FLAVIOLA

Targeted delivery of dietary flavanols for optimal human cell function: Effects on cardiovascular health

SFRBM Annual Meeting, Pre-meeting Workshop II

Flavanols in Health and Disease

Flavanol and Procyanidin Intake and Cardiovascular Health: Outcomes from Clinical Intervention Studies

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San Diego, 14 November 2012

Flavanol research in humans

- Do flavanols enhance vascular function?
- Are flavanol effects age-dependent?
- Can flavanols be protective in CV disease?

Causality criteria

1. Vascular effects not attributable to confounders?
2. Flavanols absorbed and transported to vasculature?
3. Dose-responsiveness? Temporality?
4. Pure flavanol mimicking vascular effects?
5. Inhibition of mediator pathway attenuates vascular effects?
6. Withholding of flavanols reverses vascular effects?

1. Clinical trial standards control confounders

Randomized controlled trial (RCT) according to Good Clinical Practice (GCP)

- Subjects **randomized** to treatment
- Tested against placebo **control**
- Subjects and investigators **blinded** to allocation
- Relevant groups
- Sufficiently powered
- CONsolidated Standards Of Reporting Trials*

*http://www.consort-statement.org/

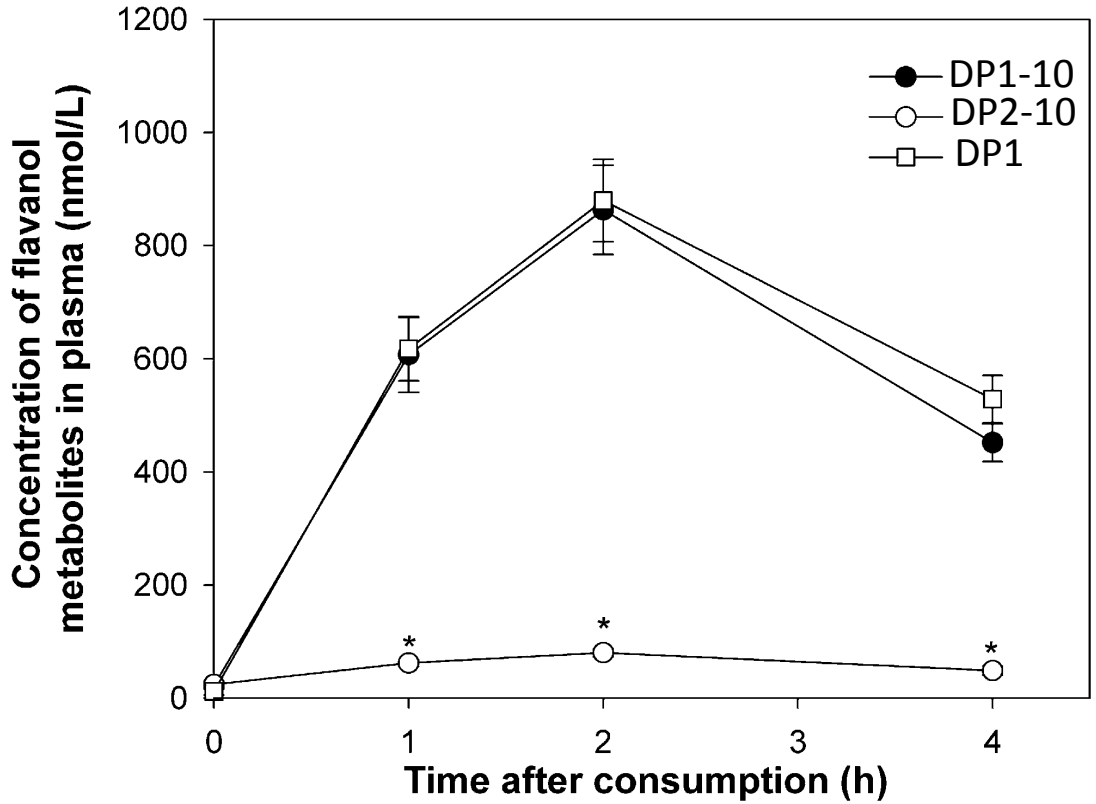
1. Clinical trial standards control confounders

Use accredited (surrogate) endpoints[#]

