Results and Discussion
## Chapter 4 Results and Discussion

### Cardiovascular disease

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CHAPTER 4 RESULTS AND DISCUSSION

Cardiovascular disease

Modifiable and Non-modifiable risk factors

A number of nonlipid risk factors are associated with increased CHD risk and must be considered in preventive efforts. Some of these factors are modifiable and are appropriate targets for intervention efforts in themselves. Several fixed risk factors cannot be modified; their presence signals the need for more intensive lowering of LDL cholesterol. ATP I/II and other guidelines have advocated adjusting the intensity of LDL cholesterol therapy in the primary prevention setting according to the absolute risk for CHD. In addition, emerging risk factors promise to provide new insights into the atherosclerotic process and potentially refine risk assessment. Certainly not all of coronary risk can be explained by the major independent risk factors. Other risk factors, some of which are yet to be identified, undoubtedly influence risk independently of the major risk factors. Some of these other factors contributing to CHD risk include the life-habit risk factors (atherogenic diet, cigarette smoking, overweight/obesity and physical inactivity), diabetes, hypertension, age, male sex, emerging risk factors and genetic/racial/ethnic characteristics.

4.1. Non-modifiable risk factors

Between April 2005 to September 2007, 300 subjects with or without CVD and 100 subjects with or without stroke were enrolled. Clinical characteristics of study patients are given in Table 4.1. Table 4.1.1 shows non-modifiable risk factors and Table 4.1.2 shows modifiable risk factor. The characteristics are compared between groups I and group II/III/IV and V, group II and group III, and between group IV and group V. The patients were categorized under Group I included 58 males and 42 females with a mean age of 54.3±6.0. Group II included 63 males and 37 females with a mean age of 58.4±6.9 and in Group III included 68 males and 32 females with a mean age of 59.4±8.2. The mean age in group II (p< 0.001) and group III (p< 0.001) was higher in patients than the control, with statistically significant differences. In all groups (I, II and III) it was identified a predominantly male cohort 58%, 63% and 68% respectively.
Table 4.1 Clinical characteristics of the study subjects
(Cardiovascular disease)

Table 4.1.1 Non-modifiable risk factors

<table>
<thead>
<tr>
<th>Non-modifiable risk factors</th>
<th>Control (n=100) Group I</th>
<th>Test group (Untreated) (n=100) Group II</th>
<th>Test group (Treated) (n=100) Group III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>54.3±6.0</td>
<td>58.4±6.9</td>
<td>59.4±8.2</td>
</tr>
<tr>
<td>Elders ≥ 65 years (%)</td>
<td>4</td>
<td>15</td>
<td>21</td>
</tr>
<tr>
<td>Sex M/F</td>
<td>58/42</td>
<td>63/37</td>
<td>68/32</td>
</tr>
<tr>
<td>Family History of CHD (%)</td>
<td>Nil (0)</td>
<td>2</td>
<td>11</td>
</tr>
</tbody>
</table>

Table 4.1.2 Modifiable risk factors with treatment of study entry

<table>
<thead>
<tr>
<th>Modifiable risk factors</th>
<th>Test group (Untreated) (n=100) Group II</th>
<th>Test group (Treated) (n=100) Group III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Food Habit - Veg/Non-Veg (%)</td>
<td>91/9</td>
<td>93/7</td>
</tr>
<tr>
<td>Cigarette Smoking - Ever/Never (%)</td>
<td>21/79</td>
<td>48/52</td>
</tr>
<tr>
<td>Alcohol Consumption - Ever/Never (%)</td>
<td>9/91</td>
<td>10/90</td>
</tr>
<tr>
<td>BMI (%)</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Obesity (%)</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Physical Activity - Low or Lack (%)</td>
<td>72</td>
<td>87</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>20</td>
<td>22</td>
</tr>
<tr>
<td>Hypertension - SBP or DBP (%)</td>
<td>32</td>
<td>44</td>
</tr>
<tr>
<td>Hypercholesterolemia (%)</td>
<td>14</td>
<td>19</td>
</tr>
<tr>
<td>Hypertriglyceridemia (%)</td>
<td>33</td>
<td>38</td>
</tr>
<tr>
<td>Low - HDLcholesterolemia (%)</td>
<td>21</td>
<td>56</td>
</tr>
<tr>
<td>High - LDLcholesterolemia (%)</td>
<td>10</td>
<td>17</td>
</tr>
<tr>
<td>Atherogenic Dyslipidemia (%)</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Metabolic Syndrome (%)</td>
<td>3</td>
<td>17</td>
</tr>
<tr>
<td>Hyperurecemia (%)</td>
<td>3</td>
<td>21</td>
</tr>
<tr>
<td>Type A Personality (%) (n=25)</td>
<td>4 (16%)</td>
<td>--</td>
</tr>
</tbody>
</table>

Treatment of study entry

<table>
<thead>
<tr>
<th>Treatment of study entry</th>
<th>Test group (Untreated) (n=100) Group II</th>
<th>Test group (Treated) (n=100) Group III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoglycemic - Oral/Insulin</td>
<td>19/1</td>
<td>42/5</td>
</tr>
<tr>
<td>ACE inhibitor (%)</td>
<td>32</td>
<td>28</td>
</tr>
<tr>
<td>Antiplatelet Therapy (%)</td>
<td>1</td>
<td>18</td>
</tr>
<tr>
<td>β - Blocker (%)</td>
<td>Nil (0)</td>
<td>12</td>
</tr>
<tr>
<td>Nitrates (%)</td>
<td>Nil (0)</td>
<td>48</td>
</tr>
<tr>
<td>Heparin (%)</td>
<td>Nil (0)</td>
<td>26</td>
</tr>
<tr>
<td>Diuretics (%)</td>
<td>Nil (0)</td>
<td>9</td>
</tr>
<tr>
<td>Atorvastatin (%)</td>
<td>Nil (0)</td>
<td>Nil (0)</td>
</tr>
<tr>
<td>Other lipid lowering drugs (%)</td>
<td>2</td>
<td>54</td>
</tr>
</tbody>
</table>
In many epidemiologic surveys, age remains one of the strongest predictors of disease. The risk of cardiovascular events increases in the older. The percentage of the study population over 65 years was 4%, 15% and 21% in group I, II and III respectively. Familial history of CHD was found significantly higher in group III (11%) than group I and II (Table 4.1.1).

