

Cocoa in cardiovascular medicine. Remedy or hype?



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Conflict of interest: none

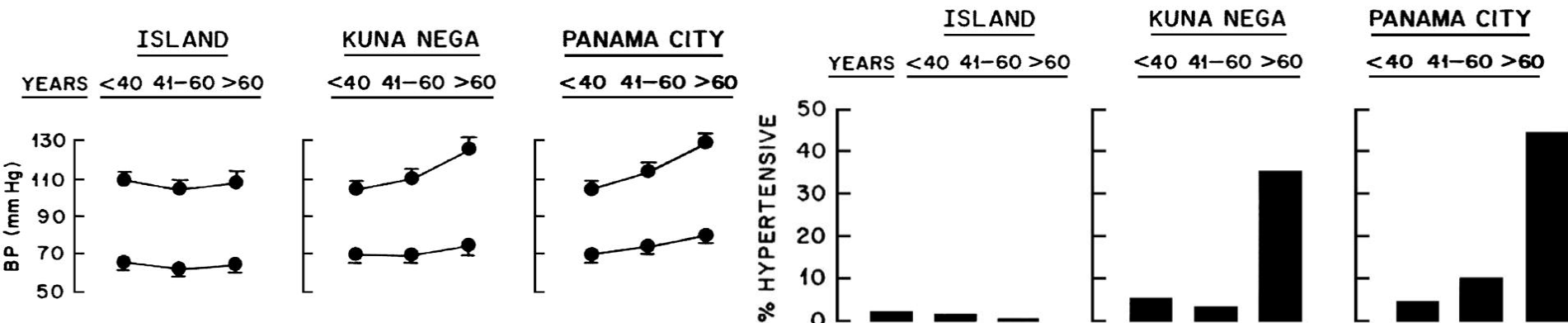
Chocolate: Popular for thousands of years

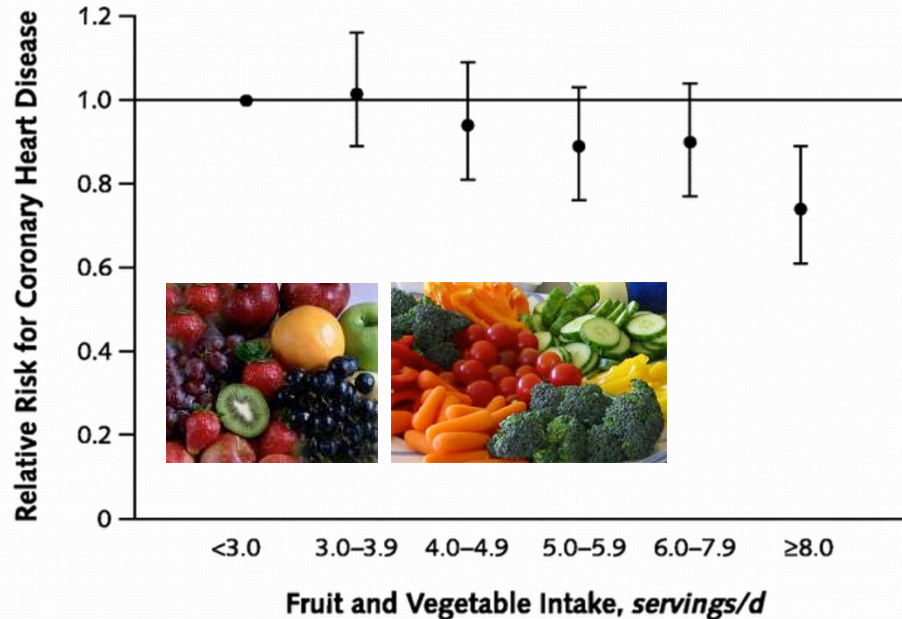
In Honduras, archaeologists uncovered elaborately designed bowls dating to 1600 BC, and believe that the Aztecs used these bowls to serve **liquid chocolate** thousands of years ago.

Cocoa was revered by Mayans, and was considered a food of the gods. This is how the cocoa tree got its scientific name *theobroma cacao*, from the Greek words "**theo**" (god) and "**broma**" (drink).



The Chocolate Story begins....





Intake of fruits and vegetables and CAD risk

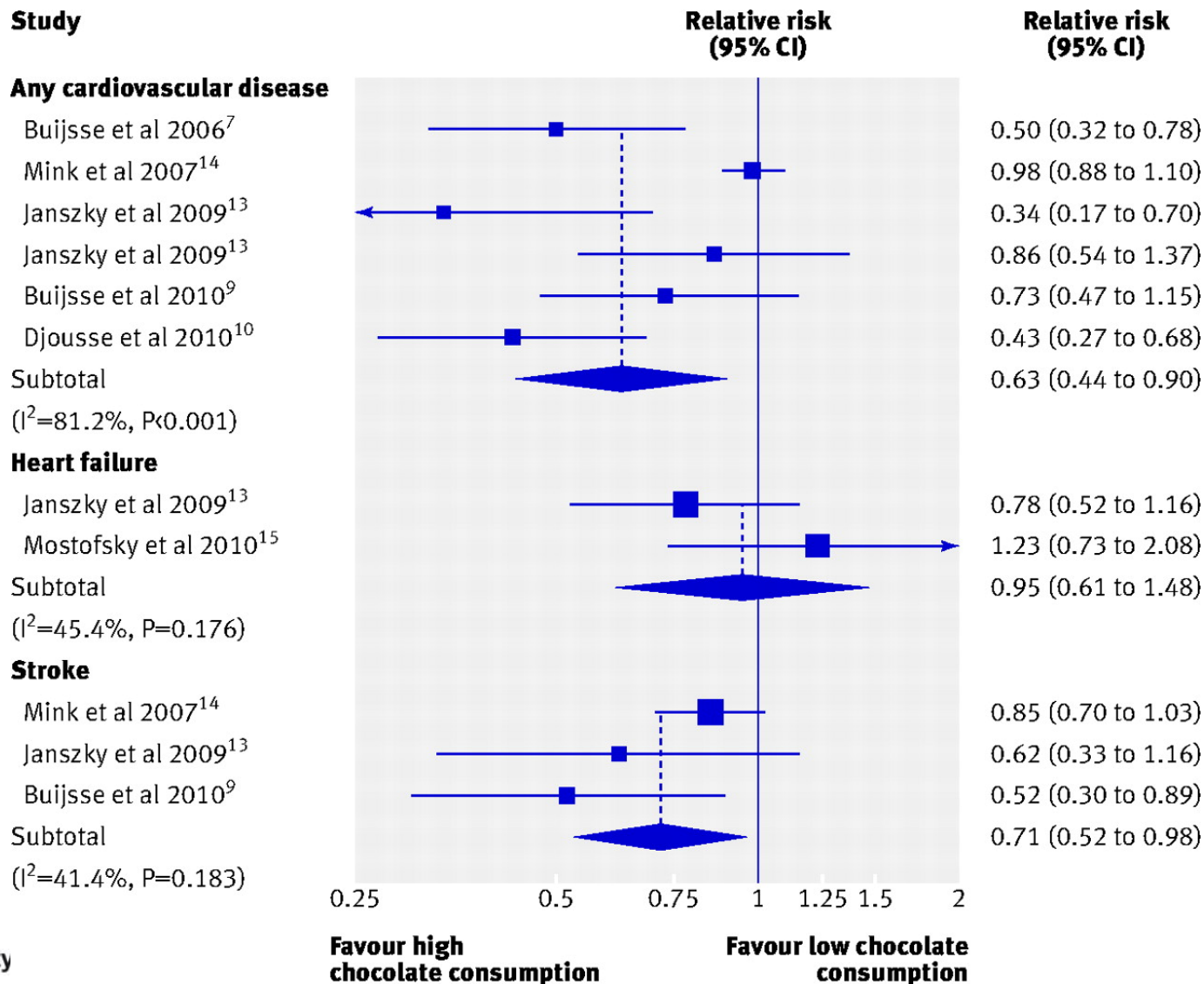
Joshiyura, K. J. et. al. Ann Intern Med 2001

Cocoa intake and 15-year mortality among elderly men (n=470)

Mortality Data	Tertile of Cocoa Intake			P Value for Trend
	Lowest (<0.50 g/d)	Middle (0.50-2.25 g/d)	Highest (>2.25 g/d)	
No. of subjects	161	147	162	NA
Person-time, person-years	1481	1573	1854	NA
All-cause mortality				
No. (%) of cases	122 (75.8)	100 (68.0)	92 (56.8)	NA
Mortality (per 1000 person-years)	82.4	63.6	49.6	NA
RR (95% CI)				
Age adjusted	1.00	0.76 (0.58-0.99) 24%	0.57 (0.43-0.75) 43%	<.001

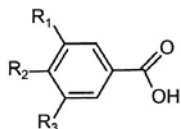


Relative Risks for CV disease, heart failure, and stroke in adults with higher levels of chocolate consumption compared with lower levels



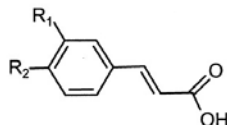
Polyphenols: Chemical Structure

Hydroxybenzoic acids



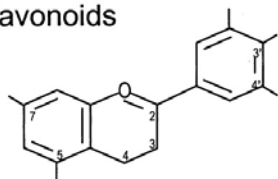
$R_1 = R_2 = \text{OH}, R_3 = \text{H}$: Protocatechuic acid
 $R_1 = R_2 = R_3 = \text{OH}$: Gallic acid

Hydroxycinnamic acids

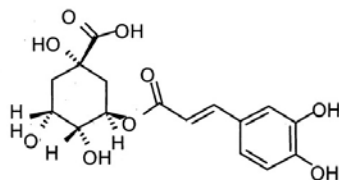


$R_1 = \text{OH}$: Coumaric acid
 $R_1 = R_2 = \text{OH}$: Caffeic acid
 $R_1 = \text{OCH}_3, R_2 = \text{OH}$: Ferulic acid

Flavonoids

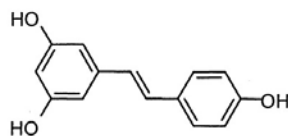


See Figure 2



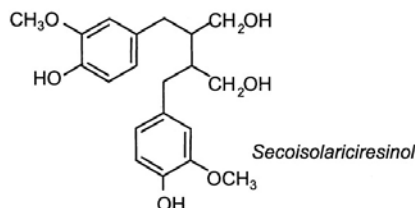
Chlorogenic acid

Stilbenes



Resveratrol

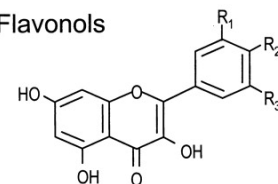
Lignans



Secoisolariciresinol

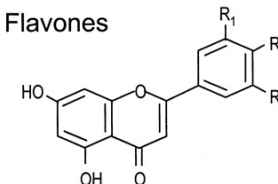
Polyphenols

Flavonols



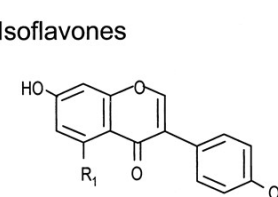
$R_2 = \text{OH}; R_1 = R_3 = \text{H}$: Kaempferol
 $R_1 = R_2 = \text{OH}; R_3 = \text{H}$: Quercetin
 $R_1 = R_2 = R_3 = \text{OH}$: Myricetin

Flavones



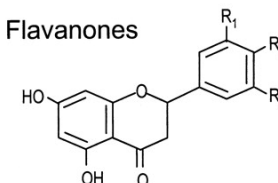
$R_1 = \text{H}; R_2 = \text{OH}$: Apigenin
 $R_1 = R_2 = \text{OH}$: Luteolin

Isoflavones



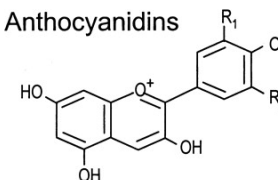
$R_1 = \text{H}$: Daidzein
 $R_1 = \text{OH}$: Genistein

Flavanones



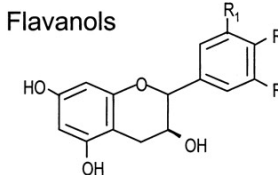
$R_1 = \text{H}; R_2 = \text{OH}$: Naringenin
 $R_1 = R_2 = \text{OH}$: Eriodictyol
 $R_1 = \text{OH}; R_2 = \text{OCH}_3$: Hesperetin

Anthocyanidins

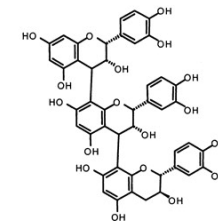


$R_1 = R_2 = \text{H}$: Pelargonidin
 $R_1 = \text{OH}; R_2 = \text{H}$: Cyanidin
 $R_1 = R_2 = \text{OH}$: Delphinidin
 $R_1 = \text{OCH}_3; R_2 = \text{OH}$: Petunidin
 $R_1 = R_2 = \text{OCH}_3$: Malvidin

Flavanols



$R_1 = R_2 = \text{OH}; R_3 = \text{H}$: Catechins
 $R_1 = R_2 = R_3 = \text{OH}$: Gallocatechin



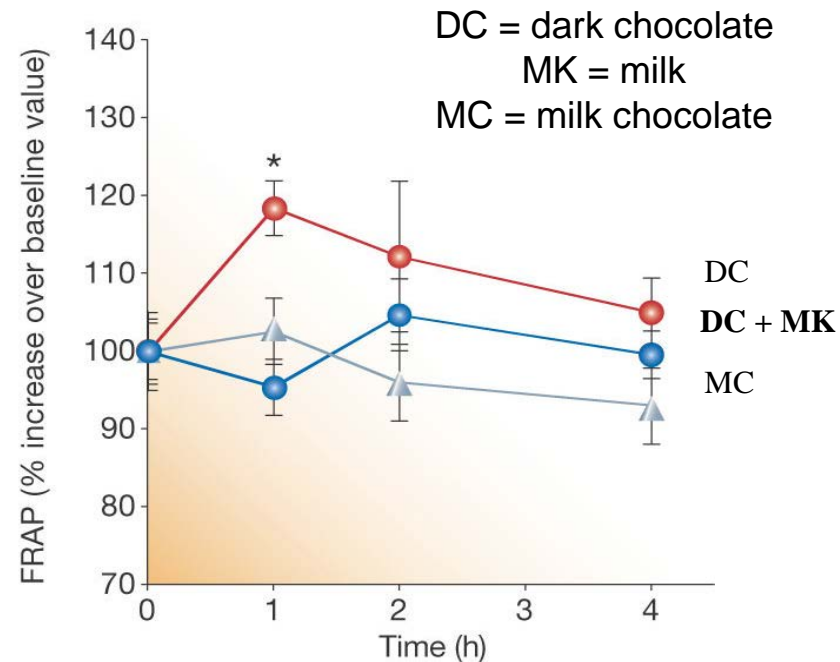
Trimeric procyanidin

Source	Flavanol content per mg/kg or mg/L
Chocolate	460-610
Beans	350-550
Apricot	100-250
Cherry	50-220
Peach	50-140
Blackberry	130
Apple	20-120
Green tea	100-800
Black tea	60-500
Red wine	80-300
Cider	40

Catechins and Epicatechins found in food

Manach C et al.
Am J Clin Nutr 2004

Plasma antioxidants from chocolate

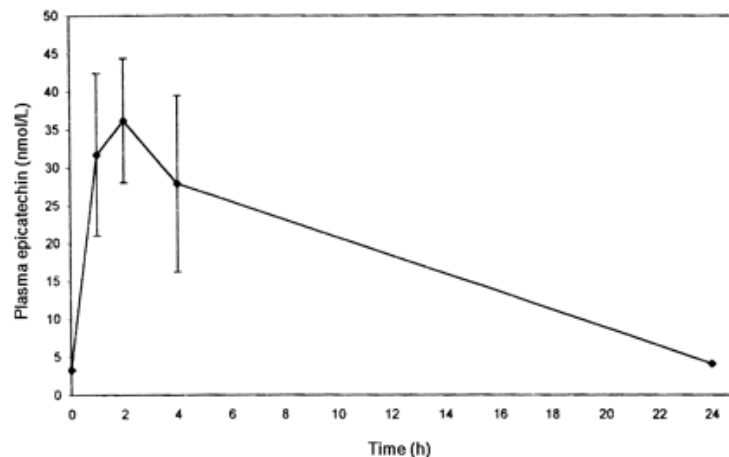


FRAP = ferric-reducing antioxidant potential

Serafini M; Nature. 2003

Plasma concentration of epicatechins after ingestion of dark chocolate

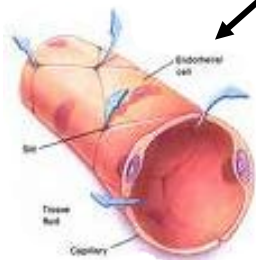
Ying Wan et al.
Am J Clin Nutr 2001



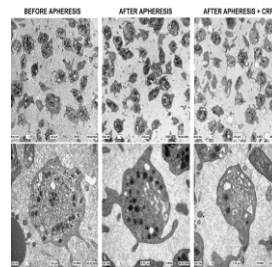
Cocoa as a remedy?



