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Endothelial Progenitor Cells and physical exercise

Cesari Francesca

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Introduction

- Postnatal neovascularization has predominantly been attributed to angiogenesis, which is characterized by mature endothelial cell proliferation, migration and remodeling. In 1997 ASAHARA et al. demonstrated that purified CD34+ hematopoietic progenitor cells from adults can differentiate ex–vivo to an endothelial phenotype

ENDOTHELIAL PROGENITOR CELLS (EPCs)

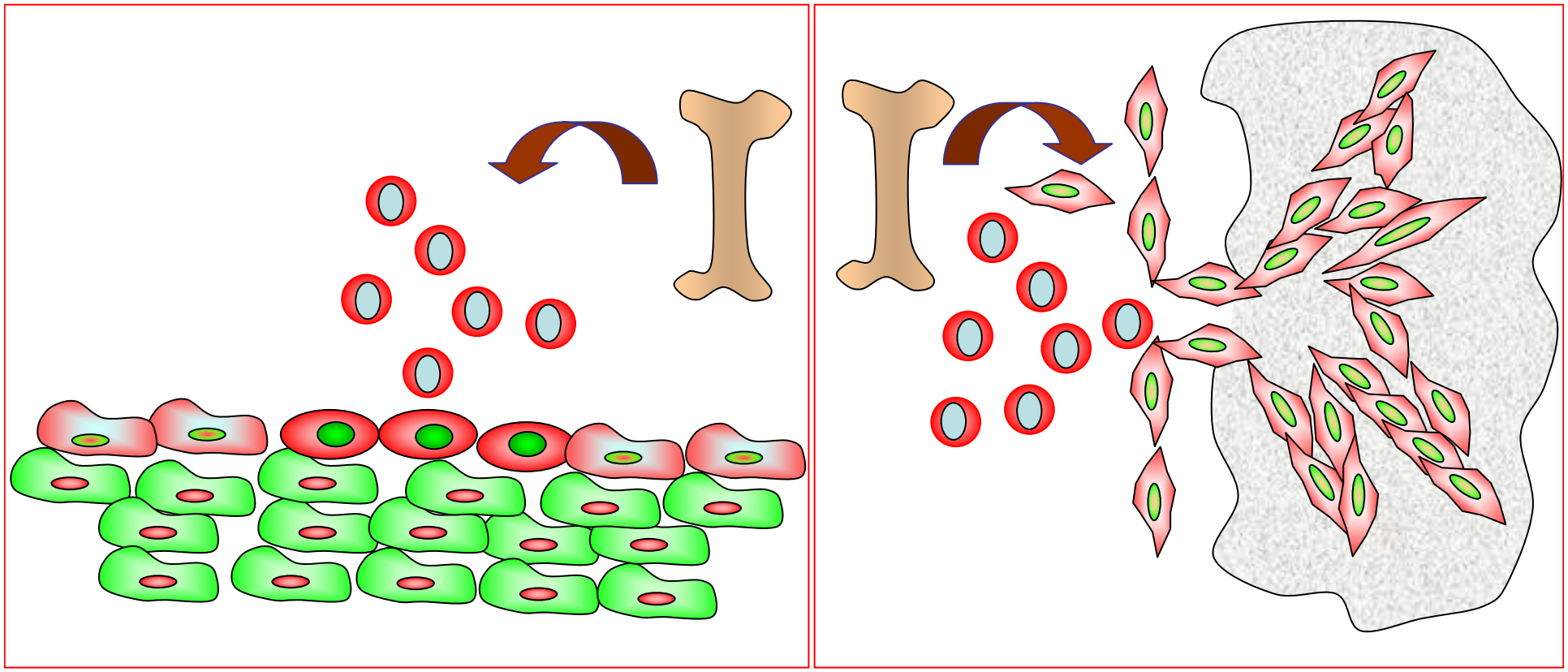
- Endothelial progenitor cells (EPCs) are bone marrow-derived progenitor cells able to differentiate into mature endothelial cells

- These cells significantly contribuite to the re-endothelialization and neovascularization after tissue ischemia in vivo

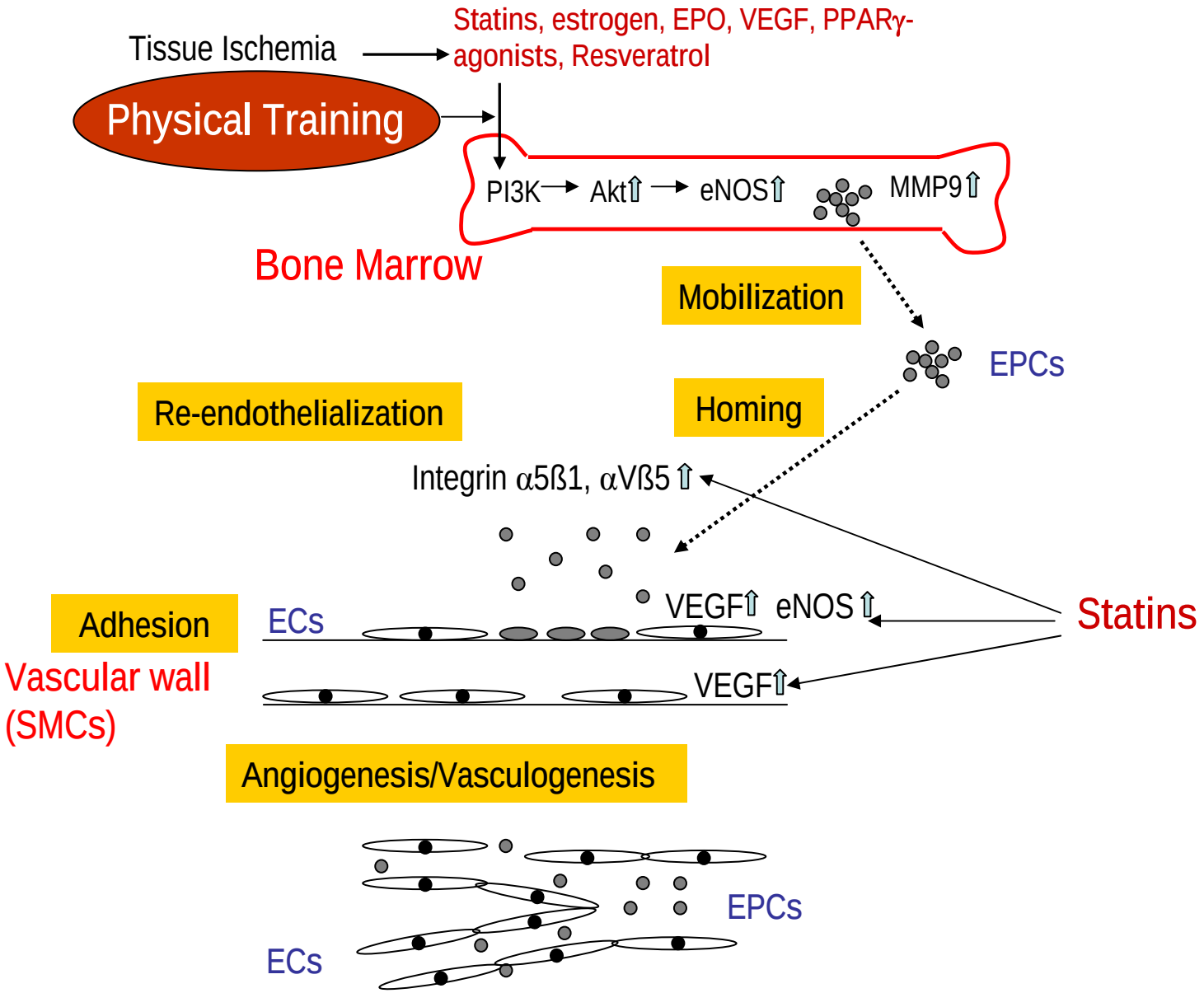
ENDOTHELIAL
PROGENITOR CELLS

RE-ENDOTHELIALIZATION

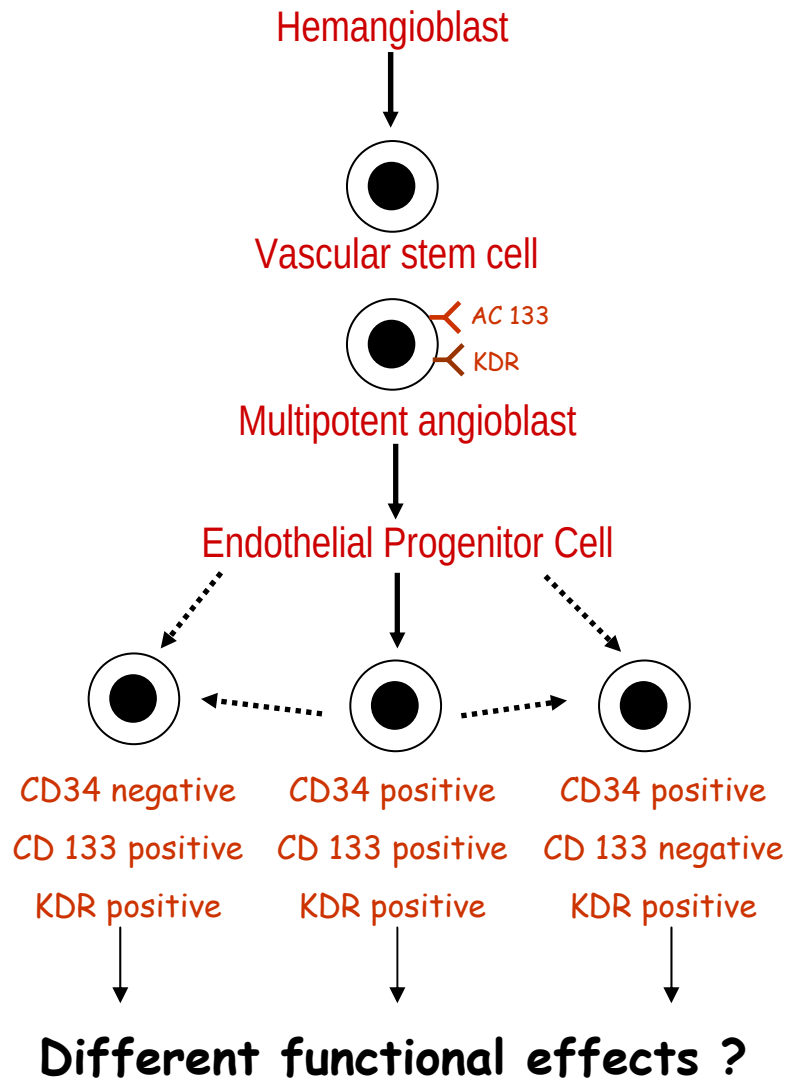
NEOVASCULARIZATION



Mechanisms of EPCs' mobilization from bone marrow and contribution to re-endothelialization and vasculogenesis

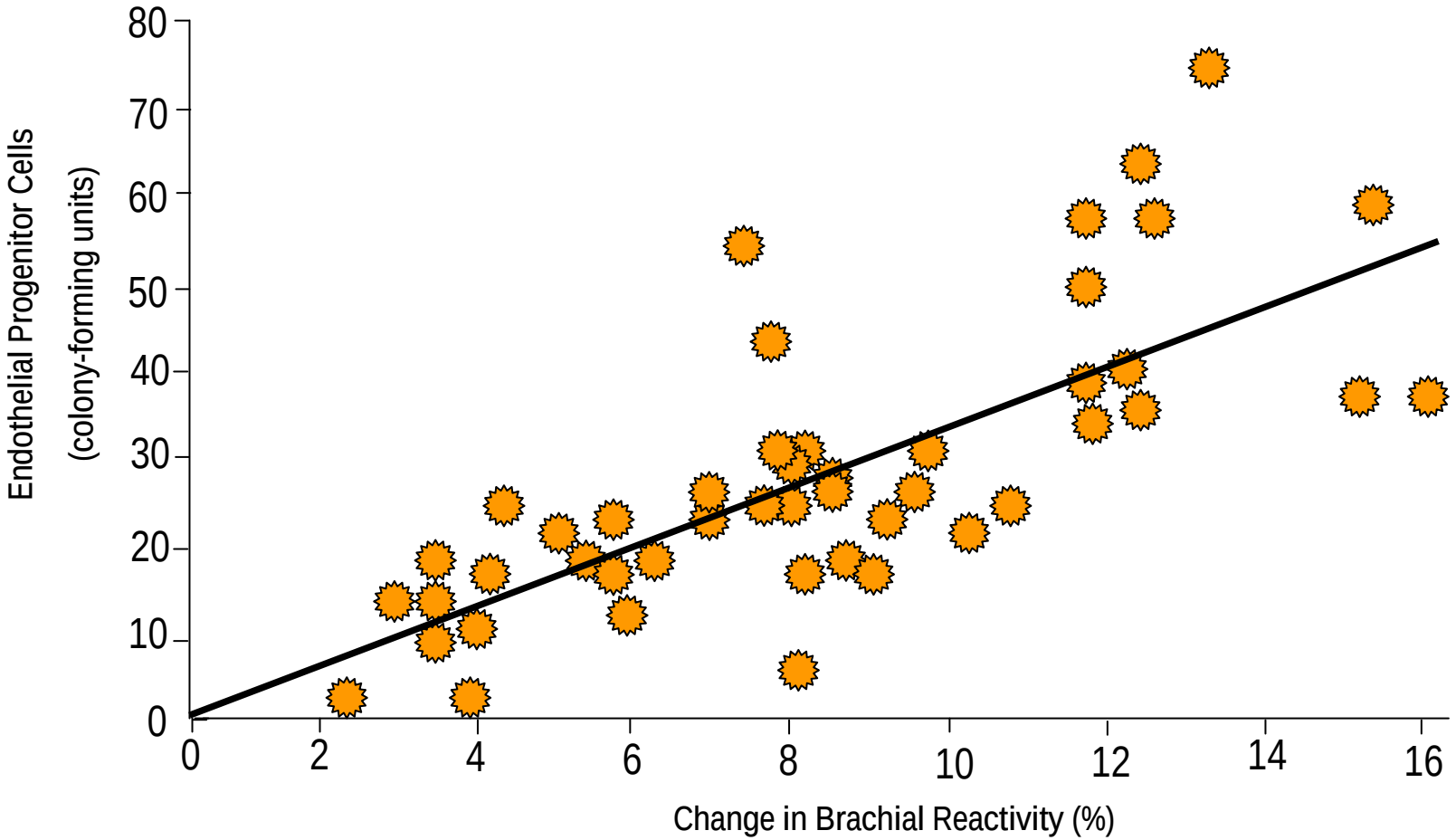


Definition of EPCs' surface markers



Relation between Endothelial Progenitor Cells and Endothelial function (n=45)

