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The JUPITER Clinical Trial

Effects of Rosuvastatin 20mg on PCSK9 Plasma Levels

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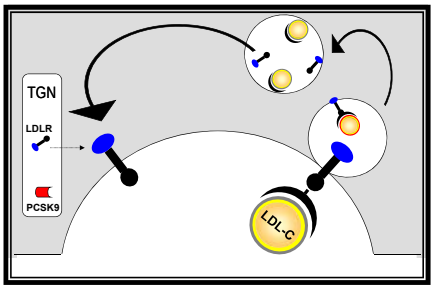
Cholesterol Metabolism



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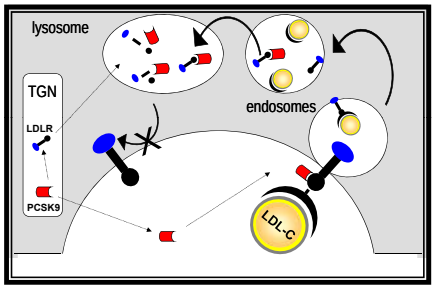
Cholesterol Metabolism



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Research Questions

- **The effect of Rosuvastatin on plasma PCSK9 levels.**
- **Relationship between PCSK9 levels and the magnitude of LDL-C reduction.**
- **Secondary aims:**
  - Effect of gender.
  - Effect of the R46L SNP on PCSK9 and LDL-C change.

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The JUPITER Clinical Trial

A Randomized Trial of Rosuvastatin in the Prevention of Cardiovascular Events Among 17,802 Apparently Healthy Men and Women With Elevated Levels of C-Reactive Protein (hsCRP): The JUPITER Trial

Paul Ridker*, Eleanor Danielson, Francisco Fonseca*, Jacques Genest*, Antonio Gotto*, John Kastelein*, Wolfgang Koenig*, Peter Libby*, Alberto Lorenzatti*, Jean MacFadyen, Borge Nordestgaard*, James Shepherd*, James Willerson, and Robert Glynn* on behalf of the JUPITER Trial Study Group

An Investigator Initiated Trial Funded by AstraZeneca, USA

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The JUPITER Clinical Trial

Multi-National Randomized Double Blind Placebo Controlled Trial of Rosuvastatin in the Prevention of Cardiovascular Events Among Individuals With Low LDL and Elevated hsCRP

No Prior CVD or DM
Men ≥50, Women ≥60
LDL <130 mg/dL
hsCRP ≥2 mg/L

→ Rosuvastatin 20mg (N=8901)
→ Placebo (N=8901)

MI
Stroke
Unstable Angina
CVD Death
CABG/PTCA

Argentina, Belgium, Brazil, Bulgaria, Canada, Chile, Colombia, Costa Rica, Denmark, El Salvador, Estonia, Germany, Israel, Mexico, Netherlands, Norway, Panama, Poland, Romania, Russia, South Africa, Switzerland, United Kingdom, Uruguay, United States, Venezuela

Ridker et al, Circulation 2003;108:2292-2297

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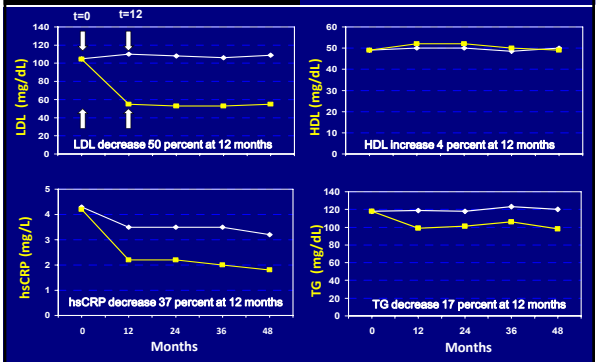
Effects of Rosuvastatin 20 mg on LDL, HDL, TG, and hsCRP



