METFORMIN FOR PERIPHERAL ARTERY DISEASE: THE PERMET RANDOMIZED CLINICAL TRIAL

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Metformin to Improve Walking Performance in Lower Extremity Peripheral Artery Disease

The PERMET Randomized Clinical Trial

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AHA Scientific Sessions

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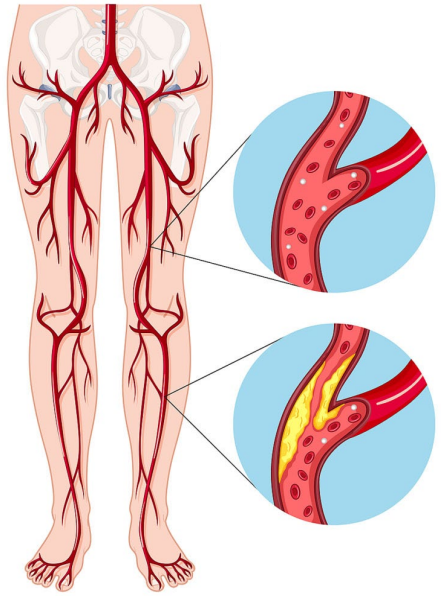
PERIPHERAL ARTERY DISEASE

- Associated with walking difficulty
  - Reduced leg perfusion
  - Impaired muscle mitochondrial activity
  - Increased oxidative stress
  - Reduced eNOS activity
- Few effective medical therapies



POTENTIAL BENEFITS OF METFORMIN

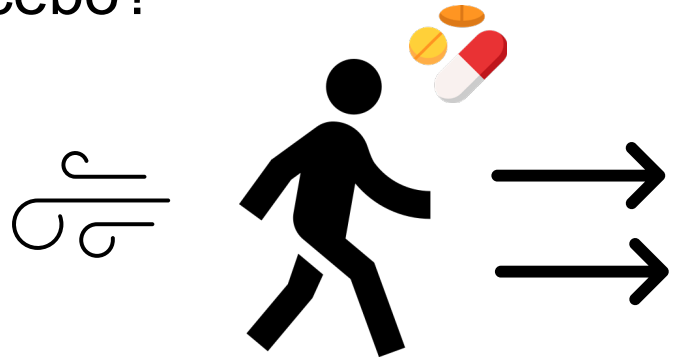
Activates AMP-activated protein kinase

- Stimulates mitochondrial biogenesis and activity
- Stimulates eNOS activity
- Reduces oxidative stress
- Increases bioavailability of nitric oxide

Preliminary evidence showed effects of metformin on improved lower extremity perfusion and treadmill walking distance in small clinical trials

PRIMARY AIM

Among people with PAD without diabetes, does metformin improve 6-minute walk at 6-month follow-up, compared to placebo?



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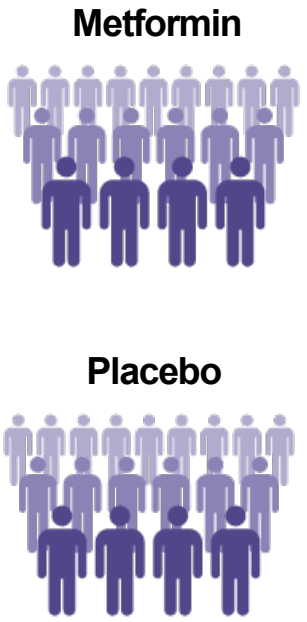
METHODS

PERMET RANDOMIZED TRIAL

- Multi-centered randomized clinical trial
  - Northwestern University, Chicago, IL
  - U. of Chicago, Chicago, IL
  - Tulane University, New Orleans, LA
  - U. of Florida, Gainesville, FL
- Participants randomized to metformin or placebo
- Double blinded
- Six month duration



INCLUSION CRITERION

- ABI ≤ 0.90 at baseline
- Toe Brachial Index of 0.70 or less

MAIN EXCLUSION CRITERIA

- Diabetes mellitus
- eGFR<45
- Walking primarily limited by a condition other than PAD
- Inability to complete 14-day metformin run-in.
- Presence of limb-threatening ischemia
- Elevated liver enzymes
- Other major medical illness (active cancer)

INTERVENTIONS ADMINISTERED IN DOUBLE BLIND FASHION

- Metformin: 2,000 mg daily
  - Administered as 2 x 500 mgs twice daily
- Placebo
  - Administered as 2 pills twice daily