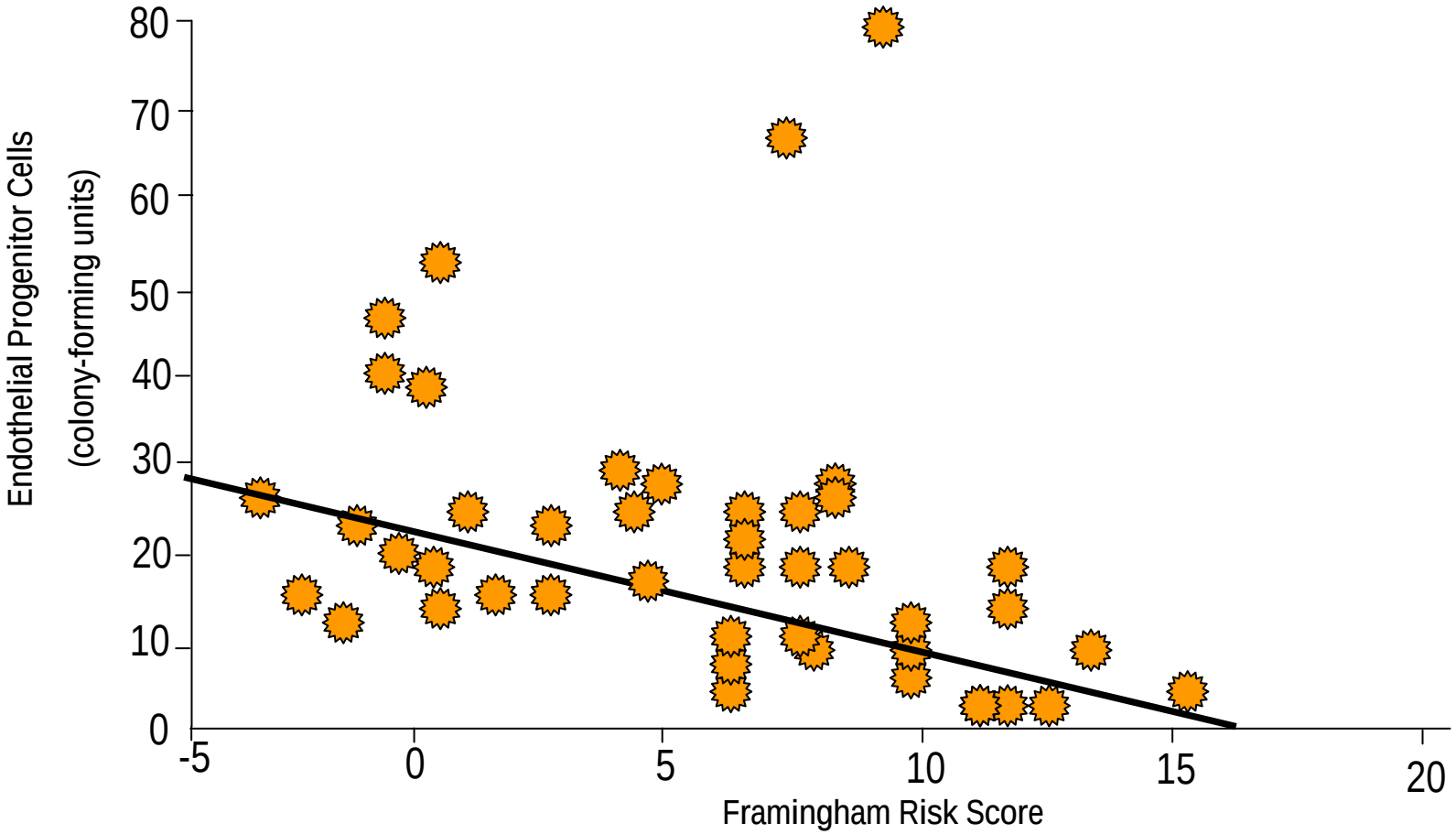
r= 0.59; p<0.001



Hill et al, N Engl J Med, 2003

Association between Cardiovascular Risk factors and Endothelial Progenitor Cell Colony Counts (n=45)

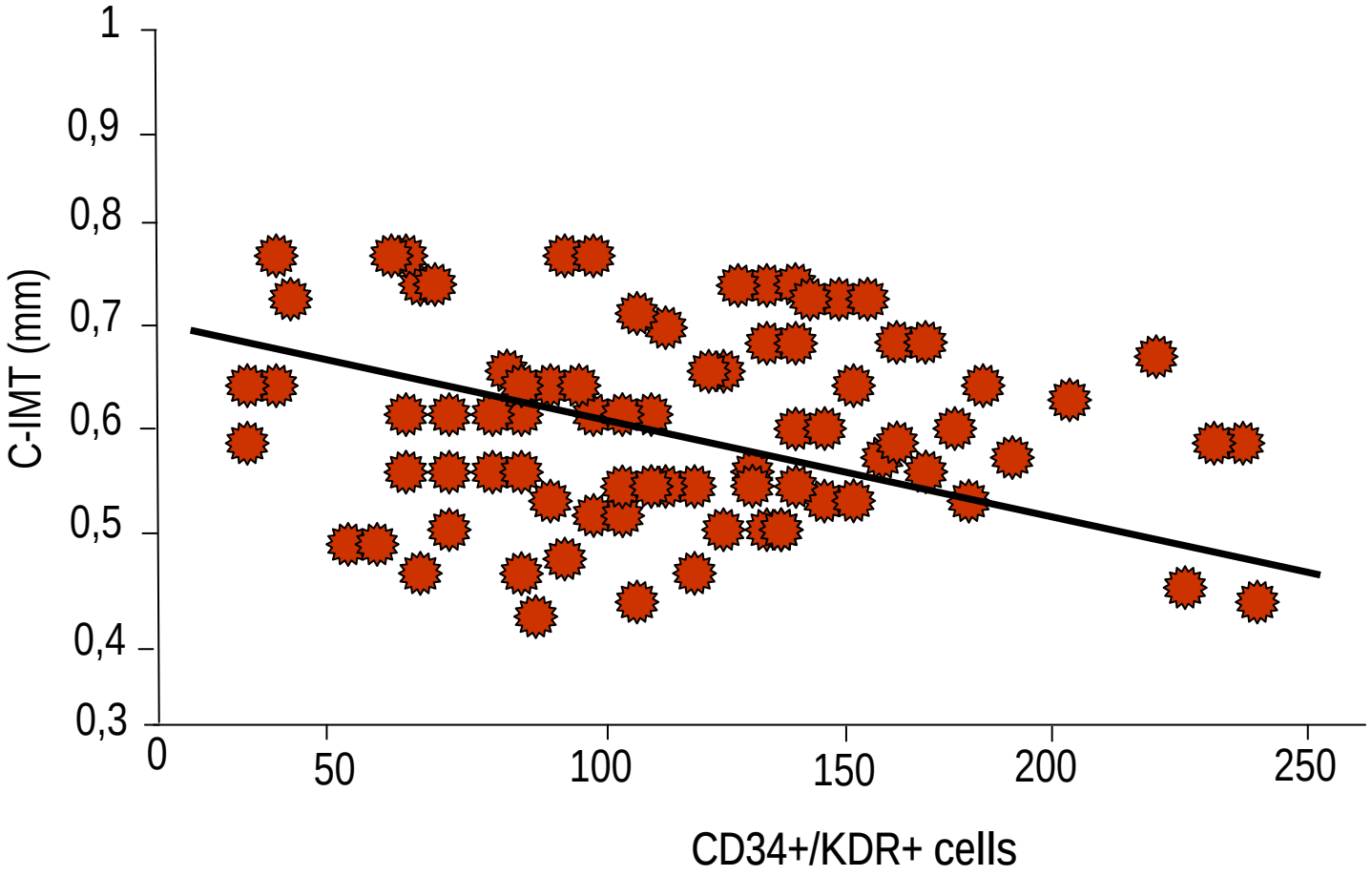
r= -0.47; p=0.001



Hill et al, N Engl J Med, 2003

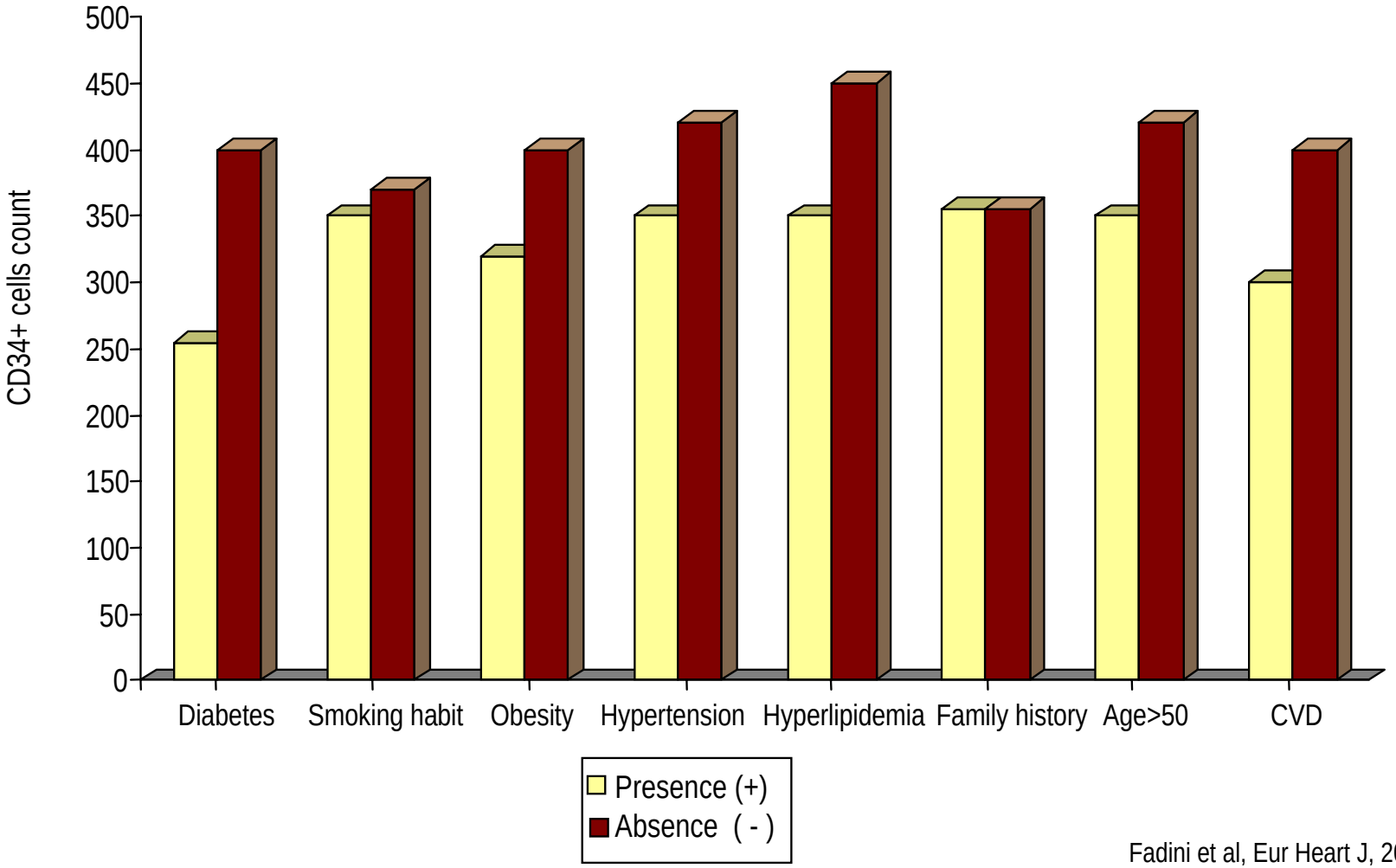
Relation between EPCs CD34+/KDR+ cell count and c-IMT (n=137)

