

The Progression and Translation of a Cardiovascular Research Project from Basic Science to Clinical Trial with a Nutritional Focus

Grant N. Pierce, OM, PhD, FACC, FAHA, FIACS, FCAHS, FISHR, FRSM, FRSC
St Boniface Hospital and the University of Manitoba



Flaxseed is an Ideal Cardiovascular Therapy



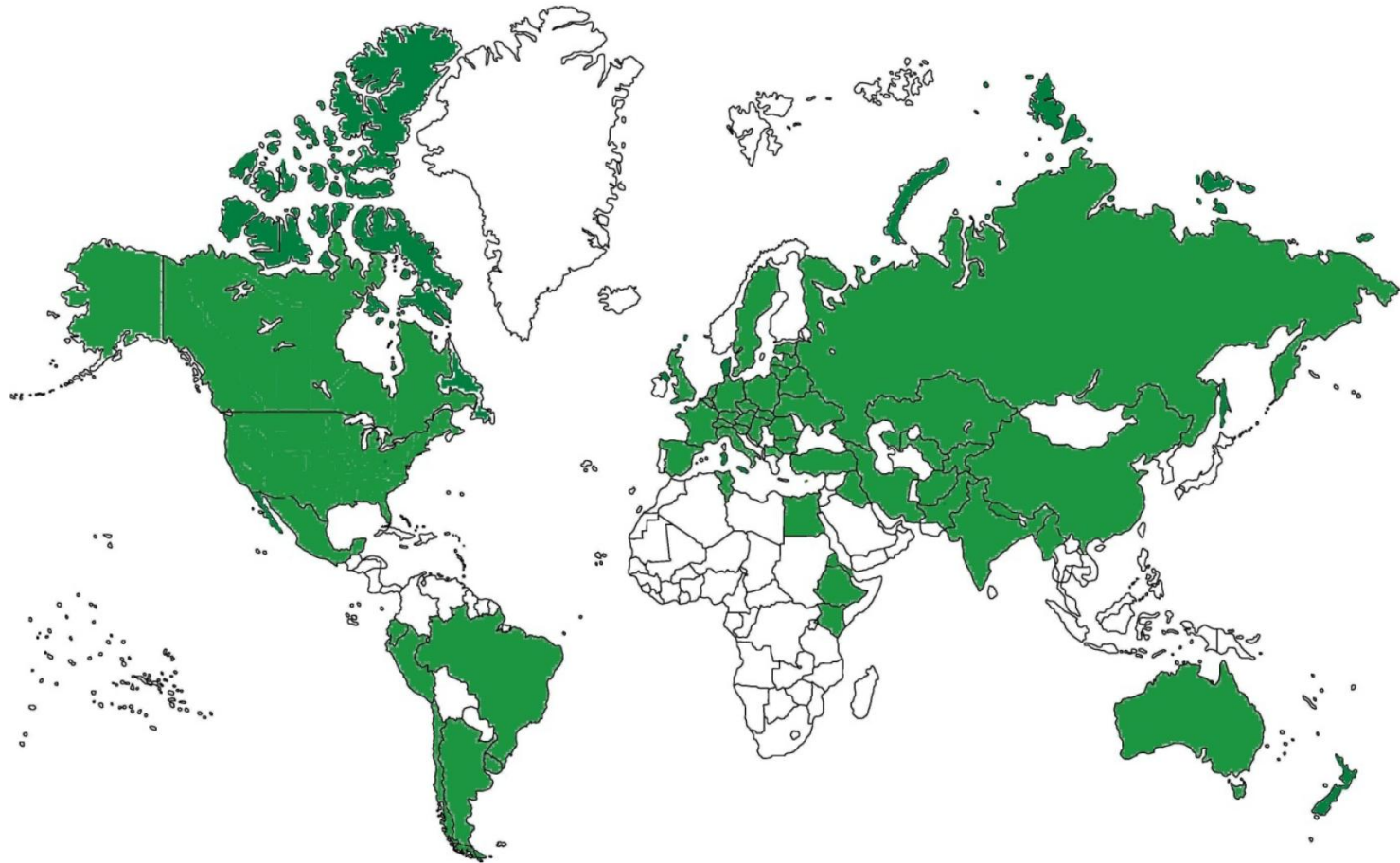


Figure 1: World Atlas of Countries Growing Flaxseed.

* Based on data from the Food and Agriculture Organization of United Nations Database (2011)

Flaxseed is a triple-threat

ALA (Omega-3 FA)



Fibre

Lignans

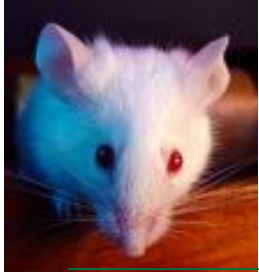
Flaxseed is a triple-threat

ANTI-INFLAMMATORY



↓ CHOL

ANTIOXIDANT

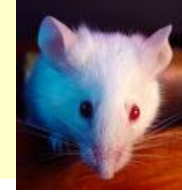


Our animal work – a glimpse into the use of flaxseed for CV health

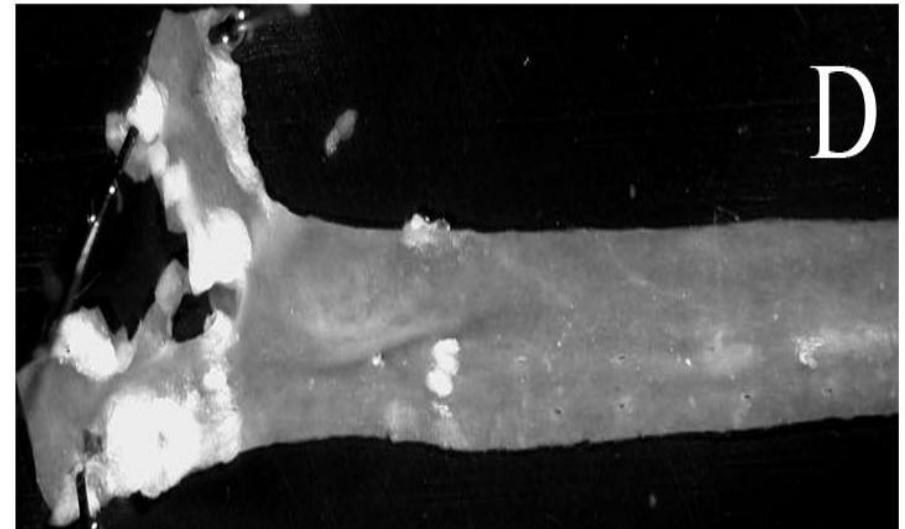
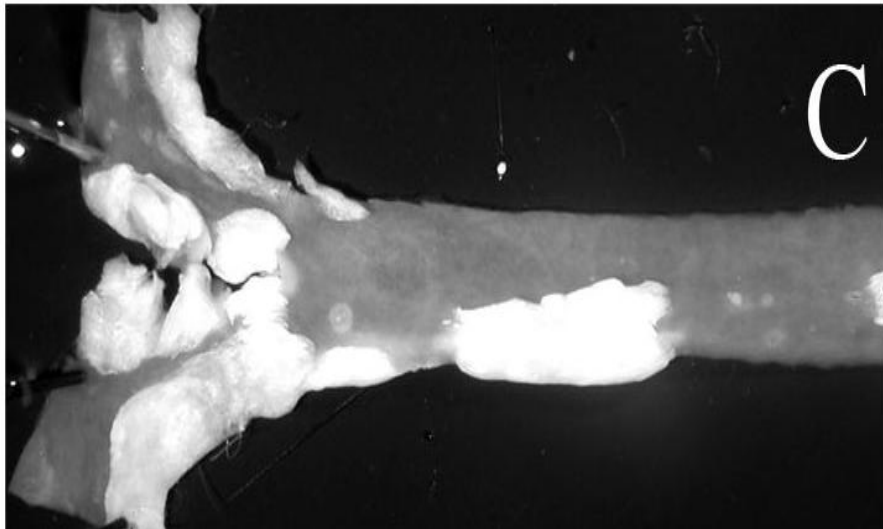
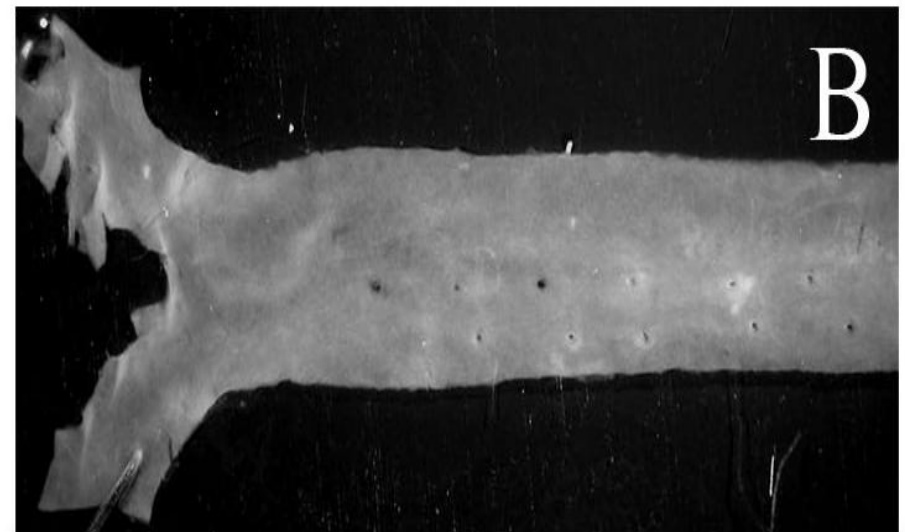
Dietary flaxseed has shown vascular and cardiac effects in animal studies:

- **Anti-atherogenic effects**
- **Ischemic heart disease**

Does flaxseed provide an anti-atherogenic effect in the LDLr KO mouse?



