Univerza v Ljubljani
Fakulteta za farmacijo

Interpretacija rezultatov kliničnih preizkušanj

Načrtovanje, analiza in interpretacija raziskav

Asist. dr. Igor Locatelli, *mag. farm.*

Ljubljana, 14. 1. 2011

Interpretacija....

Lord Rutherford famously said that 'If your experiment needs statistics, you ought to have done a better experiment', and also concluded that 'All science is either physics or stamp collecting'. Unfortunately in medicine, statistics is essential and as everyone knows, Benjamin Disraeli claimed that there are 'Lies, damned lies, and statistics'. Thus, it is important to review any study with extreme caution to try to identify the loopholes.

Značilnosti in vzročnost v biomedicini

- Statistična značilnost (testirana skupina je boljša od kontrolne skupine)
- Klinična značilnost (učinek testirane skupine je klinično bolj pomemben od kontrolne)
- Vzročna povezava (ali je kajenje vzrok za nastanek pljučnega raka);

Previdnost

- Primarni in sekundarni cilj („endpoint“)
- Zajeta populacija:
  - ITT - analiza glede na namero zdravljenja
  - PP – analiza po protokolu
  - SOT – as treated safety population
- Postavitev statističnih hipotez:
  - Superiornost
  - Neinferiornost (non-inferiority)
  - Enakost (equivalence)
- Univariatna ali multivariatna analiza
- Moteče spremenljivke

Observed Spurious Relationship*	Reason for the Relationship (the Third Variable)
Amount of ice cream sold and deaths by drownings (Moore, 1993)	Season: Ice cream sales and drownings tend to be high during the warm months of the year.
Size of left hand and size of right hand	Genetics: The size of both hands is due to genetic makeup.
Height of sons and height of daughters (Davis, 1985)	Genetics: Heights of sons and daughters are both due their parents' genetic makeup.
Ministers' salaries and price of vodka	Area (i.e., urban or rural): In urban areas, prices and salaries tend to be higher.
Shoe size and reading performance for elementary school children	Age: Older children have larger shoe sizes and read better.
Number of doctors in region and number of people dying from disease	Population density: In highly dense areas, there are more doctors and more people die.
Number of police officers and number of crimes (Glass & Hopkins, 1996)	Population density: In highly dense areas, there are more police officers and more crimes.
Number of homicides and number of churches	Population density: In highly dense areas, there are more homicides and more churches.
Number of storks sighted and the population of Oldenburg, Germany, over a six-year period (Box, Hunter, & Hunter, 1978)	Time: Both variables were increasing over time.
Number of public libraries and the amount of drug use	Time: Both were increasing during the 1970s.
Teachers' salaries and the price of liquor (Moore and McCabe, 1993)	Time: Both tend to increase over time.
Tea drinking and lung cancer	Smoking: Tea drinkers have a lower risk only because they smoke less.

Raziskava INCROSS

- Načrt raziskave
- Primarni in sekundarni markerji učinkovitosti
- Uporabljena statistična analiza
- Razlaga tabele 2 in 3
- Razlaga slike 3 in 4
- Komentar na raziskavo