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Study Design

- Random selection of men and women in the JUPITER study
- Placebo and Rosuvastatin 20mg study arms
- Blood samples at times 0 (baseline) and 1 year (12 month)
- PCSK9 determined by ELISA (Dubuc G. *et al* J Lipid Res 2010;51:140)
- Examine the PSCK9 R46L SNP on the response to Rosuvastatin

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Statistical Calculation

- We assumed a mean PCSK9 value of **89** ng/ml at baseline, a SD of **32** and an expected effect of **12.5**%, (α value of **0.001** with **90%** power).
- A minimum of **200** participants per group would be required.
- **We therefore examined 250 subjects/group:**
  - Men, Placebo (**250**) and Rosuva (**250**) at baseline.
  - Women, Placebo (**250**) and Rosuva (**250**) at baseline.
  - Men, Placebo (**250**) and Rosuva (**250**) at 1 year.
  - Women, Placebo (**250**)and Rosuva (**250**) at 1 year.

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Demographic

	Men n=500		*Women n=500*	
	Placebo	*Rosuvastatin*	*Placebo*	*Rosuvastatin*
Age	65 ±7	64 ±8	72 ±5	71 ±5
Glucose	96 ±10	96 ±9	94 ±10	93 ±9
HbA1c	5.5 ±0.4	5.6 ±0.4	5.7 ±0.3	5.6 ±0.3
Weight	202 ±39	200 ±40	165 ±34	165 ±37
BMI	30 ±6	29 ±5	29 ±6	29 ±6
Waist	41 ±5	41 ±5	37 ±6	37 ±6
SBP	132 ±14	130 ±15	133 ±16	131 ±15
DBP	78 ±8	79 ±8	77 ±8	76 ±9
Met. Syn.	95 ±38	97 ±39	99 ±40	92 ±37
Smoking	41 ±16	38 ±15	13 ±5	18 ±7

No statistically significant differences between the two groups in both genders

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Demographic

Men	*Baseline*		*12 month*	
	Placebo	*Rosuvastatin*	*Placebo*	*Rosuvastatin*
Cholesterol	182 ±22	178 ±24	183 ±25	127 ±26 *
Triglyceride	144 ±77	151 ±89	147 ±93	117 ±61 *
LDL-C	105 ±16	101 ±21	107 ±20	53 ±20 *
HDL-C	48 ±13	47 ±13	48 ±12	51 ±14 *
hsCRP	5.9 ±6.2	6.4 ±9.7	6.0 ±11.7	4.7 ±9.9
PCSK9	71 ±19	71 ±22	72 ±22	91 ±29 *

28% ↑

Woman	*Baseline*		*12 month*	
	Placebo	*Rosuvastatin*	*Placebo*	*Rosuvastatin*
Cholesterol	192 ±22	192 ±23	197 ±27 *	135 ±23 *
Triglyceride	132 ±64	129 ±55	132 ±60	103 ±41 *
LDL-C	107 ±18	106 ±17	111 ±23 *	51 ±17 *
HDL-C	59 ±15	60 ±16	60 ±15	63 ±15 *
hsCRP	6.1 ±5.8	6.8 ±6.7	5.5 ±5.2	3.5 ±4.2
PCSK9	77 ±20	77 ±19	78 ±22	103 ±31 *

34% ↑

*P value <0.005 baseline vs. 12 month

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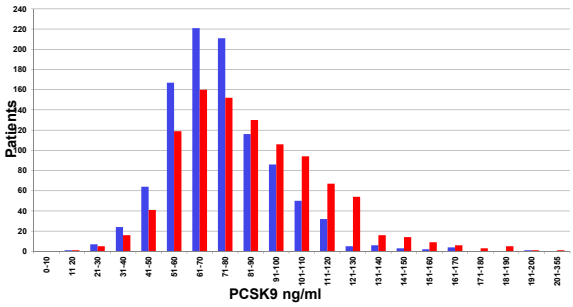
PCSK9 Distribution



