

Comments on the Milano-PILOT Trial

**AHA Scientific Sessions
Late Breaking Clinical Trials
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ApoA-I Milano



Am J Hum Genet 37:1083–1097, 1985

AI_{Milano} Apoprotein Identification of the Complete Kindred and Evidence of a Dominant Genetic Transmission

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November 5, 2003

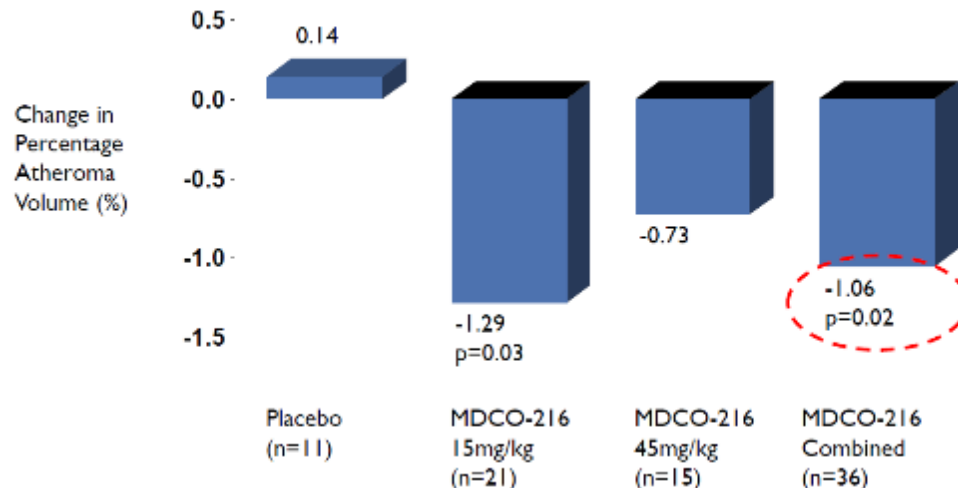
Effect of Recombinant ApoA-I Milano on Coronary Atherosclerosis in Patients With Acute Coronary Syndromes

A Randomized Controlled Trial

Steven E. Nissen, MD; Taro Tsunoda, MD; E. Murat Tuzcu, MD; [et al](#)

» [Author Affiliations](#)

JAMA. 2003;290(17):2292-2300. doi:10.1001/jama.290.17.2292



Nissen SE et al. *JAMA* 2003;290:2292–2300.

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Effect of Recombinant ApoA-I Milano on Coronary Atherosclerosis

Editorial

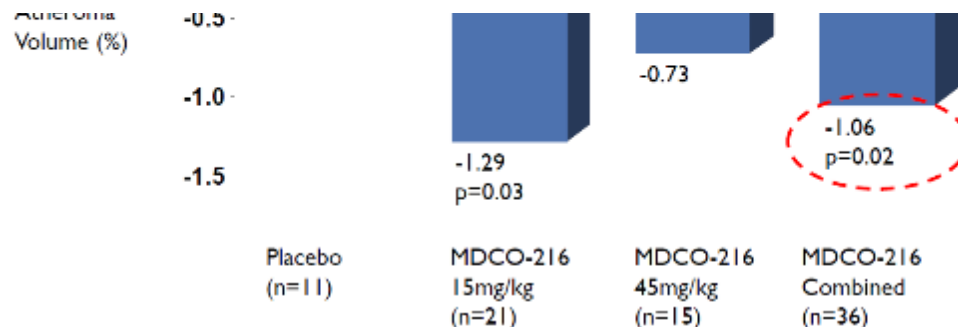
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High-Density Lipoproteins as an Emerging Therapeutic Target for Atherosclerosis

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» Author Affiliations

JAMA. 2003;290(17):2322-2324. doi:10.1001/jama.290.17.2322



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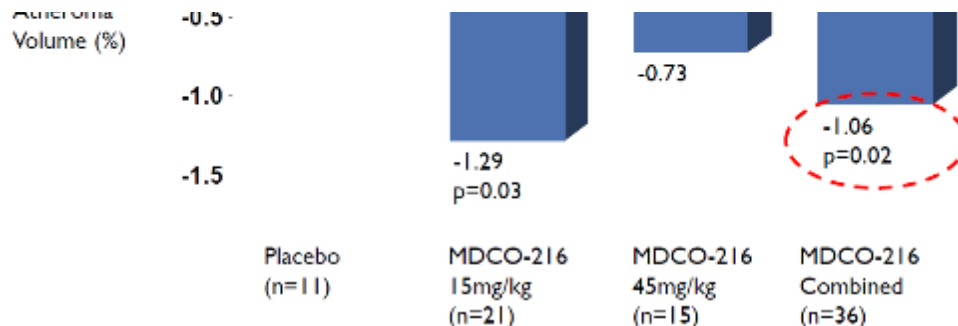
The Medicines Company Discontinues Development of MDCO-216, its Investigational Cholesterol Efflux Promoter

