Pitavastatin 4 mg vs. Pravastatin 40 mg in HIV Dyslipidemia: *Post-Hoc* Analysis of the INTREPID Trial Based on the Independent CHD Risk Factor for Age

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Disclosures

- Craig A. Sponseller, MD – employee of Kowa Pharmaceuticals America, Inc.
- Masaya Tanahashi - employee of Kowa Company, LTD, Japan
- Hideki Suganami - employee of Kowa Company, LTD, Japan
- Vladimir A. Kryzhanovski, MD, PhD – employee of Eli Lilly and Company
- Judith A. Aberg, MD (New York University School of Medicine) – INTREPID study design consultant and study investigator

Introduction

- Dyslipidemia, an established cardiovascular (CV) disease risk factor, is seen in 81% of men (median age 47 yrs) and 67% of women (median age 45 yrs) with HIV infection in the US. (Buchacz 2013)
- Advances in antiretroviral therapy (ART) continue to extend the lifespans HIV-infected individuals. By 2015, an estimated 50% of people with HIV in the US will be >50 years of age. (www.aoa.gov)
- CHD in aging HIV-infected population is an increasing medical challenge. Based on 10-year CHD risk, increase in cardiac events is expected in aging HIV-infected subjects in the next decades (≥45 years/<45 years 16.4% vs. 4.2 %, p<0.001).(Esser 2013)
- There is an estimated 50-75% increased relative risk for acute myocardial infarction (MI) in HIV-infected individuals. (Freiberg 2013, Triant 2007)

Buchacz K, et al. Antivir Ther 2013;18:65-75; Esser S, et al. Clin Res Cardiol 2013;102:203-13; Freiberg MS, et al. JAMA Intern Med. 2013;173:614-22; Triant VA. Et al. J Clin Endocrinol Metab 2007;92:2506-12; www.aoa.gov (24 Oct 2013).

NCEP ATP III Major Independent Risk Factors for CHD

- Cigarette smoking
- Hypertension (BP ≥140/90 mmHg or on antihypertensive medication)
- Low HDL-C (<40 mg/dL) (*HDL cholesterol ≥60 mg/dL = "negative" risk factor; its presence allows for subtraction of one risk factor from the count.)*
- Family history of premature CHD (CHD in male first degree relative <55 years; CHD in female first degree relative <65 years)
- Age: men ≥45 yrs; women ≥55 yrs

Circulation 2002;106:3143-421.

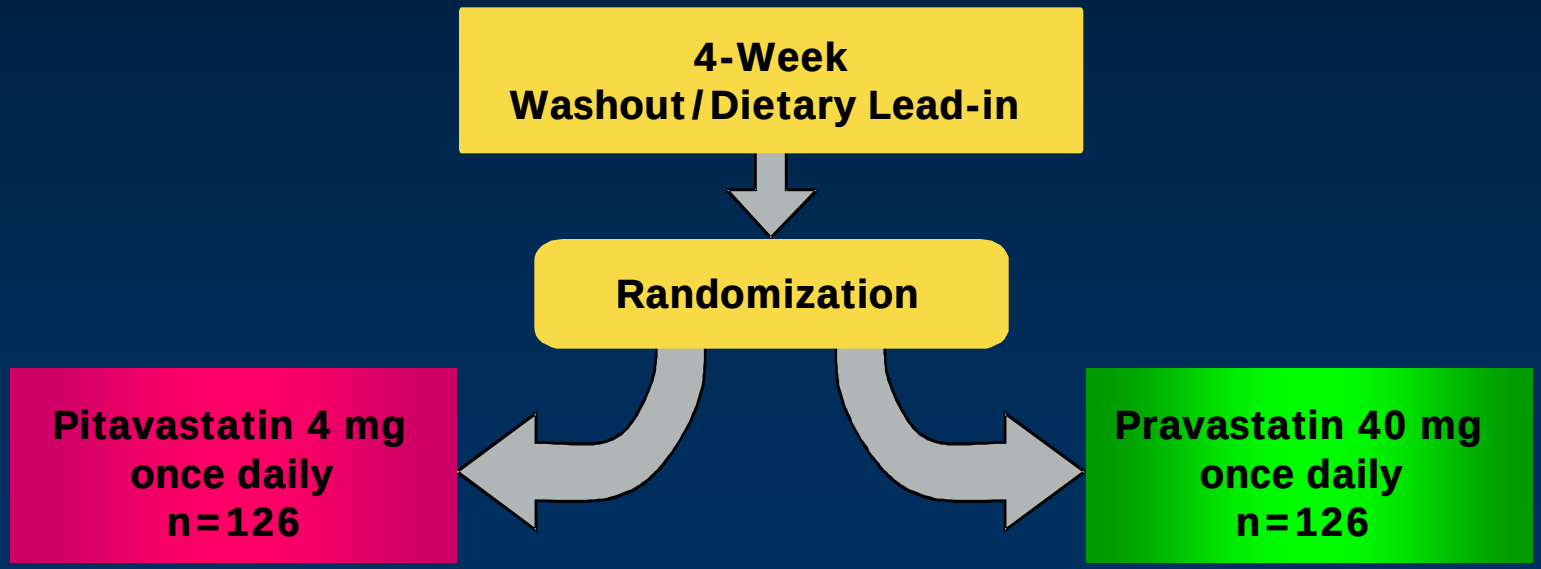
Age and Risk

- Age: a major independent risk factor for CHD; non-modifiable (men ≥45 yrs; women ≥55 yrs)
- Risk of acute MI increases significantly with age
- HIV population vs. non-HIV population
  - Rates of acute MI per 1000 person-yrs (95% CI): (Freiberg 2013)
    - 40 - 49 yrs: 2.0 (1.6-2.4) vs. 1.5 (1.3-1.7); P<0.05
    - 50 - 59 yrs: 3.9 (3.3-4.5) vs. 2.2 (1.9-2.5); P<0.05
    - 60 - 69 yrs: 5.0 (3.8-6.7) vs. 3.3 (2.6-4.2); P<0.05

Freiberg MS, et al. JAMA Intern Med. 2013;173:614-22.