- Blood pressure
- Endothelial function (FMD)
- Pulse wave velocity

[#]EFSA Journal 2011

2. Monomers, but not oligomers are absorbed and circulate primarily as metabolites



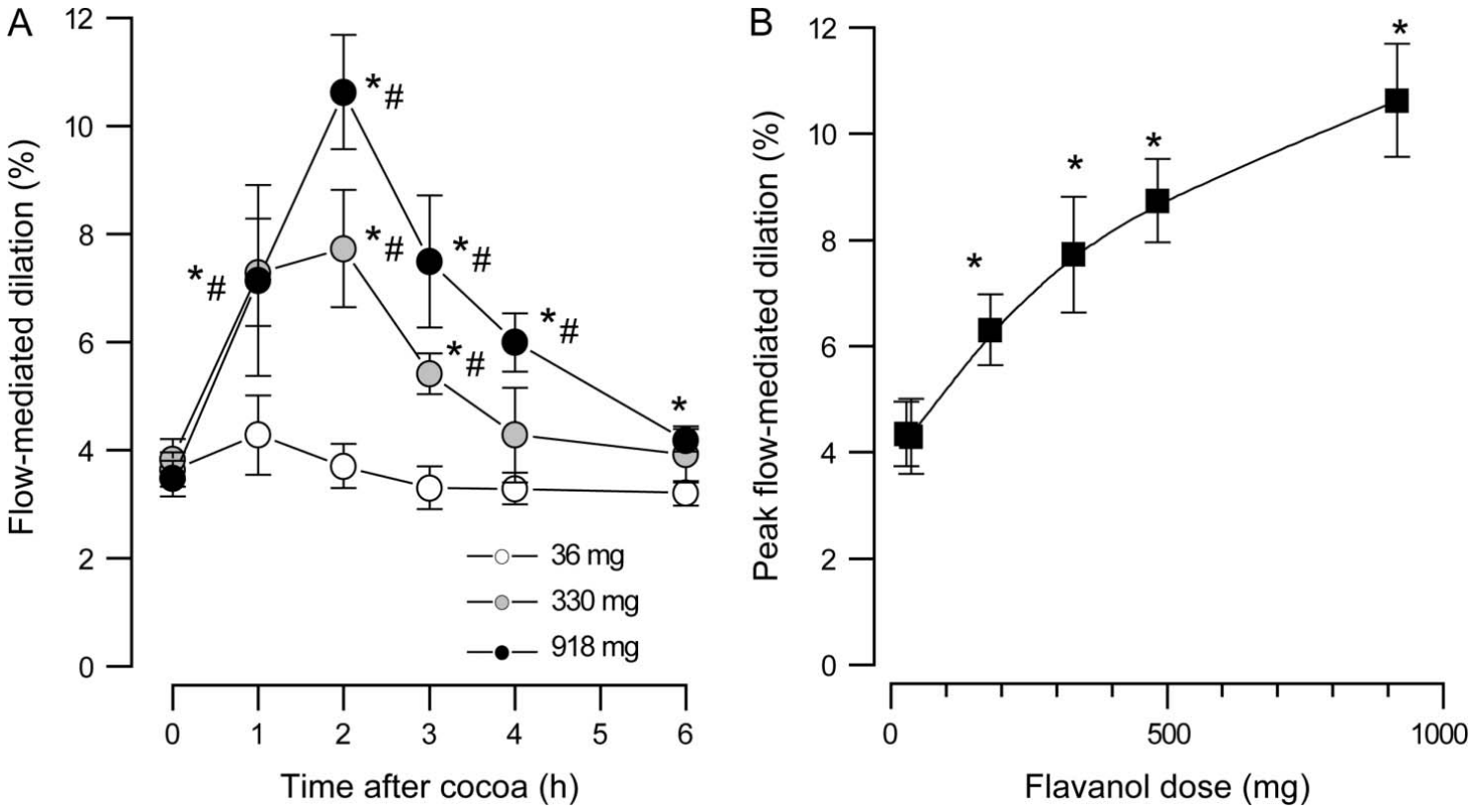
Monomers+Oligomers
Monomers

Oligomers

Ottaviani FRBM 2011

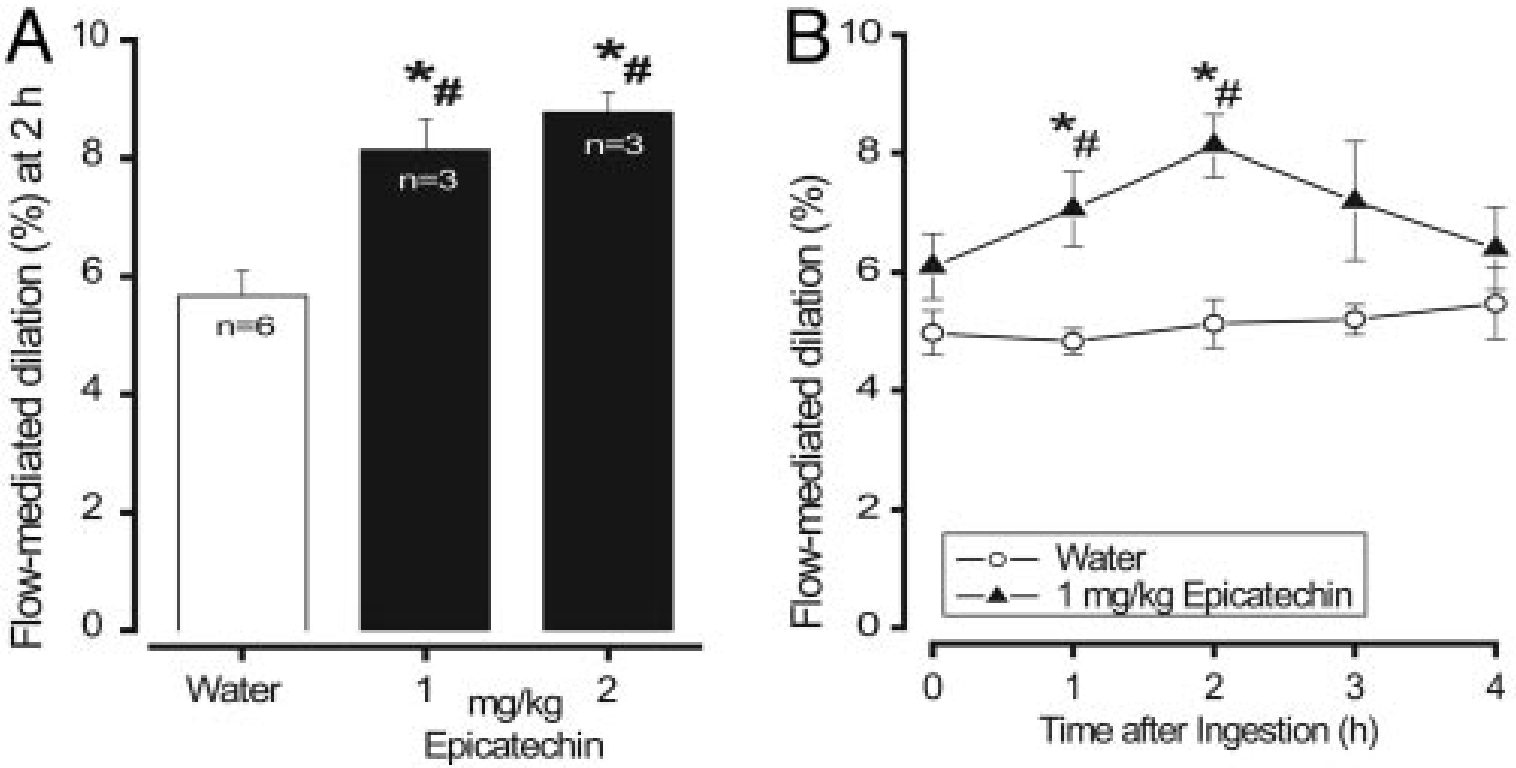
Ottaviani AJCN 2012

3. Dose-dependent improvement of endothelial function following flavanol-rich intervention



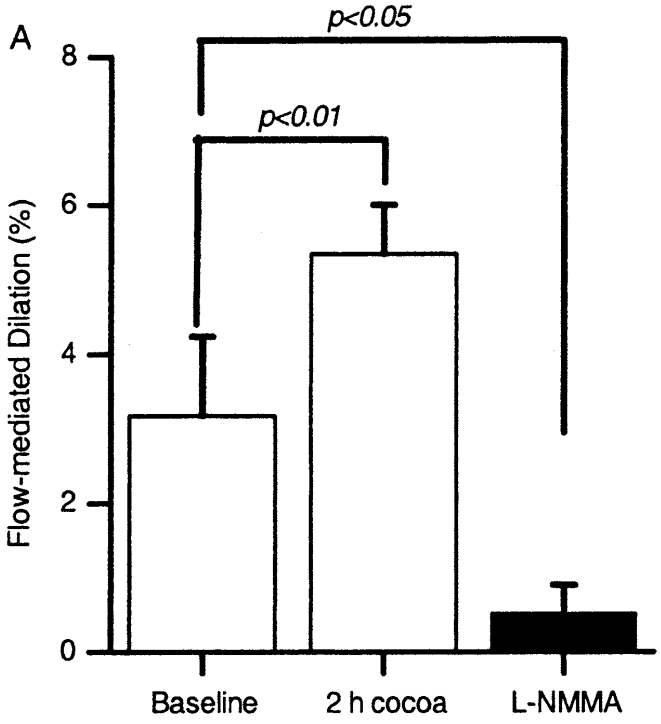
