Carnitine in Peripheral Arterial Disease

Conflicts: Consultant to Sigma Tau Pharmaceuticals

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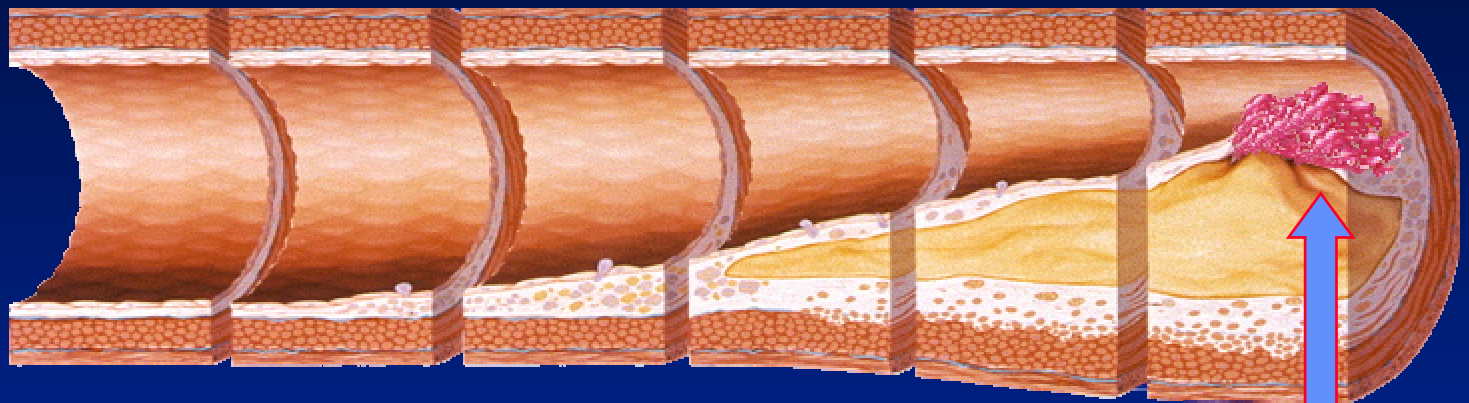
Atherothrombosis in PAD