Study Design

INTREPID = H**I**V-Infected Patie**n**ts and **Tr**eatment with **Pi**tavastatin vs. Pravastatin for **D**yslipidemia



Phase 4, double-blind, double-dummy, 12-week superiority study
(followed by a 40-week, double-blind, safety extension study)

Randomization 1:1, stratified by presence/absence of viral hepatitis B/C

Eligibility Criteria

- Subjects: HIV-infected adults (18-70 yrs) with dyslipidemia
  - Stable ART x ≥6 months
  - HIV-1 RNA viral load <200 copies/mL and CD4 count >200 cells/µL for ≥3 months
  - Fasting serum LDL-C 130 - 220 mg/dL and triglycerides ≤400 mg/dL after 4-wk washout/dietary stabilization period

Endpoints

- Primary endpoint: Superiority based on mean % change in fasting serum LDL-C from Baseline to Week 12
- Secondary endpoints: Changes in other lipid parameters (fasting serum Apo B, non-HDL-C, HDL-C, triglycerides)
- ***Post-hoc* Analysis -** Age-based evaluation of primary and secondary endpoints
- Efficacy analyses included only patients who received at least 1 dose of study drug and had a least 1 on-treatment lipid assessment.

Baseline Characteristics*

	Pitavastatin 4 mg n=126	Pravastatin 40 mg n=126
Age, mean (SD), yrs	50.1 (7.5)	49.2 (8.7)
Males, n (%)	106 (84.1)	111 (88.1)
Race, n (%)		
Caucasian	107 (84.9)	96 (76.2)
African-American	16 (12.7)	23 (18.3)
Other	3 (2.4)	7 (5.6)
Body Mass Index, mean (SD), kg/m^2	27.2 (4.5)	28.2 (4.9)

