2019 MID-ATLANTIC
CONFERENCE

9th ANNUAL CURRENT CONCEPTS IN

VASCULAR THERAPIES

2019

Hilton Virginia Beach Oceanfront
Virginia Beach, Virginia

MAY 2-4

Optimizing Medical Therapy for Patients with ~~Claudication~~ PAD

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Updates in Medical Therapy

- Evolvin[illegible]y- Does one shoe fi[illegible]ryone)
- Hyperli[illegible]tin- is that enough?
- Diabetes mellitus- do therapeutic agents matter?
- Updates on smoking cessation – helping resolve some fears.

Goals of medical therapy

1. Reduce CV morbidity and mortality
2. Reduce adverse limb outcomes

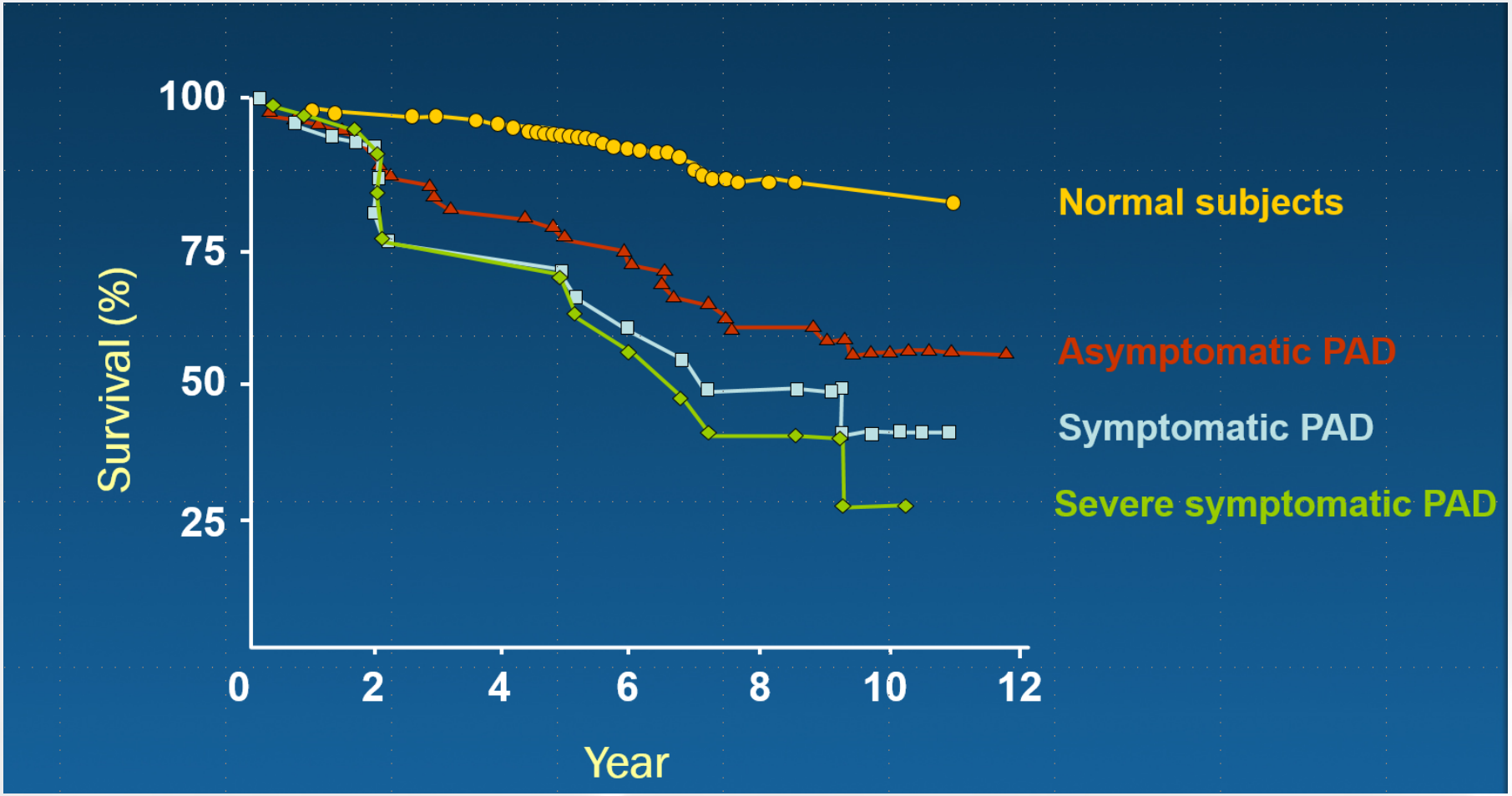
Antiplatelets

What antiplatelet therapy would you use in this patient?

– Claudicant with no known CV disease but has RF of HTN and DM-2

a. Aspirin 81 mg
b. Aspirin and Plavix
c. Aspirin and rivaroxaban 2.5 mg BID
d. Aspirin and vorapaxor
e. Plavix alone

Long-Term Survival in Patients With PAD

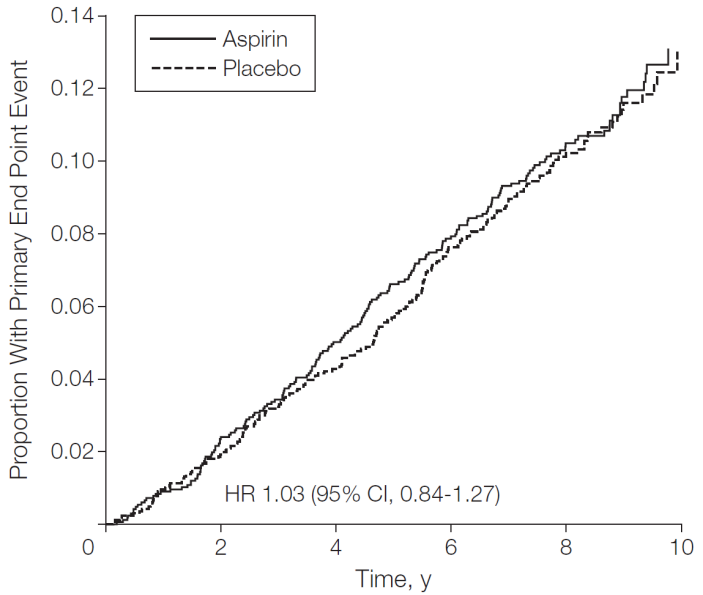


N Engl J Med. 1992;326:381-386.