4.2.1. Age

Risk for coronary disease increases steeply with advancing age in men and women. More than half of those who have heart attacks are 65 years or older, and about four out of five who die of such attacks are over the age of 65. At any given level of LDL cholesterol, risk for CHD is higher in the older than in younger people (Wilson et al., 1998). The principal reason that risk rises with age is that age is a reflection of the progressive accumulation of coronary atherosclerosis, which in turn reflects the cumulative exposure to atherogenic risk factors, both known and unknown. On the average, older persons have more coronary atherosclerosis than do younger persons. Once atherosclerosis develops, the coronary plaque itself becomes a "risk factor" for the development of clinical CHD. This is because plaque ruptures produce acute coronary events (unstable angina or MI), or when plaques grow large, coronary obstructive symptoms (angina pectoris) occur. Recent clinical trials indicate that older persons benefit from LDL cholesterol lowering therapy similarly to middle-aged individuals (Grundy et al., 2002).

4.2.2. Male Sex

The rise in absolute risk with aging becomes most clinically significant in men in their mid-forties and in women about the time of the menopause. At any given age men are at greater risk for coronary disease than are women (Wilson et al., 1998). Risk in men lags about 10 to 15 years behind that of men. The reasons for a gender difference in CHD risk are not fully understood. Part of the difference can be explained by the earlier onset of risk factors in men, e.g., elevations of LDL cholesterol and BP, and lower HDL cholesterol. However, the FHS has shown that the differences in absolute risk between the sexes cannot be explained entirely by standard risk factors. Nonetheless,
women respond to LDL cholesterol lowering therapy with a reduction in RR, similar to men.

4.2.3. Family history of premature coronary heart disease

CHD tends to cluster in families, and a positive family history of premature CHD counts as a risk factor. Several prospective studies (Barrett-Connor and Khaw, 1984; Shea et al., 1984; Conroy et al., 1985; Hunt et al., 1986; Hopkins et al., 1988; Jorde and Williams, 1988; Colditz et al., 1991; Kekalainen et al., 1996; Eaton et al., 1996; Pankow et al., 1997; Bensen et al., 1999; Li et al., 2000; Williams et al., 2001) indicate that a family history of premature CHD is an independent risk factor even when other risk factors are taken into account. RR for CHD in first-degree relatives has been reported to range from two to as high as 12 times that of the general population (Slack, 1969; Phillips et al., 1974; Rissanen, 1979). Risk increases with the number of primary relatives affected and at younger ages of onset in the probands (Pohjola-Sintonen et al., 1998; Rissanen and Nikkila, 1977). The clustering of CHD risk in families most closely resembles diseases of polygenic origin and does not follow a Mendelian recessive or dominant pattern that suggests a single gene locus (Siegmund et al., 1998). Among primary relatives, it appears that siblings of probands have the highest RR, probably due to shared sociocultural environment, exposures, and genetics.

Many prospective cohort and case-control investigations, including the recent Atherosclerosis Risk In Communities Study (ARIC) in four United States communities, show this risk to be independent of known risk factors (Bensen et al., 1999). Many risk factors are under genetic control (e.g., BP, lipids and lipoproteins, Lp (a), and obesity), but they account for only a portion of the aggregation of CHD seen in families (Snowden et al., 1982; Khaw and Barrett-Connor, 1986). While family history is immutable, a large number of modifiable risk factors are found in people with a history of premature CHD in a first-degree relative (Becker et al., 1988; Becker et al., 1998). This has been demonstrated in both genders and in most races. The FHS family history analysis does not demonstrate sufficient incremental risk for family history to be included in risk assessment equations. Nonetheless, a body of compelling case-control and cohort studies has found family history to be independently associated with higher risk status.
The variance across studies depends on the way in which family history is assessed. In the National Heart, Lung, and Blood Institute (NHLBI) Family Heart Study and in the Newcastle Family History Study (NFHS), self-report of a family history of premature CHD in a first degree relative has been found to be reasonably accurate with sensitivity above 80 percent and specificity about 90 percent (Bensen et al., 1999; Silberberg et al., 1998; Silberberg et al., 1998).

Family history may be used as a tool to educate persons about their risk and encourage behaviours that can reduce the risk of CVD (Yoon et al., 2003; Hunt et al., 2003). Modifiable CVD risk factors include hypertension, hypercholesterolemia, physical inactivity, overweight/obesity, and tobacco use (Hahn et al., 1998; Goldstein et al., 2001; American Heart Association, 2003). Modification of these risk factors through changes in diet, increased physical activity, tobacco use cessation, and pharmacotherapy (when needed) can reduce CVD risk considerably for the majority of the population (Pearson et al., 2002). Persons who are at high risk for CVD because of inherited single-gene disorders such as familial hypercholesterolemia can be referred for extensive clinical evaluation and management.

4.3. Modifiable risk factors

Cardiovascular risk factors, including smoking, obesity, hypertension and diabetes had a higher prevalence in the CVD group than in control with a relatively high percentage of non-vegetarian (91%, 95% and 93% in group I, II and III respectively) and physical inactivity (72%, 85% and 87% in group I, II and III respectively).

Smoking was reported in 33.6% of the study population. It was significantly higher in group III (48%) than group II (32%) and group I (21). 16 participants in group I, 21 participants in group II and 9 participants in group III reported that they had stopped smoking (abstained for ≥5 years), and they were therefore considered nonsmokers. Of the participants, 9%, 12% and 10% (in group I, II and III respectively) reported that they were current consumers of alcoholic beverages. 12 participants in group I, 8 participants in group II and 14 participants in group III reported that they had stopped drinking alcohol (abstained for ≥5 years), and they were therefore considered
nondrinkers. Obesity (BMI ≥30 kg/m²) was found in 5.3% of the study population. It was significantly higher in group III (8%) and in group II (6%) than group I (2%) (Table 4.1.2).

