## New Insights in the Reduction of Cardiometabolic Risk


### Abstract

Global cardiometabolic risk represents the overall risk of developing type 2 diabetes and/or cardiovascular disease (including MI and stroke), which is due to a cluster of modifiable risk factors/markers. These include classical risk factors such as smoking, high LDL, hypertension, elevated blood glucose and emerging risk factors closely related to abdominal obesity (especially intra-abdominal adiposity), such as insulin resistance, low HDL, high triglycerides and inflammatory markers.

There is increasing recognition that increased abdominal obesity, which is a strong risk factor for both cardiovascular disease as well as type diabetes, may play a key role in these various cardiometabolic risk factors.

The relatively newly discovered endocannabinoid system plays a key role in both energy balance as well as lipid and glucose and is thus an appealing target for pharmacologic intervention. By selectively blocking CB1 receptor in central and peripheral tissues, rimonabant regulates energy balance, reduces abdominal obesity, and improves glucose and lipid metabolism, thus resulting in the improvement of multiple cardiometabolic risk factors. The RIO clinical trial program has demonstrated that treatment with rimonabant results in improvements in multiple cardiometabolic risk factors in a wide range of patients with elevated cardiometabolic risk. The most frequent reported adverse events were gastrointestinal, nervous system and psychiatric in nature An increased incidence of depression-related events and anxiety was observed with rimonabant, although the overall incidence remained relatively low.


### References


Despres JP. Is visceral obesity the cause of the metabolic syndrome? Ann Med. 2006;38(1):52-63.

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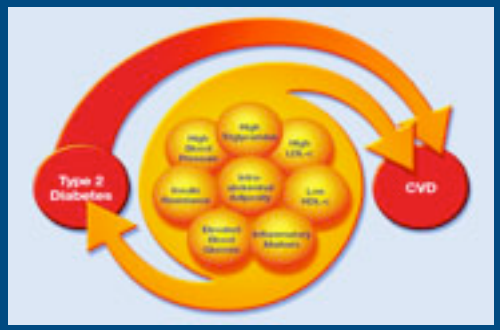
Pi-Sunyer FX, Aronne LJ, Heshmati HM, Devin J, Rosenstock J; RIO-North America Study Group. Effect of rimonabant, a cannabinoid-1 receptor blocker, on weight and cardiometabolic risk factors in overweight or obese patients: RIO-North America: a randomized controlled trial. JAMA. 2006 Feb 15;295(7):761-75.

Van Gaal LF, Rissanen AM, Scheen AJ, Ziegler O, Rossner S; RIO-Europe Study Group. Effects of the cannabinoid-1 receptor blocker rimonabant on weight reduction and cardiovascular risk factors in overweight patients: 1-year experience from the RIO-Europe study. Lancet. 2005 Apr 16-22;365(9468):1389-97.

Scheen AJ, Finer N, Hollander P, Jensen MD, Van Gaal LF; RIO-Diabetes Study Group. Efficacy and tolerability of rimonabant in overweight or obese patients with type 2 diabetes: a randomised controlled study. Lancet. 2006 Nov 11;368(9548):1660-72.

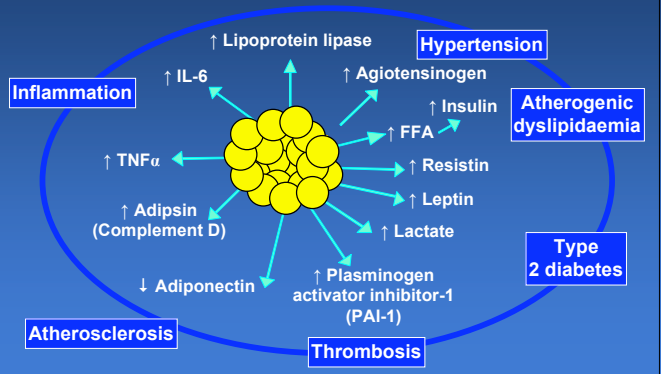
## Global cardiometabolic risk*




* working definition

Gelfand EV *et al*, 2006; Vasudevan AR *et al*, 2005

## Adverse cardiometabolic effects of products of adipocytes

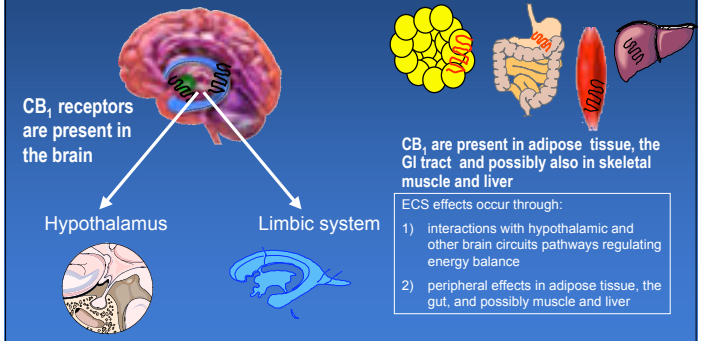



*Lyon 2003; Trayhurn et al 2004; Eckel et al 2005*

## Central and Peripheral Targets of the Endocannabinoid System (ECS)

CENTRAL NERVOUS SYSTEM

PERIPHERAL TISSUES



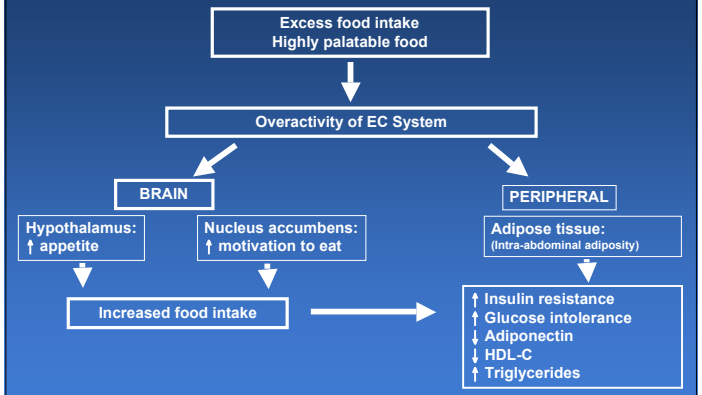



$CB_1$ are present in adipose tissue, the GI tract and possibly also in skeletal muscle and liver

