STATINS –EFFICACY AND SAFETY

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"A rare but deadly side effect of the popular cholesterol-lowering drugs known as statins has killed and injured more people than the government has acknowledged, the consumer watchdog group Public Citizen reported. The group's analysis of the Food and Drug Administration's side-effect registry linked 72 fatal and 772 non-fatal cases of muscle breakdown, known as rhabdomyolysis, to all six of the statins sold between October 1997 and December 2000", announced 'USA today' in August 2001.[1] All the print and electronic media took upon themselves to wage a war against statins . Patients taking statins got duly alarmed and turned to their doctors for the requisite information and the further plan.

Statins have been studied closely and have proven to be a safe and effective way to help patients lower their cholesterol levels. Statins, especially in combination with a good diet and regular exercise, have been proven to decrease the risk of heart attack and stroke, lessen the need for heart surgery and angioplasty, and reduce the risk of death significantly.[2-5] An overview of secondary prevention trials using both drugs and diet to lower cholesterol demonstrated an approximate 25% reduction in nonfatal and 14% in fatal MIs. The aim of this article is to objectively analyse the effects of statins on primary and secondary prevention and evaluate the side effects profile.[6,7] Many small and large studies have been conducted with HMG Co reductase inhibitors in the scenario of primary and secondary prevention. Some of the landmark studies which revolutionized the way we handle the patients of coronary artery disease will be discussed.

PRIMARY PREVENTION

The importance of dyslipidaemia as an important risk factors had always been appreciated.[2,3,7,8] Many studies done in the past employing large populations and different cholesterol lowering strategies failed to show any significant reduction in mortality.[9] Statins used in this setting, for the first time have shown very reliable data, that shows reduction of mortality in persons without any evidence of coronary artery disease.[10] The data is not only convincing for people with high cholesterol but also very encouraging in patients with not so high cholesterol.

West of Scotland Coronary Primary Prevention Study (WOSCOPS)

WOSCOPS studied the role of statin therapy in primary prevention in a relatively high-risk population. In a double-blind, placebo-controlled design, WOSCOPS evaluated the effects of either a fixed dose of pravastatin, 40 mg/d, or

↑ LDL Cholesterol ↓	Primary Prevention	Secondary Prevention
	WOSCOP 31% risk reduction nonfatal MI and CHD death	**4S** 34% risk reduction nonfatal coronary events
	AFCAPS/TexCAPS 40% risk reduction nonfatal and fatal MI	**CARE** 24% risk reduction nonfatal MI and CHD death **LIPID** 24% risk reduction nonfatal MI and CHD death **HPS** 30% risk reduction

TABLE 1

placebo over a 5-year period. The primary endpoint of WOSCOPS was the combined incidence of nonfatal myocardial infarction or death from CHD. WOSCOPS evaluated total mortality, death from cardiovascular cause, and the frequency of coronary revascularization procedures as secondary endpoints. The WOSCOPS cohort had a number of characteristics that placed them in a relatively high-risk group despite the clinical absence of atherosclerosis as defined by a prior infarction. All subjects were men who averaged 55 years of age. The average cholesterol was 272 mg/dl, which was associated with an LDL-C of 192 mg/dl. Triglycerides averaged 164 mg/dl, and HDL-C was 44 mg/dl. Approximately 5 percent of the total cohort had a positive Rose Questionnaire for anginal symptoms, 3 percent reported intermittent claudication, and 78 percent of the patients were either current or ex-smokers.[11,12]

A significant reduction of 31 percent was achieved in the primary endpoint. Total mortality was reduced by 22 percent, which closely approached statistical significance ($p = 0.051$). No increase in noncardiovascular death rates were seen in the pravastatin group. When taking into account suspected coronary events, death from CAD was decreased by 33 percent ($p = 0.042$). WOSCOPS also reported 31 and 37 percent reductions of coronary angiography and revascularization procedures, respectively ($p = 0.007$ and 0.009, respectively). The West of Scotland trial established the benefit of statin therapy in a high-risk group. Pravastatin therapy demonstrated a significant reduction in coronary death and nonfatal myocardial infarction, and the event curves began to diverge within the first 12 months of therapy.

