# CLI BEST MEDICAL THERAPY (PART II)

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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 |

# 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

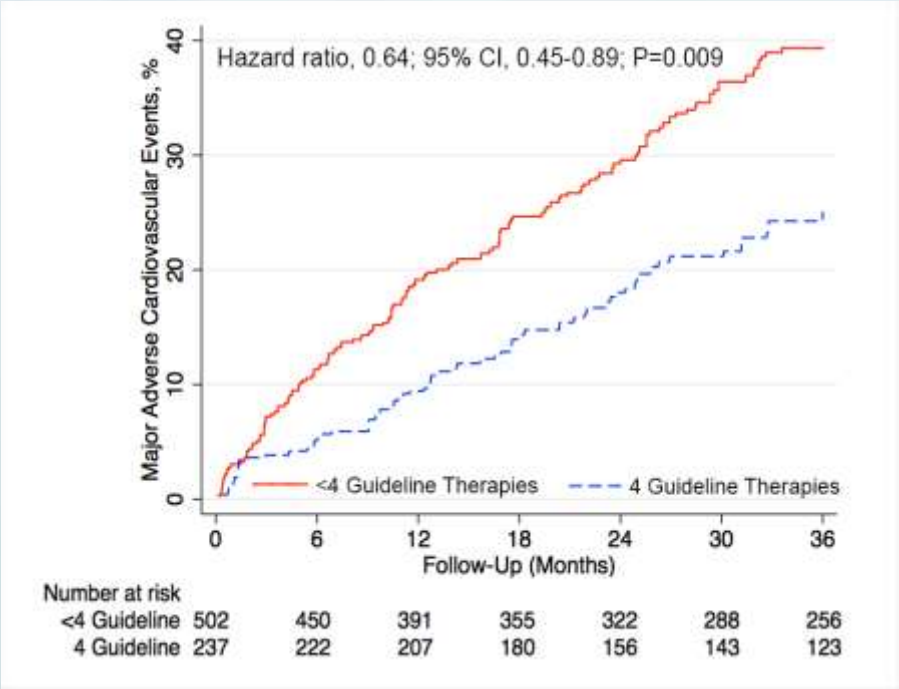
## Definitions

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

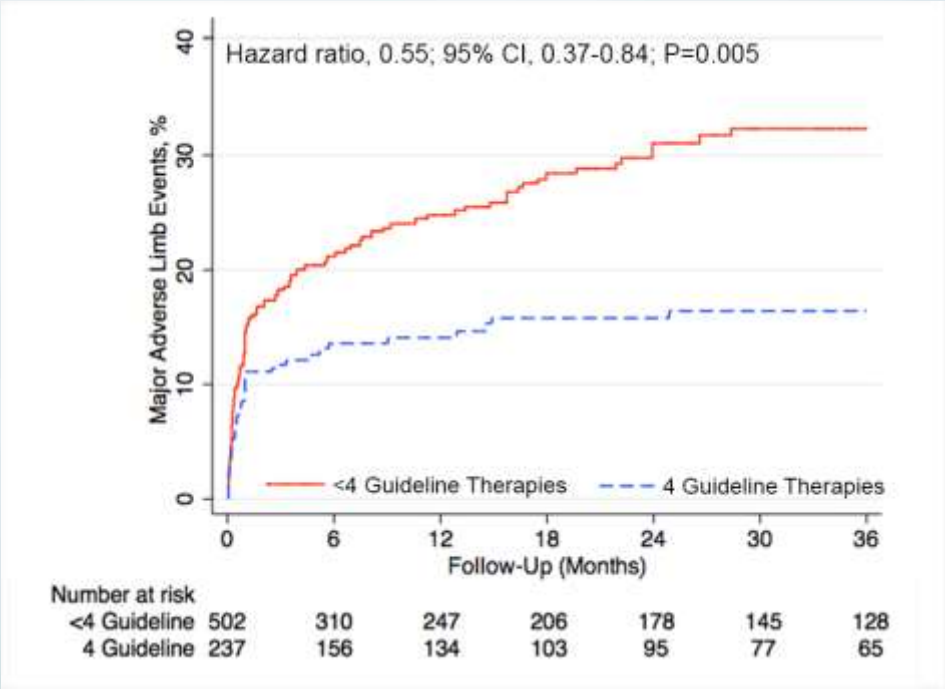
Armstrong, J Am Heart Assoc 2014

# Adherence to all 4 Guidelines Based Therapies

## 36% reduction in MACE




## 45% reduction in MALE




Armstrong, J Am Heart Assoc 2014

# Our Number One Priority!

# Smoking Prevalence

- US
  - Median adults: 20.9%
    - Lowest: Utah (10.5%); highest: Kentucky (27.6%)
- California
  - Median: 14.8%
    - Women: 11.1%; men: 18.5%
- Minnesota
  - Median: 20.7%
    - Women: 19.5%; men: 22.0%
- Nevada
  - Median: 23.2%
    - Women: 21.7%; men: 24.7%

*State-Specific Prevalence of Cigarette Smoking and Quitting Among Adults --- United States, 2004, MMWR, November 11, 2005 / 54(44);1124-1127.*

# Smoking Prevalence - Korea

- 2008 Korean Health and Nutrition Examination Survey
- 5455 individuals (2387 men and 3068 women)
- Cotinine-verified smoking rates were 50.0% for men and 13.9% for women, or 5.3% point and 8.0% point higher in absolute terms, respectively, than the self-reported rates for men and women

*Tob Control* 2012;**21**:536-542

# 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!

# Beneficial Effects of Smoking Cessation in Patients With PAD

- Decreases likelihood of:
  - Amputation[1]
  - Need for revascularization[2]
  - Failure of arterial bypass grafts[3,7]
- Improves pain free and maximal walking times compared to patients who continue to smoke[4,5]
- Improves survival[6]

1. *Lasila R, Lepantalo M. Acta Chir Scand. 1988;154:635.*
2. *Jonason T, Bergstrom R. Acta Med Scand. 1987;221:253.*
3. *Willigendael, et al. J Vasc Surg. 2005;42:67.*
4. *Gardner AW. Vasc Med. 1996;1:181.*
