Endocrinologic and Metabolic Drugs Advisory Committee

Meeting on Simvastatin/Ezetimibe

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I have no conflicts of interest

Important Differences Between Statistical and Clinical Significance

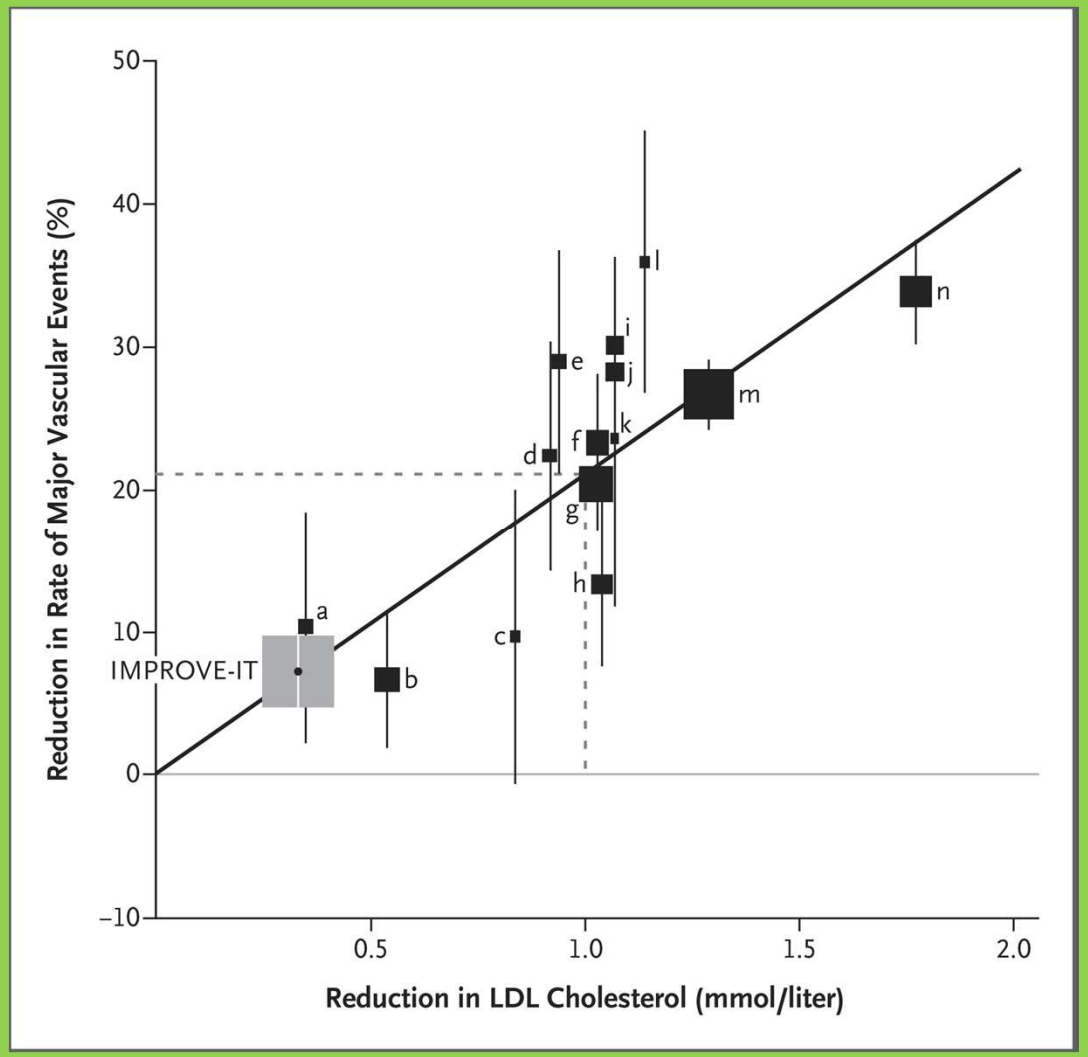
- IMPROVE-IT exemplifies not only the fragility of statistical significance, as already discussed---including missing data---but also the important difference between statistical significance and clinical relevance.

- There was a statistically significant reduction in the composite end point risk after 7 years in the 18,000 patient study.

- But, the relative risk reduction was only 6%.

- Absolute risk reduction was 2.0%

Plot of the IMPROVE-IT Trial Data and Statin Trials for Change in Low-Density Lipoprotein (LDL) Cholesterol versus Clinical Benefit.