What does it mean to our practice of medicine? Pravastatin therapy in male subjects with similar patient characteristics to the WOSCOPS trial would prevent one event in 31 subjects who take statin therapy over a 5-year period. Restriction of therapy to the 40 percent of men at highest risk (20 percent event rate in 10 years, in accord with European guidelines) reduces the number needed to treat to 22.5. A conservative estimate of the feasibility of treating patients like those in WOSCOPS was determined to be well within the range of interventions that are considered to be cost effective (approximately £8200 [$13,000 US] per year of life saved).[12]

AFCAPS/TexCAPS

The AFCAPS/TexCAPS examined the potential impact of statin therapy in subjects that included both middle-aged men and women whose total cholesterol and LDL-C approximated the average cholesterol. The AFCAPS/TexCAPS was designed in a prospective, randomized, double-blind, placebo-controlled fashion to test the hypothesis that primary prevention with a statin would reduce cardiac event rates in a relatively low-risk group of 6605 men and women with no clinical evidence of atherosclerosis The

cohort ranged from 45 to 73 years of age for men and 55 to 73 years of age for women. The entrance lipid criteria were cholesterol levels between 180 and 264 mg/dl, LDL-C of 130 to 190 mg/dl, and HDL-C of 45 mg/dl or lower in men or 47 mg/dl or lower in women. In addition to having no clinical evidence of CHD, only 12 percent of this cohort were active smokers, 22 percent were hypertensive, and 2 percent were categorized as diabetic. AFCAPS/TexCAPS is one of the first intervention trials to randomize a significant number of female subjects (n = 997).[13]

Lovastatin therapy resulted in a statistically significant 37 percent reduction in the incidence of a primary endpoint event ($p<0.001$). A total of 183 subjects in the placebo group had at least one primary endpoint compared with 116 subjects in the lovastatin group. Life-table plots suggest that a difference between treatment and placebo event curves began in the first year of therapy and continued to diverge throughout the remaining years of the trial. In absolute terms, 11 subjects per 1000 patient-years in the placebo group suffered an event compared with 7 subjects per 1000 patient-years in the lovastatin group. Lovastatin therapy resulted in consistent reductions in event rates in the secondary endpoints: a 33 percent risk reduction in revascularizations ($p = 0.001$), a 32 percent risk reduction in unstable angina ($p = 0.02$), 40 percent risk reduction in nonfatal or fatal myocardial infarctions ($p = 0.002$), and 25 percent risk reductions in both coronary and cardiovascular endpoints ($p = 0.006$ and 0.003, respectively). Among patient subgroups in the cohort (e.g., women, smokers, and hypertensives), the benefit of lovastatin treatment was comparable with the benefit in the overall cohort. The AFCAPS/TexCAPS is the first major clinical trial of a statin to demonstrate reductions in first coronary events in a low-risk subgroup whose profile approximates the general population.[14]

SECONDARY PREVENTION STUDIES

These studies, conducted in patients with established CAD, offered new insights and directions in the management of CAD. For the first time we have very convincing data that shows mortality benefit by altering dyslipidaemia favourably in patients with high and not so high cholesterol and established CAD.