Antiplatelet therapy in Asymptomatic PAD

- Community Health Registry
- N= 3350
- Age 50-75 years
- No known CV disease
- Low ABI(≤0.95)
- ASA 100 mg vs. placebo
- Results:
  - Low risk population
    - Event rate < 2%
    - No benefit with aspirin

Figure 2. Primary End Point Event by Treatment Group and Duration of Follow-up



No. at risk						
Aspirin	1675	1618	1555	1473	946	124
Placebo	1675	1634	1566	1474	935	119

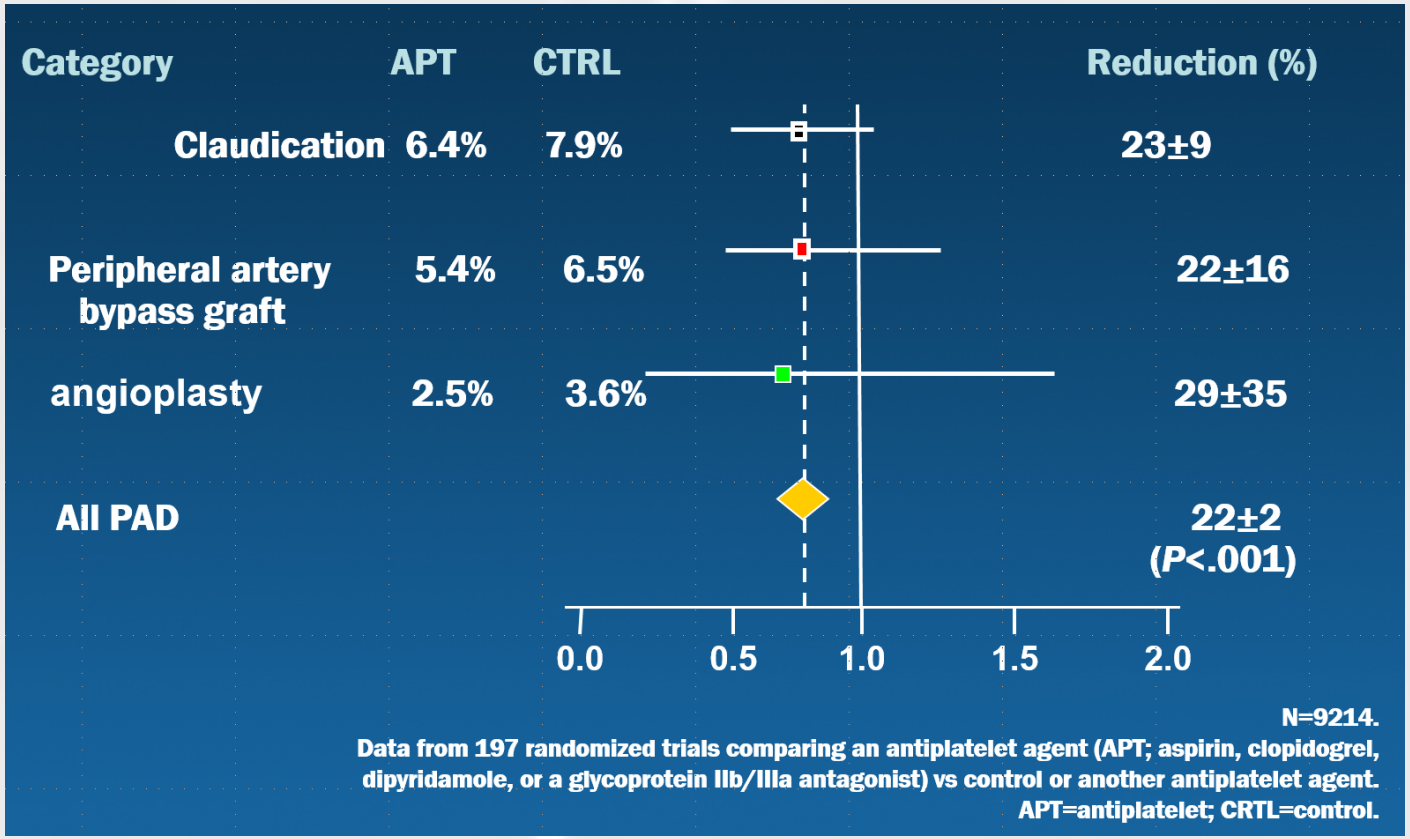
These data represent the initial event only. Primary end point events comprised fatal or nonfatal coronary event, stroke, or revascularization. CI indicates confidence interval; HR, hazard ratio.

JAMA 2010;303:841-848

Symptomatic PAD- Antiplatelet therapy

Antithrombotic Trialists' Collaboration (ATC):

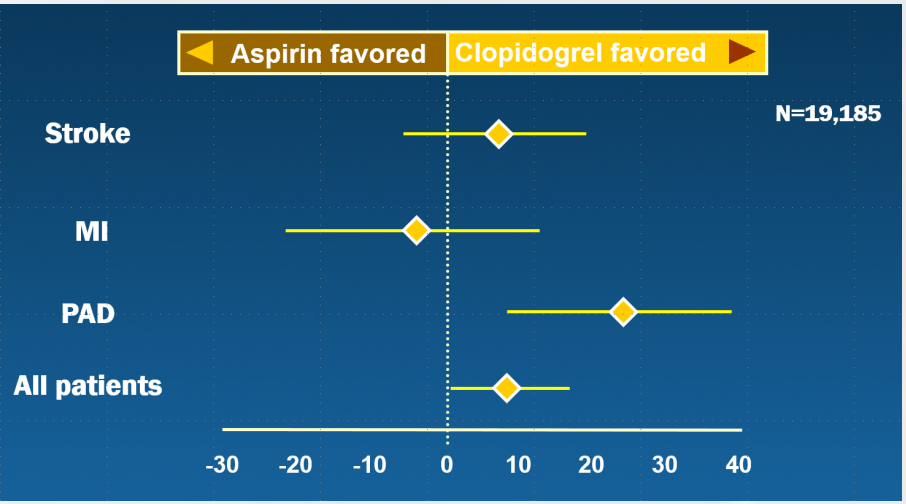
Meta-analysis of Vascular Events in Antiplatelet Trials in Patients With PAD

