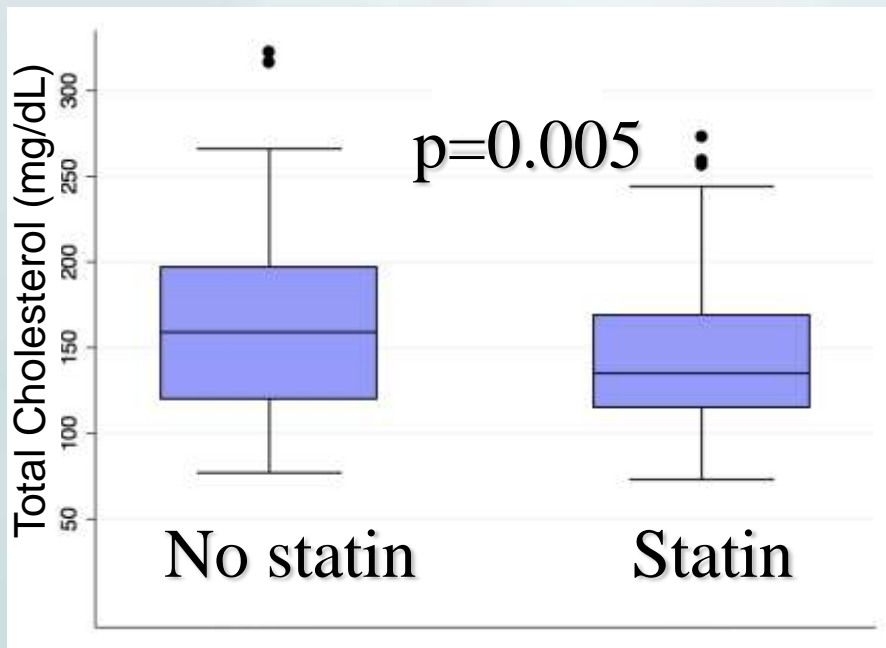
Study Population

- 337 patients with critical limb ischemia.
- 215 (64%) prescribed a statin at baseline.
- No significant change over time.