5. *Quick CR, Cotton LT. Br J Surg. 1982;69:S24.*
6. *Faulkner KW. Med J Aust. 1983;1:217.*
7. *Selvarajah S. J Vasc Surg 2014;59:1308-14.*

# 2011 ACCF/AHA Focused Update of the Guideline for the Management of Patients With Peripheral Artery Disease (Updating the 2005 Guideline)

*A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines*

| 2011 Focused Update Recommendations | Comments |
|---|---|
| 1. Patients who are smokers or former smokers should be asked about status of tobacco use at every visit (25–28). *(Level of Evidence: A)* | New recommendation |
| 2. Patients should be assisted with counseling and developing a plan for quitting that may include pharmacotherapy and/or referral to a smoking cessation program (26,29). *(Level of Evidence: A)* | New recommendation |
| 3. Individuals with lower extremity PAD who smoke cigarettes or use other forms of tobacco should be advised by each of their clinicians to stop smoking and offered behavioral and pharmacological treatment. *(Level of Evidence: C)* | Modified recommendation (wording clarified and level of evidence changed from B to C). |
| 4. In the absence of contraindication or other compelling clinical indication, 1 or more of the following pharmacological therapies should be offered: varenicline, bupropion, and nicotine replacement therapy (30–33). *(Level of Evidence: A)* | New recommendation |

*J Am Coll Cardio. 2011;58;2020-2045; originally published online Sep 29. 2011.*

# 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

J Am Coll Cardiol 2010;56:2105-12

# 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%

J Am Coll Cardiol 2010;56:2105-12

# Pharmacotherapy


- Nicotine Replacement Therapy (NRT)
  - Patches
    - Appropriate dose, may need to "double patch"
    - Can supplement with gum/lozenges
      - Use 2 mg
  - Gum
    - If monotherapy, can use 4 mg
  - Lozenges
  - Nasal spray
  - Inhaler