Scandinavian Simvastatin Survival Study (4S)

The Scandinavian Simvastatin Survival Study (4S) was a large-scale, double-blind, placebo-controlled trial that evaluated the effect of Simvastatin therapy in dyslipidemic patients who were either myocardial infarction survivors (63 percent), patients with the anginal syndrome (21 percent), or both (16 percent) in a 5.4-year trial. The age inclusion criteria ranged from 35 to 70 years. Patients were randomly assigned to receive either placebo or 20 mg of Simvastatin per day with the allowance of dosage titration in an

4S	Very high cholesterol with CHD
LIPID	Moderately high cholesterol
CARE VA-HIT (low HDL-C)	Average cholesterol with MI
WOSCOPS LRC-CPPT, Helsinki	High cholesterol without MI
AFCAPS/TexCAPS (low HDL)	Average cholesterol without CHD
HPS	Average cholesterol with and without CAD

TABLE 2

PRIMARY PREVENTION TRIALS OF STATIN THERAPY

	PRIMARY PREVENTION	
	WOSCOP	**AFCAPS/TexCAPS**
N (% women)	6596 (0)	6605 (15)
Duration	4.9	5.2
Intervention	Pravastatin 40mg/d	Lovastatin, 20-40 mg/d
Baseline lipid (mg/dl)		
TC	272	221
LDL-C	192	150
HDL-C	44	36 Men; 40 Women
TG	164	158
% Lipid Changes, Treatment vs. Placebo		
TC	-20	-19
LDL-C	-26	-26
HDL-C	+5	+5
TG	-12	-13
Endpoints (% Changes in Risk), Treatment vs. Placebo		
Nonfatal MI/CHD death	-31	-25
Fatal/nonfatal MI	-	-40
Acute major coronary events	-	-37
Total mortality	-22	+ 3 (NS)
CHD mortality	-28	Too few
Revascularizations	-37	-33
Stroke	-11 (NS)	

HMG-CoA = 3-hydroxy-3methylglutaryl coenzyme A; WOSOPS=West of Scotland Coronary Prevention Study; AFCAPS/TexCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study; TG = Total Cholesterol; LDL-C = low-density lipoprotein cholesterol; HDL-C=high-density lipoprotein Cholesterol; TG=triglycerride; MI=myocardial infarction; CHD=coronary heart disease'
NS = nonsignificant; **bold** = study's primary endpoint; - - not reported

TABLE 3

attempt to reduce the serum cholesterol to 116 to 200 mg/dl.[15]

The primary endpoint was achieved by Simvastatin therapy, with a highly statistically significant relative risk reduction of 30 percent (p = 0.0003). The absolute number of deaths totaled 438, with 256 subjects dying in the placebo group compared with 182 patients in the Simvastatin group. The absolute risk reduction was 4 percent. Adjustment for baseline covariates resulted in no difference in total mortality or other endpoints.[16-20]

The 4S study was a landmark trial and demonstrated clearly that statin therapy could reduce total mortality in a secondary prevention trial. The most significant impact on mortality was due to the reductions in cardiovascular events. A number of substudies were also performed and demonstrated that Simvastatin therapy was effective in women and older patients (age > 60 years).[21] Cerebrovascular events and new carotid bruits were also significantly reduced by Simvastatin therapy.[22] Lp(a) was also measured in the 4S study and was a major predictor of morbidity in major coronary events. The impact on clinical events is compatible with the angiographic studies (e.g., MAAS, CIS), which demonstrated that Simvastatin therapy was able to alter beneficially the progression of angiographically demonstrable coronary artery disease.[24]

Cholesterol And Recurrent Events (CARE)

The CARE trial analyzed 4159 subjects (3583 men and 576 women) who had suffered an acute myocardial infarction between 3 and 20 months before randomization and whose total cholesterol levels at baseline were less than 240 mg/dl. Additional lipid criteria required the LDL-C to be between 115 and 174 mg/dl and the fasting triglycerides to be less than 350 mg/dl. Pravastatin was administered at 40 mg/d in a fixed dose; cholestyramine, 8 to 16 g, could be added to the designated therapy if the LDL-C levels remained at 175 mg/dl or more after intensified dietary therapy in both groups. The primary endpoint analyzed in the CARE trial was nonfatal myocardial infarction and death from CHD,. which included several fatal coronary events (sudden cardiac death, death during a coronary intervention, or mortality from other coronary causes). Pravastatin therapy resulted in significant improvement in the lipid profile and was well tolerated (approximately 94 percent of the treatment group were still on the randomized medication during the final 12 months of the follow-up period). LDL-C that averaged 139 mg/dl at the time of randomization was decreased by 32 percent to 98 mg/dl during the trial duration. The total cholesterol was approximately 20 percent lower when compared with the placebo group. The HDL-C level in the group randomized to pravastatin was 5 percent higher when compared with dietary therapy, and the triglyceride decrease was approximately 14 percent.[25,26]

