Endocannabinoid system (ECS) and cardiovascular risk prevention

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Centro unificato di Ricerca Biomedica applicata

…THERE IS A LIGHT THAT NEVER GOES DOWN…..

Rimonabant In Overweight/Obesity (Phase III)

Study	Population	N=6627	Design
RIO NORTH AMERICA	**Obese or overweight with/without comorbidities** (except diabetes)	**3040**	1+1 year Re-randomized
RIO EUROPE	**Obese or overweight with/without comorbidities** (except diabetes)	**1507**	2 years
RIO LIPIDS	**Obese or overweight with untreated dyslipidaemia** (diabetes excluded)	**1033**	1 year
RIO DIABETES	**Obese or overweight with Type 2 diabetes** **Recently released at ADA**	**1047**	1 year

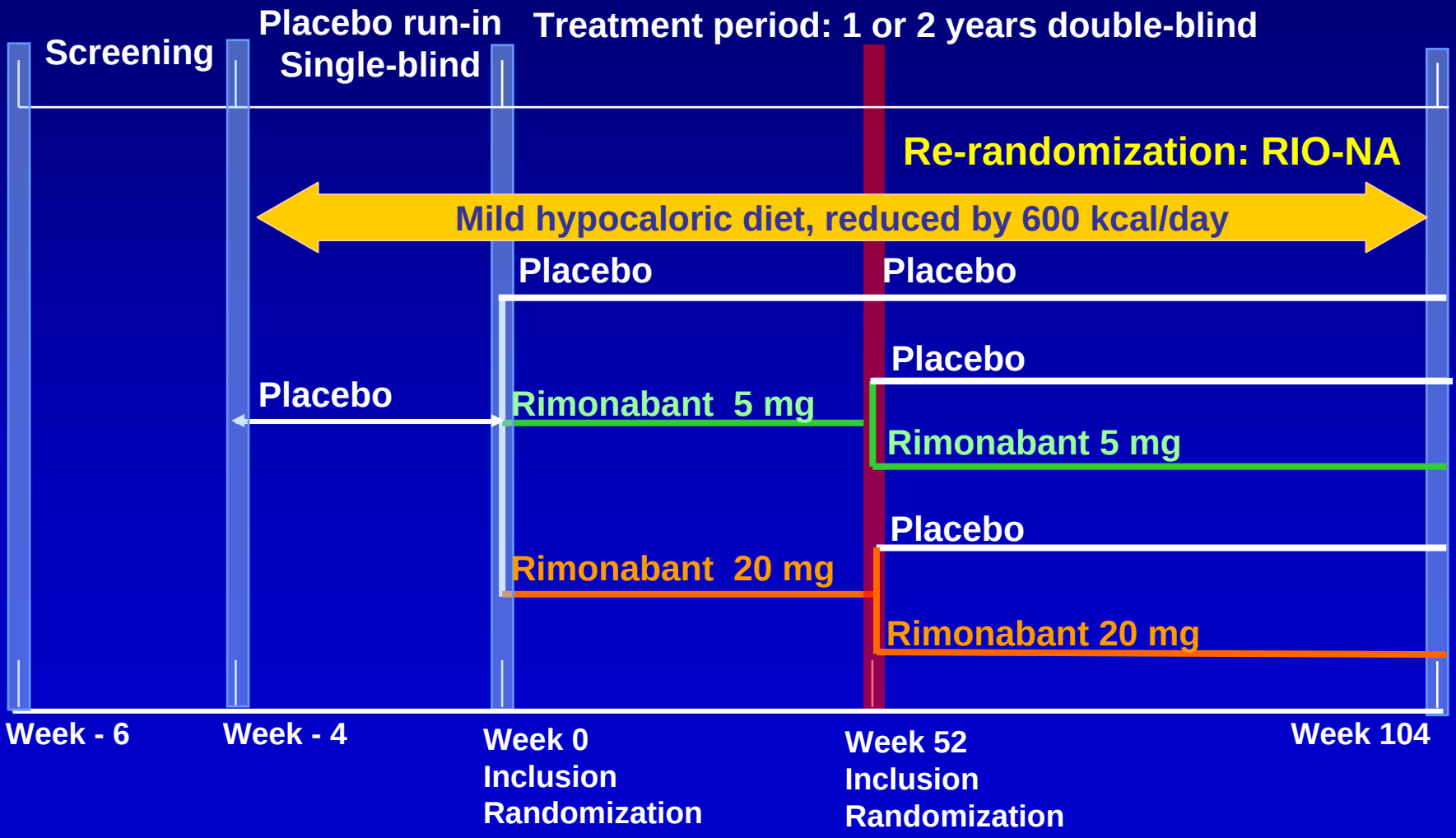
RIO programme study design

RIO EUROPE

RIO NORTH AMERICA

RIO LIPIDS

RIO DIABETES



Demographics Baseline

		RIO North America (N=3040)	RIO Europe (N=1507)	RIO Lipids (N=1033)	RIO Diabetes (N=1045)
Age (years)	Mean (SD)	45.0 (11.6)	45.0 (11.5)	47.8 (10.1)	55.6 (8.6)
Gender	Males	19.3%	20.5%	39.4%	49.1%
	Females	80.7%	79.5%	60.6%	50.9%
Race	Caucasian	84.0%	93.6%	96.8%	88.5%
	Black	11.2%	4.8%	0.6%	5.5%
	Other	4.8%	1.6%	2.6%	6.0%
Weight (kg)	Mean (SD)	104.4 (21.3)	101.0 (19.8)	94.1 (14.8)	96.3 (14.7)
Waist (cm)	Mean (SD)	105.8 (15.3)	108.4 (14.1)	105.0 (11.1)	109.0 (10.8)
BMI (kg/m^2)	Mean (SD)	37.6 (6.5)	36.0 (5.9)	33.3 (3.5)	33.7 (3.6)

CV Risk Factors Baseline

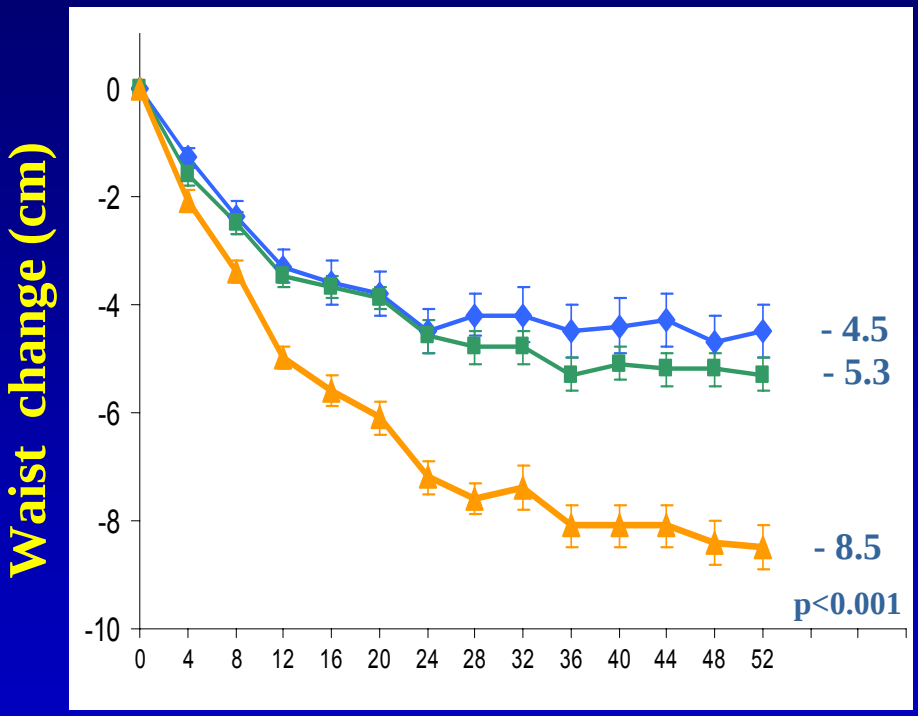
	RIO North America (N=3040)	RIO Europe (N=1507)	RIO Lipids (N=1033)	RIO Diabetes (N=1045)
Abdominal obesity Male (>102 cm)	89.6%	93.5%	78.6%	81.3%
Female (>88 cm)	86.9%	94.7%	91.2%	96.6%
Dyslipidemia	62.6%	60.7%	100 %	55.6%
TG>=1.69mmol/L	33.4%	27.4%	57.4%	53.0%
HDL-C<1.03mmol/L (men)	50.3%	50.0%	62.6%	45.1%
HDL-C<1.3 mmol/L (women)	52.8%	54.3%	70.7%	58.3%
LDLC ≥3.36mmol/L	34.9%	40.6%	58.2%	32.7%
Drug treatment if dyslipidemic	15.1%	13.7%	0%	64.9%
Diabetes	0	0	0	100%
Pre-diabetes				
Fasting glucose ≥5.55mmol/L	20.8%	29.2%	28.8 %	
2h post glucose load ≥7.77mmol/L		15.4 %	22.6 %	
Hypertension	30.4%	40.9%	27.2%	61.2%
Drug treatment if hypertensive	68.1%	55.1%	68.7%	93.0%
Metabolic syndrome (ATP III)	34.9%	41.3%	53.6%	79.1%

General efficacy aspects of CB1 Blockade

- Waist & weight changes
- Metabolic improvements
- Long-term effects

Changes in Weight & Waist Circumference

Completers

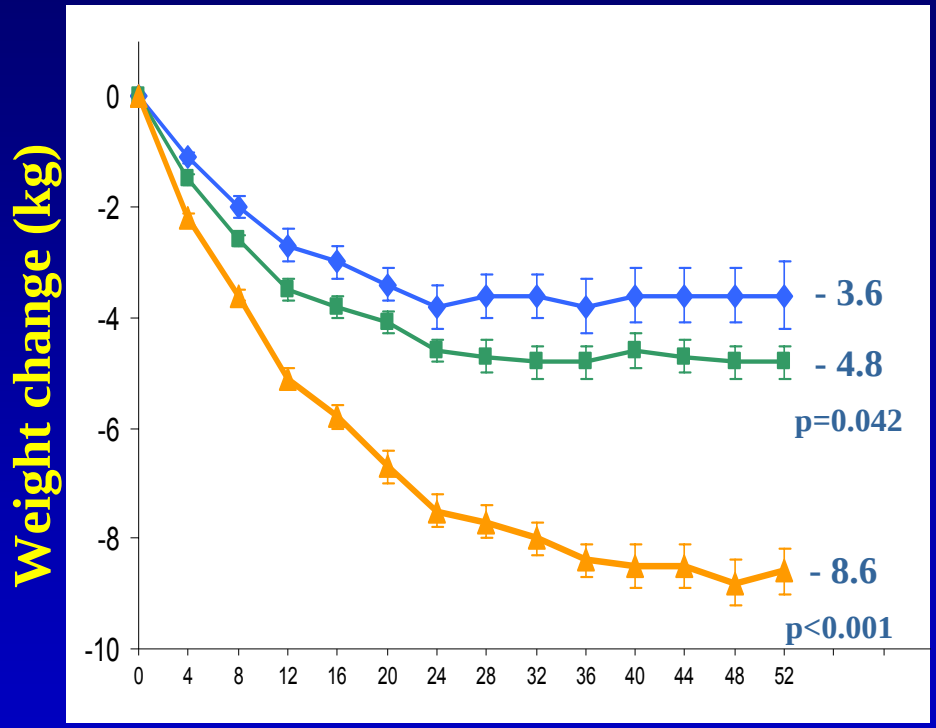


ITT LOCF

placebo: - 2.4 cm

5 mg: - 3.9 cm (p = 0.002 vs. placebo)

20 mg: - 6.5 cm (p < 0.001 vs. placebo)



ITT LOCF

placebo: - 1.8 kg

5 mg: - 3.4 kg (p = 0.002 vs. placebo)

20 mg: - 6.6 kg (p < 0.001 vs. placebo)

L. Van Gaal et al. Lancet, 2005; 365: 1389-1397

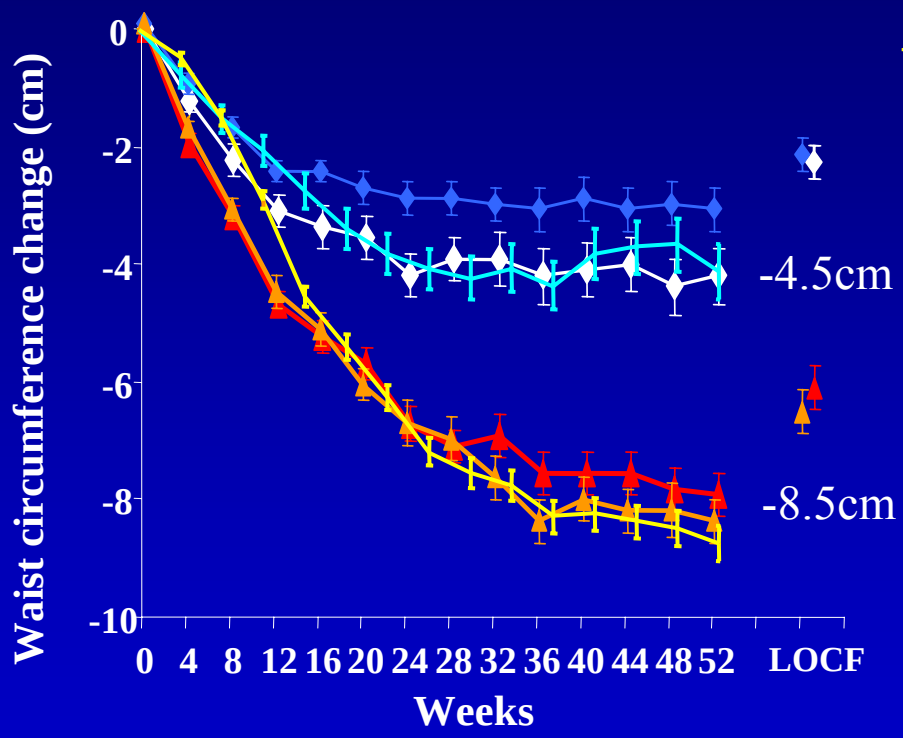
Consistent Changes in Waist Circumference

