PharmaNote®

VOLUME 24, ISSUE 9 JUNE 2009

UPDATE ON STATINS: FOCUS ON UNAPPROVED USES

Jose L. Barboza Jr, Pharm.D. Candidate

Over two decades ago, the first HMG-CoA reductase inhibitor (statin) was approved to treat hypercholesterolemia, a major modifiable risk factor for cardiovascular disease. Since then, both the number of statins approved, and indications for their use have increased. In addition to hypercholesterolemia, indications now include preventing and slowing the progression of atherosclerosis in primary and secondary cardiovascular events and coronary artery disease as well as use in Heterozygous Familial Hypercholesterolemia (HeFH) in adolescents. The six currently marketed statins are listed in Table 1.

Table 1. Currently Marketed Statins

DRUG	TRADENAME	APPROVAL DATE
Lovastatin	Mevacor®	September, 1987
Pravastatin	Pravachol®	October, 1991
Simvastatin	Zocor®	December, 1991
Fluvastatin	Lescol®	December, 1993
Atorvastatin	Lipitor®	December, 1996
Rosuvastatin	Crestor®	August, 2003

Over the last two decades, statins have become one of the most frequently prescribed drug classes among all medications. In 1992, statins accounted for 47% of all lipid lowering medications, growing to 87% in 2002.[7] Lipitor® has been the number 1 selling drug in the US this decade. In 2007, it accounted for $6.165 billion in US sales, despite a 6.3% reduction in sales compared with 2006. Crestor® had $1.367 billion US sales in 2007, an increase of 29.2% from 2006.[8]

Although statins have been commonly used for cholesterol lowering and prevention of cardiovascular disease, there is an increasing amount of attention directed towards potential new benefits of statin therapy. This article will evaluate the data on statin use for unapproved indications, including prevention of cardiovascular events in patients with high C-Reactive Protein (CRP) and Low Density Lipoprotein Cholesterol (LDL-C), prevention of venous thromboembolism, statin use in children, and use in rheumatoid arthritis. The pharmacology, clinically useful pharmacokinetics, most prevalent side effects, and prescription costs of the statins will also be covered.

INSIDE THIS ISSUE:

Table 2. Pharmacokinetic Overview of Available Statins

FACTOR	ATORVASTATIN[5]	FLUVASTATIN[4]	LOVASTATIN[1]	PRAVASTATIN[2]	ROSUVASTATIN[6]	SIMVASTATIN[3]
Absorption (%)	30	99+	30	34	40-60	85
Food Effect on Absorption (%)	↓ 9	not affected	Increased	Decreased	not affected	0
Bioavailability (%)	14	24	<5	17	20	<5
t-max (hrs)	1.0-2.0	0.5-1	2	1-1.5	3.0-5.0	1.3-2.4
Protein Binding (%)	>98	98	>95	50	88	95
Metabolizing Enzyme	CYP3A4	CYP2C9	CYP3A4	Minimal CYP	Minimal CYP	CYP3A4
Possible Drug Interactions†						
Increase Statin Levels	Itraconazole, Clarithromycin, Erythromycin, Cyclosporine, HIV Protease Inhibitors, Diltiazem, Grapefruit Juice, Oral Contraceptives	Cyclosporine, Gemfibrozil, Niacin Erythromycin, Fluconazole, Diclofenac, Cimetidine, Ranitidine, Omeprazole	Itraconazole, Clarithromycin, Erythromycin, Ketoconazole, Nefazodone, HIV Protease Inhibitors, Cyclosporine, Amiodarone, Verapamil , Gemfibrozi, Niacin (≥1 g/day), grapefruit juice (>1 quart daily)	Cyclosporine, Erythromycin, Itraconazole, Gemfibrozil, Niacin	Cyclosporine Lopinavir/ Ritonavir, Nevazodone, Clarithromycin, Gemfibrozil, Niacin	Cyclosporine, Itraconazole, Ketoconazole, Erythromycin, Clarithromycin, Nefazodone, HIV Protease Inhibitors, Amiodarone, Gemfibrozil, Verapamil,
Decrease Statin Levels	Colestipol Antacids Rifampin efavirenz Digoxin Penytoin St. John's Wort	Cholestyramine Phenytoin Rifampicin	Rifampin Phenytoin St. John's Wort	Cholestyramine Colestipol	Antacids St. John's Wort	Digoxin St. John's Wort
Prodrug	No	No	Yes	No	No	Yes
$t_{1/2}$ (hrs)	14	<3	1.1-1.7	1.3-2.8	19	1.9
Renal Clearance (%)	≤2	5	10	20	10	13
Adjustments in Renal failure	No dose adjustment necessary.	No dose adjustment necessary. No data available for 40mg in severe renal impairment	Severe renal insufficiency, CrCl <30 mL/min, use caution and carefully consider any dose above 20 mg/day	Closely monitor patients with renal impairment	Severe renal insufficiency, CrCl <30 mL/min). not on hemodialysis, dosing should be started at 5 mg/day	Severe renal impairment, dosing should be started at 5 mg/day and be closely monitored