The improvements in the lipid profile relative to the dietary intervention resulted in a significant 24 percent reduction in the primary endpoint (p = 0.003). In absolute terms, 13.2 percent of the dietary group had a qualifying recurrent event compared with 10.2 percent in the pravastatin group. In addition to the impact on the primary endpoint, the subjects randomized to pravastatin had a 26 percent reduction in the rate of coronary artery bypass procedures (p = 0.005) and a 23 percent reduction in the rate of angioplasty (p<0.001).[26]

The CARE trial was a landmark study that demonstrated significant improvement in fatal and nonfatal myocardial infarction in secondary prevention despite normal baseline cholesterol levels. Subgroup analysis of the CARE trial demonstrated reductions in stroke and improvement in diabetics, elderly patients, and women.[27-30] The CARE trial emphasizes the clinical utility of statin therapy in secondary prevention even with cholesterol levels that would be considered to be within the normal range.[31]

The Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID)

LIPID was an extremely large secondary-prevention trial that evaluated pravastatin in 9014 patients over a period of 6.1 years. Patients enrolled in the LIPID trial had a

	SECONDARY PREVENTION		
	4S	**CARE**	**LIPID**
N (% women)	4444 (19)	4159 (14)	9014 (17)
Duration (yr)	5.4	5	6.1
Intervention	Simvastatin 10-40 mg/d	Pravastatin 40 mg/d	Pravastatin 40 mg/d
Baseline lipids (Mg/dl)			
TC	261	209	218
LDL-C	188	139	150
HDL-C	46	39	36
TG	135	155	138
% Lipid changes, Treatment vs. Placebo			
TC	-26	-20	-18
LDL-C	-36	-28	-25
HDL-C	+7	+5	+5
TG	-17	-14	-11
Endpoints (% changes in Risk), Treatment vs. Placebo			
Nonfatal MI/CHD death	-34	-24	-24
Fatal/nonfatal MI	-42	-25	-24
Acute major coronary events			-29
Total mortality	-30	-9 (NS)	-22
CHD mortality	-42	-20	-24
Revascularizations	-37	-27	-20
Stroke	-30	-31	-19

HMG-CoA-3-hydroxy -3-methyulgluaryl coenzyme A; 4S=Scandinavin Simvastatin Survival Study; CARE=Cholesterol and recurrent events; LIPID= Long term intervention with pravastatin in ischemic disease; TG= Total Cholesterol; LDL-C= low-density lipoprotein cholesterol; HDL-C= high-density lipoprotein Cholesterol; TG-triglycerride; MI=Myocardial infarction; CHD=Coronary heart disease' NS = Nonsignificant; **bold** = study's primary endpoint; - - not reported

TABLE 4

broad range of cholesterol levels (155–271 mg/dl) and also included a large number of women (17 percent). Subjects randomized in the LIPID trial ranged from 31 to 75 years of age and were considered for inclusion if they had suffered an acute myocardial infarction or had a diagnosis of unstable angina that was established between 3 and 36 months before randomization. Patients were allocated to receive dietary advice and either 40 mg of pravastatin versus placebo. The primary endpoint of the lipid trial was death from CHD. A number of secondary outcomes were also tabulated, including all-cause mortality, death from CHD, nonfatal myocardial infarction, stroke, revascularization procedures, hospital days, and death due to heart failure.[32]

