

# Medical Therapy, Current Guidelines and More Things that Will Change the Management of PAD Patients

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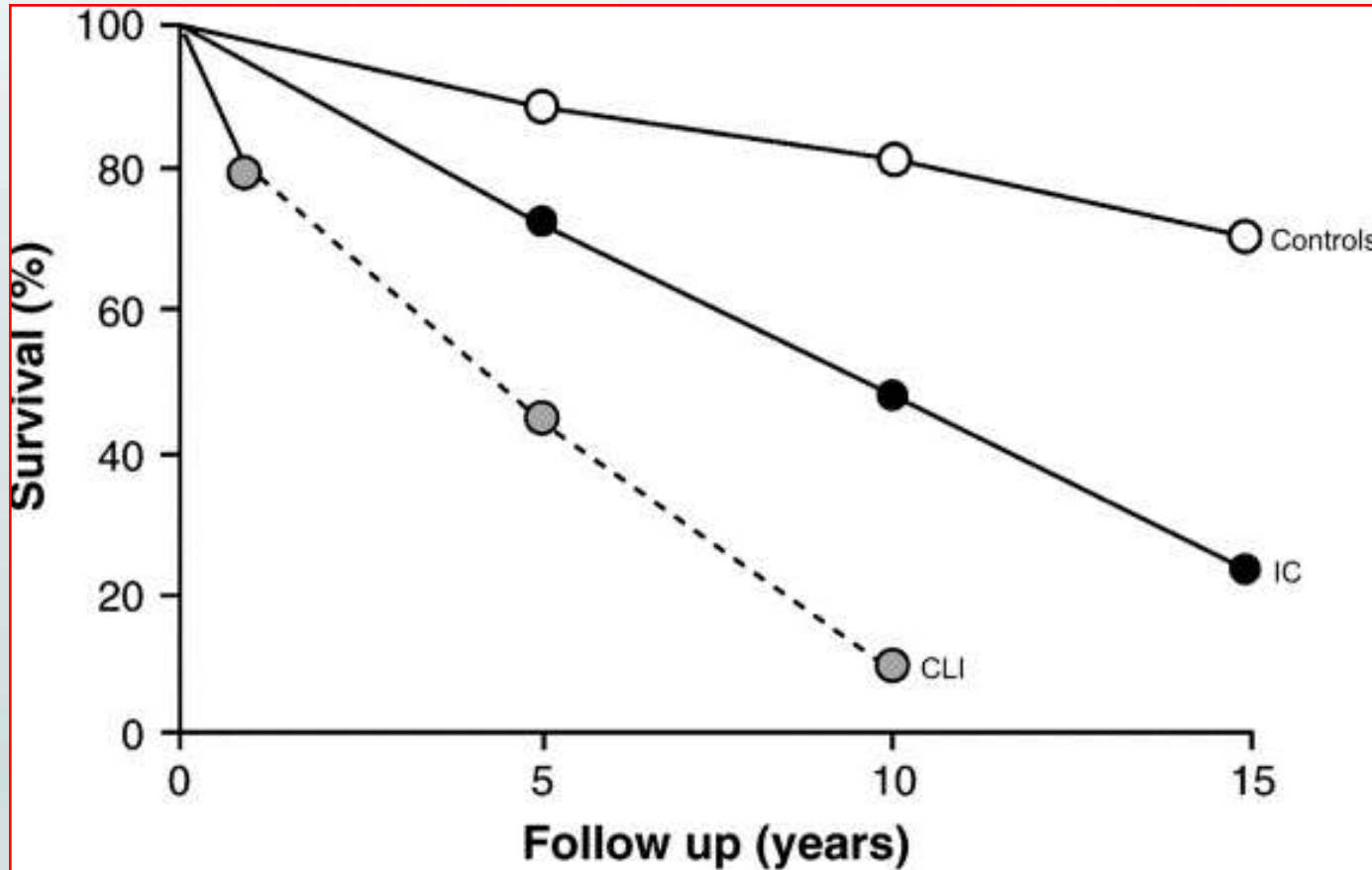
UC Davis Health

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■ Grant/Research Support	■ WL Gore, Medtronic
■ Consulting Fees/Honoraria	■ Abbott Vascular, Bard Peripheral Vascular, WL Gore, Boston Scientific, Medtronic

# The Clinical Imperative!



# 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<sup>2</sup> (OR: 1.5), BMI <18.0 kg/m<sup>2</sup> (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.