Heiss JAMA 2003, JACC 2005, JCVP 2007

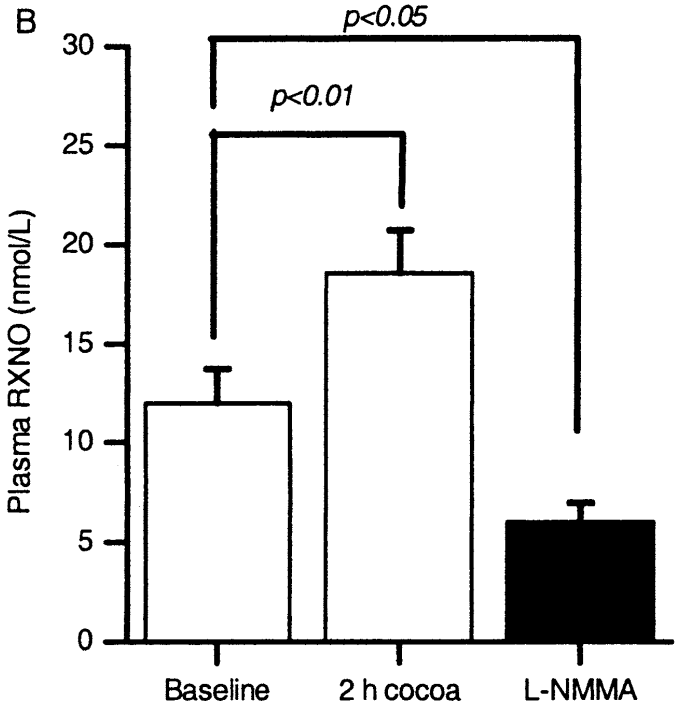
4. Pure (-)-epicatechin acutely improves endothelial function



Schroeter PNAS 2006

5. Inhibition of NO Synthase by L-NMMA inhibits vascular effects of flavanols

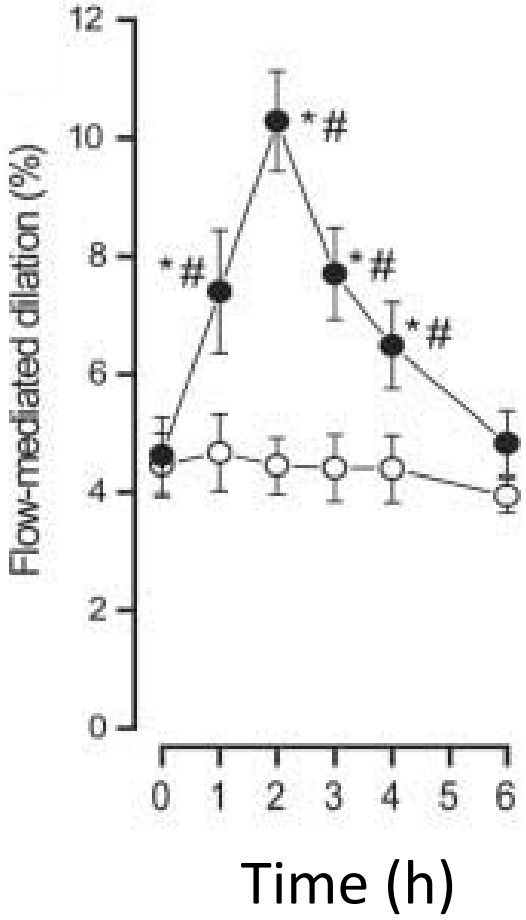




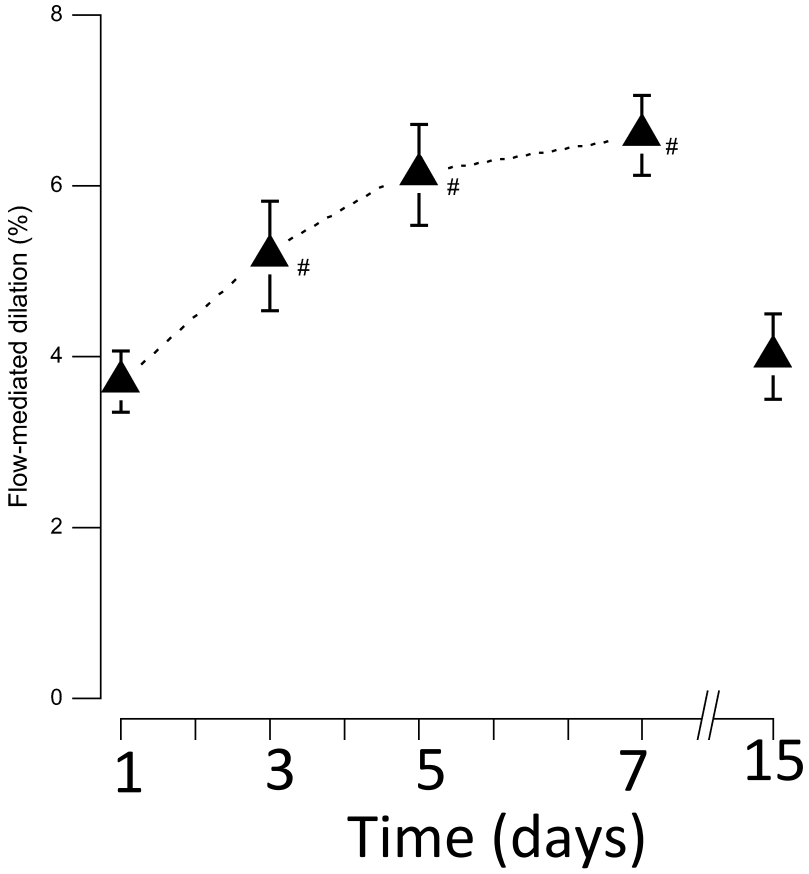
Heiss JACC 2005, Schroeter PNAS 2006

6. Withholding reverses vascular effects

Acute application (975 mg)