Pills were encapsulated to appear identical

OUTCOMES

- **Primary outcome**
  - **6-month change in six-minute walk distance**
- **Secondary outcomes**
  - 6-month change in maximal treadmill walking time
  - 6-month change in pain-free walking time
  - 6-month change in WIQ distance score
  - 6-month change in WIQ speed score
  - 6-month change in brachial artery FMD
- **Exploratory outcomes**
  - 4-meter walking velocity
    - Usual and fast pace
  - Short physical performance battery
  - WIQ stair climbing score

STATISTICAL ANALYSES PLAN

- Primary outcome (6-minute walk)
  - ANCOVA
  - Adjusting for baseline value of 6-minute walk and site
- Secondary and exploratory outcomes
  - ANCOVA
  - Adjusting for baseline value of each outcome and site
- Pre-specified statistical significance threshold
  - Two-sided P value < 0.05

POWER CALCULATIONS

212 participants provided 80% power to detect a 28 meter difference in 6-minute walk between the metformin and placebo groups, assuming a 91% follow-up rate

RESULTS

PERMET TRIAL RESULTS

- 202 participants randomized
  - May, 2017 to February, 2025
- 6-month follow-up: 179 (89%)

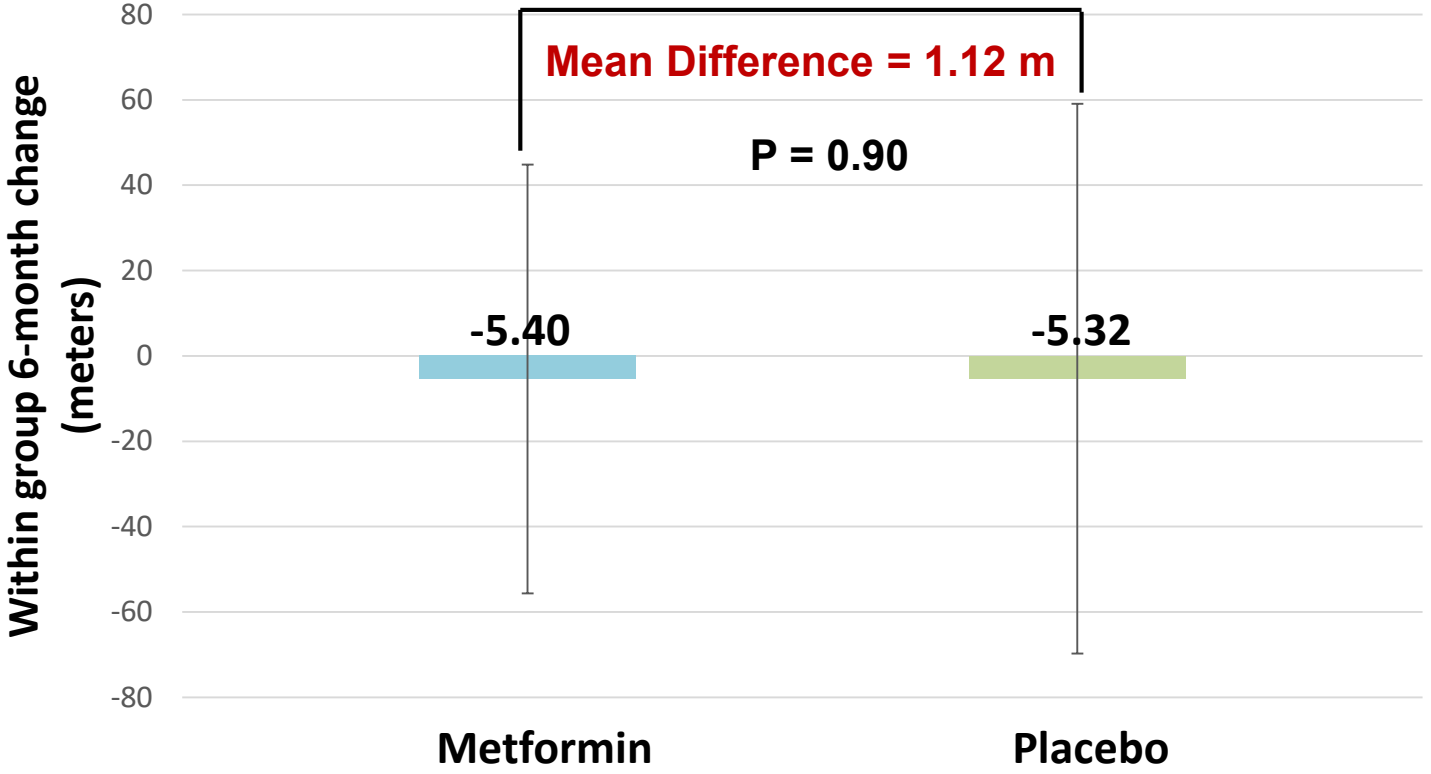
CHARACTERISTICS OF RANDOMIZED PARTICIPANTS IN THE PERMET TRIAL

Baseline variable	Overall (N=202)	Trial Assignment	
		Metformin (N=97)	Placebo (N=105)
Age (years), mean (SD)	69.6 (8.4)	69.9 (9.0)	69.3 (7.8)
Male, n (%)	146 (72.3)	65 (67.0)	81 (77.1)
Female, n (%)	56 (27.7)	32 (33.0)	24 (22.9)
Black, n (%)	79 (39.1)	41 (42.3)	38 (36.2)
Ankle brachial index, mean (SD)	0.64 (0.16)	0.63 (0.16)	0.66 (0.15)

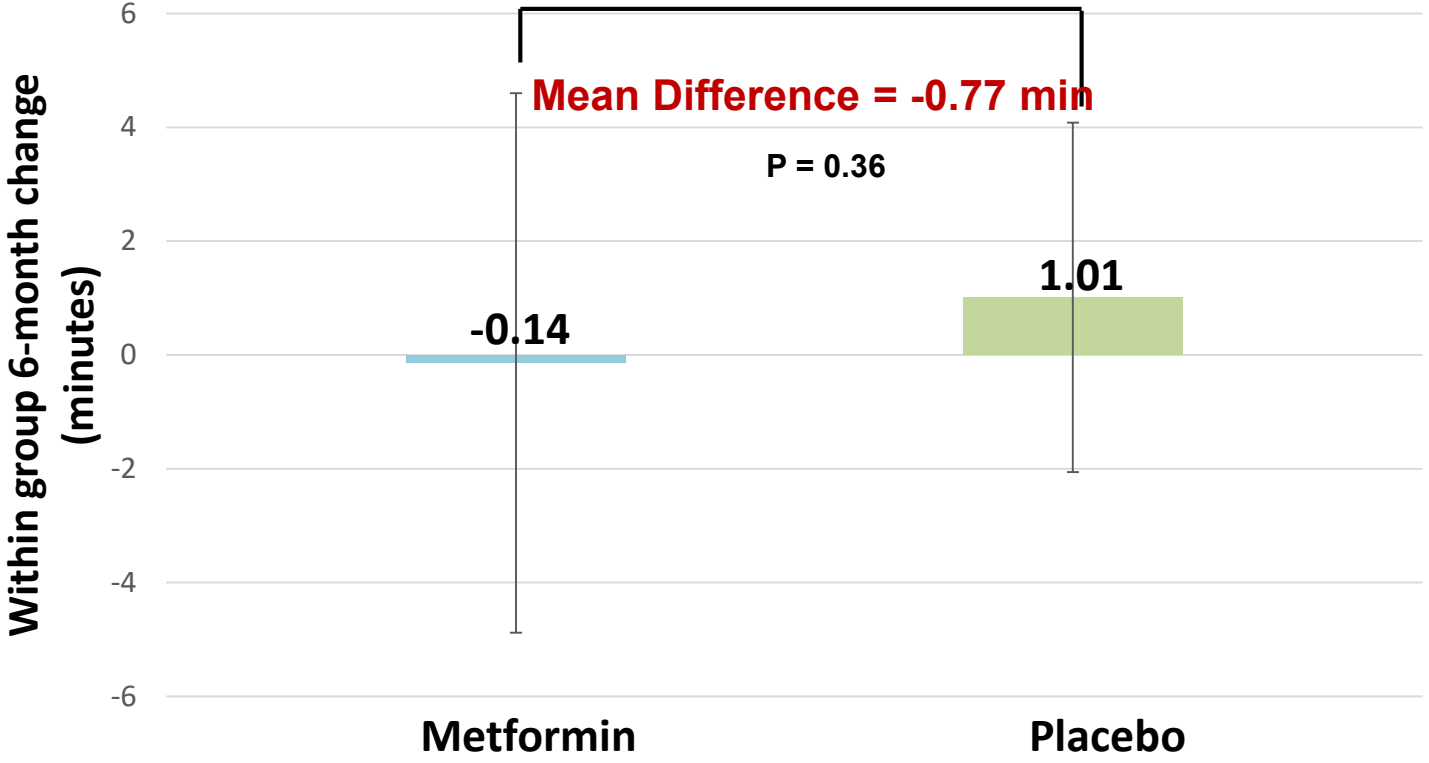
ADHERENCE TO STUDY PILLS BASED ON PILL COUNTS