# ACC/AHA Guideline-Recommended Therapies for PAD

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

## Optimal medical therapy predicts amputation-free survival in chronic critical limb ischemia

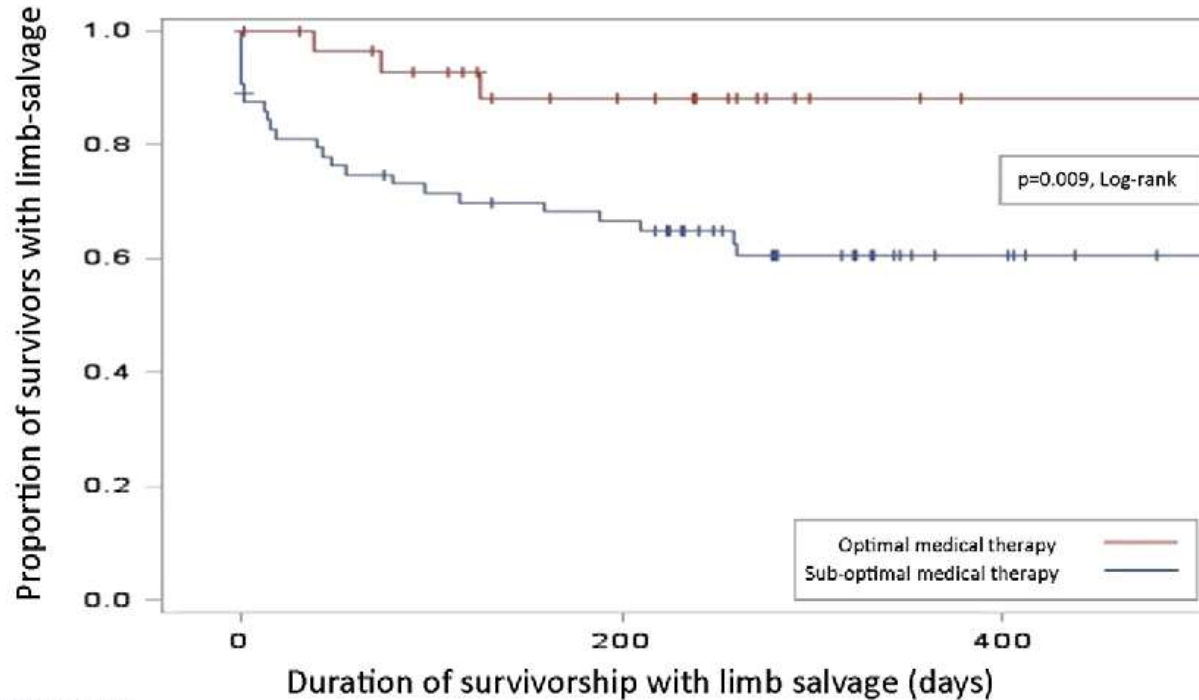
Jayer Chung, MD, David A. Timaran, MD, J. Gregory Modrall, MD, Chul Ahn, PhD,  
Carlos H. Timaran, MD, Melissa L. Kirkwood, MD, Mirza S. Baig, MD, and R. James Valentine, MD,  
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**Conclusions:** Despite guidelines advocating the optimization of atherosclerotic risk factors, less than one-third of patients with CLI present with their risk factors optimally managed. Patients who are medically undertreated have an eight-fold risk of major amputation and/or death. The magnitude of the effect suggests that future trials and quality assessments should stratify outcomes by the quality of baseline medical management. Of the risk factors affecting AFS medical therapy optimization is the variable that can be most significantly improved by vascular surgeons and the medical community. (J Vasc Surg 2013;58:972-80.)

patients (HR, 2.77; 95% CI, 1.02-8.00;  $P < .01$ ); a history of tobacco abuse (HR, 1.47; 95% CI, 0.67-3.00;  $P = .07$ ); a history of end-stage renal disease (HR, 7.97; 95% CI, 3.10-20.52;  $P < .01$ ); suboptimal medical management (HR, 4.25; 95% CI, 1.28-14.07;  $P = .02$ ); and an absence of antiplatelet agents (HR, 1.94; 95% CI, 0.92-4.11;  $P = .08$ ). Independent predictors of major amputation or death included: initial nonambulatory status (HR, 2.43; 95% CI, 1.03-2.05;  $P < .01$ ); unrevascularized status (HR, 2.43; 95% CI, 1.76-3.34;  $P = .01$ ); and suboptimal medical management at presentation (HR, 8.54; 95% CI, 2.05-35.65;  $P < .01$ ).

**Conclusions:** Despite guidelines advocating the optimization of atherosclerotic risk factors, less than one-third of patients with CLI present with their risk factors optimally managed. Patients who are medically undertreated have an eight-fold risk of major amputation and/or death. The magnitude of the effect suggests that future trials and quality assessments should stratify outcomes by the quality of baseline medical management. Of the risk factors affecting AFS medical therapy optimization is the variable that can be most significantly improved by vascular surgeons and the medical community. (J Vasc Surg 2013;58:972-80.)

The effect of optimal medical therapy upon amputation-free survival



	0	100	200	400
Optimally managed				
N	31	23	17	8
N Major amputation/death	0	2	1	0
% Survival	100	92.7	88.3	88.3
SE	0	0.05	0.06	0.06
Suboptimally managed				
N	67	43	39	23
N Major amputation/death	0	19	3	2
% Survival	100	71.5	64.9	60.4
SE	0	0.05	0.06	0.06

Fig 2. Amputation-free survival (AFS) among 98 chronic critical limb ischemia (CLI) patients stratified by optimal medical therapy at presentation. SE, Standard error.