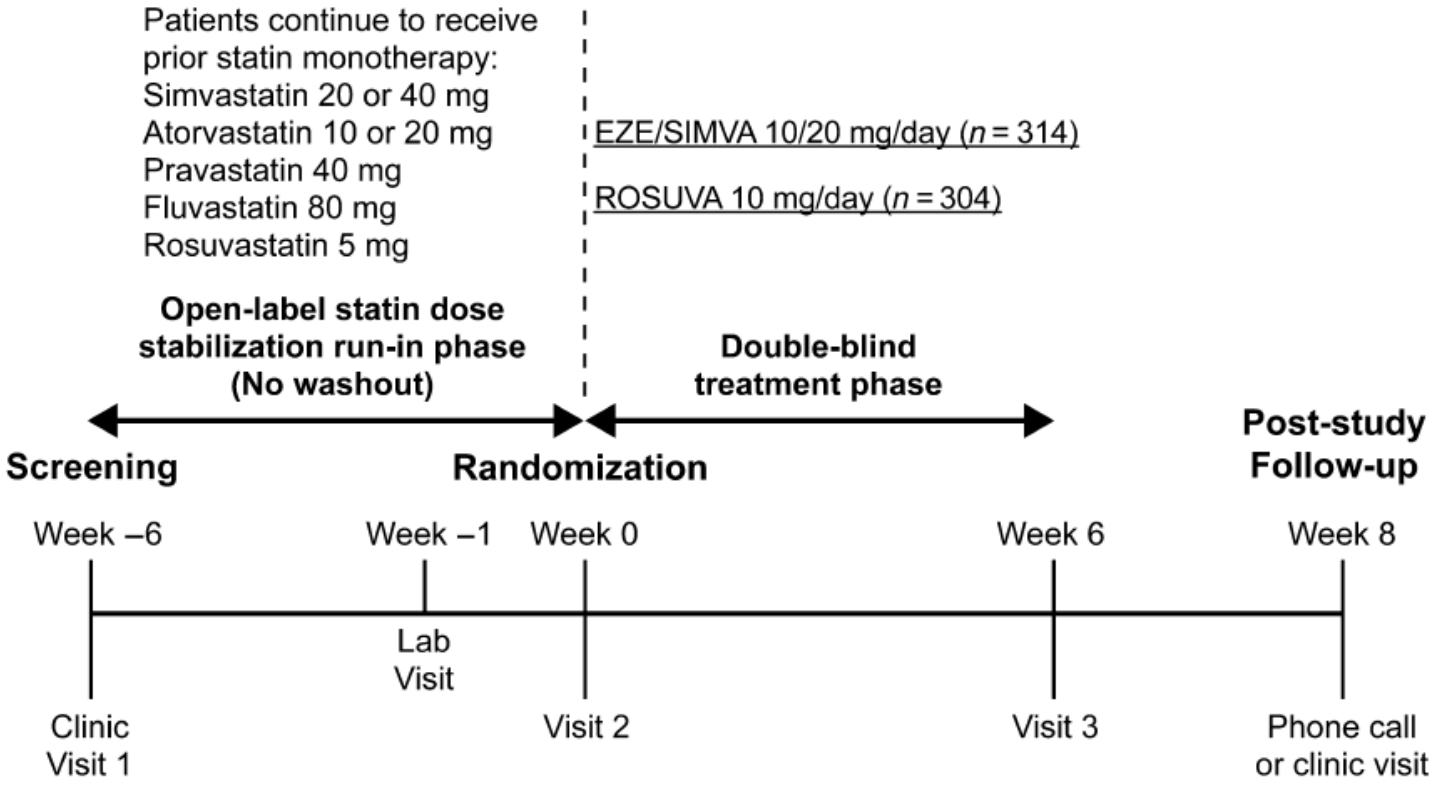
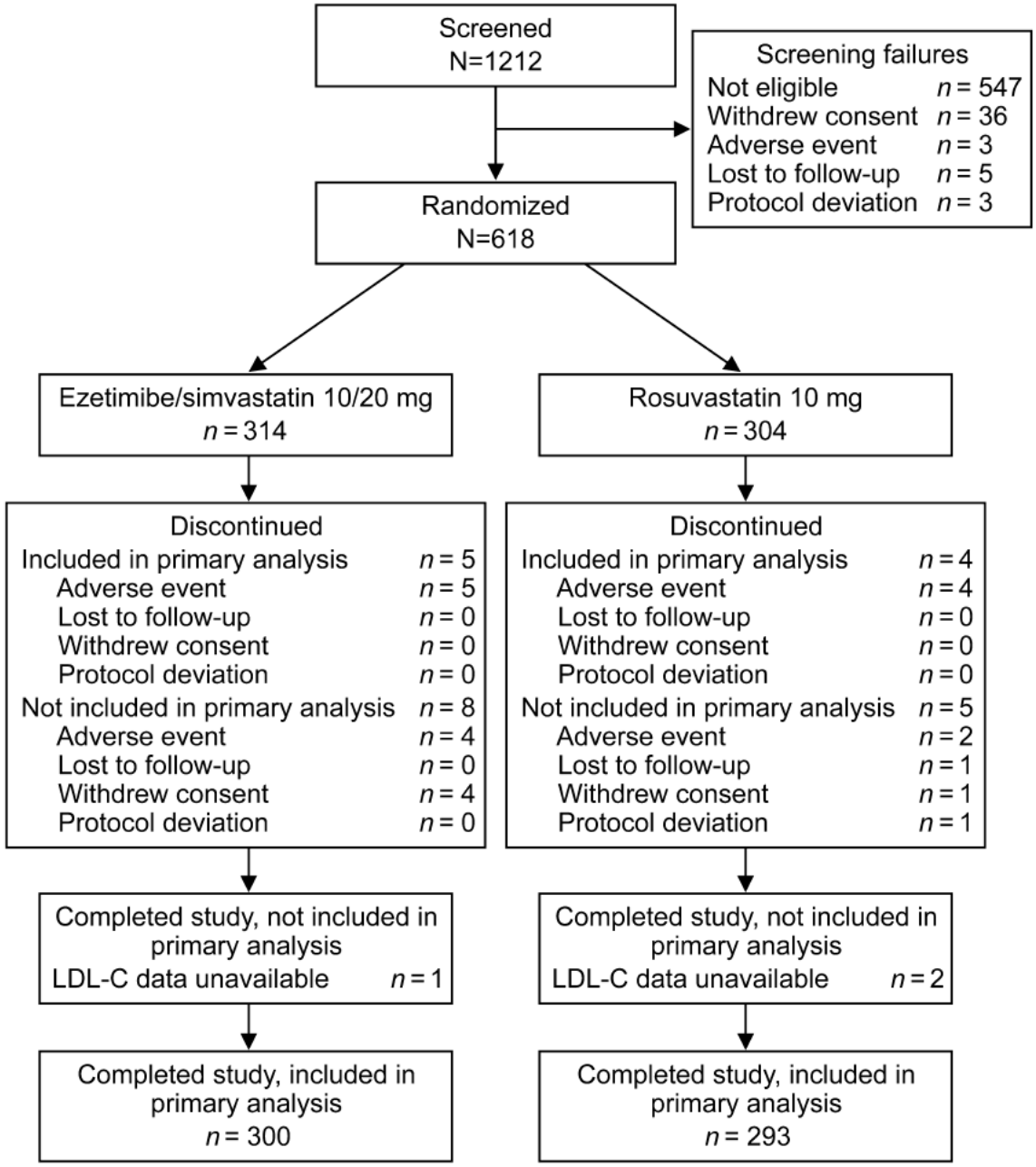