Repetitive Application (3x375 mg/d)



Heiss JCVP 2007

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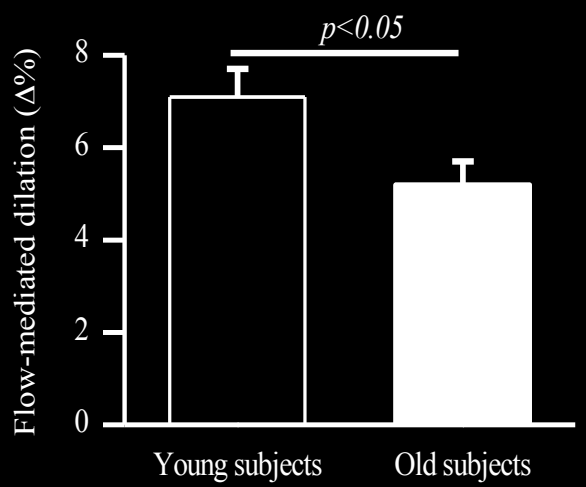
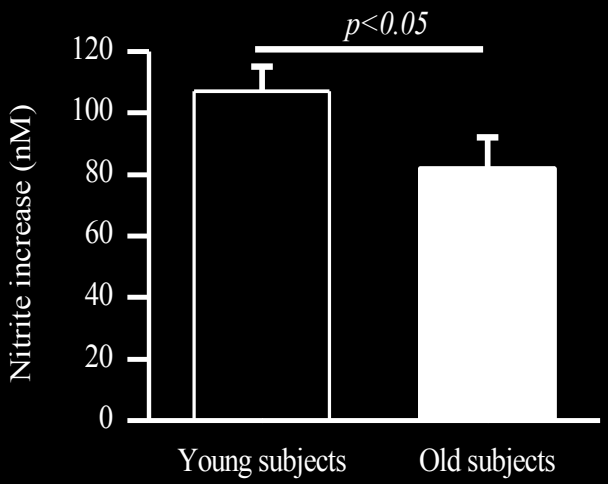
Age-related vascular changes

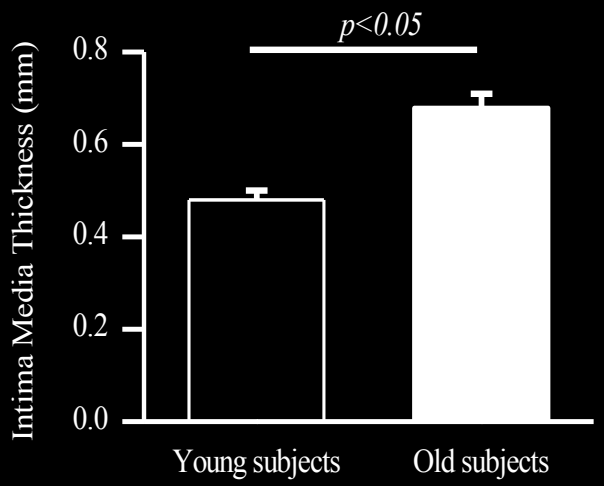
FMD



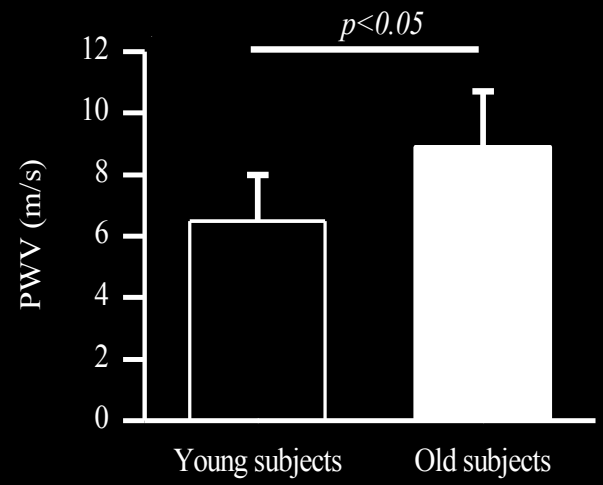
Nitrite increase



Intima media thickness



Pulse wave velocity

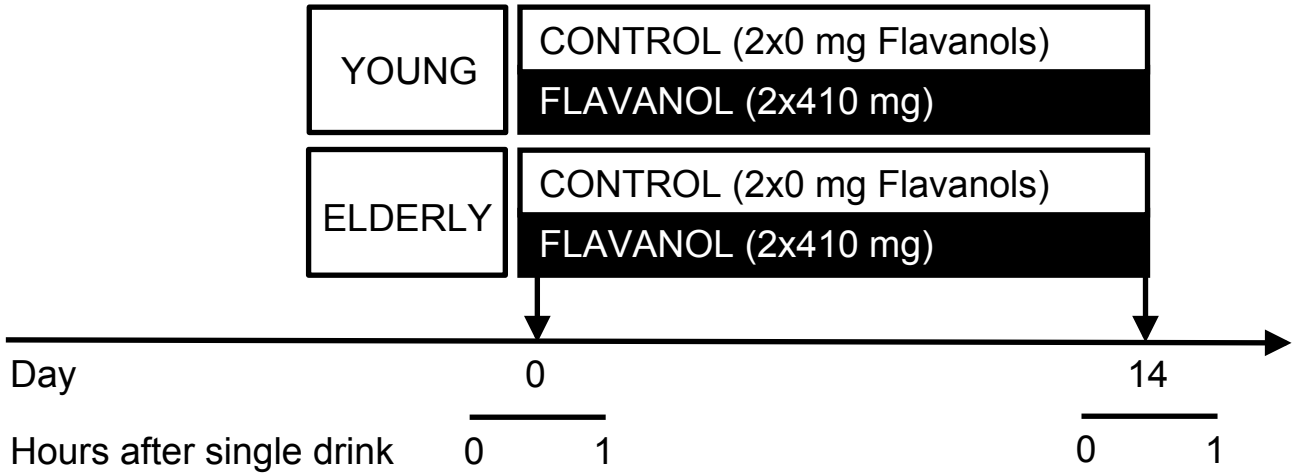


Heiss JACC 2006, Lauer, Heiss BRC 2008, Keymel BRC 2009

Study design: 4-armed randomized controlled double blind parallel group intervention study