# 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

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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 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

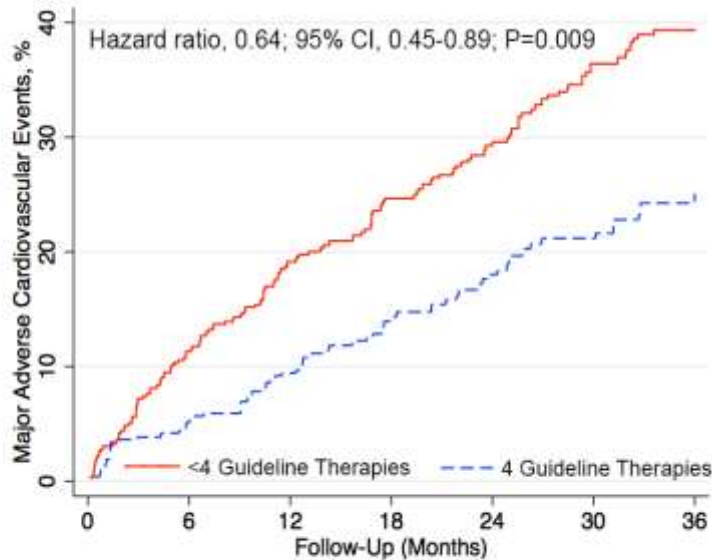
### Definitions

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

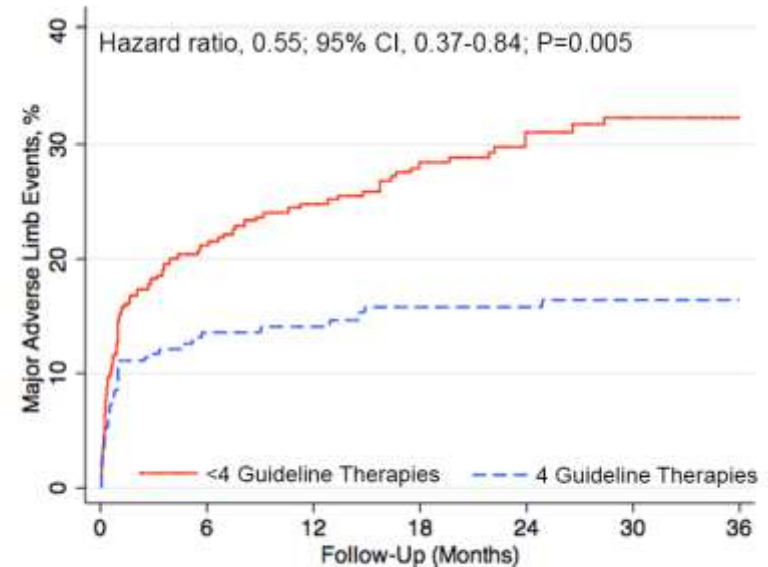
# Adherence to all 4 Guidelines Based Therapies

**36% reduction in MACE**

**45% reduction in MALE**



Number at risk	0	6	12	18	24	30	36
<4 Guideline	502	450	391	355	322	288	256
4 Guideline	237	222	207	180	156	143	123



Number at risk	0	6	12	18	24	30	36
<4 Guideline	502	310	247	206	178	145	128
4 Guideline	237	156	134	103	95	77	65

# Our Number One Priority!



# Smoking cessation is associated with decreased mortality and improved amputation-free survival among patients with symptomatic peripheral artery disease

Ehrin J. Armstrong, MD, MS,<sup>a</sup> Julie Wu, BS,<sup>b</sup> Gagan D. Singh, MD,<sup>b</sup> David L. Dawson, MD,<sup>c</sup> William C. Pevec, MD,<sup>c</sup> Ezra A. Amsterdam, MD,<sup>b</sup> and John R. Laird, MD,<sup>b</sup> *Aurora, Colo; and Sacramento, Calif*

**Objective:** Although smoking cessation is recommended for all patients with peripheral artery disease, there are little data regarding the prevalence of smoking among patients at the time of angiography or the effect of smoking cessation on clinical outcomes.

**Methods:** Consecutive patients with claudication or critical limb ischemia who underwent peripheral angiography from 2006 to 2013 were included in an observational cohort analysis. Smoking status was assessed at the time of angiography and during follow-up clinic visits. Kaplan-Meier analysis was used to assess the relationship between smoking cessation, mortality, and amputation-free survival.

**Results:** Among 739 patients (423 men and 316 women; mean age,  $60 \pm 12$  years), 204 (28%) remained active smokers at the time of lower extremity angiography. At the time of angiography, the mean number of cigarettes smoked per day was  $16 \pm 10$ , and the mean pack-years was  $40 \pm 25$ . During the course of the subsequent year, 61 patients (30%) successfully quit smoking and maintained continued abstinence. Baseline medication use between groups did not differ significantly. The mean ankle-brachial index was also similar for quitters vs nonquitters ( $0.53 \pm 0.24$  vs  $0.49 \pm 0.22$ ;  $P = .3$ ). During follow-up to 5 years, patients who quit smoking had significantly lower all-cause mortality (14% vs 31%; hazard ratio, 0.40; 95% confidence interval, 0.18-0.90) and improved amputation-free survival (81% vs 60%; hazard ratio, 0.43, 95% confidence interval, 0.22-0.86) compared with patients who continued smoking, with most of the difference driven by reduced mortality among patients who quit smoking. The findings remained significant on multivariable analysis.