RIO LIPIDS

RIO~Lipids

Placebo

R 20 mg



RIO EUROPE

RIO~Europe

Placebo

R 20 mg

RIO NORTH AMERICA

RIO~North America

Placebo

R 20 mg

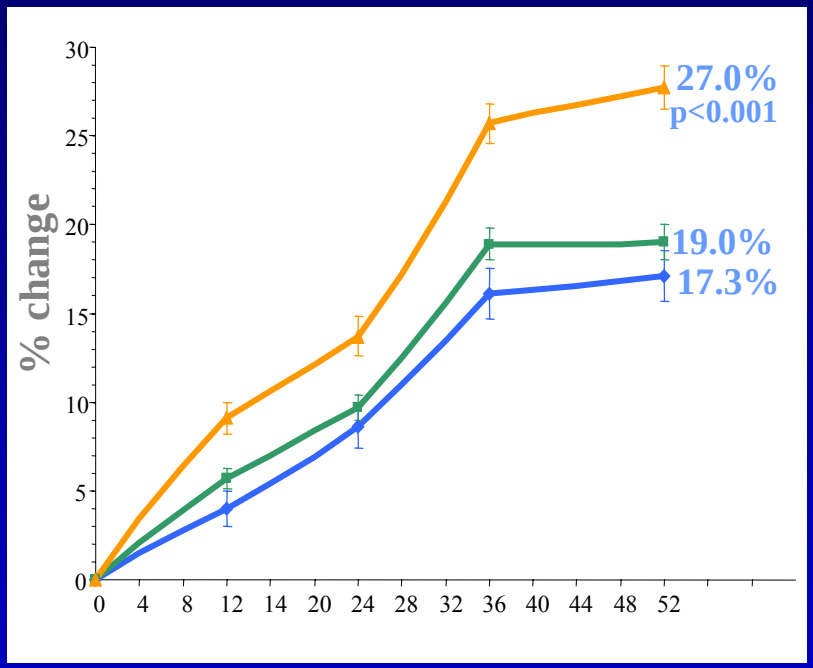
Change in lipid profile: RIO-Europe

RIO EUROPE

HDL-cholesterol

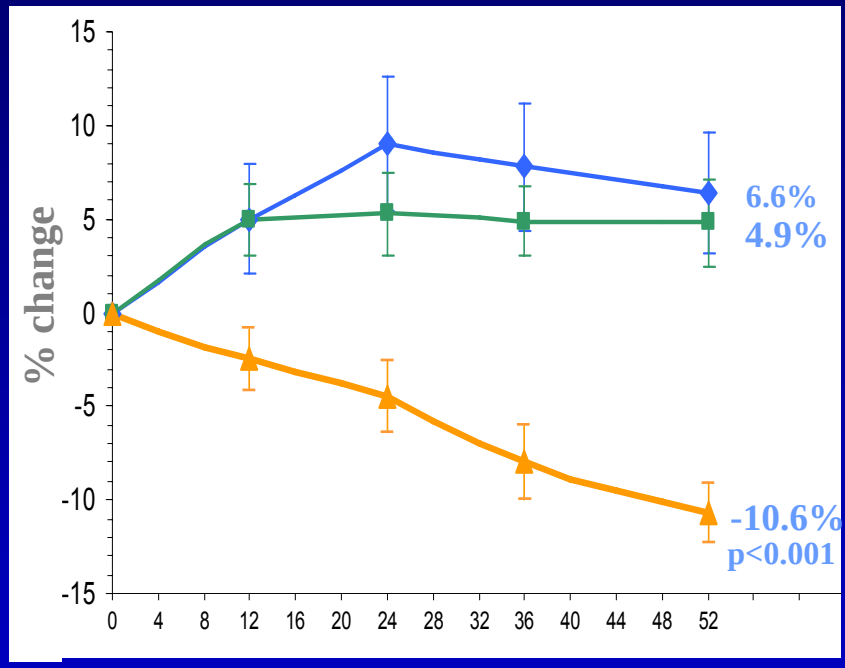
Completers

Triglycerides



Weeks

Placebo : 13.4%
5 mg : 16.2% (p=0.048 vs placebo)
20 mg : 22.3% (p<0.001 vs placebo)



Weeks

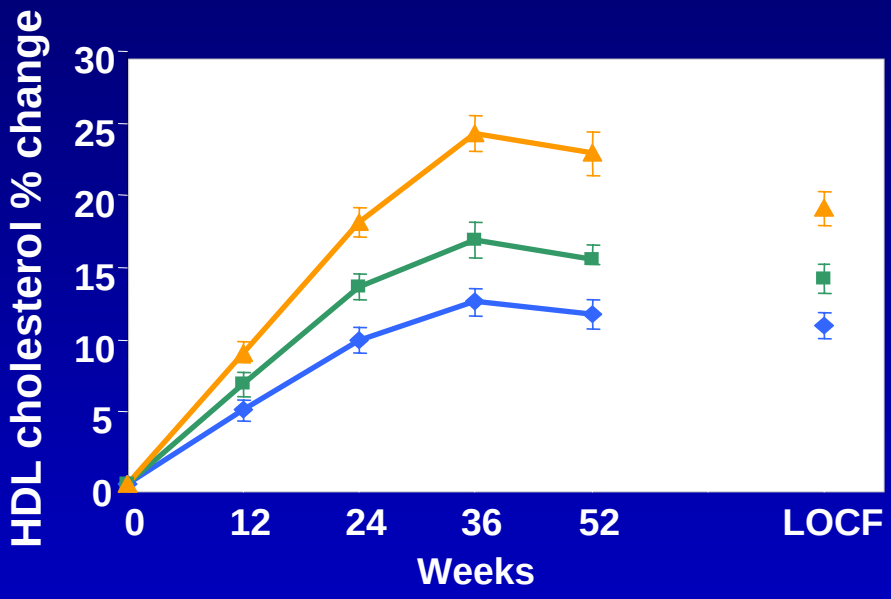
Placebo : 8.3%
5 mg : 5.7% (ns vs placebo)
20 mg : - 6.8% (p<0.001 vs placebo)

Placebo Rimonabant 5 mg Rimonabant 20 mg

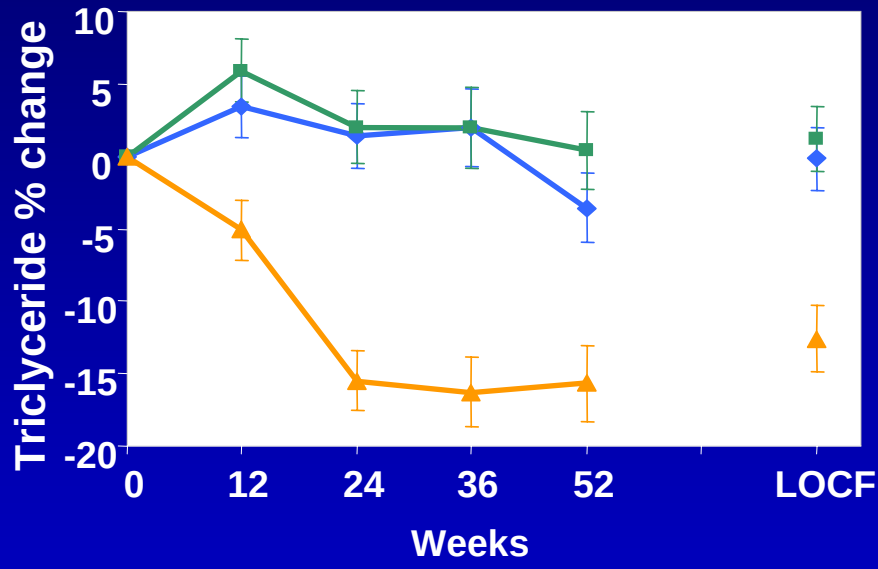
Lancet 2005

Change in HDL-Cholesterol and Triglycerides

ITT, LOCF



5 mg vs. **placebo**: p = 0.025
20 mg vs. **placebo**: p < 0.001



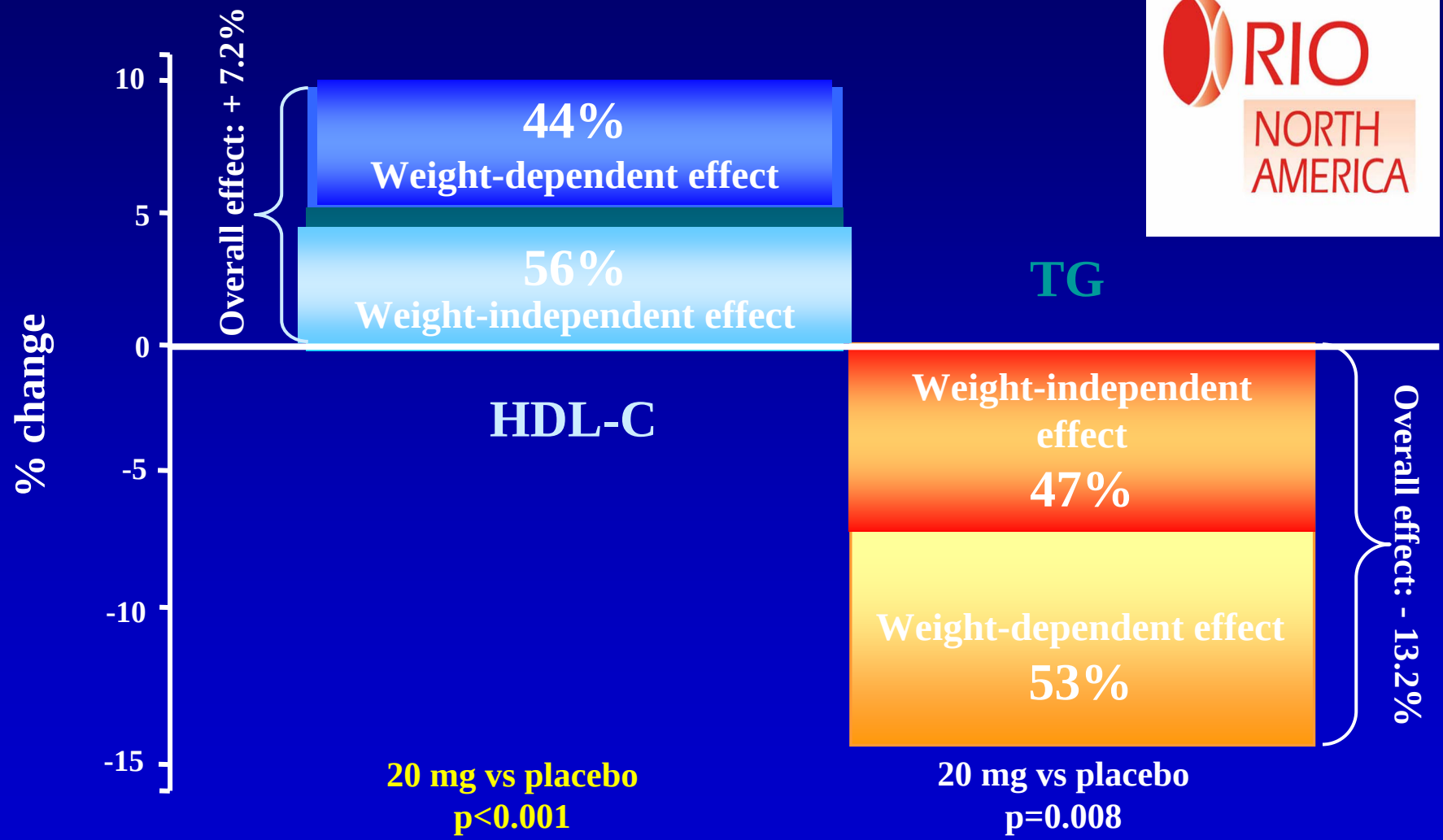
5 mg vs. **placebo**: ns
20 mg vs. **placebo**: p < 0.001