# Nicotine replacement therapy for stopping smoking

## Cochrane Review

**Table: Results from nicotine replacement therapy meta-analysis with sensitivity analysis**

| | | Patients stopped smoking at 6-12 months | | | | |
|---|---|---|---|---|---|---|
| | | NRT | | Placebo | | |
| Type of NRT | Number of trials | Number/total | Percent | Number/total | Percent | NNT (95% CI) |
| **All trials** | | | | | | |
| Gum | 48 | 1453/7387 | 20 | 1084/9319 | 12 | 12 (11 to 14) |
| Patch | 31 | 1384/9708 | 14 | 495/5969 | 8 | 17 (14 to 20) |
| Intranasal spray | 4 | 107/448 | 24 | 52/439 | 12 | 8 (6 to 14) |
| Inhaler | 4 | 84/490 | 14 | 44/486 | 8 | 12 (8 to 26) |
| Sublingual tablet | 2 | 49/243 | 20 | 31/245 | 13 | 13 (7 to 103) |

*Courtesy of Tom Rooke.*

# Pharmacotherapy

- Buproprion SR (Zyban, Wellbutrin)
  - 150 mg daily X 3 days, then twice daily for 12 weeks and re-assess
  - 29.5% quit rate at 9-12 weeks
  - Use with NRT
    - More effective

# Pharmacotherapy


- Varenicline (Chantix)
  - Partial nicotine receptor agonist
  - 0.5 mg daily X 3 days, then twice daily for 4 days, then 1 mg twice daily for 11 weeks
  - Re-assess at 12 weeks, can continue for additional 12 weeks
  - Use with caution in patients with psych history
  - Can use gum or lozenges
    - 2 mg up to 5 pieces per day

JAMA®

The Journal of the American Medical Association — To Promote the Science and Art of Medicine and the Betterment of the Public Health



Vol. 296 No. 1, July 5, 2006



Original Contribution

JAMA-EXPRESS

# Varenicline, an α4β2 Nicotinic Acetylcholine Receptor Partial A

## s44% Quit Rate at 12 Weeks …

### A Randomized Controlled Trial

David Gonzales, PhD; Stephen I. Rennard, MD; Mitchell Nides, PhD; Cheryl Oncken, MD; Salomon Azoulay, MD; Clare B. Billing, MS; Eric J. Watsky, MD; Jason Gong, MD; Kathryn E. Williams, PhD; Karen R. Reeves, MD; for the Varenicline Phase 3 Study Group

JAMA. 2006;296:47-55.

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

Ehrin J. Armstrong, MD, MS,[a] Julie Wu, BS,[b] Gagan D. Singh, MD,[b] David L. Dawson, MD,[c] William C. Pevec, MD,[c] Ezra A. Amsterdam, MD,[b] and John R. Laird, MD,[b] *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 ± 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 ± 10, and the mean pack-years was 40 ± 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 ± 24 vs 0.49 ± 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.