Dupasquier et al, Am J Physiol 293:H2394-2402, 2007



Experimental induction of Myocardial Infarction

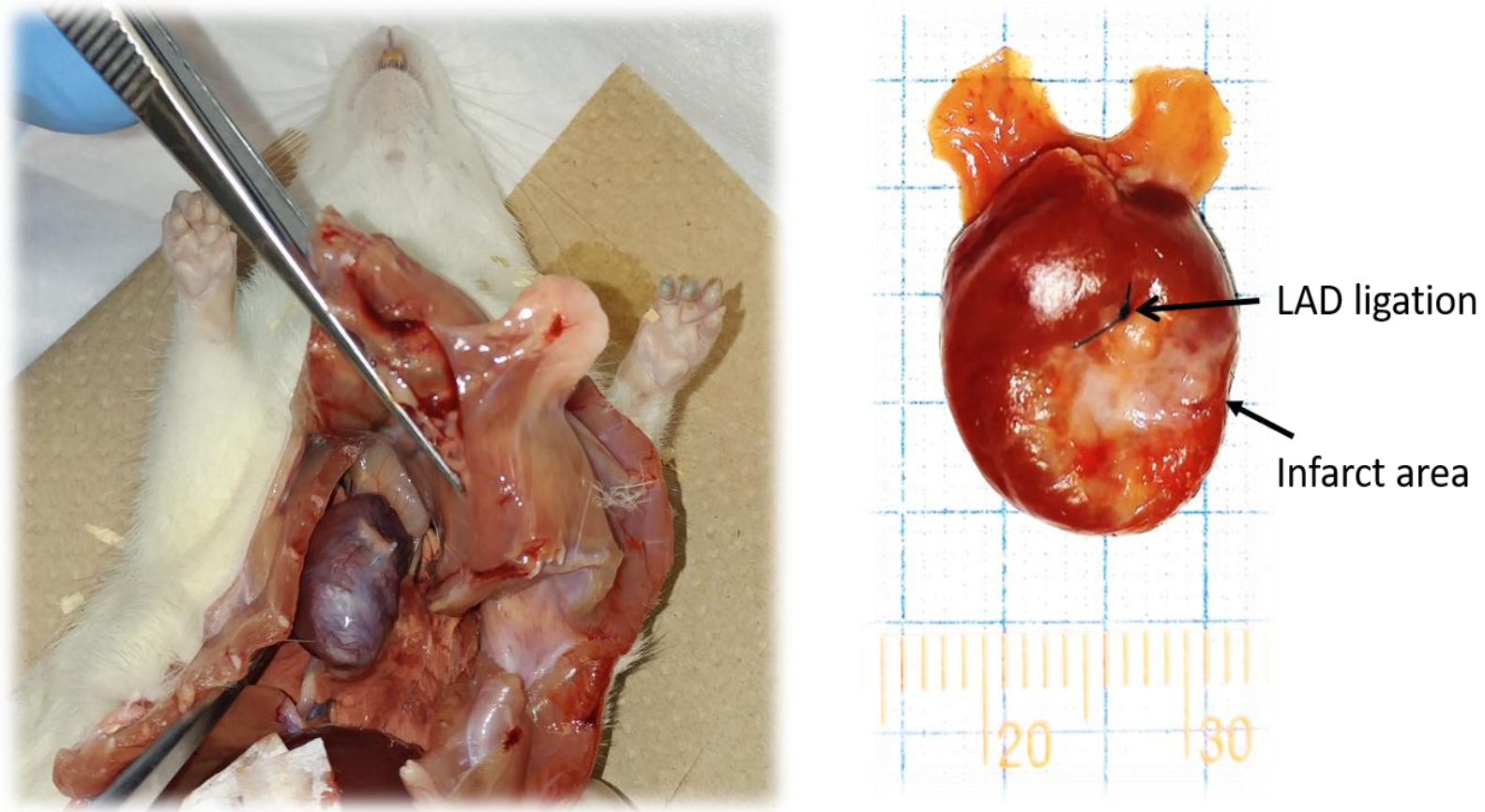
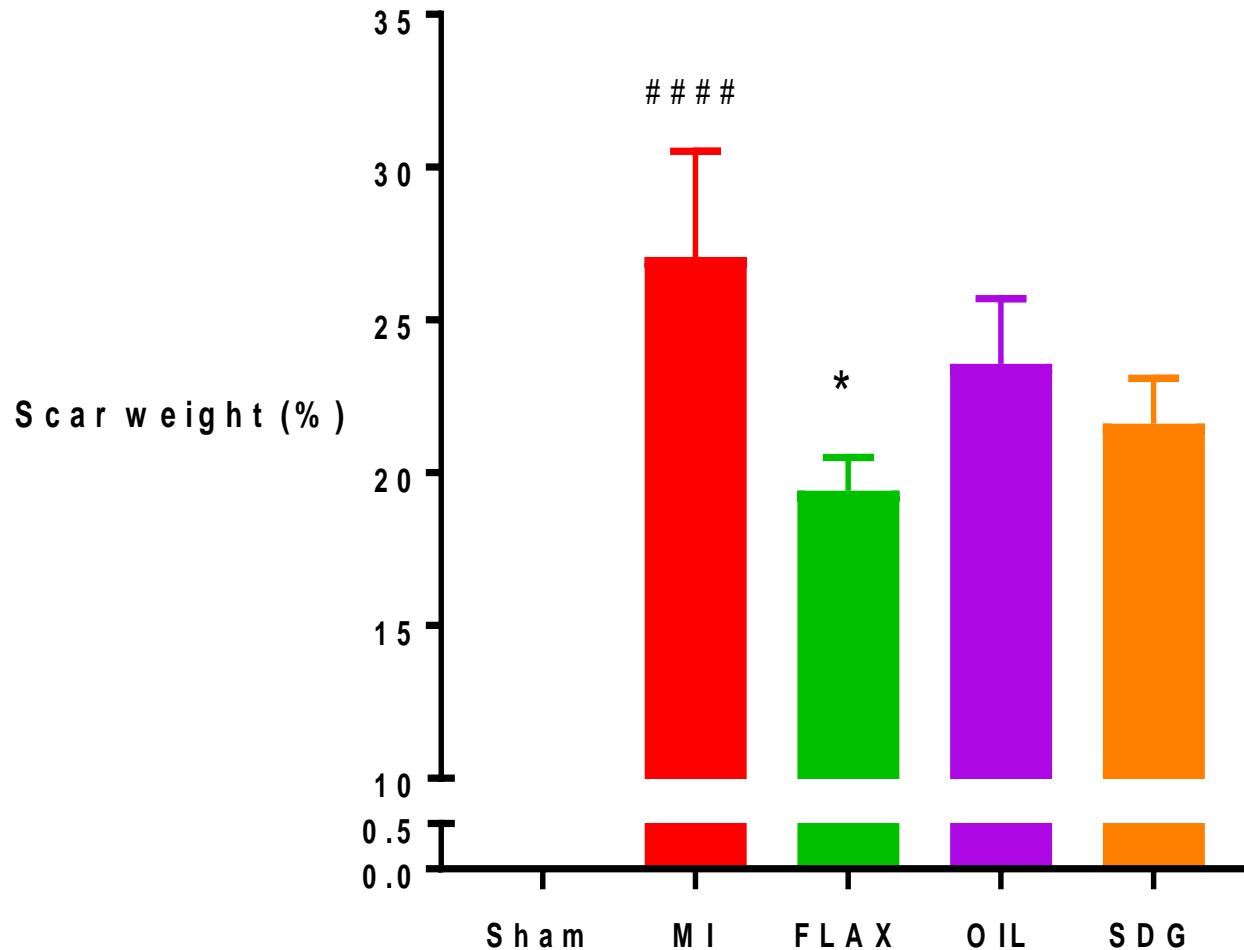


Figure 1. A, Color change from red to white indicating MI induction after the left anterior descending (LAD) coronary artery ligation. **B,** Surgical site for LAD ligation and infarct area shown in an isolated heart.

Dietary flaxseed decreases myocardial infarct size



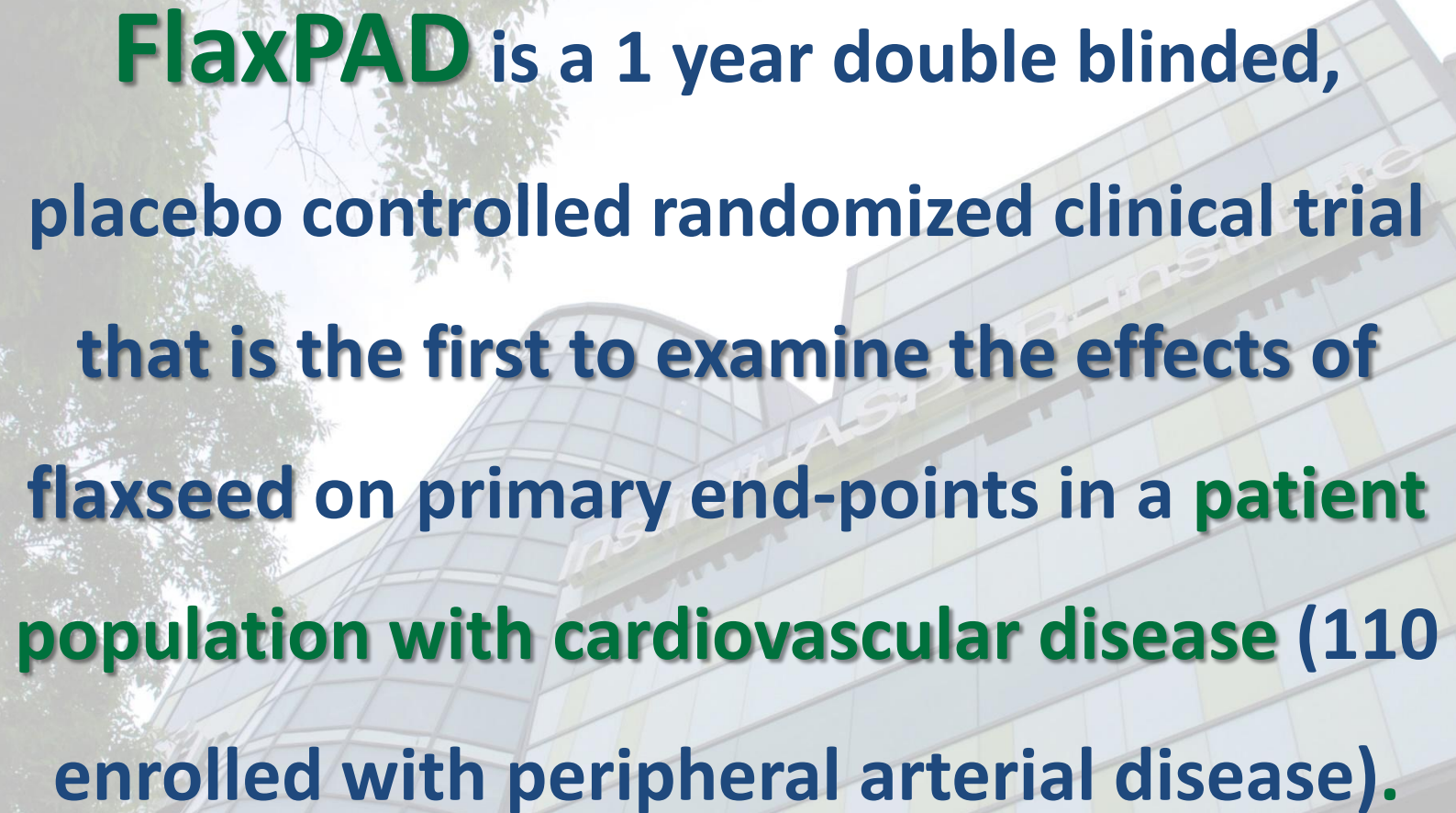
I have a choice:

- 1. Continue to squeeze out animal work or**
- 2. Dive into clinical trials**



The FlaxPAD Trial:

A Powerful Anti-Hypertensive Action of a Novel Dietary Intervention



FlaxPAD is a 1 year double blinded, placebo controlled randomized clinical trial that is the first to examine the effects of flaxseed on primary end-points in a **patient population with cardiovascular disease** (110 enrolled with peripheral arterial disease).

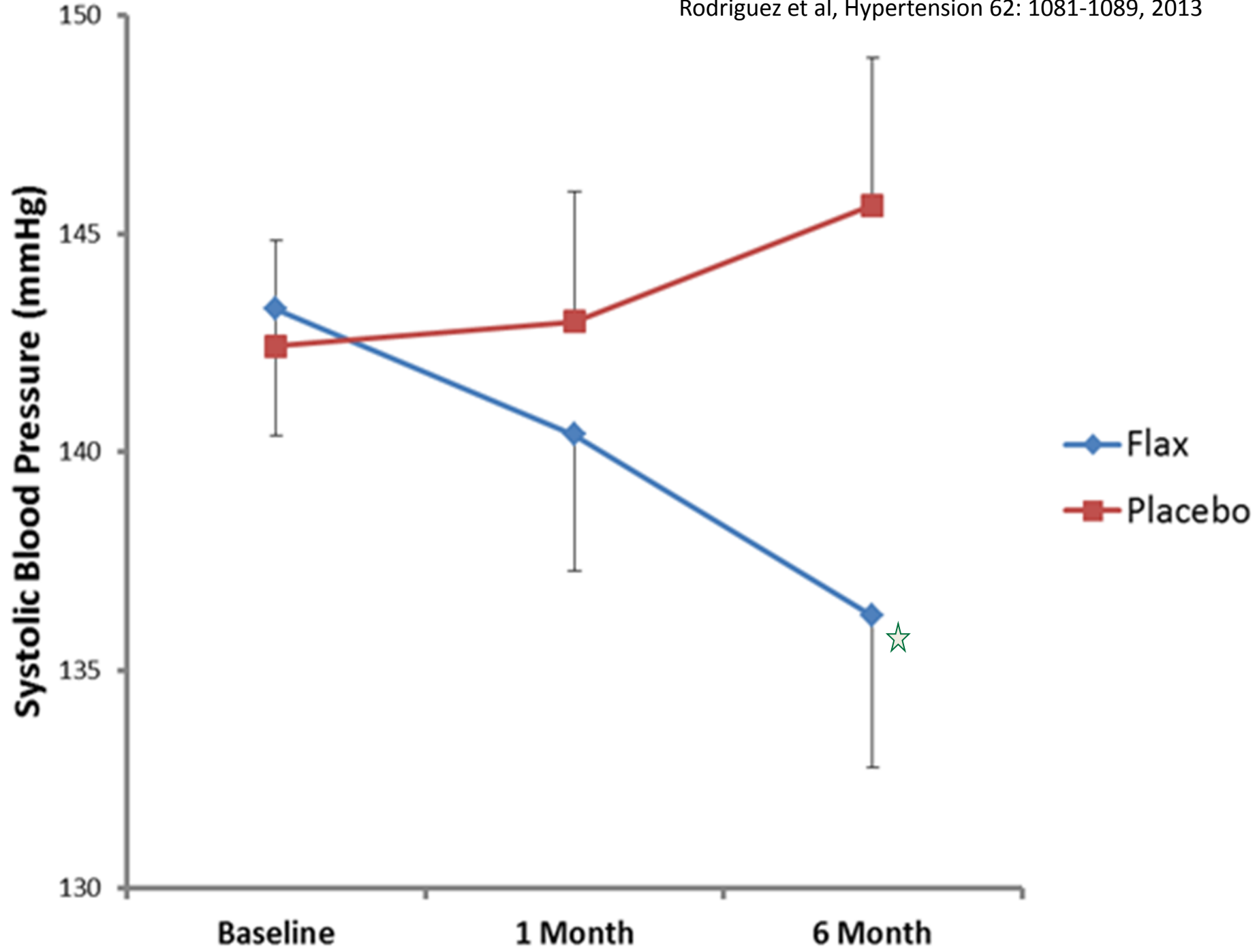


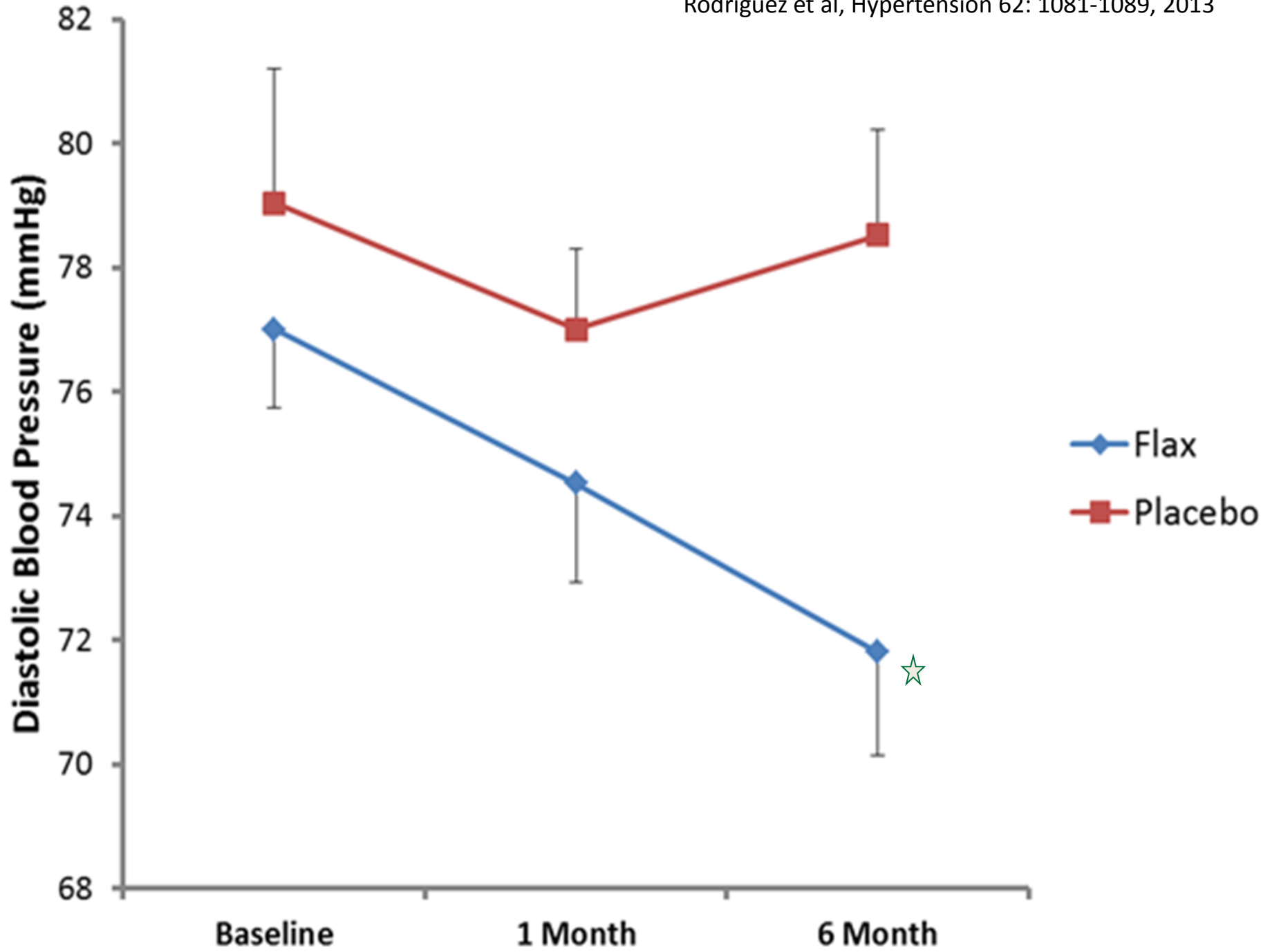
With the help of Canada Bread, CIGI and FDC, we developed foods that contained 30g of milled flaxseed or placebo.