Pravastatin therapy effectively lowered lipid values, with the total cholesterol level falling 39 mg/dl from the original average

value of 218 mg/dl. The pravastatin-induced reduction in total cholesterol was 18 percent greater than the effect of dietary therapy alone in the placebo group. The median LDL-C in the group randomized to pravastatin was initially 150 mg/dl and was reduced by 25 percent compared with placebo. Median triglyceride level was 142 mg/dl and was reduced by 11 percent. HDL-C was increased by 5 percent.[32]

The primary outcome was significantly and favorably altered by pravastatin therapy. Overall mortality was 22 percent less in the group randomized to pravastatin, which was highly statistically significant ($p<0.001$). In absolute terms, 11 percent of subjects randomized to pravastatin suffered a fatal event, compared with 14.1 percent in the placebo group. The relative risk reduction by pravastatin in deaths from CHD was reduced by 24 percent compared with placebo ($p<0.001$). In absolute terms, death from CHD was 6.4 percent in subjects randomized to pravastatin compared with 8.3 percent in the placebo group. A number of secondary endpoints, including the incidence of myocardial infarction, revascularization procedures, hospitalization for unstable angina, stroke and hospital days, were also significantly reduced by pravastatin therapy.[32]

Because of its large and diverse population, the LIPID trial provides extremely strong evidence that pravastatin therapy in secondary prevention is of clinical benefit across a broad range of baseline cholesterol values and is associated with a reduction in total and cardiac mortality without an increase in noncardiac deaths. The LIPID investigators estimated that for every 1000 patients assigned to treatment with pravastatin over a period of 6 years, a total of 30 deaths, 28 nonfatal myocardial infarctions, and nine nonfatal strokes could be avoided with effective lipid-lowering therapy.

LISA:

In the Lescol in Severe Atherosclerosis (LISA) Study, patients with symptomatic coronary heart disease and hypercholesterolemia who were given fluvastatin had 71% fewer cardiac events than those in the placebo group. These results firmly establish the desirability of lowering atherogenic serum lipid levels among patients who have recovered from AMI.[33]

Atorvastatin Versus Revascularization Treatment (AVERT)

The AVERT trial was designed to evaluate the potential benefits of aggressive lipid lowering with atorvastatin, 80 mg/d, on ischemic events in a cohort of patients with stable atherosclerosis who were scheduled to undergo a percutaneous revascularization procedure. The AVERT trial was an 18-month, open-label, randomized, multicenter study that evaluated 341 patients who were scheduled for elective angioplasty. Qualification requirements included at least one native coronary vessel with 50 percent or greater stenosis and an LDL-C in excess of 115 mg/dl. Subjects were excluded if the triglyceride levels were in excess of 500 mg/dl, ejection fraction was less than 40 percent, or the patients could not complete 4 minutes of exercise on a Bruce treadmill. Additionally, patients were excluded if angiography revealed left main or triple-vessel coronary atherosclerosis. Recent unstable angina and myocardial infarction (<14 days) also were major exclusion criteria.[34]

Lipid-lowering drugs were administered in 73 percent of patients in this group at some time during the follow-up (71 percent of the total group received statins). The subjects randomized to receive atorvastatin had a significant reduction in lipid levels with an LDL-C decrease from mean baseline value 145 to 77 mg/dl (46 percent reduction). Total cholesterol was decreased from 223 to

151 mg/dl (31 percent reduction). Triglycerides were also decreased from 168 to 139 mg/dl (11 percent reduction), and HDL-C increased from 45 to 47 mg/dl. The usual care group experienced a decrease in LDL-C from 147 to 119 mg/dl (18 percent reduction). Total cholesterol decreased from 222 to 197 mg/dl (10 percent decrease). Triglycerides increased from 161 to 165 mg/dl, and HDL-C increased from 43 to 46 mg/dl. Total cholesterol, LDL-C, and triglycerides were significantly improved by atorvastatin relative to usual care.[34]

The composite endpoint of ischemic events was reduced by atorvastatin therapy. A total of 22 ischemic events occurred in the group randomized to receive aggressive lipid-lowering therapy compared with a total of 37 events in the usual care group (36 percent reduction, $p = 0.048$). The difference in the treatment arms trended toward adjusted statistical significance because the significance level was reduced to 0.045 because of the performance of two interim analyses. An increase in ischemic events, especially as related to the potential for enhanced rate of repeat percutaneous revascularization, may be expected in the early period after angioplasty.