Of the people examined, 32% in group I, 44% in group II and 49% in group III had BP levels of 140 or 90 or higher. The prevalence of hypertension was higher in group III than the other groups. The mean DBP was significantly higher in group III (p< 0.02) and group II (p< 0.07) than the group I. There was no statistically significant difference between group II and group III. The mean SBP was significantly higher in group III (p< 0.03) than the group I and there were no significant different between group I and group II and group II and group III. The occurrence of hypertension was significantly higher in people aged 50 years and over in group I (90.6%), group II (88.8%) and group III (89.7%). In all groups (I, II and III) it was identified a predominantly male cohort 59.3%, 56.8% and 75.5% respectively. History of diabetes was found in 29.6% of the study population. It was significantly higher for group III (47%) (p< 0.001) than for both group I (20%) and group II (22%). The occurrence of diabetes was significantly higher in people aged 50 years and over in group I (28%), group II (25%) and group III (51%). There was no statistically significant difference between group I and group II. Diabetic participants had a higher prevalence of CVD at baseline. Diabetic participants also had a higher prevalence of hypertension by history (Table 4.1.2). The RR for the incidence of hypertension and diabetes in the present study were found to be 1.53 (95% CI 1.08 to 2.17) and 2.35 (1.50 to 3.66) respectively.

4.3.1. Atherogenic diet

Prospective studies in populations show that dietary patterns modify the baseline CHD risk of populations (U.S. Department of Health and Human Services, 2000; Krauss et al., 2000). In high-risk populations, some of the adverse effects of diet composition undoubtedly relate to established risk factors, e.g., effects of high intakes of saturated fatty acids and cholesterol on LDL cholesterol levels and of high salt intakes on BP. Moreover, dietary patterns appear to influence baseline risk beyond the known risk factors. For example, populations that consume diets high in fruits, vegetables, whole grains, and unsaturated fatty acids appear to be at a lower baseline risk than can
be explained by standard risk factors. The particular nutrients that impart this lower risk have not been adequately defined, but strong candidates include antioxidant nutrients, folic acid, other B-vitamins, omega-3 fatty acids, and other micronutrients (Krauss et al., 2000).

4.3.2. Cigarette smoking

Cigarette smoking has been established as a powerful contributor to risk for CHD and other forms of CVD (Doll and Peto, 1976; Doll et al., 1980; Willett et al., 1987; Colditz et al., 1988; Wolf et al., 1988; U.S. Department of Health and Human Services, 1989; LaCroix et al., 1991; McBride, 1992; Jonas et al., 1992; Pyorala et al., 1994). The relationship of smoking to CVD risk is dose dependent and observed in men and women. Observational data suggest that smoking cessation reduces the risk for CVD events and that the decline in risk begins within months after quitting (U.S. Department of Health and Human Services, 1990). Randomized clinical trials of smoking cessation in primary prevention settings have revealed substantial reductions in risk for cardiac events in those who quit (Hjermann et al., 1981; Rose et al., 1982; Multiple Risk Factor Intervention Trial Research Group, 1982). Cigarette smoking features prominently in the risk assessment component of ATP III because of the CVD risks associated with it and the substantial benefits to be derived from smoking cessation. Moreover, smokers benefit as much, if not more, from LDL cholesterol lowering therapy, as do nonsmokers.

4.3.3. Overweight/Obesity

An estimated 97 million adults in the United States are overweight or obese. Obesity is defined as a BMI (weight in kg divided by the square of height in meters) of ≥30 kg/m² and overweight as 25-29.9 kg/m² (National Institutes of Health, 1998; National Institutes of Health, 1998). Although some people classified as overweight actually have a large muscle mass, most persons with BMIs of 25 to 29.9 kg/m² have excess body fat. Overweight and obesity not only predispose to CHD, stroke, and numerous other conditions, they also are associated with a greater all-cause mortality (Hubert et al., 1983; Wilcosky et al., 1990; Manson et al., 1990; Calle et al., 1999). People who are overweight or obese have a high burden of other CHD risk factors including
dyslipidemia (high LDL cholesterol, low HDL cholesterol, and high VLDL cholesterol and TG) (Denke et al., 1993; Denke et al., 1994; Olefsky et al., 1974; Grundy et al., 1979; Garrison et al., 1980), type 2 diabetes (Hartz et al., 1983; Stern et al., 1986) and hypertension (Berchtold et al., 1981; Berchtold et al., 1981; Blair et al., 1984). Obese individuals who do not yet have these risk factors are at increased risk for developing them.

The FHS confirms that obesity is strongly predictive of CHD. Risk for CVD is particularly raised when abdominal obesity is present; abdominal obesity is defined by a waist circumference greater than 102 cm (40 inches) in men or 88 cm (35 inches) in women (National Institutes of Health, 1998; National Institutes of Health, 1998). Despite the strong association between various indicators of obesity and risk for CHD, ATP III does not list obesity among the risk factors that modify the treatment goals for LDL cholesterol. Much of the risk associated with overweight and obesity appears to be mediated through the major risk factors. The independent component of risk has not been quantified. Furthermore, the prevalence of overweight and obesity in the United States population is so high that counting them as risk factors to modify LDL cholesterol goals would enormously expand the population having multiple risk factors, causing an even greater increase in usage of LDL cholesterol lowering drugs than will result from the intensified management of persons with multiple risk factors outlined in ATP III. Instead, ATP III identifies overweight and obesity as direct targets of weight-reduction intervention; this approach will achieve more overall risk reduction than will LDL cholesterol lowering without an emphasis on weight control.