MI
ACS
CVA / TIA
Acute Leg Ischemia
CV death

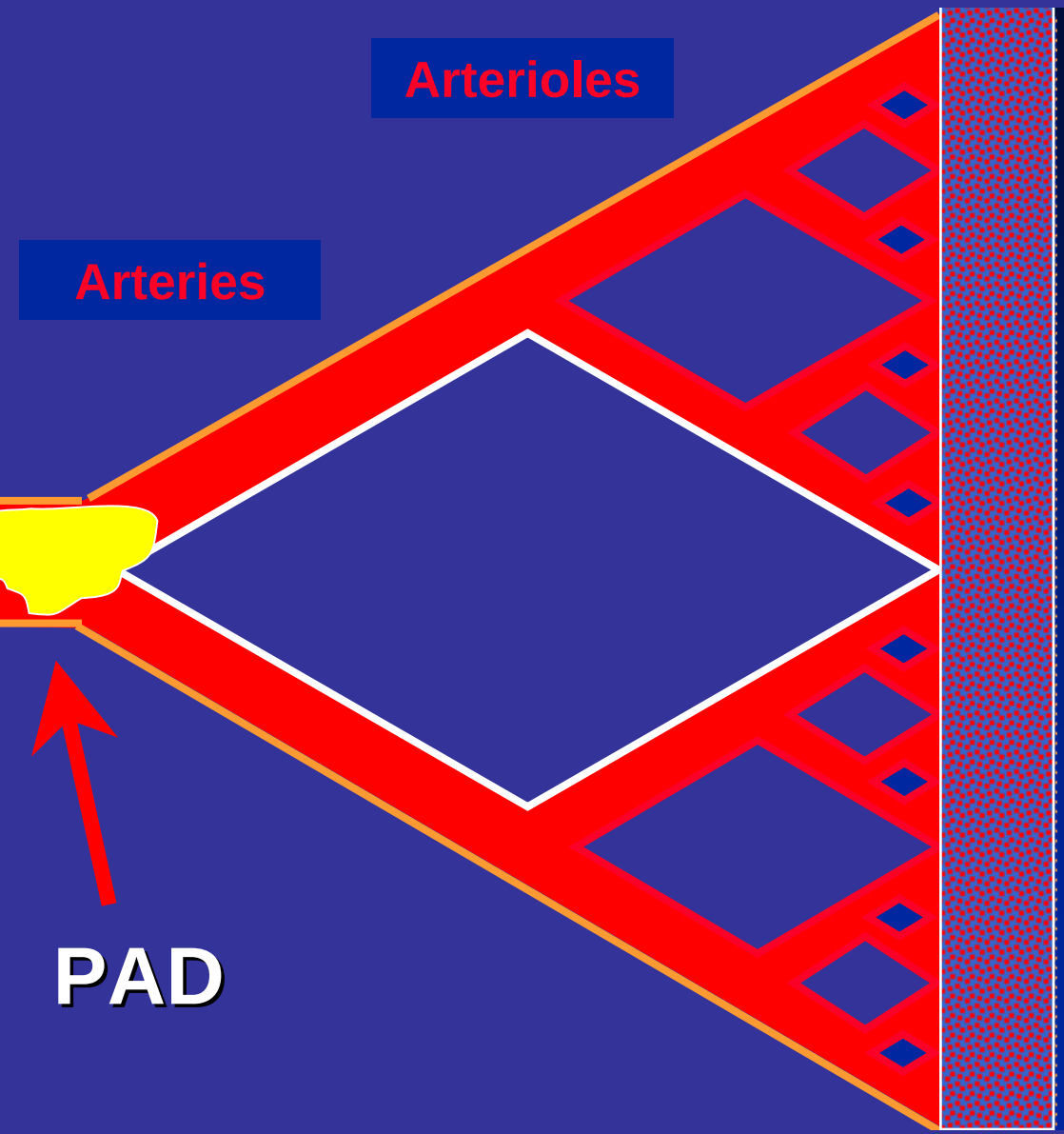
Thrombosis

Atherosclerosis
(Peripheral Artery)

Intermittent claudication
Critical Leg Ischemia

Stary HC. *Circulation*.1995;92:1355-1374.
Fuster V et al. *Vasc Med*. 1998;3:231-239.