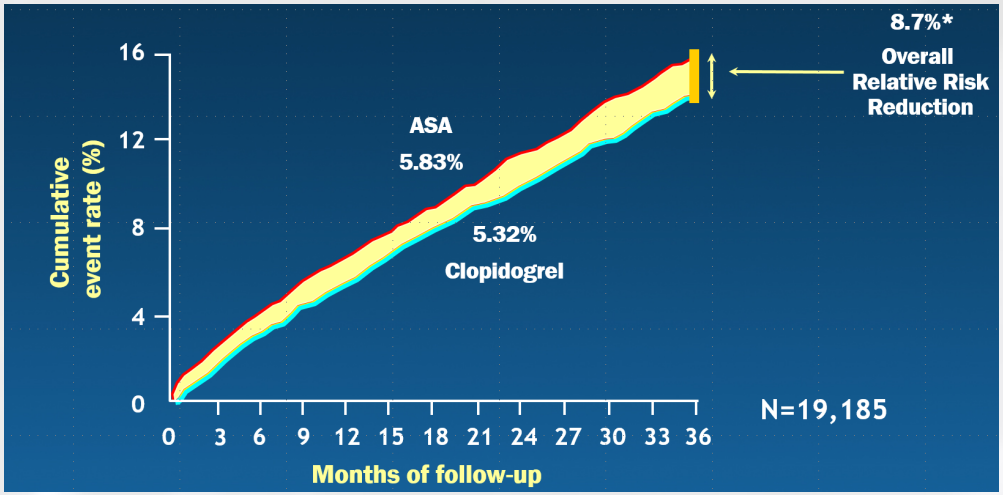


BMJ. 2002;324:71-86.

Clopidogrel Vs. Aspirin: CAPRIE Trial

Risk Reduction of Clopidogrel vs. Aspirin in Patients With Atherosclerotic Vascular Disease





Lancet. 1996;348:1329-1339.

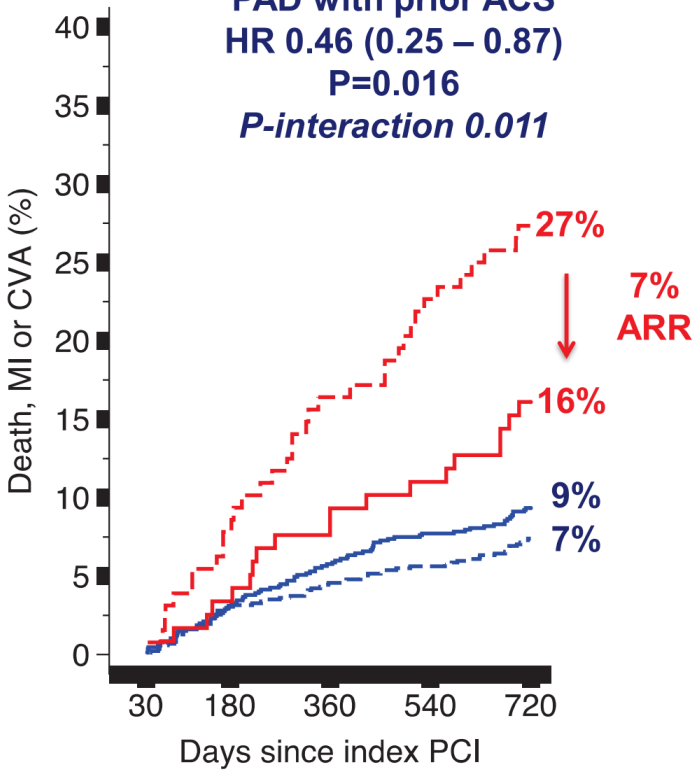
Antiplatelets: What do we know in PAD

- 2009 meta-analysis suggests aspirin not adequately proven to be anti-platelet agent of choice for preventing CV events in PAD patients
- EUCLID trial: ticagrelor monotherapy not superior to clopidogrel
- DAPT: Increased bleeding over monotherapy in PAD
- TIMI 50 trial- Novel anti-platelet agent vorapaxar in addition to anti-platelet therapy reduced MALE but increased risk of major bleeding

JAMA. 2010;303:841. N Engl J Med 2017; 376:32-40. Eur Heart J. 2009;30:192. J Vasc Surg. 2010;52:825. Circulation. 2013;127:1522.

DAPT in CAD + PAD: PRODIGY Trial

Short (≤ 6 months) versus long (24 months course DAPT in PAD after coronary stenting on MACE)



All Cause Mortality
21.1% vs 10.2%
HR 0.45 (0.23 – 0.88)
P=0.02

TIMI Major Bleeding
1.8% vs 3.5%
HR 0.50 (0.09 – 2.74)
P=0.43

GUSTO Mod/Severe
2.6% vs 2.6%
HR 1.02 (0.21 – 5.04)
P=0.51

Large reduction in MACE
Lower mortality
Modest bleeding excess

CONCLUSIONS AND RELEVANCE Peripheral artery disease confers a poor prognosis in patients undergoing PCI in the setting of stable coronary artery disease or acute coronary syndromes. Prolonged DAPT lowers the risk of ischemic events with no apparent bleeding liability in this high-risk group.

