tion. Patients were divided into good responders (GR) or poor responders (PR) based upon % change in LDL-C from baseline after initial statin dose.
Results: At baseline, PR had lower total cholesterol (TC) (227±35 vs 258±36 mg/dl;p<0.001) and lower LDL-C (149±29 vs 173±28 mg/dl; p<0.001). Initial change in LDL-C was -30.8±8.7% in GR vs. -8±7.2% in PR (p<0.01). Dose titration led to an additional 14.7±9.4% reduction in LDL-C in GR vs. only additional 7.7±11.6% in PR (p<0.001). After dose titration, PR had less change from baseline in LDL-C (-15.7±14.6% vs -45.5±12%; p<0.001). After dose titration, 18% of PR achieved LDL goal compared to 71% of GR (p<0.001). % LDL-C decrease after dose titration correlated with initial response (r^2=0.72).
Conclusions: Response to initial statin dose predicts response to dose titration. Dose titration of statins is therefore not an effective strategy to reach aggressive LDL goals in patients who have a poor initial LDL reduction. Other approaches such as combination therapy need to be evaluated in this group of patients.

LDL-C response in GR vs. PR

	Good Responders (n=38)	Poor Responders (n=38)	
Change in LDL-C after initial dose	-30.8±8.7%	-8.07.2%±	p<0.001
Change in LDL-C after dose titration (from baseline)	-45.5±12%	-15.7±14.6%	p<0.001
% at ATP III Goal	71%	18%	p<0.001

1084-172 Rosuvastatin Is Efficacious as Monotherapy in Patients With Combined Dyslipidemia

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Cardiovascular disease (CVD) risk is greater in patients with combined dyslipidemia (CDL) than in those with isolated increases in fasting plasma triglyceride (TG) or low-density lipoprotein (LDL) cholesterol (C) concentrations. Effective treatment (Rx) of CDL has been confounded by: 1) concern of the increased risk of myopathy associated with combined use of a “statin” and a fibric acid; and 2) neglecting the effect of Rx on post-prandial (PP) lipemia. This study was initiated to test the hypothesis that the magnitude of improvement in both fasting and PP lipid metabolism in rosuvastatin (RSV)-treated subjects with CDL would obviate the need for combined drug Rx. Forty nondiabetic subjects with CDL were randomly assigned to Rx with either RSV (40 mg/day) or gemfibrozil (GEM, 1200 mg/day) for 3 months, and multiple aspects of fasting and PP carbohydrate and lipid metabolism measured before and after Rx. The two groups did not differ in age, sex distribution, or BMI. Mean±SE (mg/dL) fasting plasma LDL-C levels fell (P<0.001) following RSV-Rx (138±7 vs. 62±4), but did not change in GEM-treated subjects (126±5 vs. 131±5). Fasting TG levels fell (P<0.001), and to a similar degree in GEM-treated (284±17 vs. 166±23) and RSV-treated (324±19 vs. 211±18) subjects. RSV-treated subjects also had significantly greater decreases in apo B-100, apo E, and the apo B-100/apo A-1 ratio compared to those treated with GEM. Daylong glucose, insulin, and free fatty acid levels did not change with Rx, whereas PP-TG levels fell to a similar degree in both groups (P<0.01). Although the PP-remnant lipoprotein-C levels fell significantly with Rx in both groups, the magnitude of the change was greater in the RSV-Rx group (P<0.05). Finally, RSV-Rx resulted in significant (P<0.001) reductions in C-reactive protein (median change -57.6%) compared to GEM-Rx (median change -9.1%). Conclusion: In addition to the expected substantial decrease in LDL-C, the improvement in both fasting and PP concentrations of TG-rich lipoproteins in RSV-treated subjects was equal to or greater than that seen with GEM-Rx. These results demonstrate that RSV provides effective monotherapy to decrease lipoprotein-related CVD risk factors in subjects with CDL.

1084-173 Analysis of the Renal Safety of Atorvastatin in a Broad Spectrum of Patients With Dyslipidemia