What happened to blood pressure in our **FlaxPAD** Trial?







How does flaxseed compare to anti-hypertensive medication?

Blood pressure lowering regimen	SBP	DBP
Flaxseed	- 10 mmHg	- 7 mmHg
ACE-I	- 4.4 mmHg	-2.1 mmHg
CA	-7.6 mmHg	-3.1 mmHg
ARB	-1.8 mmHg	-1.2 mmHg

Will this change in blood pressure have an impact on cardiovascular disease?

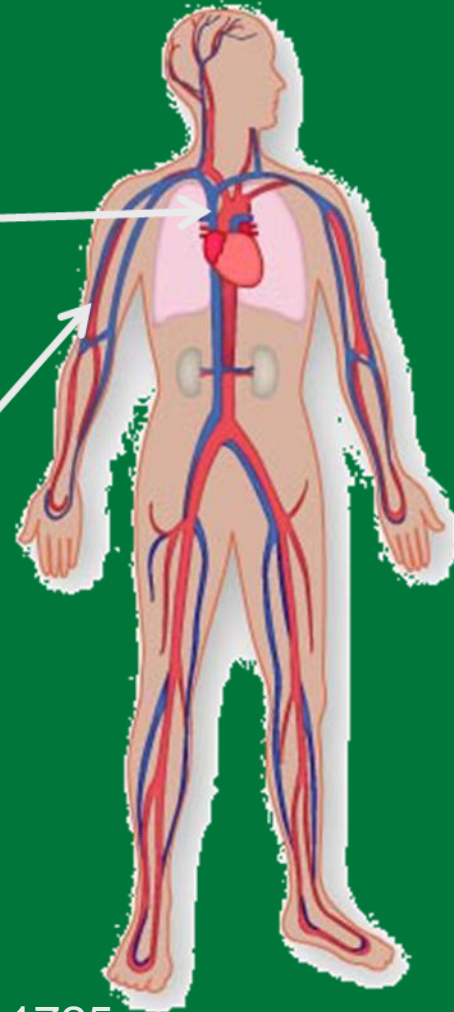
Intervention Effect of FLAXSEED.	Incidence of Stroke	Incidence of Myocardial Infarction
↓ SBP by 10 mmHg	↓ 36%	↓ 27%
↓ DBP by 7 mmHg	↓ 46%	↓ 29%

Central Blood Pressure

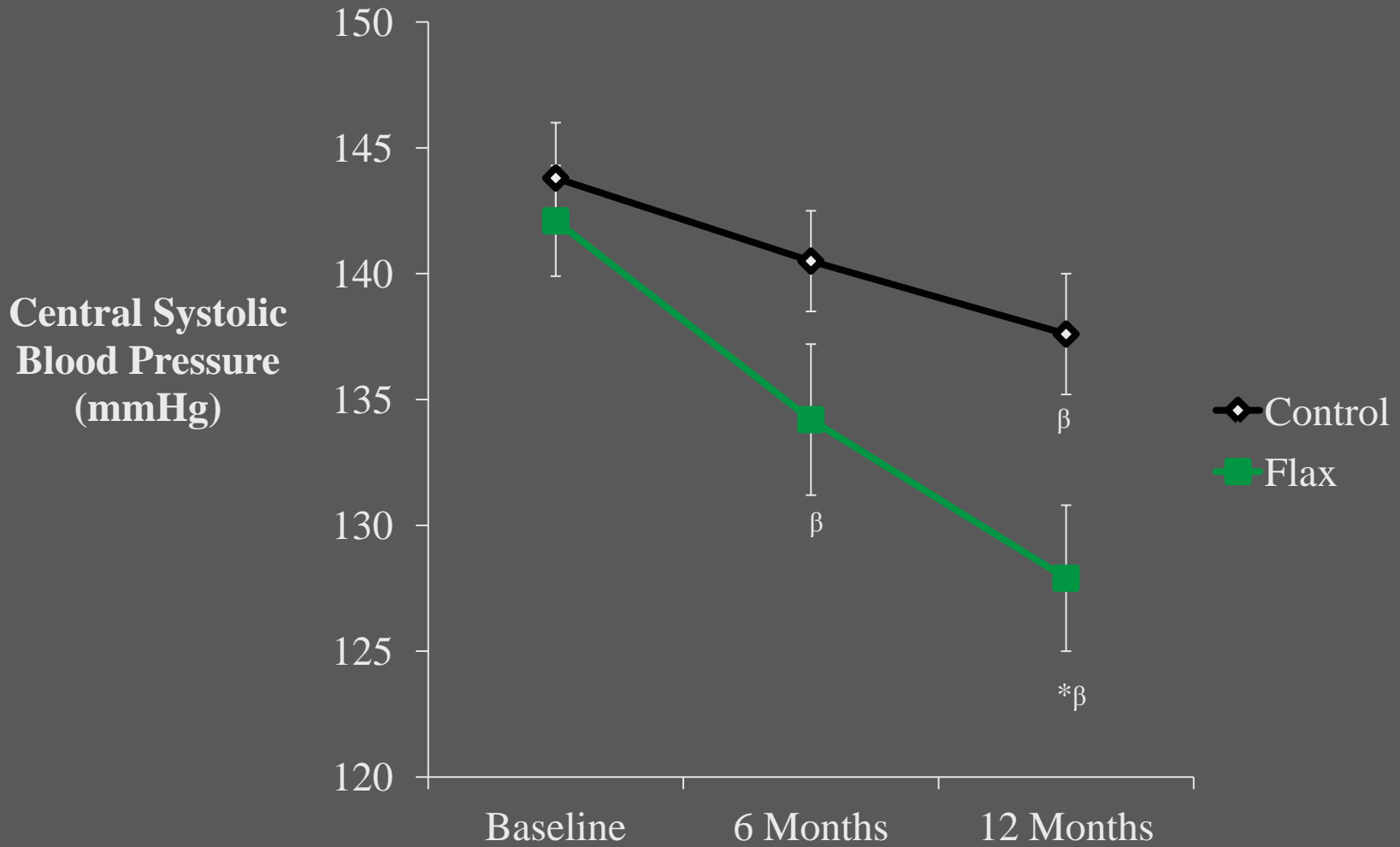
- ◆ Central blood pressure better predicts future cardiovascular events

Central Blood Pressure :
Pressure in aorta

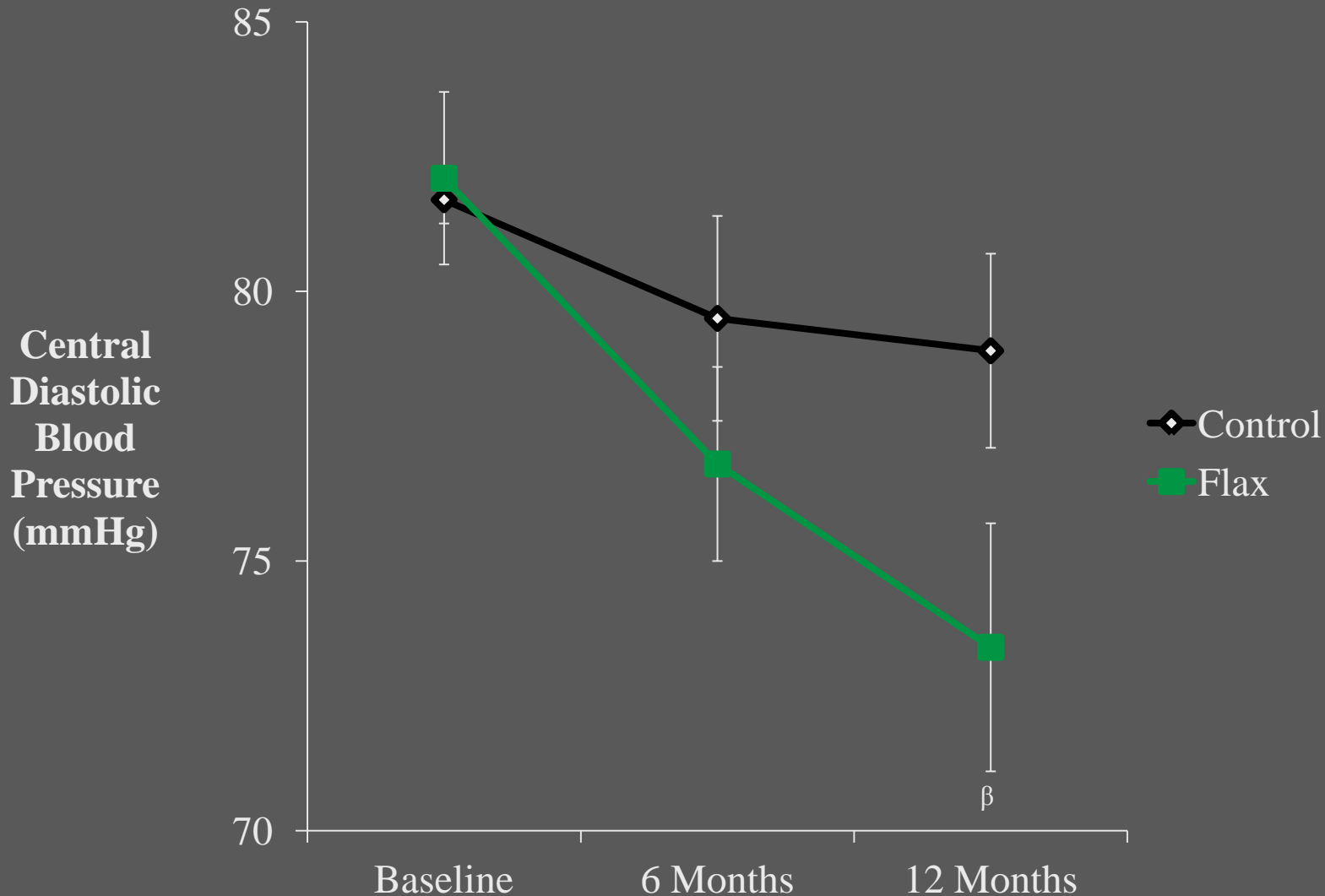
Peripheral Blood Pressure:
Pressure in Brachial artery