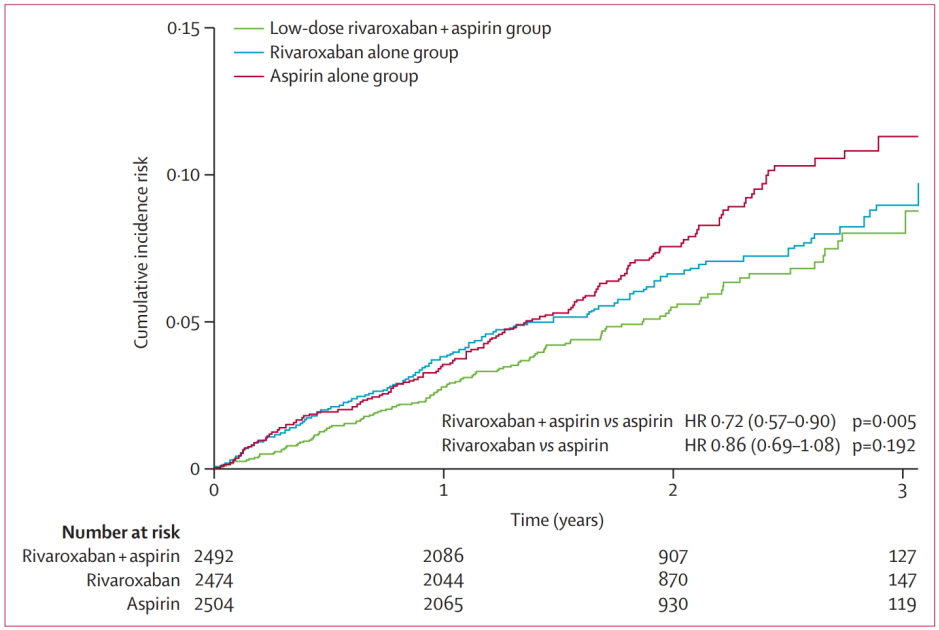


Figure 2: **Cumulative incidence of the primary efficacy outcome**

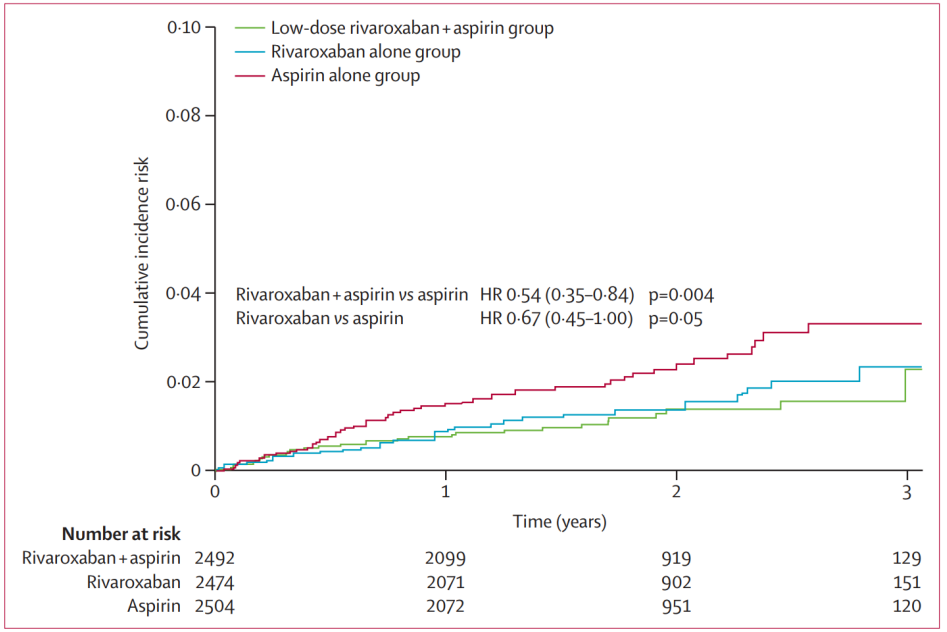


Figure 3: **Cumulative incidence of individual components of major adverse limb events including major amputation**

- 7470 patients (+/- CAD)
  - rivaroxaban 2.5 mg BID ↓ 1◦ MACE endpoint of CV death/MI/stroke (HR = 0.72, p=0.005) vs. aspirin only
  - ↓ major amputation (HR=0.33, p=0.03)
  - ↓ vascular intervention (HR=0.76, P=0.03)
  - ↓ALI+ CLI + vasc hosp. (HR=0.76,P=0.02)
  - ↑ major bleeding with aspirin + rivaroxaban vs. aspirin alone (HR=1.61, p=0.01)

Lancet 2018; 391: 219–29
J Am Coll Cardiol. 2018;2306

Approach to antiplatelet therapy in PAD

- Asymptomatic:
  - No polyvascular disease: May be aspirin
  - Polyvascular disease present: Antiplatelet monotherapy

Approach to antiplatelet therapy in PAD: Symptomatic

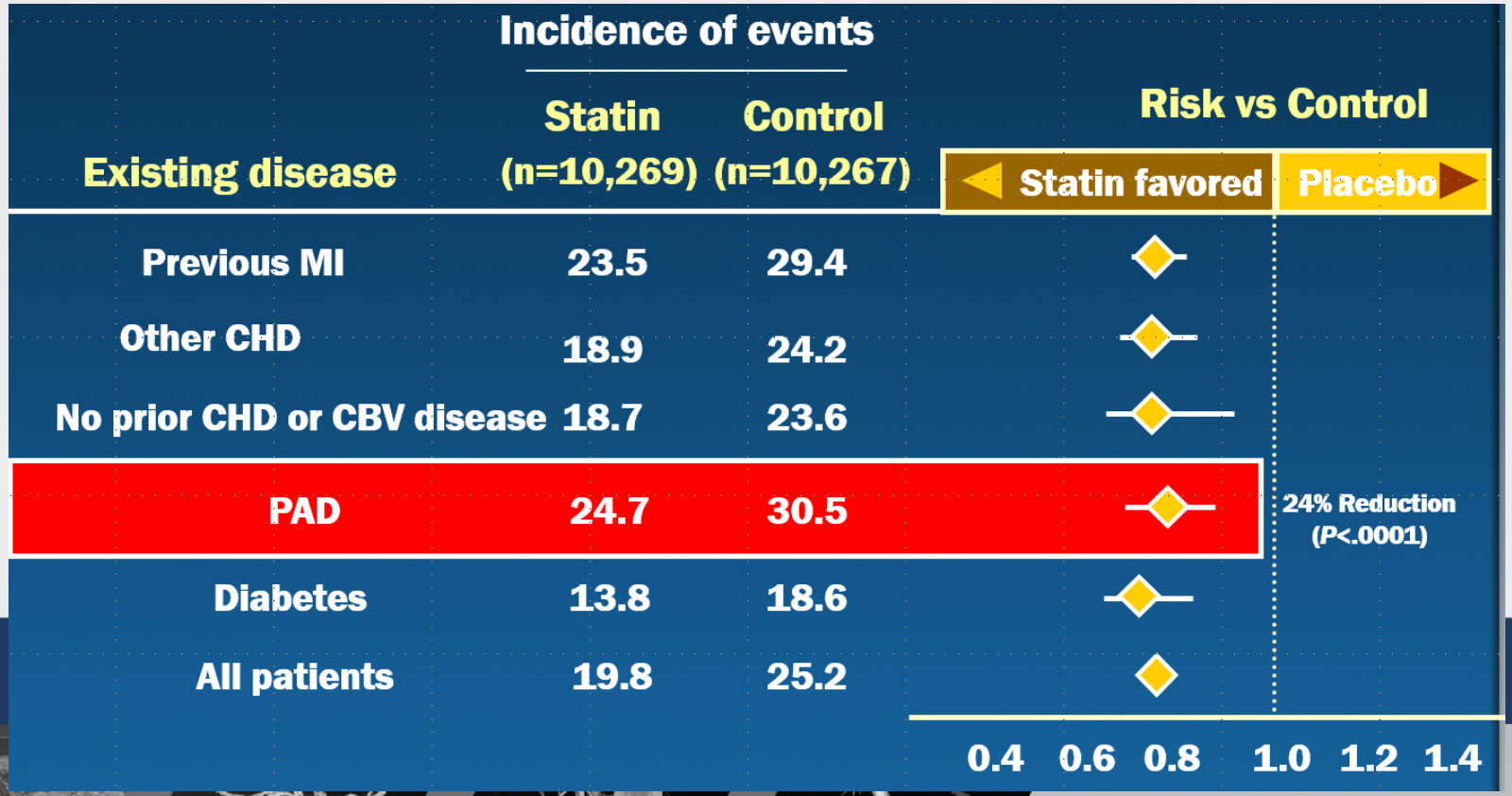
1. Bleeding risk: recent major bleeding, ICH, chronic anticoagulation, fragile
2. High MACE : Concomitant CAD or Cerebrovascular disease or DM
3. High MALE: prior revascularization, amputation, thrombosis, severe ABI