**Blood Pressure
Reduction**

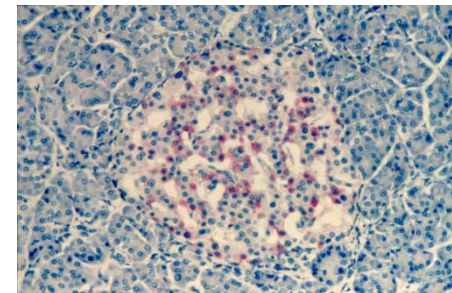


**Improved
endothelial function**



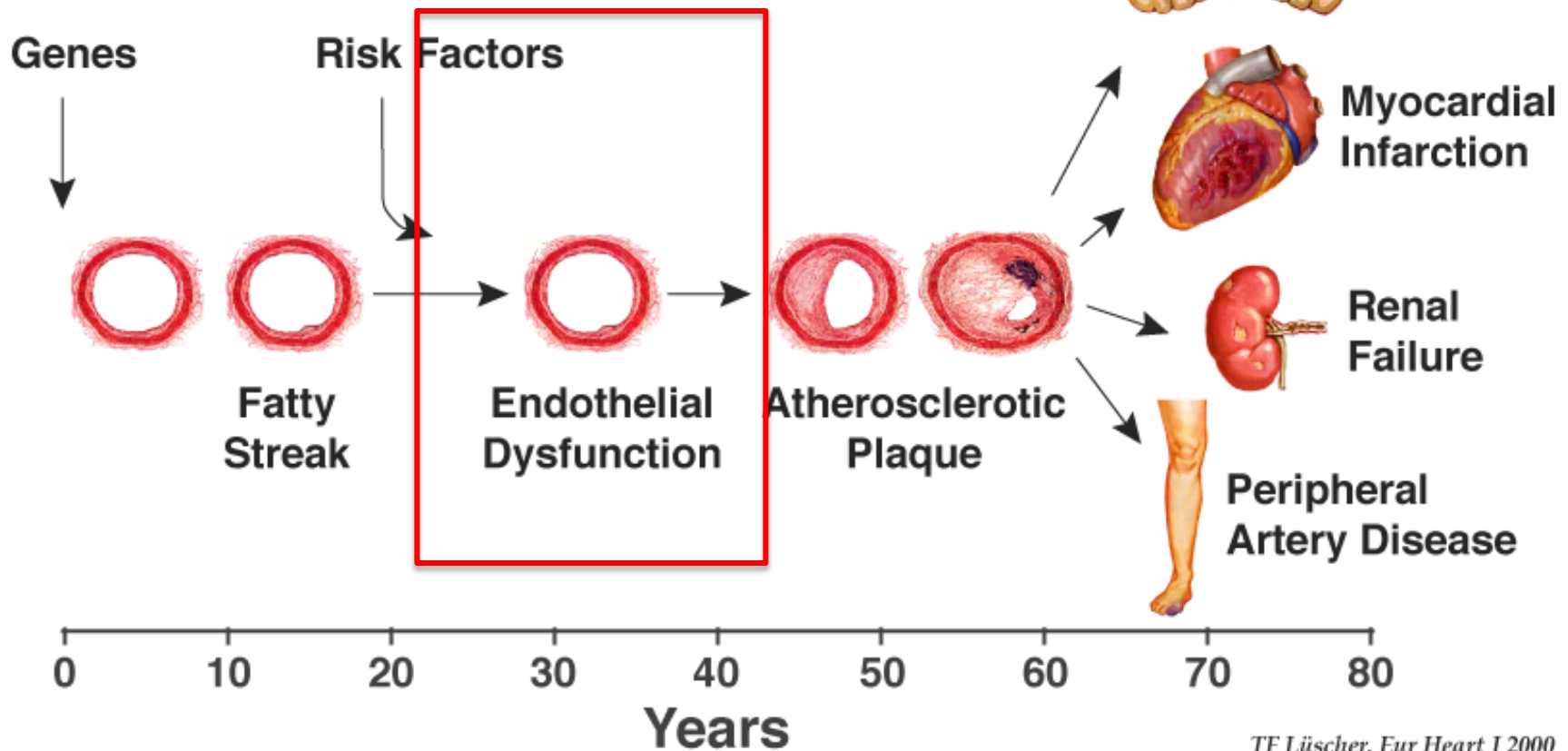
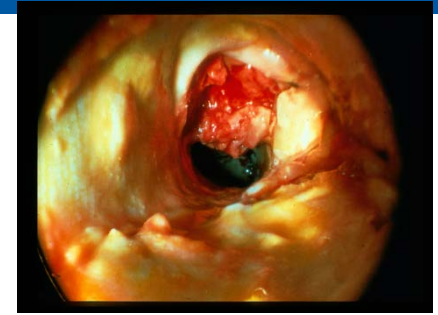
**Reduced
platelet reactivity**

**Other:
Anti-Inflammatory**

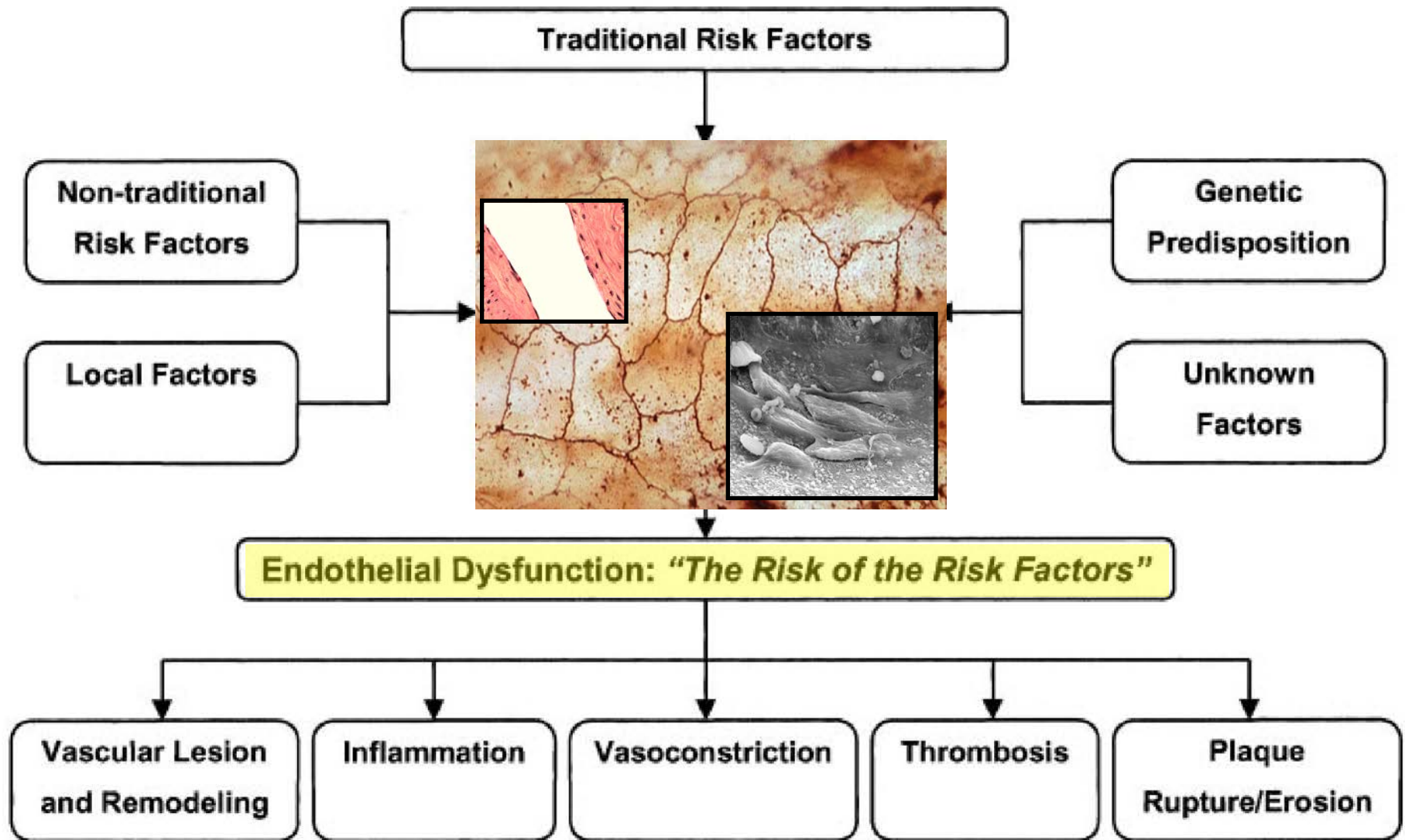


**Improved
insulin sensitivity**

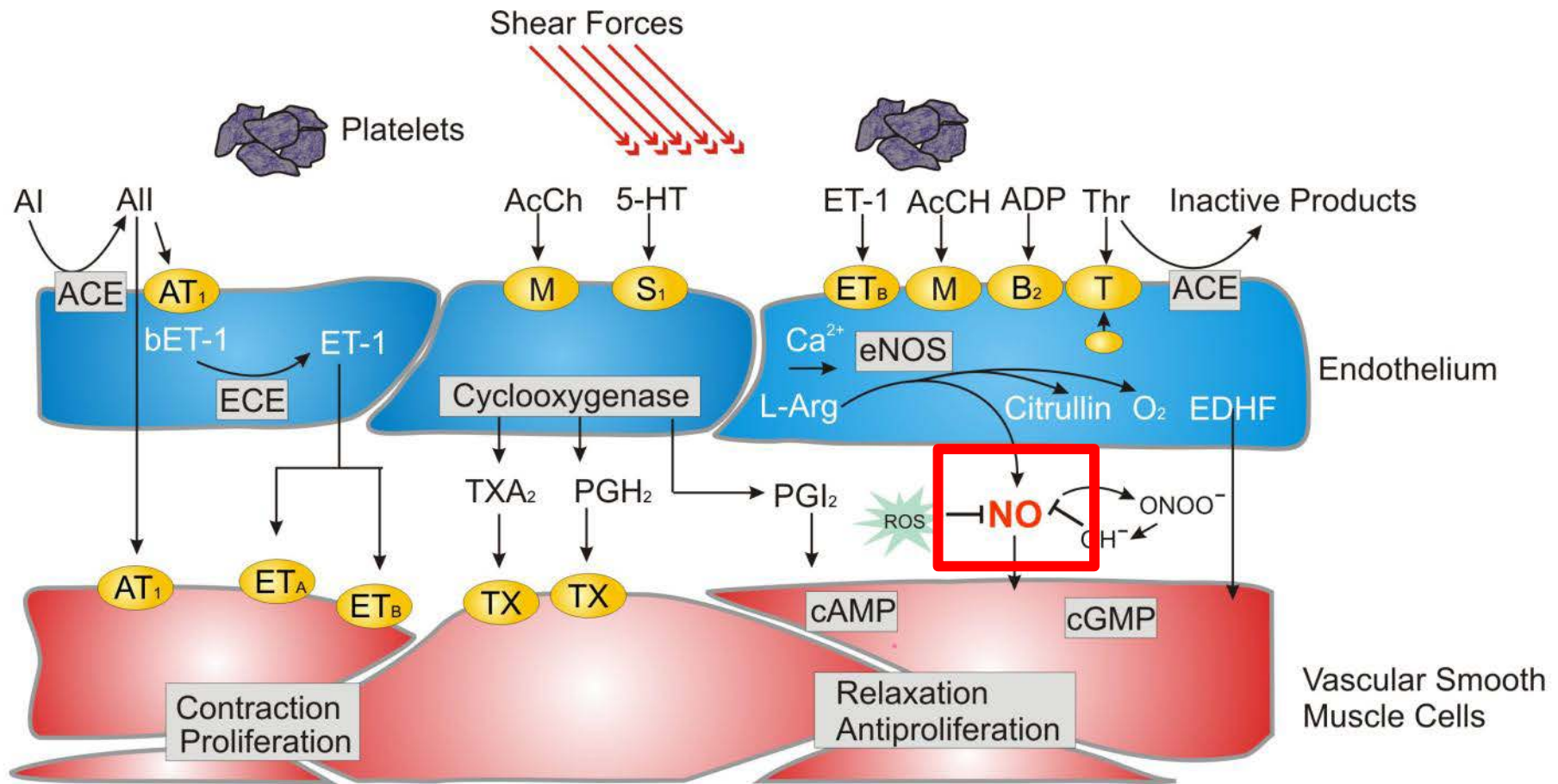
The Pathogenesis of Atherosclerosis – *Vascular function*



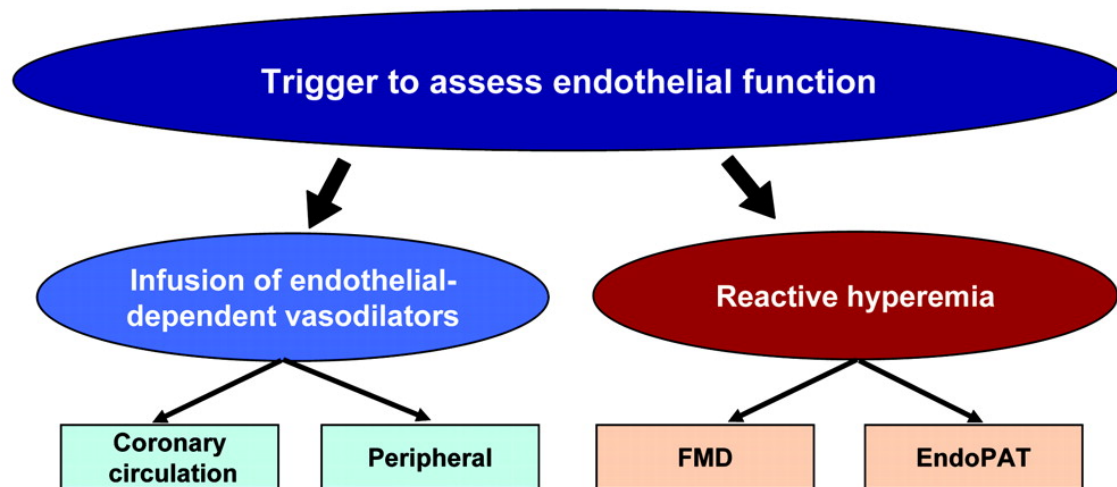
Endothelial Dysfunction



Endothelial function. Mechanisms

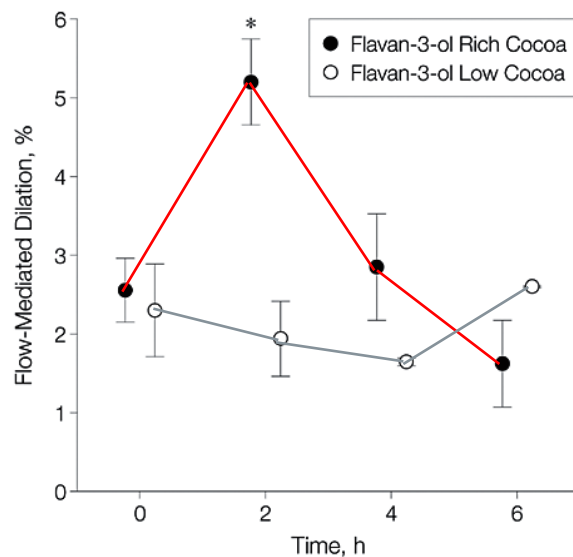
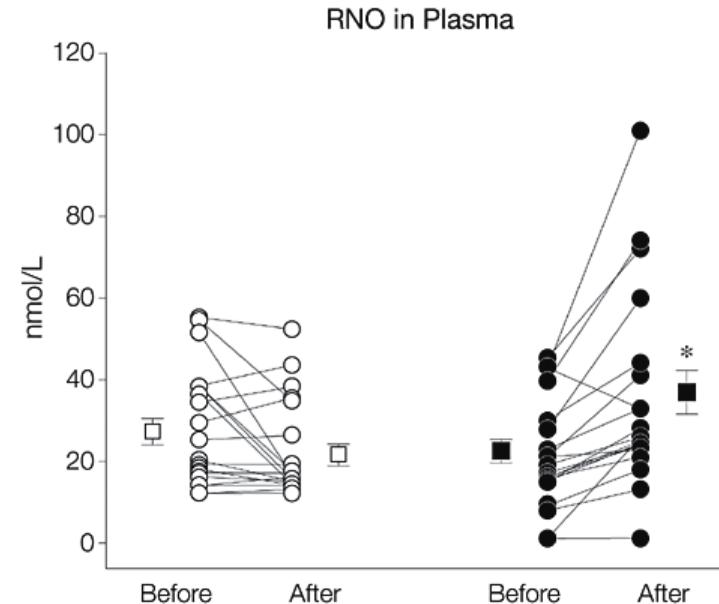
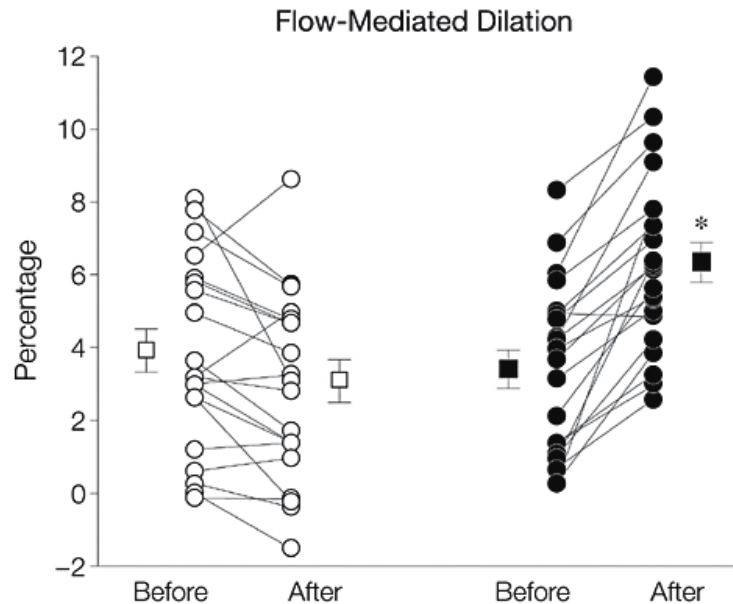