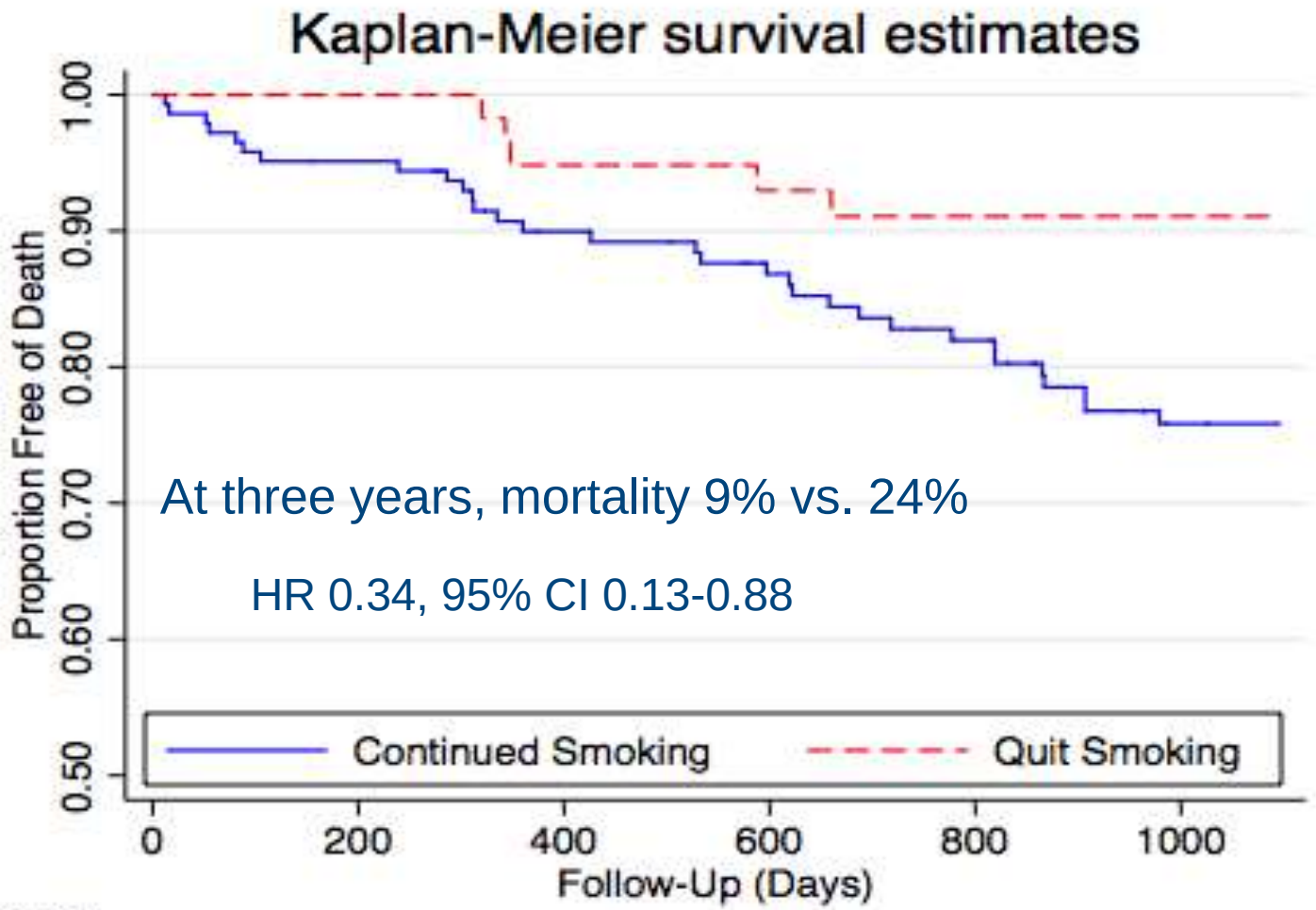
*Conclusions:* Approximately one-third of active smokers with peripheral artery disease successfully quit smoking ≤1 year after lower extremity angiography. Patients who quit smoking have lower mortality and improved amputation-free survival compared with patients who continue smoking. (J Vasc Surg 2014;60:1565-71.)