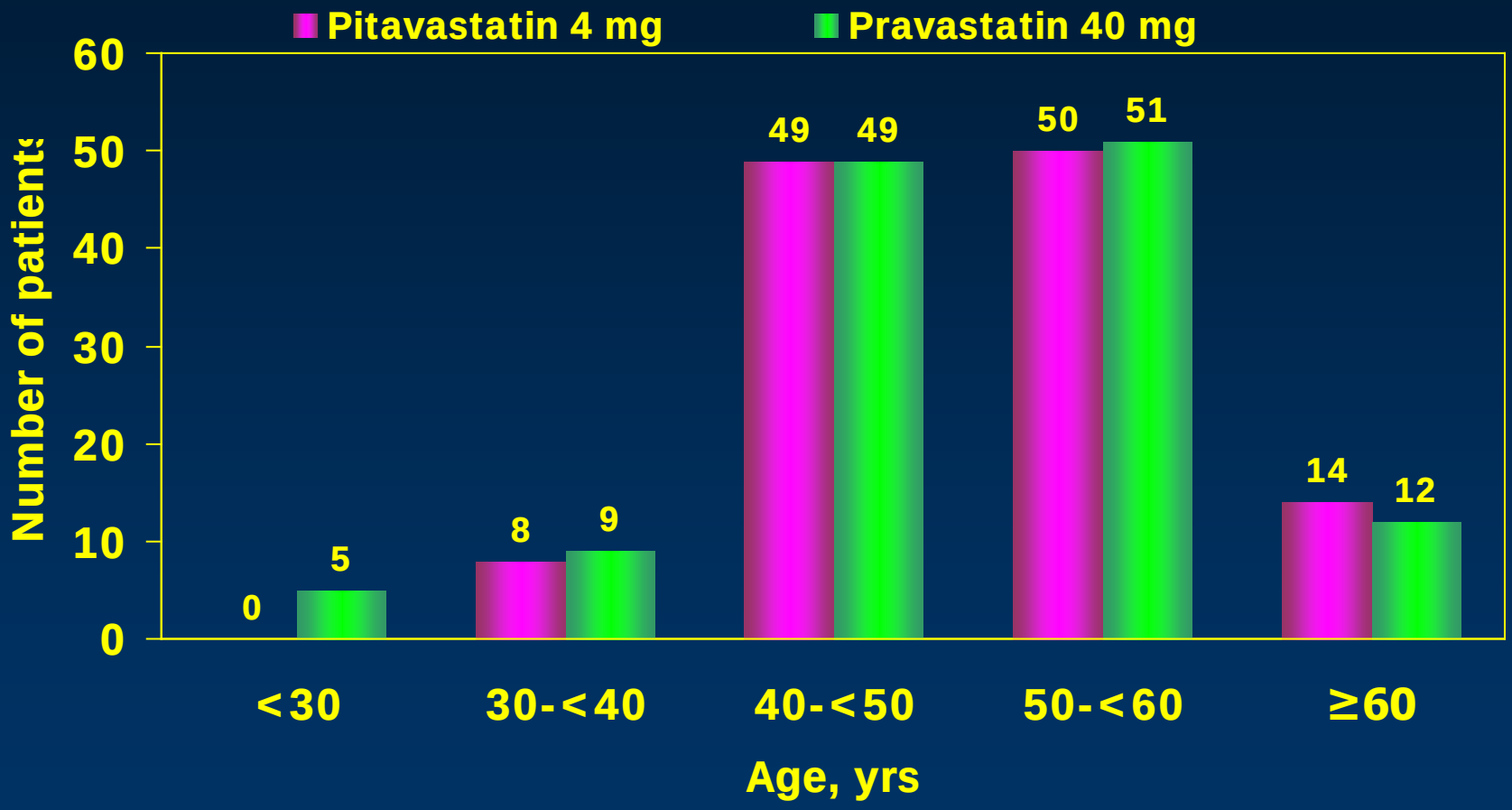
* Safety population

Baseline Characteristics*

	Pitavastatin 4 mg n=126	Pravastatin 40 mg n=126
10-year CHD Risk, n (%)		
>20%	1 (0.8)	1 (0.8)
10-20%	32 (25.4)	30 (23.8)
<10%	93 (73.8)	95 (75.4)
HIV-1 RNA viral load, mean (SD), log copies	1.2 (0.3)	1.1 (0.2)
CD4 cell count, mean (SD), cells/mm^3	648.5 (246.8)	563.7 (211.3)