The principles of the most commonly used methods to assess endothelial function



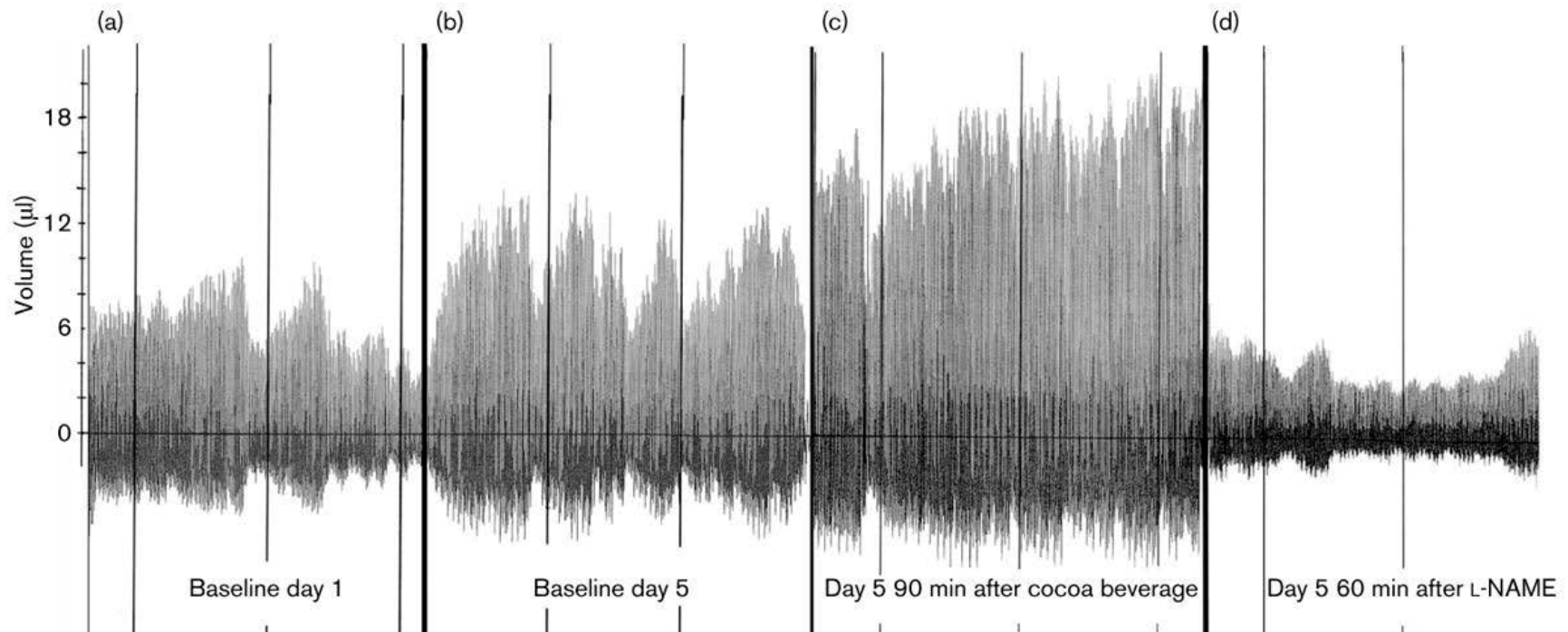
Non-Invasive	-	-	+	+
Predictive	++	++	++	+
Reversible	+	+	+	+
Control vessel	+ (control segments)	+	-	++
Not expensive	-	+	+	+/-
Low-risk	+/-	+	++	++
Operator independent	+/-	+/-	-	++
Easy to use	-	-	-	+

Acute consumption of a flavanol-rich cocoa drink reverses endothelial dysfunction in patients with cvRF



- High (176 mg/100 mL) amount of Flavan-3-ols
- Low (<10 mg/100 mL) amount of Flavan-3-ols

Central role of Nitric Oxide



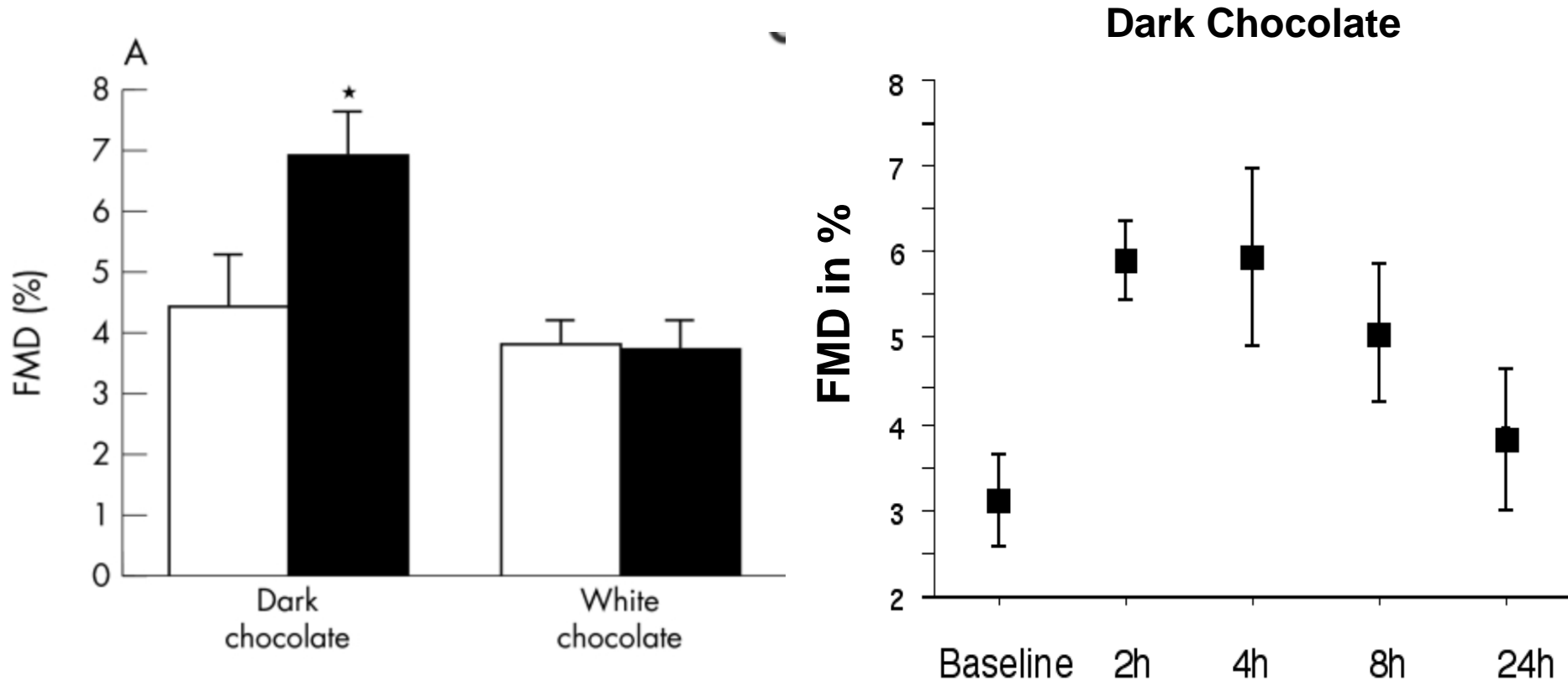
Baseline demonstrates normal variability in digital pulse wave amplitude

After 4 days of ingestion of flavanol-rich cocoa there is an increase more than 12 h after the last dose of cocoa ($P = 0.01$)

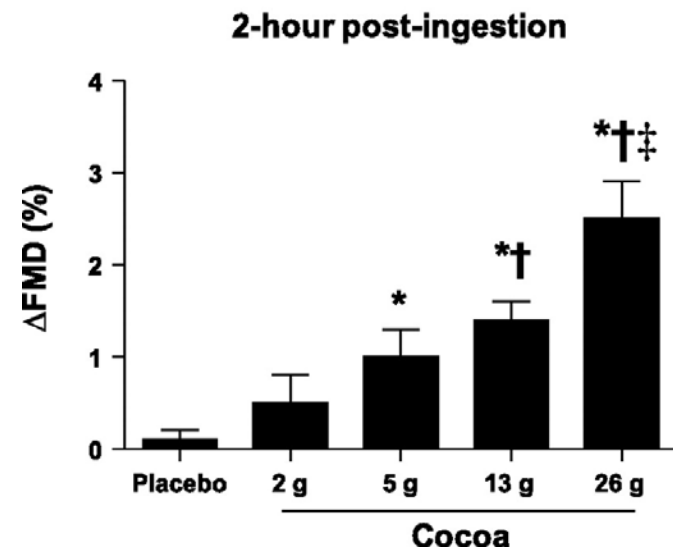
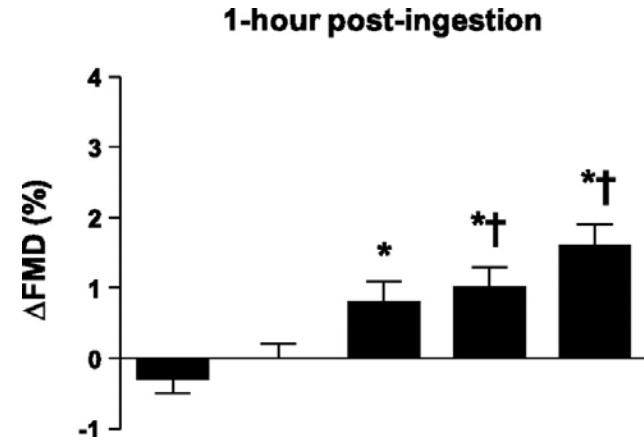
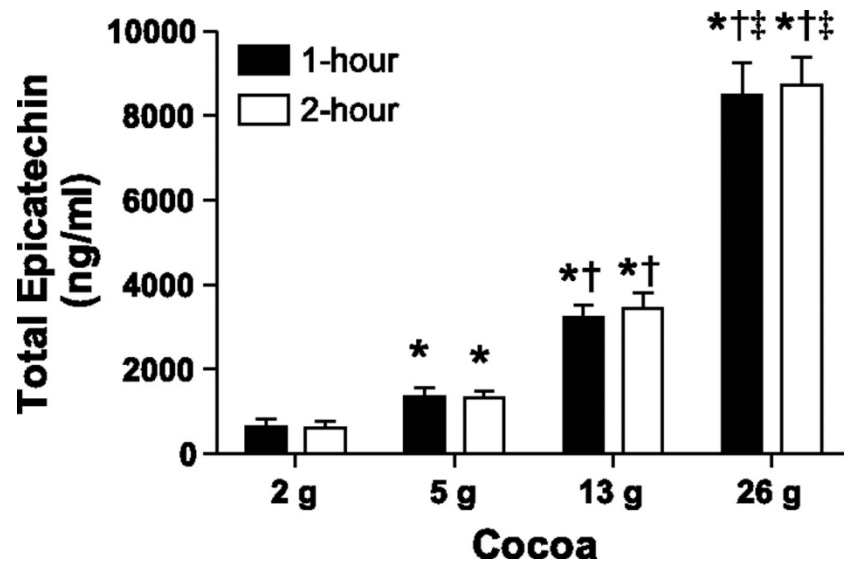
Exposure to an additional 230 ml dose of cocoa led to a further increase 90 min later ($P = 0.01$)

After ingestion of cocoa on day 5 the nitric oxide synthesis inhibitor, L-NAME, had a dramatic effect in reversing dilation ($P = 0.004$)

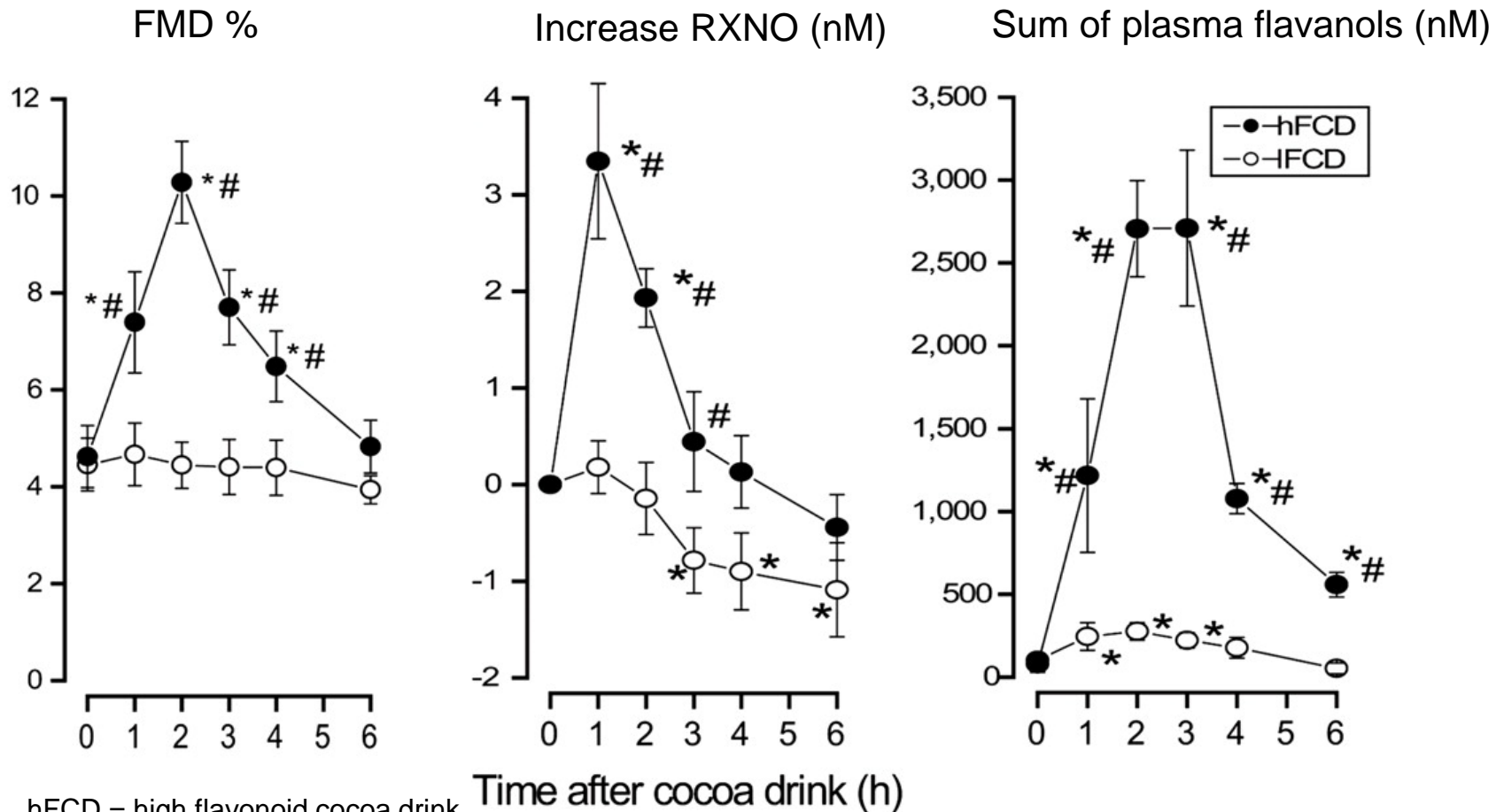
Effect and time course of commercially available flavanol-rich chocolate on vascular function in young smokers



Dose-Response relationship after Cocoa intake

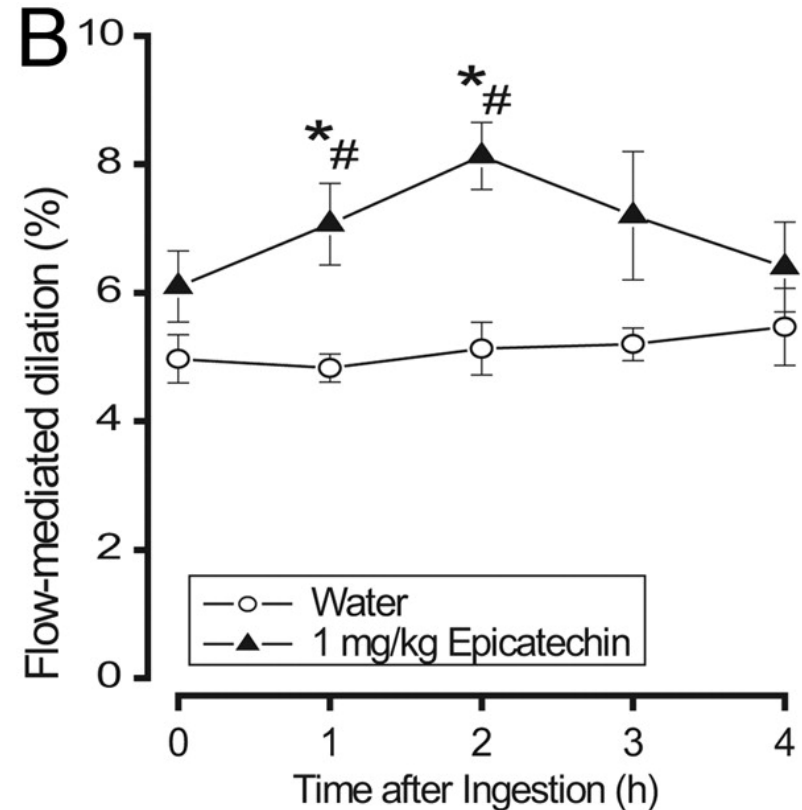
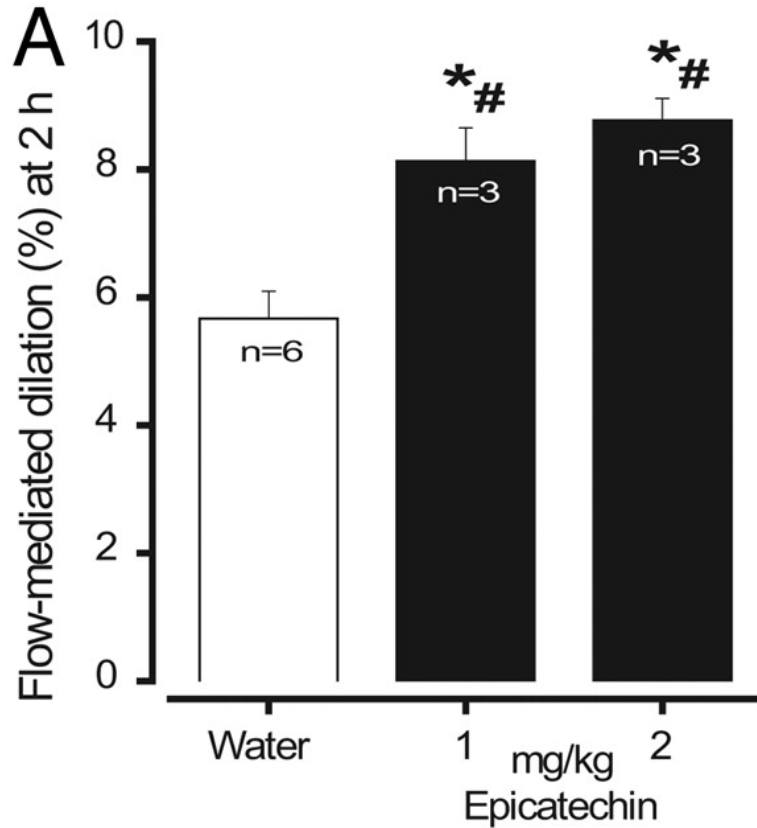