$t_{1/2}$ = half-life; **CrCl** = creatinine clearance; **CYP =** Cytochrome P450.
† Statins can potentiate the effects of warfarin

PHARMACOLOGY

Statins inhibit 3-Hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase, the rate limiting enzyme in cholesterol biosynthesis. Reduction of cholesterol biosynthesis decreases intracellular cholesterol pools in the hepatocyte, thus upregulating low-density lipoprotein (LDL) receptors. These LDL receptors remove LDL, intermediate-density lipoprotein (IDL) and very-low-density lipoprotein (VLDL) from the systemic circulation.[9]

LDL causes the upregulation of monocyte chemotactic protein (MCP-1) which recruits monocytes to the endothelium. These monocytes subsequently differentiate into macrophages which are inflammatory due to cytokine secretion. Foam cells, which are derived from accumulation of macrophages, are metabolically active and can secrete growth factors and metaloproteinases which can eventually result in ACS and coronary disease. The accumulation of foam cells over time leads to atherosclerosis as well as the development of coronary lesions. As these lesions increase, the potential for ischemia also increases due to diminished blood flow to the tissues. Alternatively, the lesions may rupture and trigger an acute coronary event.

The variable damaging mechanisms of increased LDL explain the pleiotropic effects of LDL lowering statins.[10]

PHARMACOKINETICS

Pharmacokinetic differences between statins allow clinicians to customize therapy using patient-specific factors to promote optimal response while minimizing adverse effects. When selecting a statin, the patient's renal function should be assessed to determine whether a renally-eliminated statin is an appropriate choice. Hepatically-eliminated statins may undergo metabolism by varying enzymes; therefore, the patient's medications should also be taken into account due to possible drug-drug interactions. Certain statins are affected by food, with lovastatin recommended to be taken with evening meals to increase its absorption. Table 2 outlines the significant pharmacokinetic profile for each statin. Common drug interactions which affect statin levels are listed, but this list is not all-inclusive. It should be noted that all statins are classified as pregnancy category X.

UNAPPROVED USES

Prevention of Cardiovascular Events in Patients with high CRP and low LDL

Although prevention of cardiovascular events in patients with hyperlipidemia, cardiovascular disease, and diabetes is an established and approved indication for statins, half of all myocardial infarctions and strokes occur in men and women in whom statins are not indicated. Consequently, it has been suggested that other biomarkers may exist that could more accurately distinguish those who would benefit from preventative therapy. One potential inflammatory marker filling this role is C-reactive protein (CRP). Previous studies demonstrate a relationship between CRP and future vascular events regardless of LDL levels.[11, 12] Statins reduce CRP, and by reducing CRP levels they may reduce cardiovascular events.[13] The Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein trial was a randomized, double-blind, placebo controlled, multicenter trial evaluating the effects of rosuvastatin on the rate of first major cardiovascular events in men and women who did not have hyperlipidemia but had elevated C-Reactive Protein (CRP) levels.[14] The trial's primary objective was the **J**ustification for the **U**se of Statins in **P**revention: an **I**ntervention **T**rial **E**valuating **R**osuvastatin (JUPITER).