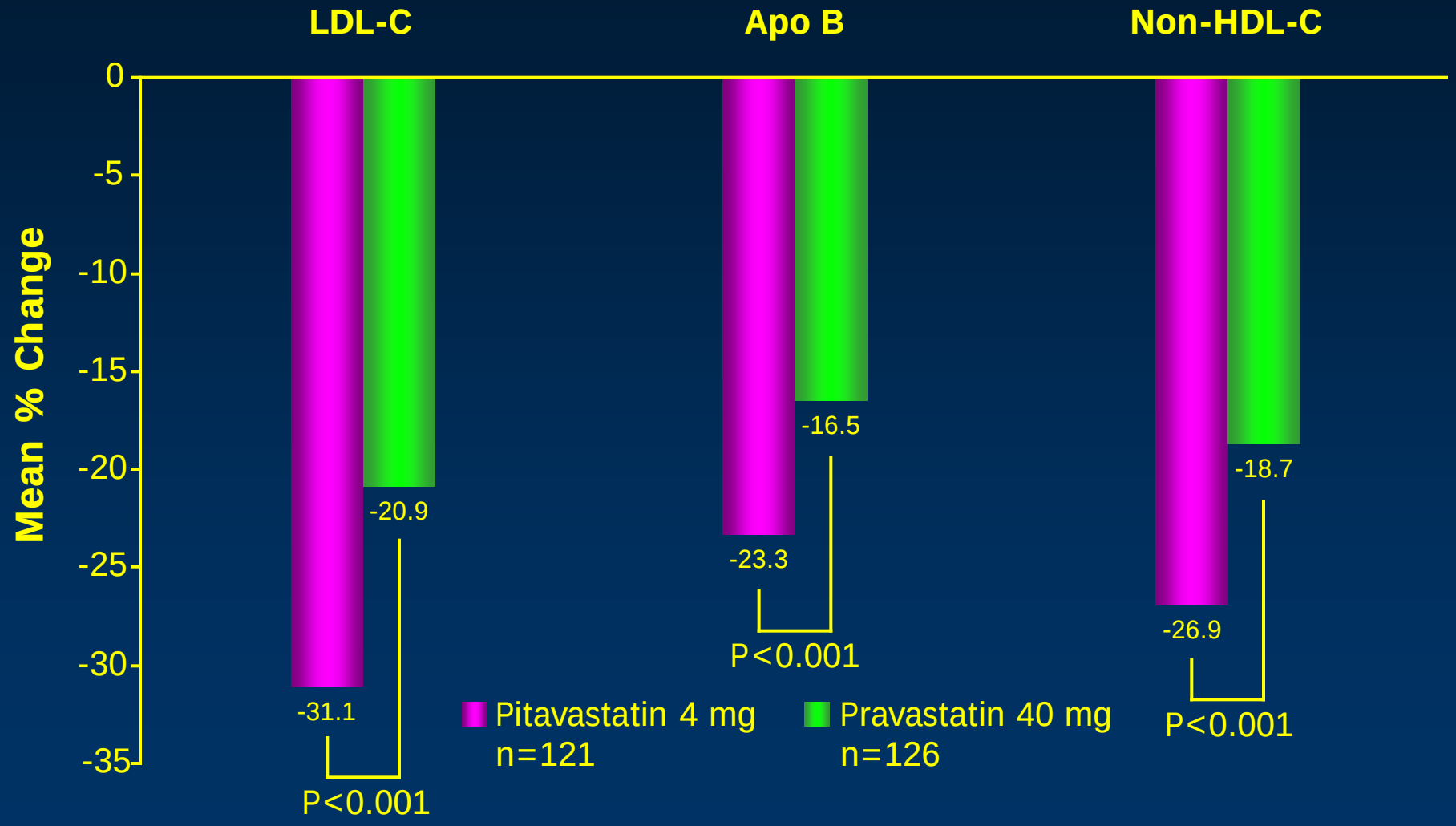
* Safety population

Patient Demographics: Age



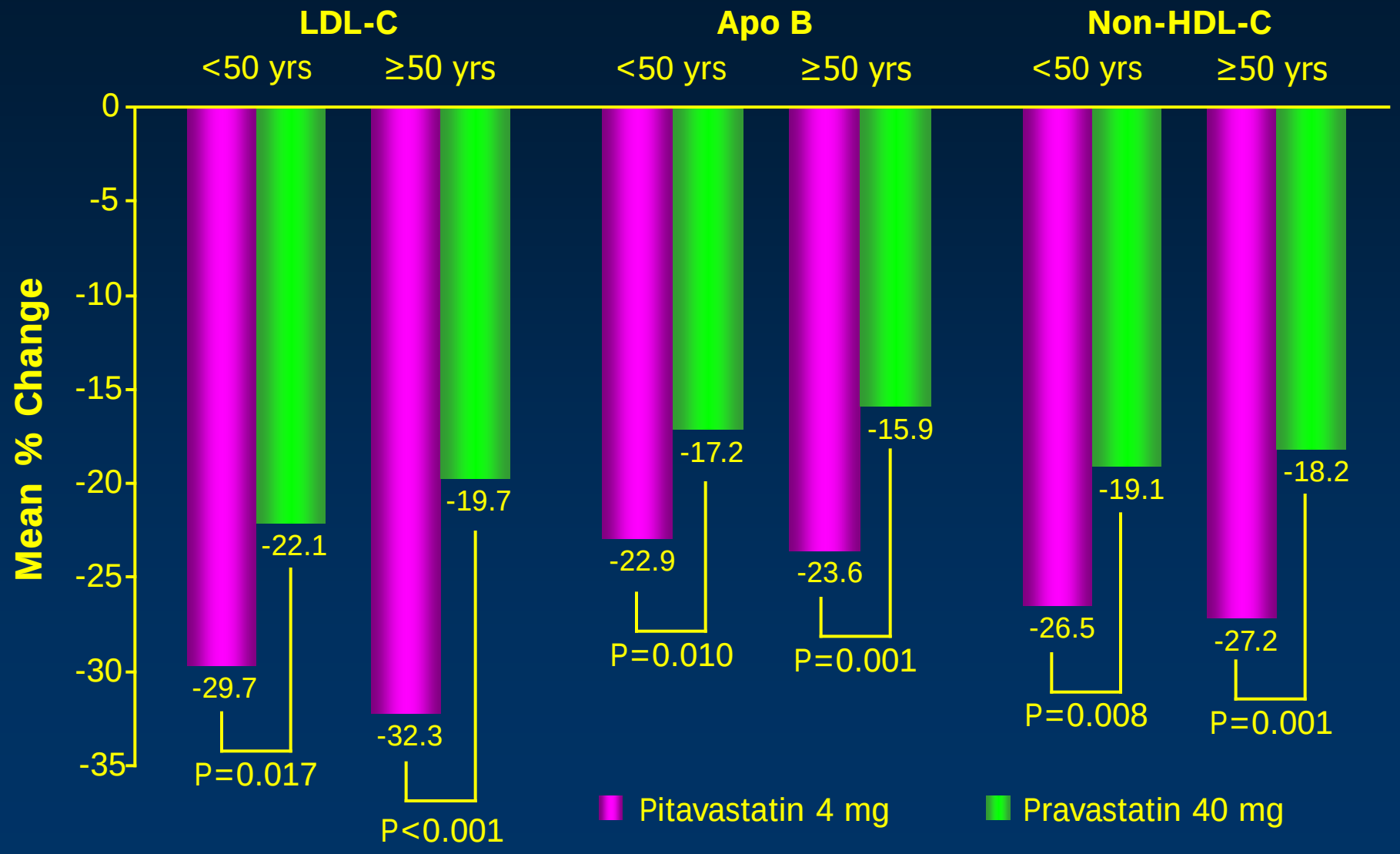
Approximately 50% of the INTREPID population was ≥50 yrs