Inclusion
- Healthy, male
- 18-30 (YOUNG)
- 50-80 (ELDERLY)
- BMI 23-30 kg/m^2

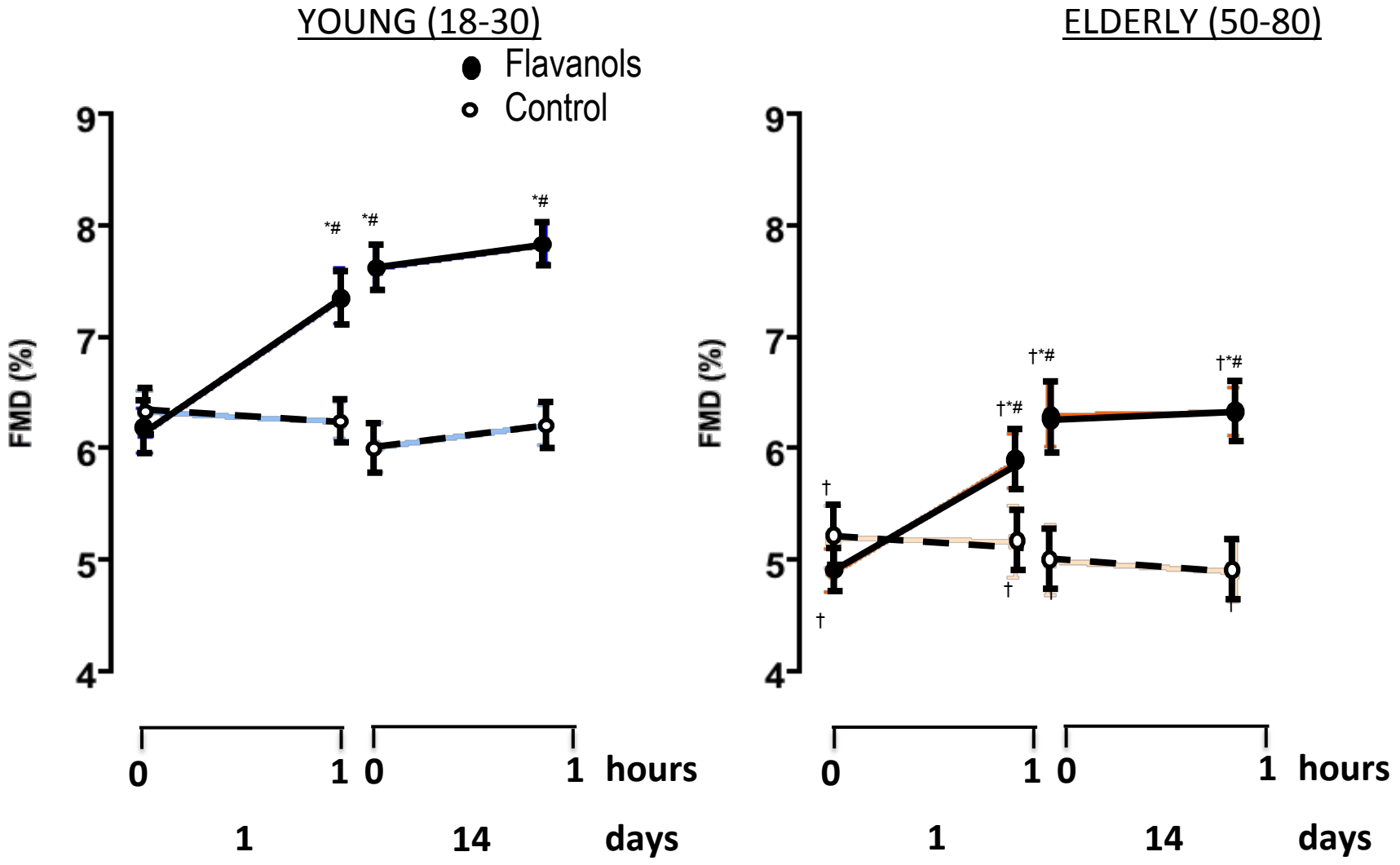
Exclusion
- Cardiovascular disease (signs, symptoms, meds)
- Diabetes mellitus
- Smoking
- Acute inflammation
- Cardiac arrythmia
- Malignancies
- Heart failure
- Renal failure



Subject characteristics

	YOUNG			ELDERLY			p-value
n	22			20			
Age (y)	26	±	3	60	±	7	**<0.001**
BMI (kg/m2)	24.9	±	3.0	26.5	±	3.0	**0.013**
Height (m)	1.83	±	0.06	1.81	±	0.04	0.453
Weight (kg)	81	±	10	88	±	11	0.079
Creatinine (mg/dl)	1.0	±	0.1	1.0	±	0.1	0.991
Total cholesterol (mg/dl)	184	±	33	225	±	32	**<0.001**
LDL cholesterol (mg/dl)	129	±	26	157	±	27	**0.005**
HDL cholesterol (mg/dl)	53	±	16	54	±	12	0.900
Triglycerides (mg/dl)	97	±	44	118	±	39	0.104
Fasting plasma glucose (mg/dl)	89	±	8	95	±	8	**0.027**
HbA1c (%)	4.8	±	1.1	4.6	±	2.0	0.554
SBP (mmHg)	120	±	9	131	±	11	**0.006**
DBP (mmHg)	77	±	7	82	±	9	**0.011**
HR (bpm)	56	±	7	56	±	7	0.908
CRP (mg/dl)	0.1	±	0.2	0.1	±	0.2	0.692
Hb (mg/dl)	15.3	±	1.0	15.4	±	1.1	0.721
Leucocytes (1000/ul)	5.5	±	1.3	5.8	±	1.4	0.489
Smoking history	0			0			
Medication	0			0			
				MV	±	SD	

Flavanols improve age-related impairment in endothelial function



* p<0.05 vs. 0 h, day 1 baseline, # p<0.05 vs. Control drink, † p< 0.05 vs. Young

FLAVIOLA Health Study

- ***Aims**: General applicability, larger population* at increased cardiovascular risk, in the context of cardiovascular health, and identify influencing factors
- ***Study Design**:* 2-armed, randomized controlled parallel-group study
- ***Sample Size**: n=100*
- ***Study Population:*** middle-aged, male, healthy subjects
- ***End points*** *1° Endothelial function*
  2° blood pressure, cholesterol, glucose
  3° Exploratory end points
- ***1 month Intervention***
  - » *Flavanol intervention 2x410 mg*
  - » *Flavanol free control*