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Background: This report summarizes the renal safety data from >9000 patients exposed to atorvastatin for up to 2 years in completed clinical trials. These data are especially important in the current climate which has seen increased scrutiny placed on all aspects of the safety of chronic statin therapy.
Methods: Data were analyzed from 16,731 dyslipidemic patients (9976 male/6755 female; median age 61 yrs) enrolled in 44 clinical trials. The studies included 9416 atorvastatin-treated patients, 1789 placebo-treated patients and 5526 patients treated with other statins (simvastatin [2771]; pravastatin [807]; lovastatin [968]; fluvastatin [744]; cerivastatin [236]). A broad spectrum of dyslipidemic patients with varying risks for cardiovascular events were evaluated for up to 2 years.
Results: Across the 44 studies analyzed, renal adverse events were rare in all 3 treatment groups. Albuminuria was observed in 7 patients receiving atorvastatin (0.07%), compared to 5 patients receiving other statins (0.09%) and 0 patients receiving placebo. No case of albuminuria was considered to be treatment related. The rate of occurrence of hematuria was also low in all treatment groups (atorvastatin, 44 patients [0.5%]; other statins, 34 patients [0.6%]; placebo, 3 patients [0.2%]). Only in 1 atorvastatin and 1 placebo patient was hematuria considered to be possibly associated with study treatment. In the subset of patients treated in placebo-controlled trials, there were no cases of albuminuria for either placebo or atorvastatin and hematuria was observed in 0.2% of patients treated with placebo (3/1789) and in 0.3% of patients treated with atorvastatin (8/2976). Overall, renal adverse events did not appear to be dose-related, and there were no discontinuations considered related to renal adverse events.
Conclusion: Specific analysis of renal adverse events in 44 clinical trials demonstrates that these occurred infrequently with atorvastatin and at similar rates to placebo. These data provide further evidence to support the favorable clinical safety profile of atorvastatin 10 mg to 80 mg in a broad range of patients.

1084-174 Efficacy of Ezetimibe-10 mg/Day Coadministered With Multiple Doses of Simvastatin in Patients With Primary Hypercholesterolemia

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Background: The cholesterol absorption inhibitor, ezetimibe (EZE), has a complementary mechanism of action to statins, which inhibit hepatic cholesterol synthesis. The purpose of this study was to evaluate the LDL-C-lowering efficacy of EZE 10 mg/d coadministered with simvastatin (SIM) 10, 20, 40, and 80 mg/d in hypercholesterolemic patients (pts).
Methods: This was a 12 wk multicenter, double-blind, randomized, placebo (PBO)-controlled study. After a 4-wk PBO/diet run-in, 887 pts with LDL-C 145 - 250 mg/dL and TG ≤350 mg/dL were randomized to one of ten daily treatments: PBO; EZE 10 mg; SIM 10, 20, 40, or 80 mg; EZE 10 mg + SIM 10, 20, 40, or 80 mg.
Results: Results for LDL-C, non-high density lipoprotein cholesterol (non-HDL-C), triglycerides (TG), and HDL-C by dose are summarized in the table. Pooled across the dose ranges, EZE+SIM was more effective (p ≤0.001) than SIM in reducing LDL-C (-53.1% vs. -38.3%), TG (-28.0% vs. -15.2%) and non-HDL-C (-48.5% vs. -34.1%), while HDL-C was increased by 8% in both groups. A greater proportion of EZE+SIM pts reached the LDL-C target of <100mg/dL (p <0.001): 82.4% (n=353) vs. 42.9% (n=345). Coadministration of EZE+SIM was well tolerated and had an overall safety profile similar to that of SIM monotherapy. However, there were more cases of consecutive ≥3 x upper limit of normal elevations of aminotransferases in the EZE+SIM group vs. SIM group.
Conclusions: Overall, EZE+SIM was well tolerated and provided superior lipid-modifying efficacy over SIM monotherapy.

Mean Percent Change from Baseline

Lipid Parameter	SIM 10mg (n=79)	EZE/SIM 10mg/10mg (n=87)	SIM 20mg (n=89)	EZE/SIM 10mg/20mg (n=86)	SIM 40mg (n=90)	EZE/SIM 10mg/40mg (n=89)	SIM 80mg (n=87)	EZE/SIM 10mg/80mg (n=91)

									LDL-C	-31.3	-46.2	-34.9	-50.5	-41.5	-54.9	-45.6	-60.8
Total C	-20.7	-31.5	-24.1	-36.5	-28.7	-39.5	-31.7	-43.0									
non-HDL-C	-26.8	-41.3	-31.2	-47.1	-37.0	-50.9	-41.4	-54.8									
TG (median)	-4.5	-20.5	-13.6	-30.7	-18.6	-32.0	-25.7	-27.8									
HDL-C	4.9	9.5	6.3	8.0	8.3	9.1	11.0	6.3									

1084-175 Changes in Coronary Plaque Color and Morphology by Lipid-Lowering Therapy With Atorvastatin: Serial Evaluation by Coronary Angioscopy