Flaxseed Significantly Reduces Central Systolic Blood Pressure

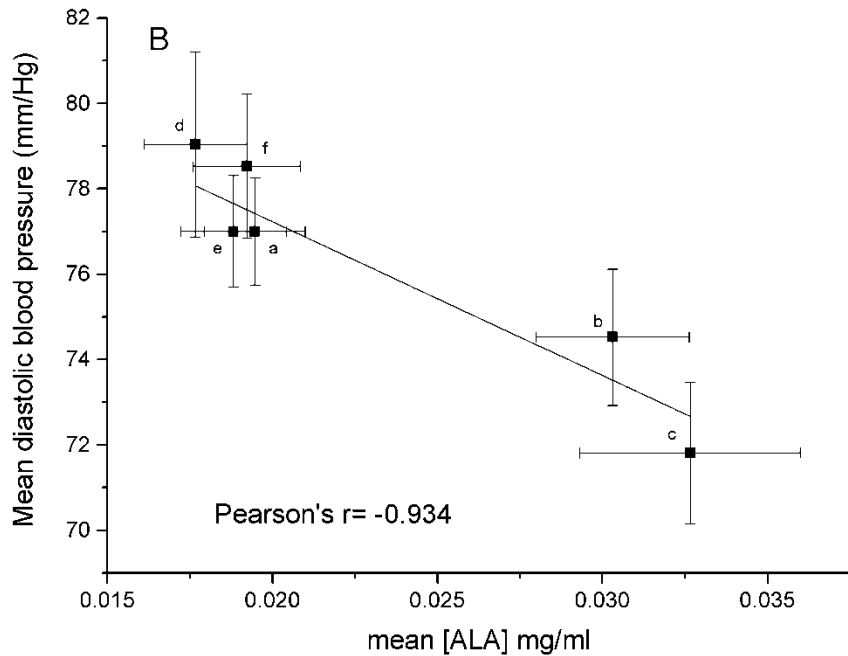
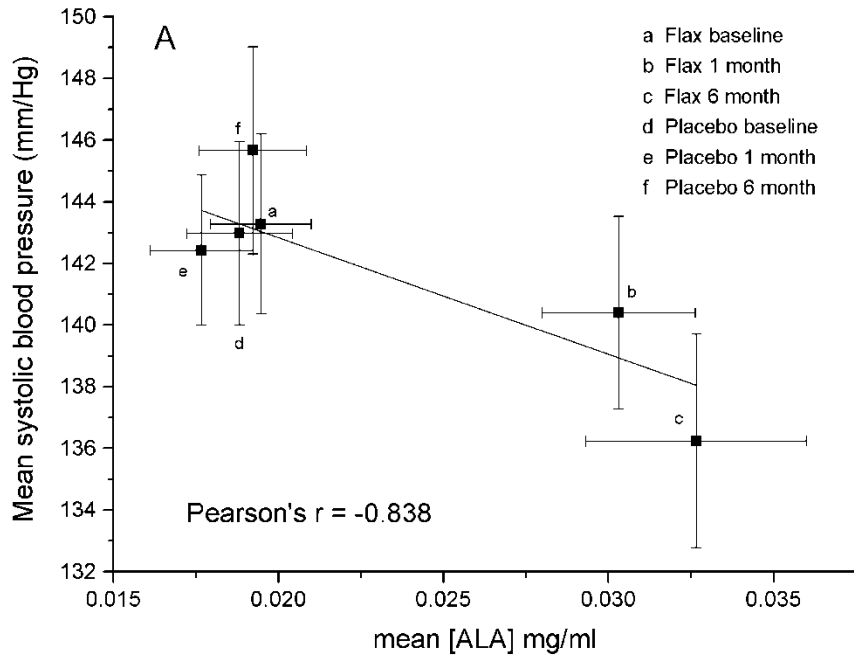


Flaxseed Significantly Reduces Central Diastolic Blood Pressure



Too good to be true???





Oxylipins

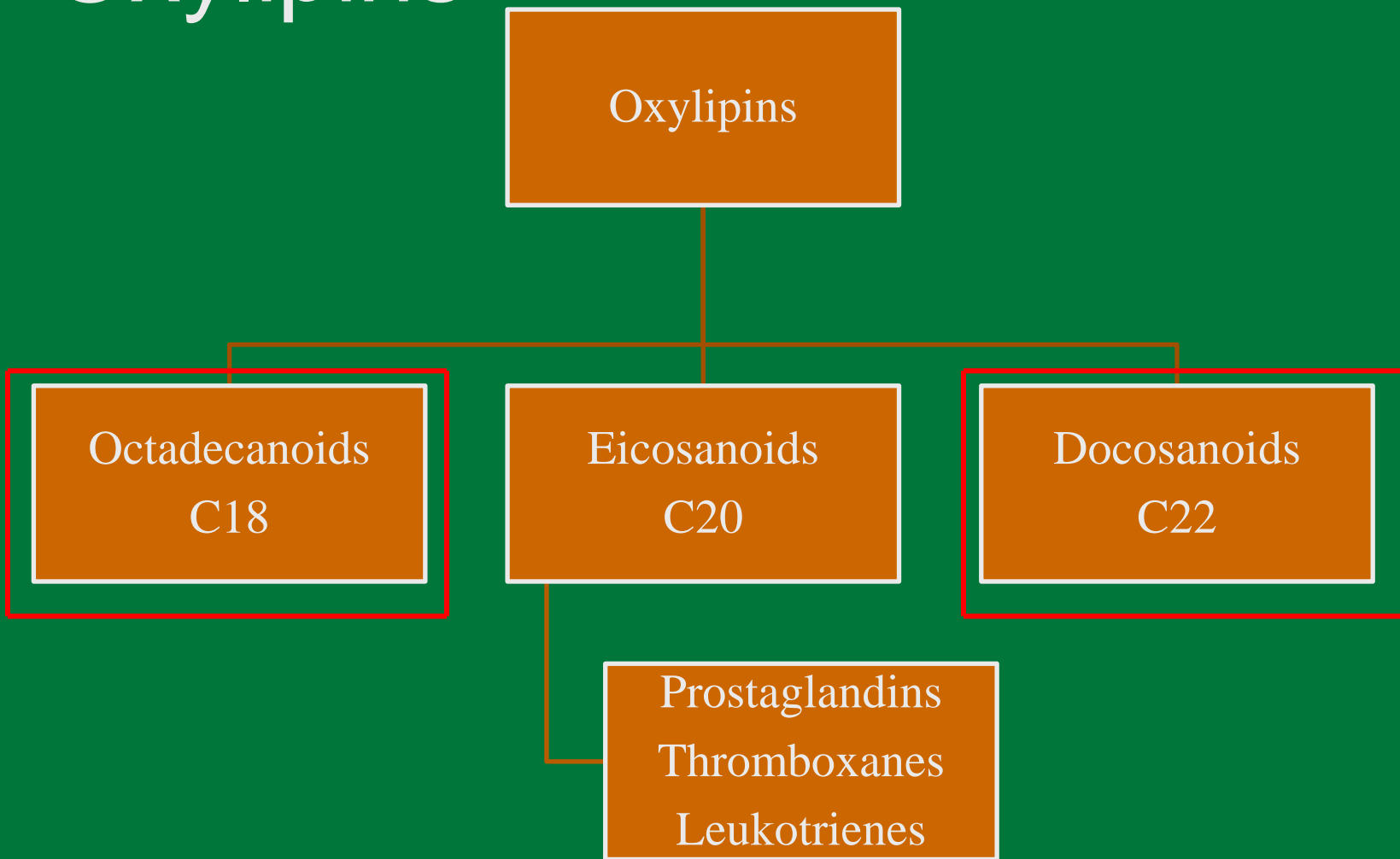
What are Oxylipins?

- ◆ A class of highly bioactive oxygenated molecules
- ◆ Endogenously produced from polyunsaturated fatty acids
- ◆ Vascular tone, inflammation, and immunity

Calder, P. C. (2006). *The American Journal of Clinical Nutrition*, 83(6 Suppl), 1505S.

Calder, P. C. (2006). *Prostaglandins, Leukotrienes, and Essential Fatty Acids*, 75(3), 197.