Placebo — Rimonabant 5mg — Rimonabant 20mg

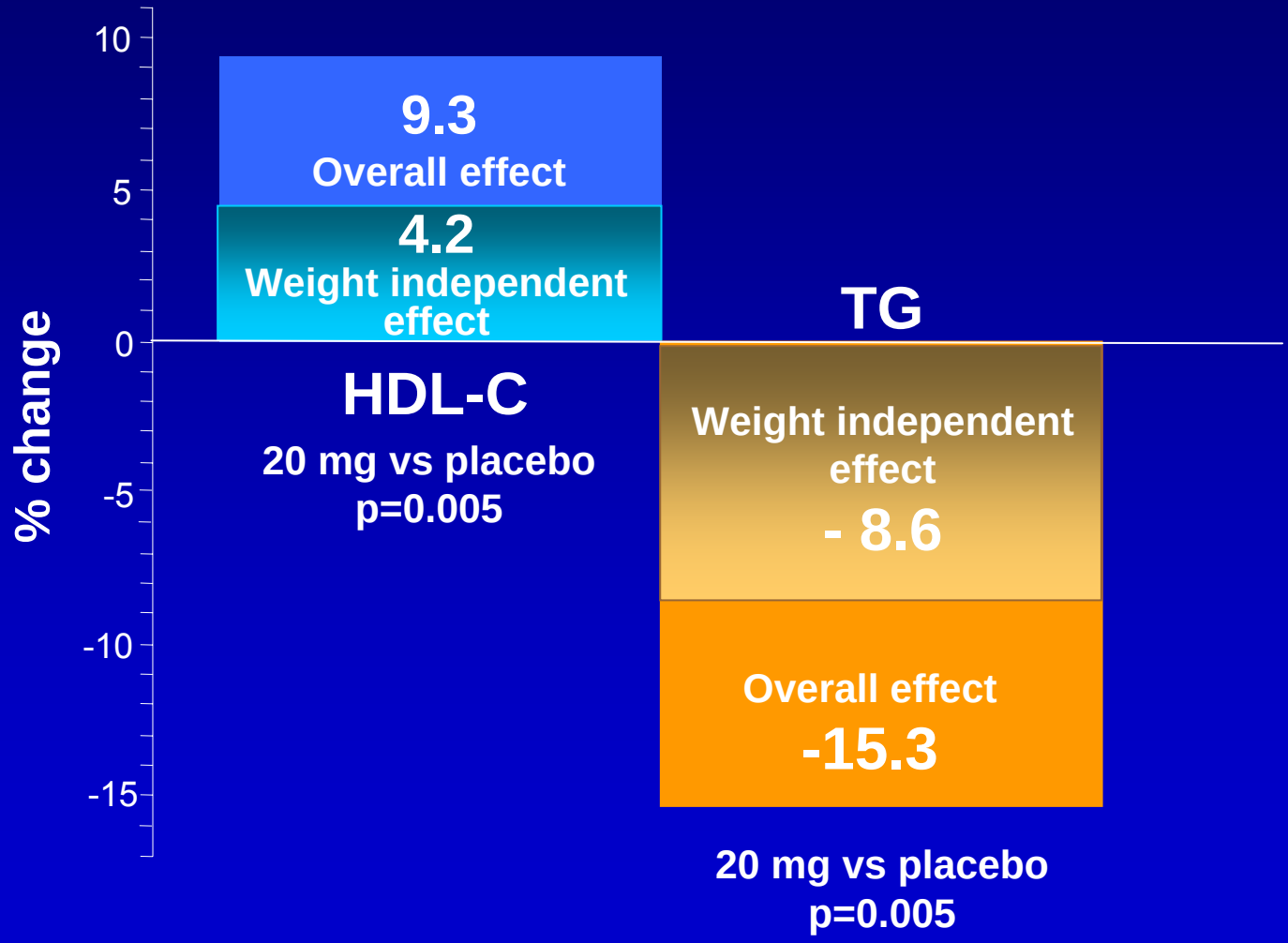
RIO LIPIDS

J.P. Després et al, NEJM, 2005

Improvements in lipids adjusted for weight loss: RIO-North America



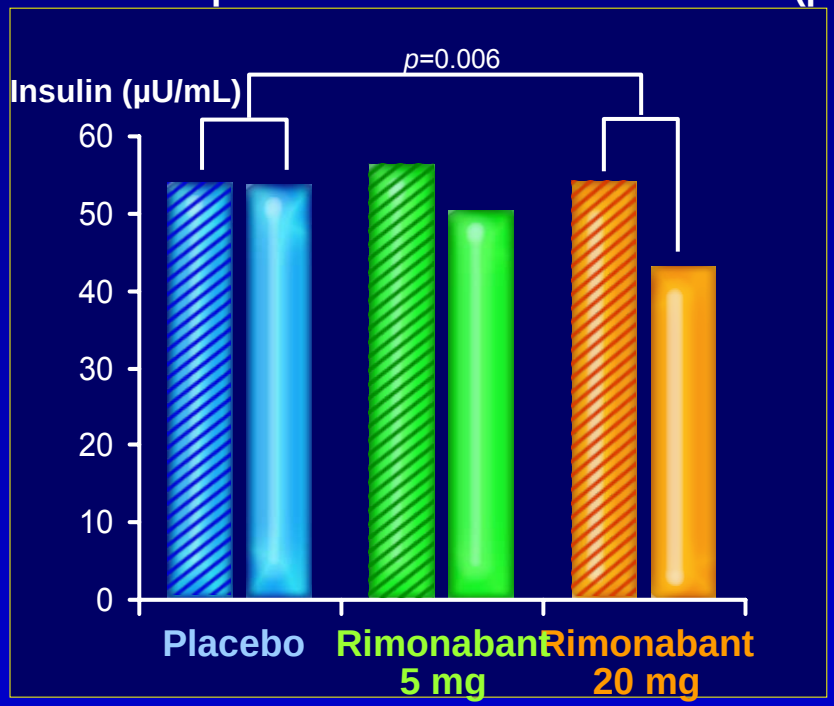
Improvements in lipid parameters are independent of weight loss



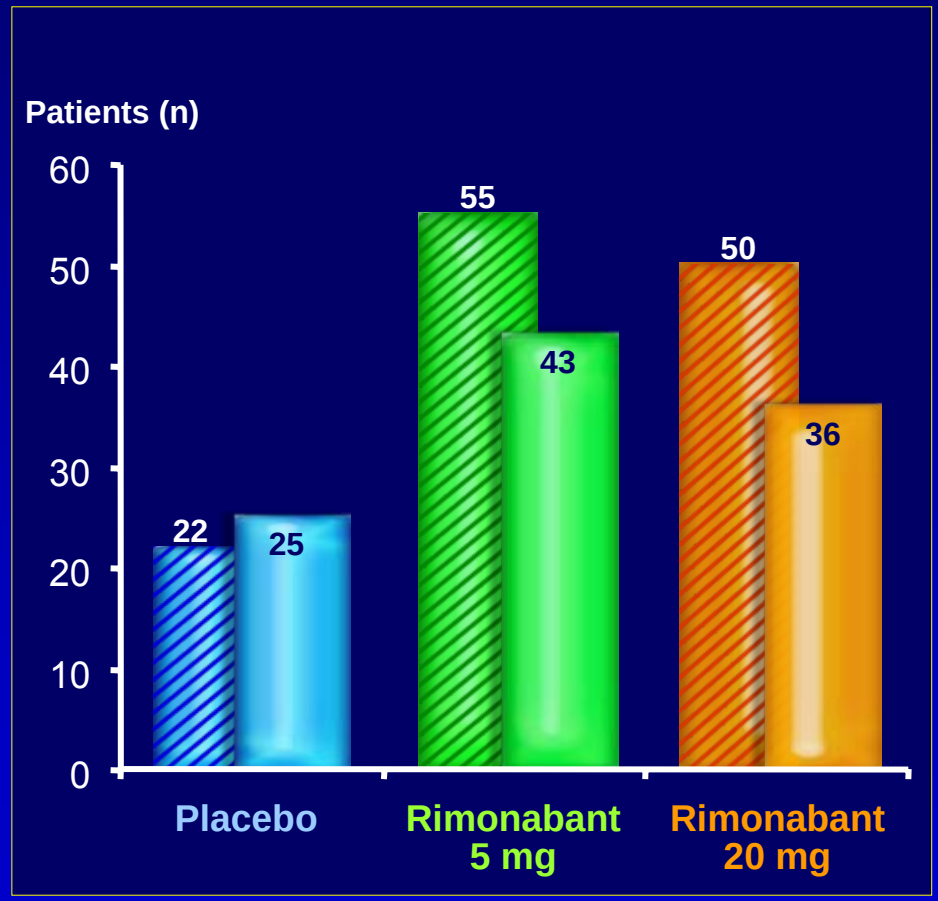
L. Van Gaal et al. Lancet, 2005; 365: 1389-1397

2 y Changes in Insulin & Glucose Tolerance

120 min post load Insulin concentrations (µU/mL)



Impaired Glucose Tolerance Status*



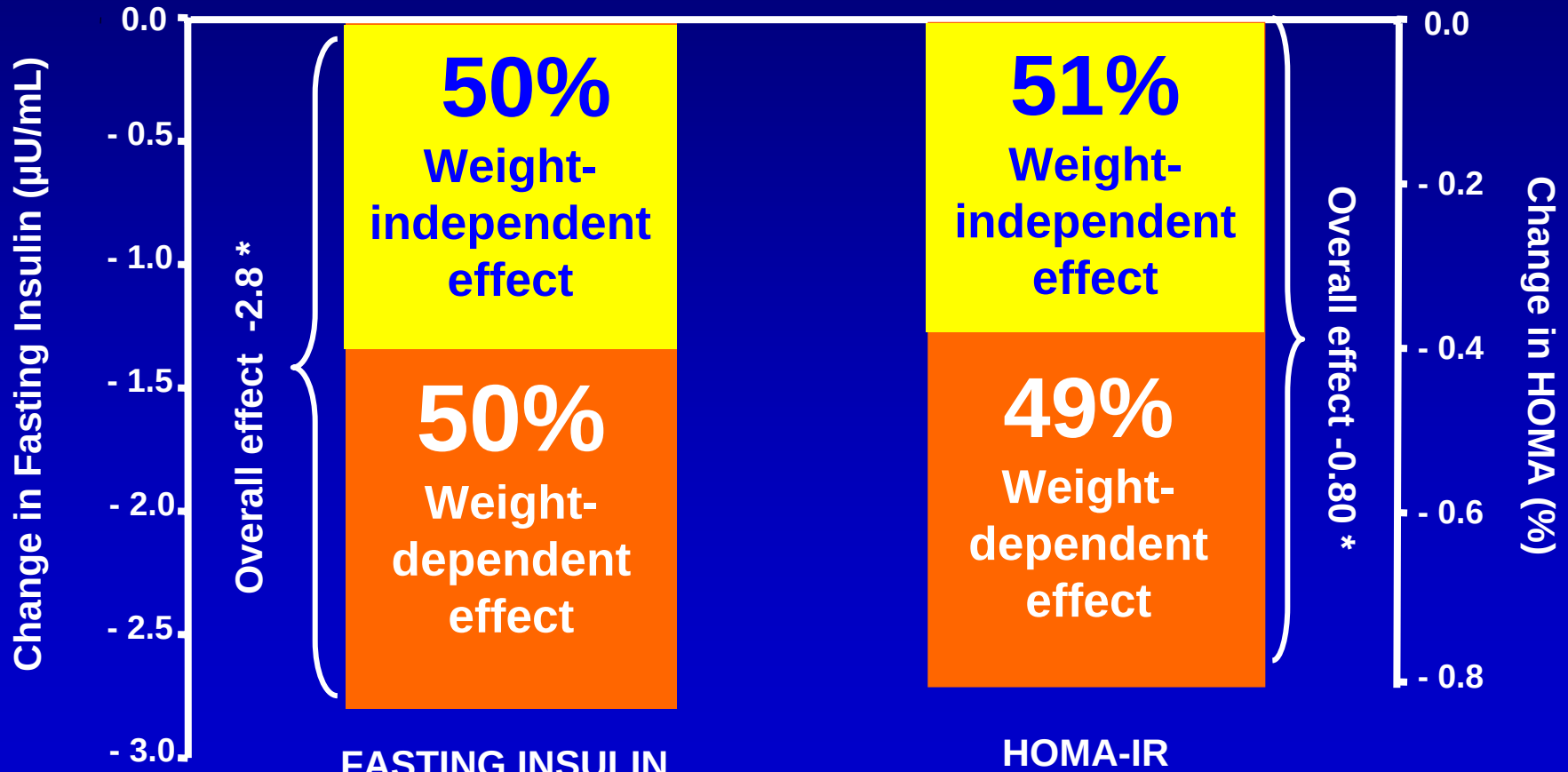
Baseline 2 year

* Change in glucose tolerance status 20mg vs placebo: (P=0.001)