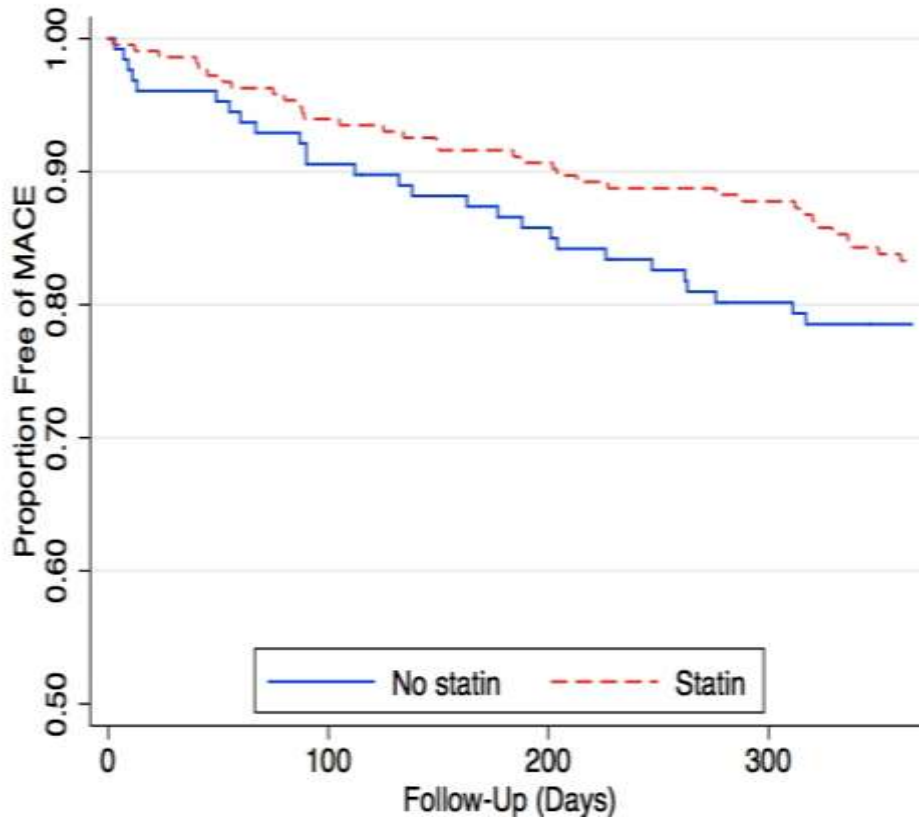


Lower Baseline LDL and Total Cholesterol in Statin Group

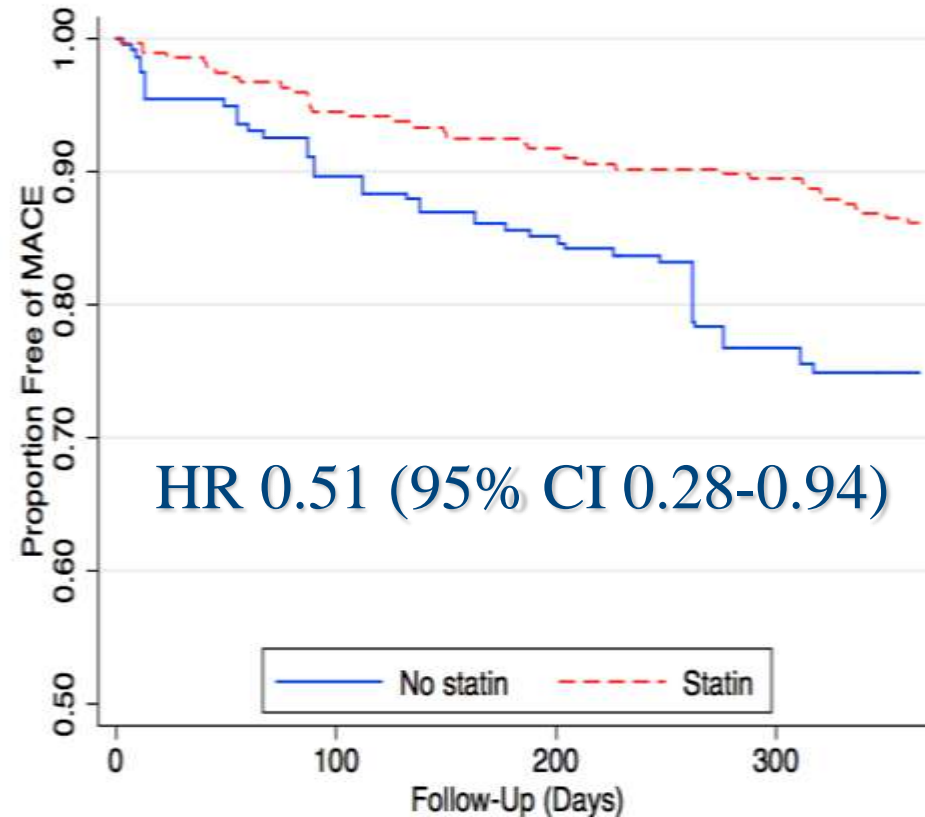
Variable	Statin (N=215)	No Statin (N=122)	p
Cholesterol, mg/dL	135	159	0.005
LDL, mg/dL	73	91	0.006
HDL, mg/dL	37	31	0.1
Triglyceride, mg/dL	113	114	0.7