r=-0.28; p=0.001



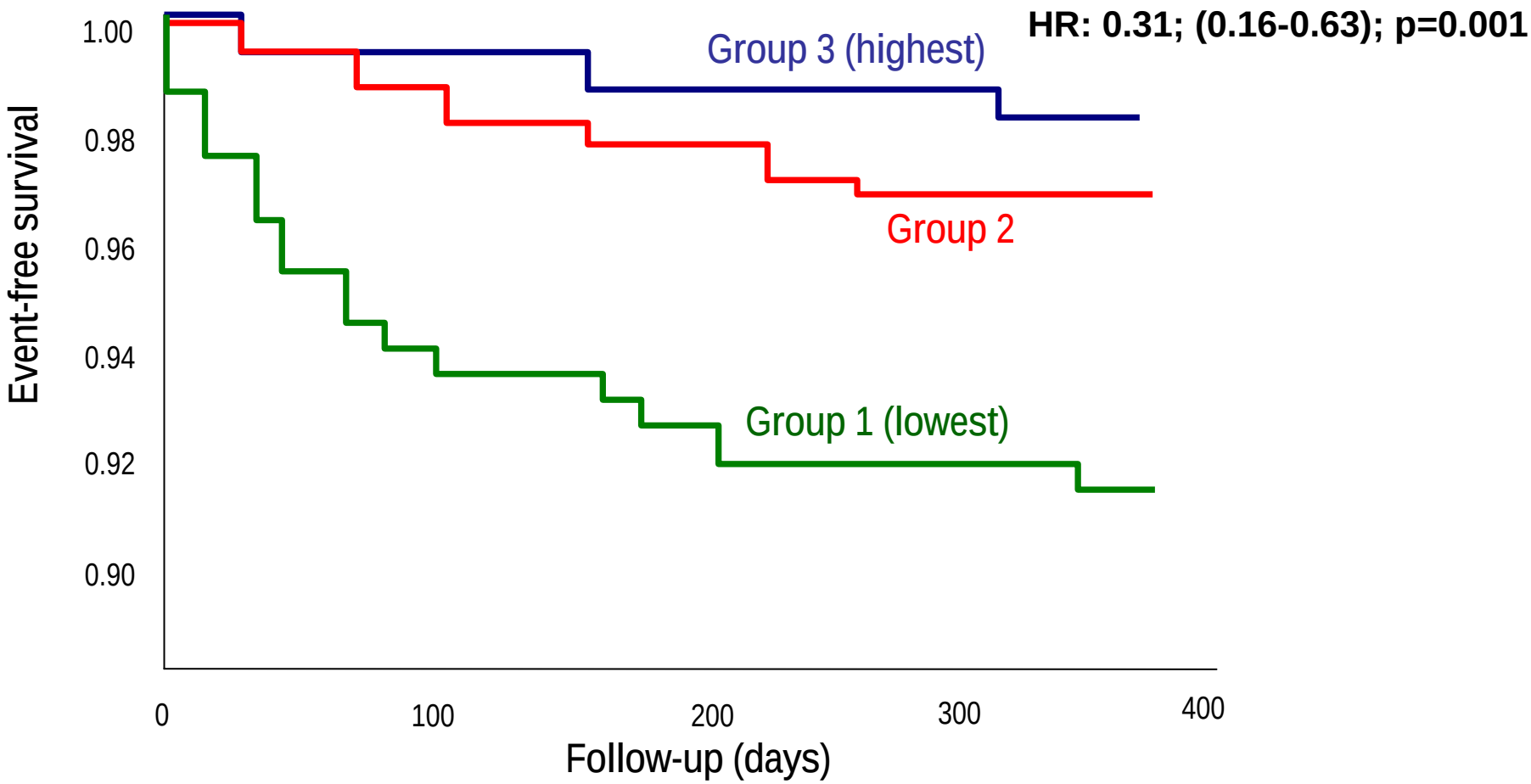
Fadini et al., Stroke 2006

CD34+ cell levels in the presence (+) or absence (-) of classical risk factors and established CVD (n=214)



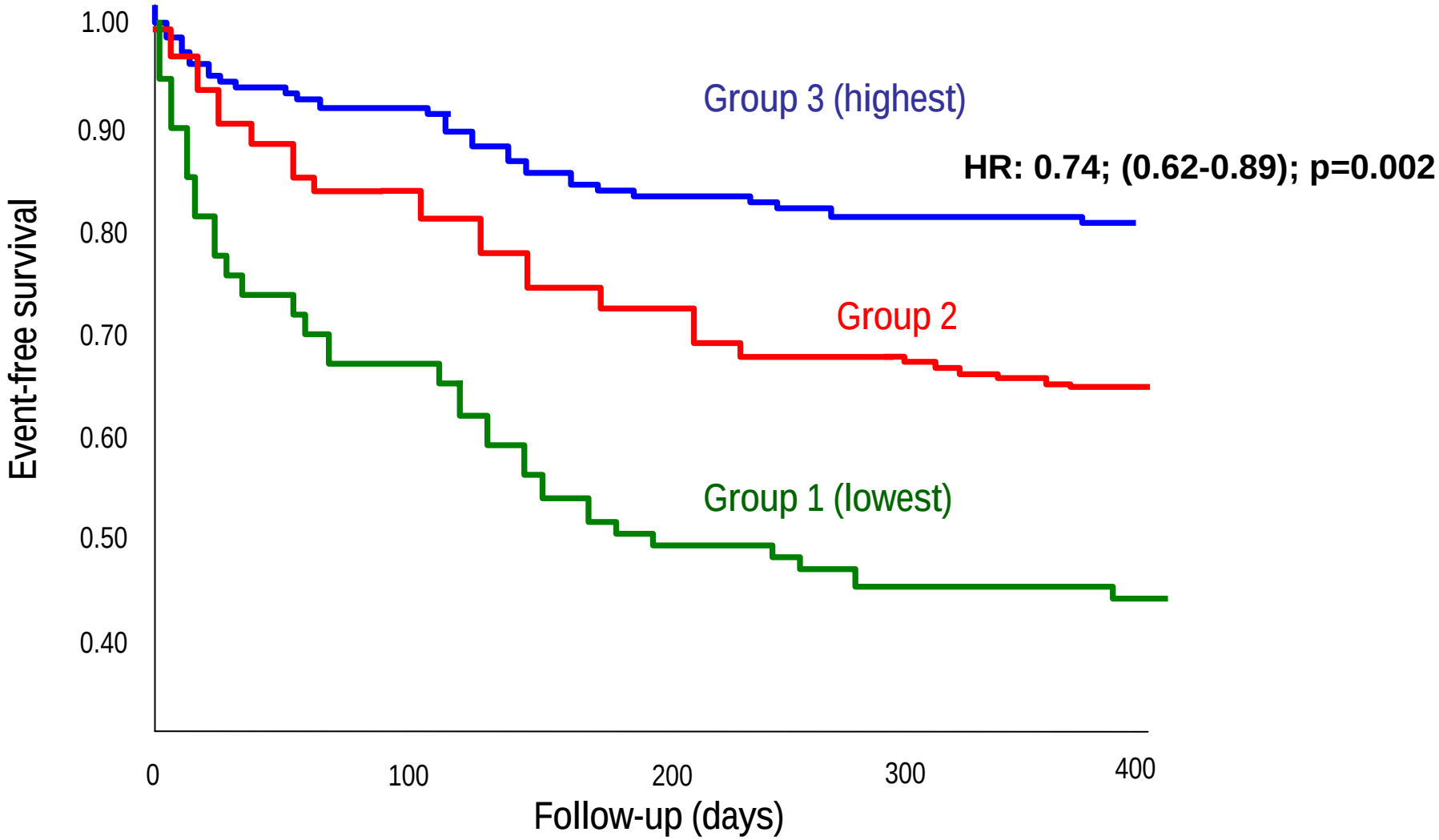
Fadini et al, Eur Heart J, 2006

Cumulative event-free survival for CV DEATH at 12 months according to circulating levels of CD34+/KDR+ EPCs (n=519)



Werner et al., NEJM 2005

Cumulative event-free survival for MACE at 12 months according to circulating levels of CD34+/KDR+ EPCs (n=519)



Werner et al., NEJM 2005

Factors influencing EPCs

Statins

Estrogen/Estradiol

Erythropoietin

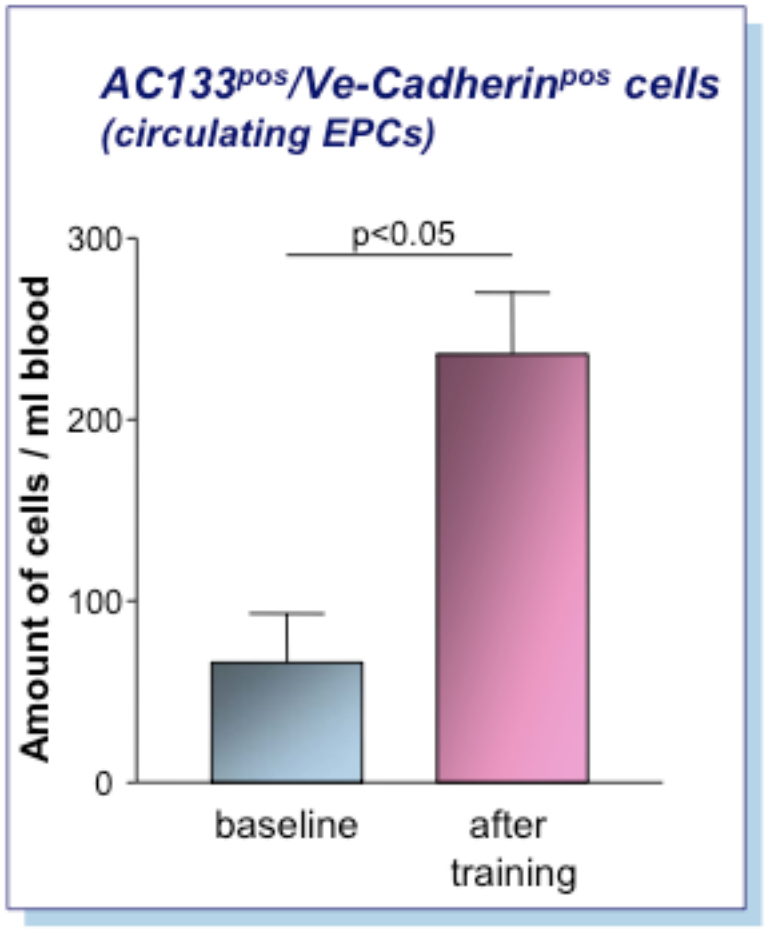
Regular physical exercise → ↑ Number and functional activity of EPCs

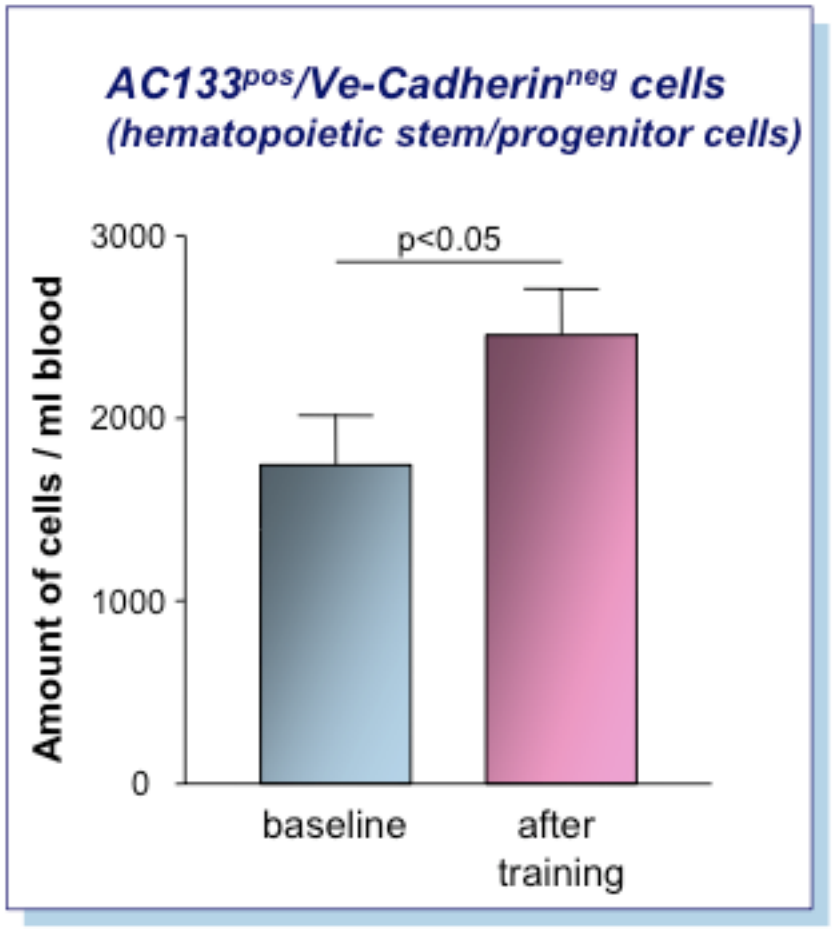
Resveratrol at low concentration

PPAR-γ agonists (rosiglitazone- pioglitazone)