RIO EUROPE

Improvement in Fasting Insulin and Insulin Resistance Adjusted for Weight Loss

1 Year Analysis

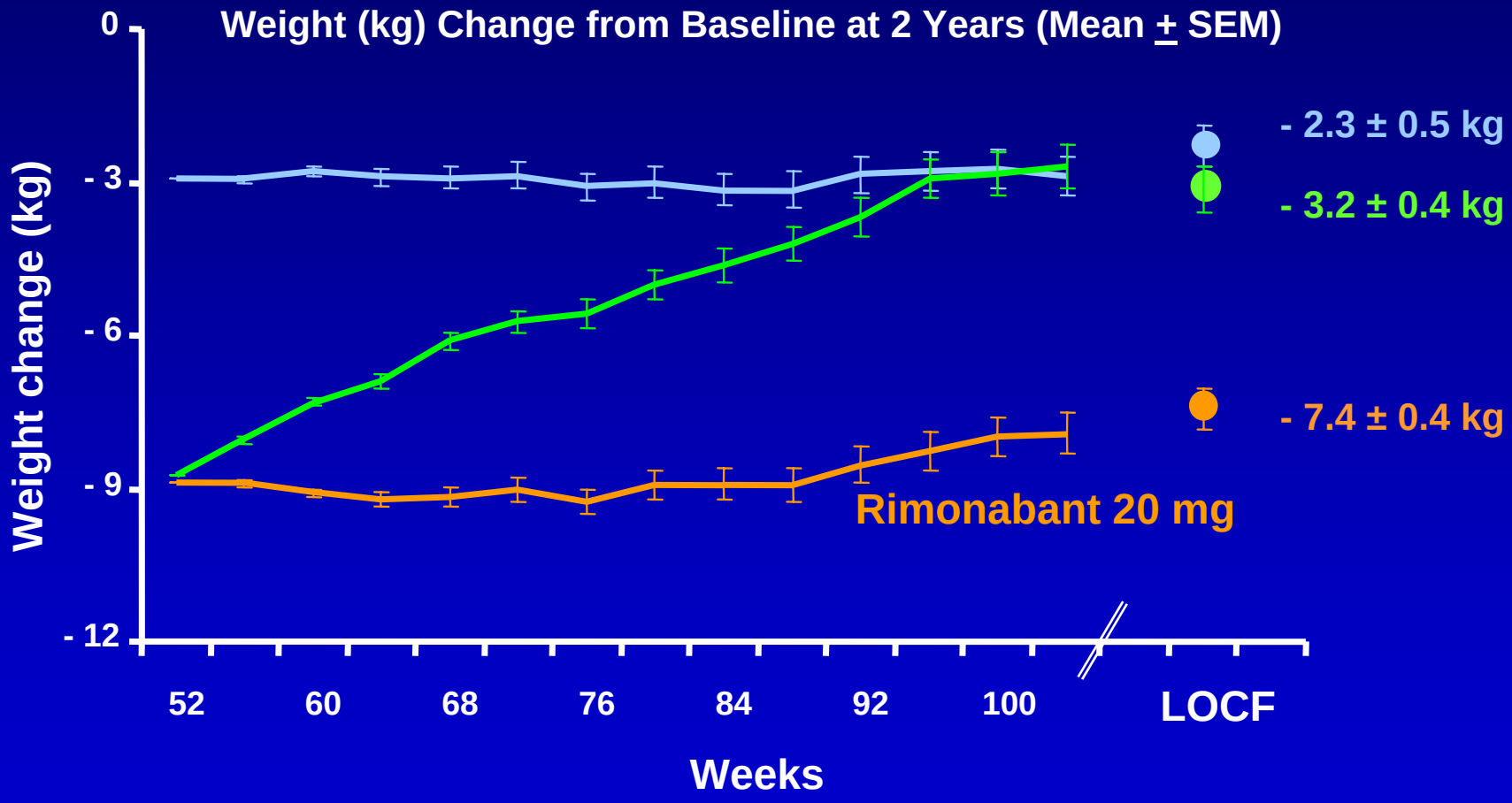


RIO NORTH AMERICA

X. Pi-Sunyer, presented AHA 2004

Prevention of Weight Regain by Chronic Therapy

ITT-LOCF

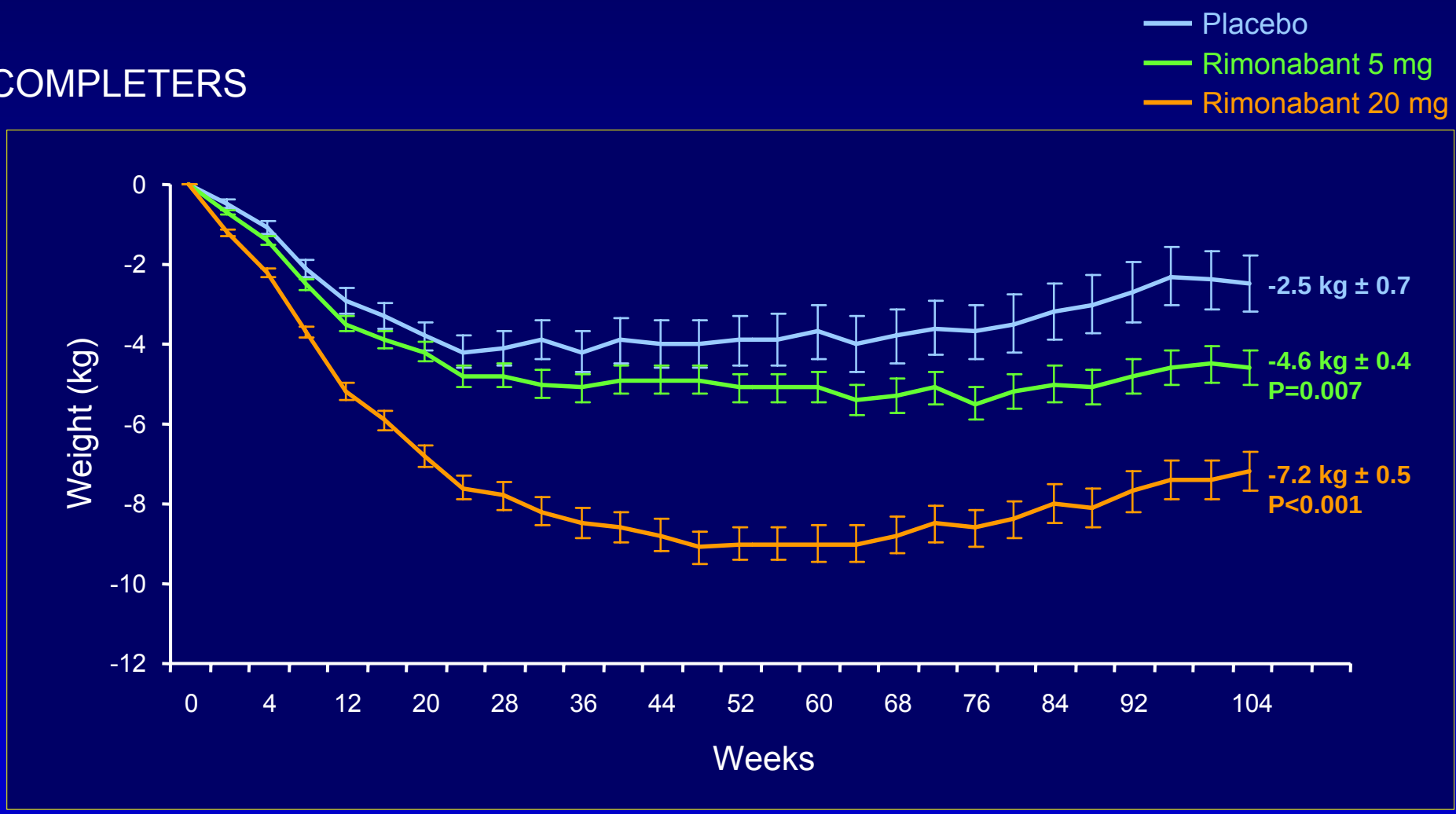


RIO NORTH AMERICA

X. Pi-Sunyer et al, JAMA 2006

Body Weight Change at 2 Years

COMPLETERS

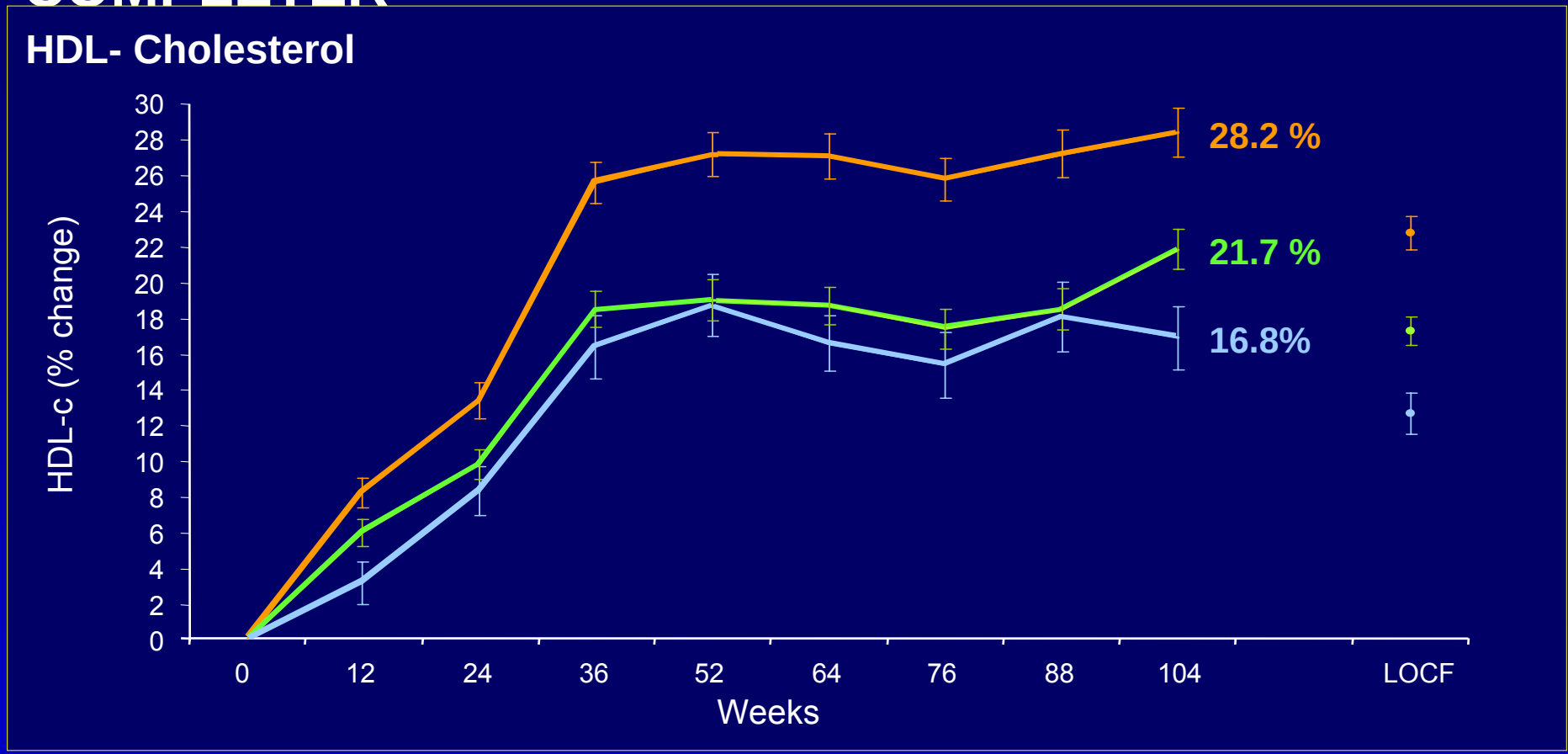


(mean change ± SEM) - Completers population

L. Van Gaal, presented ACC 2005

Change in HDL- Cholesterol

COMPLETER



R 20 mg vs placebo : $p < 0.001$
R 5 mg vs placebo : $p = 0.023$

ITT LOCF

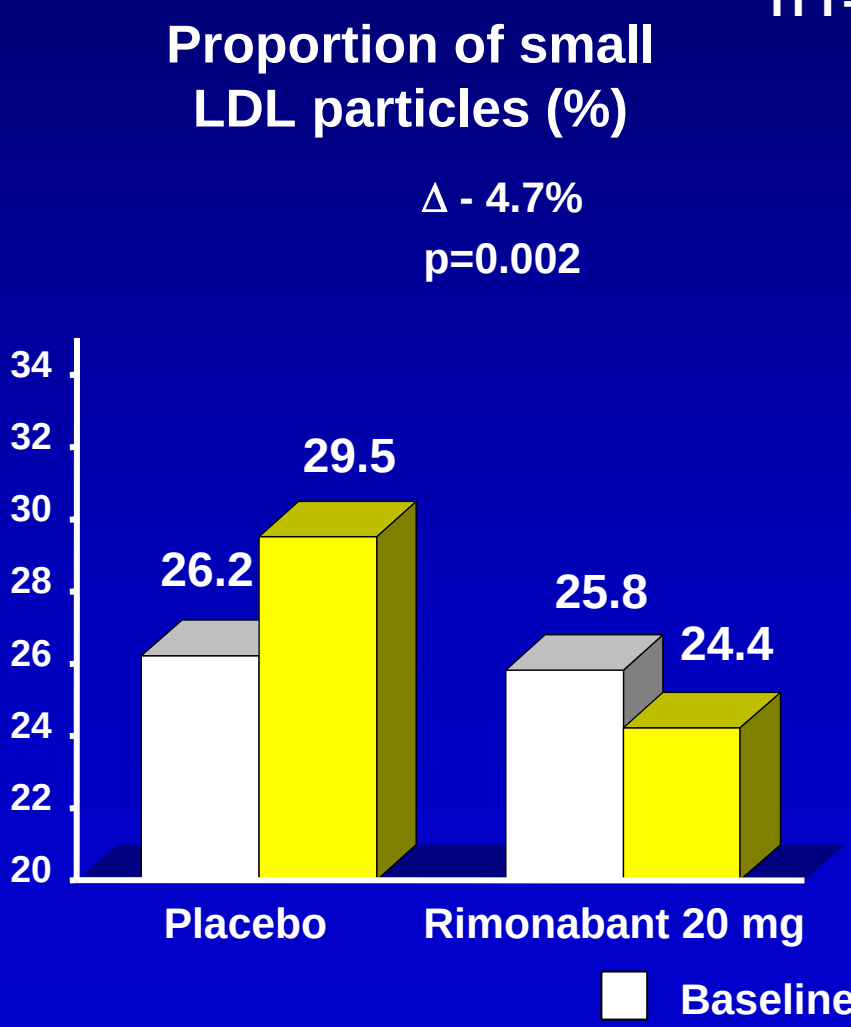
Placebo : 12.6 %
5 mg : 17.2 % (p=0.002 vs. placebo)
20 mg : 22.6 % (p<0.001 vs. placebo)