Parallel elevation of circulating NO species, plasma flavanols and enhancement of endothelial function

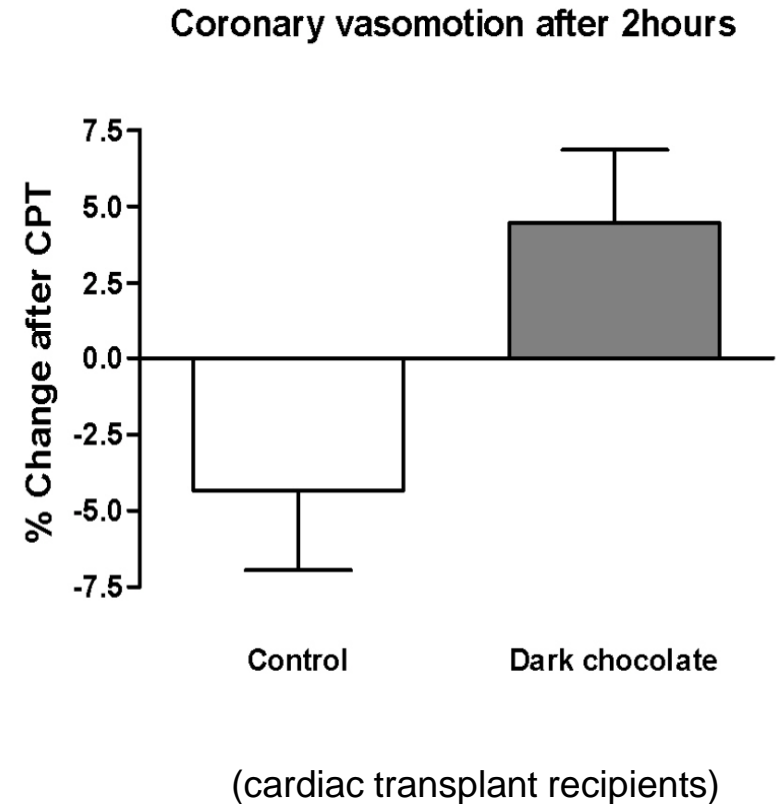
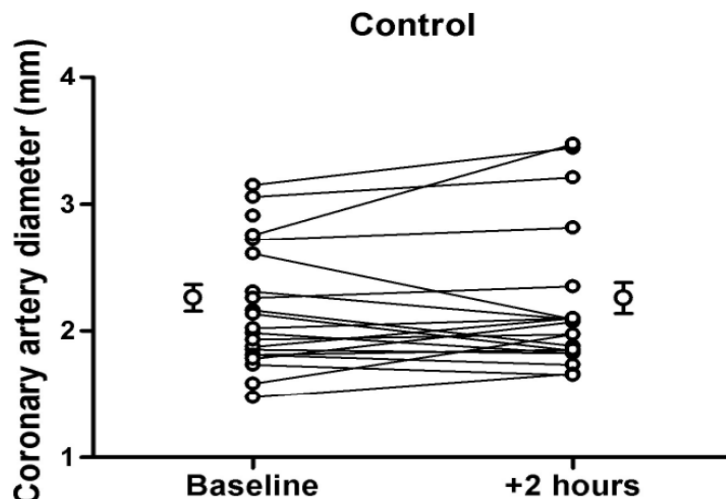
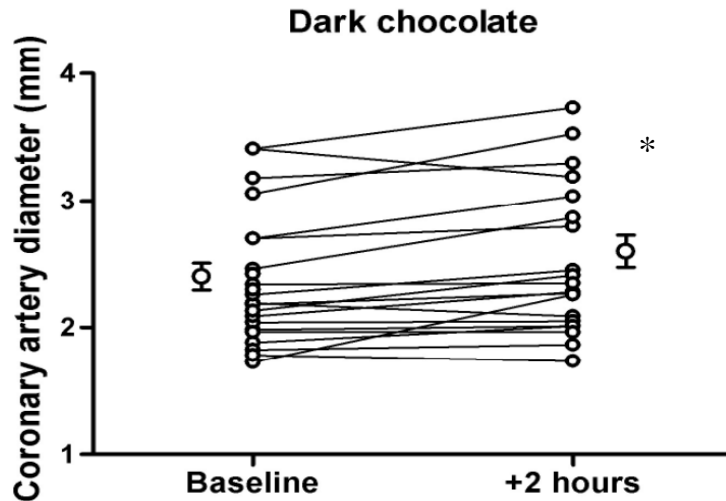


hFCD = high flavonoid cocoa drink
 lFCD = low flavonoid cocoa drink
 RXNO = plasma nitroso species

Proof of concept: Vascular response after oral ingestion of (-)-Epicatechin

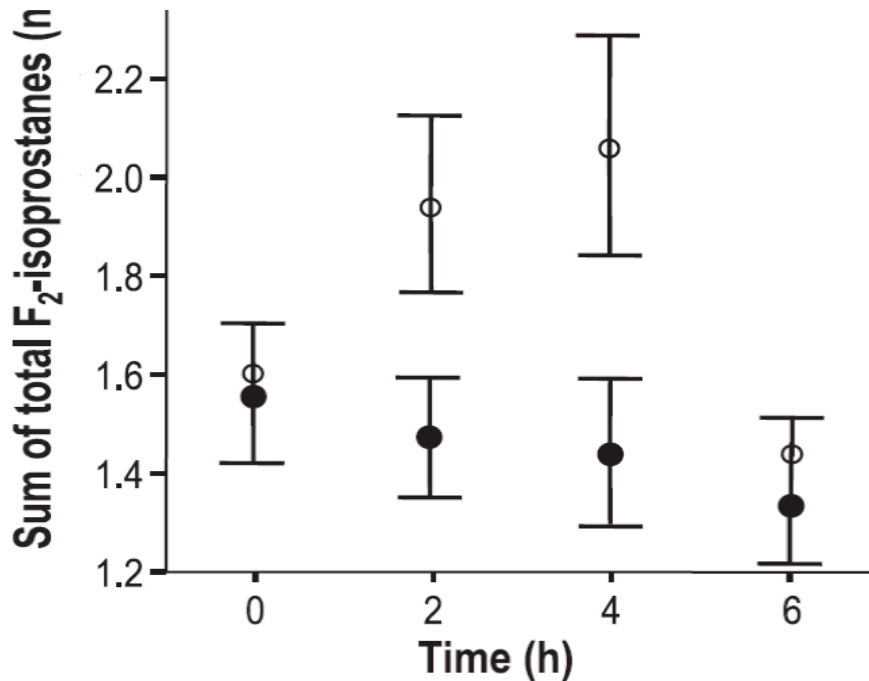


Improvement in endothelial function also at the level of the coronary arteries



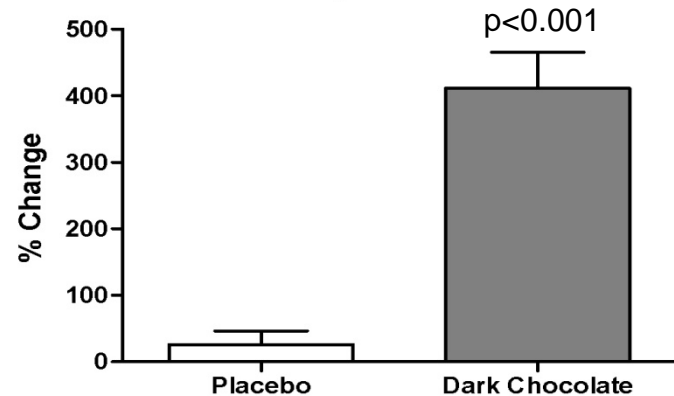
Cocoa decreases Isoprostanes (indicators of in vivo lipid peroxidation) in certain patients

Oxidative stress-mediated
increase in Isoprostanes with exercise

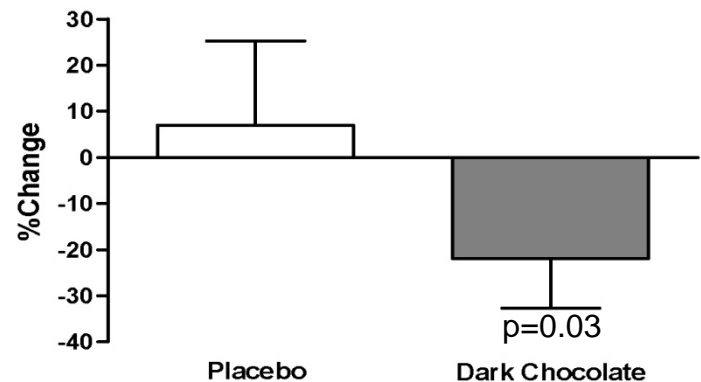


Wiswedel I et al. Free Radic Biol Med 2004

Epicatechin

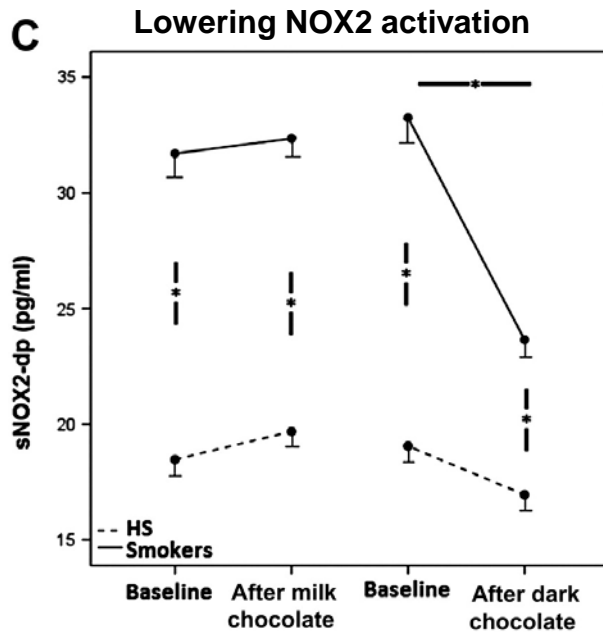


8-Isoprostanes

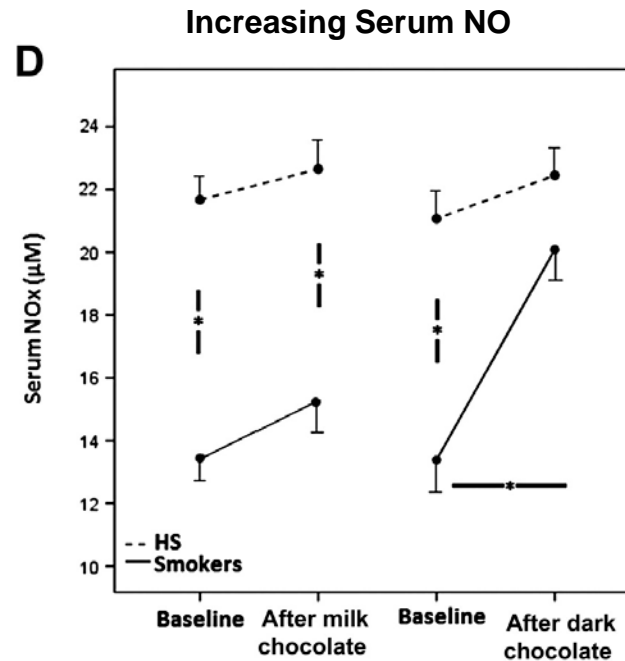


Flammer AJ, et al, Circulation 2007

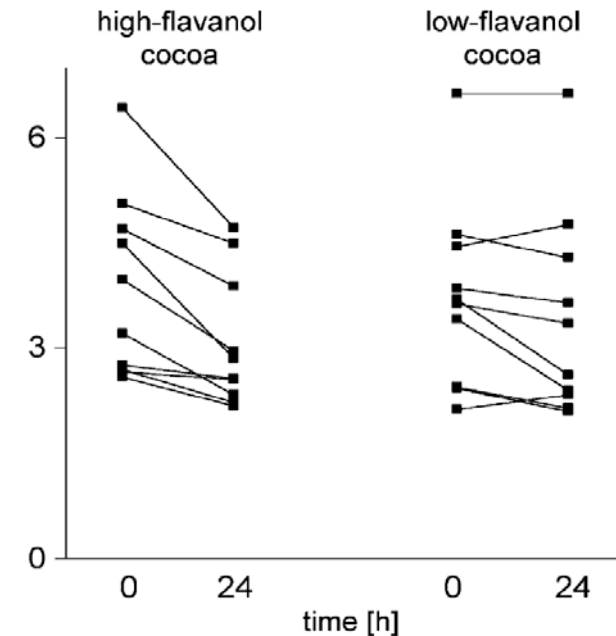
Lowering NOX2 activation (catalytic core of NADPH oxidase), increasing Serum NO and lowering arginase activity