However, in the AVERT study, the difference between usual care and aggressive medical therapy continued to remain separate during the trial period.[34]

Heart Protection Study (HPS)

It involved 20,000 volunteers aged 40-80 years who were at high risk of coronary heart disease, but for whom there was substantial uncertainty about the balance of benefits and safety of cholesterol-lowering therapy. It specifically targeted groups of patients in which there was little direct evidence of benefit-including women, the over 70s, people with diabetes, those with non-coronary vascular disease, and those with average or below-average cholesterol levels. Volunteers were allocated either 40 mg daily simvastatin as cholesterol-lowering therapy, or matching placebo tablets. Study treatment and follow-up continued for an average of five and a half years in 69 UK hospitals.

Summary of major findings were Cholesterol-lowering with statin treatment reduces the risk of heart attacks and of stokes by at least one-third, as well as reducing the need for arterial surgery, angioplasty and amputations. Reductions of at least one-third in these 'major vascular' events were found in a very wide range of high-risk patients for whom there had previously been uncertainty about using cholesterol-lowering therapy: women as well as men, people aged over 70 as well as younger people, people with blood levels of total cholesterol below 200 mg/dl (approx. 5mmol/l) or of 'bad' LDL cholesterol below 120 mg/dl Approx. 3 mmol/l), as well as those considered to have 'high' levels.[35]

About 5 years of statin treatment typically prevents heart attacks, strokes or other major vascular events in: 100 of every 1000 people who previously had a heart attack, 80 of every 1000 people with angina or some other evidence of coronary heart disease, 70 of every 1000 patients who previously had a stoke, 70 of every 1000 people with occlusive disease in leg or other arteries, 70 of every 1000 people with diabetes. In addition, cholesterol-lowering reduces the risk of being hospitalized because of worsening angina –typically, about 30 fewer admissions per 1000 treated for 5 years.

The benefits increase throughout the study treatment period (so more prolonged therapy might be expected to produce even bigger benefits), and are additional to those of other treatments used to prevent heart attacks and strokes.[35]

This trial provides uniquely reliable evidence about the safety of this simvastatin

regimen, with no support for previous concerns about possible adverse effects of lowering cholesterol on particular non-vascular causes of death, on cancer or one stroke due to bleeding.

SIDE EFFECTS PROFILE

Main side effects pertaining to statins are the effects on skeletal muscles, and liver and are considered below: *Skeletal Muscle*:

The muscles can be effected by statins ranging from asymptomatic rise in creatine kinase and myalgia to frank rhabdomylosis. The evidence that statin drugs may also be associated with development of rhabdomyolysis and kidney failure is understandably of concern. But we have to be careful to understand the extent of problem and not to throw the baby out with the bath water. Whether different statin-fibrate combinations have different risks for rhabdomyolysis is not yet known. In fact, several recent studies have shown other statins and combinations to be effective without evidence of abnormal biochemical test results.[11,16,32] in this large patient data base employing different statins rhabdomyolysis was extremely rare. Rise in CPK indicating muscle involvement is comparable with placebo. However this side effect should be kept in mind and drugs which increase the likehood of myopathy should be avoided. Patients on statins present with muscle pain and aches should have their CPK checked. The drug should be discontinued if myopathy is suspected, if CPK levels rise markedly, or if the patient has risk factors for rhabdomyolysis.