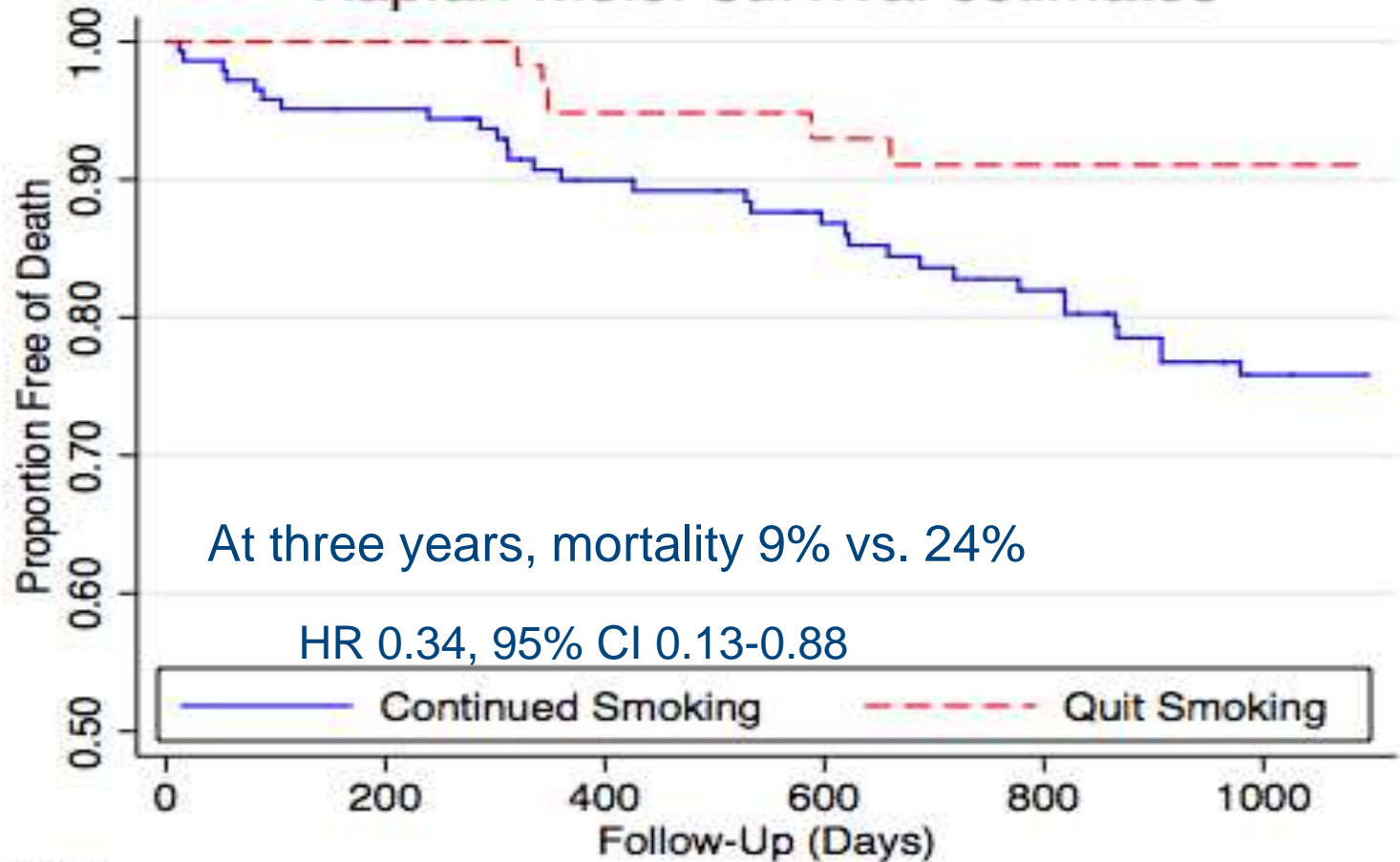
**Conclusions:** Approximately one-third of active smokers with peripheral artery disease successfully quit smoking  $\leq 1$  year after lower extremity angiography. Patients who quit smoking have lower mortality and improved amputation-free survival compared with patients who continue smoking. (J Vasc Surg 2014;60:1565-71.)