Decreased Hazard of MACCE in Statin Group

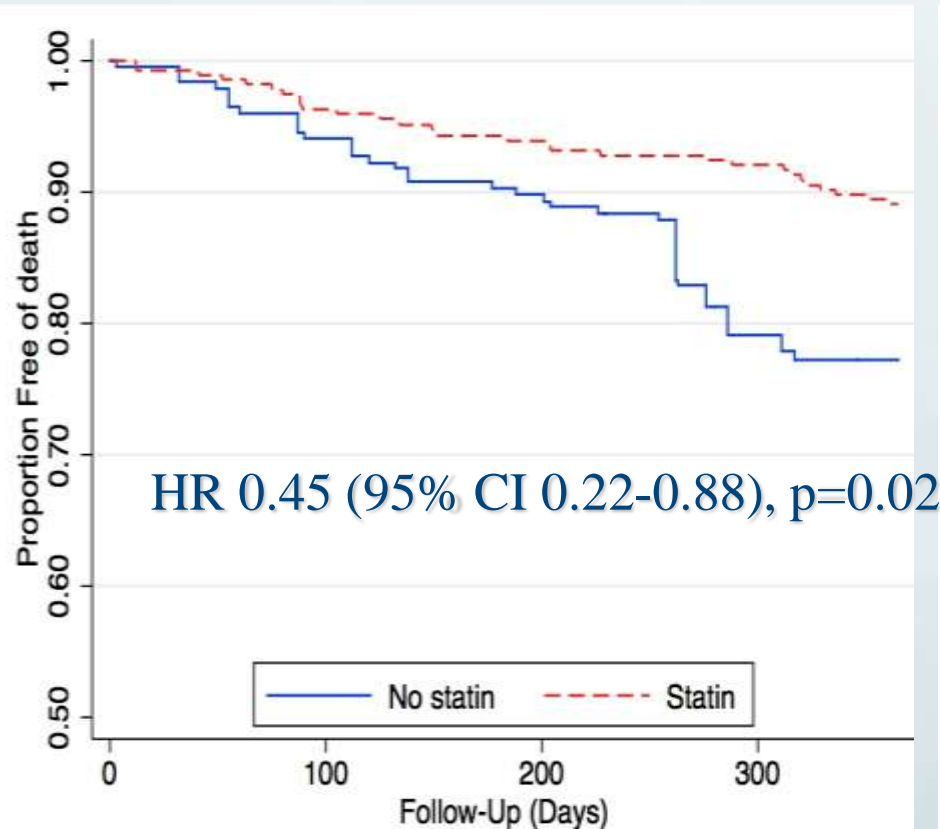


Unadjusted

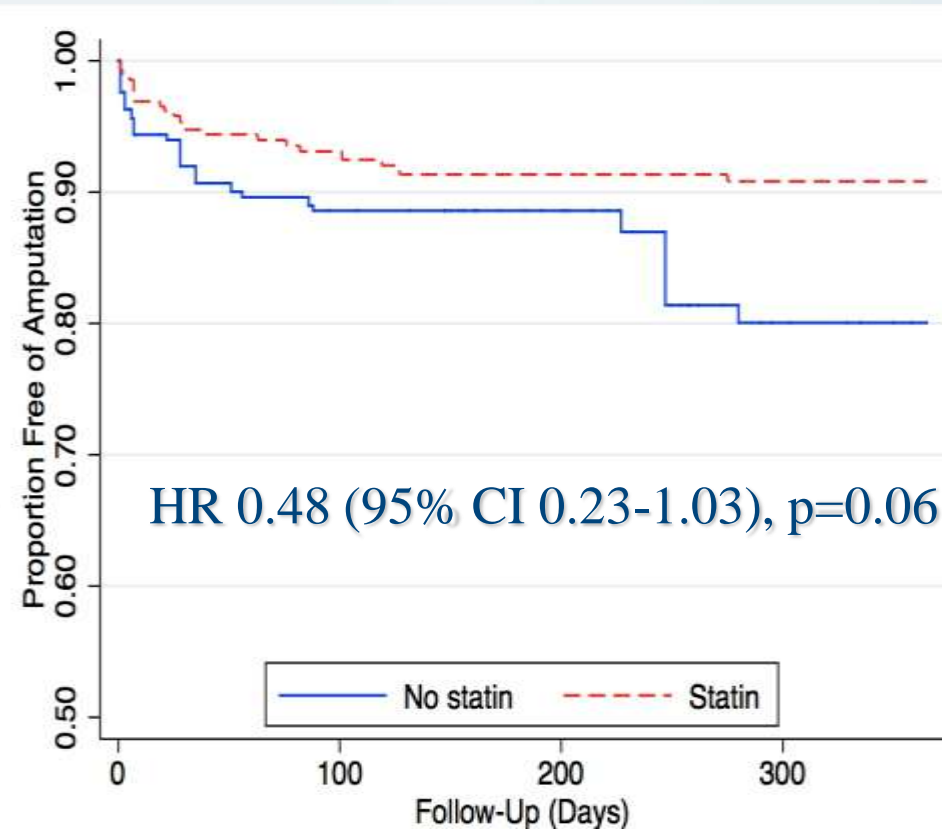


Propensity Weighted

Lower Mortality and Trend Towards Fewer Major Amputations in Statin Group