7 Nov 2016

— Top-line efficacy data from the MILANO-PILOT trial, which enrolled 126 patients, provide insufficient basis for further investment by the Company —



JAMA. 2003;290(17):2292-2300. doi:10.1001/jama.290.17.2292



Nissen SE et al. JAMA 2003;290:2292–2300.

MILANO-PILOT

- Well-executed IVUS trial by world class investigators
- Three times the size of the original apoA-I Milano IVUS trial
- Unexpected regression in the placebo group
- Convincing negative results

ApoA-I Milano is very different structurally from wild-type apoA-I

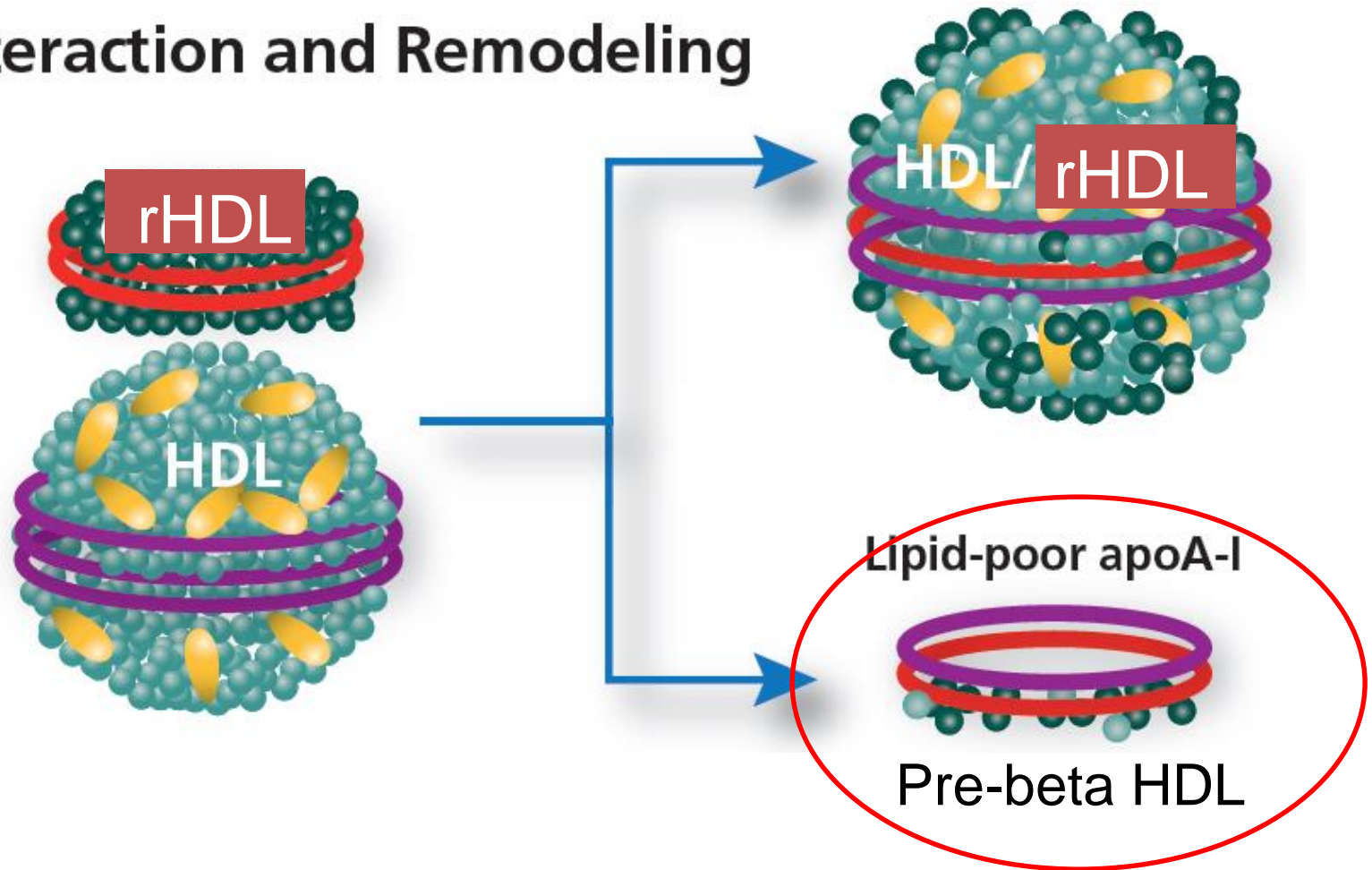
- Arginine 173 replaced with cysteine leading to disulfide dimer formation
- Rapidly catabolized leading to reduced levels of HDL-C