G-CSF

Influence of a single exercise bout on EPCs in healthy subjects





Rehman et al, JACC 2004

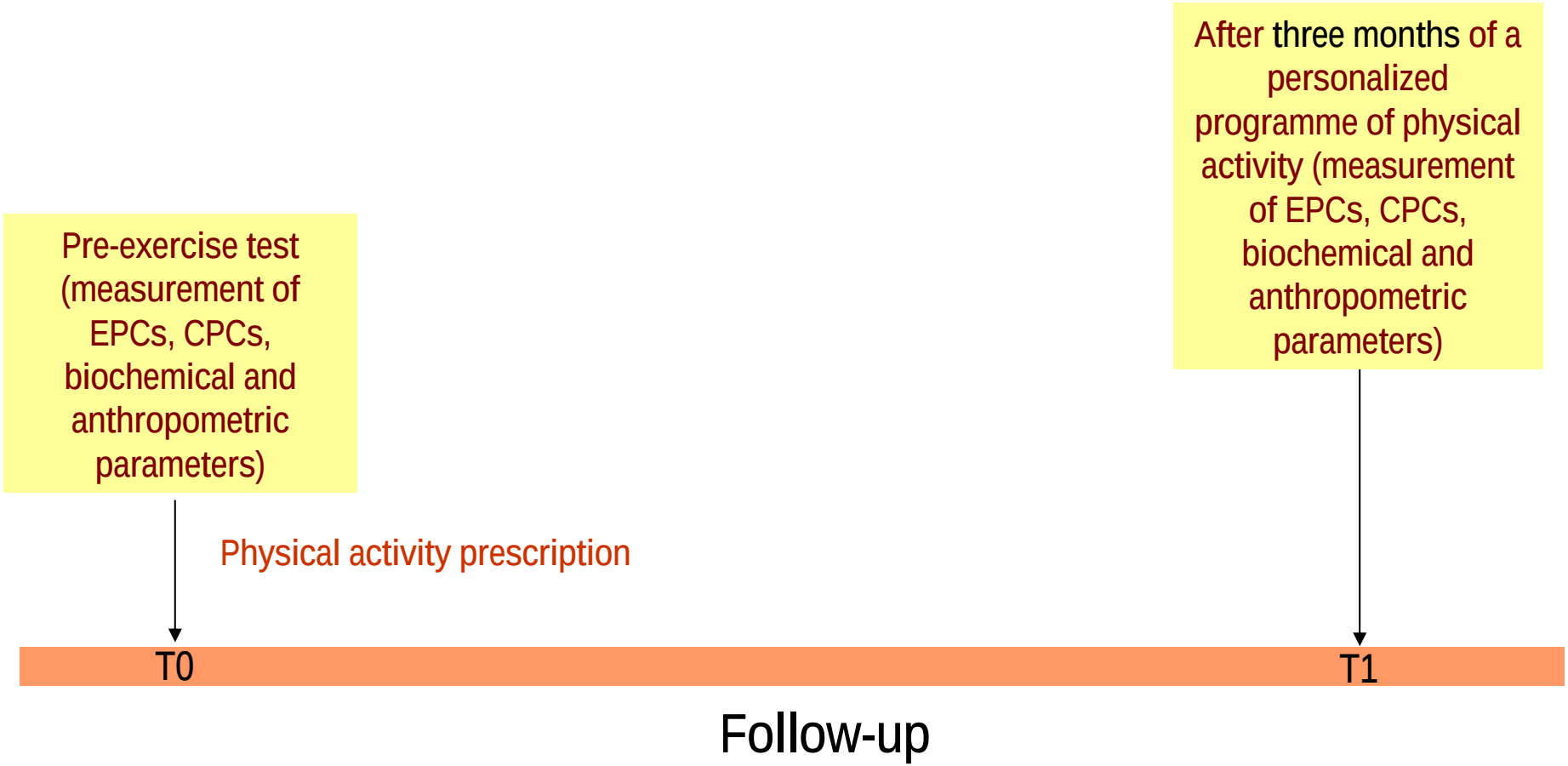
Effect of a personalized physical activity programme on circulating endothelial progenitor cells and weight loss

Cesari F, Sofi F §°, Gori AM, Corsani I, Capalbo A, Caporale R*, Abbate R, Gensini GF°, Casini A§

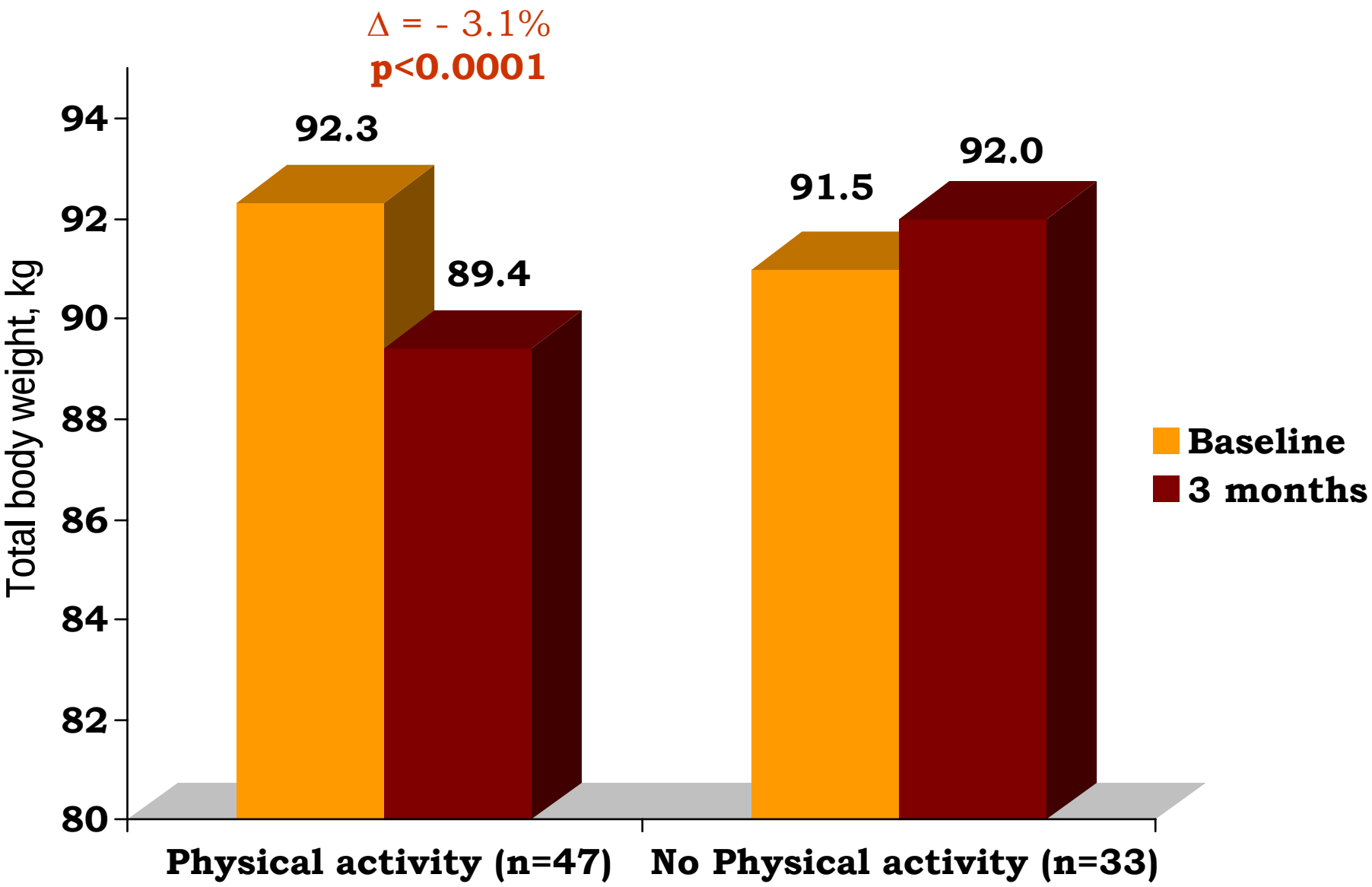
Department of Medical and Surgical Critical Care, Thrombosis Centre, University of Florence; § Regional Agency for Nutrition, University of Florence; *Central Laboratory, Azienda Ospedaliero-Universitaria Careggi, Florence, Italy;°Don Carlo Gnocchi Foundation Onlus, IRCCS, Impruneta, Florence;

Design of the study

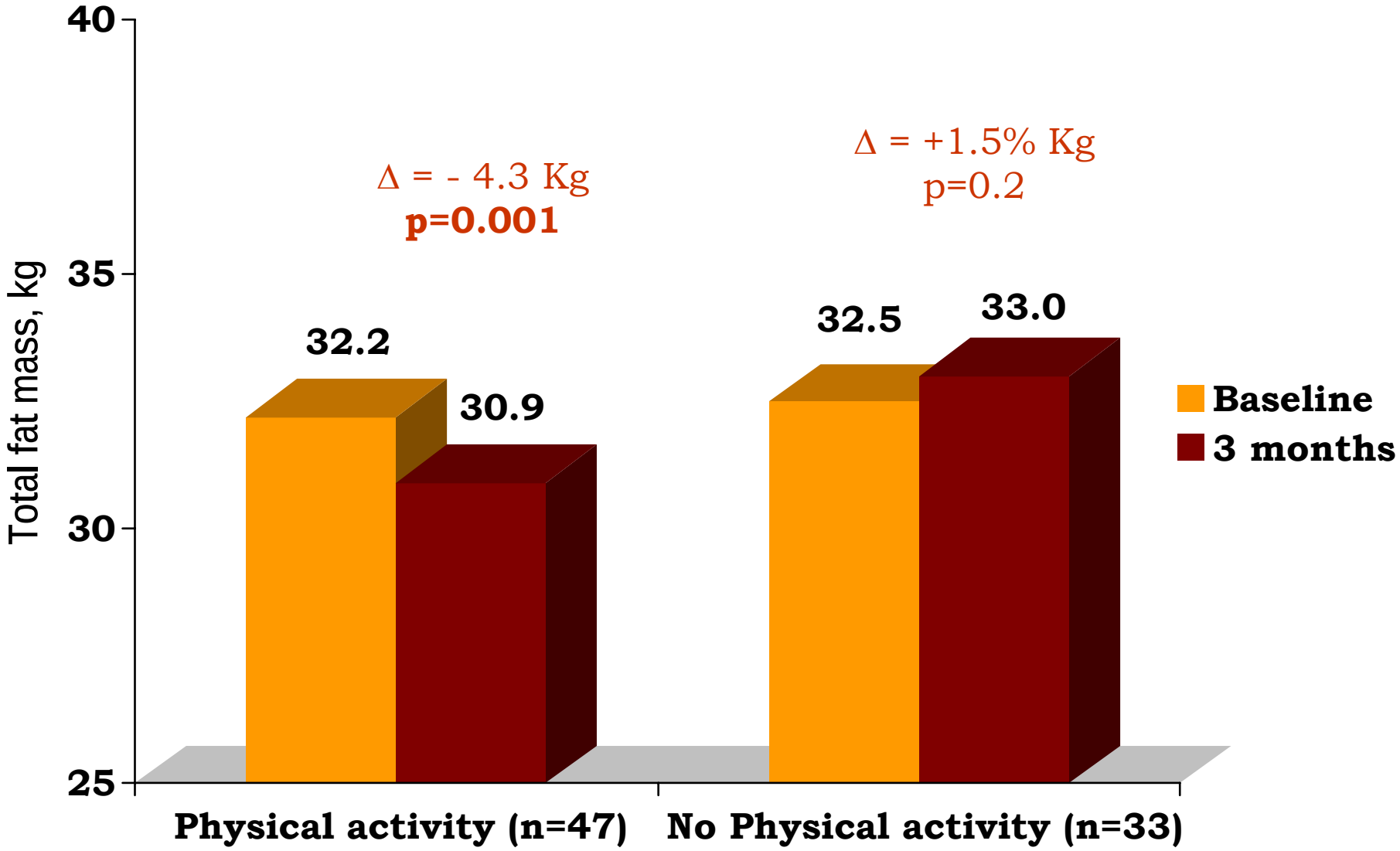
80 overweight non-diabetic subjects with a median age of 44 (range: 24-65) years and a mean BMI of 31.2±4.9 underwent a maximal stress exercise test with maximal oxygen uptake (VO2max)