Classic pathophysiology



Arterial stenosis/occlusion

↓

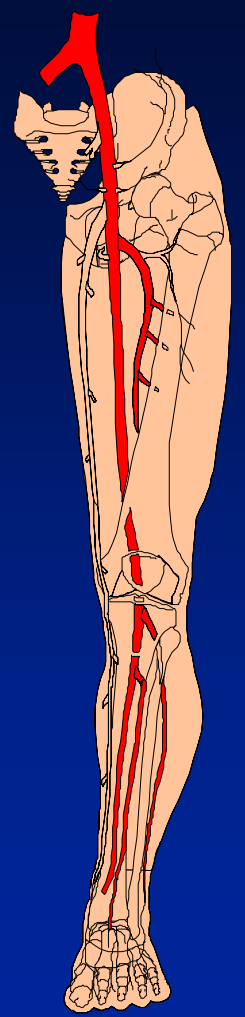
↓ Pressure & flow

↓

↓ O_2 supply
Muscle ischemia

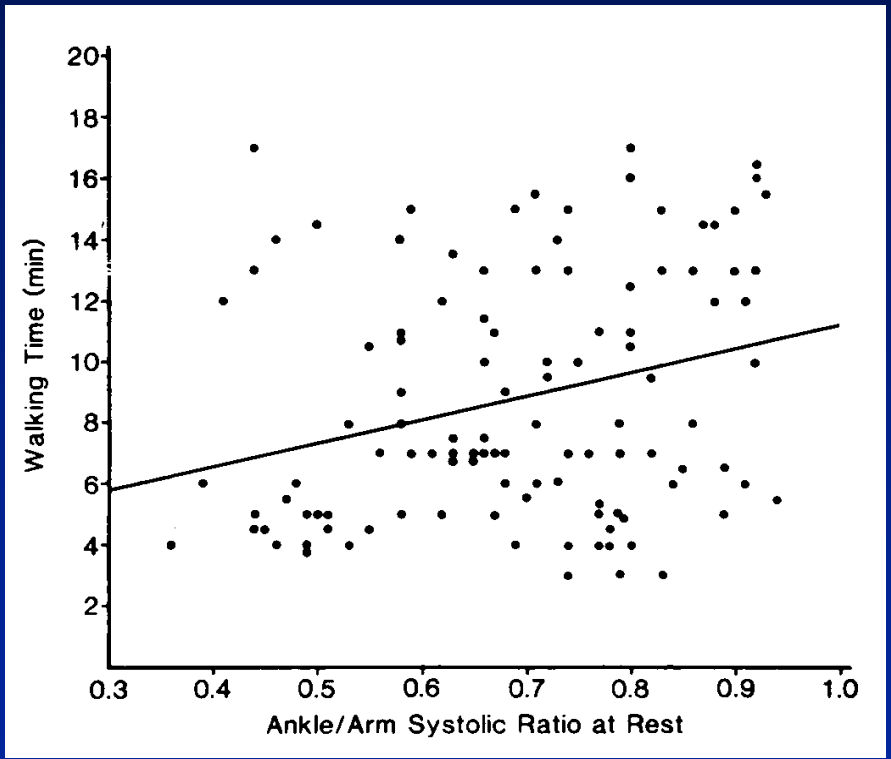
↓

Claudication



Claudication Pathophysiology
NOT Just Hemodynamics

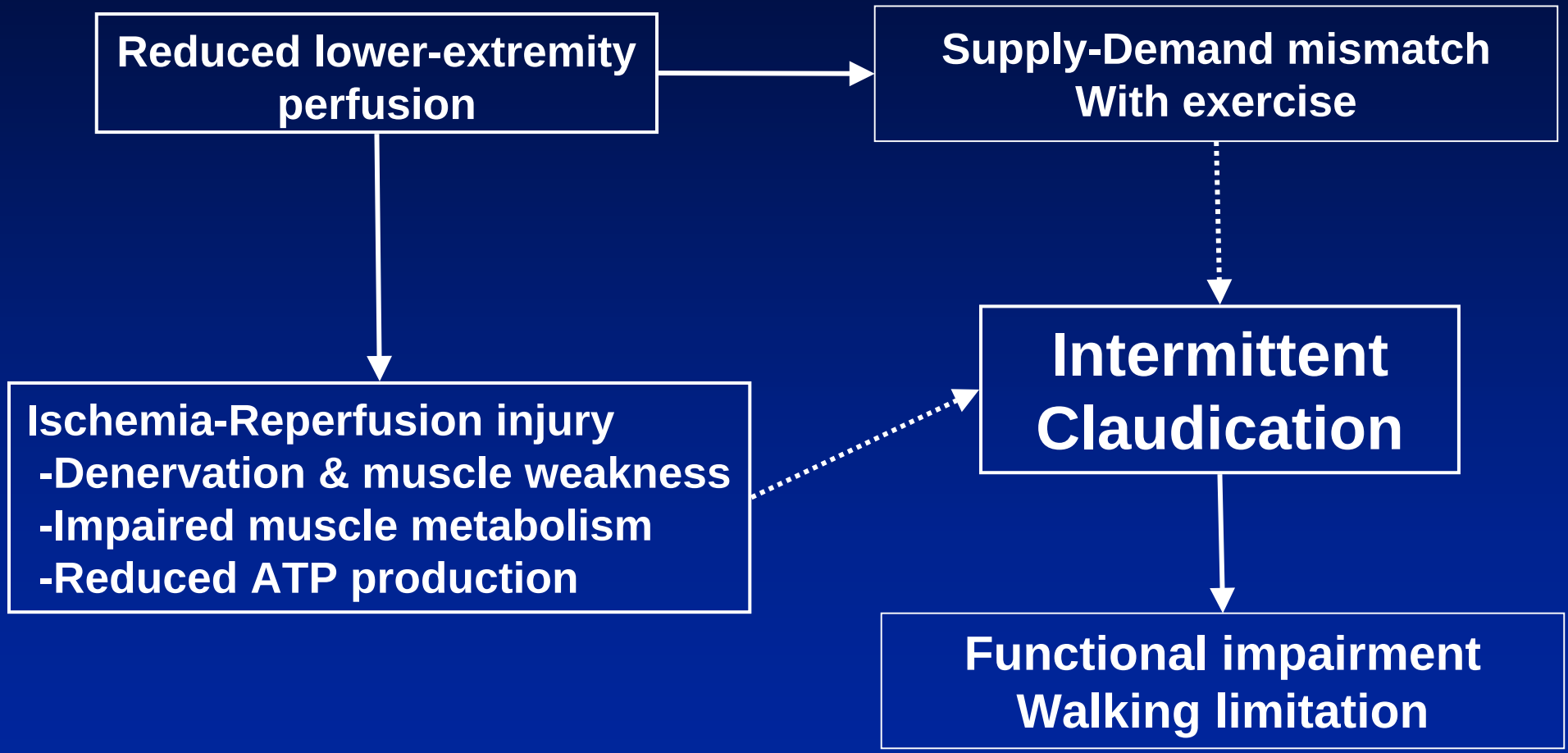
Hemodynamics do not explain performance



- **Microcirculatory changes**
  - Endothelial injury
  - Increased viscosity
- **Oxygen free radicals**
  - Muscle fiber injury
  - Mitochondrial DNA injury
- **Altered muscle metabolism**
  - Accumulation of acylcarnitines
  - Impairment in electron transport