# Smoking Cessation

## UCD PAD Registry

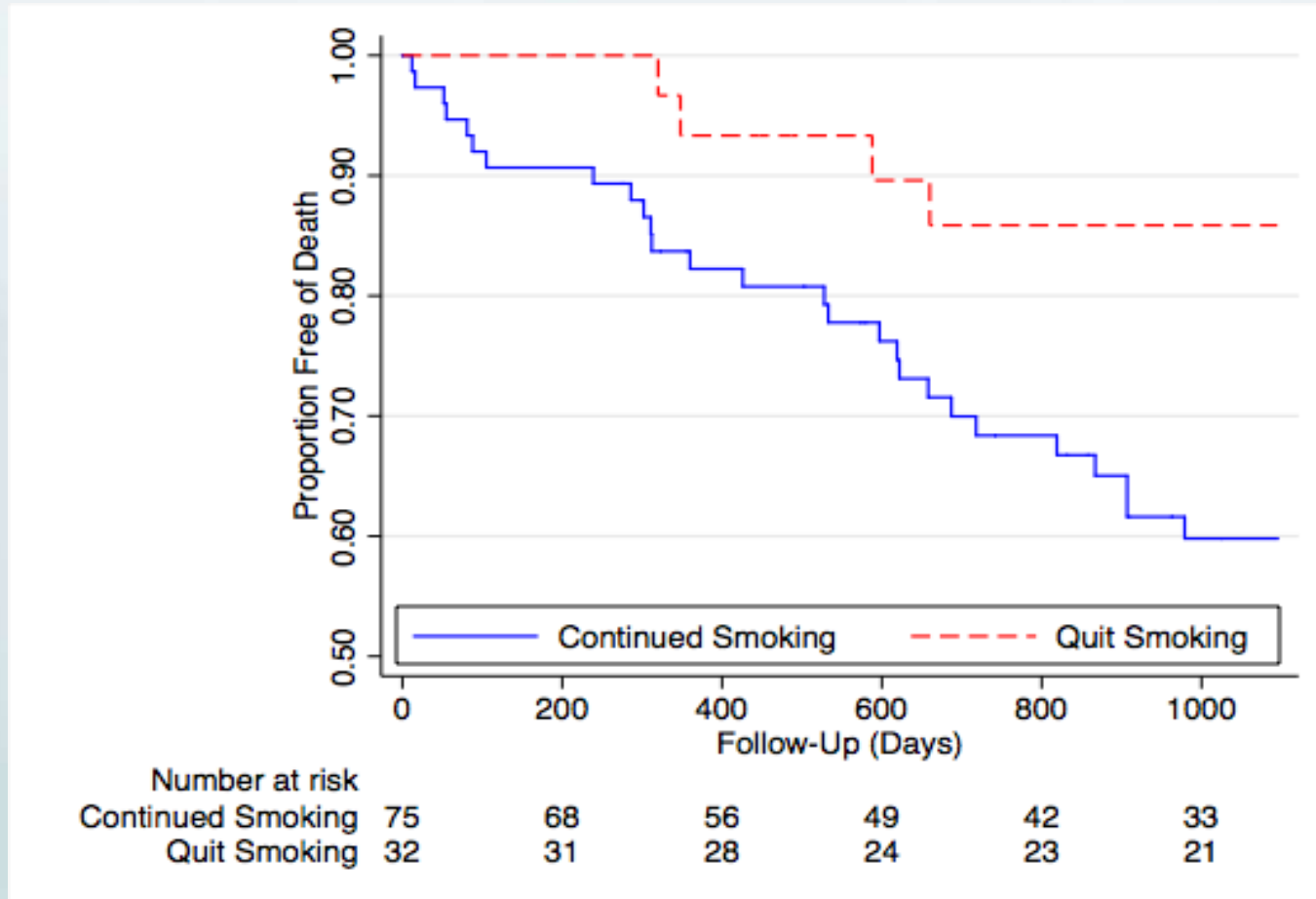
- Among 739 patients with claudication or CLI, 204 (28%) remained active smokers at the time of LE angiography.
- Mean number of cigs/day 16, mean pack-years 40
- In subsequent year, 61 (30%) patients successfully quit smoking.

### Kaplan-Meier survival estimates



	0	200	400	600	800	1000
Number at risk						
Continued Smoking	143	135	118	109	98	80
Quit Smoking	61	60	55	50	48	45