4.3.4. Physical inactivity

Physical inactivity is associated with increased risk for CHD. Conversely, physical activity favorably modifies several risk factors; it has been reported to lower LDL cholesterol and TG levels, raise HDL cholesterol, improve insulin sensitivity, and lower BP (Blair et al., 1983; King and Kriska, 1992; Helmrich et al., 1991; Haskell et al., 1994). Evidence that physical activity can reduce risk for CHD comes from multiple observational studies (Leon et al., 1987; Ekelund et al., 1988; Blair et al., 1989; Morris et al., 1990; Sandvik et al., 1993; Paffenbarger et al., 1993). Therefore, physical inactivity is
widely designated to be a major risk factor for CHD (National Cholesterol Education Program, 1993; National Cholesterol Education Program, 1994; Fletcher et al., 1996; U.S. Department of Health and Human Services, 1996). In ATP III, physical inactivity also is listed as a major modifiable risk factor.

The mechanisms whereby physical inactivity raises risk for CHD are not fully understood and are probably multifactorial. Physical inactivity reduces caloric expenditure and probably contributes to obesity and to its associated lipid and nonlipid risk factors (Grundy et al., 1999), as well as to insulin resistance (Perseghin et al., 1996). Beyond its effects on standard risk factors, physical inactivity may have adverse effects on cardiovascular fitness and function.

Many of the adverse effects of a sedentary lifestyle that raise CHD risk can be inferred from the actions of increased physical activity, which include reduction in insulin resistance, lowering of BP, reducing serum TG, raising HDL cholesterol, and improving cardiovascular risk (U.S. Department of Health and Human Services, 1996). Although ATP III specifies physical inactivity as a major modifiable risk factor, it does not list it as a risk factor that modifies LDL cholesterol goals. Because of the collinearity of physical inactivity with other independent risk factors, there is some confounding between physical inactivity and the risk factors that modify LDL cholesterol goals.

Nonetheless, physical inactivity is designated as a major target of intervention for therapeutic lifestyle changes. Undoubtedly some of the benefit of increased physical activity is mediated through mechanisms other than the measured risk factors. In addition, after setting LDL cholesterol goals with standard risk factors, a physician can take into account a person's levels of physical activity and fitness when adjusting the intensity of LDL cholesterol lowering therapy.

It has been suggested that a history of regular physical activity should count as a "negative risk factor," similarly to high HDL cholesterol. Although regular physical activity undoubtedly reduces baseline risk for CHD and should be encouraged, ATP III does not specifically count it as a negative risk factor for setting the goal level for LDL cholesterol.
4.3.5. Hypertension

The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High BP (JNC VI) (Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, 1997) defines categorical hypertension as a BP ≥140 mmHg systolic or ≥90 mmHg diastolic or current use of antihypertensive medication. Numerous observational studies have demonstrated unequivocally a powerful association of high BP with risk for CHD (MacMahon et al., 1990; Selmer, 1992; Stamler et al., 1993; Staessen et al., 1997; Franklin et al., 1999; van den Hoogen et al., 2000). This association holds for men and women and younger and older persons. Even below categorical hypertension, subjects with high-normal BP (130-139 mmHg systolic and/or 85-89 mmHg diastolic) are at increased risk for CHD compared with those with optimal values (Rodgers and MacMahon, 1999; Vasan et al., 1999).

Clinical trials have established that BP reduction in people with hypertension reduces risk for a variety of BP-related endpoints including CHD (Cutler et al., 1995). This is true even for older people with isolated systolic hypertension (SHEP Cooperative Research Group, 1991; Staessen et al., 1997). Following the approach taken in ATP II, (National Cholesterol Education Program, 1993; National Cholesterol Education Program, 1994), JNC VI (Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, 1997) employed the level of BP and the concomitant presence of risk factors, coexisting CVD, or evidence of target-organ damage to classify BP severity and to guide treatment. Hypertension and high serum cholesterol often occur concomitantly (Working Group Report on Management of Patients with Hypertension and High Blood Cholesterol, 1990; Working Group Report on Management of Patients with Hypertension and High Blood Cholesterol, 1991; Meigs et al., 1997).

4.3.6. Diabetes

Diabetes is defined as fasting blood glucose of 126 mg/dL or greater (Gavin et al., 1998). Risk for all forms of CVD, including CHD is increased substantially with type 1 and type 2 diabetes mellitus (Kannel and McGee, 1979; Kannel and McGee, 1979;
Wingard and Barrett-Connor, 1995; Pyorala et al., 1987; Bierman, 1992). Furthermore, the mortality rate in diabetic subjects who have experienced CHD is much higher than in non-diabetic subjects (Abbott et al., 1988; Herlitz et al., 1992; Miettinen et al., 1998). The increase in risk attributed to hyperglycemia per se is independent of the overweight/obesity and dyslipidemia commonly observed in persons with diabetes. Tighter glycemic control reduces risk for microvascular complications of diabetes such as renal impairment and retinopathy. Thus far, however, improved glucose control in diabetic people has not been definitively shown to reduce macrovascular disease (CHD), although a trend toward benefit has been observed (Diabetes Control and Complications Trial Research Group, 1993; UK Prospective Diabetes Study Group, 1998; UK Prospective Diabetes Study Group, 1998).

Importantly, management of other risk factors effectively reduces the incidence of major coronary events in persons with diabetes. This has been shown for tight BP control (UK Prospective Diabetes Study Group, 1998; UK Prospective Diabetes Study Group, 1998). Analyses of diabetic subgroups within large placebo-controlled trials of cholesterol- and TG-lowering therapy have indicated that the benefits of treatment are comparable among diabetics and non-diabetics (Koskinen et al., 1992; Pyorala et al., 1997; Goldberg et al., 1998; Long-Term Intervention with Pravastatin in Ischaemic Disease Study Group, 1998; Downs et al., 1998; Hoogwerf et al., 1999; Haffner et al., 1999). A growing body of literature reveals that higher-risk people with diabetes carry an absolute risk for major coronary events similar to that of non-diabetic people with established CHD (Haffner et al., 1998; Haffner et al., 2000; Malmberg et al., 2000; Hu et al., 2000). Although some populations with diabetes do not reach this risk level (Simons and Simons, 1998), the very high morbidity and mortality after onset of CHD makes it appropriate to place most people with diabetes in a separate category of risk.