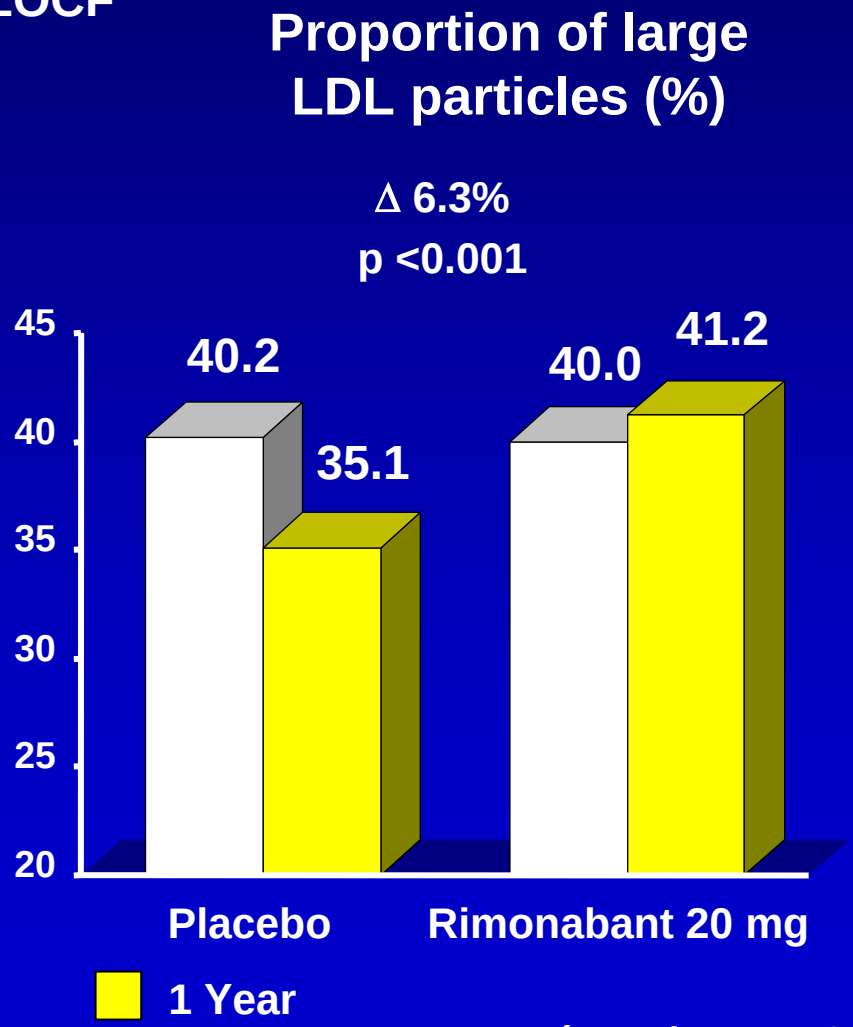
Special aspects of CB1 Blockade

- Lipoprotein particles change
- Inflammatory aspects
- Adiponectine

Change in Proportion of Small and Large LDL Particles

ITT-LOCF





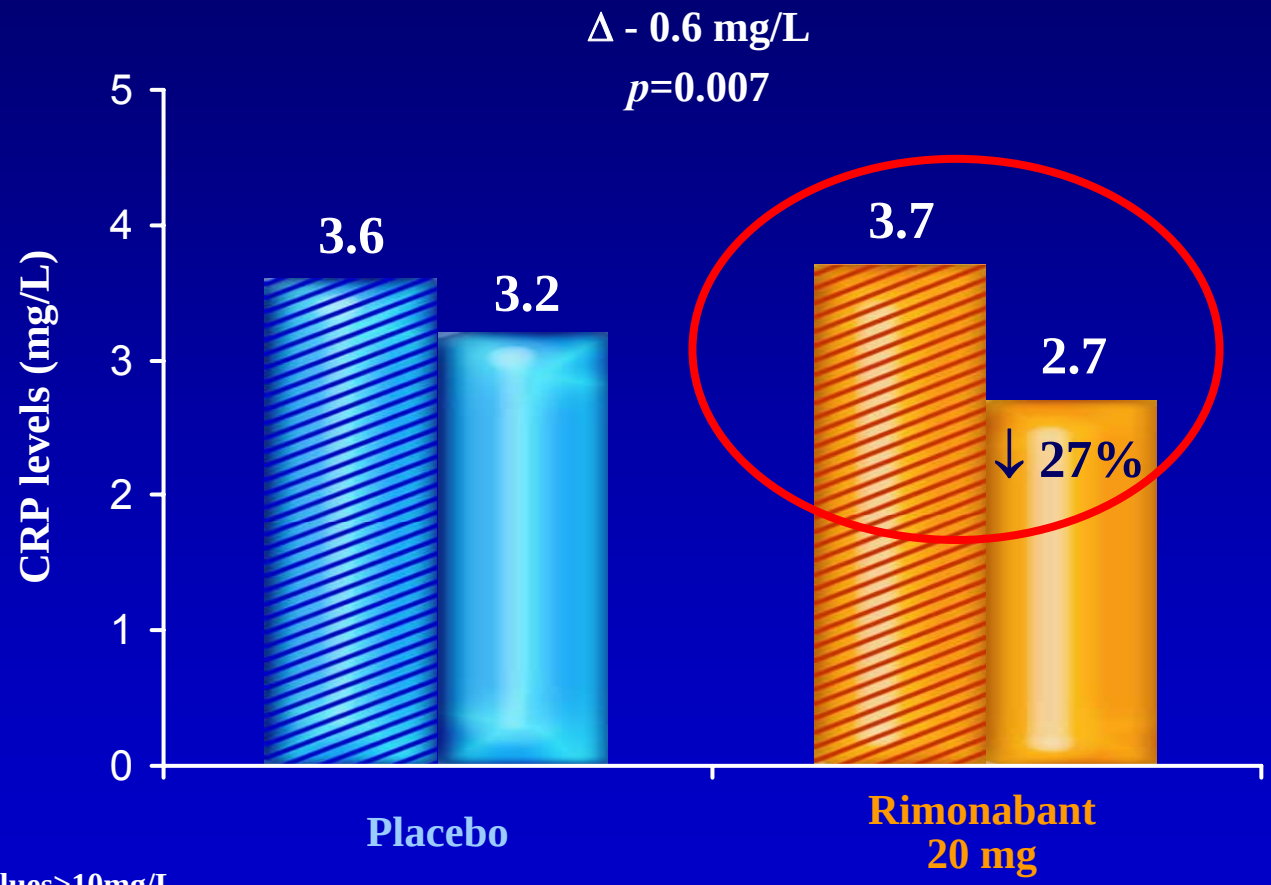
Baseline

1 Year

J.P. Després et al, NEJM, 2005

RIO~Lipids: C-reactive Protein

ITT, LOCF

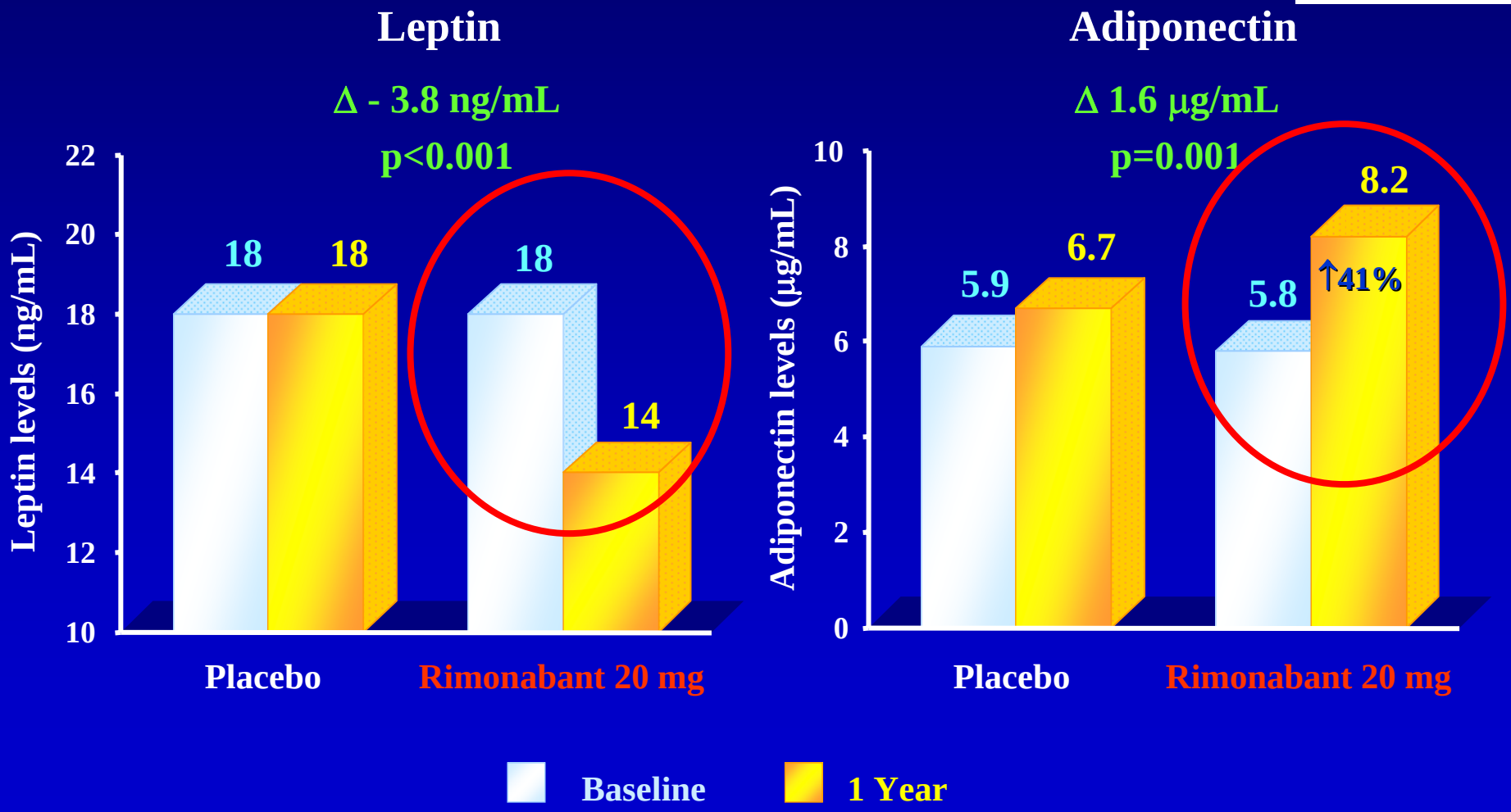


* Excluding values>10mg/L

R, Després J-P. Presented at the ACC congress, March 2004, Abstr. 409-1

Changes in leptin and adiponectin: RIO-Lipids

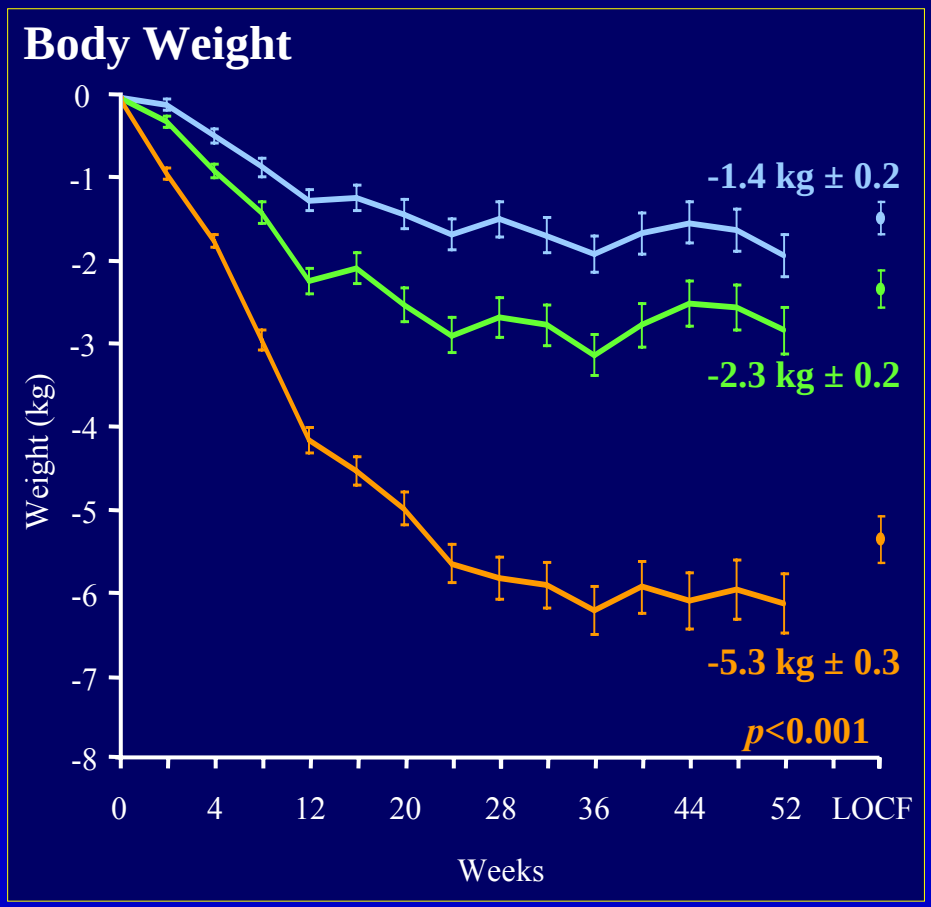
ITT-LOCF

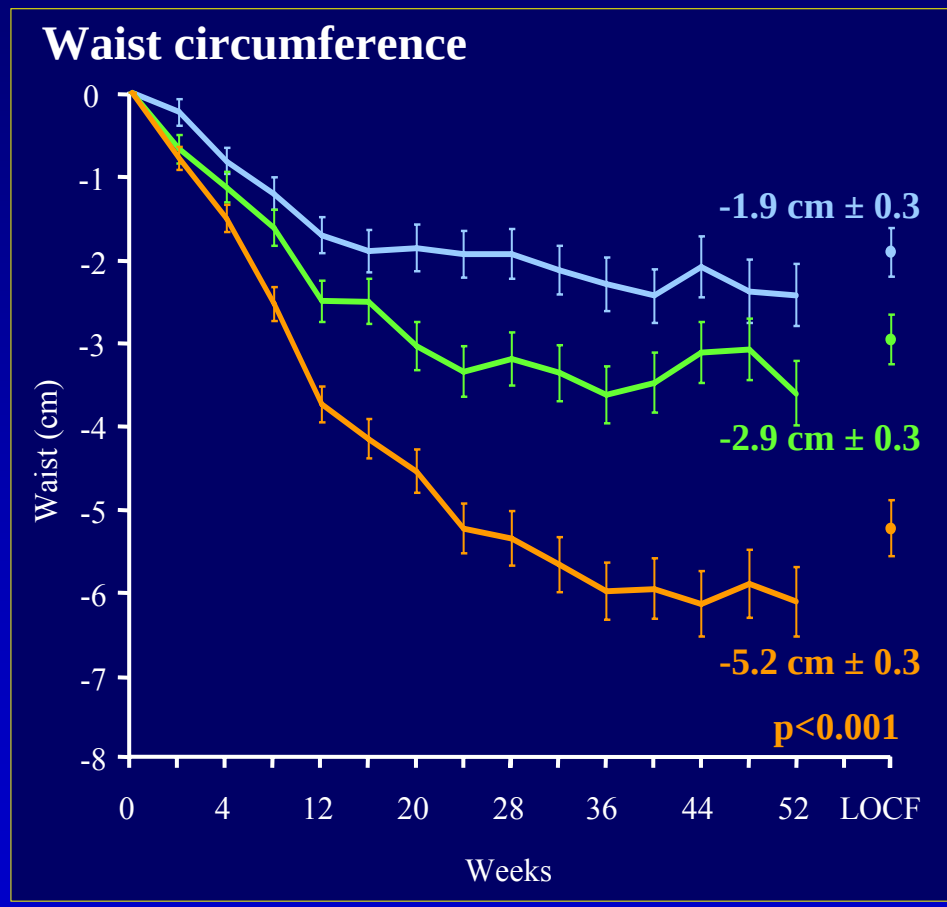


RIO~DIABETES
change in weight and waist circumference

ITT, LOCF

(mean change ± SEM)





Completers

R 5 mg v. placebo : -2.8 kg v. -1.9kg, *ns*
R 20 mg v. placebo : -6.1 kg v. -1.9kg, *p*<0.001

Completers