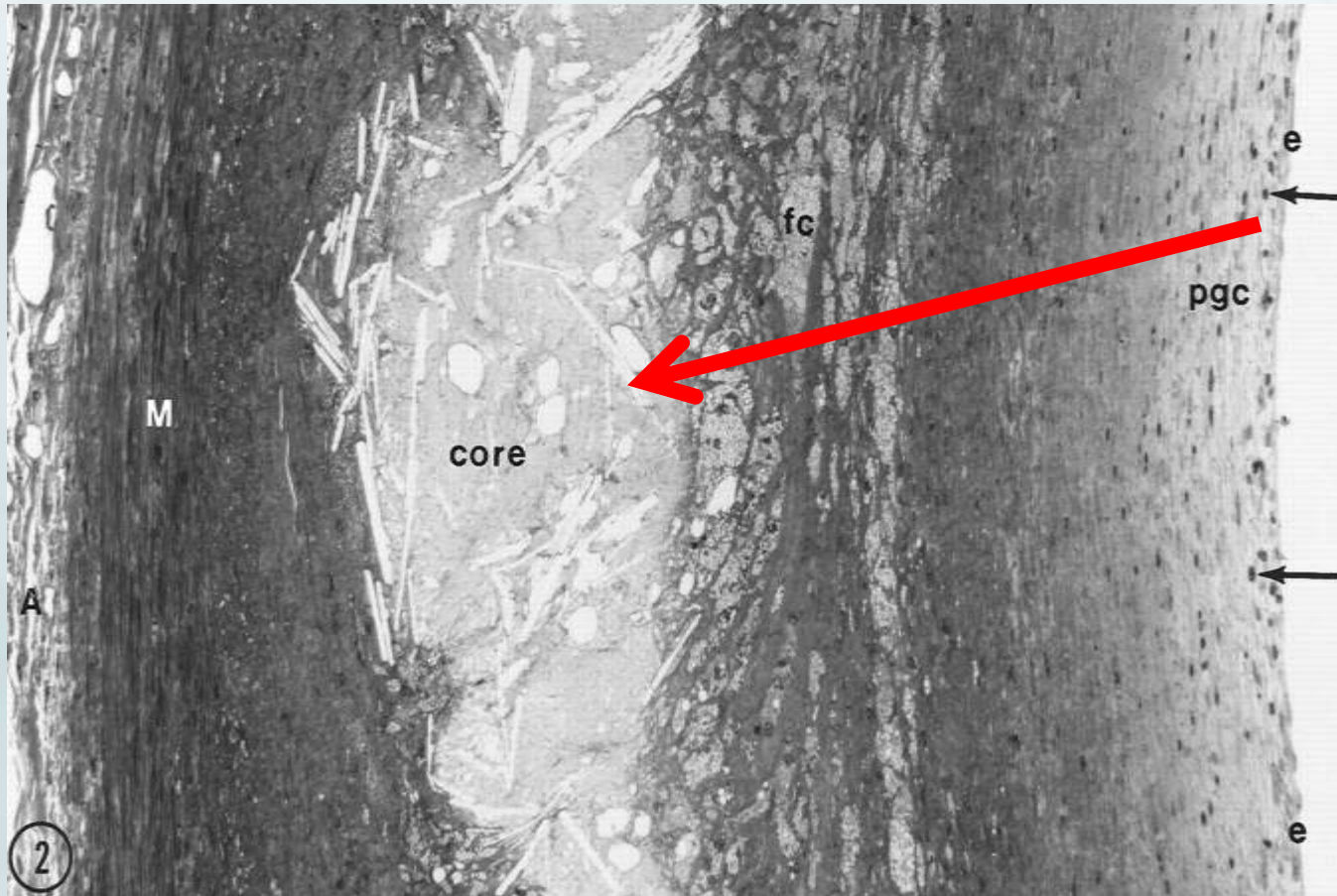
# Dramatic difference in survival for patients with critical limb ischemia!





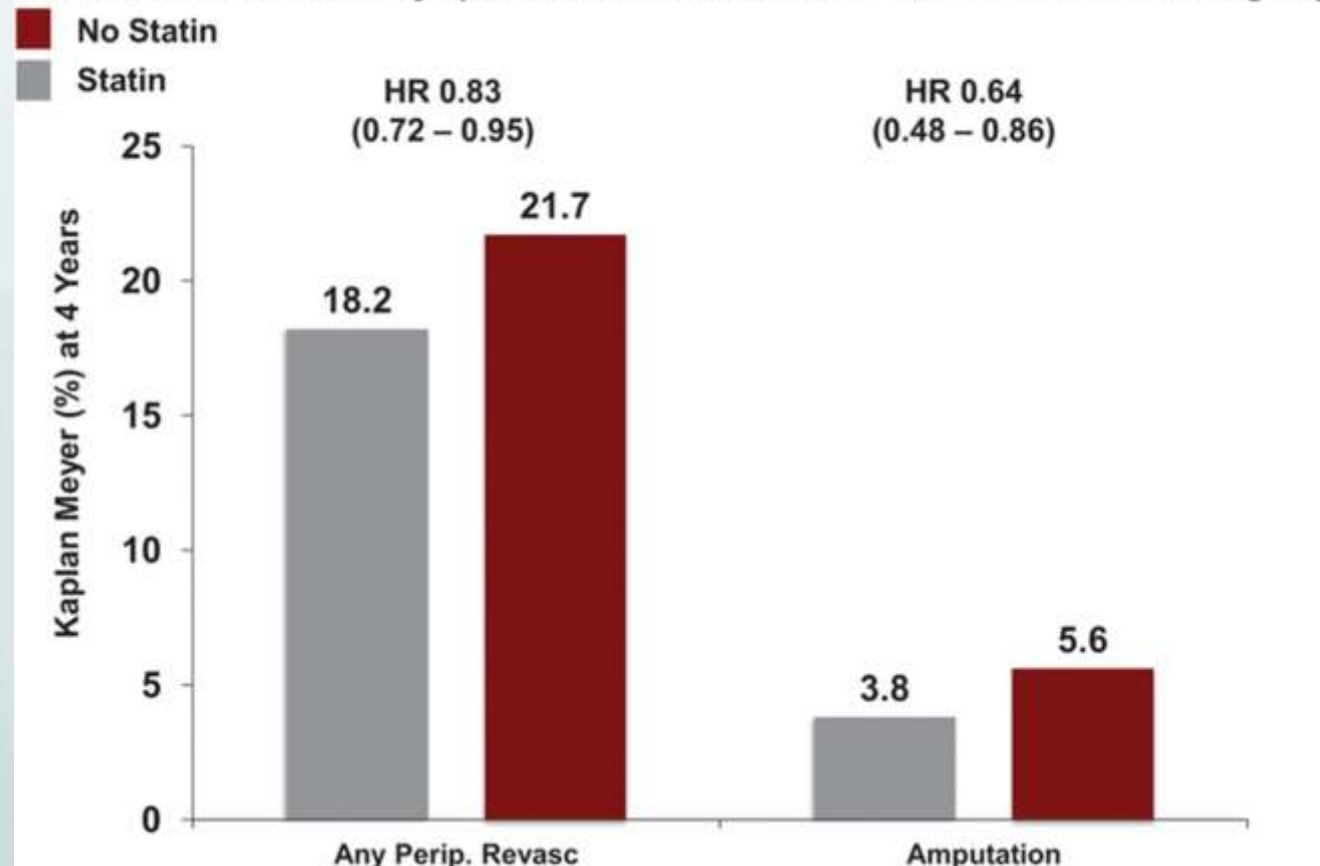
# What About Statins in PAD and CLI?