Rhabdomyolysis is the actual death (necrosis) of skeletal muscle tissue, which leads to disintegration or dissolution of muscle fibers. Such extensive muscle damage results in the release of the contents of muscle cells into the bloodstream. Rhabdomyolysis, with or without acute renal failure secondary to myoglobinuria, has been reported rarely. Rhabdomyolysis can be seen alone or together with other muscle problems, such as muscular weakness and pain. Patients can present with muscle pain, tenderness, or weakness. This musculoskeletal disease is rare and usually caused by a crush injury to muscle. It can also be caused by prolonged immobilization, particularly after drug overdose or intoxication. Exertional rhabdomyolysis is an even more uncommon form of rhabdomyolysis, in which damaged muscle tissue is caused by intense and prolonged physical exertion. The major complication of rhabdomyolysis is acute kidney failure, which is caused by the kidney's filters getting clogged by proteins (myoglobins) released from the muscle cells.[35]

Myopathy Caused by Drug Interactions: Concomitant use of Simvastatin with itraconazole, ketoconazole, erythromycin, clarithromycin, HIV protease inhibitors, nefazodone, or large quantities of grapefruit juice (>1 quart daily) is not recommended because of the risk of myopathy. In patients taking concomitant cyclosporine, fibrates, or niacin, the dose of statins should be regulated carefully as the risk of myopathy increases substantially at higher doses.[35]

Diagnosis is relatively straightforward. Marked elevation of creatine kinase in the blood is a biochemical indicator of skeletal muscle necrosis, and a simple blood test can verify diagnosis. The presence of myoglobin in the urine also indicates rhabdomyolysis and kidney failure.

Evidence: In a long term trial using Simvastatin the overall incidence of myopathy was 0.7% (5/669) and 0.2% (1/436) at the 80-mg and 40-mg doses, respectively.[36] Simvastatin demonstrated an excellent long-term safety profile in 4S study. The single reported case of myopathy reversed upon

discontinuation (N=2,221).[16-20] The number of patients in WOSCOPS reporting myalgia or elevated enzymes were also comparable between the two groups.[11,12] In AVERT study rhabdomyolysis was not seen in either group.[34]

Laboratory variables in LIPID study, including liver function tests and creatine kinase levels associated with myopathy, were evaluated and were essentially similar in the two groups.[32]

In HPS, elevated CK 4-10 times of upper limit normal was seen in 0.19% in Simvastatin and 0.13% in placebo group CK levels more than 10 times of normal were seen in 0.11% in Simvastatin and .06% in placebo. Rhabdomylosis was diagnosed in .05% in Simvastatin and .03% in placebo group.[35]

Liver can be effected by statins. Effects can be asymptomation mild to marked rise of serum transaminase or frank jaundice. In majority of case the rise of enzyme is transitory and almost always reversible on discontinuation of therapy. Mild increase in transaminsase, time does not warrant cessation (2-4 upper limit of normal) of therapy. Close monitoring and reduction of dose is usually sufficient. If the rise is more than 4 times then the drugs should be stopped. A different statin at a lower dose may be reinitiated and the dose built up slowly.

Liver: Liver function should be monitored before treatment is started and periodically thereafter (eg, semiannually) for the first year of treatment or until 1 year after the last elevation in dose. Patients titrated to high dosage should receive an additional liver function test at 3 months. If serum transaminase levels rise, monitor more often; if they persist at three times the upper limit of normal, discontinue the drug.