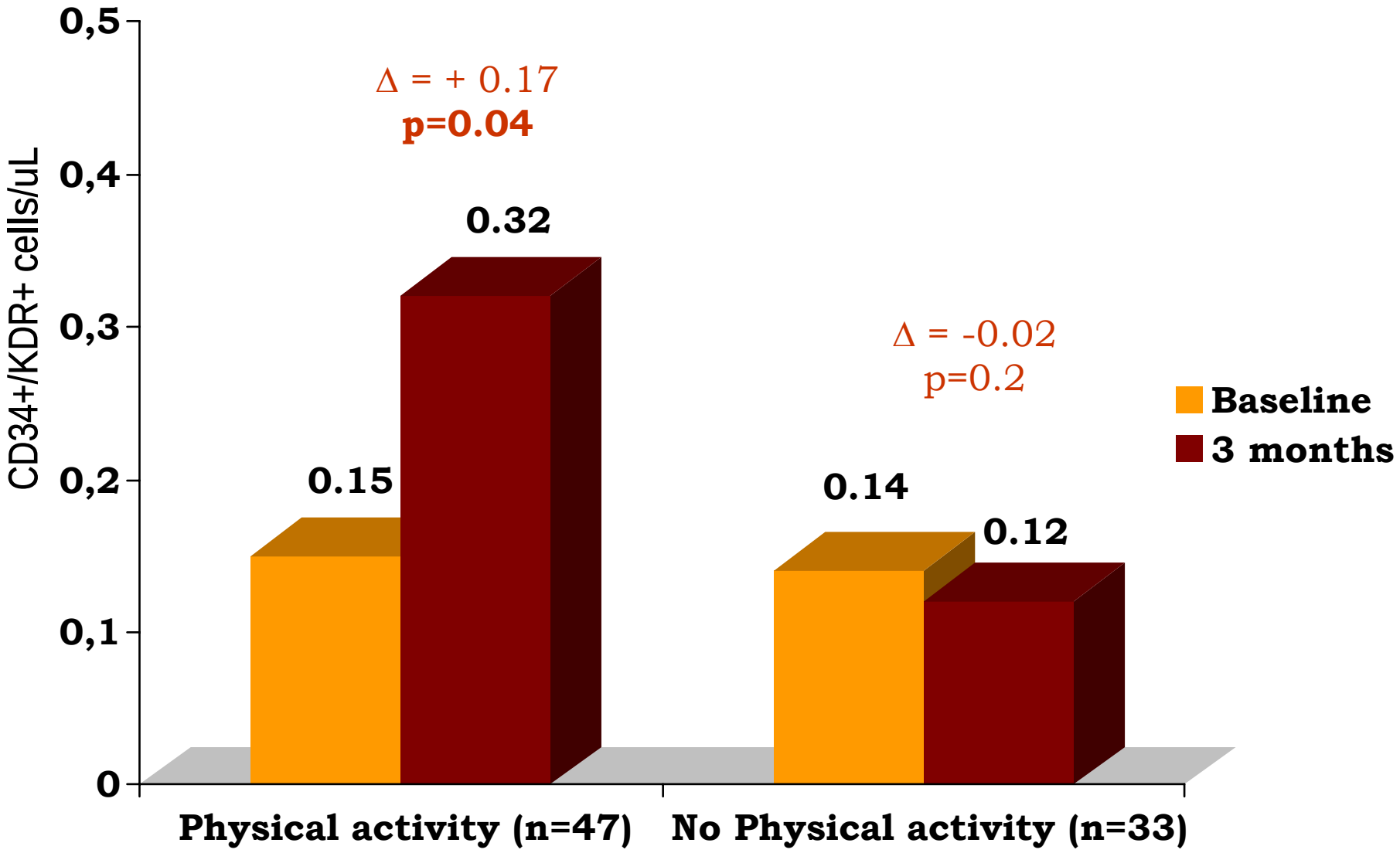
Changes of total body weight



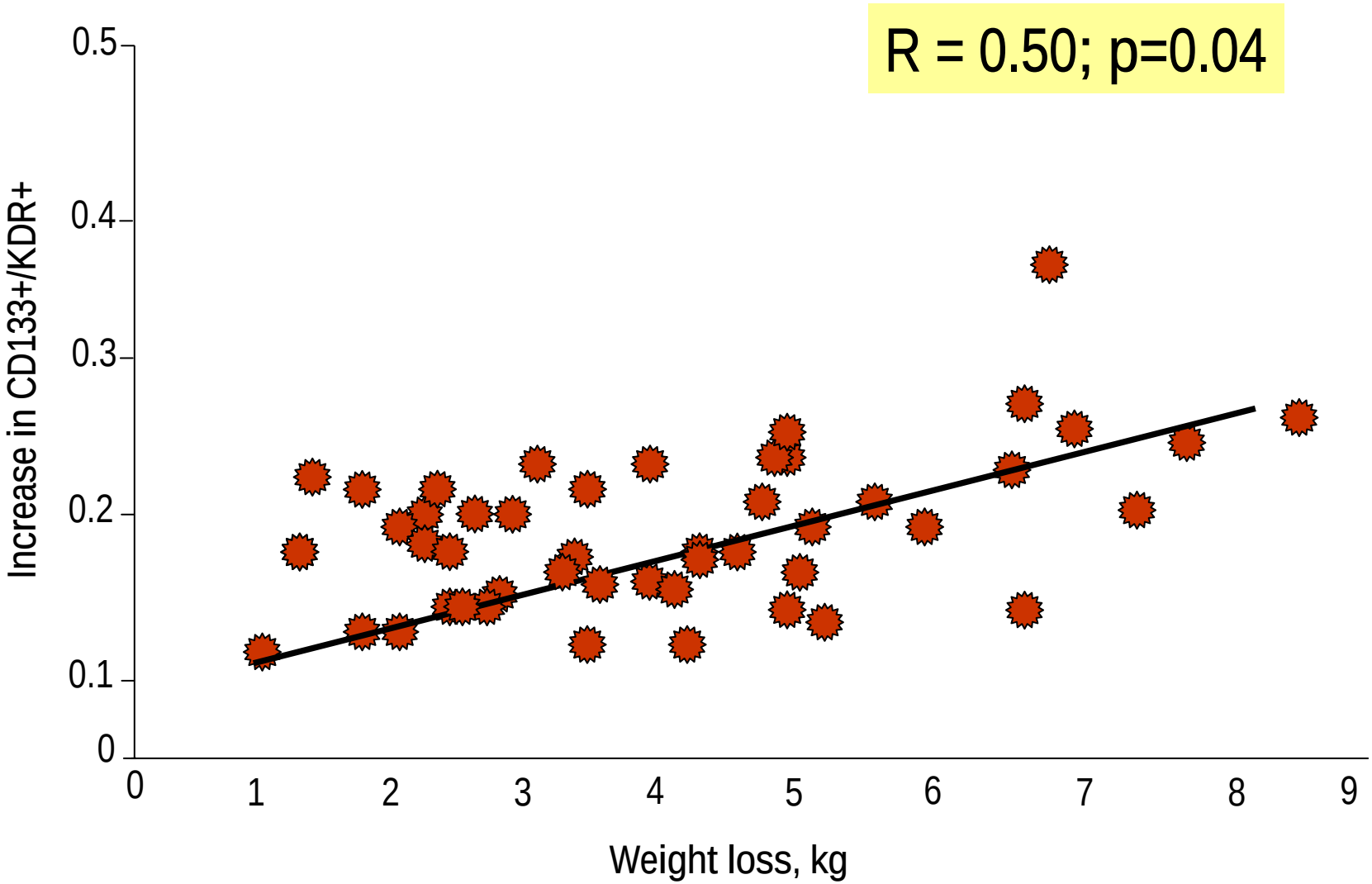
Changes of total fat mass



Changes of CD34+/KDR+ EPCs



Correlation analysis between CD133+/KDR+ EPCs and weight loss



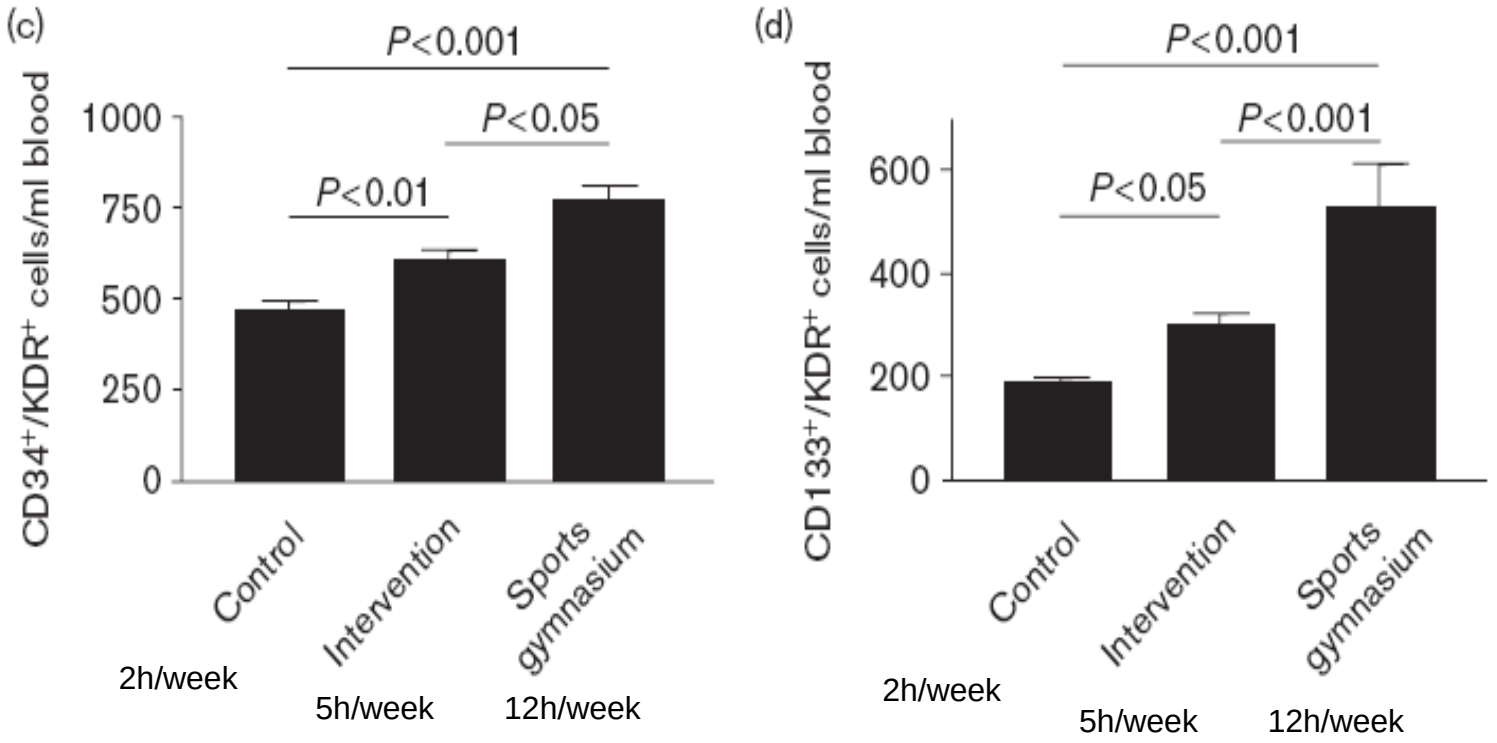
EUROPEAN SOCIETY OF CARDIOLOGY®

European Journal of Cardiovascular Prevention and Rehabilitation 2008, 15:416–422

Increasing physical education in high school students: effects on concentration of circulating endothelial progenitor cells

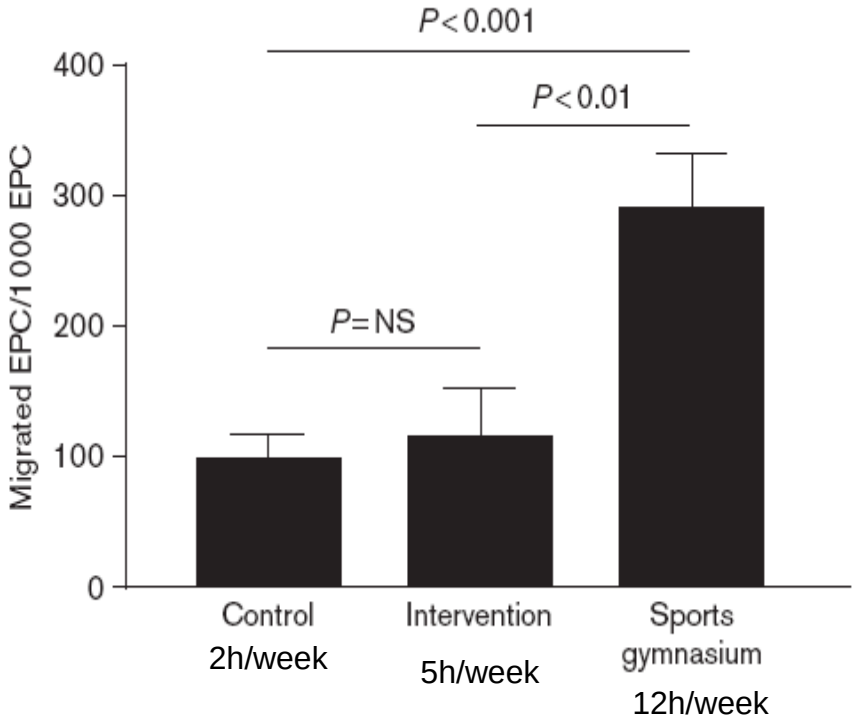
Claudia Walther[a,*], Volker Adams[a,*], Inga Bothur[a], Kati Drechsler[a], Sven Fikenzer[c], Melanie Sonnabend[a], Beatrice Bublitz[a], Antje Körner[b], Sandra Erbs[a], Martin Busse[c] and Gerhard Schuler[a]

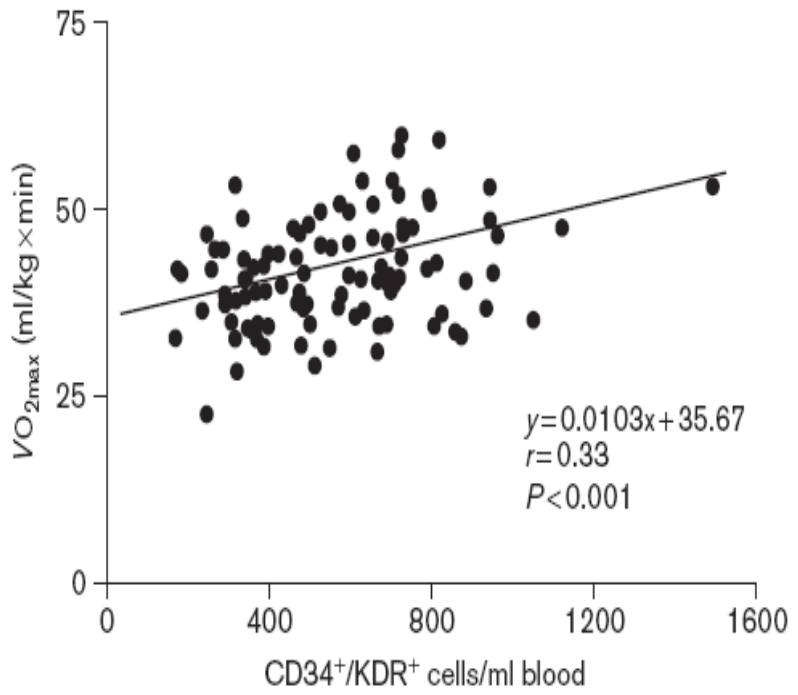
Differences on CD34+/KDR+ and CD133+/KDR+ cells in students in relation to a physical education program (n=92)



Walther et al, Eur J Card Prev Rehab, 2008

Migratory capacity of EPCs and correlation analysis between EPCs and exercise capacity of the school children (n=92)