## Lipid Lowering and Plaque Stabilization



# Effect of Statin Treatment on *Limb Vascular Events*

Limb Vascular Events in Symptomatic\* PAD Patients at 4 Years in the REACH Registry



# 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  $\beta$ -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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## 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.

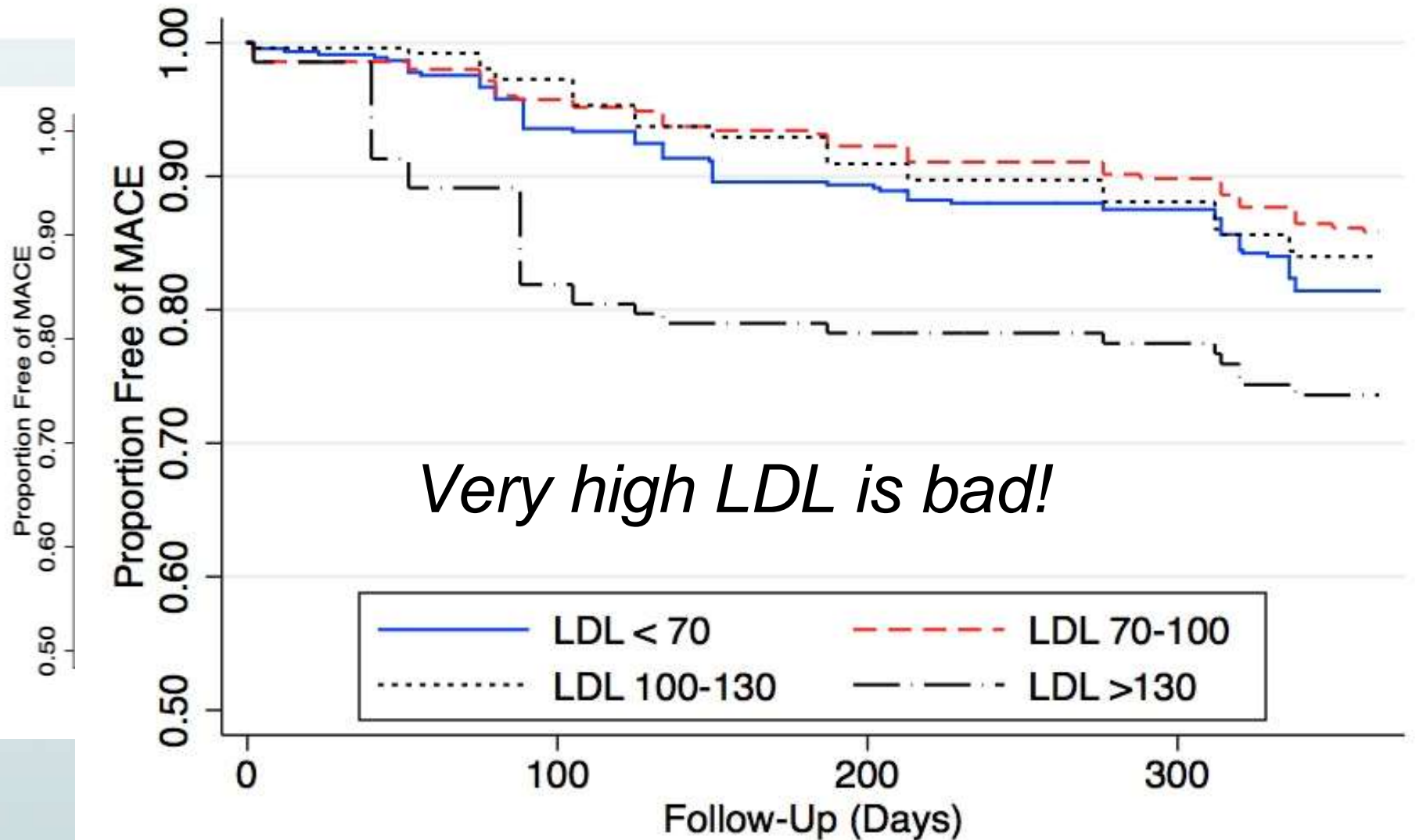
## Results

Statin use was prescribed for 246 (65%) patients. The mean serum low-density lipoprotein (LDL) level was lower in patients prescribed statins ( $75 \pm 28$  mg/dl vs.  $96 \pm 40$  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

Statin use is 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

# Decreased Hazard of MACE in Statin Group



# Should CLI patients be treated with Dual Antiplatelet Therapy?

# 2016 PAD Guideline Focused Update Recommendations for Antiplatelet and Antithrombotic Drugs (MODIFIED)

- Antiplatelet therapy (ASA or clopidogrel) for symptomatic PAD to *reduce CV complications* (I-A)
- DAPT for symptomatic PAD to *reduce CV complications* (II-B)
- Vorapaxar added to existing antiplatelet therapy for symptomatic PAD (II-B)



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

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**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.