The primary endpoint was the occurrence of the first cardiovascular event, defined as nonfatal myocardial infarction, nonfatal stroke, hospitalization from unstable angina, arterial revascularization procedure, or cardiovascular mortality. Results of the JUPITER trial are summarized in Table 3. The primary endpoint was significantly reduced in rosuvastatin-treated patients with event rates of 0.77 vs. 1.36 per 100 person-years ($p<0.00001$) of follow-up in the rosuvastatin and placebo groups, respectively. Secondary endpoints of all-cause mortality, myocardial infarction, stroke, revsascularization or unstable angina, and cardiovascular mortality were also significantly reduced in the rosuvastatin group. Additionally, the rates of death from any cause were decreased in the rosuvastatin group (1.00 vs. 1.25; $p=0.02$). In summary, there was a significant reduction in the incidence of major cardiovascular events attributed to the rosuvastatin group. It is unclear whether these effects are related to statins as a class or rosuvastatin only.

Table 3. Summary of JUPITER Trial.[14]

DESIGN	n	INCLUSION CRITERIA	SERIOUS ADVERSE EVENTS	RESULTS
• RCT • DB • MC	• Ro=8,901 • PCB=8,901	• CRP ≥ 2.0mg/L • LDL < 130 mg/dL • Age (Men ≥ 50, Women≥ 60) • TG < 500mg/dL	No significant differences seen except: • Physician reported diabetes: 270 for the rosuvastatin group and 216 for the placebo group (P=0.01) • 1 nonfatal rhabdomyolysis in the rosuvastatin group	Rosuvastatin significantly reduced the incidence of major CV events in non-hyperlipidemia patients with high CRP and reduced high sensitivity CRP by 37%. Rates of Ro vs. PCB: • Primary endpoint: 0.77 vs. 1.36 per 100 PYF (P<0.00001) • MI: 0.17 vs. 0.37(p = 0.0002) • Stroke 0.18 vs. 0.34 (p = 0.002) • RV or UA: 0.41 vs. 0.77 (p < 0.00001) • Combined endpoint of MI, stroke, death from CV causes: 0.45 vs. 0.85 (p < 0.00001) • Death from any cause: 1.00 vs. 1.25 (p = 0.02) • No significant incidence of myopathy or cancer

RCT = randomized controlled trial; **DB** = double-blind; **MC** = multi-center; **Ro** = rosuvastatin 20mg; **PCB** =Placebo; **MI** = myocardial infarction; **RV** = revascularization; **UA** = unstable angina; **PYF** = person-years of follow-up; **CRP** = C-reactive protein; **CV** = cardiovascular; **LDL** = low-density lipoprotein cholesterol.

Venous Thromboembolism Prevention

There has been conflicting evidence associating statin use with a reduction in venous thromboembolism (VTE). The mechanism by which statins can potentially decrease VTE is not fully understood; however, it is thought to be through inhibition of isoprenylation of signaling proteins as well as reduction in tissue factor expression, thrombin generation, attenuated fibrinogen cleavage, and activation of factors V and VII. A substudy of the JUPITER trial analyzed the effects of rosuvastatin 20mg vs. placebo on venous thromboembolism or pulmonary embolism in men and women who, at the time of the trial, had no indications to be on statin therapy (See table 2 for specifics of the trial).[15] There were 34 thromboembolic events in the rosuvastatin arm compared to 60 in the placebo arm. This accounts for rates of 0.18 vs. 0.32 events per 100 person-years for the rosuvastatin and placebo groups, respectively (p=0.007). For provoked and unprovoked venous thromboembolisms, the rates for deep-vein thrombosis rates were 0.09 vs. 0.20 per 100 patient years (p=0.004) and 0.09 vs. 0.12 (p=0.42), respectively. In summary, there was a significant reduction in the incidence of venous thromboembolism. Other studies are needed to confirm these findings in addition to clarifying the mechanism and evaluating statin use in high risk patients. The authors did not suggest whether these effects were related to statins as a class or rosuvastatin in particular.[15]