Figure 1 Study design. Patient's medical history and current brand/dose of statin reviewed at Visit 1. Eligibility of study entry based on LDL-C ≥ 2.59 mmol/l and ≤ 4.92 mmol/l. Randomisation to treatment (ezetimibe 10/20 mg or rosuvastatin 10 mg) at Visit 2 after stratification by baseline statin potency (low or high) and eligibility based on acceptable serum chemistry values for alanine aminotransferase, aspartate aminotransferase, creatine kinase, triglycerides and low-density lipoprotein cholesterol (LDL-C)


Screened
N=1212
Screening failures
Not eligible n = 547
Withdrew consent n = 36
Adverse event n = 3
Lost to follow-up n = 5
Protocol deviation n = 3
Randomized
N=618
Ezetimibe/simvastatin 10/20 mg
n = 314
Rosuvastatin 10 mg
n = 304
Discontinued
Included in primary analysis n = 5
Adverse event n = 5
Lost to follow-up n = 0
Withdrew consent n = 0
Protocol deviation n = 0
Not included in primary analysis n = 8
Adverse event n = 4
Lost to follow-up n = 0
Withdrew consent n = 4
Protocol deviation n = 0
Discontinued
Included in primary analysis n = 4
Adverse event n = 4
Lost to follow-up n = 0
Withdrew consent n = 0
Protocol deviation n = 0
Not included in primary analysis n = 5
Adverse event n = 2
Lost to follow-up n = 1
Withdrew consent n = 1
Protocol deviation n = 1
Completed study, not included in primary analysis
LDL-C data unavailable n = 1
Completed study, not included in primary analysis
LDL-C data unavailable n = 2
Completed study, included in primary analysis
n = 300
Completed study, included in primary analysis
n = 293

The primary efficacy variable was mean per cent change in LDL-C from baseline (week 0) to study end-point (last postbaseline measurement during the 6-week active treatment period). Key secondary efficacy variables were the percentages of patients achieving LDL-C < 2.59 mmol/l (< 100 mg/dl) and < 1.81 mmol/l (< 70 mg/dl) at study end-point. Predefined secondary efficacy variables included the mean per cent change at study end-point in total cholesterol (TC), TG, high-density lipoprotein cholesterol (HDL-C), non-HDL-C, LDL-C/HDL-C and TC/HDL-C ratios, apolipoprotein (apo) B and high-sensitivity C-reactive protein (hs-CRP).