Mean % Change Baseline to Week 12:
Primary Study Population



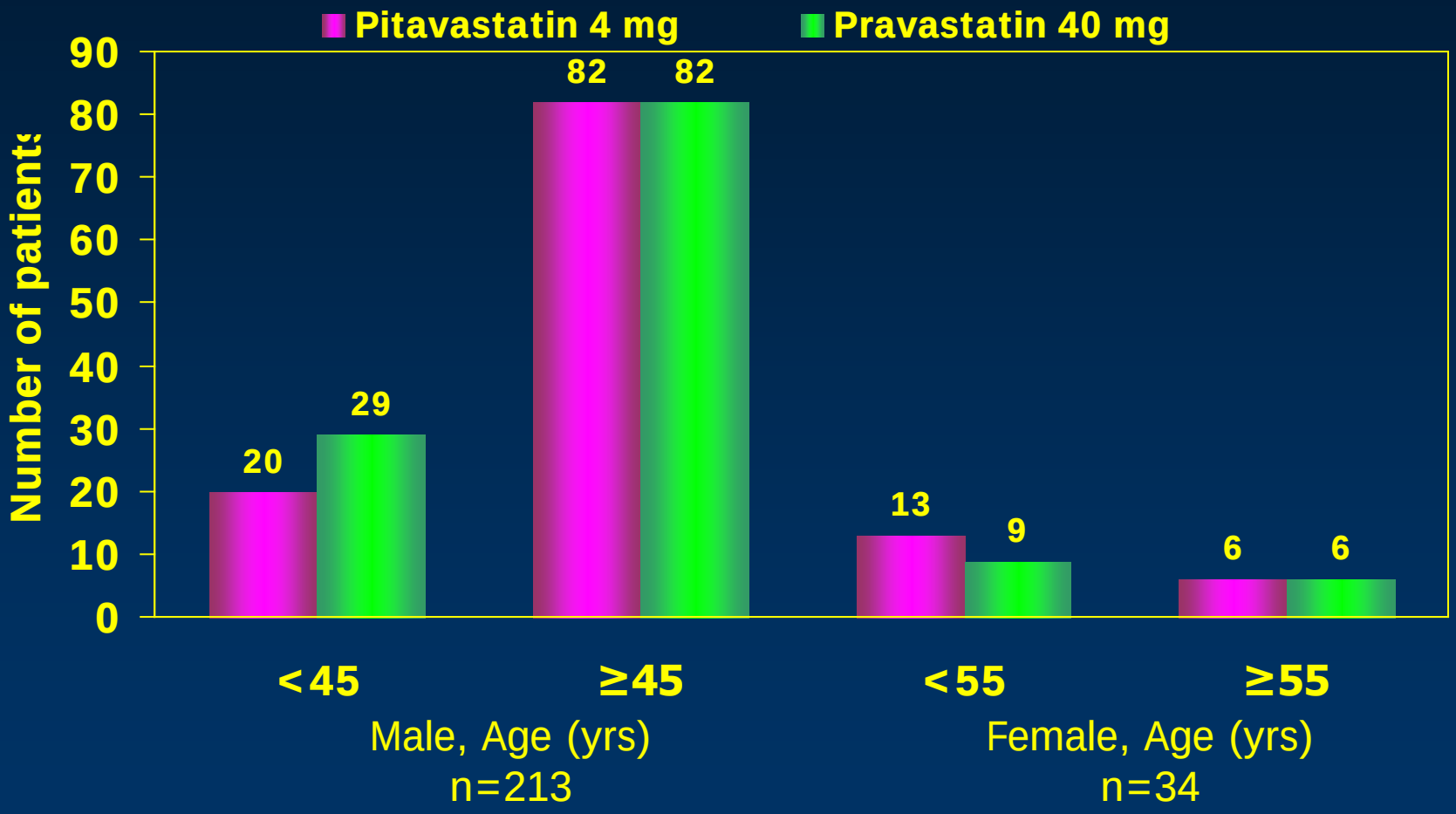
P-values for between-treatment comparisons based on LS mean % change.

Mean % Change Baseline to Week 12



P-values for between-treatment comparisons based on LS mean % change.

Patient Demographics: Sex and Age



71% of the population had age as a major independent risk factor for CHD

Mean Baseline Lipid Measurements

	Pitavastatin 4 mg N=121		Pravastatin 40 mg N=126	
LDL-C, mg/dL	n		n	
Male <45 yrs	20	154.4	29	158.0
Male ≥45 yrs	82	153.2	82	154.1
Female <55 yrs	13	164.2	9	150.1
Female ≥55 yrs	6	163.7	6	151.2