Walther et al, Eur J Card Prev Rehab, 2008

Pediatric Cardiology

Effect of Increased Exercise in School Children on Physical Fitness and Endothelial Progenitor Cells

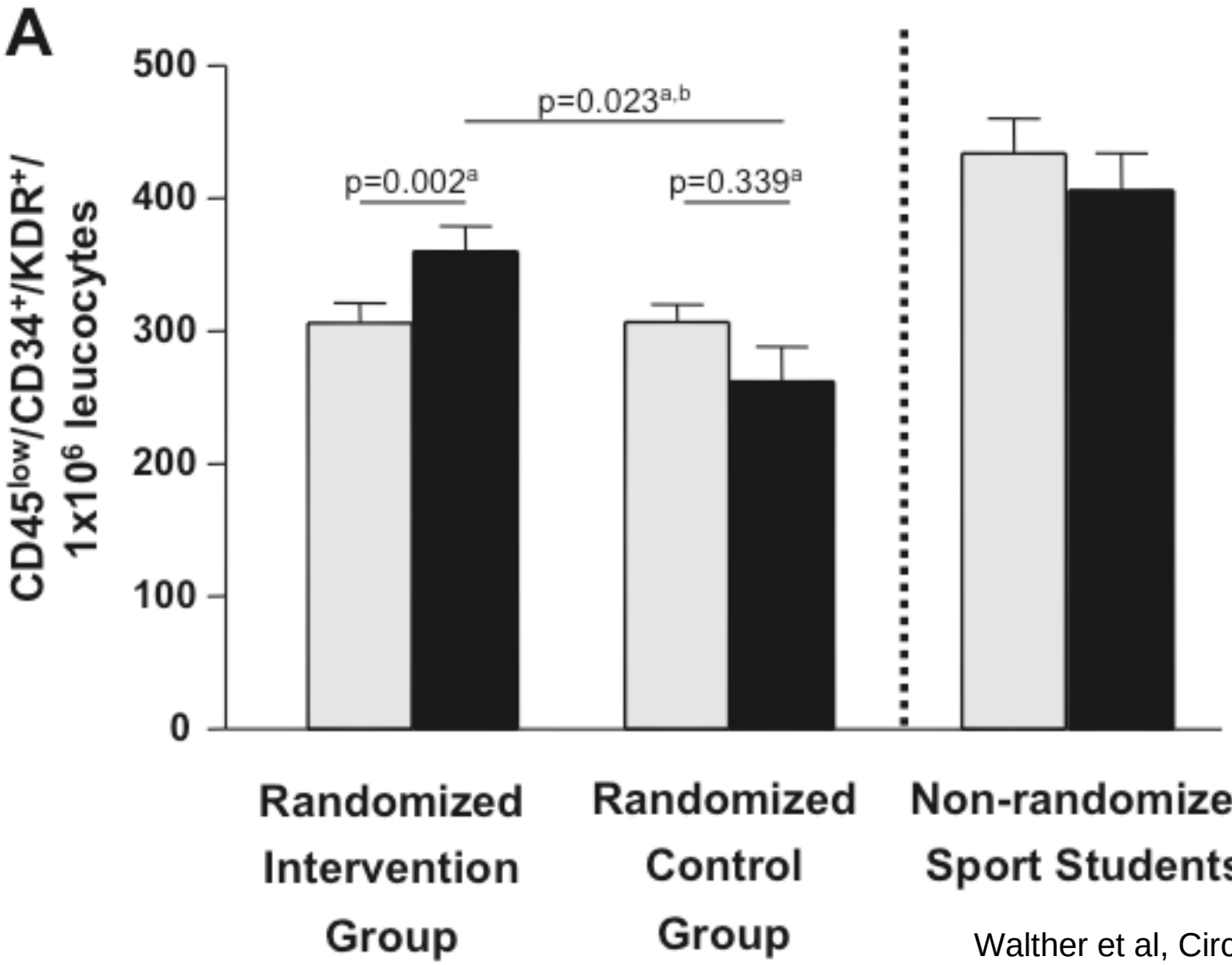
A Prospective Randomized Trial

Claudia Walther, MD; Luise Gaede, BS; Volker Adams, PhD; Götz Gelbrich, MD, PhD; Alexander Leichtle, MD; Sandra Erbs, MD; Melanie Sonnabend, MS; Kati Fikenzer, MD; Antje Körner, MD; Wieland Kiess, MD; Mathias Bruegel, MD; Joachim Thiery, MD; Gerhard Schuler, MD

A randomized trial on **182 children** (mean age 11.1 years) were randomized to an **intervention group** with daily school exercise lessons for 1 year and a **control group** with regular school sports twice weekly

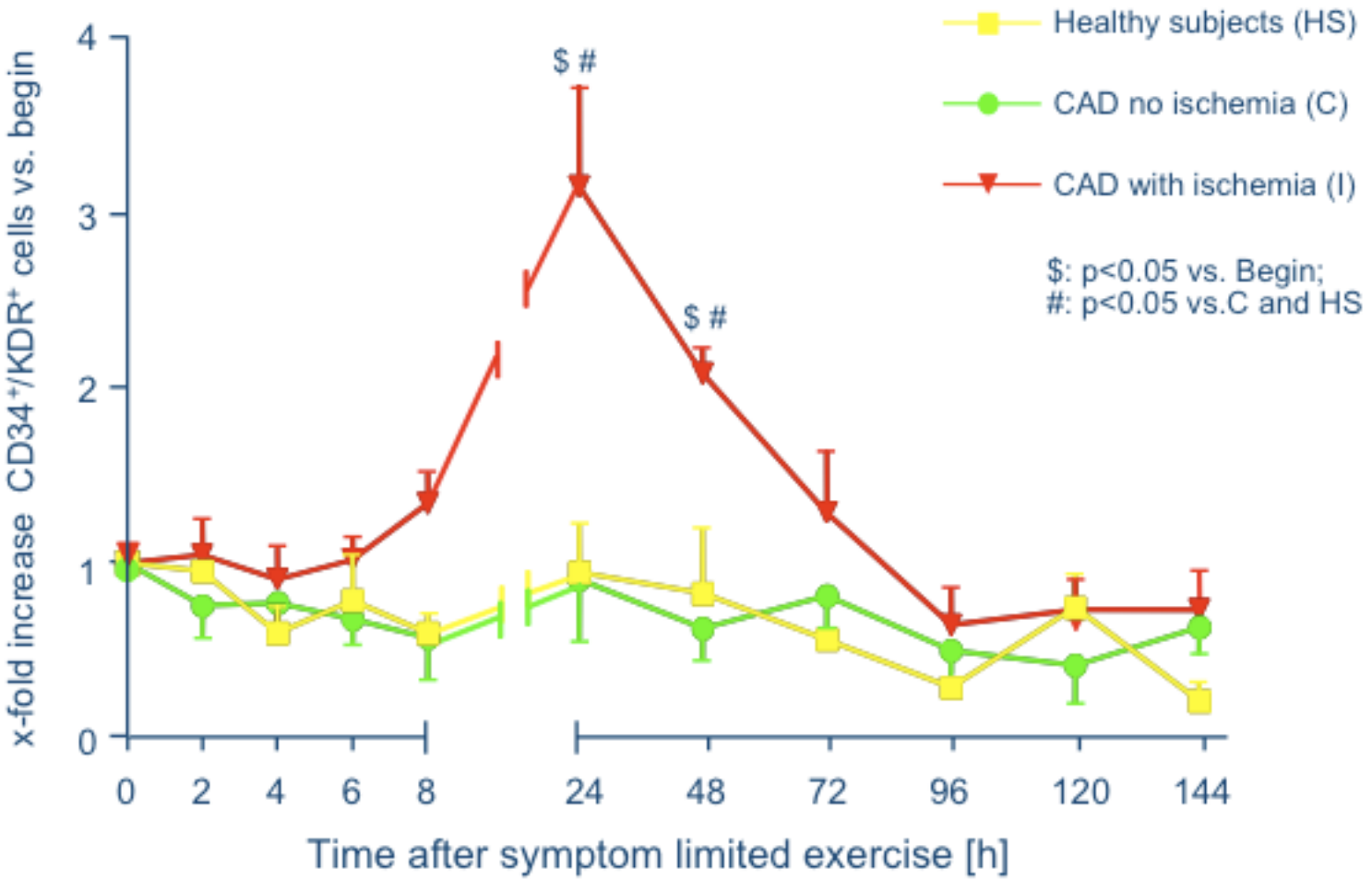
Walther et al, Circulation 2009

Effect of increased exercise in school children on endothelial progenitor cells - A prospective randomized trial



Walther et al, Circulation 2009

Impact of symptoms-limited exercise on EPCs' mobilization



Adams V et al, ATVB 2004

Physical training and EPCs

19 patients with clinically stable CAD

↓

Quantification of EPCs by FACS analysis

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4-week controlled exercise program

- bicycle ergometer training
- Moderate strength training
- 60 – 80% max. heart rate
- no signs of myocardial ischemia

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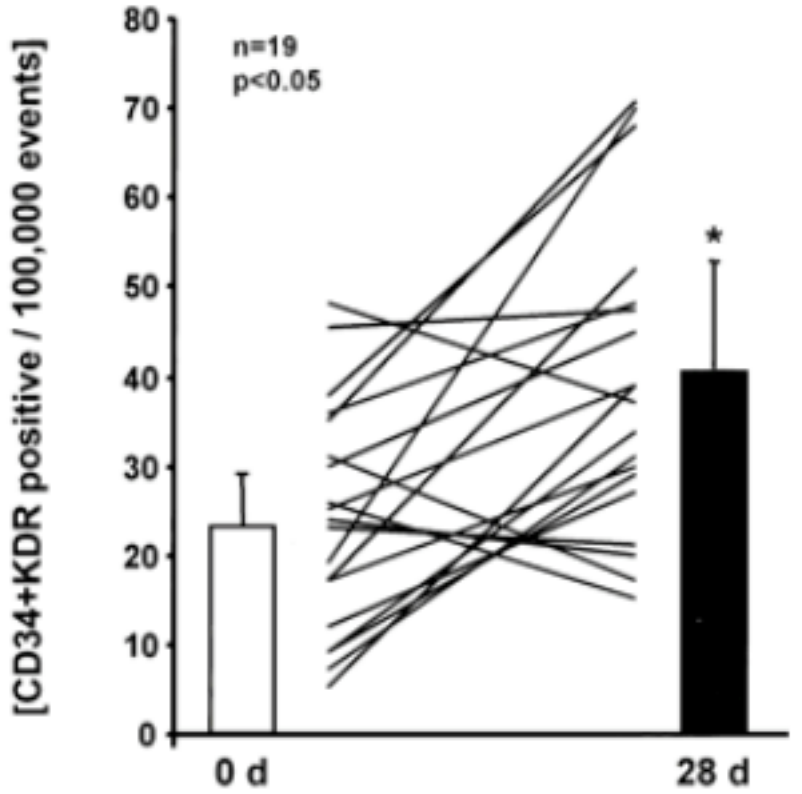
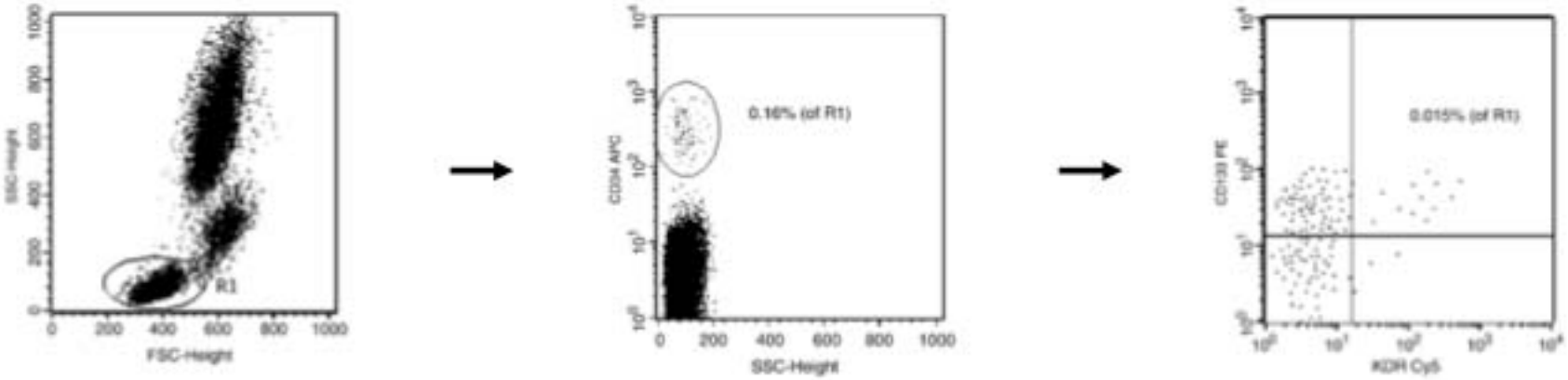
Quantification of EPCs by FACS analysis



Laufs et al, Circulation 2004

Endurance training and EPCs

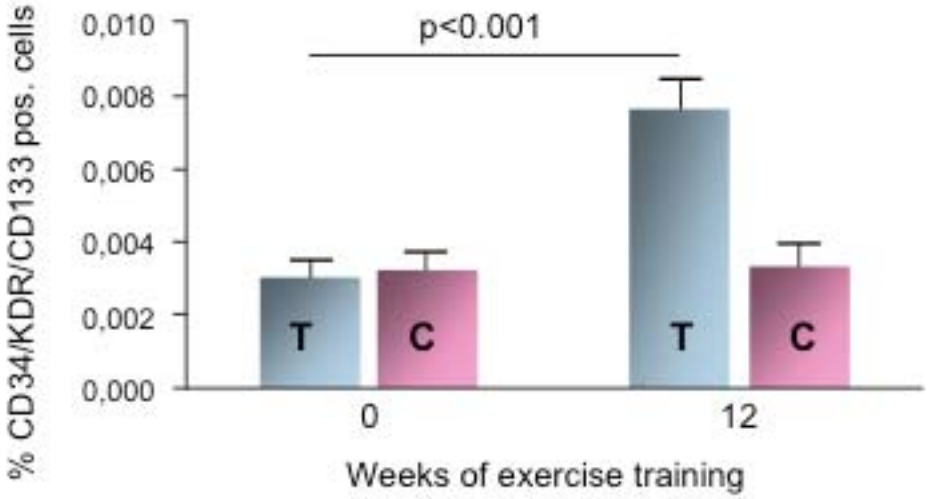


40 asymptomatic CAD patients with no signs of ischemia during bicycle ergometry.