Table 2 Baseline LDL-C concentrations and number (%) of patients in each statin potency stratum receiving specific brands and doses of statin monotherapies

	EZE/SIMVA 10/20 mg (*n* = 314)		ROSUVA 10 mg (*n* = 304)	
	Baseline LDL-C (mmol/l)	No. of patients (%)	Baseline LDL-C (mmol/l)	No. of patients (%)
Low potency statin (Stratum 1)	3.25 (0.42)	189 (60.2)	3.23 (0.44)	180 (59.2)
Fluvastatin 80 mg	3.12 (0.48)	18 (9.5)	3.20 (0.45)	17 (9.4)
Lovastatin 20 mg*	–	0	2.75 (–)	1 (0.6)
Pravastatin 40 mg	3.39 (0.39)	40 (21.2)	3.20 (0.39)	30 (16.7)
Atorvastatin 10 mg	3.23 (0.40)	66 (34.9)	3.30 (0.49)	63 (35.0)
Simvastatin 20 mg	3.22 (0.44)	65 (34.4)	3.19 (0.41)	69 (38.3)
High potency statin (Stratum 2)	3.16 (0.42)	125 (39.8)	3.27 (0.43)	124 (40.8)
Atorvastatin 20 mg	3.10 (0.41)	52 (41.6)	3.21 (0.38)	51 (41.1)
Rosuvastatin 5 mg	3.22 (0.42)	44 (35.2)	3.33 (0.49)	50 (40.3)
Simvastatin 40 mg	3.16 (0.44)	29 (23.2)	3.24 (0.40)	23 (18.5)

*One patient taking lovastatin 20 mg was allowed to participate in this study.
EZE/SIMVA, ezetimibe/simvastatin; LDL-C, low-density lipoprotein cholesterol; ROSUVA, rosuvastatin.

Table 3 Least squares mean percent change from baseline and between-group differences (EZE/SIMVA – ROSUVA) in efficacy parameters at the last available postbaseline evaluation during the 6-week study period

Efficacy parameter	Least-squares mean % change (95% CI)		Between-group difference (95% CI)	p-value
	EZE/SIMVA 10/20 mg (*n* = 301–305)‡	ROSUVA 10 mg (*n* = 292–297)‡		
LDL-C	−27.7 (−30.3, −25.0)***	−16.9 (−19.6, −14.3)***	−10.7 (−14.1, −7.3)	≤ 0.001
TC	−17.5 (−19.4, −15.7)***	−10.3 (−12.2, −8.5)***	−7.2 (−9.6, −4.8)	≤ 0.001
HDL-C	2.1 (0.3, 3.9)**	3.0 (1.2, 4.9)***	−0.9 (−3.2, 1.4)	0.433
TG†	−11.0 (−15.3, −6.8)***	−5.3 (−9.9, −1.2)**	−5.1 (−9.6, −0.3)	0.056
non-HDL-C	−23.4 (−25.8, −21.0)***	−14.0 (−16.5, −11.6)***	−9.4 (−12.5, −6.3)	≤ 0.001
apo B	−17.9 (−20.1, −15.7)***	−9.8 (−12.0, −7.6)***	−8.1 (−10.9, −5.3)	≤ 0.001
LDL-C/HDL-C ratio	−27.4 (−30.4, −24.4)***	−17.8 (−20.9, −14.8)***	−9.6 (−13.5, −5.7)	≤ 0.001
TC/HDL-C ratio	−17.8 (−19.9, −15.6)***	−11.5 (−13.7, −9.3)***	−6.3 (−9.1, −3.4)	≤ 0.001
hs-CRP†	−8.3 (−16.7, 0.0)**	0.0 (−7.1, 6.3)	−6.7 (−16.7, 2.9)	0.172

**p ≤ 0.05 vs. baseline; ***p ≤ 0.001 vs. baseline.

†Expressed as median study endpoint value (95% CI of median); the difference in medians was obtained by Hodges-Lehman estimation.