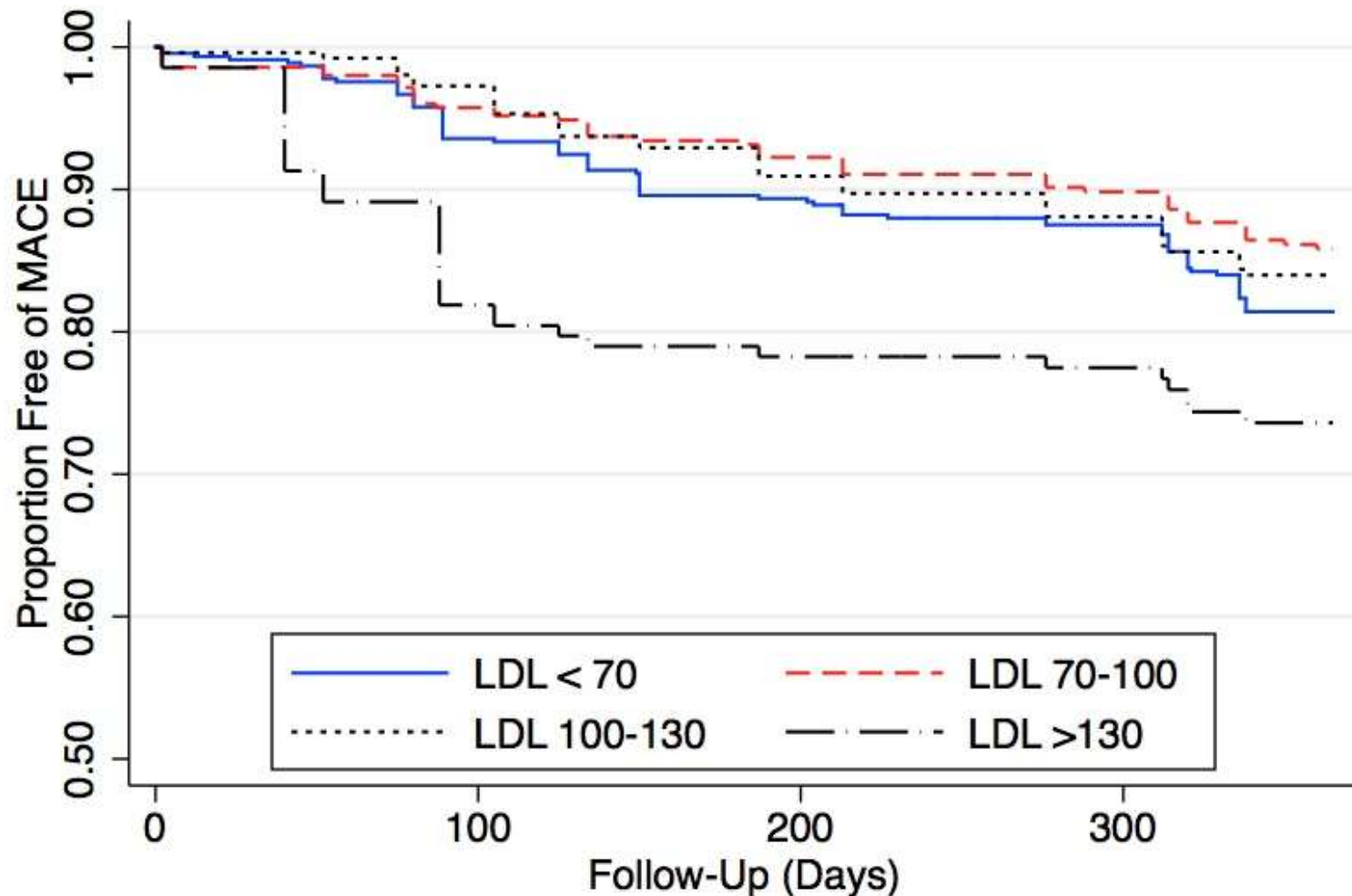


Death



Major Amputation

LDL > 130 mg/dL Associated With Increased MACCE



HR = 1.6 (95% CI 1.09-2.37) for LDL >130 vs. <70 (p=0.02)

Should PAD patients be treated with Dual Antiplatelet Therapy?