Use in Children

There is controversy in the prescribing of statins to children, with concern for both the adverse event profile, including the stunting of growth, as well as with critics who state that the main focus in this population should be on lifestyle changes rather than drug therapy. Statins are currently approved in children ≥ 10 years of age (in ≥ 8 for pravastatin) who have HeFH, a genetic disorder in which one or both strands of DNA responsible for LDL receptor protein are altered, subsequently causing increased LDL levels. Current evidence correlates childhood cholesterol levels to fatty streak formation and to an elevated incidence of coronary heart disease in adulthood; therefore, statins may benefit children who have high cholesterol regardless of familial hypercholesterolemia.[16]

Jongh and colleagues, in a multicenter, randomized, double blind, placebo-controlled study evaluated 173 children with HeFH over 48 weeks.[17] The study found that simvastatin was well tolerated with no deleterious effects on growth and pubertal development, as well as beneficial modified lipid/

lipoprotein profiles in children. Compared to placebo, there was a significant reduction in total cholesterol, LDL, and apoB levels. Simvastatin 40mg did not have clinically meaningful effects on gonadal function in children and adolescent boys or girls nor did it affect normal growth. With the exception of decreases in dehydroepiandosterone, significant changes from baseline in adrenal, gonadal, and pituitary hormones were not found in either group. There were no cases of myopathy, and no significant differences were observed between the treatment groups regarding the number of clinical and laboratory AEs, drug related AEs, or clinically meaningful elevations in hepatic transaminases (ALT and AST) and creatine phosphokinase. This study demonstrated the safety and efficacy of simvastatin ≤ 40 mg/day in children aged 10 to 17 years.[17]

Avis and colleagues performed a meta-analysis of randomized, double-blind, placebo controlled trials that evaluated statin therapy in children aged 8 to 18 years with HeFH.[18] The analysis included 6 trials accounting for 798 children and the length of treatment varied between 12 to 104 weeks. Significant reductions were noted among levels of total cholesterol, LDL cholesterol, and apolipoprotein B, whereas HDL and apolipoprotein A1 levels were increased. With respect to the adverse effect profile, including sexual development, liver toxicity, or muscle toxicity, there were no statistically significant differences found between statin and placebo treated children. In summary, the study suggests that statin treatment may be considered for all children aged 8 to 18 with HeFH due to both the safety and efficacy of statin treatment.[18]

McCrindle and colleagues, in a multicenter, randomized, double-blinded, placebo controlled trial evaluated the safety and efficacy of atorvastatin 10-20 mg in decreasing LDL-C in patients with FH.[19] The patients were 10 to 17 years old with FH or severe hyperlipidemia, defined as LDL-C > 190mg/dL or > 160mg/dL with positive family history or documented premature cardiovascular disease in a 1st or 2nd degree relative. All patients who completed the double blind phase were eligible to continue treatment for 26 more weeks in an open label atorvastatin 10mg study. Overall, no clinically significant increases in the incidence or severity of treatment adverse events were observed in the statin groups compared to placebo. None of the patients discontinued treatment as a result of increased ALT or AST. In summary, there were significant reductions in LDL-C, TC, TG, apolipoprotein B, and increased HDL-C in the atorvastatin group. The study showed safety and efficacy in the treatment of elevated lipid levels in children and adolescents with known FH or severe hypercholesterolemia.[19]

Although evidence supports the safety and efficacy of statins in children aged ≥ 8 years, the topic remains controversial with many clinicians preferring lifestyle changes over drug therapy.

Table 4: Studies Evaluating Rheumatoid Arthritis and Statins.

STUDY	DESIGN	n	INCLUSION CRITERIA	STUDY LENGTH	RESULTS
Okamoto, et al. (2007)[22]	Single institute, prospective observational cohort	7,512 enrolled Analyzed cross sectional data of 4,152, of which 279 (6.7%) took statins	• RA diagnosis • Pt age 18-65 years • Active disease	Cross sectional data was analyzed	Statin vs. non-statin patients showed: • Lower C-reactive protein (0.85 vs 1.24 mg/dL) (p < 0.0001) • Lower swollen joint counts (1.80 vs 2.55) (p ≤ 0.0001) • More frequently used corticosteroids (avg. dosage of 2.88 vs 2.40 mg/day) (p < 0.05)
McCarey, et al. (2003)[23]	Randomized, double blind, placebo-controlled	116 pts receiving DMARD therapy received either atorvastatin(n=58) or placebo(n=58)	• ACR criteria for RA • Symptomatic AR despite DMARD treatment	6 months	Atorvastatin 40mg vs. placebo: • DAS28 improvement (-0.5 vs. 0.03) (p = 0.004) • Achieved EULAR response: (31% vs. 10%) (p = 0.006) • CRP: (-0.46 vs 0.12) (p < 0.0001) • ESR: (-5.03 vs. 1.91) (p = 0.005) • SJC: (-2.69 vs. -0.53) (p = 0.0058)