Cannon CP et al. N Engl J Med 2015;372:2387-2397

The NEW ENGLAND JOURNAL of MEDICINE

Studies Leading to FDA Clinical Indication for Statins

Pub year	Drug/ control	Primary/ Secondary	Study Name	# of Patients	Rel. risk red'n	Abs. risk red'n	Upper 95% CI
1995	Prava vs placebo	Primary	WOSCOPS	6595	31 %	2.4 %	.43
1996	Prava vs placebo	Secondary	CARE	4159	24%	3.0%	.36
2002	Fluva vs placebo	Secondary	LIPS	1677	20%	5.3%	.95
2006	10 vs 80 Atorva	Secondary	TNT	10,000	22%	2.2	.89

IMPROVE-IT

Pub year	Drug/ control	Primary/ Secondary	Study Name	# of Patients	Rel. risk red'n	Abs. risk red'n	Upper 95% CI
2015	Simva vs Ezet/sim	Secondary	IMPROVE IT	18,000	6 %	2.0 %	.99

Sources: www.accessdata.fda.gov/drugsatfda_docs/nda/2010/021366s016MedR.pdf. (pdf pages 21-23) and published studies

Statin Studies with Similarly Small Treatment Effects as IMPROVE-IT but not Statistically Significant

a. GISSI Prevenzione Investigators. Results of the low-dose (20 mg) pravastatin GISSI Prevenzione trial in **4271 patients with recent myocardial infarction**: do stopped trials contribute to overall knowledge? Ital Heart J 2000;1:810-820

"During the study 256 (6.0%) patients either died or had a non-fatal stroke or a myocardial infarction, 136 (6.4%) in the control group and 120 (5.6%) in the pravastatin group **(relative risk 0.90, 95% confidence interval 0.71-1.15, p = 0.41)**; 160 patients died, 88 (4.1%) in the control group and 72 (3.4%) in the pravastatin group (relative risk 0.84, 94% confidence interval 0.61-1.14, p = 0.26)." The reduction of cardiovascular events was more evident in the by-treatment analysis, with coronary heart disease deaths being significantly decreased (relative risk 0.60, 95% confidence interval 0.38-0.96, p = 0.04)."

Small Treatment Effect Studies (cont'd)

b. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in **moderately hypercholesterolemic, hypertensive patients** randomized to pravastatin vs usual care: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). JAMA 2002;288:2998-3007 **[10,355 patients]**

"All-cause mortality was similar for the 2 groups (relative risk [RR], 0.99; 95% confidence interval [CI], 0.89-1.11; P =.88), with 6-year mortality rates of 14.9% for pravastatin vs 15.3% with usual care. **CHD event rates were not significantly different between the groups (RR, 0.91; 95% CI, 0.79-1.04; P =.16),** with 6-year CHD event rates of 9.3% for pravastatin and 10.4% for usual care."

Small Treatment Effect Studies (cont'd)

c. Holdaas H, Fellstrom B, Jardine AG, et al. Effect of fluvastatin on cardiac outcomes **in renal transplant recipients**: a multicentre, randomised, placebo-controlled trial. Lancet 2003;361:2024-2031 **[2012 patients**]

"After a mean follow-up of 5.1 years, fluvastatin lowered LDL cholesterol concentrations by 32%. **Risk reduction with fluvastatin for the primary endpoint (risk ratio 0.83 [95% CI 0.64-1.06], p=0.139) was not significant, although there were fewer cardiac deaths or non-fatal MI (70 vs 104, 0.65 [0.48-0.88] p=0.005)"**

Small Treatment Effect Studies (cont'd)

Rossebo AB, Pedersen TR, Boman K, et al. Intensive lipid lowering with simvastatin and ezetimibe in **aortic stenosis**. N Engl J Med 2008;359:1343-1356 **[total 1873 patients]**

(patients received either 40 mg of simvastatin plus 10 mg of ezetimibe or placebo daily)

During a median follow-up of 52.2 months, the primary outcome occurred in 333 patients (35.3%) in the simvastatin–ezetimibe group and in 355 patients (38.2%) in the placebo group (hazard ratio in the simvastatin–ezetimibe group, 0.96; 95% confidence interval [CI], 0.83 to 1.12; P = 0.59).

Important Differences Between Overall Clinical Significance and Subgroup Significance

Subgroup	n	HR (95% CI)	P	P (interaction)
Non-Diabetics	13202	0.98 (0.91, 1.04)	0.49	0.023
Diabetics	4933	0.86 (0.78, 0.94)	0.001	
Age <75	15338	0.97 (0.91, 1.03)	0.34	0.005
Age ≥75	2797	0.80 (0.70, 0.90)	0.0003	

"There was no effect seen among the under 75, nondiabetic subgroup (Table 11), which were a majority of the study population." FDA Briefing: PDF page 24

Question about Approval

Do the efficacy and safety data from the IMPROVE-IT trial provide substantial evidence to support approval of a claim that adding ezetimibe to statin therapy reduces the risk of cardiovascular events?

No, Because statistical significance is fragile and marginal and……

overall clinical relevance is quite small, with any relevance limited to a minority of patients studied: people diabetic or over 75