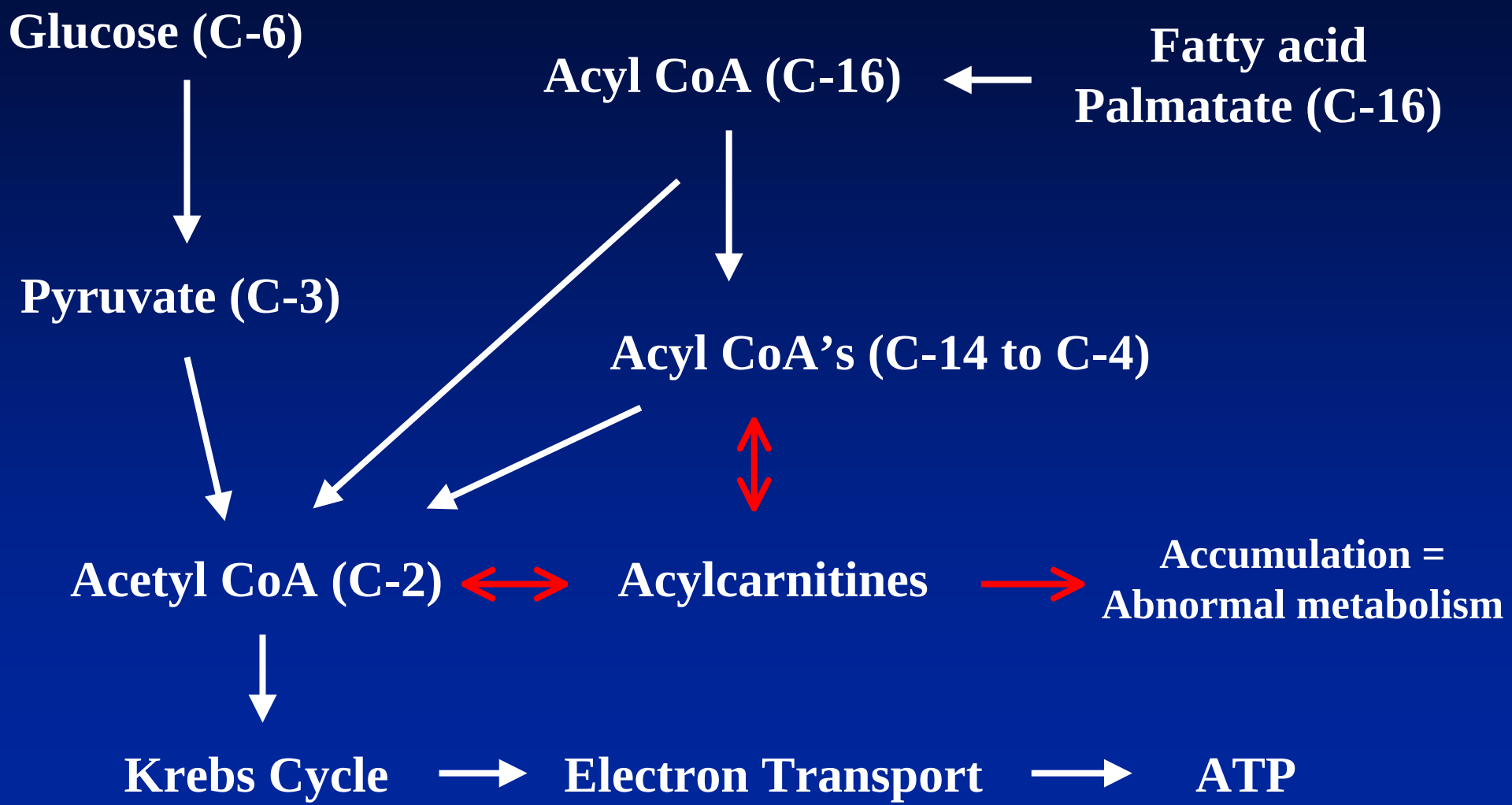
J Cardiopulmonary Rehab 1988;12:525-532
Vasc Med 2000;5:55-59