R 5 mg v. placebo : -3.6 cm v. -2.4cm, *p*=0.034
R 20 mg v. placebo : -6.0 cm v. -2.4cm, *p*<0.001

RIO~DIABETES: Change in HbA1c

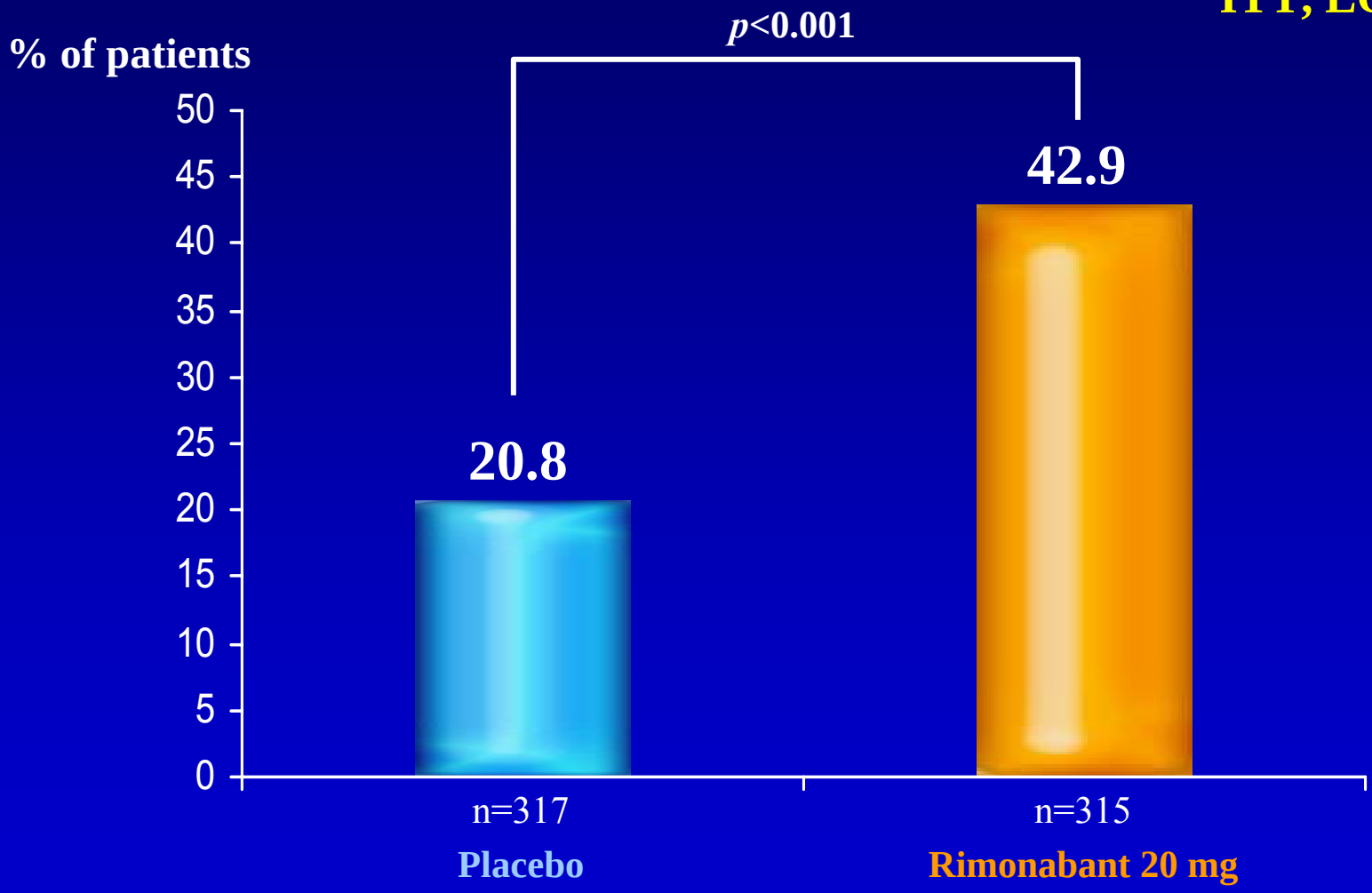
ITT, LOCF

% (Mean ± SD)	Placebo n=317	Rimonabant 5 mg n=330	Rimonabant 20 mg n=315
Baseline	7.2 ± 0.9	7.3 ± 0.8	7.3 ± 0.8
Year 1	7.3 ± 1.1	7.2 ± 1.1	6.7 ±0.9
Change	0.1 ± 1.0	-0.1 ± 1.0	-0.6 ± 0.8
Difference rimonabant v. placebo (SEM)		-0.2 (0.1)*	-0.7 (0.1)**
		*p=0.034	**p< 0.001

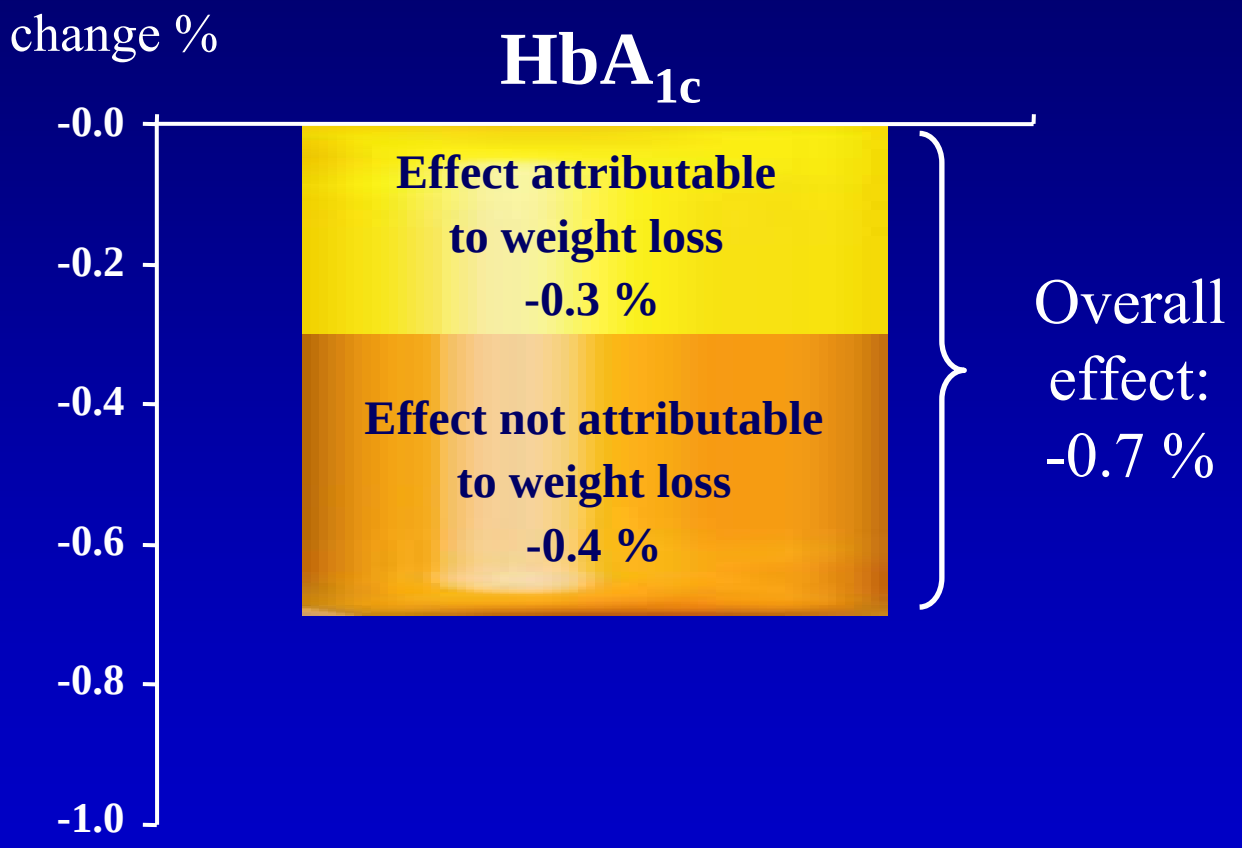
Completers:
R5mg vs Placebo : -0.1% v. +0.1%, p=0.035
R20mg vs Placebo : -0.7% v. +0.1%, p<0.001

RIO~DIABETES: Patients achieving HbA1c< 6.5% at 1 Year

ITT, LOCF



RIO~DIABETES: Improvement in HbA1c attributable to weight loss*

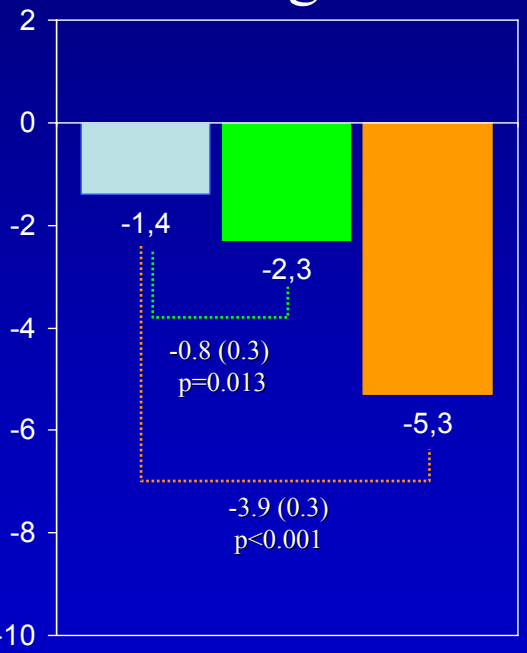


* Analysis of covariance

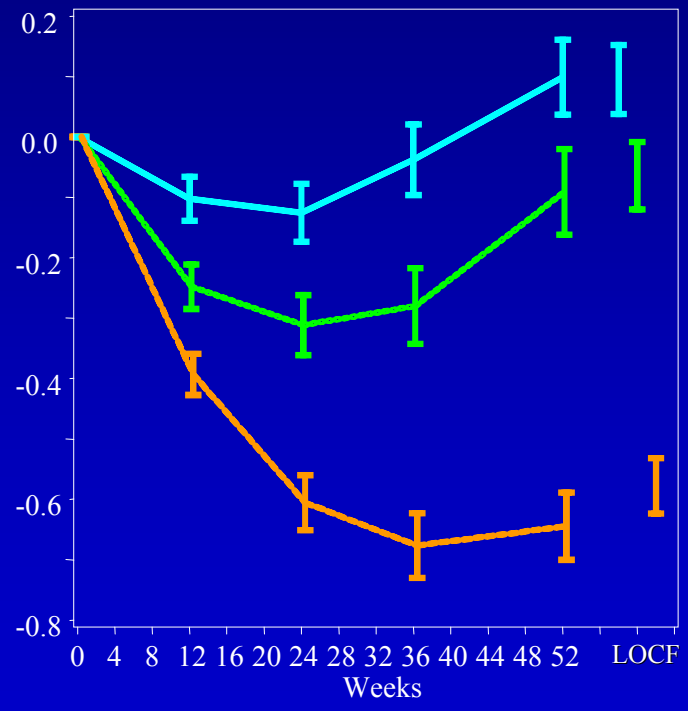
RIO Diabetes
Lower Weight, Lower HbA1C and FPG