# 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.

J Vasc Surg 2014;60:1565-71



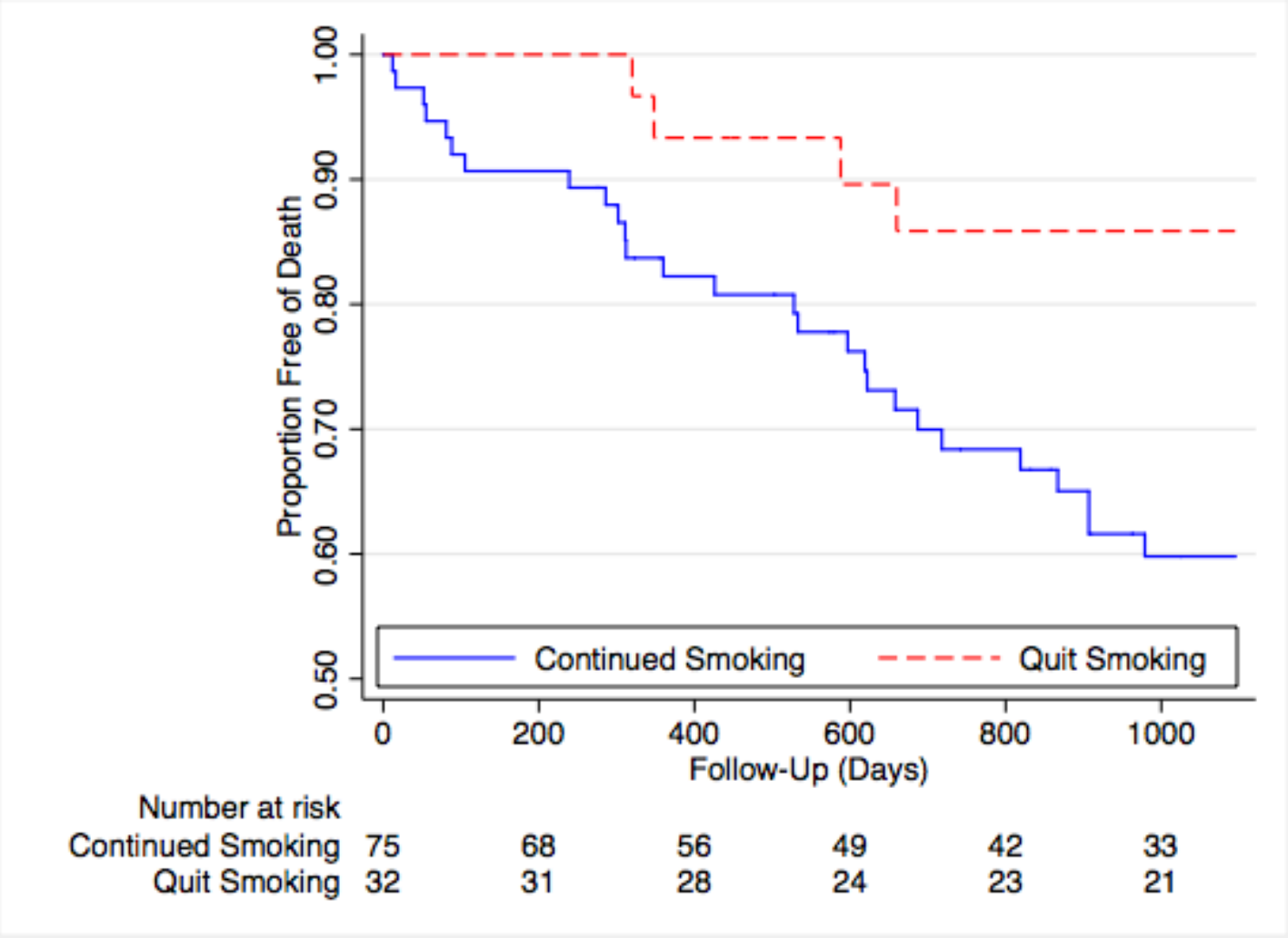

At three years, mortality 9% vs. 24%

HR 0.34, 95% CI 0.13-0.88

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

J Vasc Surg 2014;60:1565-71

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




J Vasc Surg 2014;60:1565-71

# Conclusions

- Adherence to guidelines recommended therapies can impact survival and limb outcomes in our patients with PAD
- Aggressive medical intervention may be most important for CLI patients, who are the highest risk group for cardiovascular complications
- Smoking cessation is the single most important intervention that we can make for our PAD patients