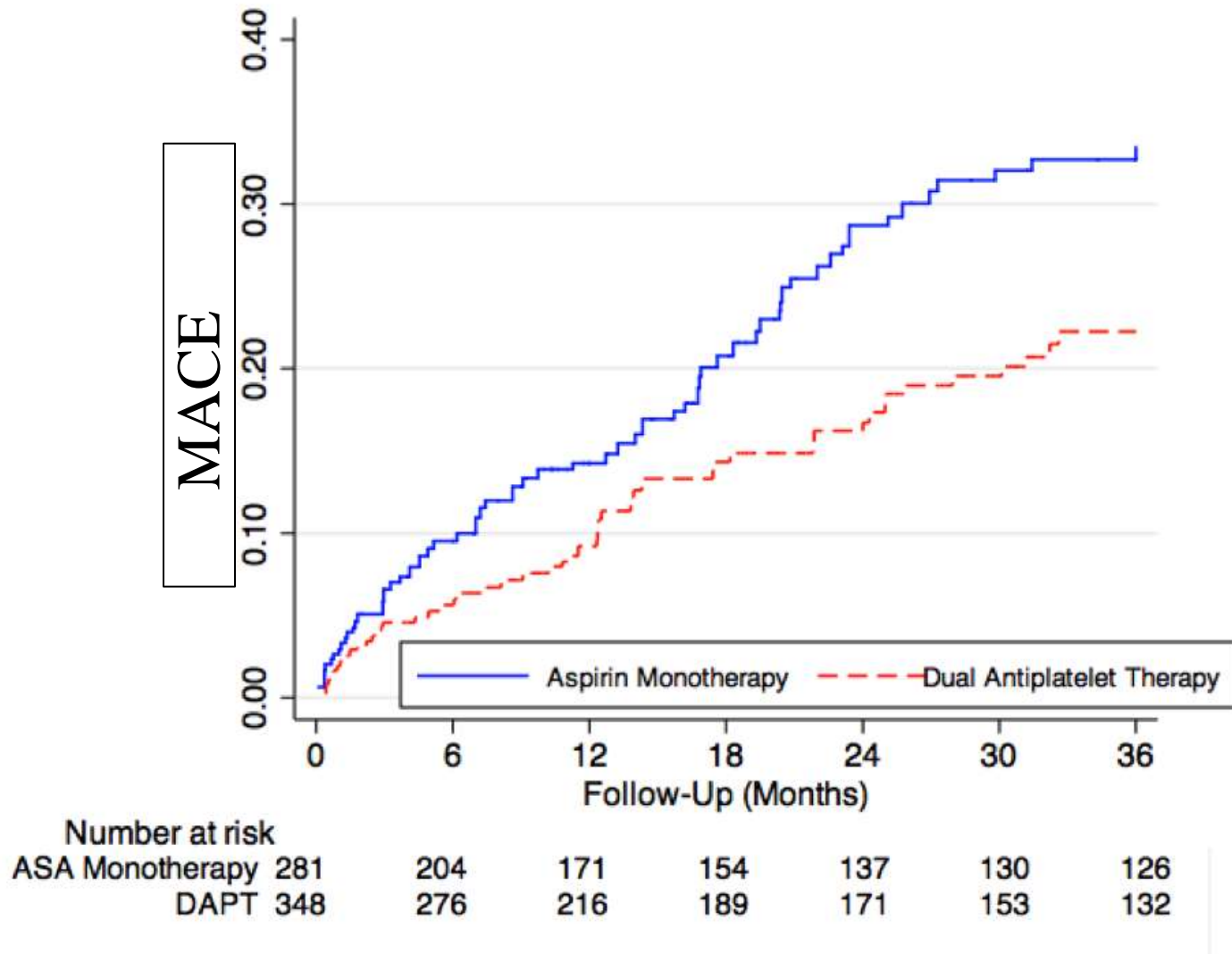
**Methods:** This was an observational cohort analysis that included 629 patients with claudication or critical limb ischemia. The prevalence of patients taking ASA monotherapy vs DAPT was assessed monthly for up to 3 years. A propensity model was constructed to adjust for baseline demographic characteristics 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



Adjusted HR 0.65 (95% CI 0.44-0.96)

# PCSK9 Inhibitors

## *The Future of Medical Therapy for PAD?*

### ■ The GLAGOV Study

- Mean LDL-C of 36.6 mg/dl for those treated with statin plus evolocumab (-59.8% from baseline)
- 5.8 mm<sup>3</sup> reduction in total atheroma volume (0.9mm<sup>3</sup> for statin alone)
- Plaque regression in 64.3% of patients treated with statin plus evolocumab (compared with 47.3% with statin alone,  $p < 0.0001$ )
- Reduction in first Major Cardiovascular Event (12.2% vs. 15.3%)

# 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