

# Safety and Tolerability of Pravastatin in Long Term Clinical Trials: Pravastatin Pooling Project

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## Abstract (P1530)

Prospective pravastatin pooling (PPP) project: the tolerability and safety of pravastatin based on a 112,000 patient year experience in placebo-controlled trials

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## Background

Therapeutic decisions for utilization of pharmacologic therapy for risk factor modification should be based on safety and tolerability as well as efficacy data. Individual placebo (PLA) controlled trials designed for efficacy estimates generally need to be combined to generate reliable data on relatively uncommon but important safety concerns.

## Methods

West of Scotland Coronary Prevention Study (WOSCOPS), Cholesterol and Recurrent Events (CARE), and Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) trials collectively accumulated over 112,000 person-years of exposure in double-blind randomized trials to conventional therapy plus either PLA or pravastatin (PRAVA), 40 mg once daily. Prior published efficacy data showed fewer deaths in those randomized to PRAVA with no difference in the non-cardiovascular fatalities. This analysis used patient data from these 3 trials to specifically address tolerability and safety issues. A Cox model considering treatment group, age, diabetes, smoking, primary or secondary prevention study and cardiovascular serious adverse events was utilized to determine the likelihood of discontinuing study medication.

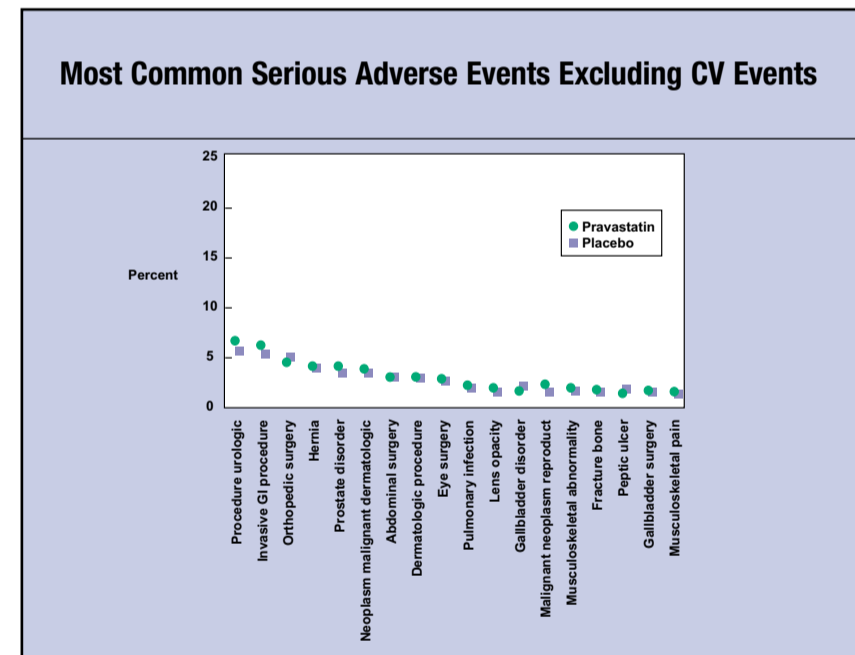
## Results

Tolerability, assessed as % of patients not permanently discontinuing study medication for any reason, was numerically greater with PRAVA (7,592/9,809, 77% vs. 7055/9783, 72%, p=0.0001). There was no particular imbalance of non-cardiovascular reasons for discontinuation of PRAVA compared to PLA. Tolerability was similar in men and women as well as between those < 65 and > 65 years of age. After adjustment for potential confounders, PRAVA-assigned patients remained less likely than PLA to discontinue study medication. With over 230,000 blood sample analyses, the % of patients with an abnormal liver function test was similar in PRAVA and PLA groups (> 3xULN, ALAT: 128, 1.4% vs. 131, 1.4%; PRAVA vs. PLA, respectively). Three PRAVA and 7 PLA patients were withdrawn from study medication due to CPK elevations. No cases of severe myopathy were reported.