Mean Baseline Lipid Measurements

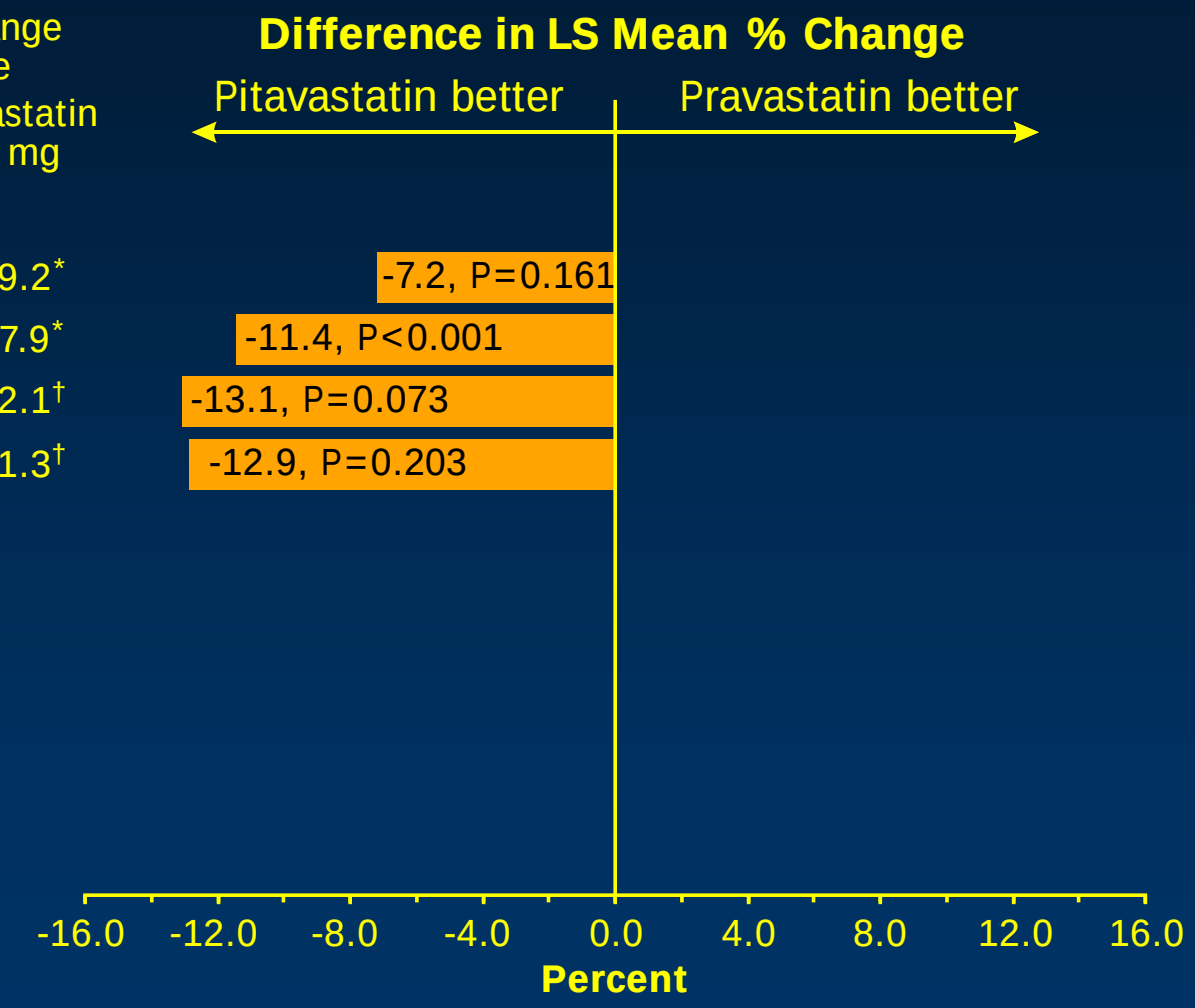
	Pitavastatin 4 mg	Pravastatin 40 mg
Apo B, mg/dL		
Male <45 yrs	124.8	129.7
Male ≥45 yrs	122.5	126.7
Female <55 yrs	125.8	132.2
Female ≥55 yrs	136.2	122.5
Non-HDL-C, mg/dL		
Male <45 yrs	187.4	196.1
Male ≥45 yrs	186.9	187.3
Female <55 yrs	197.8	187.0
Female ≥55 yrs	199.7	181.0

Mean Baseline Lipid Measurements

	Pitavastatin 4 mg	Pravastatin 40 mg
HDL-C, mg/dL		
Male <45 yrs	52.4	47.2
Male ≥45 yrs	46.9	48.7
Female <55 yrs	58.9	53.8
Female ≥55 yrs	57.0	57.3
Triglycerides, mg/dL		
Male <45 yrs	169.2	187.4
Male ≥45 yrs	173.8	165.8
Female <55 yrs	182.2	199.6
Female ≥55 yrs	179.7	148.8