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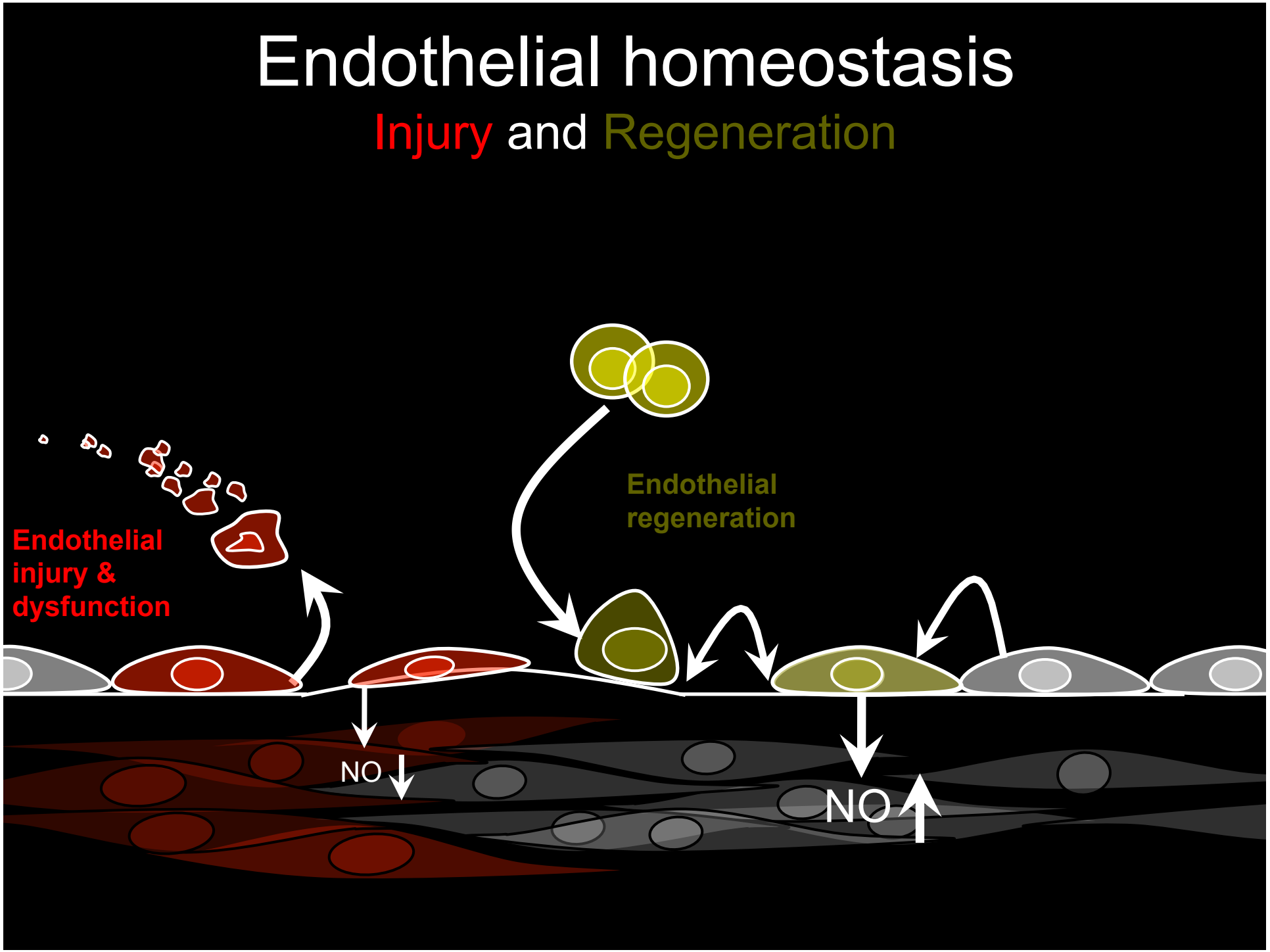
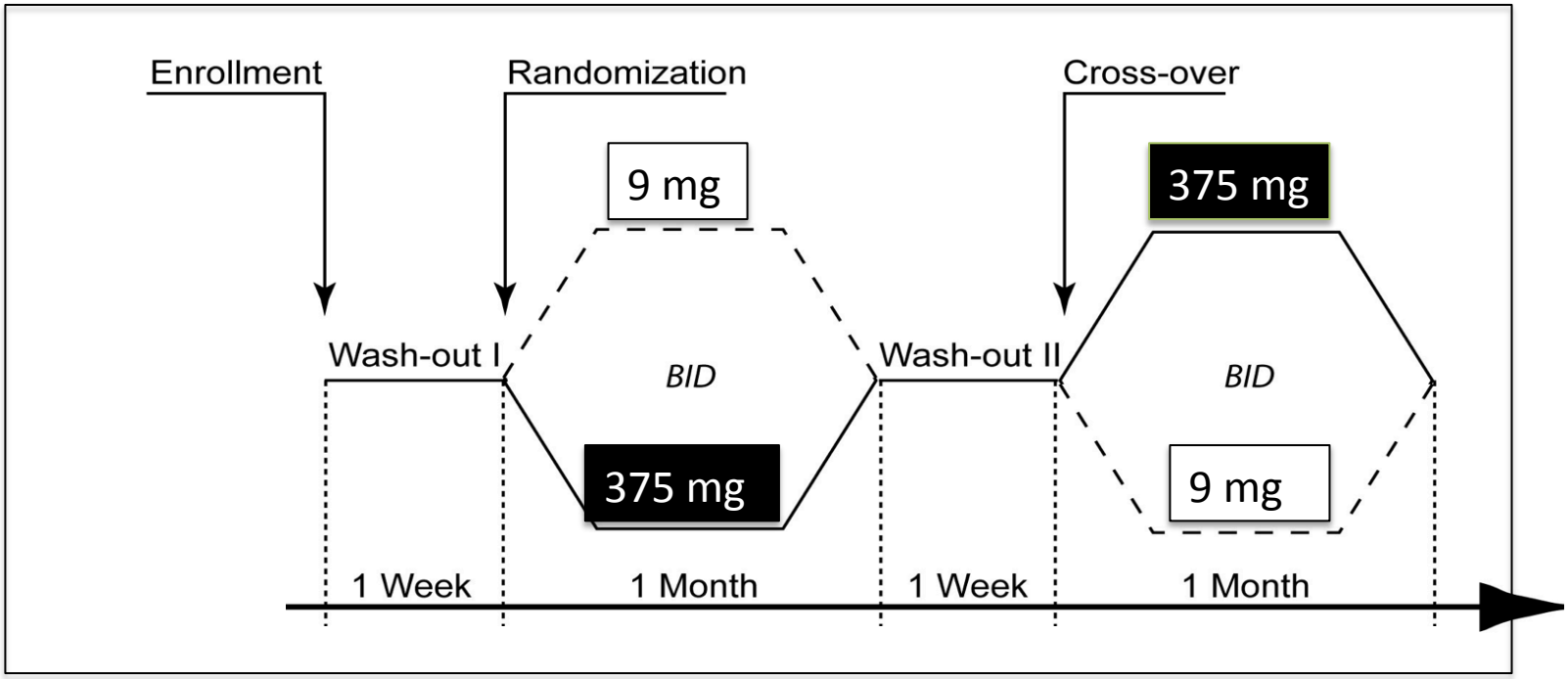
Endothelial homeostasis