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Background: The concept of coronary plaque stabilization by statin therapy has been clarified. However, serial changes of coronary plaques by statin therapy in human have not been examined in detail.
Methods: Thirty-one patients with coronary artery disease were devided into either the comparison group (n=16) or the atorvastatin group (n=15). Before treatment and 12 months after, the color and complexity of 145 coronary plaques were determined according to angioscopic findings. The yellow score of the plaque was defined as 0 (white), 1 (light yellow), 2 (yellow), or 3 (dark yellow), and its disrupted score was defined as 0 (smooth surface) or 1 (irregular surface) and as 0 (without thrombus) or 1 (with thrombus). In each patient, the mean yellow score and mean disrupted score were calculated.
Results: Mean low-density lipoprotein cholesterol (LDL-C) decreased by 45% in the atorvastatin group, whereas an increase of 9% was seen in the comparison group. The mean yellow score decreased from 2.03 to 1.13 in the atorvastatin group, whereas it increased from 1.67 to 1.99 in the comparison group. There was a good correlation between the change in the mean yellow score and the change in LDL-C levels (r=0.81, p<0.0001). The change in the mean yellow score and mean disrupted score differed significantly between the two groups (p=0.002 and p=0.03, respectively).
Conclusions: This study indicated that lipid-lowering therapy changes plaque color and morphology and should then lead to coronary plaque stabilization.

1084-176 Efficacy of Ezetimibe Coadminstered With Simvastatin Versus Atorvastatin in Patients With Hypercholesterolemia

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Background: This study was designed to evaluate the efficacy and safety of ezetimibe coadministered with simvastatin (EZ/S) vs atorvastatin (A) in adults with hypercholesterolemia.
Methods: After a four-week diet/placebo run-in period, eligible patients were randomized 1:1:1 to 3 treatment groups, each for four 6-week periods: (1) A10 mg titrated to A20 mg, A40 mg, and A80 mg through Periods 1-4; (2) EZ/S 10 mg (10/10) titrated to EZ/S 20 mg

(10/20), EZ/S 40 mg (10/40), and EZ/S 80 mg (10/80) through Periods 1-4; and (3) EZ/S 20 mg titrated to EZ/S 40 mg (for Periods 2 and 3), then EZ/S 80 mg for Period 4. Primary endpoint was % change from baseline in LDL-C after the initial 6-week period. Secondary endpoints included % change from baseline in LDL-C to ends of Periods 2, 3, and 4; and HDL-C to ends of Periods 1, 2, 3, and 4. Safety measurements were clinical and laboratory adverse events including ALT or AST _3x upper limit of normal (ULN), CK _10x ULN.

Results: Baseline LDL-C and HDL-C levels were comparable between treatment groups. At the end of Period 1, mean LDL-C reduction and mean HDL-C increase were significantly (p_0.01) greater for the EZ/S 10 mg and EZ/S 20 mg groups compared with the A10 mg group (see Table). At the end of Period 4, comparing maximum doses, EZ/S 80 mg was superior to A80 mg in LDL-C reduction (–59.4 vs –52.5) and HDL-C increase (12.3 vs 6.5).

Table. Summary of Endpoints

				LS-Mean Percent Change from Baseline in:	
Period	Group	Treatment	n available for analysis†	LDL-C	HDL-C
1	1	Atorvastatin 10 mg	250	—37.2	5.1
	2	Ezetimibe/Simvastatin 10 mg	252	—46.1‡	8.0‡
	3	Ezetimibe/Simvastatin 20 mg	253	—50.3‡	9.5‡
2	1	Atorvastatin 20 mg	235	—44.3	6.9
	2	Ezetimibe/Simvastatin 20 mg	239	—50.2‡	9.0
	3	Ezetimibe/Simvastatin 40 mg	243	—54.3‡	12.4‡
3	1	Atorvastatin 40 mg	228	—49.1	7.8
	2&3*	Ezetimibe/Simvastatin 40 mg	466	—55.6‡	11.4‡
4	1	Atorvastatin 80 mg	223	—52.5	6.5
	2&3*	Ezetimibe/Simvastatin 80 mg	441	—59.4‡	12.3‡

LS means and p-values are from analysis of variance model with terms for treatment and baseline LDL-C strata. †Baseline values for LDL-C (mg/dL) were: (Group 1, 180.6; Group 2, 180.0; Group 3, 179.2), for HDL-C: (Group 1, 46.9; Group 2, 46.6; Group 3, 46.8). ‡p_0.01 for difference with Atorvastatin in the specified period.
*Treatment Groups 2 and 3 combined in Periods 3 and 4.

Conclusion: Greater LDL-C reduction and HDL-C increase can be attained by treating with EZ/S compared with atorvastatin. Treatments with EZ/S and A were well-tolerated.

1084-178 Trends in Use of Statins in Older Patients With Acute Myocardial Infarction

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Background: Treatment with HMG CoA Reductase Inhibitors (statins) decreases cardiovascular events and mortality in patients with coronary artery disease (CAD). Little is known regarding trends in the use of statins in a population-based sample of older patients surviving acute myocardial infarction (AMI).