Pathophysiology of Intermittent Claudication

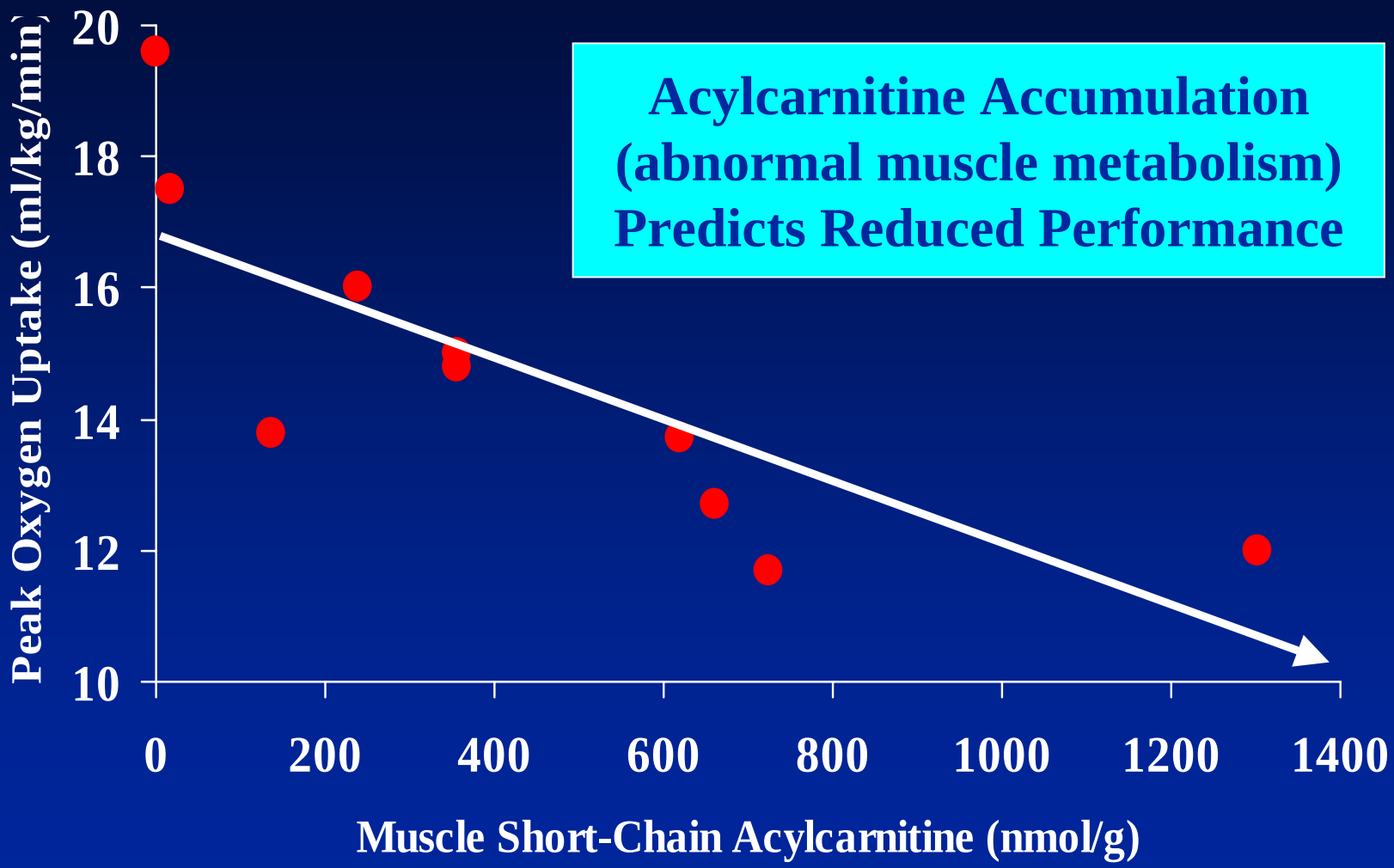


Creager M, ed. *Management of Peripheral Arterial Disease. Medical, Surgical, and Interventional Aspects.* 2000.

PAD Muscle Metabolism



PAD Muscle Metabolism



J Appl Physiol 1992;73:346-53

PAD Muscle Metabolism

- Accumulation of metabolic intermediates
  - Increased skeletal muscle acylcarnitine content inversely correlated with claudication-limited peak $V0_2$
- Specific electron transport chain defects in PAD
- Alterations in muscle metabolism partially account for reduced PAD exercise performance

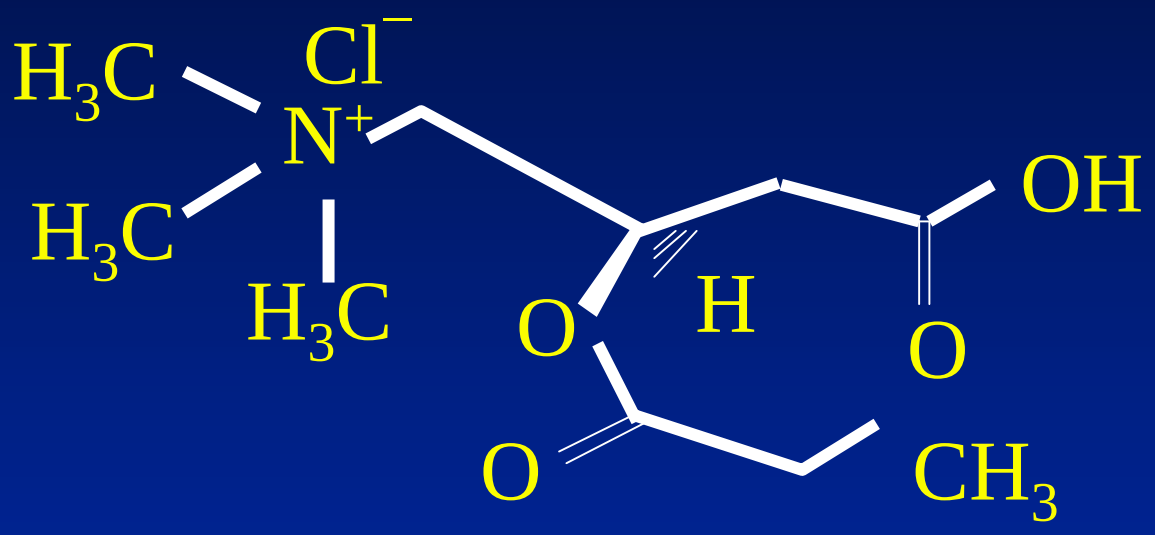
J Appl Physiol 1992;73(1):346-353, J Appl Physiol 1996;81(2):780-788

PAD Symptom Severity

- Maximal walking speed
  - Normal = 3-4 mph
  - PAD = 1-2 mph
- Maximal walking distance
  - Normal = unlimited
  - PAD, 31% difficulty walking in home
  - PAD, 66% difficulty walking 1/2 block
- Peak VO_2
  - PAD reduced 50% (NYHA class III CHF)

Otsuka data set, J Appl Physiol 1992;73:346

Structure of Propionyl-L-Carnitine



Potential Mechanism of Action of Propionyl-L-Carnitine

- Increased carnitine availability to ischemic skeletal muscle

  Removal of accumulated acyl-CoA's improves metabolism
- Anaplerotic effect of the Krebs cycle

  Conversion to succinyl-CoA improves energy flux
- Vascular endothelial effects

  Propionyl L-Carnitine improves endothelial function
- In patients with PAD, improved muscle energy metabolism and vascular endothelial function may improve claudication symptoms and walking ability