Injury and Regeneration



Study design

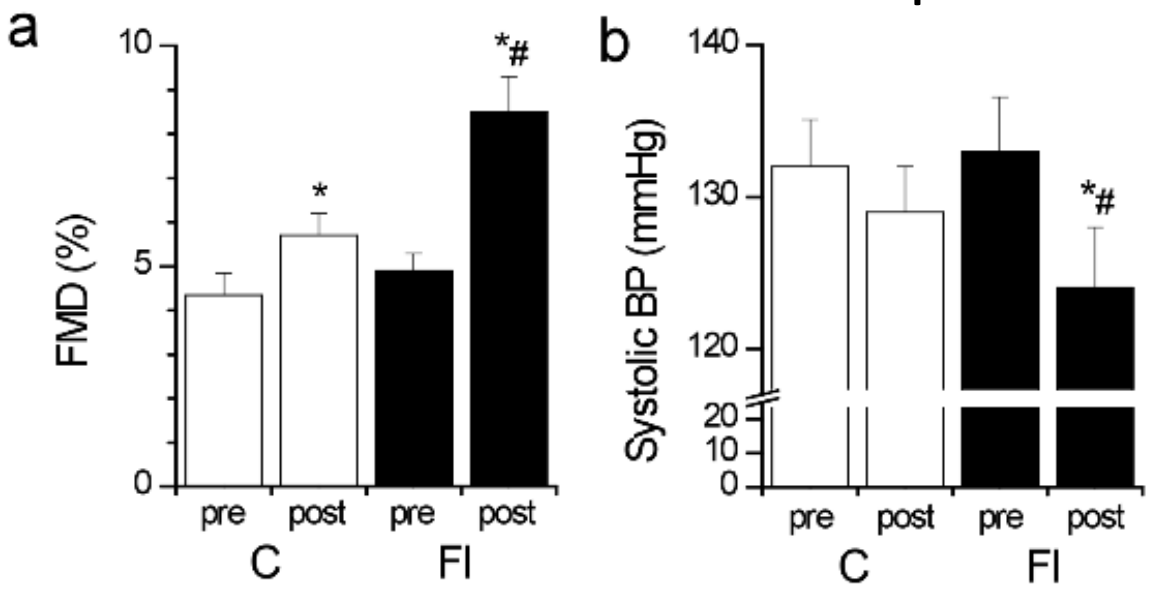
- Randomized controlled crossover double blinded trial
- N=16 Patients with **coronary artery disease** on **optimal medical therapy**
- **30 days** *high flavanol intervention (2 x 375 mg/d)* & *low flavanol control (2 x 9 mg/d)*