Oxylipins

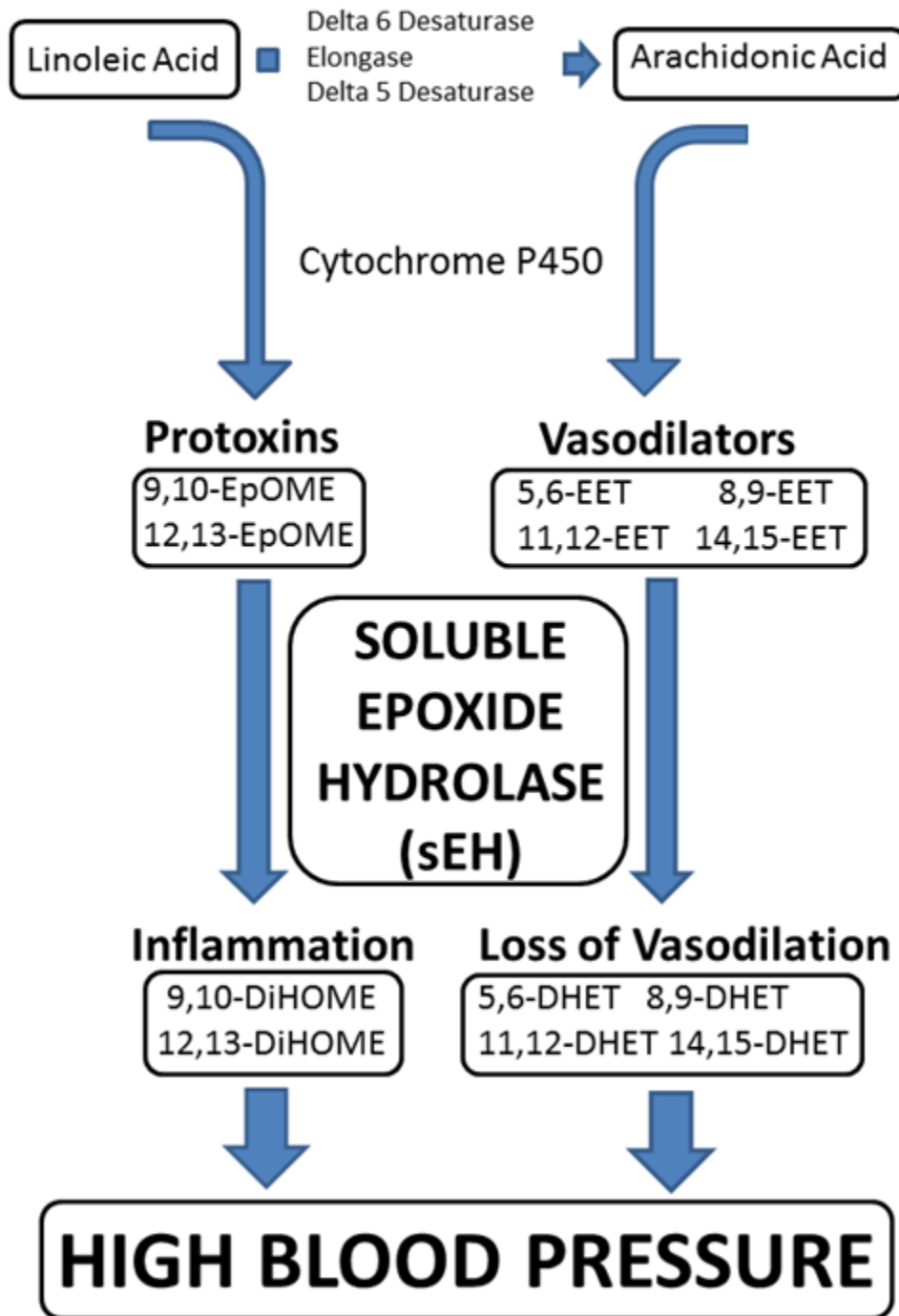


Oxylipins

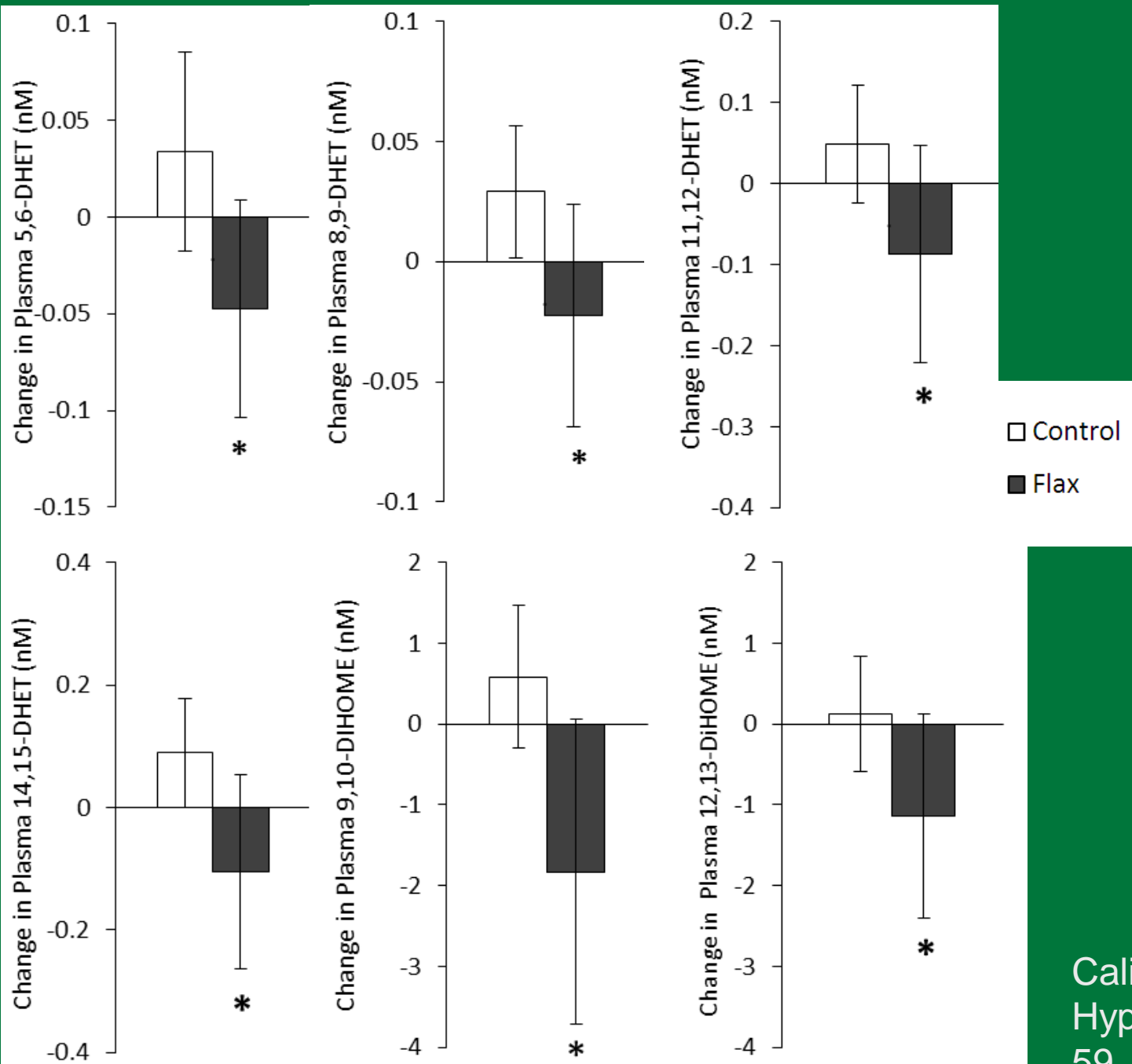
- ◆ Enzymatically produced by:
 - Cyclooxygenase
 - Lipoxygenase
 - Epoxygenase (Cytochrome P450)

Calder, P. C. (2006). *The American Journal of Clinical Nutrition*, 83(6 Suppl), 1505S.

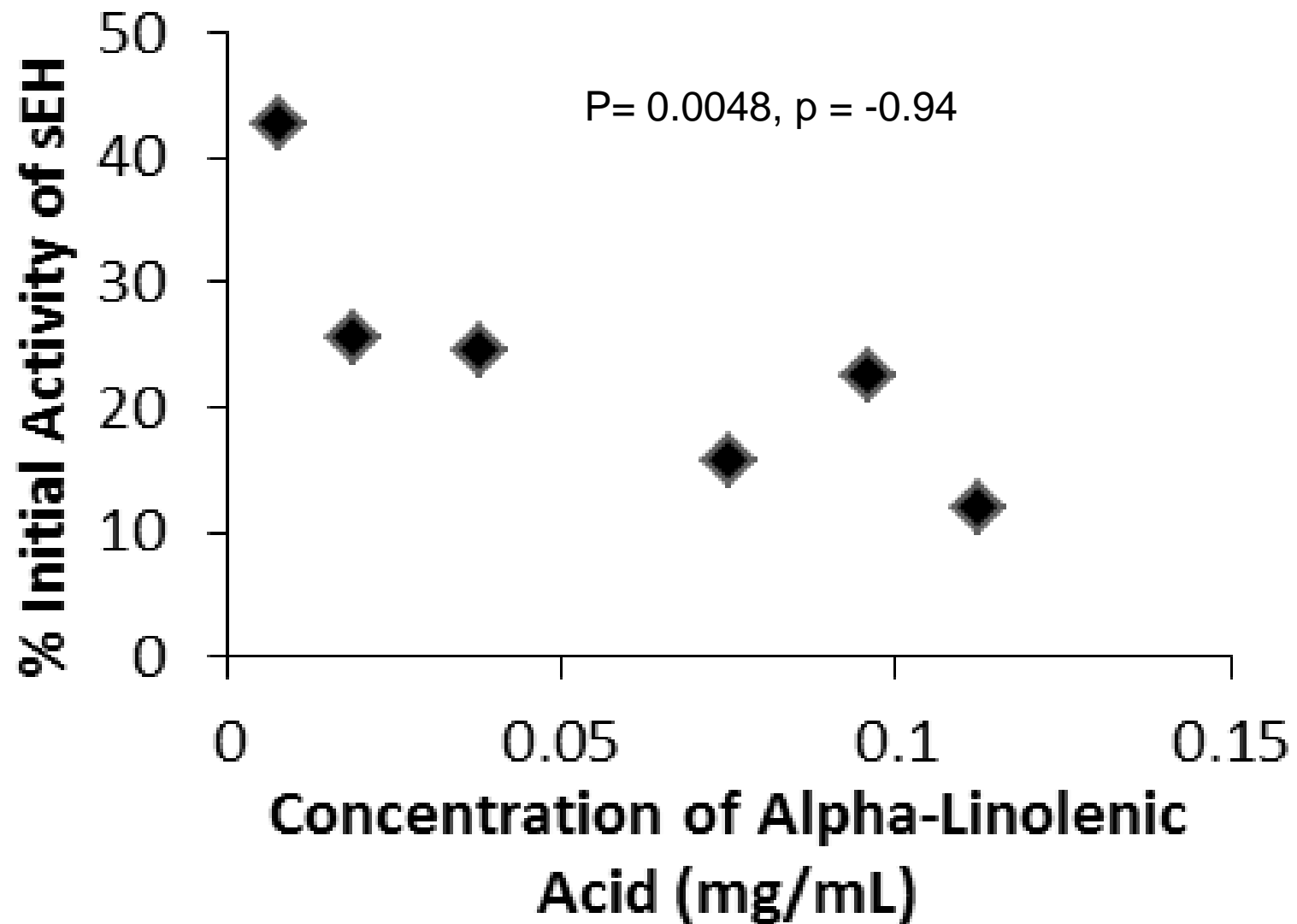
Calder, P. C. (2006). *Prostaglandins, Leukotrienes, and Essential Fatty Acids*, 75(3), 197.