- High bleeding risk : Monotherapy
- Low bleeding risk:
  - Low MACE or MALE: Aspirin or Plavix or ticagrelor alone
  - High MACE or MALE: Aspirin+ rivaroxaban 2.5mg BID or aspirin + clopidogrel/ticagrelor
    - Recent MI or PCI: Aspirin+ clopidogrel/ticagrelor x 1 year
    - Recent peripheral stenting: Aspirin+Plavix initially
      - Both groups: later → aspirin + rivaroxaban 2.5 mg BID

Hyperlipidemia: Statins and Beyond

Heart Protection Study: Vascular Event by Prior Disease

simvastatin, 40 mg daily, for 5 years would prevent about 100 people per 1000 from having at least one major vascular event



. Lancet. 2002;360:7-22

ACC/AHA Prevention Guideline

OPEN

2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults

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

Endorsed by the American Academy of Physician Assistants, American Association of Cardiovascular and Pulmonary Rehabilitation, American Pharmacists Association, American Society for Preventive Cardiology, Association of Black Cardiologists, Preventive Cardiovascular Nurses Association, and WomenHeart: The National Coalition for Women With Heart Disease

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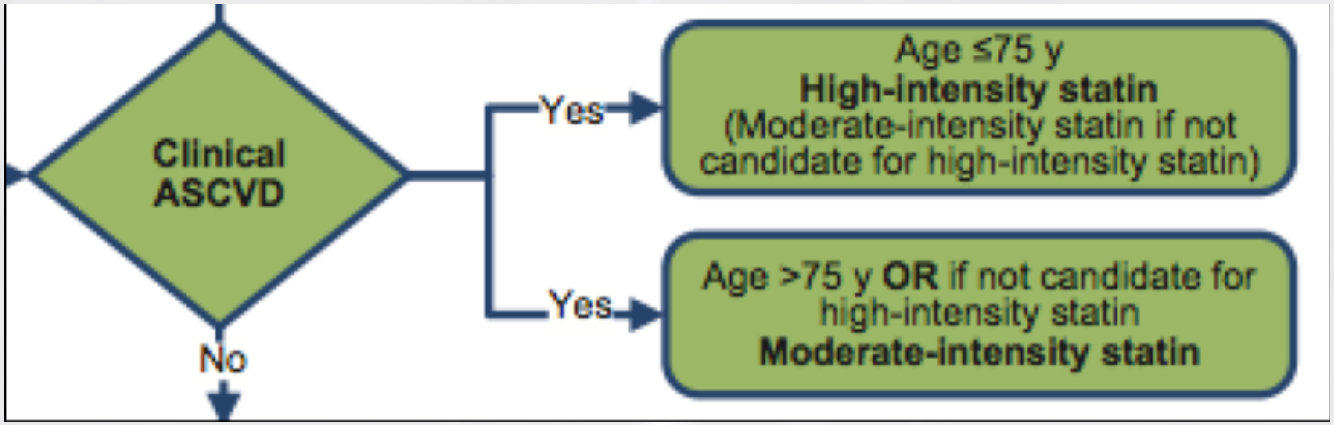


Clinical ASCVD includes ACS, history of MI, stable or unstable angina, other arterial revascularization, stroke, TIA or peripheral artery disease…..

Circulation. 2017 Mar 21;135(12):e726-e779.

Intensity of Statin Therapy

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL–C on average, by approximately ≥50%	Daily dose lowers LDL–C on average, by approximately 30% to <50%	Daily dose lowers LDL–C on average, by <30%
Atorvastatin (40†)–80 mg **Rosuvastatin 20** *(40)* **mg**	**Atorvastatin 10** *(20)* **mg** **Rosuvastatin** *(5)* **10 mg** **Simvastatin 20–40 mg‡** **Pravastatin 40** *(80)* **mg** **Lovastatin 40 mg** *Fluvastatin XL 80 mg* **Fluvastatin 40 mg bid** *Pitavastatin 2–4 mg*	*Simvastatin 10 mg* **Pravastatin 10–20 mg** **Lovastatin 20 mg** *Fluvastatin 20–40 mg* *Pitavastatin 1 mg*

J Am Coll Cardiol. 2014 Jul 1;63(25 Pt B):2935-59.