RA = rheumatoid arthritis; **DMARD** = disease-modifying antirheumatic drug therapy; **DAS28** = Disease Activity Score (http://www.das-score.nl); **EULAR** = European League Against Rheumatism; **CRP** = C-reactive protein; **ESR** = erythrocyte sedimentation rate; **SJC** = swollen joint count; **ACR** = American College of Rheumatology.

Beneficial Uses in Rheumatoid Arthritis

Rheumatoid arthritis (RA) and atherosclerosis have a similar pathogenesis, with inflammation being a major causative agent.[20] Both atherosclerosis and RA are characterized by increases in T-cell, B-cell, monocyte, and endothelial cell activations, as well as increased CRP levels. Statins block the immunosuppressive and anti-inflammatory effects of the mevalonate pathway. They selectively inhibit leukocyte function antigen-1 (LFA-1) mediated adhesion. The LFA-1 is expressed on the surface of leukocytes and binds to the intermolecular adhesion molecule 1 when activated.[21] LFA-1 cells promote immunosuppression by co-stimulating T cells. Blocking these two immune responses may improve rheumatoid arthritis symptoms and disease course. Two studies in particular have observed benefits with statin use in this population as shown in Table 4.[22, 23]

Both Okamoto and McCarey observed benefits in reduced swollen joint counts and CRP levels in those on statin therapy. However, in the case of Okamoto, et al., statin users had a higher percent of corticosteroid use (statin users: 62% vs. non statin users: 52.5%) and higher doses; therefore, the lower disease activity in this study could be attributed to increased corticosteroid use. The McCarey et al. study showed a stronger relationship between statin use and RA prevention. The atorvastatin group showed a decrease of 0.52 in DAS28, a decrease of 2.16 in swollen joint count, and a decline in CRP and ESR of 50% and 28% respectively compared to placebo. The results in these studies show that statins could be used to improve RA symptoms in combination with DMARDS. Before statins can be routinely recommended in RA therapy, larger, more highly powered studies, preferably linked to one specific DMARD, will be needed. It is unknown whether these benefits are a class effect or applicable to specific statins only; however, Okamoto and colleagues observed benefits with the use of four different statins, with pravastatin being the most prevalent at 49%.

ADVERSE EVENTS

Table 4 summarizes the most common side effects of the various commercially available statins. Adverse effects associated with statin therapy are generally mild but can occasionally be of significant consequence.

Table 4: Percent of Patients Experiencing Adverse Events with Currently Available Statins.

	Rosuvastatin[6] 10mg	Atorvastatin[5] 10mg	Simvastatin[3] 20-40mg	Pravastatin[2] 40mg	Lovastatin[1] 20mg	Fluvastatin[4] 20, 40, 80mg*
Headache	5.0 (4.9)	5.4 (7.0)	2.5 (2.1)	1.9 (1.8)	2.6 (2.7)	8.9 (7.8)
Abdominal Pain	1.8 (2.4)	2.8 (0.7)	5.9 (5.8)	2.4 (2.5)	2.0 (1.6)	4.9 (3.8)
Dyspepsia, Heartburn or Gastritis		2.3 (4.1)	4.9 (3.9)	3.5 (3.7)	1.3 (1.9)	4.9 (4.2)
Diarrhea		2.7 (1.5)			3.7 (4.2)	7.9 (3.2)
Flatulence		2.1 (3.3)		1.2 (1.1)	2.6 (2.3)	2.6 (2.5)
Myalgia	1.3 (2.1)	3.2 (1.1)	3.7 (3.2)	1.4 (1.4)	2.6 (1.7)	5.0 (4.5)
Constipation	2.4 (2.1)	2.1 (1.8)	2.2 (1.6)	1.2 (1.3)	2.0 (1.9)	
Nausea	3.1 (3.5)			1.6 (1.6)	1.9 (2.5)	3.2 (2.0)
Dizziness	4.0[(24)] (2.8)			2.2 (2.1)	0.7 (0.7)	
Rash		3.9 (0.7)		2.1 (2.2)	0.8 (0.7)	
Sinusitis		2.8 (2.6)	2.3 (1.8)			
Arthralgia	7.1[(24)] (10.1)	2.0 (1.5)		6.0 (5.8)		
Asthenia/Fatigue	2.6 (3.2)	2.2 (1.9)		3.4 (3.3)		