Baseline mean (SD)

96.3 (14.7) Kg
Weight

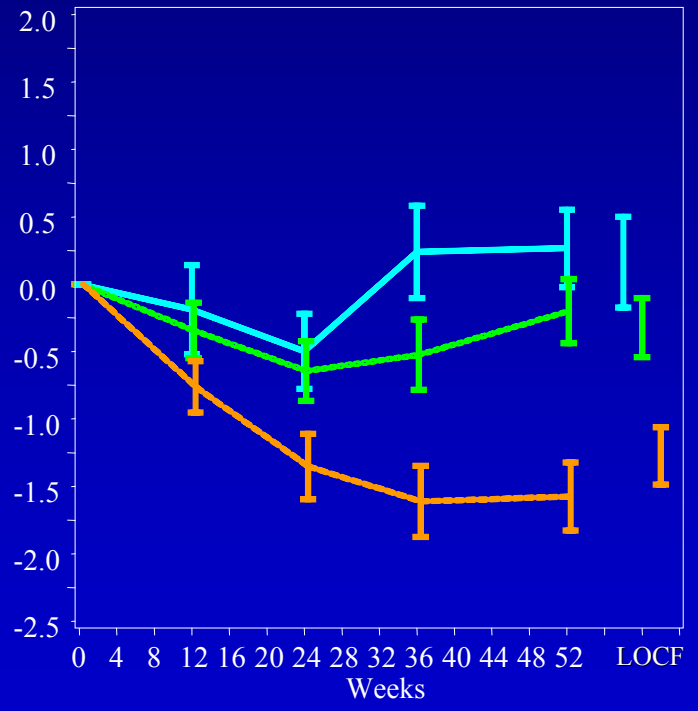


7.3 (0.9)%
HbA_{1c}



Difference between groups, mean (SEM)
LOCF 5mg vs Pbo -0.2 (0.1) (p=0.034)
20mg vs Pbo -0.7 (0.1) (p<0.001)

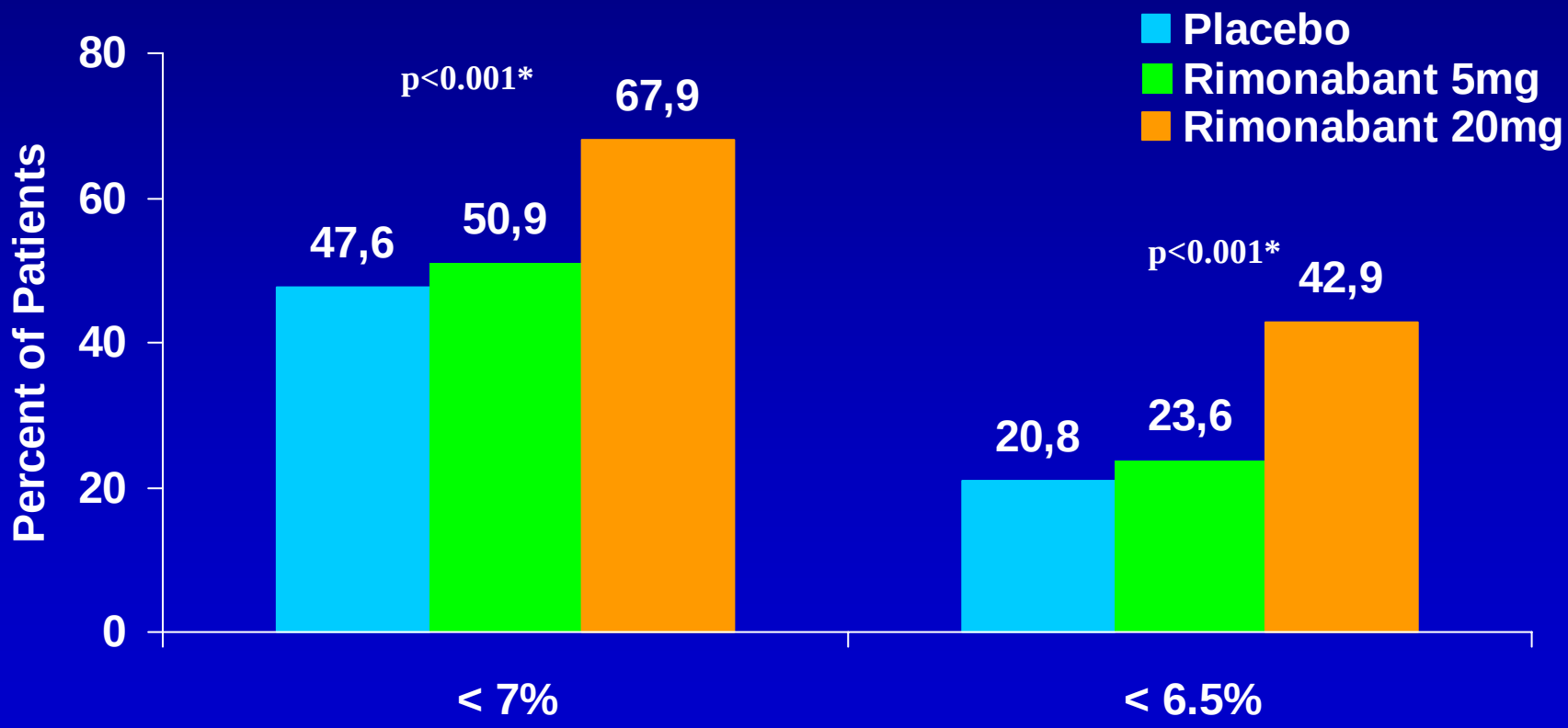
8.3 (2.1)mmol/L
Fasting Glucose



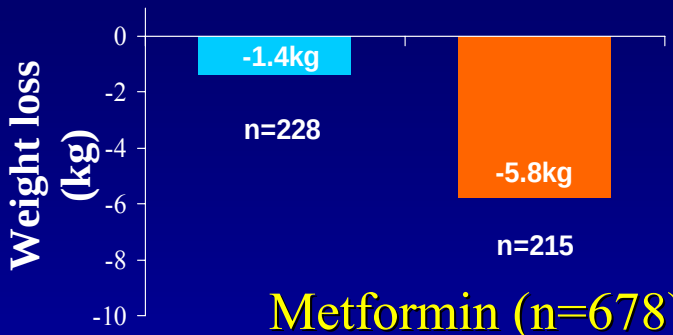
Difference between groups, mean (SEM)
LOCF 5mg vs Pbo -0.03 (0.17) (p=0.858)
20mg vs Pbo -0.97 (0.17) (p<0.001)

RIO Diabetes
Patients at HbA1c Target at 1 Yr

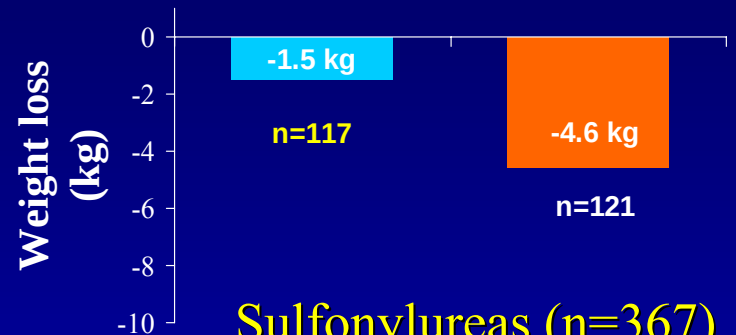
HbA_{1c} goal at 1 Year (LOCF)



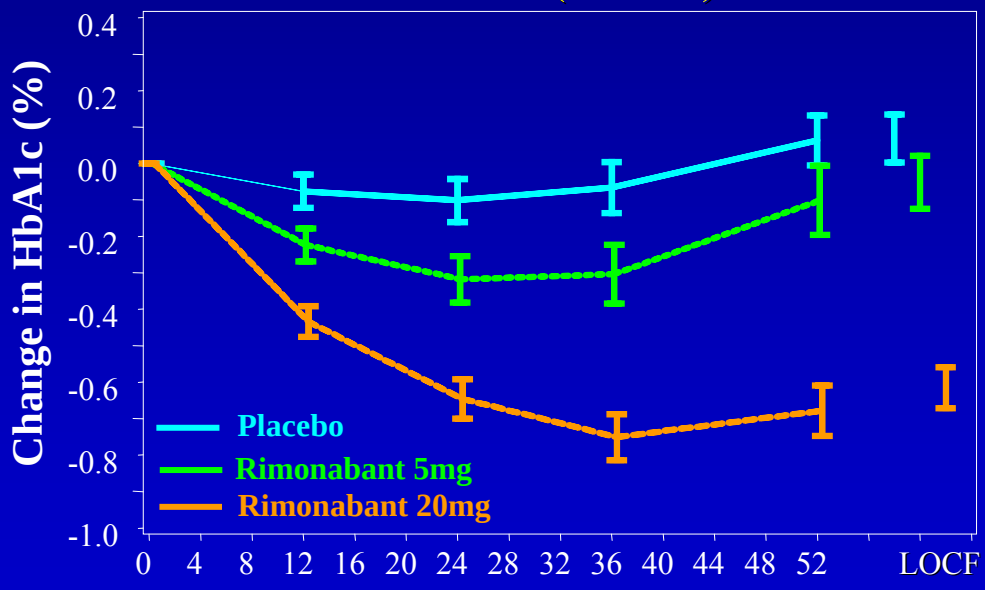
RIO-Diabetes: Metformin and Sulfonylurea Subgroups Change in Weight (kg) and HbA1C (%)



Metformin (n=678)

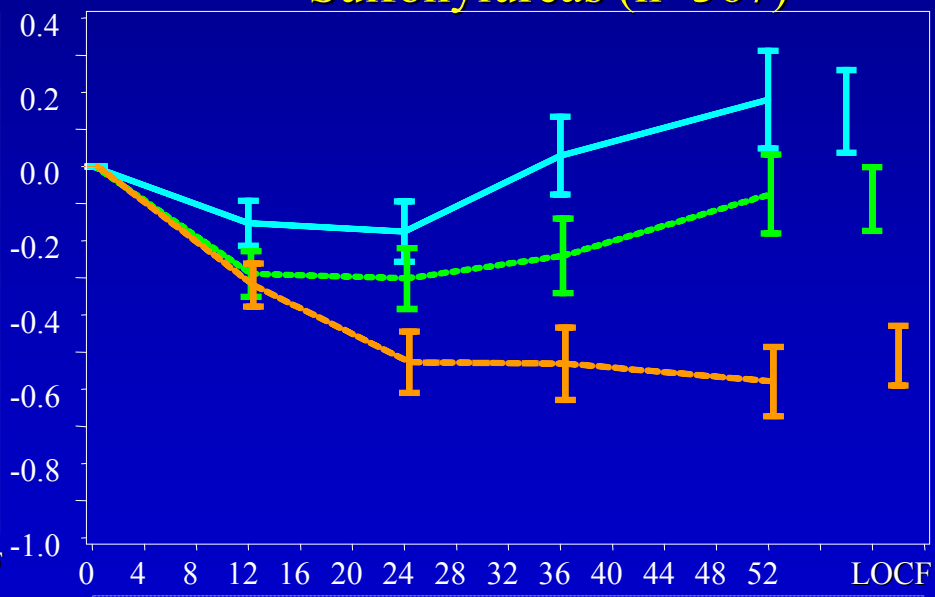


Sulfonylureas (n=367)



Difference between groups, mean (SEM)

LOCF	5mg vs Pbo	-0.1(0.1) (p=0.194)
	20mg vs Pbo	-0.7 (0.1) (p<0.001)



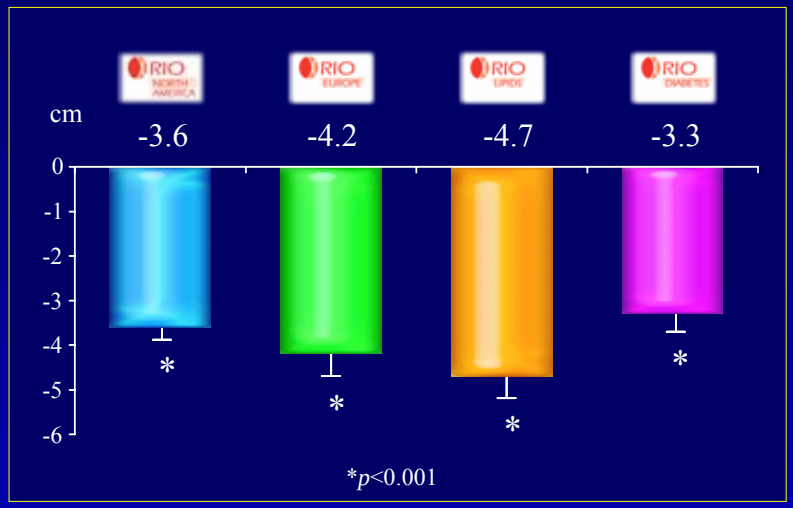
Difference between groups, mean (SEM)