The 12-month incidences of persistent hepatic transaminase elevations without regard to drug relationship were 2.1% (80 mg) and 0.9% (40 mg). No patients developed persistent liver function abnormalities following the initial 6 months of treatment at a given dose.[36] In 4S study 8 patients on Simvastatin (vs 5 on placebo) discontinued therapy because of elevated transaminases (6 were on Simvastatin 40 mg) The Simvastatin Survival Study (4S) was not designed to compare the relative safety of Simvastatin 40 mg and 20 mg. Patients were not randomized to 40 mg at the start of the study but were titrated to 40 mg if TOTAL-C was >200 mg/dL.[16-20] The number of patients in WOSCOPS reporting myalgia or elevated liver enzymes were also comparable between the two groups.[11,12] Laboratory variables, in LIPID study including liver function tests and creatine kinase levels associated with myopathy, were evaluated and were essentially similar in the two groups.[32] The AVERT study was evaluated for safety, and there was no clinically significant differences in other adverse events. A total of 2.4 percent of patients in the atorvastatin group had persistently elevated levels of aspartate aminotransferase and alanine aminotransferase compared with no patients in the angioplasty and usual care group.[34]

In HPS serum alamin transaminse was increased 2-4 fold of upper limit normal in 1.35% in Simvastatin group and 1.28% in placebo group. It was more than 4 folds increased so,[arab;u as 0.425 om Simvastatin and 0.3% om placebo group.[35]

Noncardiac mortality:

In earlier trials conducted, inspite of reduction in cholesterol and CAD, there was no definite decrease in mortality. Increase in mortality due to noncardiac causes was reported in patients on hypolipidaemic drugs.[37] This is for the first time that we have a very robust data showing definite decrease in mortality and morbidity. In WOSCOPS in the pravastatin group, 116 subjects had incident

cancers compared with 106 in the placebo group; the difference was not significant.[11,12] In CARE study the safety analysis demonstrated no increase in noncardiac mortality with lovastatin therapy.[28-30] The safety analysis revealed no statistically significant alteration in the number of deaths from noncardiovascular causes when the Simvastatin and placebo groups were compared. Specifically, there was no increase in the incidence of malignancies or violent deaths associated with hypolipidemic therapy that had been implicated in other epidemiological and intervention trials.[16-20] In LIPID study Pravastatin therapy did not result in an increase in noncardiac deaths, and there were actually fewer deaths from cancer, trauma, or suicide in the group randomized to drug therapy, although this did not achieve statistical significance The LIPID trial evaluated a number of safety parameters, including malignancy. A total of 403 primary cancers occurred in patients randomized to receive pravastatin compared with 417 cancers in the control group, indicating no increase in malignancy from statin therapy. Deaths from violent behavior, suicide, or accidents were also not increased in the treatment group.[32]

Discontinuation of therapy:

In 4S study the total frequency of adverse experience was similar within the treated and placebo group. A total of 6 percent of the patients, who were equally distributed in both active therapy and placebo, discontinued the study medication secondary to adverse events. 2.3% patients on 20 mg and 40 mg discontinued the therapy as against 2.6% patients on placebo.[16-20] In CARE study the discontinuation rate was similar in the placebo and lovastatin-treated groups.[28-30] In AVERT study seventeen serious adverse events were reported in the atorvastatin group, although none was attributed to atorvastatin. Twenty-eight of the patients in the angioplasty group had serious adverse events; six of these patients had events attributable to the angioplasty.[34]

Effectiveness and safety:

An average reduction of cholesterol by 40 mg/dl for about 05 years will result in reduction in non fatal myocardial infarction and coronary death by about 25%. The effects are seen for people with no evidence of CAD and having high or not so high cholesterol. The data is quite encouraging for patients with evidence of CAD and having high or normal levels of cholesterol.[36-45]

The side effects may sound alarming but are very rate and do not require very close monitoring in majority of patients: these side effects should not prevent the more side spread application of this date like "new aspirin".

ACC & AHA reassured patients about statin effectiveness and safety and declared.

"While statins like all other drugs have side effects the benefits of using statins to manage patients' cholesterol far outweighs the risk of serious side effects from their use We want to reassure patients that statins have proven to be safe and very effective drugs and we urge patients who are taking statins and have no side effects to continue taking the drug." Douglas P Zipes President ACC.

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