LDL-C: Change from Baseline to Week 12

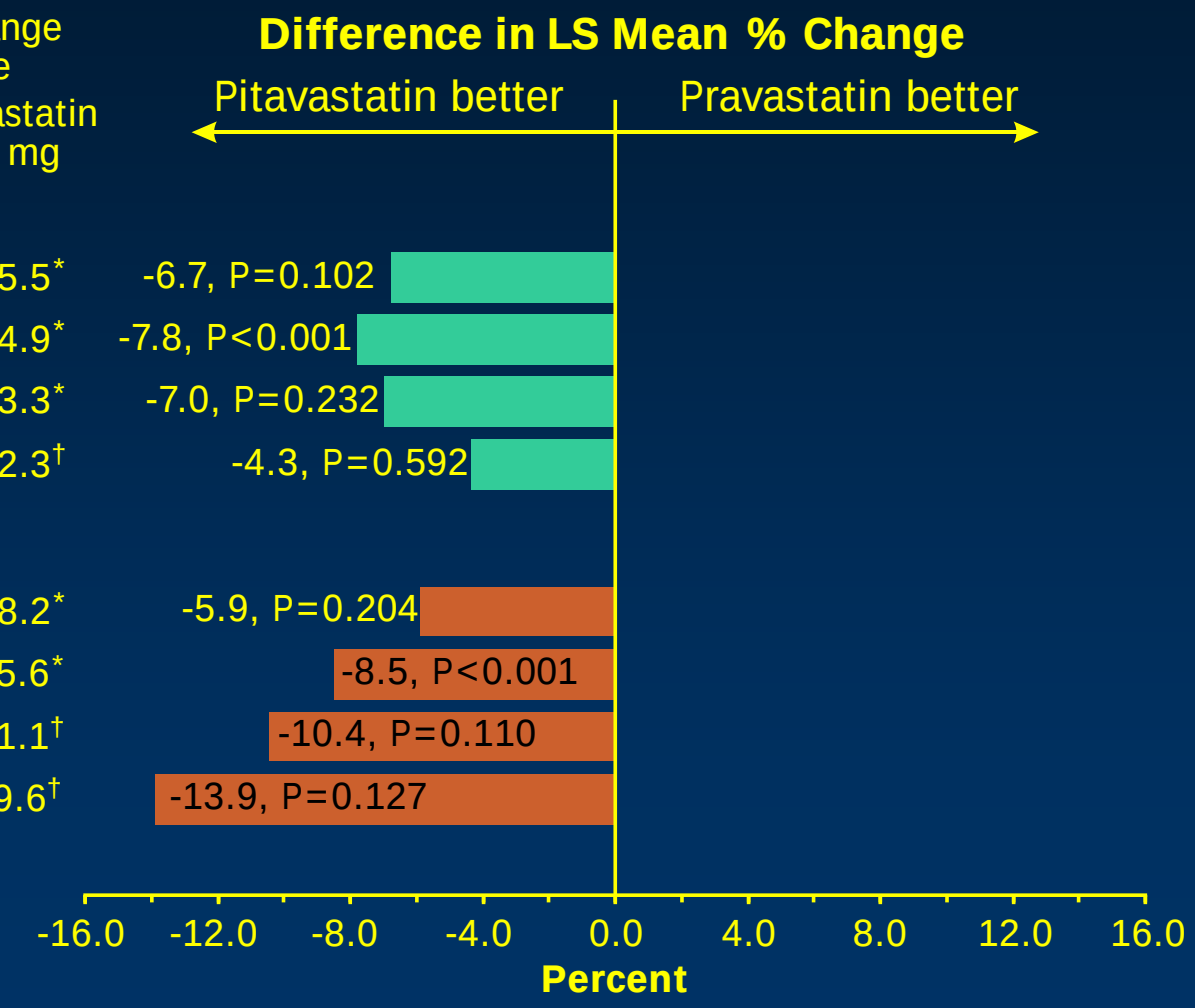
	LS Mean % Change from Baseline	
	Pitavastatin 4 mg	Pravastatin 40 mg
LDL-C		
Male <45 yrs	-26.4*	-19.2*
Male ≥45 yrs	-29.4*	-17.9*
Female <55 yrs	-25.2*	-12.1†
Female ≥55 yrs	-24.1*	-11.3†



*P≤0.01 †P>0.05

Apo B and Non-HDL-C: Change from Baseline to Week 12

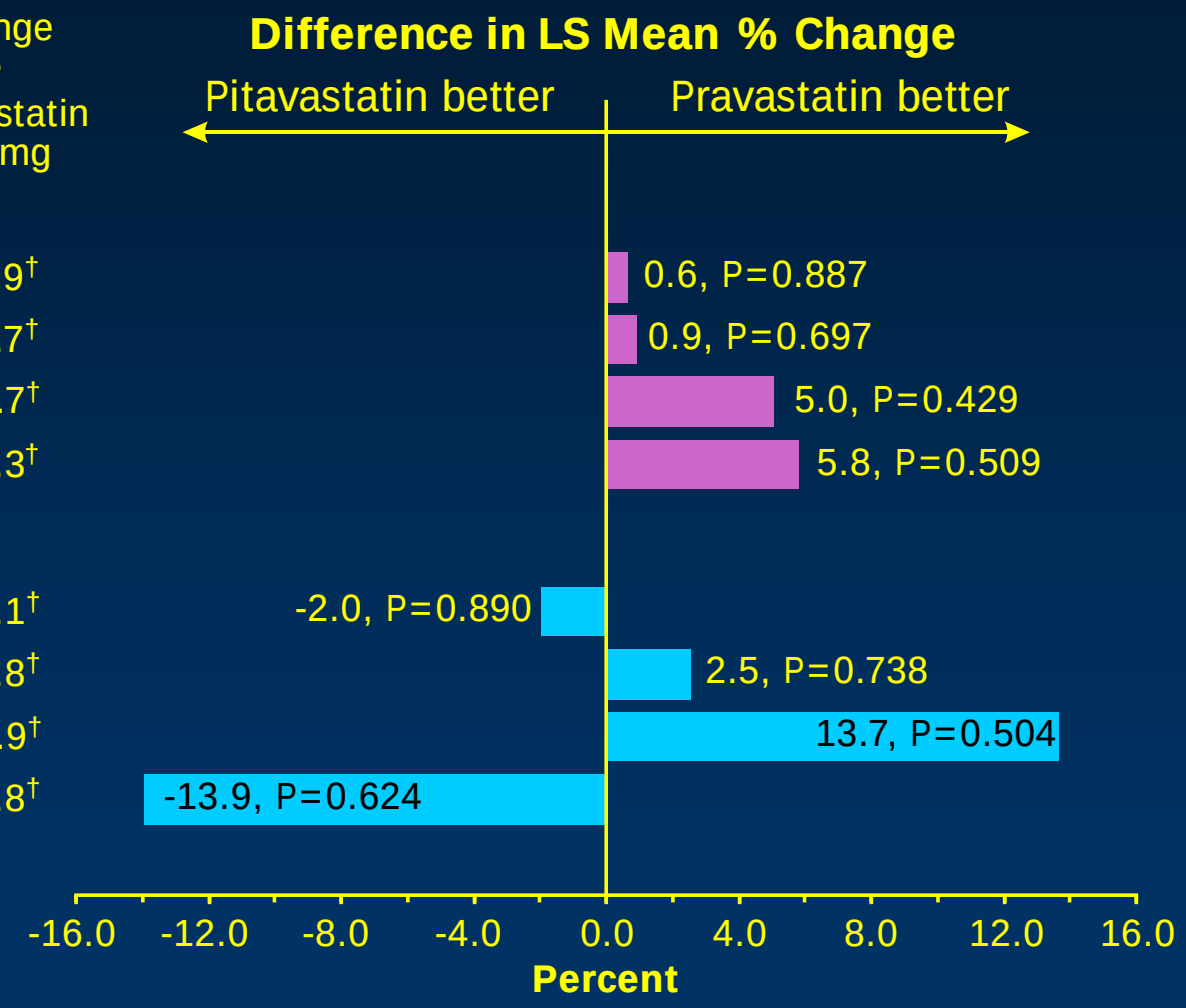
	LS Mean % Change from Baseline	
	Pitavastatin 4 mg	Pravastatin 40 mg
Apo B		
Male <45 yrs	-22.2*	-15.5*
Male ≥45 yrs	-22.7*	-14.9*
Female <55 yrs	-20.3*	-13.3*
Female ≥55 yrs	-16.7*	-12.3†
Non-HDL-C		
Male <45 yrs	-24.0*	-18.2*
Male ≥45 yrs	-24.0*	-15.6*
Female <55 yrs	-21.5*	-11.1†
Female ≥55 yrs	-23.5*	-9.6†