From the studied parameter such as, age, male sex, family history of CHD, atherogenic diet, cigarette smoking, obesity, physical inactivity, hypertension and diabetes were positively associated with CVD. In particular age, male sex, atherogenic diet, cigarette smoking, physical inactivity, hypertension and diabetes are proven as risk factor in CVD.
4.4. High sensitivity C-reactive protein

Table 4.2 summarizes the biochemical parameters examined in serum samples of all patients divided according to the groups. Although debate persists regarding the precise physiologic role of hsCRP, the prognostic value of hsCRP as a marker of cardiovascular risk is now firmly established. HsCRP predicts future cardiovascular risk in a wide variety of clinical populations, including healthy individuals without CVD, patients presenting with ACS, patients with stable angina or in the stable phase after MI, and patients with the metabolic syndrome, diabetes, or renal disease. The patients had significant higher concentration of mean hsCRP levels in group III (p<0.001) and group II (p< 0.05) when compare with the healthy control (group I). There was also a significant difference between group I and group II (p< 0.001). The mean values of group I was found to be 0.9±0.5, in group II 1.0±0.9 and in group III 1.9±1.1 (Table 4.2).

Prospective epidemiologic studies with follow-up periods ranging from 3 to 20 years have found that a single hsCRP measurement is a strong predictor of MI or CHD mortality (Kuller et al., 1996; Ridker et al., 1997; Tracy et al., 1997; Ridker et al., 1998; Koenig et al., 1999; Danesh et al., 2000; Mendall et al., 2000; Roivainen et al., 2000; Ridker et al., 2000; Ridker et al., 2000; Packard et al., 2000; Lowe et al., 2001; Park et al., 2002; Folsom et al., 2002; Ridker et al., 2002; Pradhan et al., 2002; Rifai et al., 2002; Sakkinen et al., 2002; Witherell et al., 2003; Van der Meer et al., 2003) stroke (Ridker et al., 1997; Ridker et al., 1998; Gussekloo et al., 2000; Ridker et al., 2000; Rost et al., 2001; Rifai et al., 2002; Ridker et al., 2002; Curb et al., 2003; Cao et al., 2003) PVD (Ridker et al., 1998; Ridker et al., 2001) CHF (Vasan et al., 2003; Cesari et al., 2003) atrial fibrillation, (Aviles et al., 2003) and sudden cardiac death (Albert et al., 2002) in individual without a history of CVD. Taken in the aggregate, epidemiologic studies indicate that participants with baseline hsCRP levels in the top quartile of the sample distribution are 2 to 3 times more likely to have a future vascular event than are those in the bottom hsCRP quartile. In most instances, the association between hsCRP and subsequent vascular events exhibits a linear “dose-response” shape and is independent of age, smoking, hypertension, dyslipidemia, and diabetes, the traditional risk factors evaluated in daily practice and included in global cardiovascular prediction algorithms such as that derived from the FHS.
Table 4.2 Baseline mean levels of the biochemical parameters examined in serum samples of all patients

<table>
<thead>
<tr>
<th>Nonlipid risk factors/risk markers</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (n = 20)</td>
<td>23.5±2.7</td>
<td>24.6±3.4</td>
<td>26.4±4.3</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>123.5±11.3</td>
<td>126.0±14.1</td>
<td>127.3±14.7</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>81.8±7.8</td>
<td>83.9±8.9</td>
<td>84.4±8.9</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>0.9±0.5</td>
<td>1.0±0.9</td>
<td>1.9±1.1</td>
</tr>
<tr>
<td>Apolipoprotein AI</td>
<td>72.0±40.6</td>
<td>77.0±17.1</td>
<td>85.9±18.6</td>
</tr>
<tr>
<td>Apolipoprotein B</td>
<td>54.6±15.9</td>
<td>78.2±21.7</td>
<td>64.5±14.3</td>
</tr>
<tr>
<td>Uric acid</td>
<td>4.5±1.0</td>
<td>5.4±1.4</td>
<td>6.0±1.4</td>
</tr>
<tr>
<td>Glucose</td>
<td>111.6±18.1</td>
<td>112.8±35.52</td>
<td>134.6±46.8</td>
</tr>
</tbody>
</table>

Lipid risk factors

| Total Cholesterol                | 165.3±29.9    | 170.2±33.72   | 202.0±41.4     |
| Triglycerides                    | 140.4±67.3    | 149.5±75.0    | 175.6±86.2     |
| High-density lipoprotein cholesterol | 42.1±8.3     | 38.4±6.5      | 36.9±6.1       |
| Low-density lipoprotein cholesterol | 95.2±25.6    | 102.0±28.7    | 137.4±41.9     |
| Very Low-density lipoprotein cholesterol | 28.2±13.7    | 29.8±14.9     | 35.1±16.9      |
| Non-HDL cholesterol              | 123.3±27.1    | 131.8±31.5    | 164.9±39.9     |
For example, 8-year follow-up data from 2 large primary prevention cohorts, the PHS and the WHS, indicate that, after adjustment for traditional risk factors, for each quintile increase in baseline hsCRP, the risk of a future cardiovascular event increases by 26% for men (Ridker et al., 1997) and 33% for women (Ridker et al., 2000). A meta-analysis of 14 prospective long-term studies (2,557 cases; mean age at baseline, 58 years; mean follow-up, 8 years) of hsCRP and risk of nonfatal MI or CHD death yielded an adjusted summary RR of 1.9 for individuals in the top tertile of baseline hsCRP as compared with those in the bottom tertile (Danesh et al., 2000).