Loffredo L et al. Heart 2011

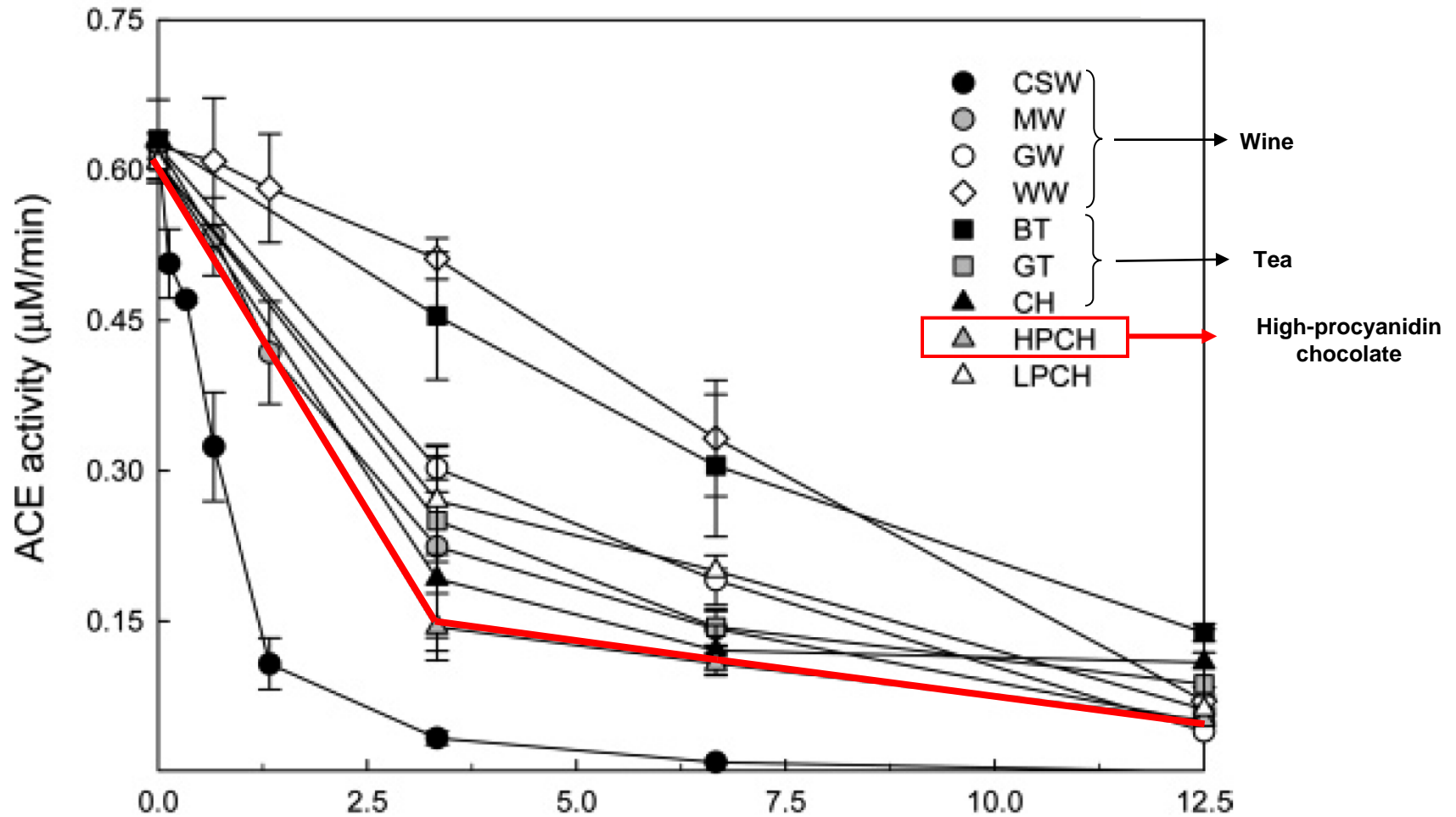


Erythrocyte arginase activity in vivo

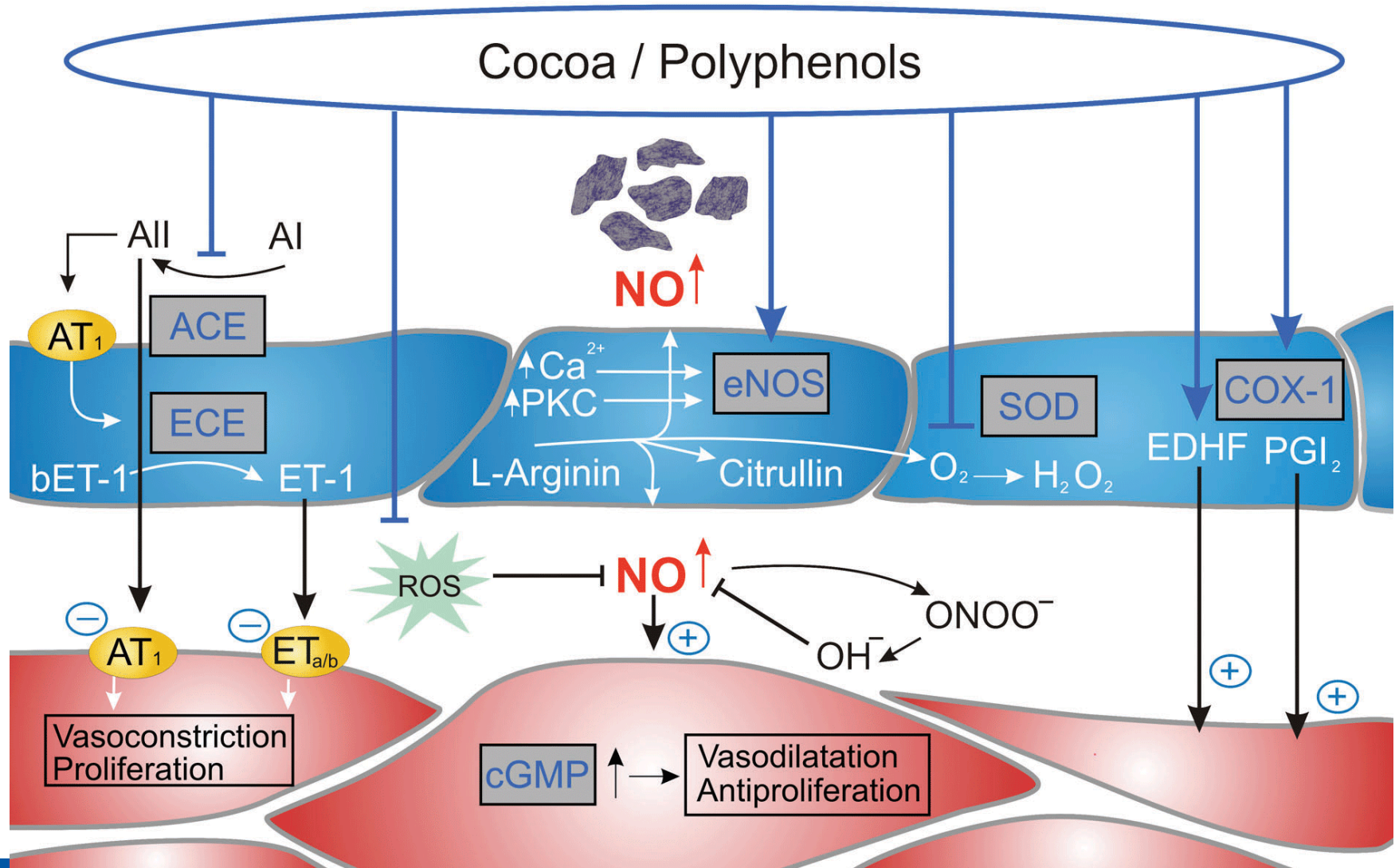


Schnorr O et al. Arch Biochem Biophys. 2008

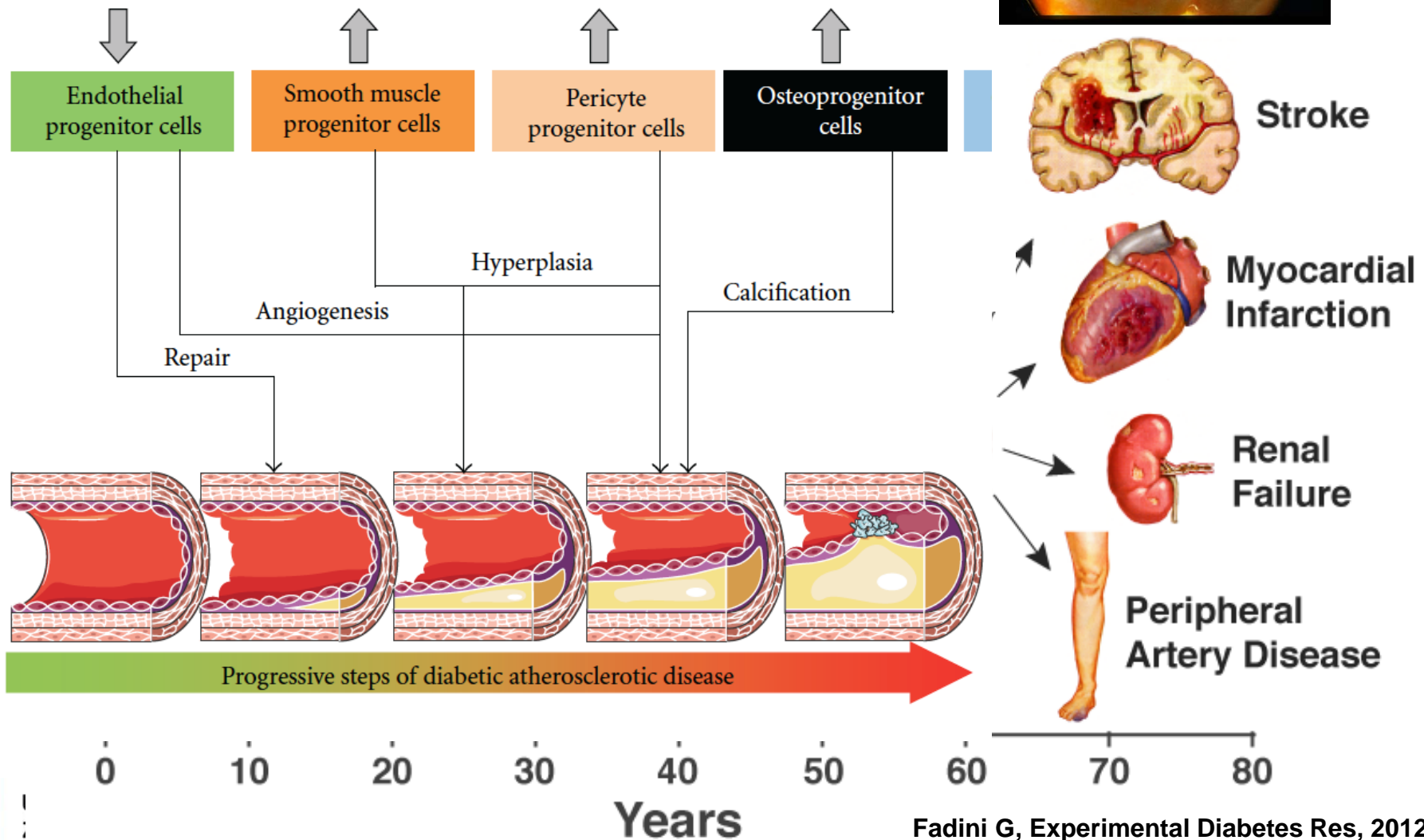
Effect of flavanol-rich foods on ACE activity in vitro



Summary of potential mechanisms

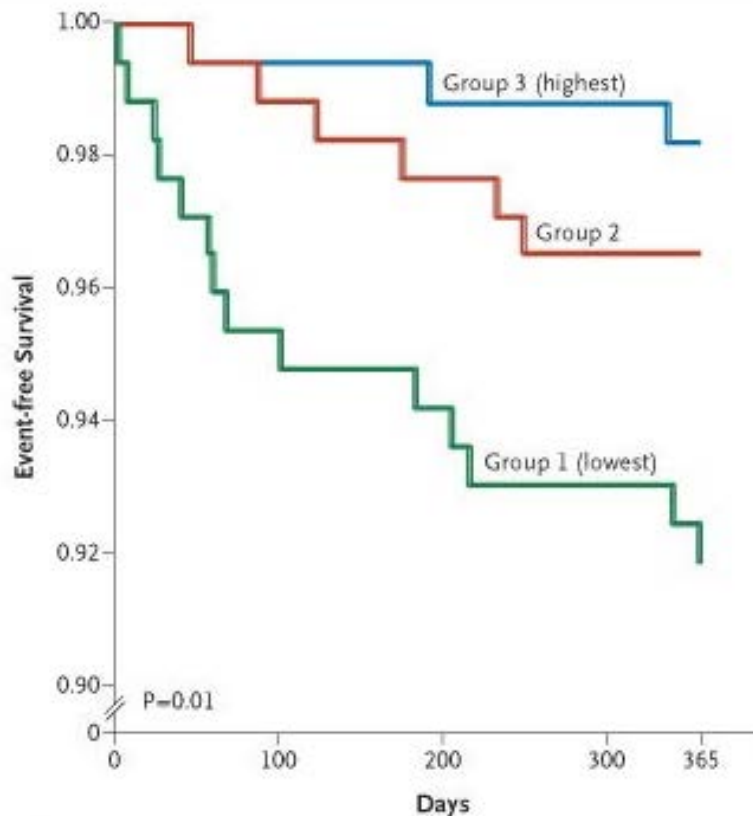


The Pathogenesis of Atherosclerosis – *vascular repair and calcification*



Progenitor Cells in cardiovascular disease

Lower event-free survival with lower numbers of circulating EPCs (CD34/KDR)

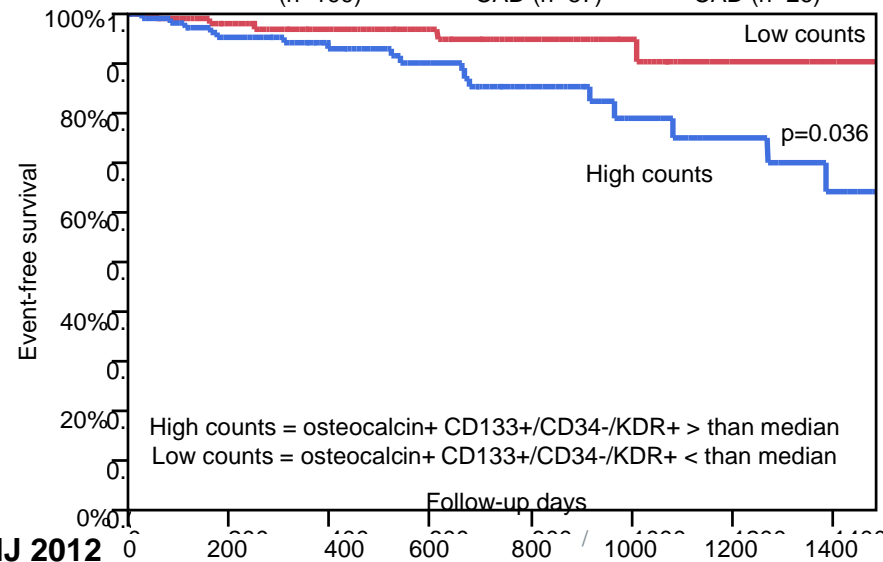
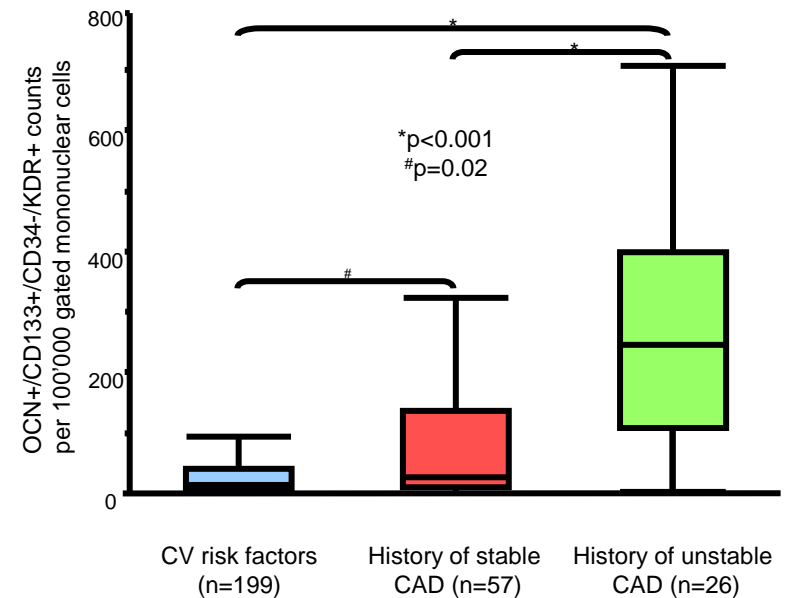


Werner, N, et al. NEJM 2005



University Hospital
Zurich

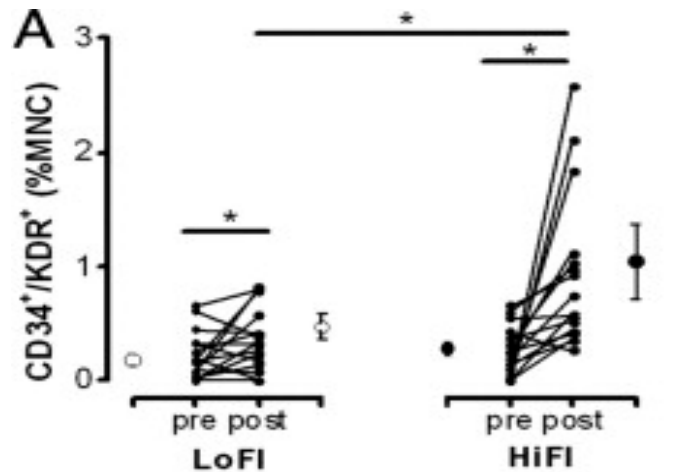
Osteocalcin co-expressing EPCs as a marker for CAD



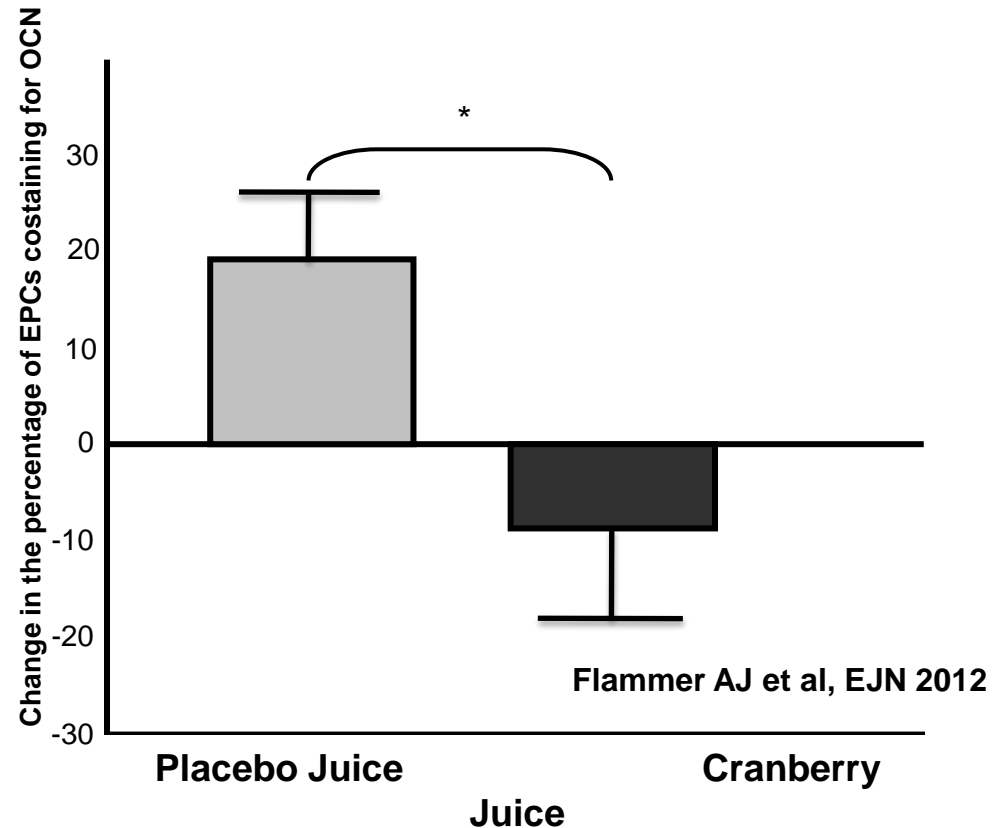
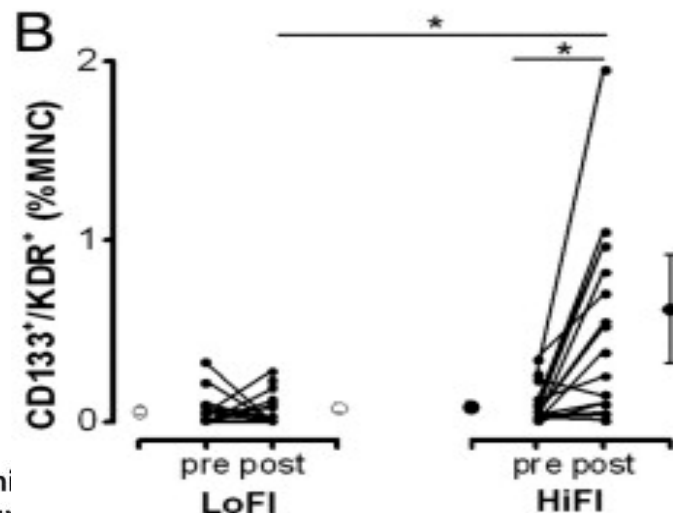
Flammer AJ et al, EHJ 2012