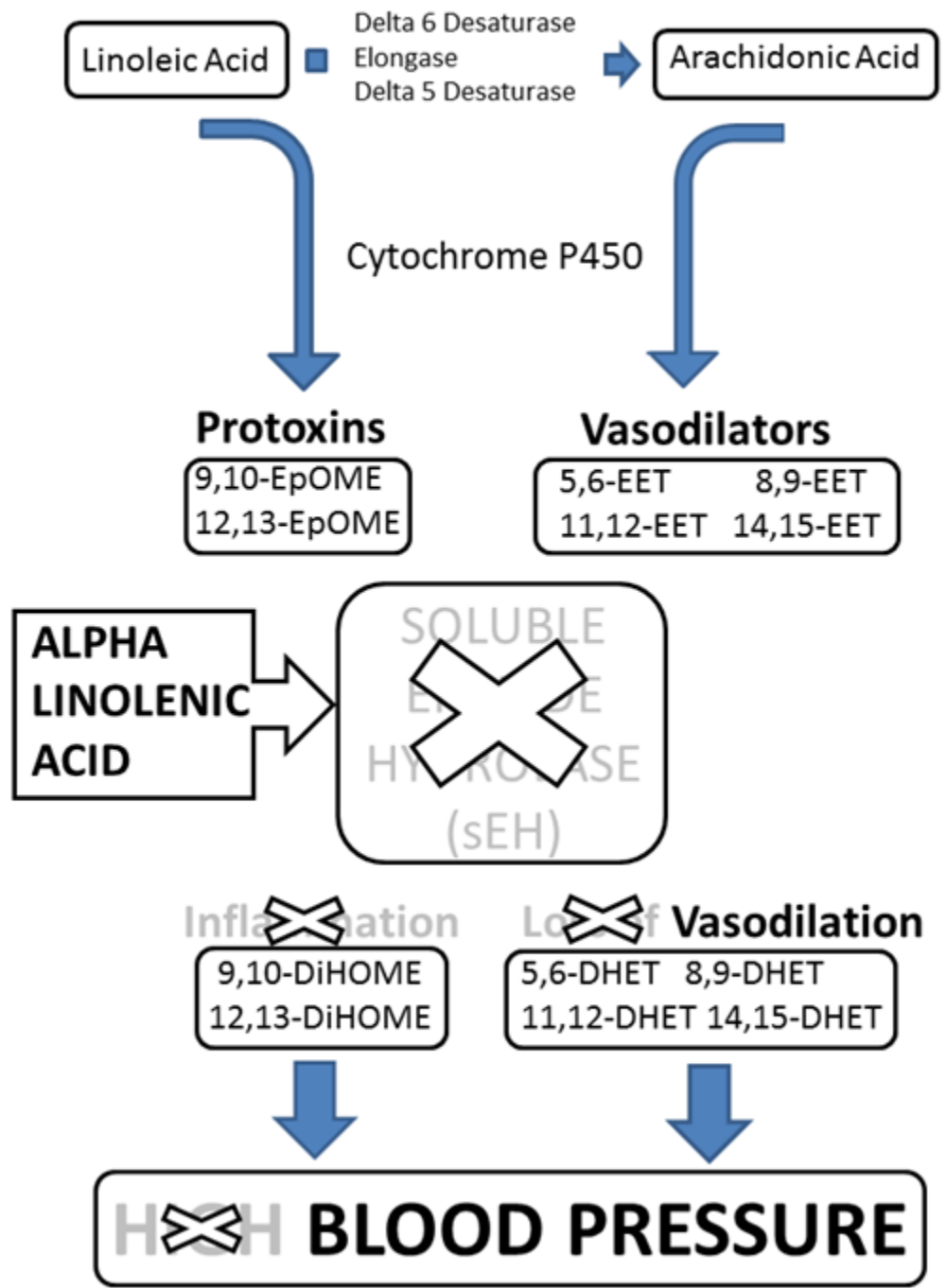
Changes in Oxylipins during the FlaxPAD Trial



Caligiuri et al,
Hypertension 64: 53-59, 2014



ALA Inhibits Soluble Epoxide Hydrolase



Flax-PAD Trial Final Conclusions

- Dietary flaxseed induced potent reductions of SBP and DBP in patients with PAD.**
- The magnitude of the effect on BP would be expected to result in a significant decrease by over 50% in the incidence of cardiovascular events over time.**
- Dietary flaxseed decreases total and LDL cholesterol in PAD patients.**
- THIS IS THE LARGEST EFFECT ON BP EVER SHOWN BY A DIETARY INTERVENTION**

Is it time to think of new ways to control hypertension?

Why not?

- Current therapies are partly effective (33% is uncontrolled)
- Diet can control cholesterol & BP
 - Diet is cheaper than drugs
 - Flaxseed tastes better than a pill
 - It has less side effects
- It provides critical alternatives for 3rd world countries that cannot afford medication
- It can stimulate ag economies like Canada & the USA



MY THANKS TO THE PEOPLE!

Janice Meseyton; Bruce McKeown;

**Linda Malcolmson; Tony Tweed;
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Kelley Fitzpatrick

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Drs Harold Aukema & Michel Aliani

Drs Amir Ravandi & Bram Ramjiawan





MY THANKS TO OUR PARTNERS!

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Food Development Centre

AAFC; CIGI; Pizzey's

St Boniface Hospital Foundation

CIHR; Western Grains Res Fdn

Manitoba Health Research Council

**Heart & Stroke Foundation of
Canada**





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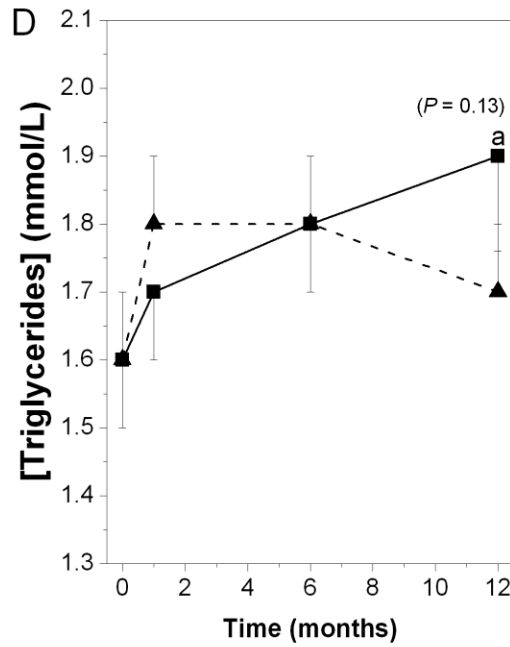
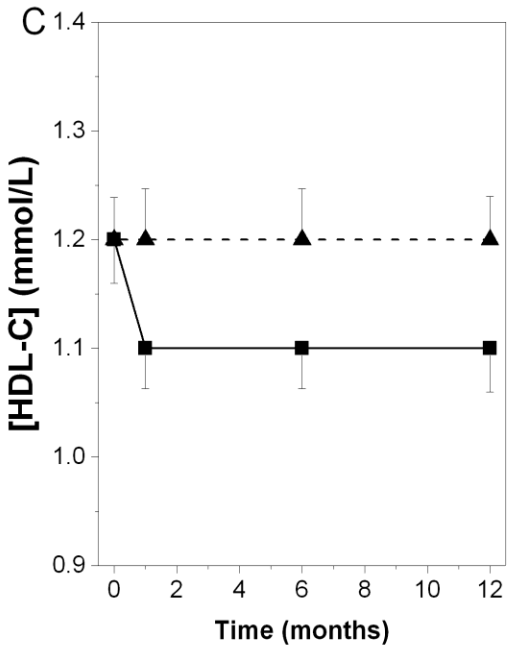
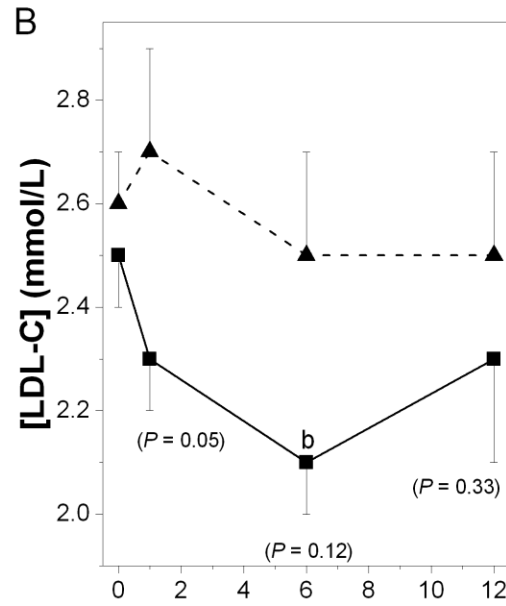
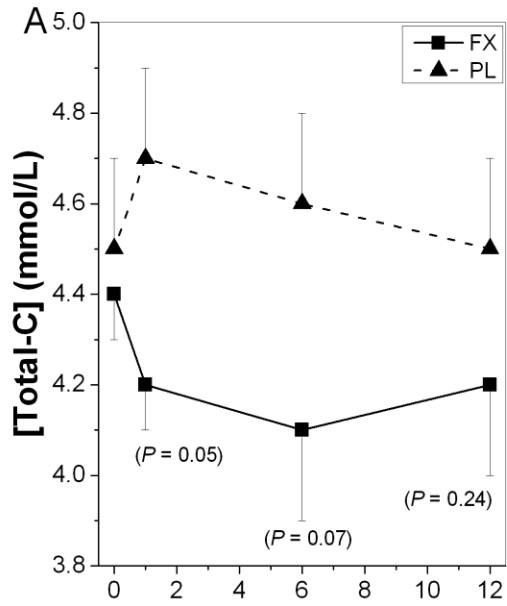
Chantal Bassett, Amanda Patenaude, Brad Ander, Alex Austria, Andrea Edel, Mirna Chahine; Elena Dibrov, Renee LaVallee, Thane Maddaford, Justin Deniset, Dave Blackwood, Andrew Francis, Melanie Richard, Richelle McCullough, Delfin Rodriguez, and Stephanie Caligiuri



Who needs Red Bull??