The association between hsCRP and CVD has been observed in the United States and Europe, in the middle-aged and elderly, and in high and usual-risk populations. The association is apparent even in studies with follow-up periods exceeding 10 years. For example, elevated hsCRP levels at baseline were predictive of 17-year coronary mortality in the MRFIT (Kuller et al., 1996) and of sudden cardiac death in the PHS (Albert et al., 2002). Among Japanese-American men participating in the Honolulu Heart Program (HHP) hsCRP was a strong predictor of MI (Sakkinen et al., 2002) and thromboembolic stroke (Curb et al., 2003) up to 20 years after initial blood samples had been drawn. However, the HHP is 1 of only a handful of studies of nonwhite populations; data on the predictive utility of hsCRP in such populations are sparse. Much of the available data on hsCRP and incident CVD have been derived from nested case-control studies, which permit estimation of RRs of disease but not of absolute risks within risk factor strata. However, event-free survival data from several large cohorts, including the WHS, (Ridker et al., 2002) the AFCAPS/TexCAPS, (Ridker et al., 2001) the multiethnic ARIC study in the United States, (Ballantyne et al., 2004) and the MONitoring of trends and determinants in CArdiovascular disease (MONICA) Augsburg study in Europe, (Koeing et al., 2004) have recently become available, allowing a straightforward interpretation of hsCRP levels in terms of population-based quintiles or simple cut points.

The latter approach, in which hsCRP levels of less than 1, 1 to 3, and greater than 3 mg/L represent low-, moderate-, and high-risk groups, respectively, provides comparable predictive utility as the former approach and has greater clinical appeal.
Data from the WHS also confirm previous work from the PHS (Ridker et al., 1998) and AFCAPS/TexCAPS (Ridker et al., 2001) demonstrating that hsCRP levels clearly add to the predictive value of cholesterol screening. Ridker et al., (2002) survival data shows that for participants with LDL cholesterol above or below the study median of 124 mg/dL and hsCRP above or below the study median of 1.52 mg/L (Ridker et al., 2002). As expected, event-free survival was poorest for persons with elevations in both LDL cholesterol and hsCRP, and the best survival was observed for those with low values on both tests. Women with an elevated reading on one test but not the other had an intermediate risk. However, contrary to many clinicians' expectations, event-free survival was significantly worse for those with high hsCRP and low LDL cholesterol as compared with those with high LDL cholesterol and low hsCRP. HsCRP levels minimally correlate with lipid levels, and it is not possible to predict hsCRP levels from knowledge of levels of TC, HDL cholesterol, or LDL cholesterol.

In assessments of more than 25,000 patients, lipid parameters accounted for less than 3% to 5% of the variance in hsCRP (Ridker et al., 2001; Albert et al., 2001; Bermudez et al., 2002; Ridker et al., 2002). Moreover, in a recent cross-sectional survey of 1,600 individuals without CVD, hsCRP level was only modestly correlated with the 10-year Framingham CHD risk score (Albert et al., 2003). Thus, hsCRP measurement does not replace but rather complements the evaluation of lipids and other classic coronary risk factors. Support for the utility of hsCRP testing as an adjunct in CHD risk assessment in primary prevention settings has been demonstrated in many investigations (Ridker et al., 1998; 2000; 2001; 2002; Ridker, 2001).

For example, data from the WHS indicate that hsCRP, trichotomized as less than 1, 1 to 3, and greater than 3 mg/L, not only adds prognostic information at all levels of risk defined by current LDL cut points of the NCEP (Expert panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001) but also at all levels of risk specified by the Framingham algorithm (Ridker et al., 2002). These striking additive effects of hsCRP beyond the traditional Framingham risk score have been confirmed in the ARIC (Ballantyne et al., 2004) and MONICA Augsburg (Koeing et al., 2004) cohorts.
The predictive value of hsCRP is also an additive to that of the metabolic syndrome (Sattar et al., 2003; Ridker et al., 2004) hypertension, (Blake et al., 2003) and various markers of subclinical atherosclerosis (Park et al., 2002; Cao et al., 2003). Results from a very recent study of more than 6,400 men and women from Iceland further highlight the clinical utility of hsCRP as an independent predictor of risk (Danesh et al., 2004). In this 20-year investigation, baseline levels of hsCRP were associated with an approximate 50% increase in future vascular risk not only after adjustment for traditional risk factors included in the Framingham risk score but also after further simultaneous control for diabetes, TG, BMI, and indices of pulmonary function (hsCRP ≥2.0 mg/L vs. <0.78 mg/L). Moreover, in the first 10 years of follow-up, an even higher overall risk estimate was observed. These data demonstrate the clinical utility of hsCRP in a population that is relatively hyperlipidemic in comparison to available United States cohorts. It should be noted that the reported RRs from Iceland were calculated using a hsCRP cut point of 2.0 mg/L rather than 3.0 mg/L and thus likely underestimate the predictive ability of hsCRP. Even so, the prognostic utility of hsCRP in these data was virtually identical to that of high BP and statistically similar to that of smoking. Although clinical interpretation of hsCRP is best performed by using ranges of less than 1, 1 to 3, and greater than 3 mg/L, recent data from the WHS indicate that the cardiovascular risk gradient is continuous across the full spectrum of measurable hsCRP levels. That is, the absolute risk of CVD is extremely low for those 10% to 15% of individuals with hsCRP levels below 0.5 mg/L, and the risk continues to increase as hsCRP levels exceed 10 or even 20 mg/L (Ridker and Cook, 2004). Thus, contrary to early expectations, markedly elevated levels of hsCRP do not appear to be false-positive readings attributable to an acute-phase response. Rather, chronic elevations of hsCRP above 10 mg/L are indicative of very high cardiovascular risk.

4.4.1. High-sensitivity C-reactive protein, metabolic syndrome, diabetes, hypertension, atherogenic dyslipidemia and cardiovascular disease

As shown in Table 4.3 the prevalence of higher levels of hsCRP was found in patients with metabolic syndrome, diabetes, hypertension, atherogenic dyslipidemia and CVD.
Table 4.3 Percentage of high-sensitivity C-reactive protein among individuals with the metabolic syndrome, diabetes, hypertension, atherogenic dyslipidemia and cardiovascular disease

<table>
<thead>
<tr>
<th></th>
<th>HsCRP (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group I</td>
</tr>
<tr>
<td>Metabolic Syndrome</td>
<td>33</td>
</tr>
<tr>
<td>Diabetes</td>
<td>40</td>
</tr>
<tr>
<td>Hypertension</td>
<td>44</td>
</tr>
<tr>
<td>Atherogenic Dyslipidemia</td>
<td>Nil (0)</td>
</tr>
<tr>
<td>Cardiovascular Disease</td>
<td>Nil (0)</td>
</tr>
</tbody>
</table>
The prevalence of hsCRP in patients suffered from metabolic syndrome in group I (33%), in group II (41%) and in group II (81%). The percentage of hsCRP in diabetic patients found to be in group I (40%), in group II (55%) and in group II (85%). The occurrence of hsCRP in hypertension found to be in group I (44%), in group II (35%) and in group II (93%). The percentage of hsCRP in atherogenic dyslipidemic patients found to be in group II (80%) and in group II (76%). The prevalence of hsCRP in patients with CVD found to be in group II (41%) and in group III (76%).