Mobilization of EPCs in Patients with CAD after high flavanol intake

Flavanol-rich drink (Cranberry juice) lowers the fraction of osteogenic progenitors



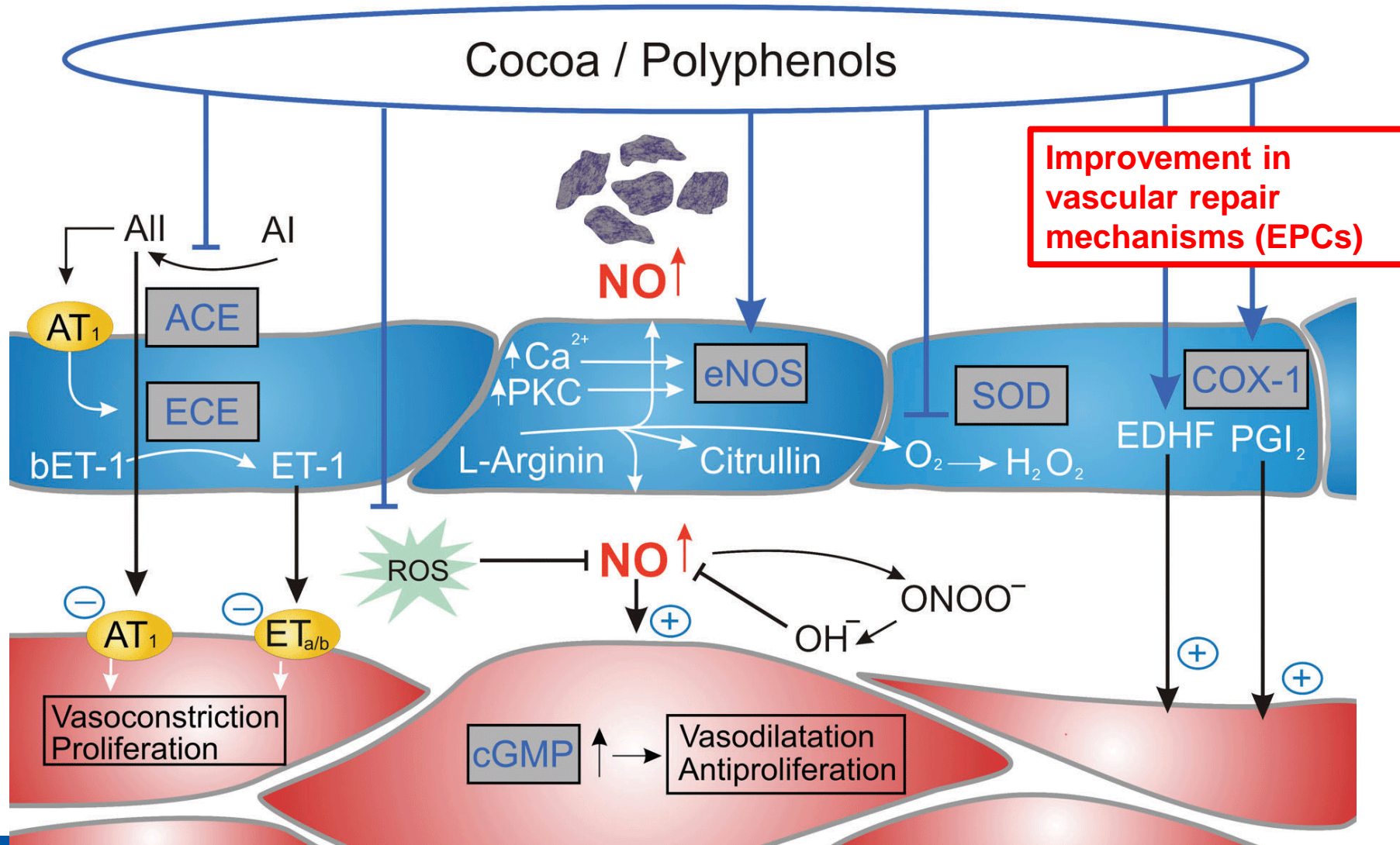
Heiss C, et al, JACC 2010



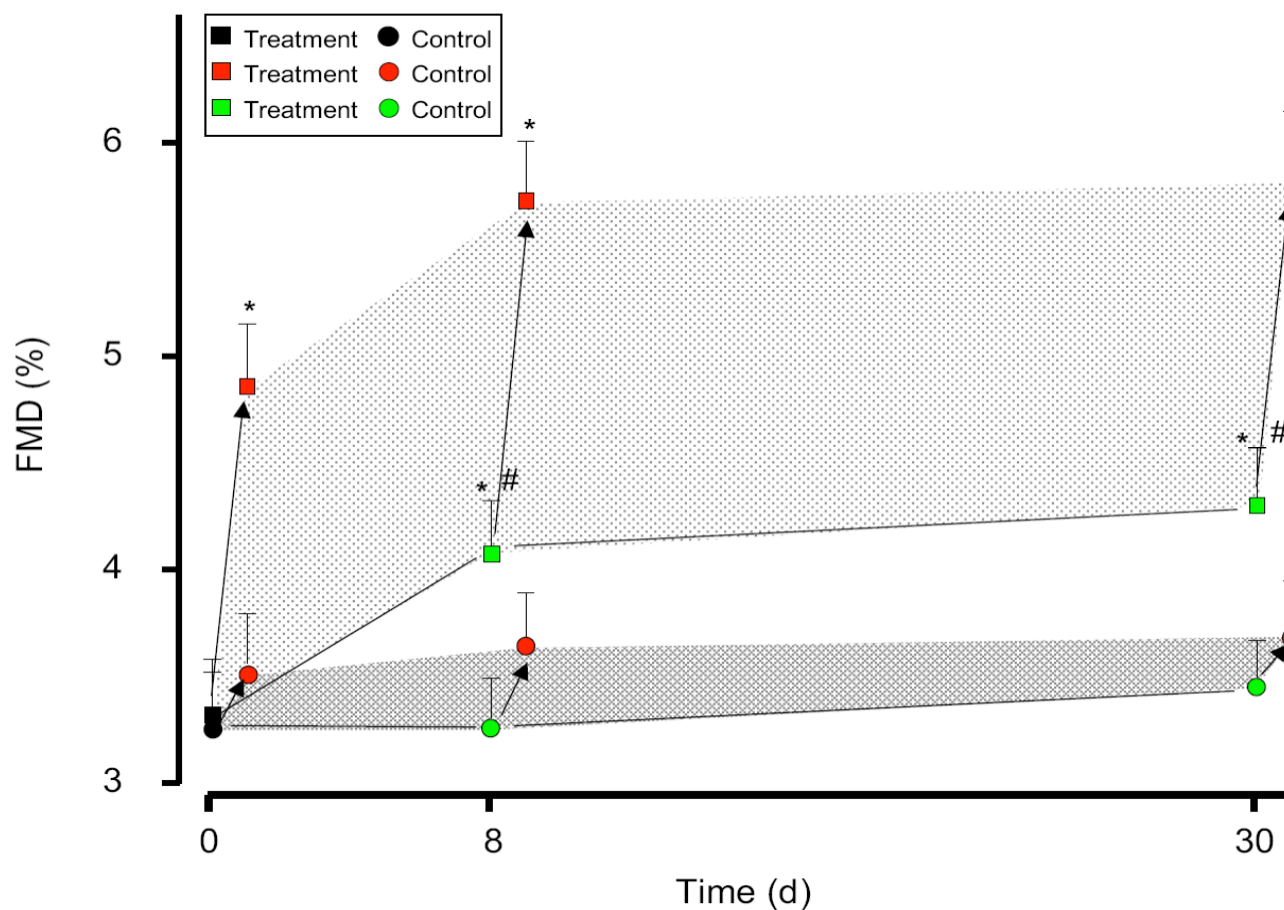
Flammer AJ et al, EJN 2012

- Cranberry Juice (n=31), as compared to placebo (n=37), induced a decrease in the fraction of EPCs co-expressing OCN (-8.64 ± 48.98 and $19.13 \pm 46.11\%$, respectively, $p=0.019$).

Summary of potential mechanisms



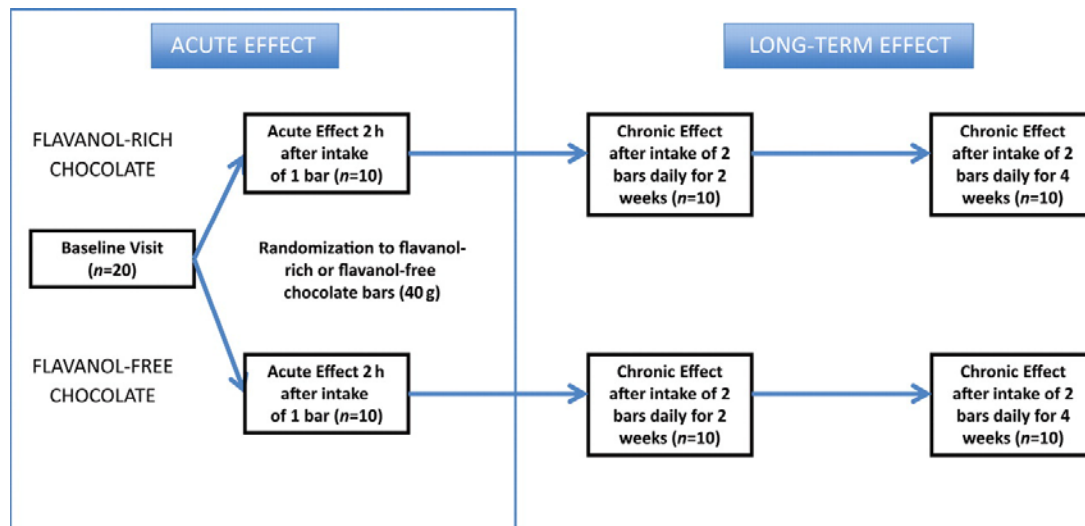
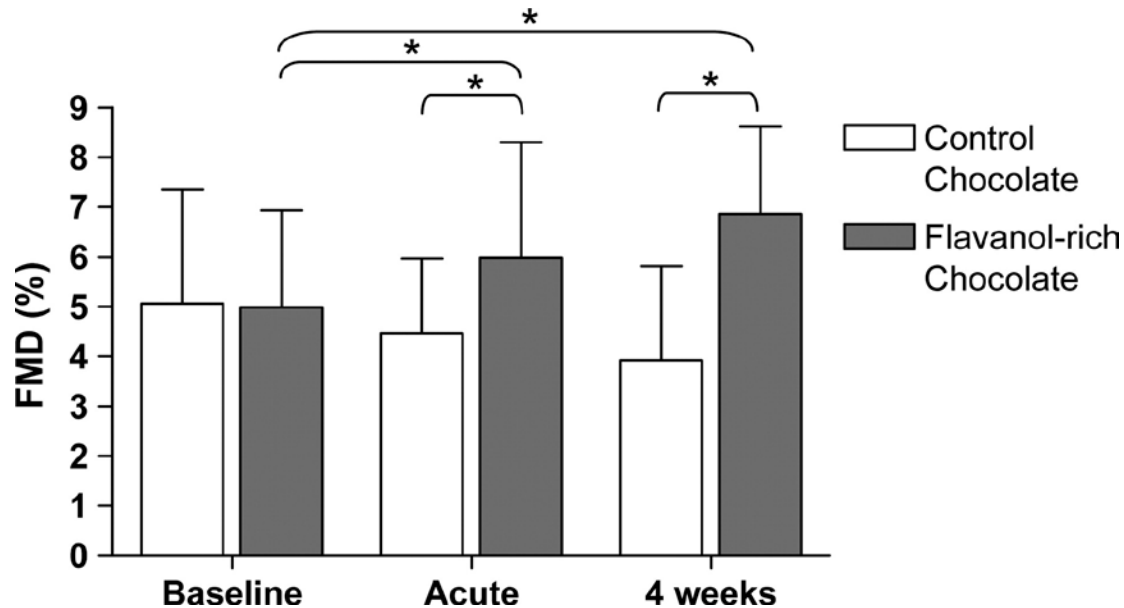
Long-term benefits in diabetes patients



N = 41 medicated diabetic patients

flavanol-rich cocoa (321 mg flavanols per dose) or a nutrient-matched control (25 mg flavanols per dose)

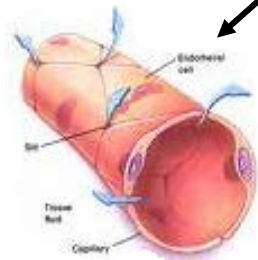
Sustained effects in patients with heart failure



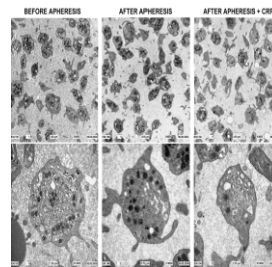
Cocoa as a remedy?



**Blood Pressure
Reduction**

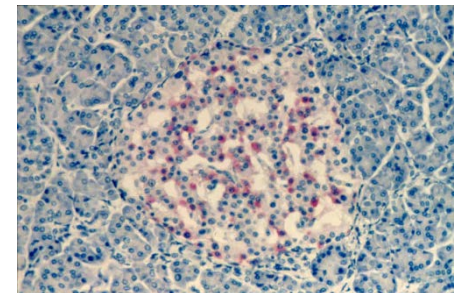


**Improved
endothelial function**



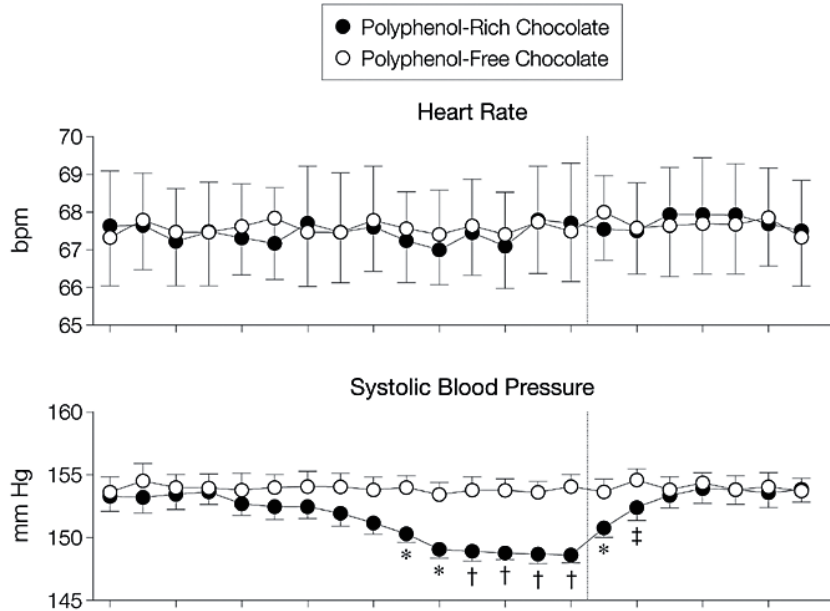
**Reduced
platelet reactivity**

**Other:
Anti-Inflammatory**

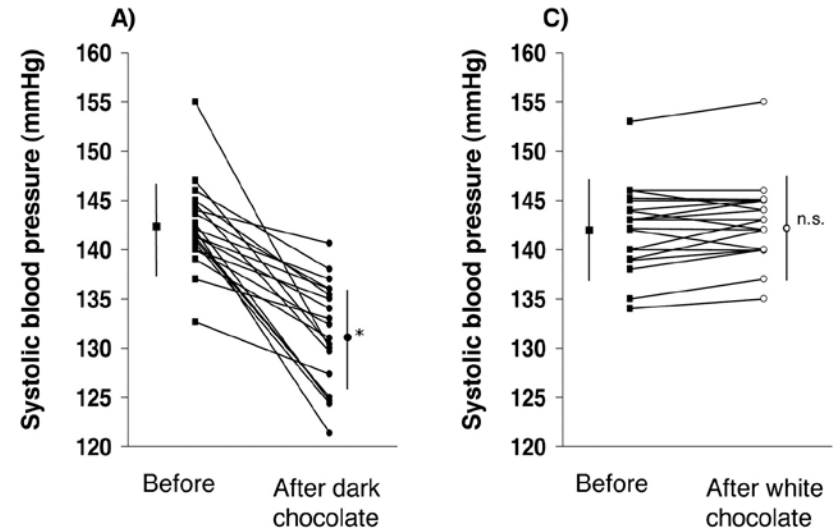


**Improved
insulin sensitivity**

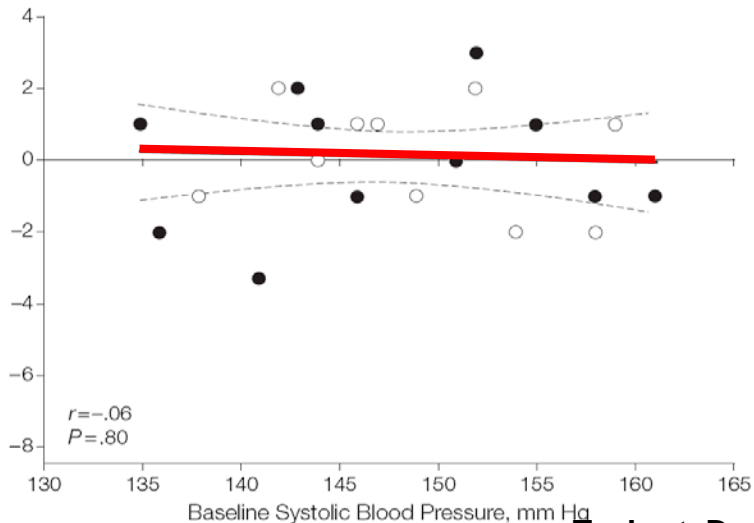
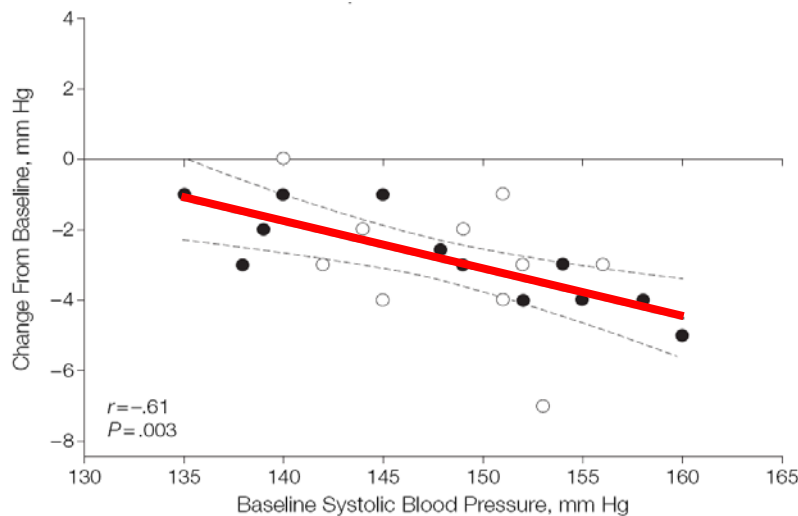
Cocoa and blood pressure