ApoA-I Milano differs from wild-type apoA-I with regard to several functions

- Reduced generation of pre-beta HDL

Recombinant HDL infusion generates pre-beta HDL

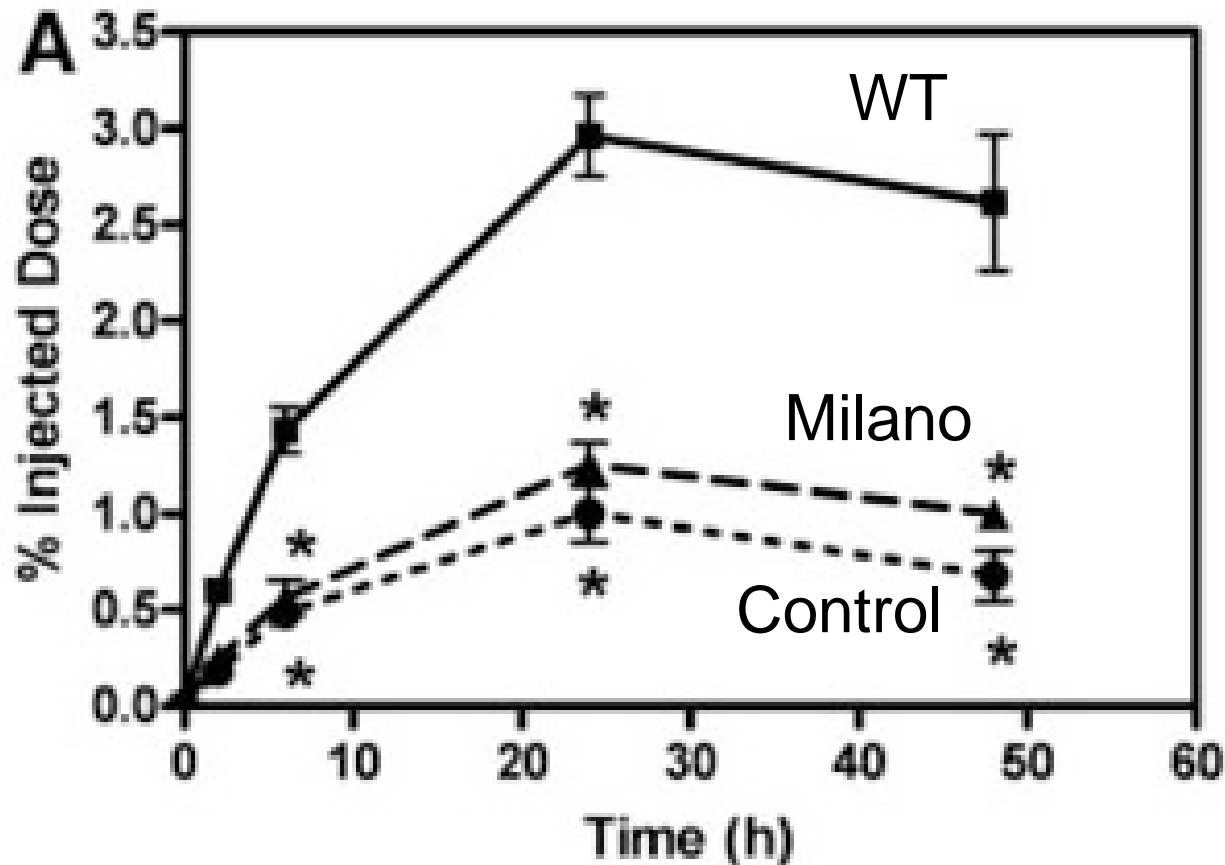
Interaction and Remodeling



ApoA-I Milano differs from wild-type apoA-I with regard to several functions

- Reduced generation of pre-beta HDL
- Reduced promotion of cholesterol efflux

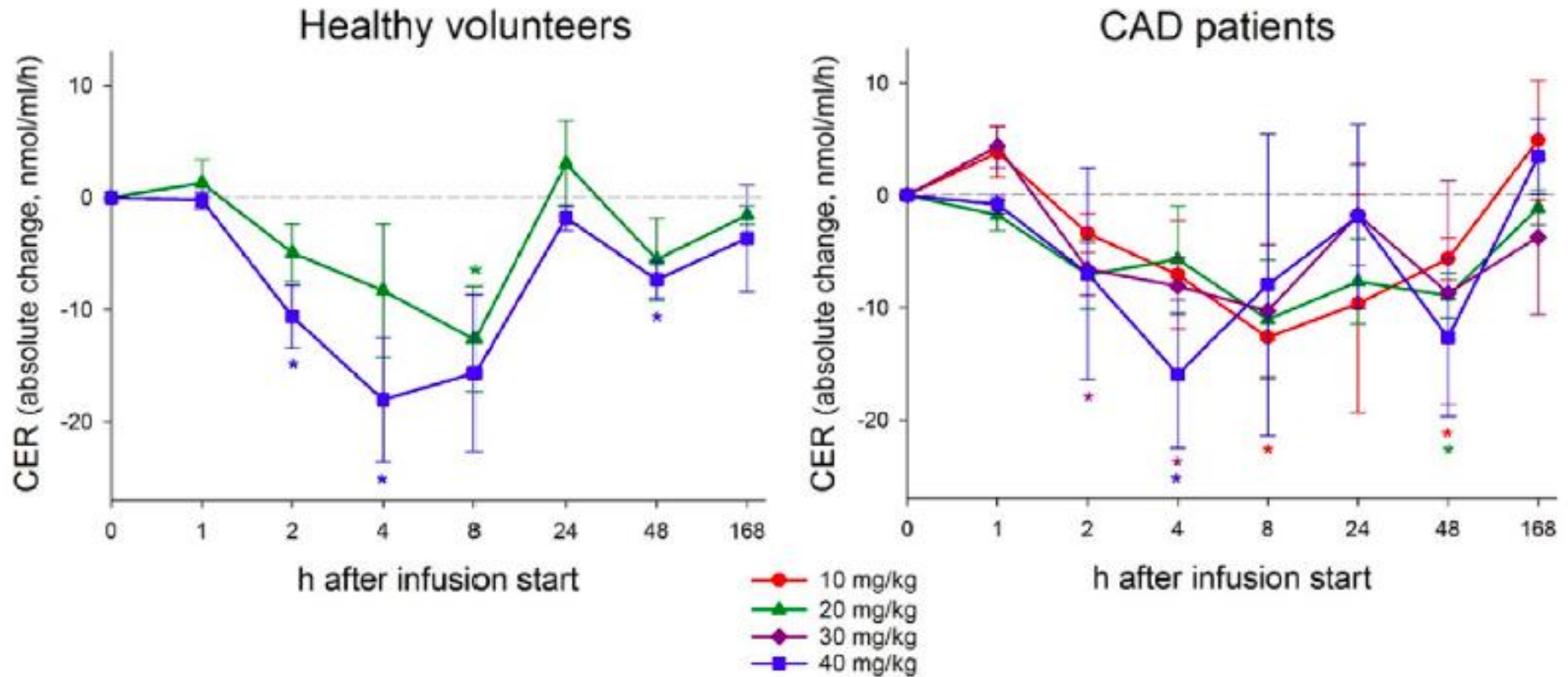
ApoA-I Milano does not mobilize macrophage cholesterol In vivo as efficiently as wild-type apoA-I



ApoA-I Milano differs from wild-type apoA-I with regard to several functions

- Reduced generation of pre-beta HDL
- Reduced promotion of cholesterol efflux
- Reduced activation of LCAT

ApoA-I Milano rHDL infusion suppresses the LCAT-mediated cholesterol esterification rate



Promoting cholesterol efflux and reducing cardiovascular events with apoA-I infusion?