‡The number of patients contributing to the efficacy analyses varied for each of the parameters shown.

apo, apolipoprotein; CI, confidence interval; EZE/SIMVA, ezetimibe/simvastatin; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; ROSUVA, rosuvastatin; TC, total cholesterol; TG, triglycerides.

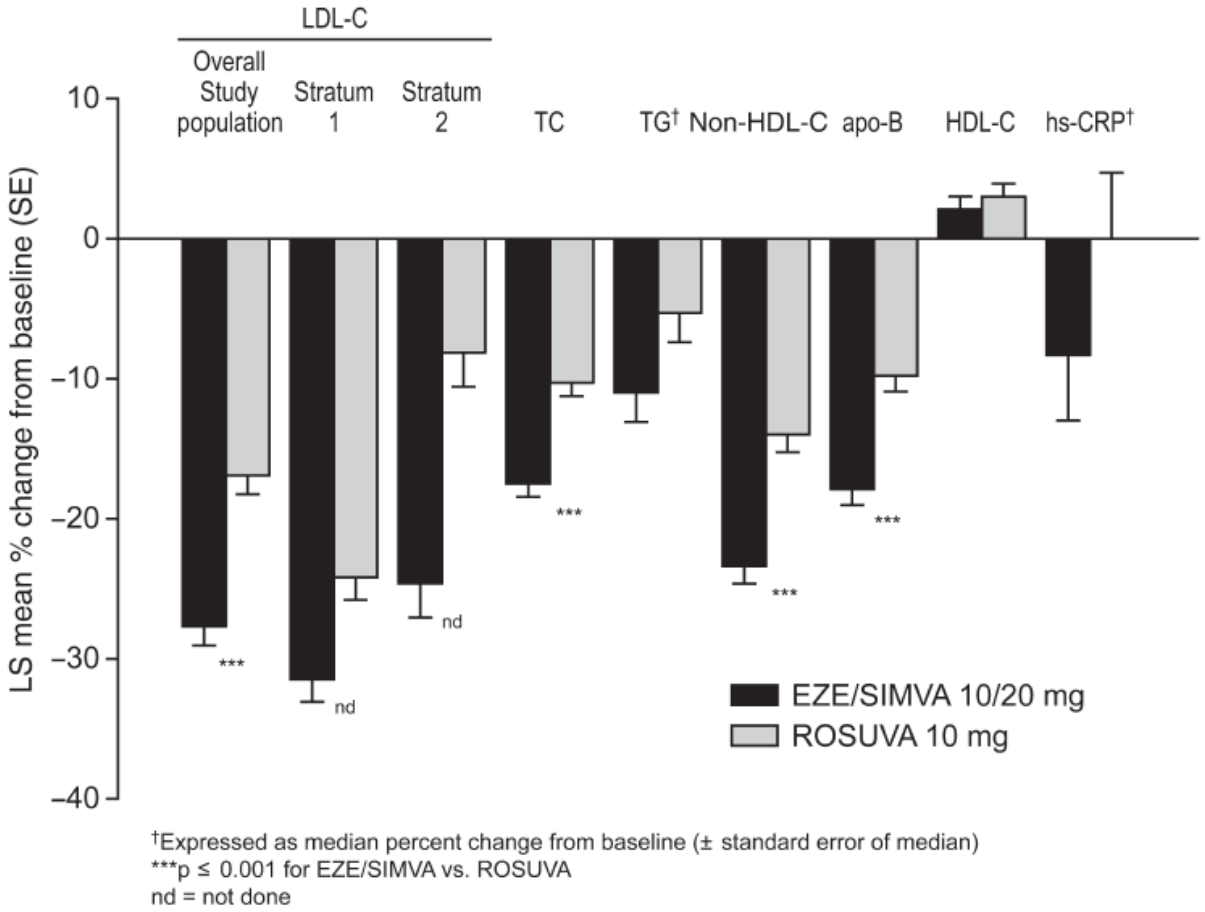


Figure 3 Mean per cent change (±standard error) from baseline in lipid parameters following 6 weeks of treatment with ezetimibe/simvastatin (EZE/SIMVA) 10/20 mg or rosuvastatin (ROSUVA) 10 mg