Clinical Scenario

- Patient with claudication
  - Obtain LDL levels and LFTs
  - Started on atorvastatin 40 mg daily
  - Now what ?
  - Follow up in 6-12 weeks: LDL levels
    - > 50% reduction of LDL (LDL < 70 mg/dl)
    - Do I have to really do this?

Individual Variability in Statin Response

VOYAGER: individual patient database of 32,258 patients from 37clinical trials comparing the lipid-modifying effects of atorvastatin 10, 20, 40, or 80 mg, rosuvastatin5, 10, 20, or 40 mg, and simvastatin 10, 20, 40, or 80 mg.

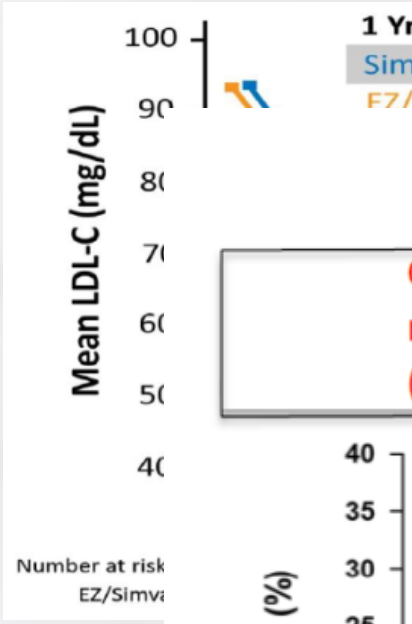
% failing to achieve the following reductions in LDL-C

	15%	30%	50%
Atorvastatin 20 mg daily:	4.3%	12.8%	67.7%
Atorvastatin 40 mg daily:	2.8%	7.6%	52.6%
Atorvastatin 80 mg daily:	4.7	11.3%	42.5%
Rosuvastatin 10 mg daily:	7.8%	17.5%	59.6%
Rosuvastatin 20 mg daily:	4.8%	9.4%	42.7%
Rosuvastatin 40 mg daily:	2.7%	5.3%	26.2%

European Heart J-Cardiovascular Pharmacotherapy 2016;2:212-7

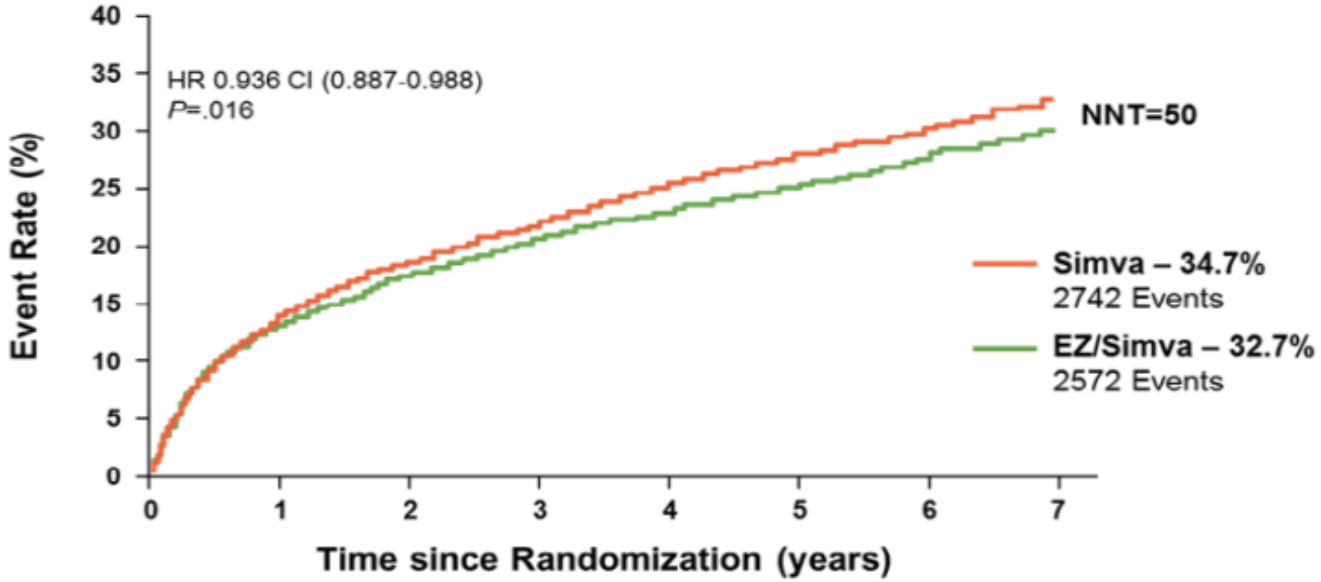
IMPROVE-IT: Role for Ezetimibe

1 Yr Mean	LDL-C	TC	TG	HDL	hsCRP
Simva	69.9	145.1	137.1	48.1	3.8
EZ/Simva	53.2	125.8	120.4	48.7	3.3



Primary Endpoint: ITT

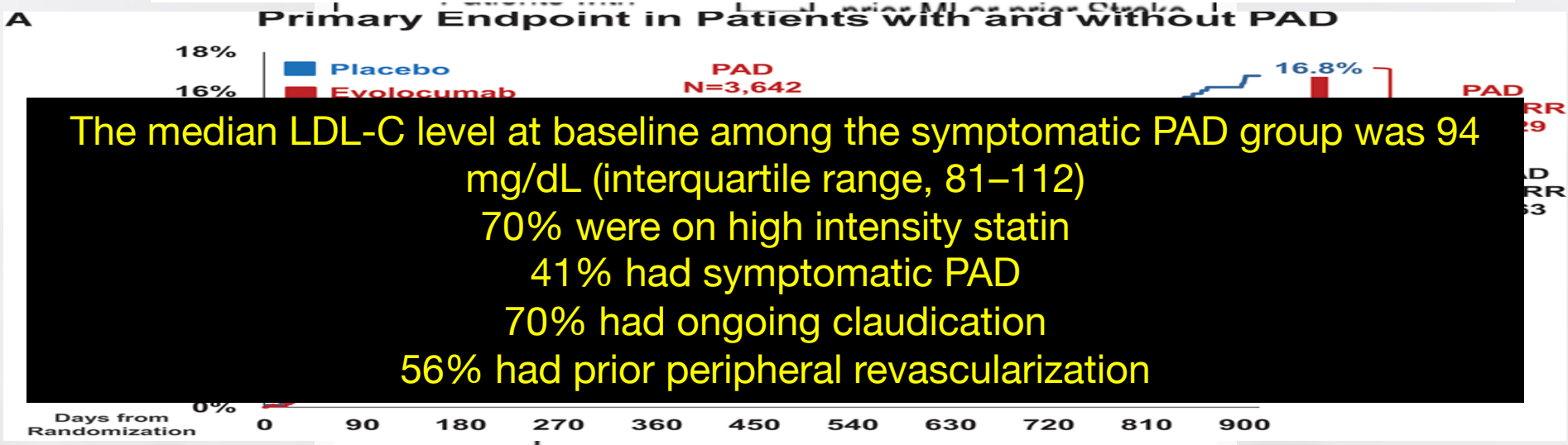
CV death, MI, documented unstable angina requiring hospitalization, coronary revascularization (≥30 days) or stroke