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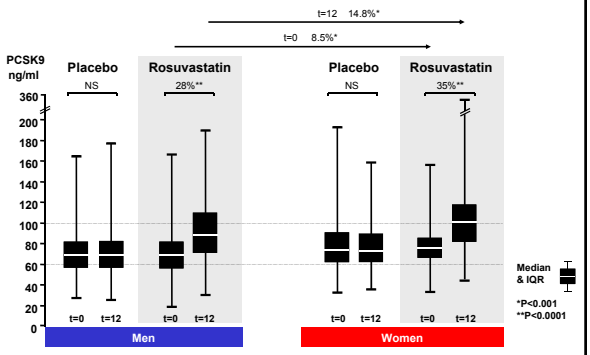
PCSK9 Respond to Rosuvastatin



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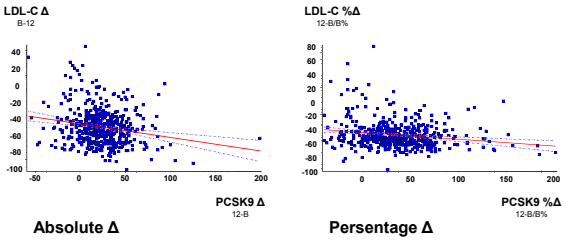
Correlation Between PCSK9 & LDL-C Changes



Absolute Δ

Number of points = 499
r = -0.15 (corrected for ties)
95% confidence interval: -0.24 to -0.06
The two-tailed P value is 0.0007

Persentage Δ

Number of points = 499
r = -0.16 (corrected for ties)
95% confidence interval: -0.25 to -0.08
The two-tailed P value is 0.0003

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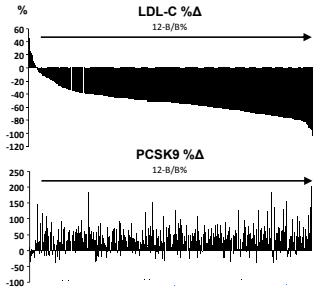
Individual LDL-C and PCSK9 Change



Individual percent LDL-C change in response to Rosuvastatin 20mg ranked by magnitude of effect

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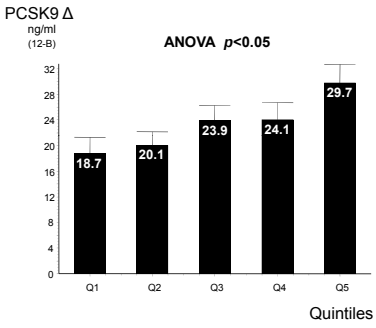
ANOVA on Quintiles



Changes in PCSK9 by quintiles of percent LDL-C change

Mean and Standard Error

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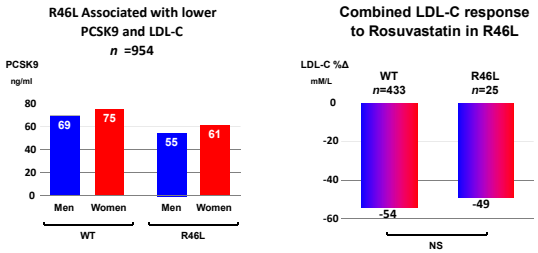
Effects of the R46L SNP on PCSK9



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Summary

- **Rosuvastatin increase plasma levels of PCSK9.**
- **Women have higher levels of PCSK9 than men and this is further exaggerated when Rosuvastatin 20mg is given.**
- **Circulating PCSK9 as a marker is stable over time.**

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Summary

- PCSK9 increase modulate the statin-mediated LDL-C lowering within a quintile range.
- The magnitude of response to Rosuvastatin was not influenced by the presence of the R46L SNP.

Discussion

- The observation that statin-mediated increase in PCSK9 is not associated with a blunting of the response to statins is counter-intuitive and warrants further explanations.

Questions

Thank You