12-weeks training

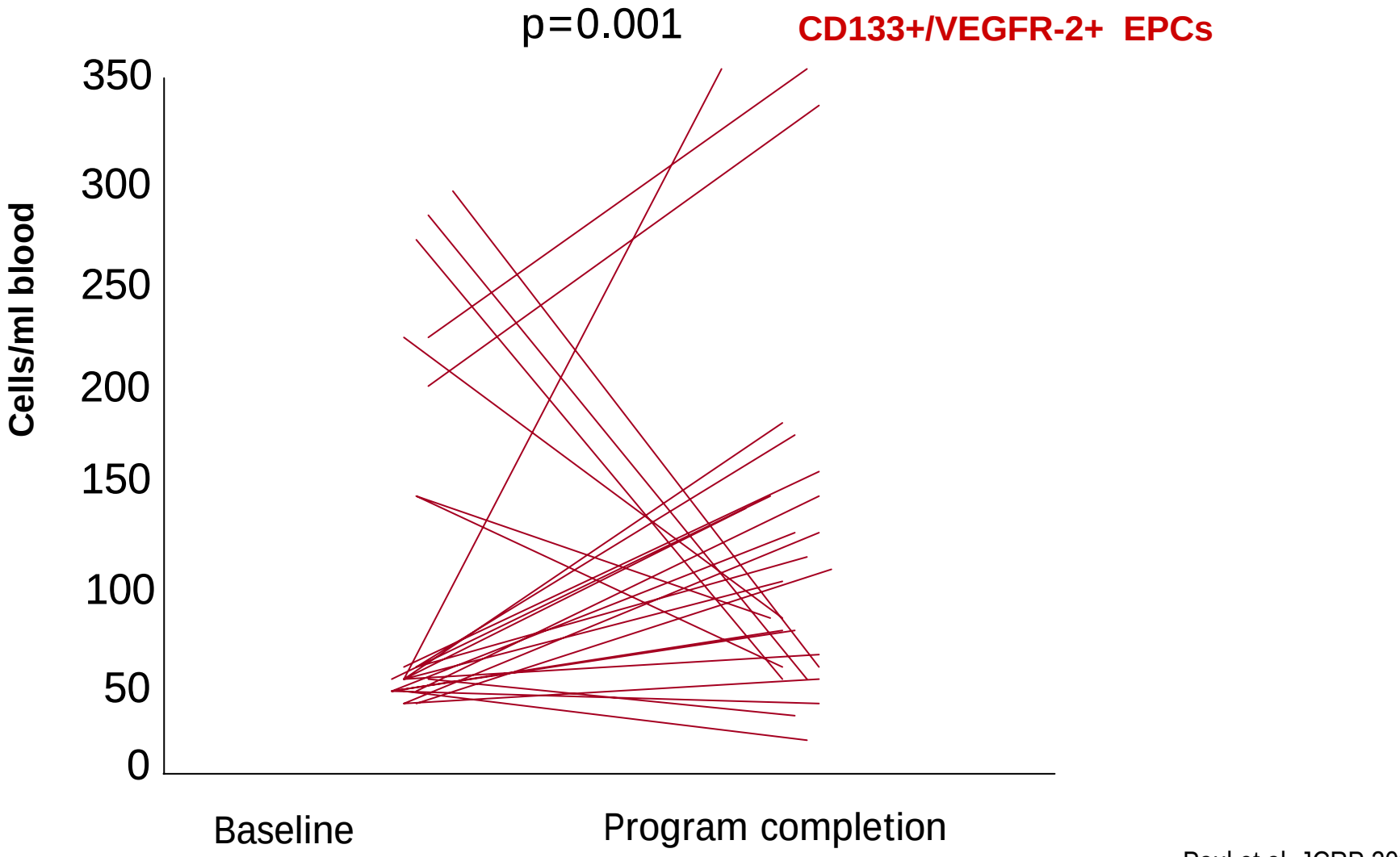
Sedentary control group

Quantification of EPCs at begin and after 12 weeks



Steiner et al, Atherosclerosis 2005

EPCs' mobilization after 3 months of cardiac rehabilitation n=45



Paul et al, JCRP 2007

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Atherosclerosis 199 (2008) 138–146

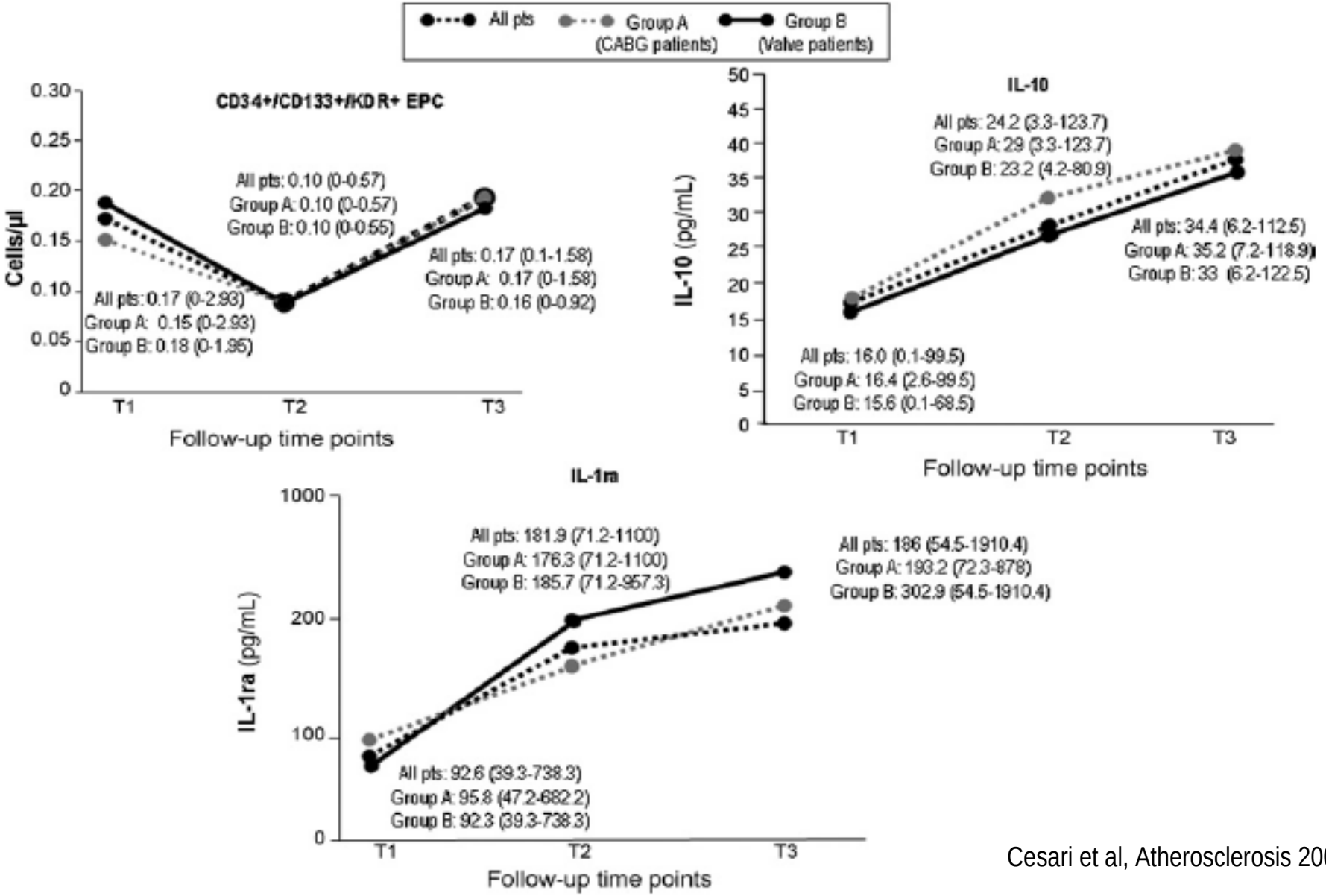
ATHEROSCLEROSIS

www.elsevier.com/locate/atherosclerosis

NT-proBNP and the anti-inflammatory cytokines are correlated with endothelial progenitor cells' response to cardiac surgery

Francesca Cesari [a,b,*], Roberto Caporale [d], Rossella Marcucci [a,b], Sabina Caciolli [c], Pier Luigi Stefano [c], Andrea Capalbo [a,b], Claudio Macchi [f], Mauro Vannucci [e], Gian Franco Gensini [f], Rosanna Abbate [a,b], Anna Maria Gori [a,b]

Circulating Endothelial Progenitor Cells and inflammation in patients before and after cardiac surgery (n=92)



Cesari et al, Atherosclerosis 2008

Cardiac rehabilitation program

Cardiac rehabilitation program lasts for 15 days and consists of 2 phases:

- Clinical rehabilitation program:
  - Pulmonary rehabilitation
  - Active and passive mobilization with onset of deambulation

- Rehabilitation Gym:
  - Pulmonary rehabilitation
  - Free exercises
  - Aerobic training stationary bicycles and trademill

Relationship between exercise capacity, endothelial progenitor cells and cytochemokines in patients undergoing cardiac rehabilitation

Francesca Cesari[1]; Francesco Sofi[1,6]; Roberto Caporale[2]; Andrea Capalbo[1]; Rossella Marcucci[1]; Claudio Macchi[3]; Raffaele Molino Lova[3,4]; Tommaso Cellai[5]; Mauro Vannucci[5]; Gian Franco Gensini[6]; Rosanna Abbate[1]; Anna Maria Gori[1,6]

Differences in EPC number, cytochemokines, hs-CRP and NT-ProBNP according to the median improvement in 6MWT at the end of the rehabilitation program (n=86)

Variable	<23%	≥23%	p
CD34+/ KDR+ (cells/μl)	0.17 (0-3.92)	0.32 (0-2.71)	**<0.05**
CD133+/ KDR+ (cells/μl)	0.20 (0-0.87)	0.32 (0-1.66)	**<0.05**
CD34+/CD133+/ KDR+ (cells/μl)	0.13 (0-0.81)	0.21 (0-1.43)	**<0.05**
hs-CRP, mg/L	10 (3.2-74)	10 (1.4-75)	n.s.
IL-6, pg/mL	17.9 (10.4-152.1)	19.1 (11.5-33.7)	n.s.
VEGF, pg/mL	174.7 (15.3-730.6)	131.4 (17.5-776.2)	n.s.
IL-8, pg/mL	20.2 (6.9-80.8)	19.7 (8-317.0)	n.s.
IL-10, pg/mL	32.7 (5.4-98.3)	28.0 (3.4-136.9)	n.s.
IL-1ra, pg/mL	183.5 (77.5-1105.0)	147.5 (59.8-898.8)	<0.05
NT-ProBNP, pg/mL	711(248.9-5439.0)	811.0(126.4-8967.0)	n.s.