4.4.1.1. High-sensitivity C-reactive protein and metabolic syndrome

That hsCRP evaluation is a valuable addition to LDL cholesterol for risk assessment may partly reflect the fact that inflammation, in contrast to LDL cholesterol, plays a key role in processes associated with the metabolic syndrome, a condition that confers increased cardiovascular risk (Lakka et al., 2002). HsCRP levels are positively correlated not only with components of the syndrome that are commonly assessed in clinical practice, such as elevated TG, low HDL cholesterol, obesity, high BP, and high fasting glucose, but also with other components that are not easily captured in such settings, such as fasting insulin, microalbuminuria, and impaired fibrinolysis. Among participants without diabetes in the WHS, hsCRP and BMI were the only independent correlates of fasting insulin level modeled as a continuous dependent variable. After adjustment for BMI and other risk factors for diabetes, the RR for elevated fasting insulin increased with tertile of hsCRP (Pradhan et al., 2003). These associations were observed among both lean and overweight women. Whether knowledge of hsCRP status improves cardiovascular risk prediction beyond that of the metabolic syndrome status as assessed in clinical practice was also tested in the WHS (Ridker et al., 2003).

HsCRP levels of below 1, 1 to 3, and above 3 mg/L successfully differentiated women with the metabolic syndrome into low-, moderate-, and high-risk groups. In analyses directly comparing the predictive ability of hsCRP alone (≥3 vs <3 mg/L) with that of the metabolic syndrome alone, the areas under the receiver operating characteristic curve were 0.77 for hsCRP and 0.78 for the metabolic syndrome, indicating that the 2 variables are equally useful for cardiovascular risk assessment. However, as with LDL cholesterol and the Framingham risk score, the addition of hsCRP to the
traditional definition of the metabolic syndrome provided the best predictive algorithm. A similar pattern of results was observed in the WOSCOPS, which followed 6,447 middle-aged men for 5 years (Sattar et al., 2003) hsCRP, coded as \( \geq 3 \) mg/L versus \(< 3 \) mg/L, was strongly predictive of incident CHD after stratification by metabolic syndrome status. Among men in the “low- hsCRP/metabolic syndrome absent”, “high- hsCRP/metabolic syndrome absent”, “low- hsCRP/metabolic syndrome present”, and “high- hsCRP/metabolic syndrome present” groups, the RRs for incident CHD were 1.0 (referent), 1.6, 1.6, and 2.75, respectively.

4.4.1.2. High-sensitivity C-reactive protein and diabetes

Elevated hsCRP levels have also been implicated in the development of type 2 diabetes mellitus, a powerful risk factor for CVD. Prospective studies have found strong, graded relations between hsCRP and incident diabetes, which in many instances persisted after adjustment for BMI and other covariates. In the West of Scotland Coronary Prevention Study (WOSCOPS), the top quintile of hsCRP was associated with a 3-fold risk of incident diabetes over a 5-year period (hsCRP \( > 4.18 \) mg/L vs \( \leq 0.66 \) mg/L), (Freeman et al., 2002) and hsCRP remained significantly predictive after stratification by metabolic syndrome status. Among men in the “low- hsCRP/metabolic syndrome absent”, “high- hsCRP/metabolic syndrome absent”, “low- hsCRP/metabolic syndrome present”, and “high- hsCRP/metabolic syndrome present” groups, the RRs for incident diabetes were 1.0 (referent), 1.8, 3.6, and 5.3, respectively (Sattar et al., 2003).

In the WHS, women in the top quartile of the hsCRP distribution were more than 4 times as likely to develop diabetes than were women in the bottom quartile during 4 years of follow-up (hsCRP \( > 6.1 \) vs \(< 1 \) mg/L) (Pradhan et al., 2001). Among 5,888 participants 65 years or older in the CHS, the extreme hsCRP quartile comparison showed a near doubling of risk over 4 years (hsCRP \( > 2.86 \) mg/L vs \(< 0.82 \) mg/L) (Barzilay et al., 2001). In contrast, despite strong age-adjusted associations between hsCRP and incident diabetes in the 7-year MONICA Augsburg study of 2,052 middle aged men (Thorand et al., 2003) and the 5-year Insulin Resistance Atherosclerosis Study (IRAS) (Festa et al., 2002) of 1,047 middle-aged men and women, hsCRP was no longer predictive of diabetes in these 2 cohorts after factoring out the effects of BMI.
Nevertheless, these data, taken as a whole, support the hypothesis that inflammation, atherothrombosis, and diabetes are tightly interrelated disorders of the innate immune system.

4.4.1.3. High-sensitivity C-reactive protein and hypertension

Accumulating data also suggest a link between BP and vascular inflammation, perhaps mediated by angiotensin II (Libby, 2001). For example, angiotensin II infusion activates NF-k B, leads to increased IL-6 expression in human VSMCs (Kranzhofer et al., 1999) and appears to induce aortic accumulation of vascular adhesion molecule mRNA in animal models (Tummala et al., 1999). Further, inflammatory macrophages and CD4+ and CD8+ lymphocytes accumulate preferentially within the arterial wall of hypertensive as compared with normotensive rats (Nicoletti et al., 1996). In humans, cross-sectional studies also demonstrate graded linear relations between IL-6 and ICAM-1 and both SBP and DSP (Chae et al., 2001). Recent studies indicate that these relations may also be mediated by hsCRP. The relation among BP, hsCRP, and incident cardiovascular events was examined in the WHS (Blake et al., 2003). In cross-sectional analysis, median hsCRP levels for women with BPs below 120/75, 120 to 129/75 to 84, 130 to 139/85 to 89, 140 to 159/90 to 94, and 160/95 mm Hg or above were 0.96, 1.42, 2.20, 2.82, and 3.34 mg/L, respectively.