Taubert, Jama 2003



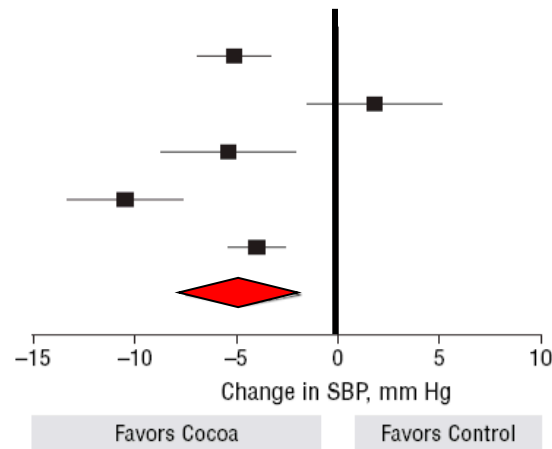
Grassi, D. et al. Hypertension 2005



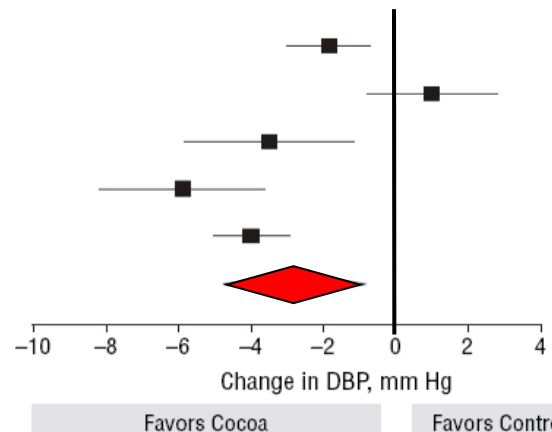
Taubert, D. et al. JAMA 2007

Blood pressure lowering effects of cocoa in controlled studies of cocoa administration

Source	Cocoa, n/ Δ SBP/SD	Control, n/ Δ SBP/SD
Taubert et al, ²⁰ 2003	13/-4.7/2.7	13/0.4/1.9
Engler et al, ²¹ 2004	11/-1.0/4.9	10/-2.8/2.5
Grassi et al, ²² 2005	15/-5.9/5.4	15/-0.5/3.7
Grassi et al, ²³ 2005	20/-11.0/6.3	20/-0.5/1.6
Fraga et al, ²⁴ 2005	28/-6.0/2.6	28/-2.0/2.6
Pooled Estimate		



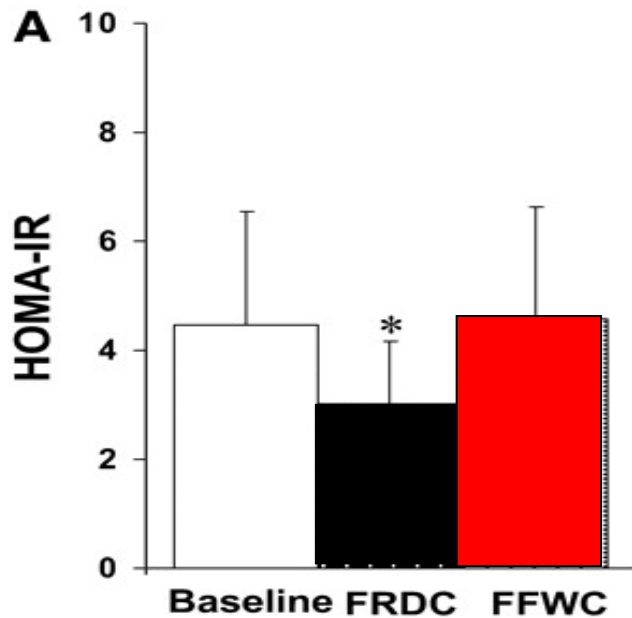
Source	Cocoa, n/ Δ DBP/SD	Control, n/ Δ DBP/SD
Taubert et al, ²⁰ 2003	13/-1.6/1.4	13/0.2/1.6
Engler et al, ²¹ 2004	11/0.9/2.3	10/-0.1/1.9
Grassi et al, ²² 2005	15/-4.1/4.1	15/-0.6/2.1
Grassi et al, ²³ 2005	20/-6.2/4.2	20/-0.3/3.1
Fraga et al, ²⁴ 2005	28/-5.0/2.0	13/-1.0/2.0
Pooled Estimate		



Meta-analysis of controlled studies of cocoa administration (173 subjects, mean duration 2 weeks)

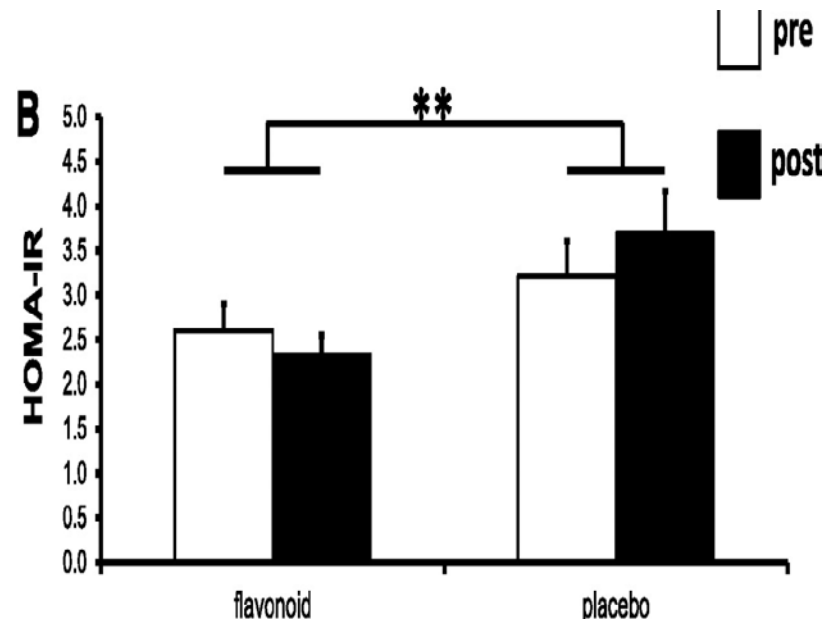
Effect of Cocoa on Insulin resistance

Cocoa improves insulin resistance in patients with impaired glucose tolerance



Grassi, D. et al. J. Nutr. 2008

1-year flavonoid intervention on insulin resistance

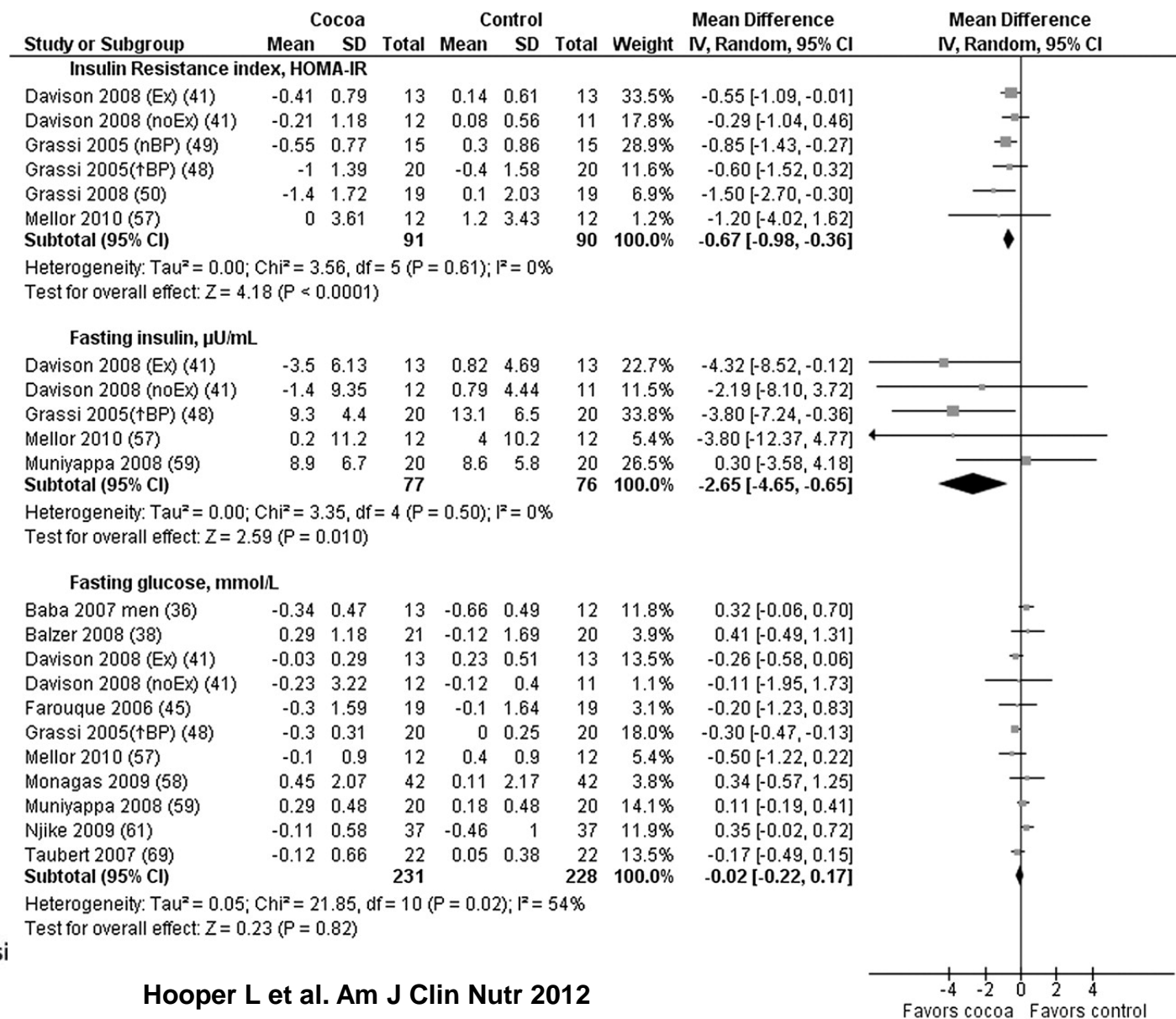


Curtis P J et al. Dia Care 2012

HOMA-IR =

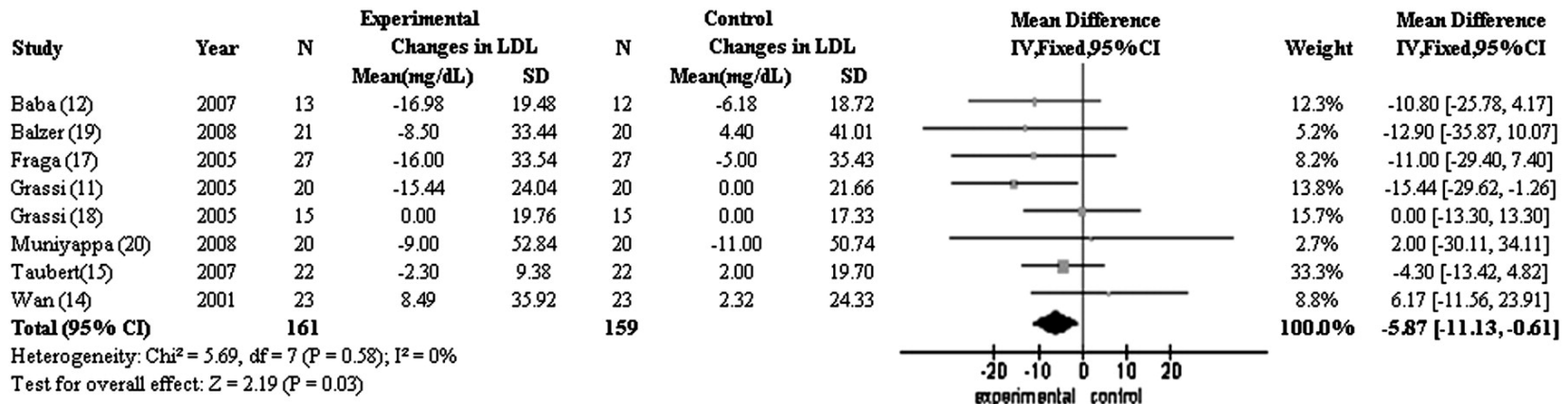
homeostasis model assessment of insulin resistance =
fasting insulin*glucose/22.5

Effect of chocolate/cocoa flavan-3-ols on measures of glucose and insulin metabolism or homeostasis

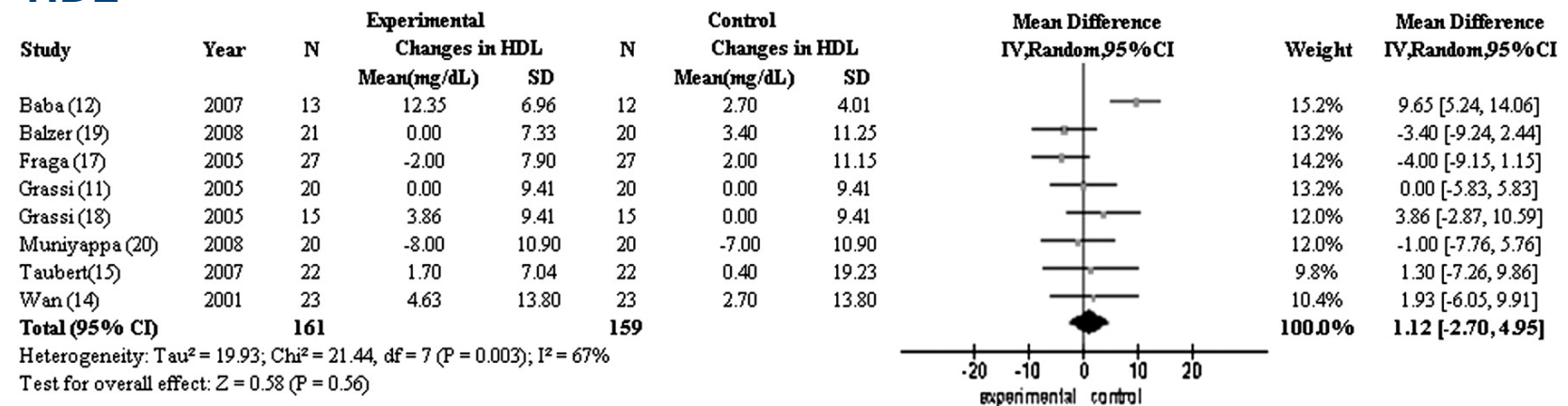


Meta-analysis of the effect of cocoa consumption blood lipids as compared with placebo

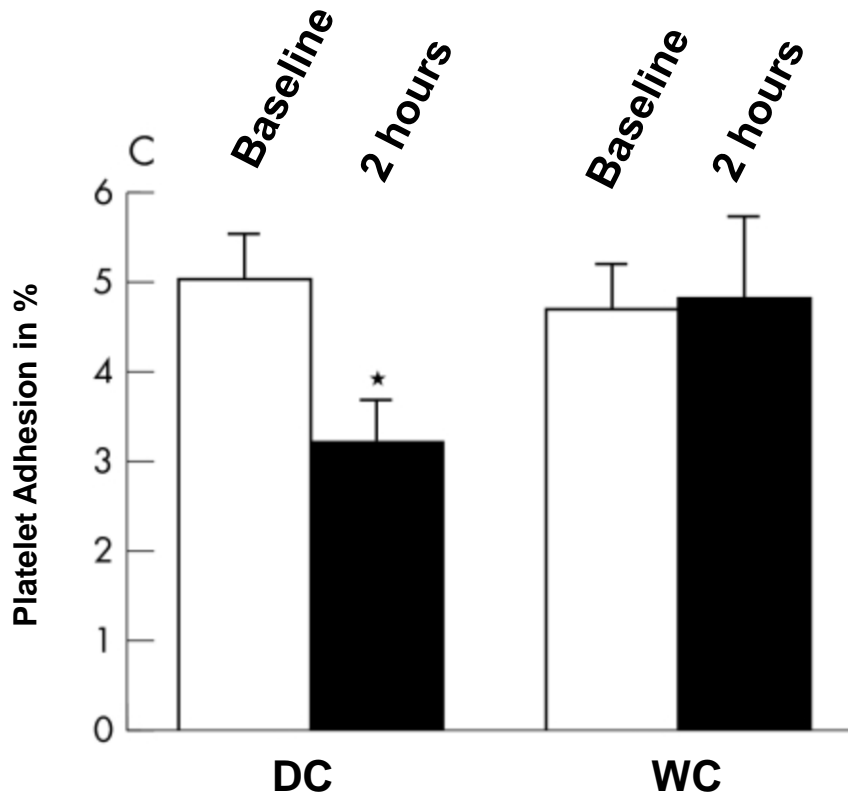
LDL



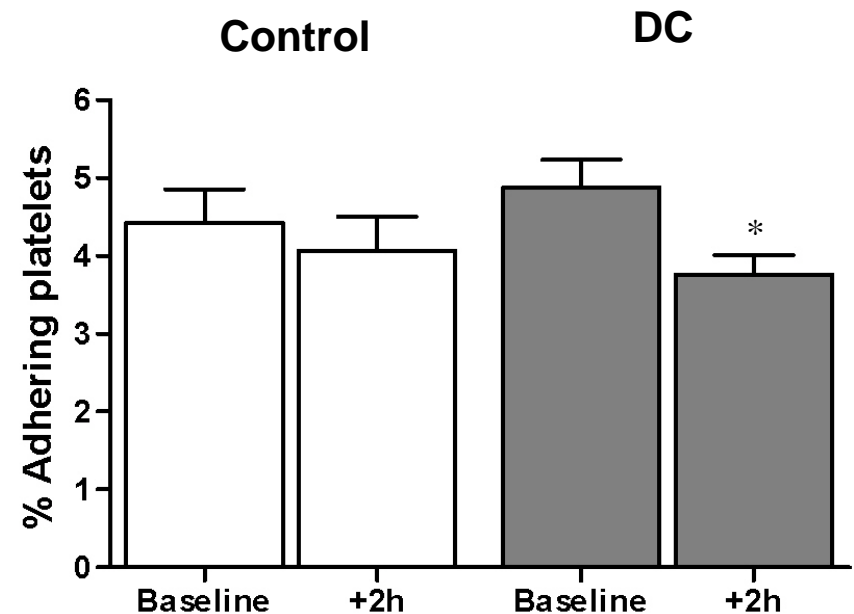
HDL



Less platelet adhesion after Cocoa intake



F. Hermann, *Heart* 2006



Flammer AJ, et al, *Circulation* 2007

Assessed by a cone and
platelet analyzer

Chocolate as medicine?