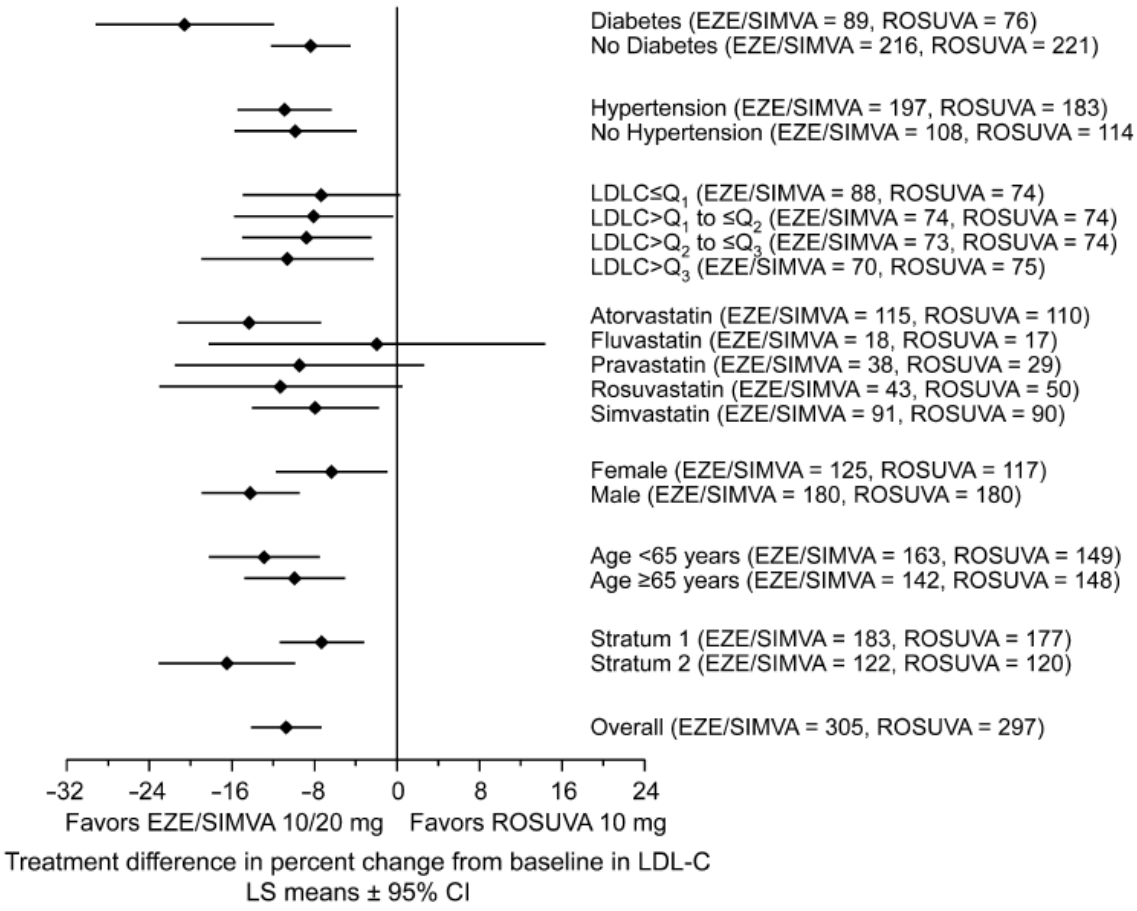


Figure 4 Between-treatment group differences (ezetimibe/simvastatin vs. rosuvastatin) in least squares mean per cent change in low-density lipoprotein cholesterol (LDL-C) at study end-point (95% CI) in the overall study population and within subgroups defined by statin potency stratum [use of low (Stratum 1) and high (Stratum 2) potency statin monotherapy prior to randomisation], statin brand used prior to randomisation, gender, age, baseline LDL-C (stratified by quartile) and prior history of diabetes or hypertension. Numbers in parentheses indicate number of patients in each treatment group in the respective subcategory

Komentar IN-CROSS

It appears that the Farnier study inclusion criteria were designed to select patients who would be likely not to respond to increase in statin dose, but can we predict what will happen when those patients are started on a cholesterol absorption blocker? It has been shown that patients who are hyporesponders to statins are hyperresponders to ezetimibe (5). A range of estimates for the extra LDL-lowering resulting from addition of ezetimibe to statin therapy have been published, with a typical extra reduction of about 18%, but that was in a mixed population and not a statin-non-responsive one. Therefore, it is possible that the Farnier trial participants may have had a greater than 18% response.