*P≤0.01 †P>0.05

HDL-C and Triglycerides: Change from Baseline to Week 12

	LS Mean % Change from Baseline	
	Pitavastatin 4 mg	Pravastatin 40 mg
HDL-C		
Male <45 yrs	5.3†	5.9†
Male ≥45 yrs	0.8†	1.7†
Female <55 yrs	5.6†	10.7†
Female ≥55 yrs	1.5†	7.3†
Triglycerides		
Male <45 yrs	-9.1†	-7.1†
Male ≥45 yrs	4.4†	1.8†
Female <55 yrs	0.8†	-12.9†
Female ≥55 yrs	-18.7†	-4.8†



†P>0.05

HIV-1 RNA Viral Load and CD4 Cell Count: Change from Baseline to Week 12

Parameter	Pitavastatin 4 mg		Pravastatin 40 mg		P-Value
	n	Mean Δ from Baseline (SD)	n	Mean Δ from Baseline (SD)	
HIV-1 RNA viral load, log copies	107	-0.02 (0.3)	112	0.08 (0.4)	0.06
CD4 count, cells/mm^3	110	-8.9 (154.9)	110	13.6 (120.6)	0.29

P-values from ANCOVA model of mean % change from baseline.

Safety Outcomes*

	Pitavastatin 4 mg N=126	Pravastatin 40 mg N=126
	n (%)	
Treatment Emergent Adverse Event (TEAE)		
Any TEAE	77 (61.1)	79 (62.7)
Any drug-related TEAE	14 (11.1)	12 (9.5)
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	3 (2.4)	4 (3.2)
Myalgia	1 (0.8)	3 (2.4)
Back pain	1 (0.8)	2 (1.6)
Pain in extremity	2 (1.6)	3 (2.4)

* Safety population

Safety Outcomes*

	Pitavastatin 4 mg N=126	Pravastatin 40 mg N=126
	n (%)	
Laboratory Enzymes		
ALT >2 x ULN	4 (3.2)	3 (2.4)
AST >2 x ULN	0 (0.0)	0 (0.0)
CK >5 x ULN	2 (1.6)	0 (0.0)
Virologic Status		
Virologic failure	3 (2.4)	4 (3.2)

* Safety population

Virologic failure: defined as HIV-1 RNA viral load >200 copies/mL and a >0.3 log increase from baseline.

Summary

- INTREPID population: 86% male; 71% had age as a major independent risk factor for CHD.
- In the male subgroups, age ≥45, <45:
  - Atherogenic lipid factors (LDL-C, Apo B, and non-HDL-C) were significantly reduced for both pitavastatin 4 mg and pravastatin 40 mg.
  - Pitavastatin 4 mg reduced these parameters significantly more than pravastatin 40 mg in males ≥45 yrs, an independent risk factor for CHD.
- In the female subgroups:
  - Pitavastatin 4 mg showed statistically significant reductions in atherogenic lipids/lipoproteins LDL-C, Apo B, and non-HDL-C in females <55 and ≥55 yrs.
  - Pravastatin 40 mg showed a statistically significant reductions only in Apo B in females <55 yrs.
  - No between-treatment differences in lipid parameters, likely due to small samples sizes.
- There were no between-treatment differences in HDL-C or triglycerides in either the male or female subgroups.

Conclusions

- Pitavastatin 4 mg demonstrated a superior reduction in LDL-C compared with pravastatin 40 mg in HIV-infected adults with dyslipidemia in the overall study population.
- Pitavastatin 4 mg significantly reduced atherogenic lipid parameters (LDL-C, Apo B, and non-HDL-C) in men age ≥45 yrs and women age ≥55 yrs.
- Pitavastatin 4 mg demonstrated significantly greater reductions in LDL-C, Apo B, and non-HDL-C vs. pravastatin 40 mg in men with the major independent risk factor for age ≥45 yrs.
- The overall adverse event profiles appeared similar between treatment arms.