## Exposure and Adverse Events

Total Extent of Exposure to Study Medication			
	Pravastatin 40 mg	Placebo	
Number of subjects receiving at least one dose of study medication	n=9,809	n=9,783	
Extent of exposure to study medication	Years		
Mean ± SD	4.6 ± 1.7	4.5 ± 1.8	
Median	5.0	5.0	
Min. (days)	1	1	
Max. (years)	7.1	7.1	
Extent of exposure to study medication	Number of Subjects (%)		
<1 year	755 (8)	826 (8)	
1 - <2 years	431 (4)	538 (5)	
2 - <3 years	339 (3)	449 (5)	
3 - <4 years	579 (6)	710 (7)	
4 - <5 years	2,527 (26)	2,465 (25)	
5 - <6 years	3,488 (36)	3,322 (34)	
≥6 years	1,690 (17)	1,473 (15)	

Percentages for extent of exposure are based on the number of subjects who received at least one dose of study medication; 1 year = 365.25 days.



### Primary Cancer: Incidence by Body System

Body System	Pravastatin n (%)	Treatment Group Placebo n (%)	p-value
Total number of subjects with at least one primary cancer adverse event*	946 (9.6)	914 (9.3)	0.480
Dermatologic	357 (3.6)	330 (3.4)	0.313
Endocrine/Metabolic/Electrolyte Imbalance	24 (0.2)	12 (0.1)	0.065
Gastrointestinal	137 (1.4)	149 (1.5)	0.475
General	16 (0.2)	21 (0.2)	0.417
Hematopoietic	38 (0.4)	52 (0.5)	0.140
Hepatic/Biliary	10 (0.1)	6 (<0.1)	0.454
Musculoskeletal/Connective Tissue	9 (<0.1)	1 (<0.1)	0.021
Nervous System	16 (0.2)	12 (0.1)	0.571
Renal/Genitourinary	266 (2.7)	247 (2.5)	0.421
Respiratory	122 (1.2)	133 (1.4)	0.489
Special Senses	4 (<0.1)	3 (<0.1)	>0.999

\*48 pravastatin and 107 placebo-treated patients had more than one body system cancer.

## Blood analysis (243,506 samples analysed)

### Incidence of Post-baseline Abnormalities of ALT

	Pravastatin 40 mg	Placebo	C.I.
	n (%)	n (%)	
ALT	804/9,185 (8.8%)	746/9,152 (8.2%)	-0.21, 1.42
>1.5 x ULN, ≥3 x ULN	676 (7.4)	615 (6.7)	-0.11, 1.39
>3 x ULN, ≥5 x ULN	84 (0.9)	90 (1.0)	-0.36, 0.22
>5 x ULN, ≥7 x ULN	24 (0.3)	19 (0.2)	-0.10, 0.21
>7 x ULN, ≥9 x ULN	6 (<0.1)	9 (<0.1)	-0.13, 0.06
>9 x ULN	14 (0.2)	13 (0.1)	-0.11, 0.13