Methods and Results: In two national cohorts of 31,399 and 31,759 older patients hospitalized between 1998-9 and 2000-1 with confirmed AMI, we identified patients who survived to discharge. We assessed change in rates of use of statins at discharge in 'ideal candidates' without contraindications to statins. Overall, 27.5% and 46.2% of patients were discharged in 1998-9 and 2000-1, respectively. Of those patients with an LDL-c greater than the guideline-based threshold of 130 mg/dL, 55% received lipid-lowering therapy in 1998-9 compared to 71% in 2000-1. In general, women and the elderly were consistently less likely to receive statins on discharge.

Conclusions: In a national sample of older AMI survivors, significant increases in discharge prescription of statins occurred irrespective of patient age, sex, race and LDL cholesterol. Despite these increases, a significant proportion of older patients do not receive guideline-based lipid management.

Rates of Statin Use in Older AMI Survivors

	1998-9 N =14,808 %	2000-1 N =14,606 %
Overall Use	27.5	46.2
Age >/= 75 years *	21.6	40.1
LDL <100 mg/dL	28.8	47.4
LDL 100-129 mg/dL	34.7	56.2
LDL >/=130 mg/dL	55.0	71.3
* in ideal patients with LDL-c ³ 130 mg/dL		

1084-179 Ezetimibe/SimvastatinTherapy Is More Effective Than Simvastatin Alone at Reducing Remnant-Like Particle Cholesterol

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Background: Levels of remnant lipoproteins are independent predictors of future coronary events in patients with coronary artery disease. We evaluated the effects of ezetimibe/simvastatin (EZE/SIM) combination therapy versus SIM alone on remnant-like particle cholesterol (RLP-C) in hypercholesterolemic patients.

Methods: After a 6- to 8-wk washout and a 4-wk diet/placebo run-in, 1528 patients with LDL-C 145 - 250 mg/dL and triglycerides ≤350 mg/dL, were randomized to one of the following daily treatments for 12 wks: EZE/SIM tablet (10/10, 10/20, 10/40, or 10/80 mg/mg); SIM alone (10, 20, 40, or 80 mg); EZE 10 mg; or placebo. The primary endpoint was % change from baseline in LDL-C for pooled EZE/SIM vs pooled SIM alone. RLP-C levels were measured using an immune separation assay.

Results: EZE/SIM produced significantly greater reductions in RLP-C than did SIM alone (table). For each SIM dose comparison, RLP-C was reduced more by the EZE/SIM combination (range: -31.8% to -47.4%) than by the corresponding dose of SIM alone (range: -22.5% to -37.5%; p<0.001 for all comparisons). The effects of EZE/SIM on RLP-C were consistent with the effects on LDL-C (-53.1% vs -39.0%; p<0.001); apolipoprotein B (-42.4% vs -31.6%; p<0.001); non-HDL-C (-48.7% vs -35.9%; p<0.001); and triglyceride (-24.3% vs -20.8%; p<0.001).

Conclusion: EZE/SIM in a single tablet (10/10 to 10/80 mg/mg) is more effective than the corresponding dose of SIM alone in reducing plasma levels of potentially atherogenic remnant lipoproteins.

Effect of Treatment on RLP-C

	Pbo (N=141)	EZE 10 mg (N=144)	Pooled SIM (N=597)	Pooled EZE/SIM (N=570)
Baseline RLP-C (mg/dL)	13.3	14.0	14.0	14.0
% Change from baseline	5.4	-15.6^	-29.31^	-40.6*^

*p<0.001 versus Pooled SIM; ^p<0.001 versus Pbo
RLP-C: remnant-like particle cholesterol; Pbo: placebo; EZE: ezetimibe; SIM: simvastatin

POSTER SESSION

1085

Hypertension Treatment Effects

Monday, March 08, 2004, Noon-2:00 p.m.
Morial Convention Center, Hall G
Presentation Hour: 1:00 p.m.-2:00 p.m.

1085-165 Aliskiren, a Novel, Orally Effective Nonpeptide Renin Inhibitor, Lowers Blood Pressure After Once-Daily Dosing in Marmosets, Rats and Humans

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Background: Renin inhibitors (RIs) provide an attractive new therapeutic approach to the treatment of hypertension, as they block the first and rate-limiting step of the renin-angiotensin system (RAS). The present study investigates the in vivo effects of aliskiren, the first of a new class of non-peptide RIs.

Methods: Aliskiren was administered orally to normotensive, sodium-depleted marmosets and to hypertensive (mean systolic BP ≥ 140 mmHg) human patients, and subcutaneously to spontaneous hypertensive rats (SHR). In animal studies, changes in mean arterial pressure (MAP; mean±s.e.mean) and heart rate were measured continuously by telemetry; 24 h ambulatory BP measurement was used in humans. Plasma renin activity was measured by antibody trapping assay.