Flavanol intervention reverses endothelial dysfunction in CAD patients

FMD

Blood pressure

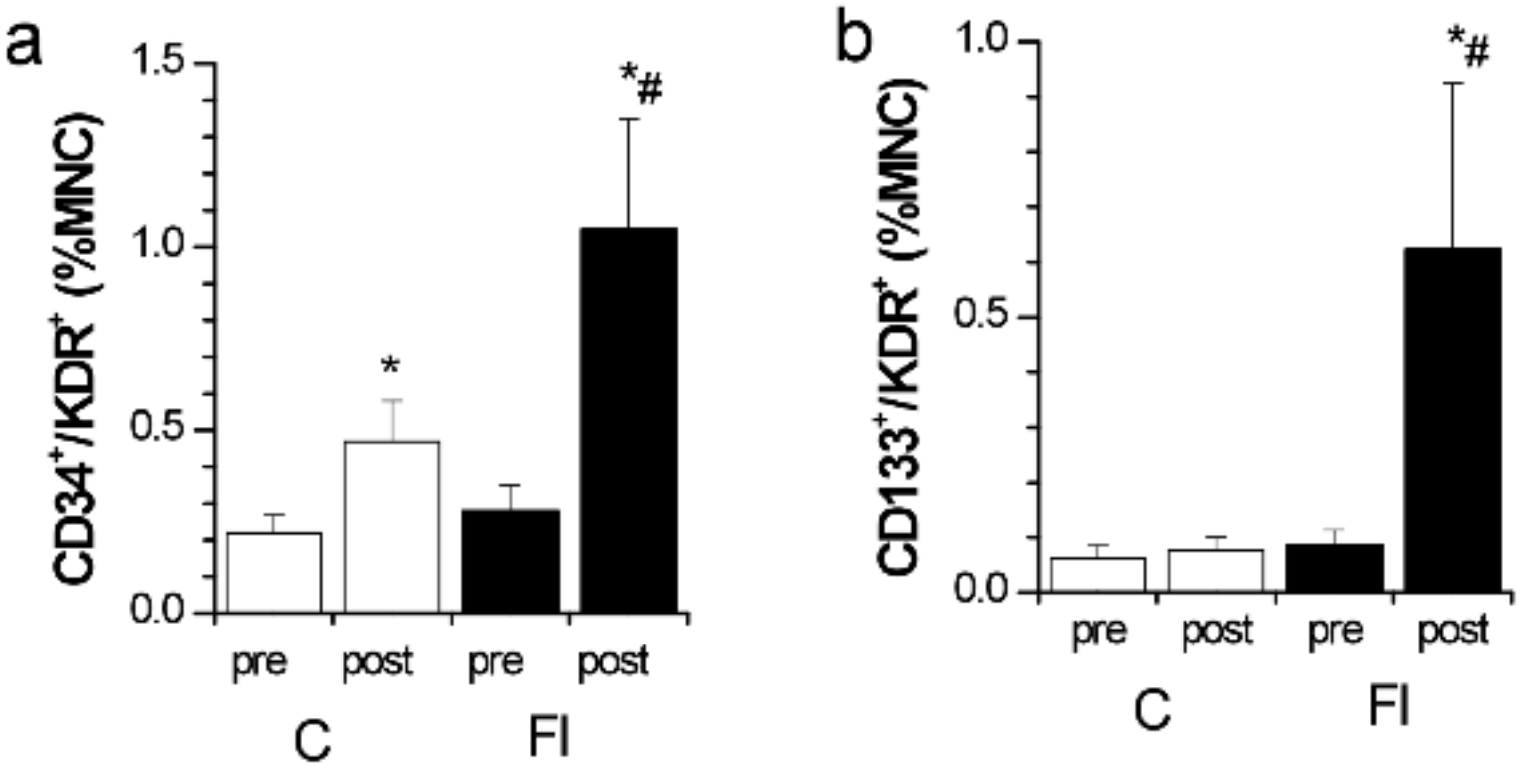


FI high flavanol interventions (2x375 mg 30d)

C low flavanol control (2x9 mg 30 d)

* p<0^.05 vs respective pre, # p<0.05 vs C

Flavanol intervention mobilizes functional CACs



Heiss JACC 2010

Flavanol research in humans

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Clinical intervention studies

Conclusion

Flavanols and their metabolites are vasoactive in young, elderly, healthy and diseased humans

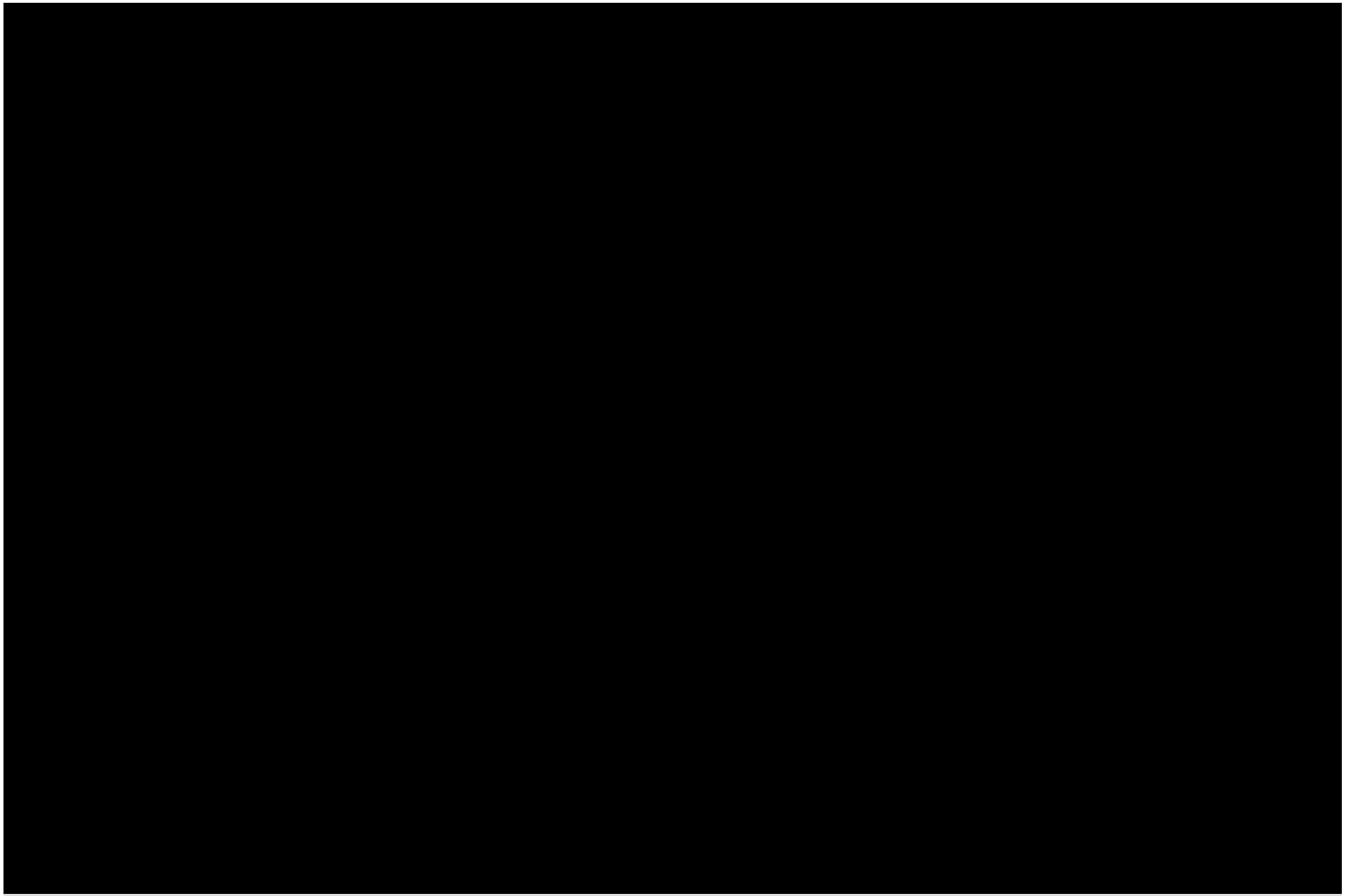
Clinical intervention studies

Conclusion

Flavanols and their metabolites are vasoactive in young, elderly, healthy and diseased subjects

Perspectives

Flavanols and their metabolites harbor vasculoprotective potential for primary and secondary CVD prevention



Take-home Message: ***Flavanols Session***

- ‚**Bioactives**' rather than (only) ‚Antioxidants'

- *Active Compounds*: Flavanol *Metabolites from Monomer, (-)-Epicatechin; Oligomers (Procyanidins) do NOT contribute*

- *Epidemiology: blood pressure lowering in human intervention studies at >50 mg flavanol (monomer)/day*

-

• *Mechanism of Action*: prooxidant enzymes, reactive oxygen species (*in vitro*, cell culture expts); inflammatory markers; master switches: *Nrf2, NFkappaB*

• *Cardiovascular Health*:
Flavanols and metabolites vasoactive are vasoactive in young, elderly, healthy and diseased subjects

•*Flavanols and their metabolites harbor vasoprotective potential for primary and secondary CVD prevention*

FLAVIOLA international workshop on Flavanols in Cardiovascular Health

Brussels, 24 January 2012

www.flaviola.org/project/events/workshop/index.php