Phase III Trials of Propionyl-L-Carnitine

- **European and USA/Russia studies**
- **Inclusion Criteria:**
  - **PAD with intermittent claudication (IC)**
  - **Use of ABI and MWD criteria**
  - **Age 40 - 80 years**
- **Exclusion Criteria:**
  - **Critical leg ischemia**
  - **Symptoms other than claudication limiting MWD**
  - **Severe concomitant disease**

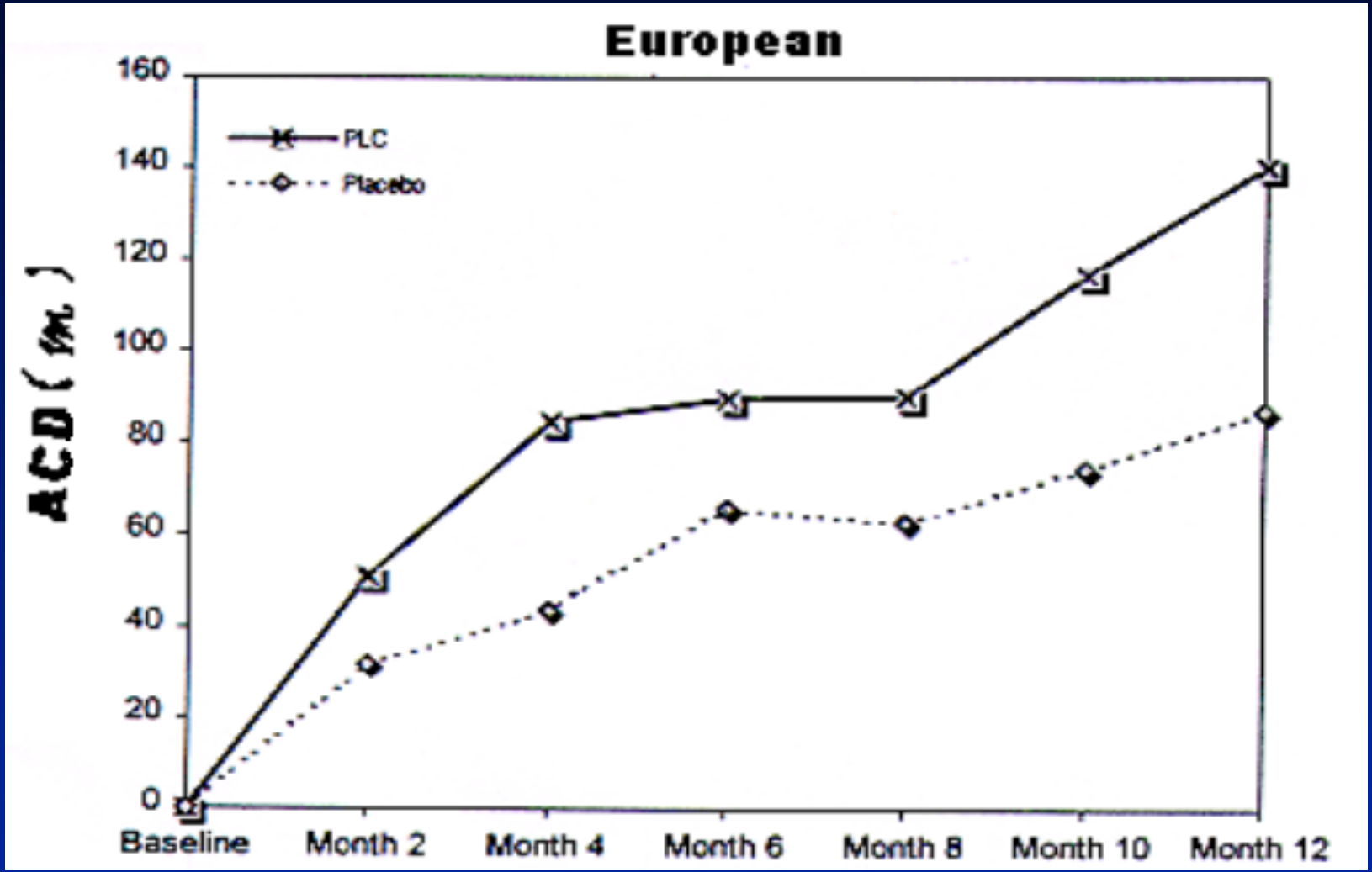
European Study

- Study conducted: 1991 - 1995
- 33 Western European, 6 Eastern European sites
- Treadmill at 3 km/h, 7% grade
- ABI $\leq$ 0.90
- Dose of PLC = 2 g/d
- Study duration = 12 months

J Am Coll Cardiol 1999;34:1618-24

European Study

- **485 ITT patients stratified into 4 groups at randomization:**
  - **S1 = MWD 50-250m, MWD variability ≤ 25%**
  - **S2 = MWD 50-250m, MWD variability 26%-50%**
  - **S3 = MWD 251-400m, MWD variability ≤ 25%**
  - **S4 = MWD 251-400m, MWD variability 26%-50%**
- **S1 = Primary analysis, n = 163**


European
160
140
120
100
80
60
40
20
0
ACD (mL)
PLC
Placebo
Baseline
Month 2
Month 4
Month 6
Month 8
Month 10
Month 12

European Study: Quality of Life

PLC showed improvement vs. placebo in the following:

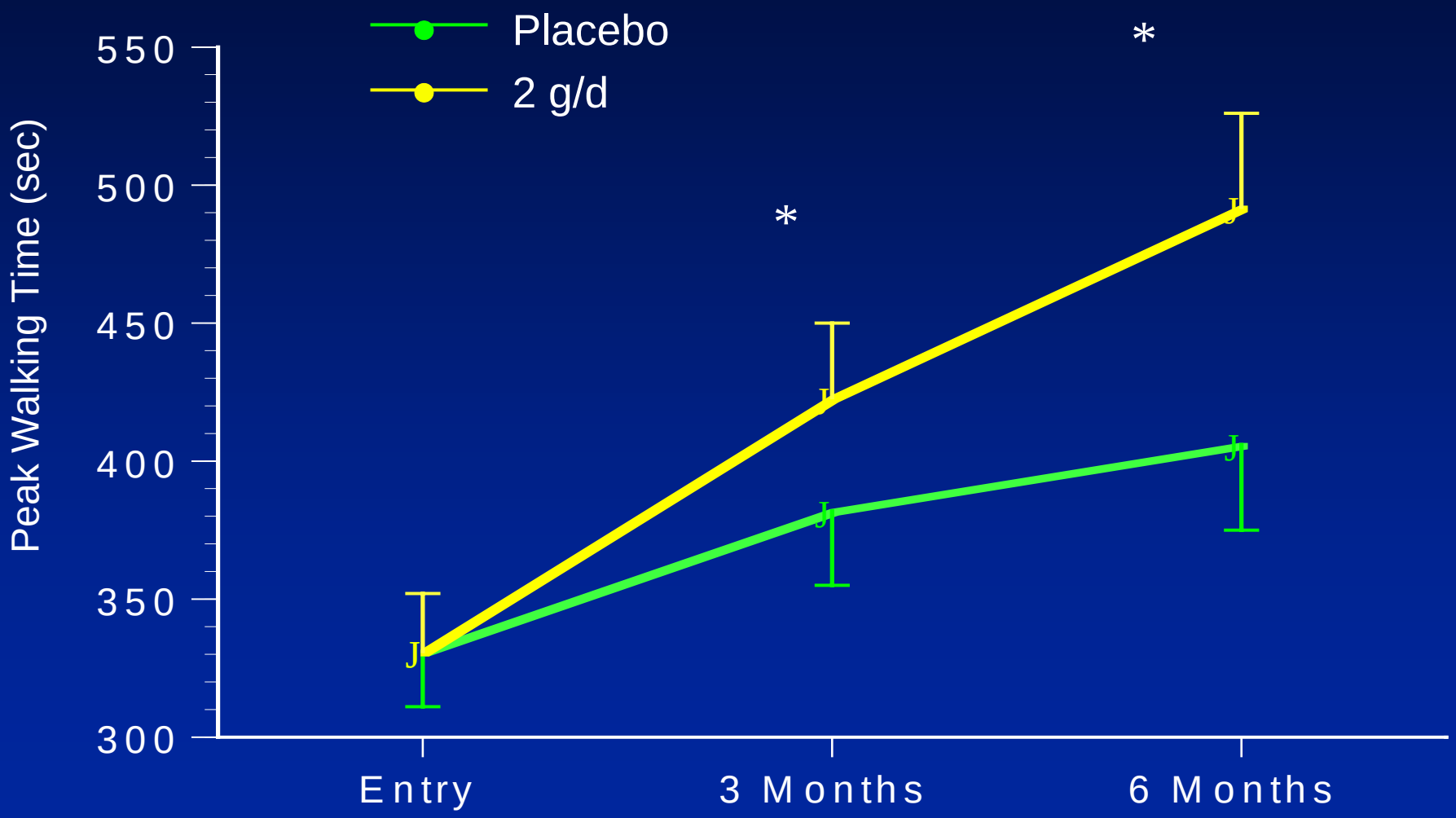
- **Walking pain** **(p = 0.017)**
- **Physical evaluation** **(p = 0.046)**
- **Psychological attitudes** **(p = 0.001)**

American-Russian Study

- Study conducted: 1994 - 1996
- 6 US, 4 Russian sites
- Treadmill at 2 mph, 12% grade
  - MWD 50-250 meters
- Efficacy Treadmill: 2 mph, graded 2% every 2 min
  - ≤ 20% variability over 2 entry tests
- Subjects: n=155, entry ABI ≤ 0.80
- Dose of PLC = 2 g/d
- Study Duration = 6 months