### Incidence of Post-baseline Abnormalities of ALT in Subgroup of 579 Patients with Abnormal Baseline ALT

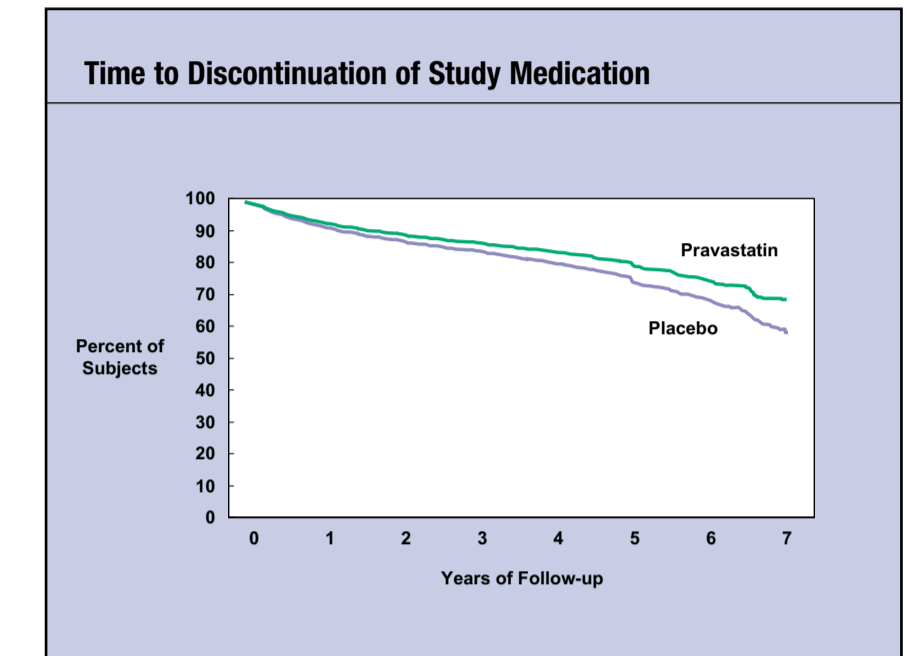
	Pravastatin 40 mg	Placebo	95% C.I.
	n (%)	n (%)	
ALT	127/317 (40.1%)	101/262 (38.5%)	
3 x ULN or greater	16/317 (5.0%)	19/262 (7.3%)	

### Incidence of Post-baseline CPK Abnormalities

	Pravastatin 40 mg	Placebo	95% C.I.
	(5,245)	(5,233)	
	n (%)	n (%)	
CPK	587 (11.2)	563 (10.8)	-0.78, 1.65
>1.5 x ULN, ≥3 x ULN	480 (9.2)	460 (8.8)	-0.75, 1.48
>3 x ULN, ≥5 x ULN	84 (1.6)	79 (1.5)	-0.40, 0.59
>5 x ULN, ≥7 x ULN	8 (0.2)	16 (0.3)	-0.36, 0.05
>7 x ULN, ≥9 x ULN	6 (0.1)	6 (0.1)	-0.15, 0.15
>9 x ULN	9 (0.2)	2 (<0.1)	-0.02, 0.28

No cases of myopathy (muscle weakness with CPK > 10 x UNL) or confirmed rhabdomyolysis in either group

## Tolerability



### Cox Model for Discontinuation

Parameter	Hazard Ratio	95% C.I.	p-value
Treatment Group	0.69	0.64, 0.74	0.0001
Age	1.00	1.00, 1.01	0.4718
Gender	0.83	0.76, 0.91	0.0001
Primary/Secondary Prevention	1.15	1.04, 1.26	0.0042
History of Diabetes	1.34	1.21, 1.49	0.0001
Smoking Status	1.25	1.16, 1.36	0.0001
Presence of an SAE in the CV Body System	0.76	0.71, 0.81	0.0001
Treatment by Primary/Secondary Prevention Interaction	1.40	0.24, 1.57	0.0001

\*For primary prevention studies (WOSCOPS) the hazard ratio for treatment is 0.96 (0.87, 1.05); for secondary prevention (LIPID/CARE) the hazard ratio for treatment is 0.69 (0.64, 0.74). Averaging across the interaction, the hazard ratio for treatment is 0.78.

Note: The presence of a serious AE in the Cardiovascular Body System should not be added to the model since many subjects with these events discontinued (which is the outcome).

## Conclusions

This prospective PPP analysis provides reassuring data that during a prolonged exposure, PRAVA 40 mg is well tolerated with no augmentation in non-cardiovascular serious adverse events including liver function abnormalities and laboratory and clinical evidence for myositis. This extensive safety and tolerability data with 40 mg of pravastatin provides important additional information for therapeutic decisions regarding this pharmacologic agent.