LOCF	5mg vs Pbo	-0.2 (0.1) (p=0.073)
	20mg vs Pbo	-0.7 (0.1) (p<0.001)

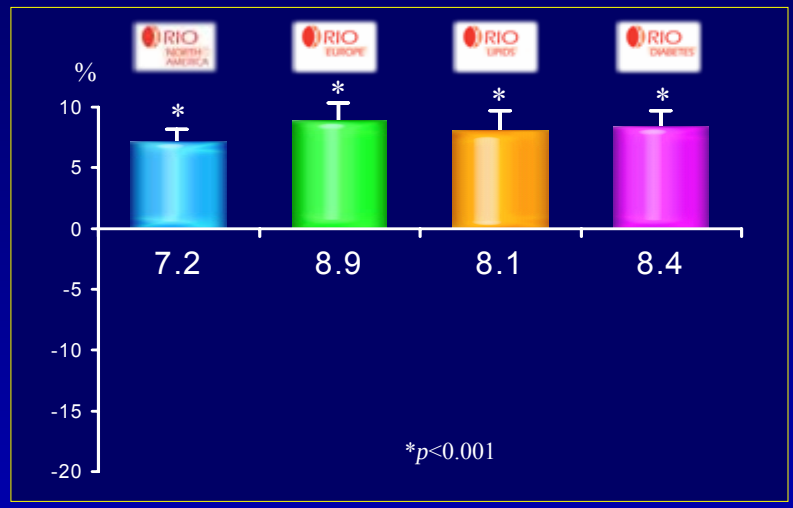
RIO~Programme: Placebo-substracted change for metabolic syndrome parameters

ITT, LOCF

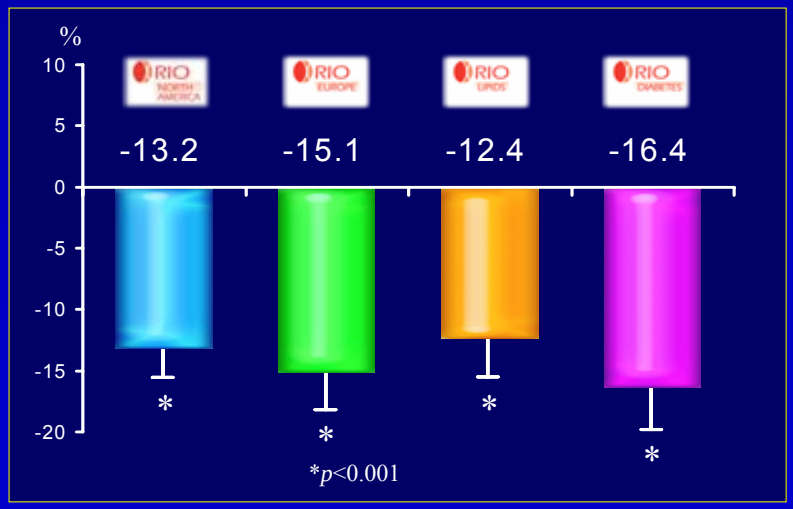
Waist circumference (cm)



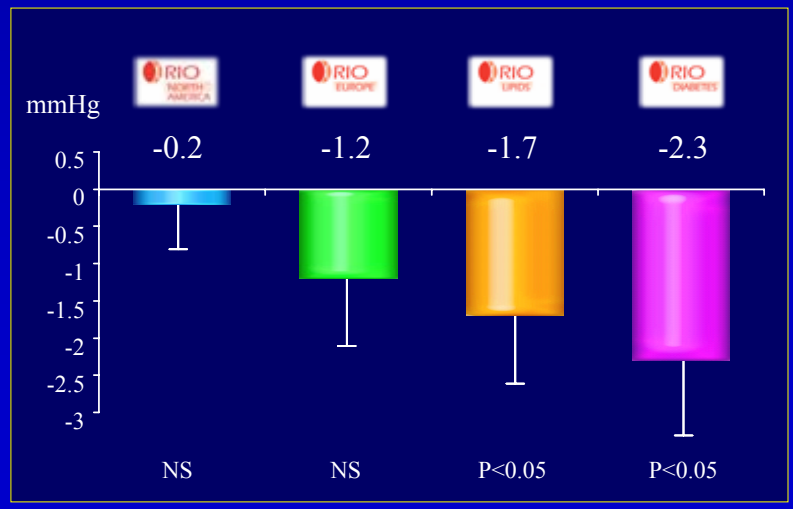
HDL-cholesterol (%)



Triglycerides (%)



SBP (mmHg)



Mean (+ SEM)

Is Rimonabant Well Tolerated ?

Issues about Neuropsychiatric Aspects

RIO 1-year data: overall safety

	Year 1		Year 2	
	Placebo (n=1602)	Rimonabant 20 mg (n=2503)	Placebo (n=466)	Rimonabant 20 mg (n=688)
Subjects with any adverse event	81.8 %	86.0 %	77.0 %	76.7 %
Subjects with any serious adverse event	4.2 %	5.9 %	5.4 %	4.5 %
Subjects discontinued due to adverse event	7.2 %	13.8 %	4.7 %	4.7 %

Data on file

Pooled RIO studies: adverse events leading to discontinuation (year 1)

%	Placebo n=1602	Rimonabant 20 mg n=2503
Any class – any event	7.2	13.8
Depressive disorders	0.8	1.9
Nausea	0.1	1.4
Mood alterations with depressive symptoms	0.6	1.0
Anxiety	0.3	1.0
Dizziness	<0.1	0.7
Pregnancy	0	0.5

According to MedDRA, preferred terms ≥0.5% in any rimonabant group

Data on file

RIO programme exclusion criteria related to neuro- and psychiatric disorders

- Presence of any clinically significant neurological or psychiatric disease according to the investigator
- History of stroke within 6 months prior to screening visit
- Presence of treated epilepsy
- Presence or history of DSM-IV bulimia or anorexia nervosa
- Presence or recent history (within 6 months prior to screening visit) of DSM-IV substance abuse or dependence

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders – 4th Edition

Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMEA)

Rimonabant 20 mg

"As an adjunct to diet and exercise for the treatment of obese patients (BMI ≥30 kg/m²), or overweight patients (BMI >27 kg/m²) with associated risk factor(s), such as type 2 diabetes or dyslipidaemia.

It is estimated that half of the observed improvement on HbA_{1c} and HDL-C in patients who received rimonabant 20 mg was beyond that expected from weight loss alone"

Use of ACOMPLIA®: Right Patient Profile (1)

- Overweight/obese patients (BMI >27 kg/m^2) with abdominal obesity (as defined by a large waist circumference) and CMR factor(s)
  - Optimal use
    - Patients most likely to benefit from ACOMPLIA® are those with multiple CMR factors that are improved by the drug
      - Patients having BMI >27 kg/m^2 with abdominal obesity and type 2 diabetes or dyslipidaemia (low HDL and/or high TG)

Use of ACOMPLIA®: Right Patient Profile (2)

- Suboptimal use
  - Patients who may not derive the maximal benefit from rimonabant usage
    - Patients with BMI and risk factors as per label, but not ready to embrace long-term treatment and concomitant lifestyle changes

Non-appropriate use of ACOMPLIA® (1)

- Patients for whom ACOMPLIA® is not indicated
  - Patients with BMI below 27 kg/m^2
  - Patients with BMI between 27 and 29.9 kg/m^2, but no associated CMR factor(s)

- Patients for whom ACOMPLIA® is contraindicated/ not recommended
  - Pregnant or breast-feeding women
  - Children below age 18 years
  - Patients with uncontrolled serious psychiatric illness such as major depression
  - Patients receiving antidepressant medication
  - Patients with severe renal/hepatic impairment

Depressive Disorders

- Higher incidence on rimonabant 20 mg vs. placebo
  - 3.2% rimonabant 20 mg vs. 1.6% placebo
- No relationship to gender, age, race, history of depressive disorders
- No argument for increased suicidality
- Similar to placebo for:
  - Intensity: generally mild or moderate
  - Corrective treatment
  - Discontinuations
  - HAD depression maximal sub-scores
  - Slightly higher recovery rate with shorter time to recovery

Data on file

Mood Alterations with Depressive Symptoms

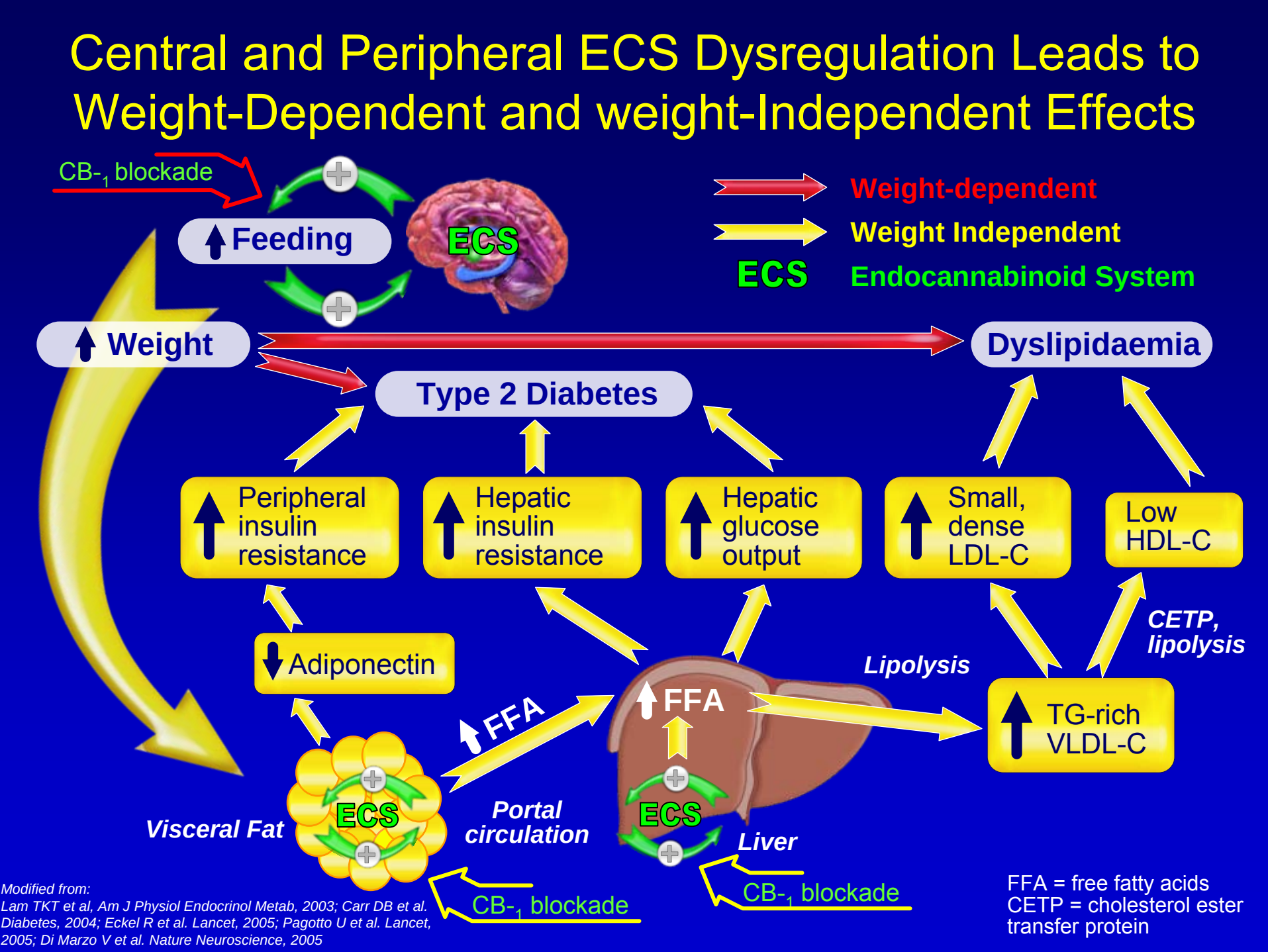
- Higher incidences on rimonabant 20 mg vs. placebo
  - 4.8% rimonabant 20 mg vs. 3.1% placebo
- No relationship to gender, age, race, history of depressive disorders
- Similar to placebo for:
  - Intensity: generally mild or moderate, no serious events
  - Corrective treatment (primarily antidepressants)
  - Time to recovery
  - HAD depression maximal sub-scores

Data on file

Non-appropriate use of ACOMPLIA® (2)

- Patients in whom ACOMPLIA® should be used with caution:
  - Patients receiving potent CYP3A4 inhibitors (including ketoconazole, itraconazole, ritonavir, telithromycin, clarithromycin, nefazodone)
  - Patients treated for epilepsy

Central and Peripheral ECS Dysregulation Leads to Weight-Dependent and weight-Independent Effects



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FFA = free fatty acids
CETP = cholesterol ester transfer protein

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