The numbers inside the parenthesis "( )" are the placebo side effects seen in each study. *The Fluvastatin® package insert does not specify which placebo controlled trials was used. Blank cells represent categories not measured in the specific trials.
Graham et al, studied the rates of rhabdomyolisis in lipid lowering drugs and found that the incidence per 10,000 person-years of monotherapy with atorvastatin, simvastatin, or pravastatin was 0.44.[25]

Monitoring Parameters

The National Lipid Association Statin Safety Assesment Task Force released their recommendations on monitoring parameters in 2006.[26]

Liver function tests (LFTs) should be obtained at baseline, and monitored 12 weeks after initiating therapy or after a dose increase and periodically thereafter. The National Lipid Association Statin Safety Assessment Task force recommend that routine monitoring is not supported by the available evidence and current recommendations for monitoring need to be reconsidered by the FDA. Monitoring for patient complaints of jaundice, malaise, fatigue, lethargy, and related symptoms should also be implemented.

Obtaining a baseline creatinine phosphokinase (CK) should be considered in patients who are at high risk of muscle toxicity. The levels should be obtained in symptomatic patients in order to help measure the severity of muscle damage and to facilitate the decision about whether to continue therapy or alter doses. CK levels should not be measured routinely in non-high risk patients, nor should they be measured in asymptomatic patients during the course of statin therapy.[26]

COSTS

Average monthly costs for currently available prescriptions are summarized in Table 5. Generically-available statins average approximately $25/month, whereas brand-only statins are associated with a four-fold increase in cost.

Table 5. Monthly Costs of Available Statins.

BRAND	GENERIC	PRICE (#30)
Crestor® 10mg	Rosuvastatin	$123.61
Lipitor® 10mg	Atorvastatin	$89.99
Zocor® 20mg	Simvastatin	$27.99 (generic)
Pravachol® 40mg	Pravastatin	$25.99 (generic)
Mevacor® 20mg	Lovastatin	$22.99 (generic)
Lescol® 20mg	Fluvastatin	$94.50

Prices obtained from www.drugstore.com

SUMMARY

Statins are being studied for a variety of new indications. Of these potential new indications, the JUPITER[12] study showed that rosuvastatin caused a significant reduction in the incidence of major cardiovascular events in patients without hyperlipidemia, who have high C-reactive protein. This study also illustrates the benefits of rosuvastatin on reducing the incidence of VTE.[13] Available data suggests that statins are safe in children; however, more clinical trials are needed in order to define their place and role. Statins also appear efficacious in treating rheumatoid arthritis, though larger clinical trials are needed to fully elucidate these benefits. Ongoing studies are assessing the potential benefits of statins in cancer and dementia prevention, cognitive function disorders, and other indications. With a few exceptions, it is unclear whether these benefits are attributable to statins as a class or to a particular statin.