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

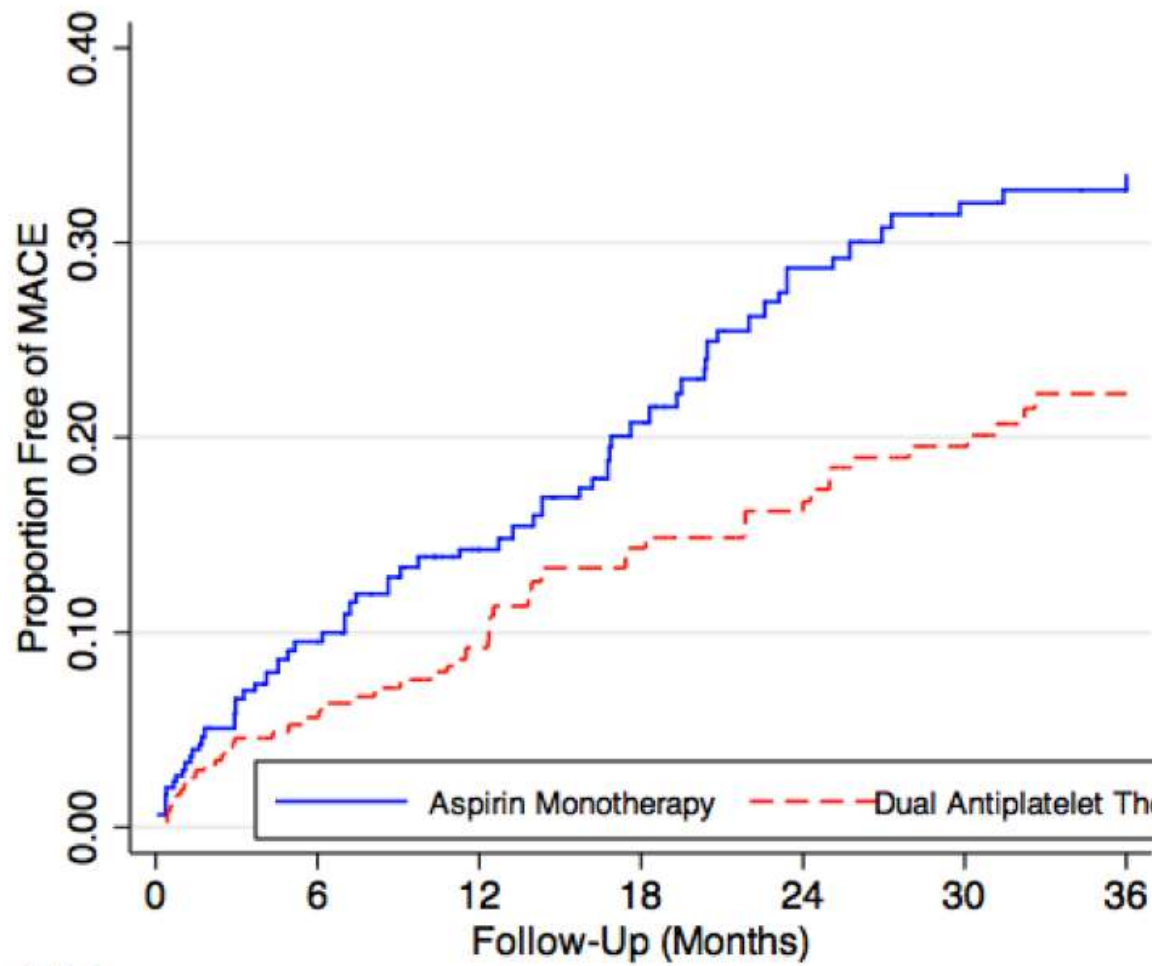
- Among patients with PAD, dual antiplatelet therapy possibly associated with reduced myocardial infarction.
- Event rates are much lower for patients with stable PAD on optimal medical therapy.

Dual Antiplatelet Therapy in Symptomatic PAD

UCD PAD Registry

- 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

MACE



Number at risk		0	6	12	18	24	30	36
ASA Monotherapy	281	204	171	154	137	130	126	
DAPT	348	276	216	189	171	153	132	

- Adjusted HR 0.65 (95% CI 0.44-0.96)

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 and may benefit the most from aggressive medical intervention