Hippocrates: “let food be the medicine”!



High caloric load and high sugar content of commercially available chocolate!

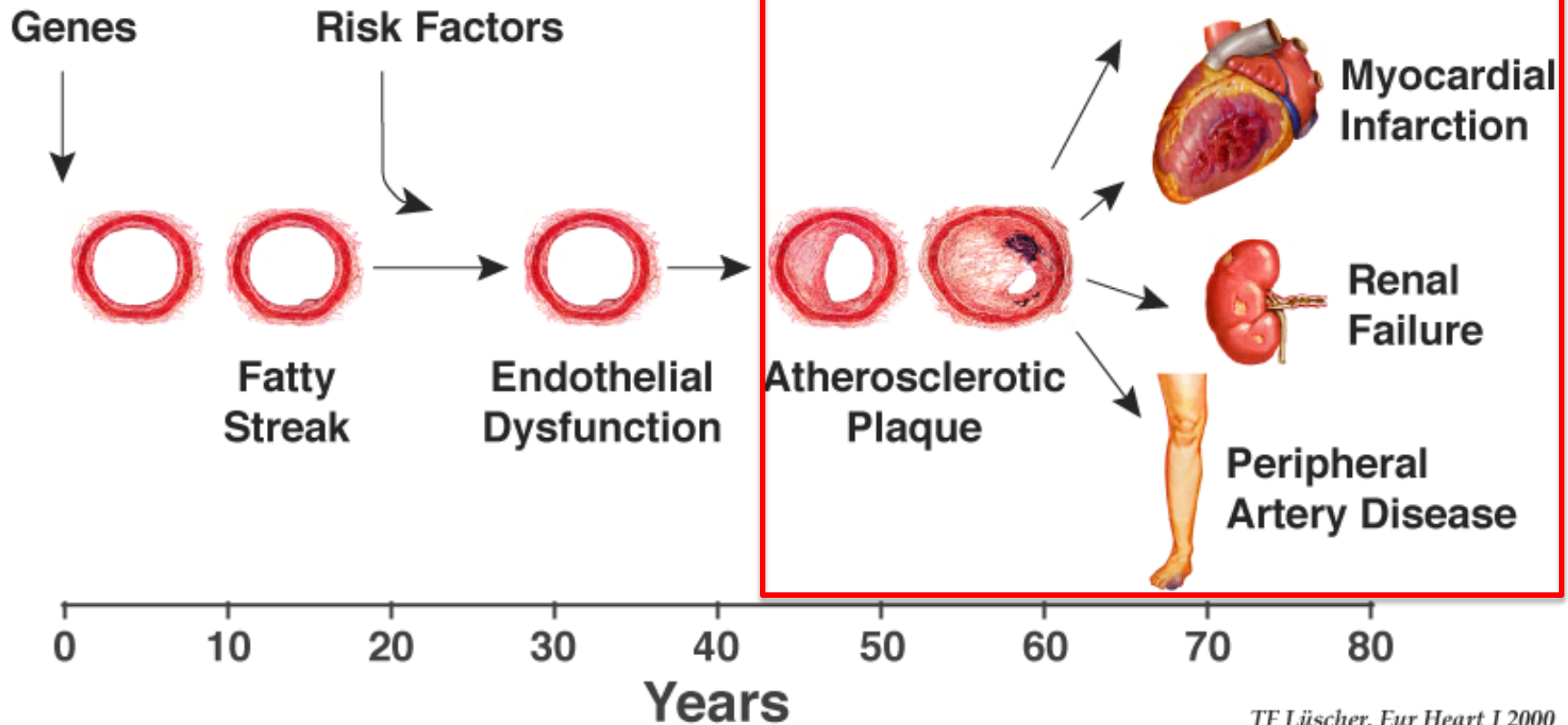
Direct supplementation with flavanols should be evaluated in more detail

At this point, recommendation of flavanol supplementation (similar as with vitamins) appears problematic (pro-oxidative effects?)

However, as with pharmaceuticals, nutraceuticals should undergo the same strict evaluation of potential benefit or harm

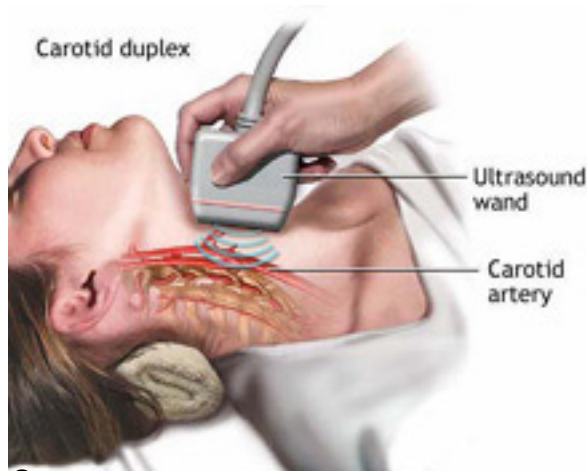
To clarify protective effects, further studies are necessary, particularly on morbidity and mortality

Effect of cocoa on structural changes or hard endpoints?



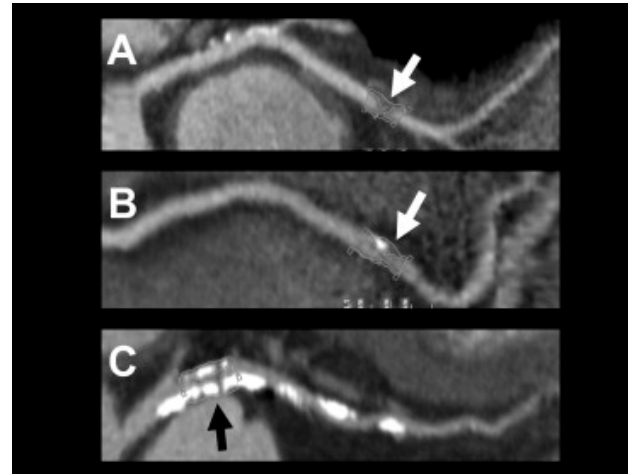
Structural vascular disease markers

Carotid Intima Media Thickness



© Sononet

Coronary Calcifications



Ferencik M, et al
AJC 2012

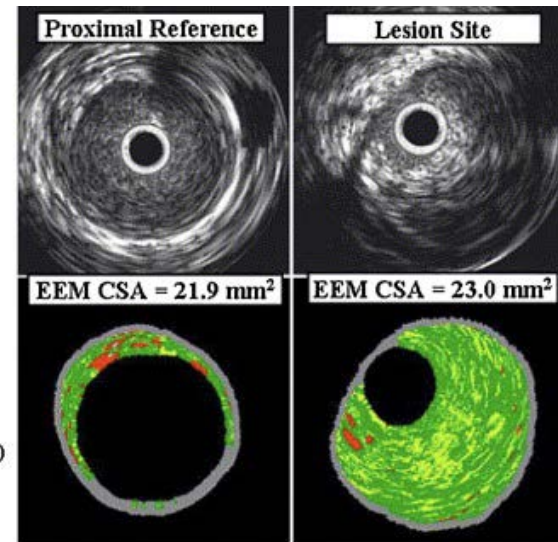
Intravascular Ultrasound with Virtual Histology

A

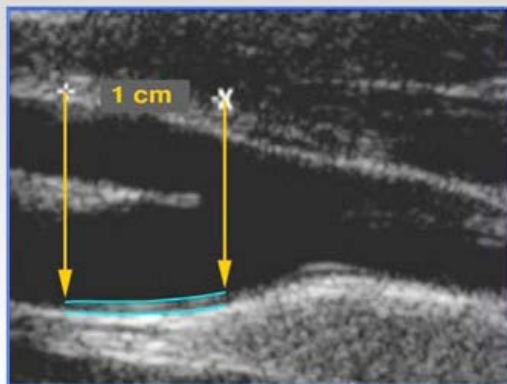
Conventional
IVUS

IVUS-VH

- Fibrous (42.3%)
- Fibro-fatty (41.4%)
- Dense Calcium (0.9%)
- Necrotic Core (5.4%)
- Media



Mario Gossl/Amir Lerman MCNA07

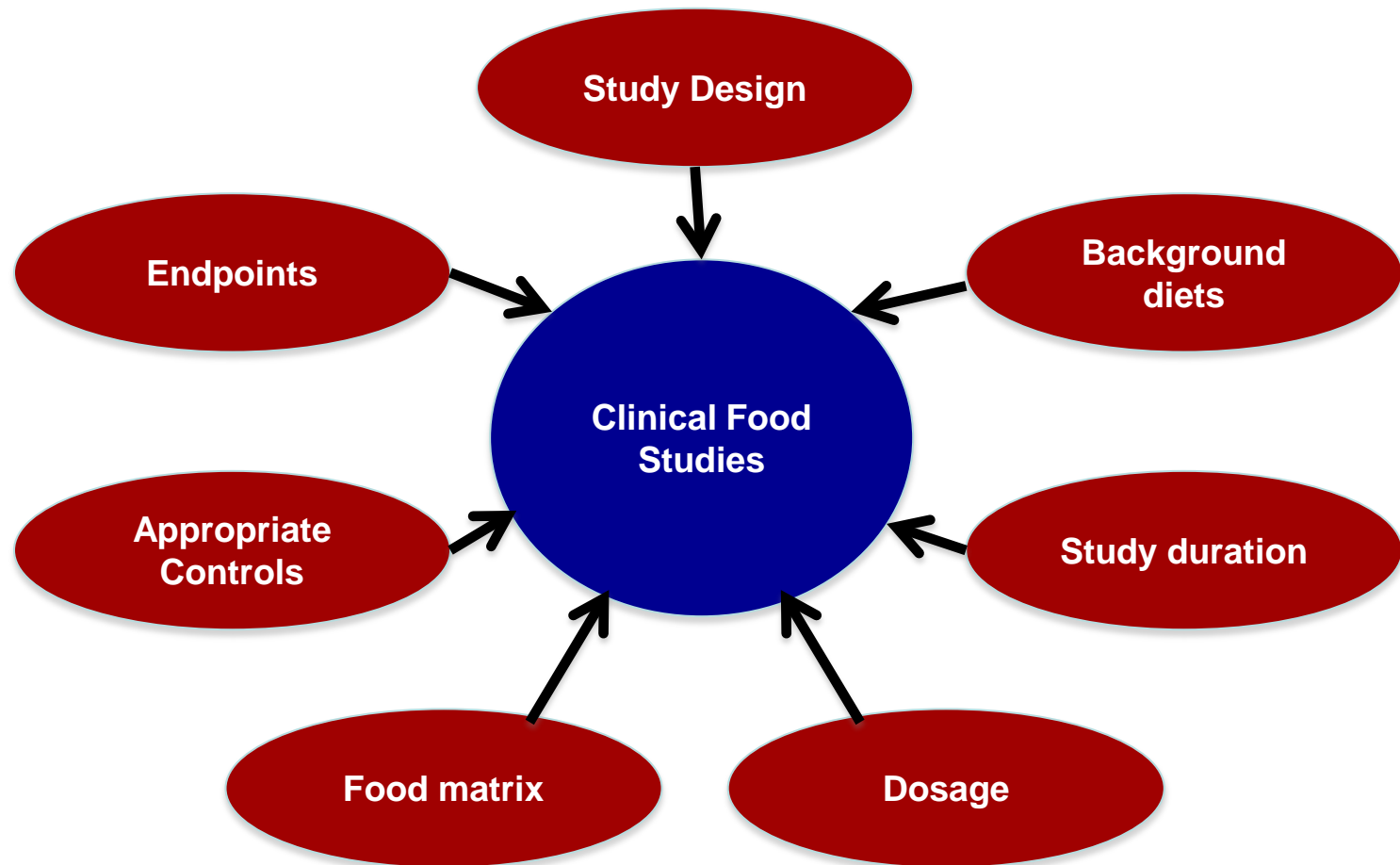


Nicholls SJ: The Heart.org



UniversityHospital
Zurich

Issues with non-pharmacological studies (nutrition, nutraceuticals...)



[Chocolate is not equal to Cocoa]

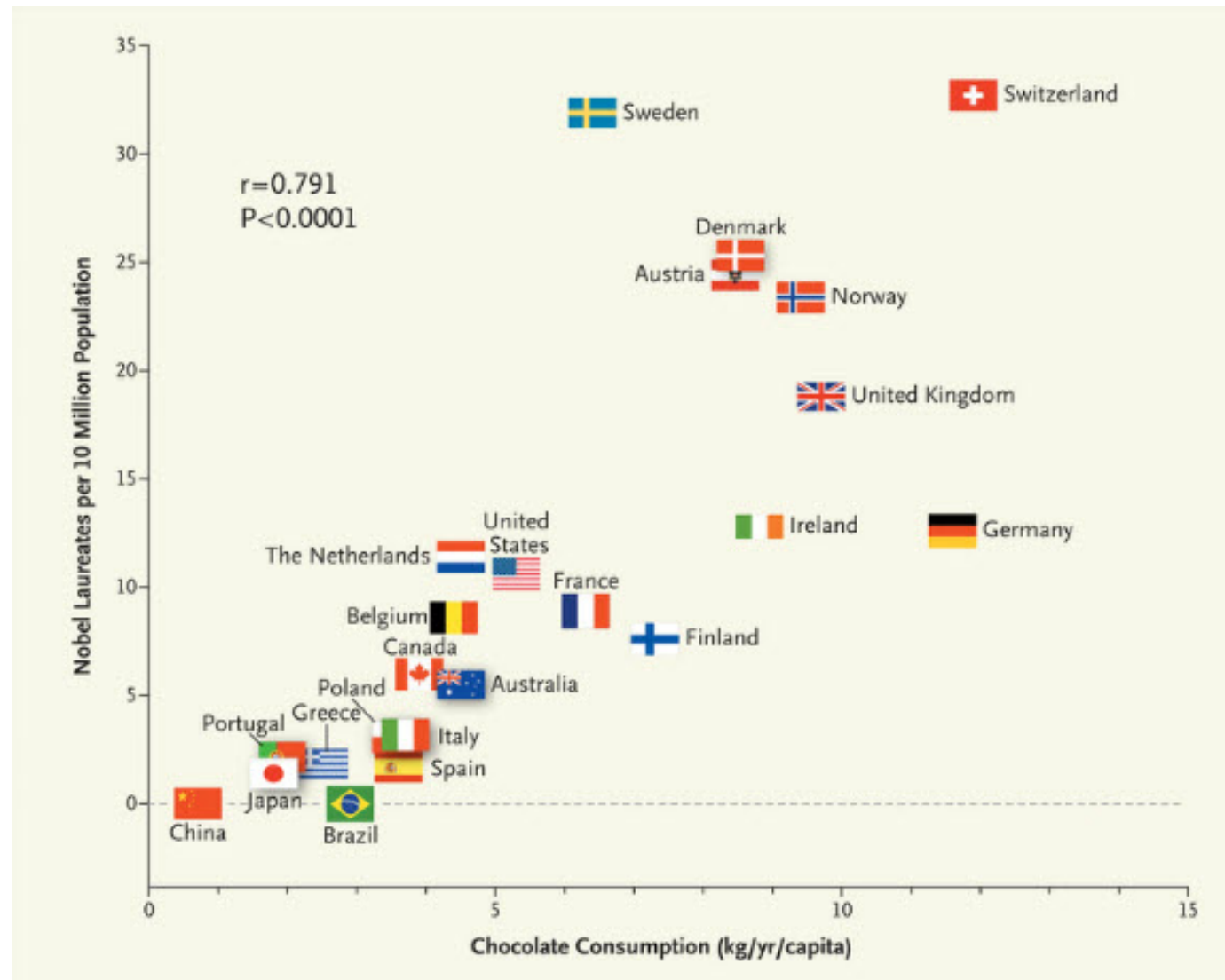
During conventional chocolate manufacturing the concentrations of polyphenols markedly decrease

In particular fermentation and roasting have detrimental impact

Polyphenol concentration depend on the agricultural origin of raw cocoa



Correlation between Countries' Annual Per Capita Chocolate Consumption and the Number of Nobel Laureates per 10 Million Population



Thank you!



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