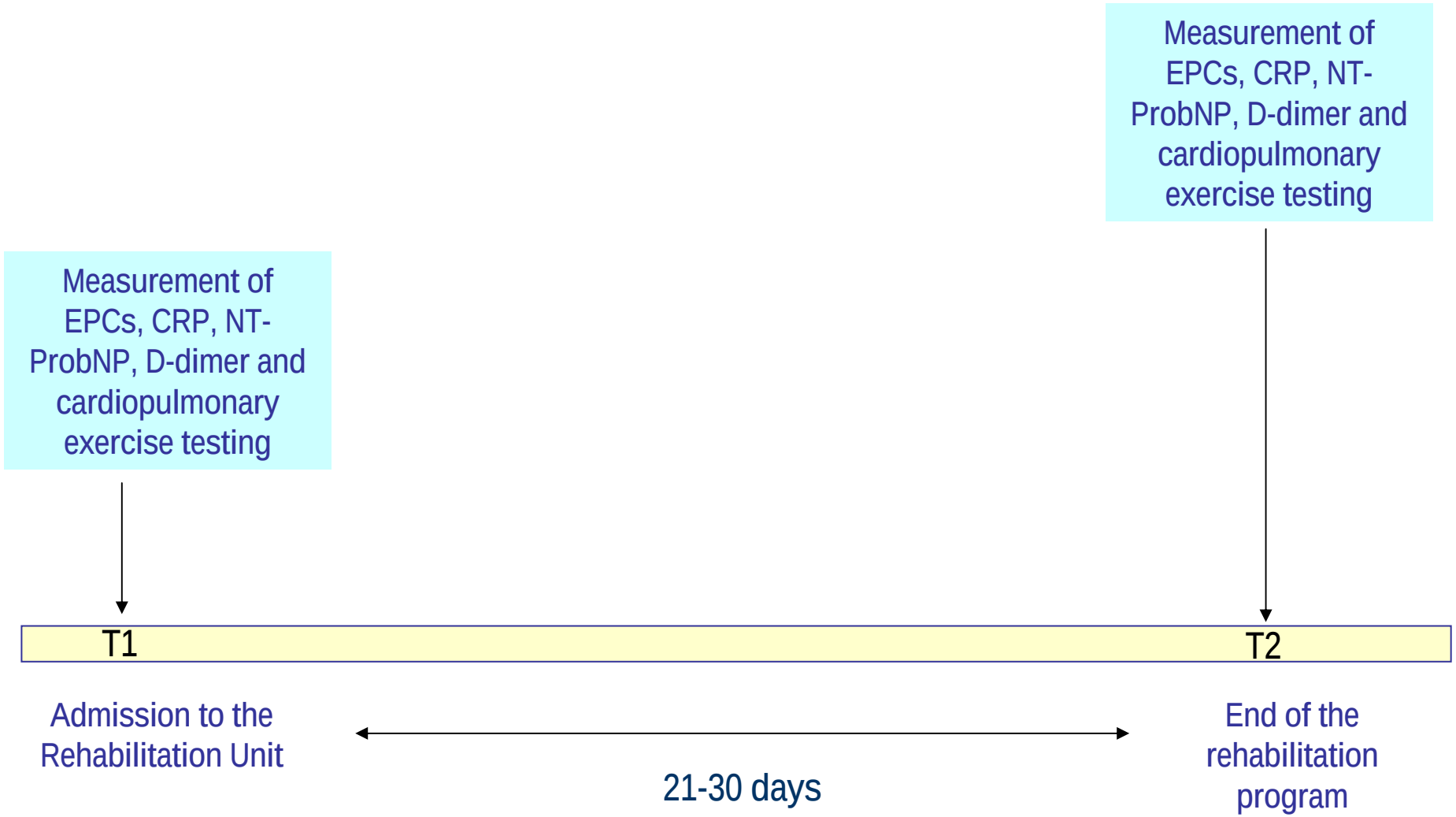
Cesari et al, Thrombosis and Haemostasis 2009

Endothelial Progenitor Cells and inflammation after cardiac rehabilitation on patients undergoing percutaneous coronary intervention after acute coronary syndrome

Cesari F, Marcucci R, Sofi F°, Gori AM°, Burgisser C, Luly S, Abbate R, Gensini GF°, Fattirolli F^

Department of Medical and Surgical Critical Care, Thrombosis Centre, University of Florence; *Central Laboratory,Azienda Ospedaliero-Universitaria Careggi, Florence, Italy;°Don Carlo Gnocchi Foundation Onlus, IRCCS, Impruneta, Florence; ^Cardiac Rehabilitation Center, Unit of Gerontology and Geriatrics, University of Florence

Clinical design of the study



Study population

55 patients (45M; 10F); median age: 58 (41-74) years

Admitted to a four weeks exercise-based cardiac rehabilitation (CR) program after acute coronary syndrome (ACS) and percutaneous coronary intervention (PCI)

Inclusion criteria were:

- Age below 75 years
- Under statins treatment
- Onset of the CR program at least 30 days after PCI

Cardiac rehabilitation program

Cardiac rehabilitation program lasts for 30 days and consists of:

Rehabilitation gym:

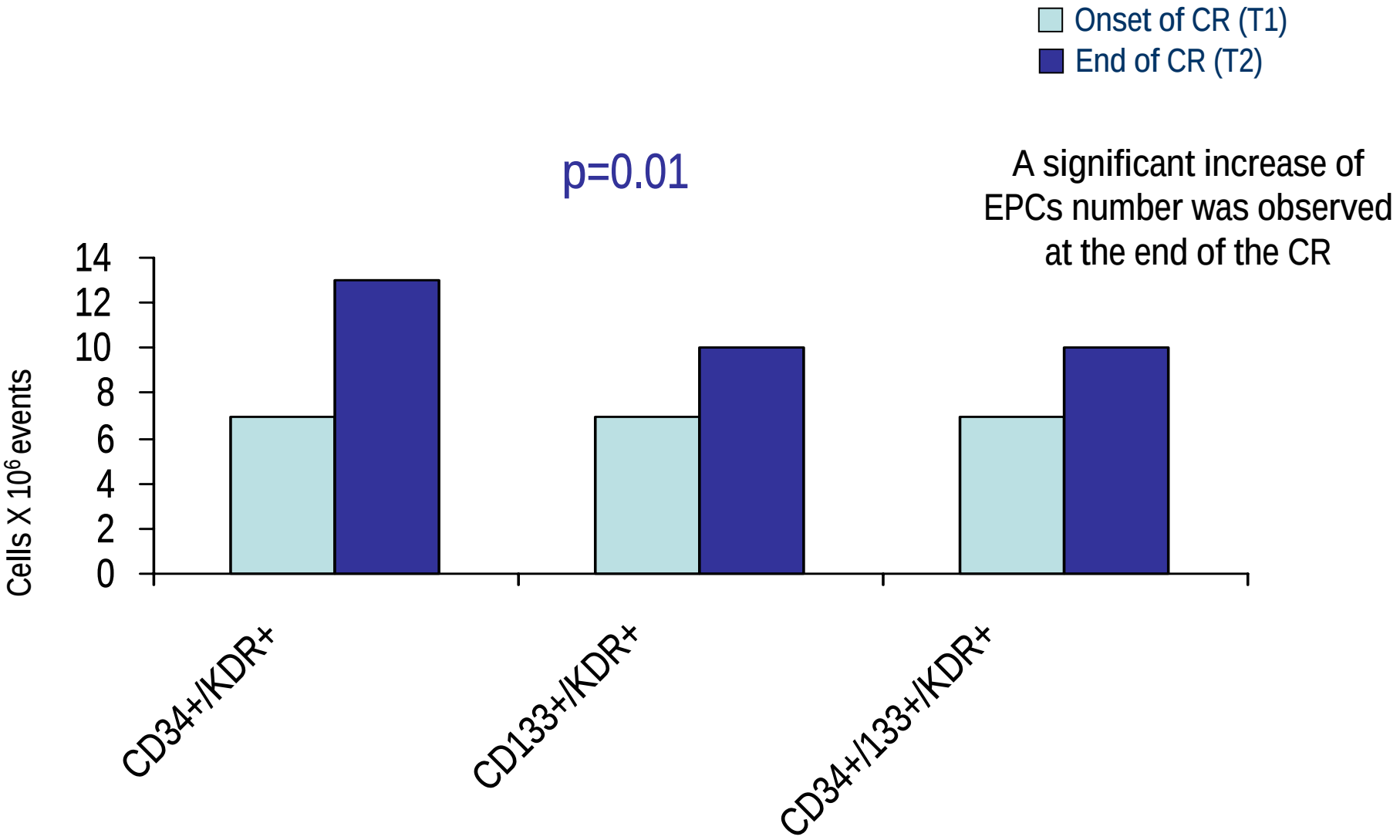
- Stretching and flexibility exercises
- Aerobic training on a stationary bicycle or on a trademill
- Cardiovascular risk factors management counseling

EPCs number at baseline and clinical characteristics (n=55)

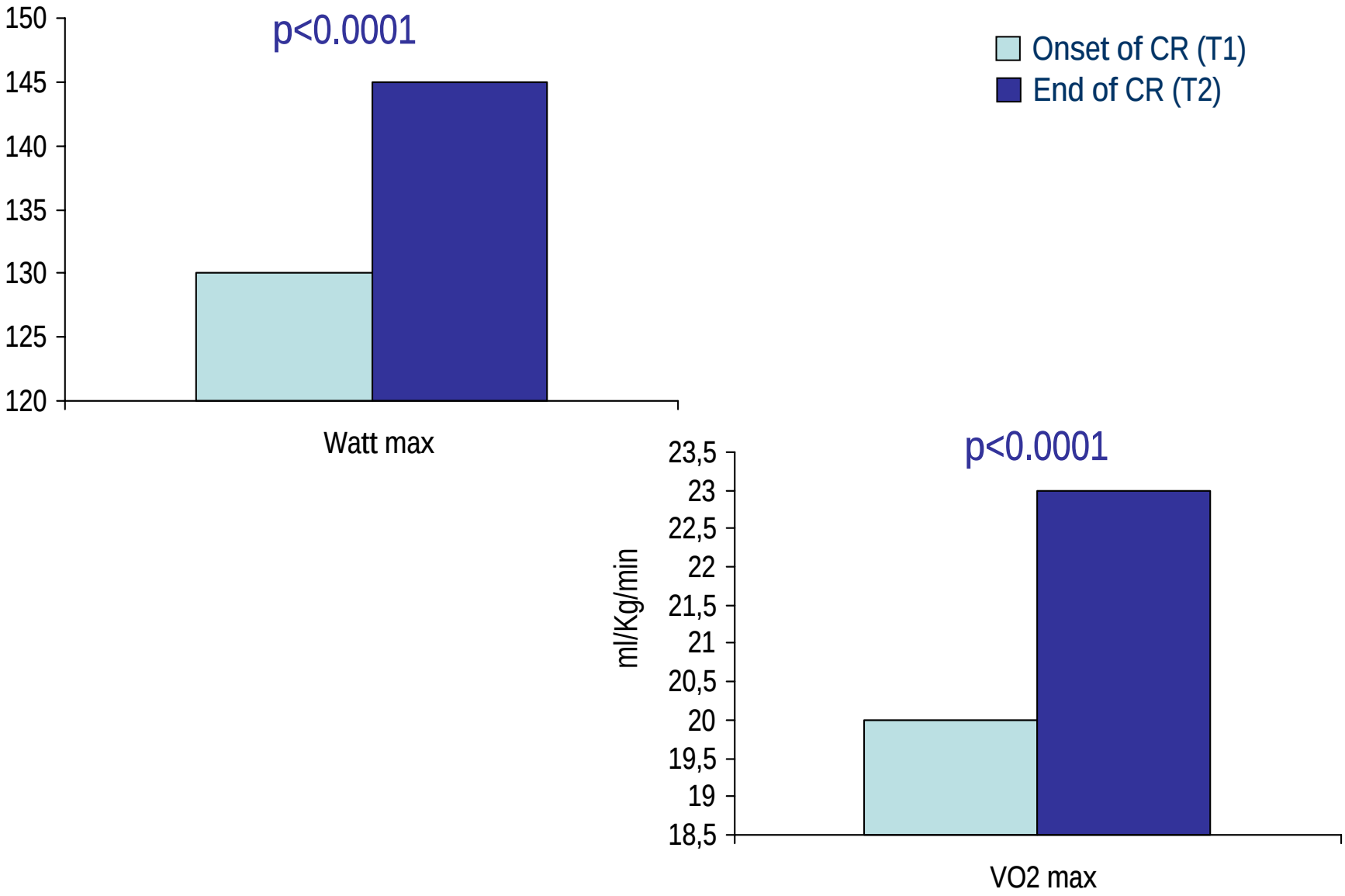
EPC T1	STEMI	NSTEMI	p
CD34+/KDR (x 10^6 events)	10 (0-27)	3 (0-10)	*0.05*
CD133+/KDR+ (x 10^6 events)	10 (0-27)	3 (0-7)	*0.08*
CD34+/CD133+/KDR+ (x 10^6 events)	10 (0-27)	3 (0-7)	*0.04*

EPC T1	PTCA+BMS	PTCA+DES	p
CD34+/KDR (x 10^6 events)	10 (0-27)	7 (0-20)	*0.04*
CD133+/KDR+ (x 10^6 events)	10 (0-27)	7 (0-17)	*0.07*
CD34+/CD133+/KDR+ (x 10^6 events)	10 (0-27)	7 (0-17)	*0.03*

EPCs modifications at the end of the rehabilitation period (n=55)



Cardiopulmonary parameters modifications at the end of the rehabilitation period (n=55)



Correlation analyses between EPCs and cardiopulmonary parameters (n=55)

EPCs	Watt max	VO_{2max}
CD34+/KDR	r=0.30 p=0.03	r=0.30 p=0.03
CD133+/KDR+	r=0.30 p=0.03	r=0.30 p=0.03
CD34+/CD133+/KDR+	r=0.30 p=0.03	r=0.32 p=0.02

EPCs	Δ Watt max	Δ VO_{2max}
△ CD34+/KDR	r=0.30 p=0.02	r=0.30 p=0.23
△ CD133+/KDR+	r=0.30 p=0.03	r=0.30 p=0.12
△ CD34+/CD133+/KDR+	r=0.30 p=0.05	r=0.30 p=0.05

Clinical parameters in group A and group B patients

Clinical Parameters	A (n=35)	B (n=20)	p
Age (years)	56±8	61±8	0.05
FC at rest (bpm)	60±9	64±8	0.09
Watt max T0	140±137	115±32	0.02
VO_2 max T0 (ml/Kg/min)	21±5	18±4	0.03
CRP T0 (mg/l)	3.4±3	5.2±3	0.03

Group A: patients with an increase of EPCs

Group B: patients with a decrease or with no increase of EPCs

Prevalence of cardiovascular risk factors in group A and group B patients

Risk factors	A (n=35)	B (n=20)	p
Smoking Habit	46%	75%	0.03
Dyslipidemia	43%	45%	0.9
Diabetes	30%	20%	0.8
Obesity	3%	20%	0.03
Hypertension	31%	45%	0.32

Group A: patients with an increase of EPCs

Group B: patients with a decrease or with no increase of EPCs

Conclusions

- Circulating EPCs are associated with cardiovascular risk profile and physical fitness
- Short and mid-term exercise regimens have a beneficial effects on the mobilization of EPCs in adults healthy subjects, CAD patients and in school children
- Long-term observations are required to establish the real impact of physical exercise on EPCs in reducing the cardiovascular risk burden