♦ ♦ ♦

REFERENCES

1. Merck & Co., Inc. MEVACOR® (Lovastatin) package insert. Whitehouse Station, NJ; 2006.
2. Bristol-Myers Squibb Co. PRAVACHOL® (Pravastatin sodium) package insert. Princeton, NJ 08543 USA; 2007.
3. Merck & Co., Inc. ZOCOR® (Simvastatin) package insert. Whitehouse Station, NJ; 2008.
4. Novartis Pharmaceuticals Corp. LESCOL® (fluvastatin sodium) package insert. East Hanover, New Jersey 07936; 2006.
5. Pfizer Inc. LIPITOR® (Atorvastatin calcium) package insert. New York, NY 10017; 2006.
6. AstraZeneca Pharmaceuticals LP. CRESTOR® (Rosuvastatin) package insert. Wilmington, DE 19850; 2007.
7. Mah J, Sehgal N, Ayanian J, et al. National trends in statin use by Coronary Heart Disease Risk Category. PLoS Medicine 2005;2(5):e123.
8. Retrieved April 18, 2009 from Drugs.com Website: http://drugs.com/top200.html
9. Rosenson RS, Tangney CC. Antiatherothrombotic properties of statins: implications for cardiovascular event reduction. JAMA 1998;279

(20):1643-50.
10. Palinski W, Tsimikas S. Immunomodulatory effects of statins: mechanisms and potential impact on arteriosclerosis. J Am Soc Nephrol 2002;13: 1673–81.
11. Pai JK, Pischon T, Ma J, et al. Inflammatory markers and the risk of coronary heart disease in men and women. N Engl J Med 2004;351:2599-610.
12. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N Engl J Med 2000;342:836-43.
13. Albert MA, Danielson E, Rifai N, Ridker PM. Effect of statin therapy on C-reactive protein levels: the Pravastatin Inflammation/CRP Evaluation (PRINCE), a randomized trial and cohort study. JAMA 2001;286:64-70.
14. Ridker PM, Danielson D, Fonseca FAH, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008;359:2195-207.
15. Glynn RJ, Danielson E , Fonseca FAH, et al. A Randomized Trial of Rosuvastatin in the Prevention of Venous Thromboembolism. N Engl J Med 2009;360:1851-61.
16. Berenson GS, Srinivasan SR, Bao W, Newman WP 3rd, Tracy RE, Wattigney WA. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults: the Bogalusa Heart Study. N Engl J Med 1998;338:1650-6.
17. de Jongh S, Ose L, Szamosi T, et al. Efficacy and safety of statintherapy in children with familial hypercholesterolemia: a randomized, double-blind, placebo-controlled trial with simvastatin. Circulation 2002;106(17):2231–7.
18. Avis HJ, et.al. A systematic review and meta-analysis of statin therapy in children with familial hypercholesterolemia. Arterioscler Thromb Vasc Biol 2007;27(8):1803-10.
19. McCrindle BW, L Ose, et al. Efficacy and safety of atorvastatin in children and adolescents with familial hypercholesterolemia or severe hyperlipidemia: a multicenter, randomized, placebo-controlled trial. J Pediatr 2003;143(1):74-80.
20. Hermann F, Forster A, Chenevard R, et al. Simvastatin improves endothelial function in patients with rheumatoid arthritis. J Am Coll Cardiol 2005;45:461–4.
21. Penney CJ. Statins in rheumatology. Rheumatol 2005;32(1):17-9.
22. Okamoto H, Koizumi K, Kamitsuji S, et al. Beneficial action of statins in patients with rheumatoid arthritis in a large observational cohort. J Rheumatol 2007;34:964–8.
23. McCarey DW, McInnes IB, Madhok R, et al. Trial of Atorvastatin in Rheumatoid Arthritis (TARA): double-blind, randomised placebo-controlled trial. Lancet 2004;363:2015–21.
24. Crouse JR 3rd, Grobbee DE, et al. Measuring Effects on intima media Thickness: an Evaluation Of Rosuvastatin in subclinical atherosclerosis--the rationale and methodology of the METEOR study. Cardiovasc Drugs Ther 2004;18 (3):231-8.
25. Graham DJ, Staffa JA. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. JAMA 2004;292(21):2585-90.
26. McKenney JM, et al. Final Conclusions and Recommendations of the National Lipid Association Statin Safety Assessment Task Force. Am J Cardiol 2006;97[suppl]:89C-94C.
27. Retrieved April 10, 2009, from Drugstore.com Web site: http://www.drugstore.com/

♦ ♦ ♦

The PharmaNote is Published by:
The Department of Pharmacy Services, UF Family Practice Medical Group, Departments of Community Health and Family Medicine and Pharmacotherapy and Translational Research
University of Florida