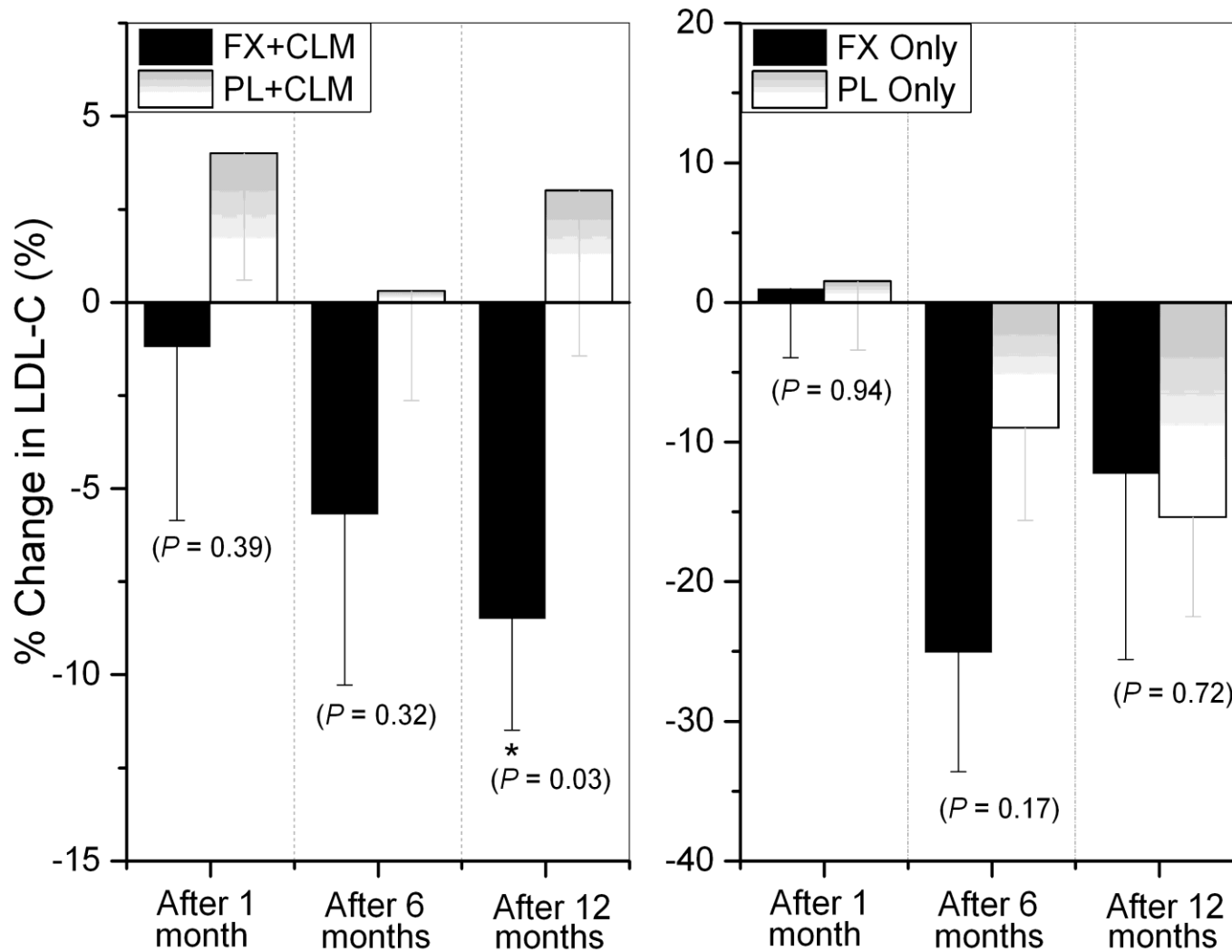
Flaxseed can
make you fly!!!



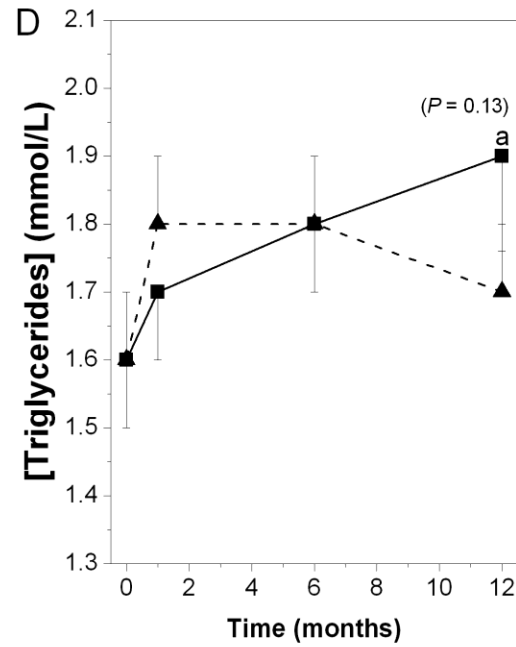
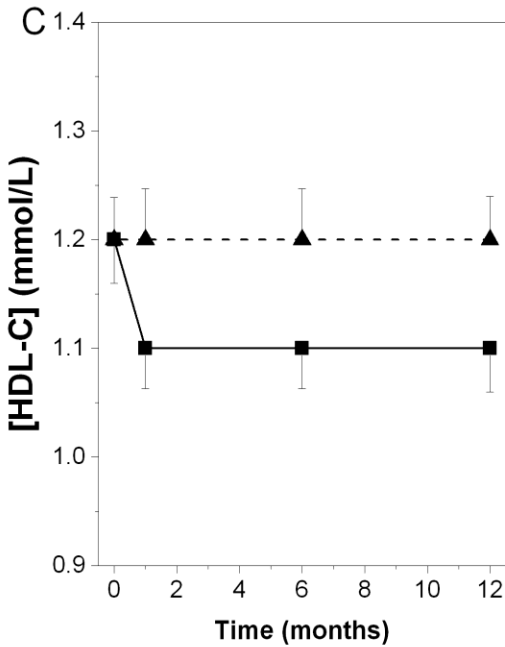
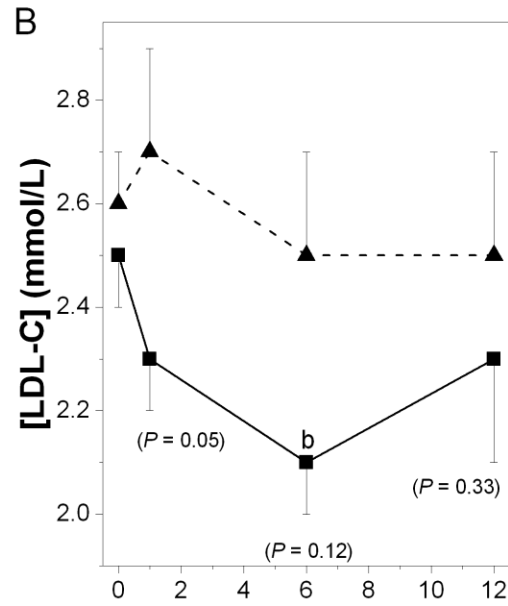
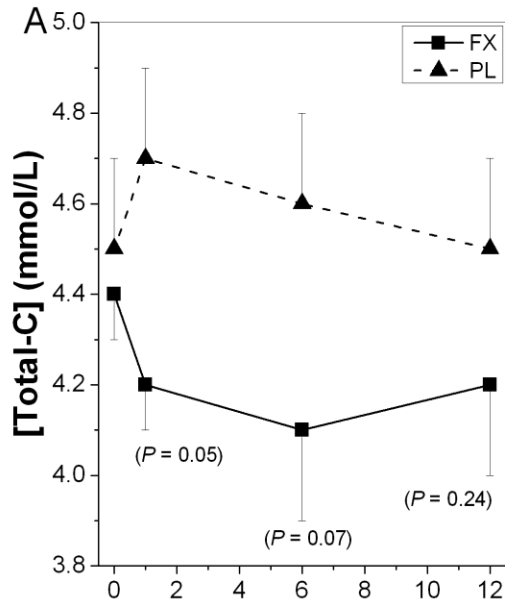


What about circulating LDL and total cholesterol?

Does flaxseed interfere or help with the action of cholesterol-lowering medications?







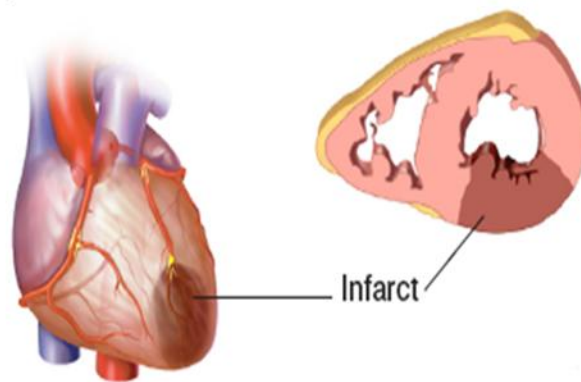
What about circulating LDL and total cholesterol?

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- **Diet can control cholesterol & BP**
- **Diet is cheaper than drugs**
- **Flaxseed tastes better than a pill**
- **It has fewer side effects**
- **It provides critical alternatives for developing nations that cannot afford medication**
- **It can stimulate ag economies in Canada**

Dietary flaxseed decreases myocardial infarct size

Every 5% increase in infarct size is associated with a 20% increase in 1-year all-cause mortality or heart failure hospitalization.



Dietary flaxseed reduces cardiac fibrosis and inflammation