ECS effects occur through:

1) interactions with hypothalamic and other brain circuits pathways regulating energy balance
2) peripheral effects in adipose tissue, the gut, and possibly muscle and liver

## Effects of EC system overactivity



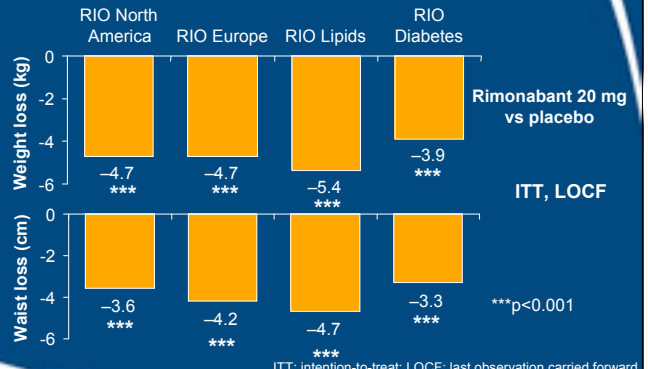

U. Pagotto, presented as a poster in IASO congress 2004

## Rimonabant in overweight/obesity

| Study | Population | N=6633 | Design |
|---|---|---|---|
| RIO North America | **Obese or overweight with/without comorbidities** (excluding diabetes) | **3045** | **1+1 year Re-randomized** |
| RIO Europe | **Obese or overweight with/without comorbidities** (excluding diabetes) | **1507** | **2 years** |
| RIO Lipids | **Obese or overweight with untreated dyslipidaemia** (excluding diabetes) | **1036** | **1 year** |
| RIO Diabetes | **Obese or overweight with type 2 diabetes** (suboptimally controlled by metformin or sulphonylurea) | **1045** | **1 year** |

Pi-Sunyer FX *et al*, 2006; Després JP *et al*, 2005; Van Gaal L *et al*, 2005; Scheen A *et al*, 2006

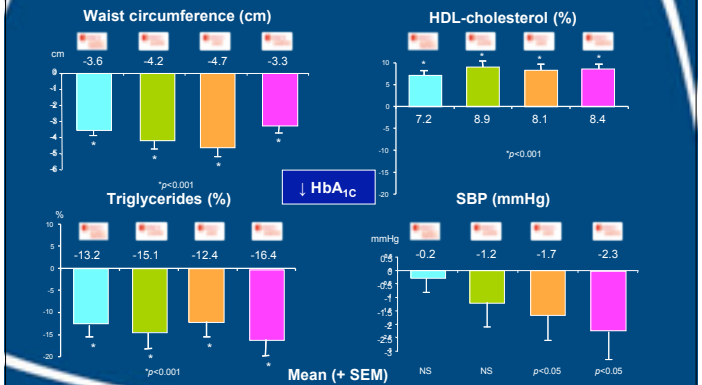
## Weight and waist loss: the consistency of RIO results




ITT: intention-to-treat; LOCF: last observation carried forward

Pi-Sunyer FX *et al*, 2006; Van Gaal L *et al*, 2005; Scheen A *et al*, 2006; Després JP *et al*, ACC 2004

## RIO programme: placebo-subtracted change for multiple cardiometabolic risk factors




ITT, LOCF

Pi-Sunyer FX *et al*, 2006; Van Gaal L *et al*, 2005; Scheen A *et al*, 2006

## Rimonabant clinical safety: summary

- Safety assessment based on extensive exposure >13,000 subjects in RIO (metabolic) and STRATUS (smoking cessation) programmes up to 2 years
  - 11,370 subjects exposed to multiple doses in Phase III
  - 2,852 subjects exposed for more than 1 year
- Most frequent reported adverse events were gastrointestinal, nervous system and psychiatric in nature
- Adverse events usually occurred during the first months and were generally of mild to moderate intensity

## Rimonabant safety conclusions

- Psychiatric events
  - Increased incidence of depression-related events and anxiety on rimonabant, overall incidence remained relatively low
  - Most adverse events were mild to moderate intensity and non-serious
  - Similar qualitative characteristics between rimonabant 20 mg vs placebo
  - No evidence of increased suicidality
- Long-term exposure did not identify new or increased risks
- No adverse changes in laboratory variables, electrocardiogram variables or vital signs

## Summary

- Global cardiometabolic risk represents the overall risk of developing type 2 diabetes and/or cardiovascular disease which is due to a cluster of modifiable risk factors/markers
- Abdominal obesity is linked to multiple cardiometabolic risk factors as well as an increased risk for both CAD and DM
- The endocannabinoid system plays a key role in energy balance and lipid and glucose metabolism and there is evidence that it is overactive in obesity
- Rimonabant selectively blocks $CB_1$ receptor in both central and peripheral tissues, thereby regulating energy balance, reducing abdominal obesity, and improving multiple cardiometabolic risk factors