- Overall adherence
  - Metformin: 84.7%
  - Placebo: 87.8%
- Medication discontinuation
  - Metformin: 19.8%
  - Placebo: 9.6%
- Mean dose
  - Metformin: 1,322 mg
  - Placebo: 1,548 mg

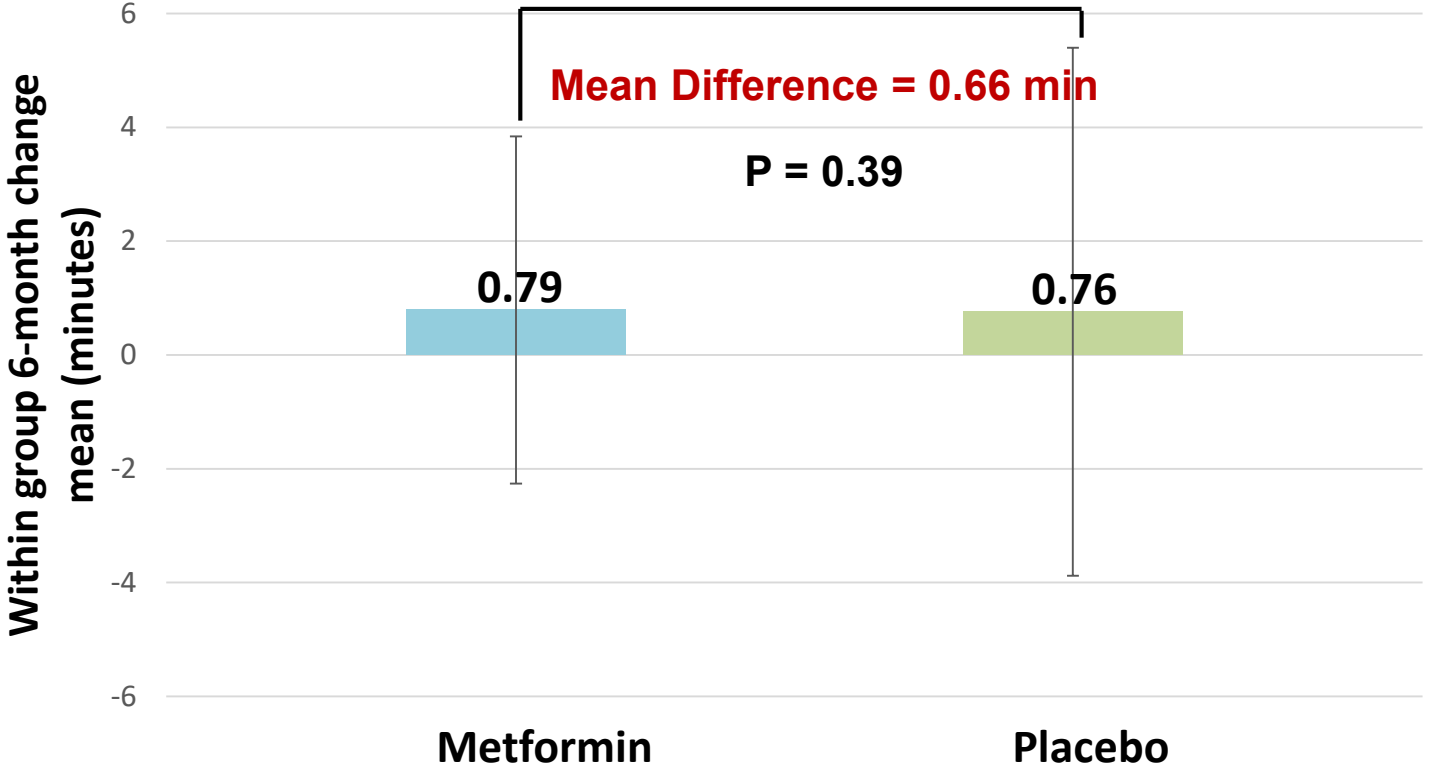
6-MONTH CHANGES IN 6-MINUTE WALK DISTANCE