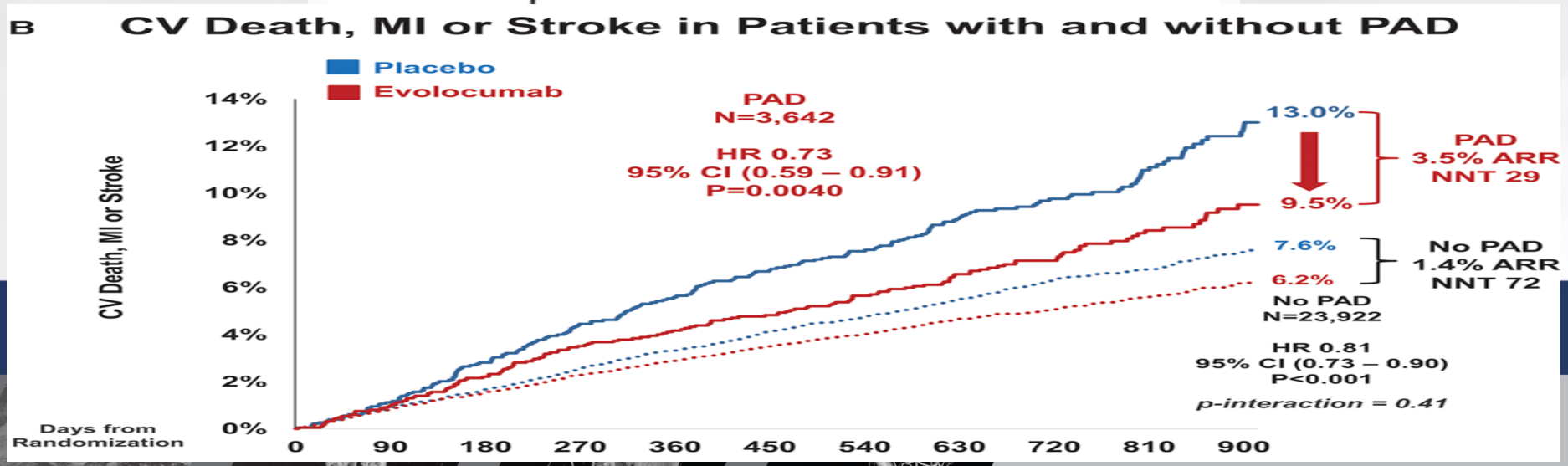
N Engl J Med 2015; 372:2387-2397

A Newer Paradigm: PCSK9 Inhibitor: **Evolocumab**

The primary composite end point (cardiovascular death, myocardial infarction, stroke, unstable angina, coronary revascularization)



The median LDL-C level at baseline among the symptomatic PAD group was 94 mg/dL (interquartile range, 81–112)
70% were on high intensity statin
41% had symptomatic PAD
70% had ongoing claudication
56% had prior peripheral revascularization



Approach to PAD and Hyperlipidemia

- On maximally tolerated statin? If not then do so
- Follow up in 4-6 weeks
  - Achieved LDL-C goals?
    - > 50% LDL-C reduction
    - Also consider LDL-C < 70 or 100 mg/dl
  - NO then do the following:
    - Question adherence and lifestyle changes
    - 1st line: Ezetimibe
    - 2nd line: PCSK9 inhibitor (in addition to ezetimibe or replacing it)

2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk

J Am Coll Cardiol 2016;68:92–125

Diabetes and PAD

- ARIC & Strong Heart have demonstrated ↑ risk of major limb events and amputation among patients with PAD with poor glycemic control

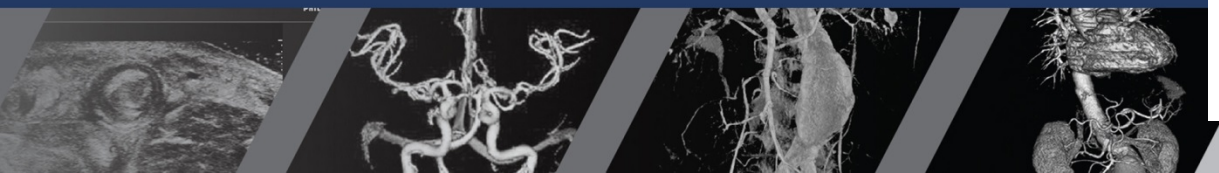
- However, recent observational data from case cohort studies of patients with PAD + CLI suggests benefit of more intensive glycemic control among diabetics with CLI undergoing revascularization

Diabetes Care 2006;29:877.
Diabetes Care. 2004;27:1885.
Diabetes Care. 2010;33:2538.
VascMed 2014;19:307.

Diabetic medications and amputations

- **CANVAS trial: Sodium–glucose cotransporter 2 (SGLT2) inhibitor canagliflozin**
  - ↓ risk of major CV event but was associated with an ↑ risk of amputation vs. placebo during mean f/u of ~ 3.6 yrs
- **EMPA-REG OUTCOMES trial: SGLT-2 inhibitor empagliflozin**
  - ↓ risk of major CV event (including CV death) among pts with T2DM but not found to have signal of amputation risk (median f/u 3.1 yrs)
- **LEADER trial**: **glucacon-like peptide 1 (GLP-1) liraglutide**
  - 35% RR ↓ amputation vs. placebo among patients with T2DM (up to 5 yr f/u)
  - But no difference in % diabetic foot ulceration, peripheral revascularization

N EnglJ Med. 2017;377:644.
N EnglJ Med. 2015;373:2117.
Diabetes Care.2018;41:e4.
Diabetes Care 2018;41:2229.