Am J Med 2001;110:616-22

American-Russian Study



American-Russian Study
Treatment by Country Effect

USA	**Increase in PWT**
PLC	22 ± 56%
Placebo	13 ± 38%

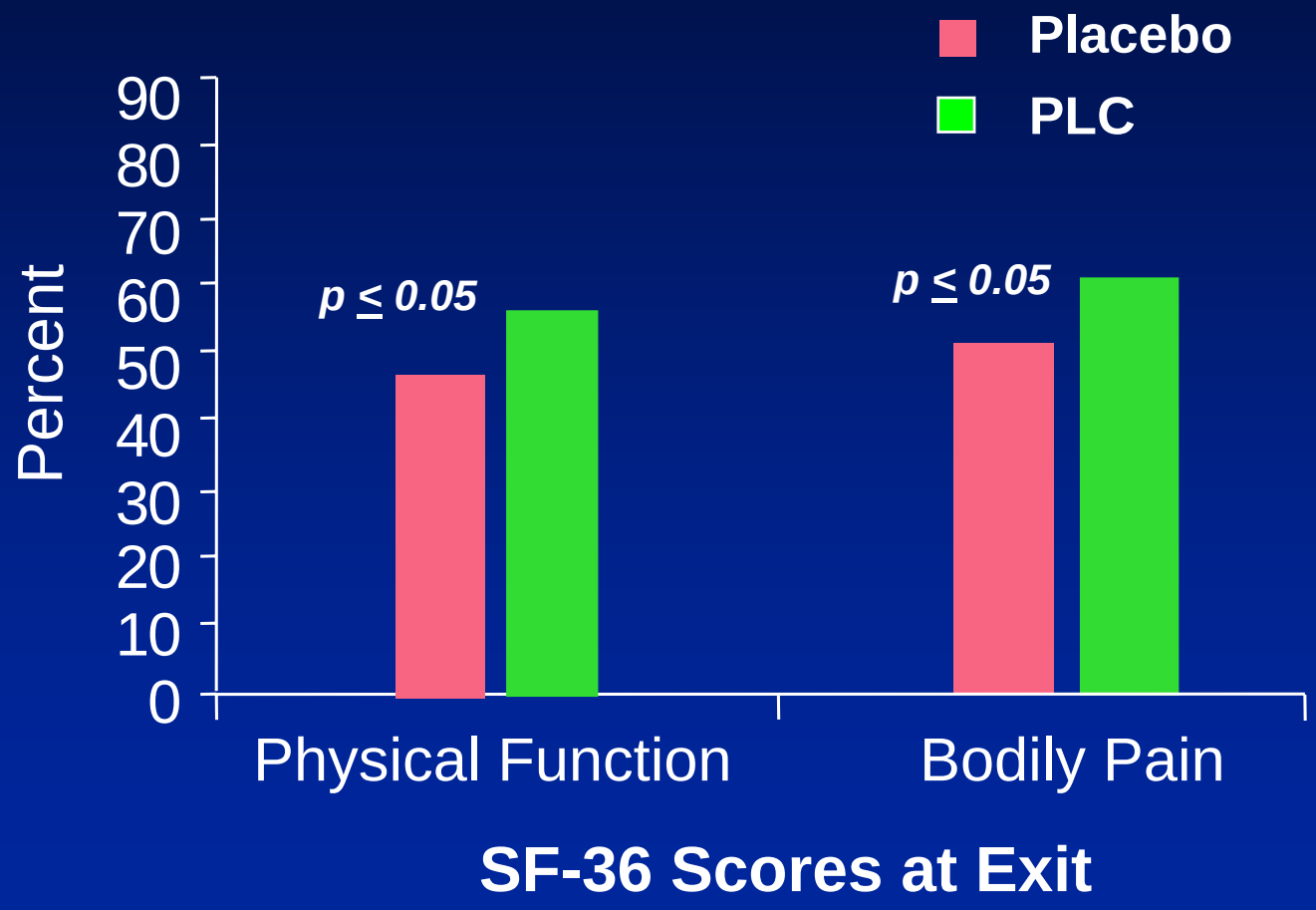
Russia	**Increase in PWT**
PLC	84 ± 92%
Placebo	35 ± 74%

Significant treatment by country interaction

American-Russian Study

Effect of Treatment on WIQ scores

American-Russian Study
Effect of Treatment on SF-36 scores



American-Russian Study: Effect on Quality of Life

QOL Domain	PLC vs. Placebo
• **WIQ**	
– **Walking distance**	**($p \leq 0.05$)**
• **MOS SF-36**	
– **Physical Function**	**($p \leq 0.05$)**
– **Bodily Pain**	**($p \leq 0.05$)**
– **Vitality**	**($p \leq 0.05$)**
– **Health Transition**	**($p \leq 0.01$)**

PLC Phase III Trials: Summary

- **European Study**
  - **Positive; 2g/d in S1 population at 12 months**
- **American-Russian Study**
  - **Positive; 2 g/d at 6 months**
  - **Significant country effect**

Safety Profile of PLC

- **The incidence of adverse events with PLC has not differed significantly from that observed in placebo-treated patients.**
- **Most common AEs seen (no significant difference compared with placebo): flu-like syndrome, PAD aggravation, body pain, and rhinitis.**

Future Research Directions

1. Need to understand the specific acylcarnitine that accumulate in PAD muscle to identify the specific metabolic disruption
2. Relate the muscle metabolic abnormalities to functional endpoints
3. Conclude the clinical development of propionyl L-Carnitine in PAD

Conclusions

- Propionyl L-Carnitine improves treadmill exercise performance in patients with intermittent claudication due to peripheral arterial disease
- Propionyl L-Carnitine improves quality of life
- PLC is associated with a low rate of adverse events.