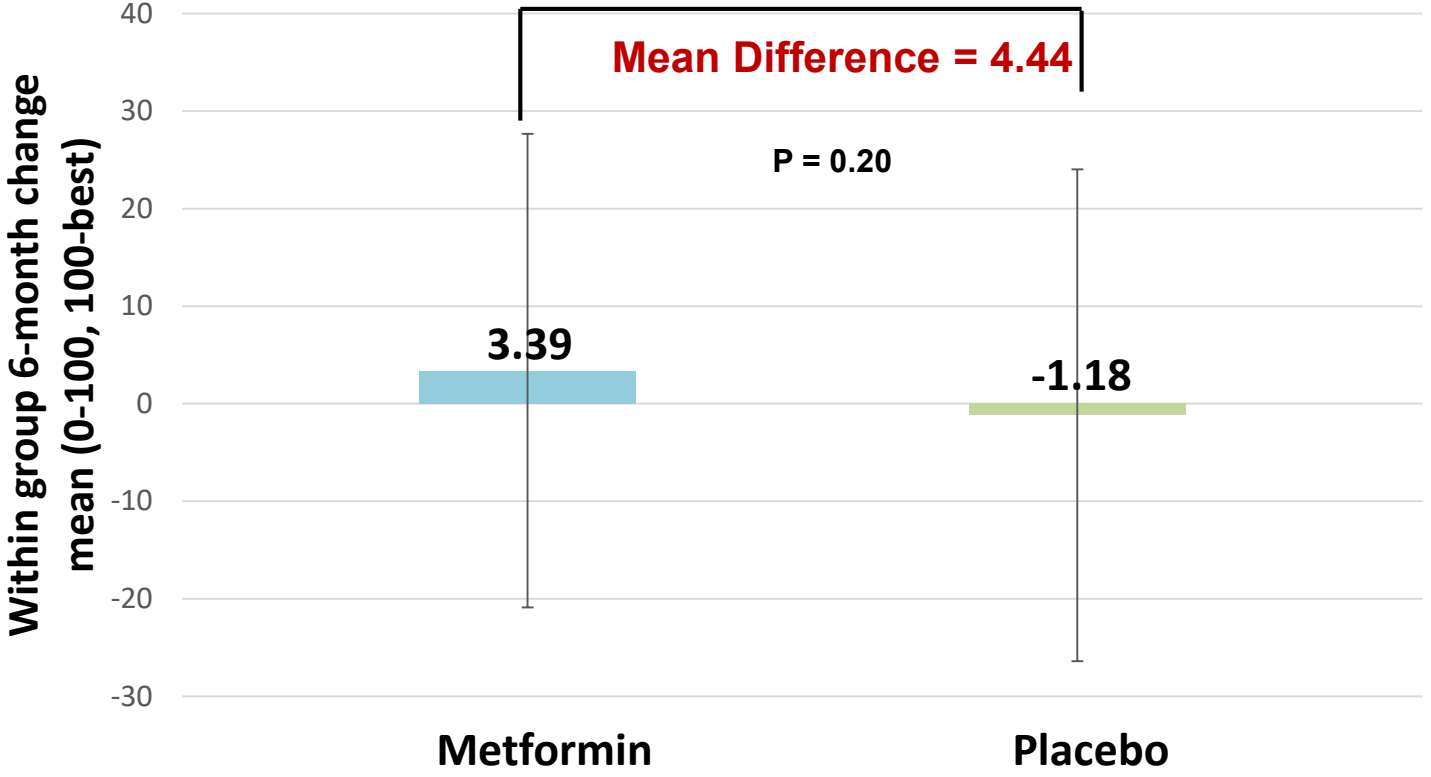
6-MONTH CHANGES IN MAXIMAL TREADMILL WALKING TIME



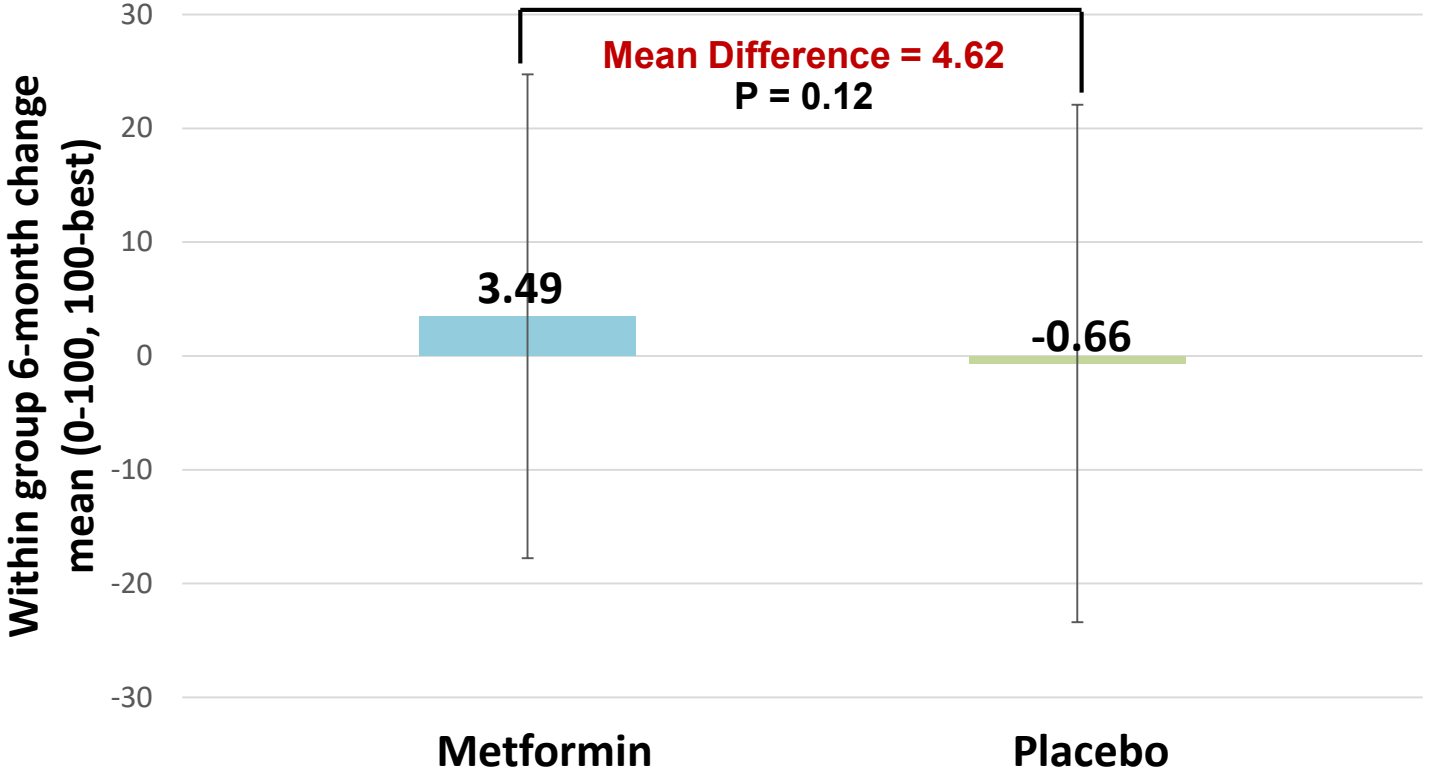
6-MONTH CHANGES IN PAIN-FREE TREADMILL WALKING DISTANCE



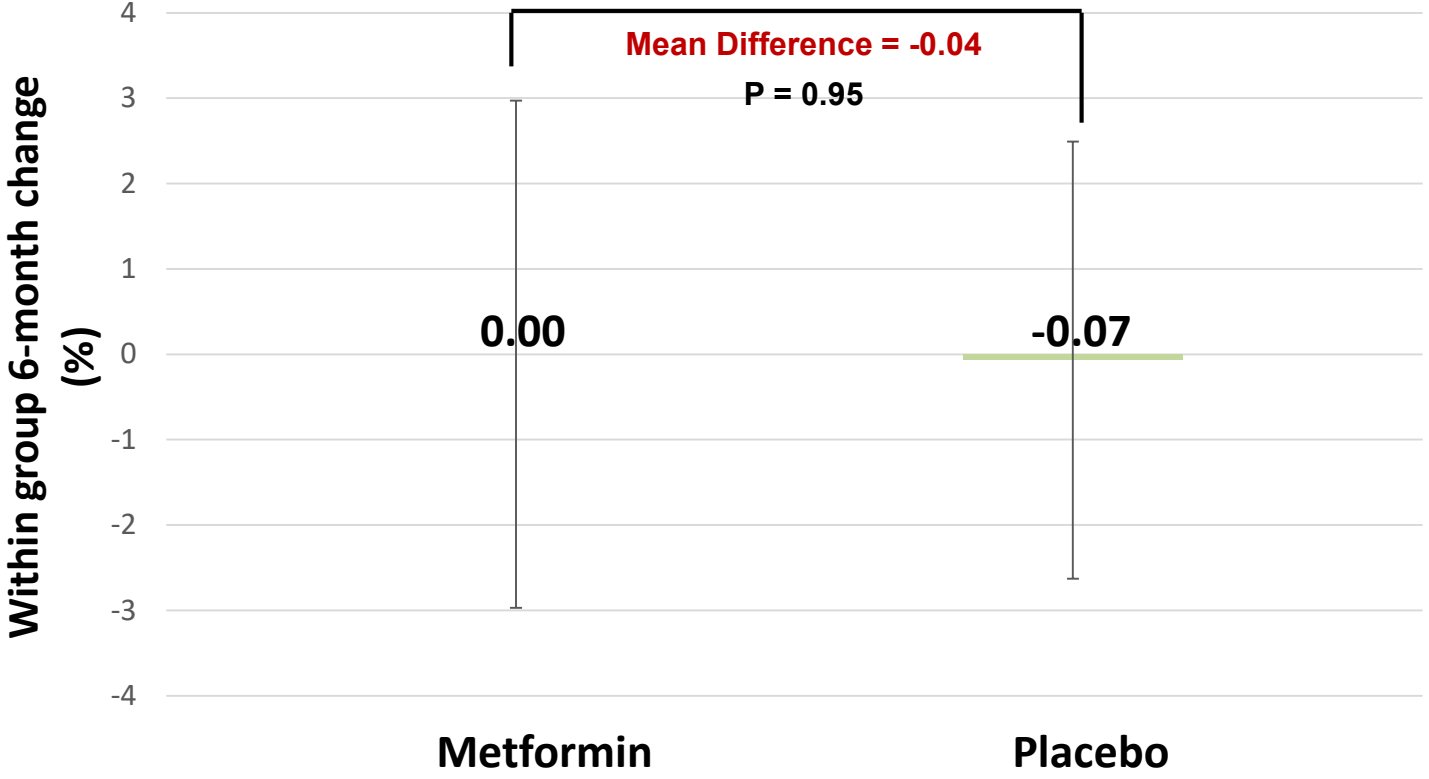
6-MONTH CHANGES IN WALKING IMPAIRMENT QUESTIONNAIRE DISTANCE SCORE



6-MONTH CHANGES IN WALKING IMPAIRMENT QUESTIONNAIRE SPEED SCORE



6-MONTH CHANGES IN BRACHIAL ARTERY FLOW-MEDIATED DILATION PERCENT CHANGE



RESULTS (CONTINUED)

No beneficial effects of metformin, compared to placebo, on exploratory outcomes

- WIQ speed score
- Four-meter walking velocity (usual pace)
- Four-meter walking velocity (fast pace)
- Short physical performance battery

ADVERSE EFFECTS

- Serious adverse events
  - Metformin: 11.3%
  - Placebo: 13.3%
- Cardiovascular events
  - Metformin: 3.1%
  - Placebo: 1.9%
- Indigestion/stomach upset
  - Metformin: 64.9%
  - Placebo: 40.6%

POTENTIAL EXPLANATIONS FOR LACK OF METFORMIN BENEFIT

- AMP activated kinase may already be maximally stimulated in PAD if low oxygen tension causes a high AMP/ATP ratio
- Potential adverse effects of metformin on cardiorespiratory adaptations to exercise

STUDY LIMITATIONS

- Enrollment ended at 95% of target sample size
- Drop-out slightly higher in the metformin, compared to placebo, group.
- Small proportion of women

PERMET TRIAL CONCLUSIONS

Results of the PERMET Trial do not support metformin to improve walking performance in people with peripheral artery disease

THANK YOU

- National Heart Blood and Lung Institute
- Study participants
- Data Safety Monitoring Board members
- Northwestern University Feinberg School of Medicine