Smoking Cessation

COR	LOE	Recommendations
I	A	Patients with PAD who smoke cigarettes or use other forms of tobacco should be advised at every visit to quit.
I	A	Patients with PAD who smoke cigarettes should be assisted in developing a plan for quitting that includes pharmacotherapy (i.e., varenicline, buproprion, and/or nicotine replacement therapy) and/or referral to a smoking cessation program.
I	B-NR	Patients with PAD should avoid exposure to environmental tobacco smoke at work, at home, and in public places.

EAGLES Trial

- Neu…opsychiatric safety and efficacy of varenicline, bupropion, and …ric diso…
- RC…
- prir… neu…
- 814… patients planned
  - 4116: psychiatric cohort
  - 4028: non-psychiatric cohort

Non-psychiatric cohort* (n=3984)

Varenicline (n=990)	Bupropion (n=989)	Nicotine patch (n=1006)	Placebo (n=999)
13 (1·3%)	22 (2·2%)	25 (2·5%)	24 (2·4%)

Psychiatric cohort* (n=4074)

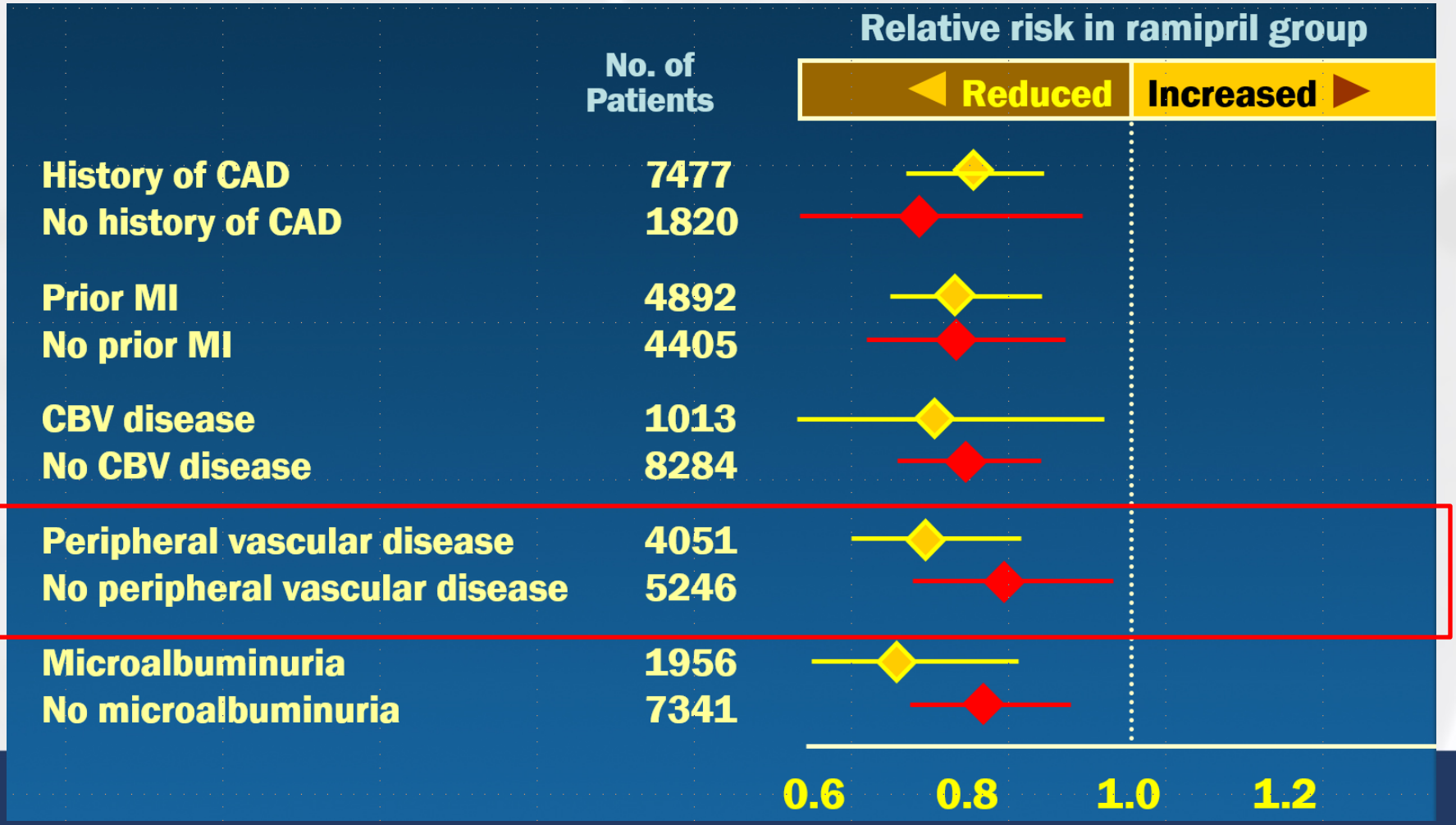
Varenicline (n=1026)	Bupropion (n=1017)	Nicotine patch (n=1016)	Placebo (n=1015)
67 (6·5%)	68 (6·7%)	53 (5·2%)†	50 (4·9%)

CV safety: 8058 patients→ < 0.5% MACE and <0.8% MACE+

Lancet 2016; 387: 2507–20
JAMA 2018 May; 178(5): 622–631.

Hypertension Management: HOPE trial

9297 high-risk patients with evidence of vascular disease or diabetes



N Engl J Med. 2000;342:145-153

Optimal Medical Therapy in PAD

- Tailor PAD patients antiplatelet therapy based on symptoms, bleeding, MACE and MALE risk
- Consider new diabetic medications tailored to reduction in CV events and amputations
- Smoking cessation therapies are safe
- High intensity statins are standard of care and we have to consider therapies beyond statins
- ACEI and ARB should be first line anti-hypertensive therapies