Despite their strong correlation, hsCRP and BP were independent determinants of future cardiovascular events during an 8-year follow-up period, and hsCRP retained incremental prognostic value at all levels of BP. Compared with women with BPs below 120/75 mm Hg and hsCRP levels below 3 mg/L, women with BPs of 160/95 mm Hg or higher and hsCRP levels of 3 mg/L or higher were more than 8 times as likely to have a future cardiovascular event. When participants were categorized into 4 groups on the basis of hsCRP (<3 vs ≥3 mg/L) and BP level (<130/85 vs ≥130/85 mm Hg), the adjusted RRs were 1.0 (referent) for low hsCRP/low BP, 1.87 for high hsCRP/low BP, 2.54 for low hsCRP/high BP, and 3.27 for high hsCRP/high BP. HsCRP also predicts incident hypertension. In the WHS, after adjustment for multiple potential confounders, the RRs of incident hypertension for increasing hsCRP quintiles were 1.00 (referent), 1.07, 1.17, 1.30, and 1.52, respectively (Sesso et al., 2003). Moreover, an elevated hsCRP level was
associated with an increased risk of incident hypertension at all baseline BPs and among individuals without traditional coronary risk factors.

### 4.4.1.4. High-sensitivity C-reactive protein, atherogenic dyslipidemia and cardiovascular disease

HsCRP is predictive of recurrent vascular events and death among patients with ACS (Liuzzo et al., 1994; Haverkate et al., 1997; Toss et al., 1997; Morrow et al., 1998; Biasucci et al., 1999; Tommasi et al., 1999; Heeschen et al., 2000; Lindahl et al., 2000; Kennon et al., 2001;) or stroke (Di Napoli and Papa, 2002) among patients in the stable phase after MI (Ridker et al., 1998; Retterstol et al., 2002) and among patients with documented CAD (Tracy et al., 1997; Anderson et al., 2000; Zebrack et al., 2002). An elevated preprocedural hsCRP also portends a worse prognosis among patients undergoing percutaneous transluminal coronary angioplasty (PTCA) (Buffon et al., 1999; Walter et al., 2001; Chew et al., 2001; Walter et al., 2001; Mueller et al., 2002; de Winter et al., 2003) coronary artery bypass grafting (Milazzo et al., 1999) and coronary artery stenting (Gaspardone et al., 1998; Dibra et al., 2003).

A seminal study by Liuzzo et al., (1994) found that patients presenting with unstable angina and elevated plasma levels of hsCRP and SAA had a higher rate of adverse coronary outcomes than did patients without elevated levels of inflammatory markers, even in the absence of troponin elevation. Data from the Thrombolysis In Myocardial Infarction (TIMI) investigators indicate that the increased cardiac risk associated with high hsCRP levels may be evident as soon as 14 days after presentation with an ACS (Morrow et al., 1998). The Chimeric c7E3 AntiPlatelet Therapy in Unstable angina REfractory to standard treatment (CAPTURE) trial of the glycoprotein IIa/IIb inhibitor abciximab found that, although not predictive in the initial 72-hour period, hsCRP predicted risk of mortality or MI at 6 months (Heeschen et al., 2000) and at 4 years (Lenderink et al., 2003). Among patients in the FRagmin during InStability in Coronary artery disease (FRISC) trial of low-molecular weight heparin, the risk associated with elevated hsCRP levels at the time of the index event (unstable angina in 61% and MI in 39% of participants) continued to increase during a 3-year follow-up period (Lindahl et al., 2000). To assess the clinical utility of testing for hsCRP among
patients with ACS, it is necessary to evaluate the predictive value of hsCRP in relation to established biochemical markers of MI.

In the TIMI, CAPTURE, and FRISC studies, the predictive value of hsCRP was shown to be independent of, and additive to, troponin. Thus, hsCRP has prognostic value even in patients without evidence of myocyte necrosis. A multimarker approach using hsCRP, troponin I, and B-type natriuretic peptide has been shown to improve risk prediction in patients with ACS (Sabatine et al., 2002). Among 450 patients in the TIMI trial who were categorized on the basis of the number of elevated biomarkers at presentation, there was a near doubling of the 30-day mortality risk for each additional biomarker that was elevated. Similar relations also existed for the endpoints of MI and CHF, and for the composite of the 3 outcomes, at 30 days and at 10 months. In a validation cohort, the number of elevated biomarkers remained a significant predictor of the composite outcome; after adjustment for confounders, compared with those with no elevated biomarkers, patients with 1, 2, and 3 elevated biomarkers had 2.1, 3.1, and 3.7 times the risk, respectively, of experiencing the composite endpoint by 6 months.

Evidence that hsCRP is a predictor of adverse events in the stable phase after MI is less consistent than evidence of its prognostic ability in primary prevention or in acute coronary settings (Blake and Ridker, 2002). In the CARE secondary prevention trial of pravastatin, patients with elevated hsCRP levels at 3 to 20 months after the index MI were at higher risk of recurrent events during the 5-year follow-up period (Ridker et al., 1998). A Norwegian study of 247 patients with premature MI also found hsCRP to be a strong predictor of future coronary death (Retterstol et al., 2002). In this cohort, the 10 year RR of cardiac mortality doubled with increasing hsCRP quartiles; patients in the top quartile had 6 times the risk of cardiac death than did patients in the bottom quartile. Adjustment for age, left ventricular ejection fraction, serum TC, fibrinogen, smoking, and hypertension somewhat attenuated but did not eliminate the association. In contrast, the THROMBOgenic risk factor study, which followed 1,045 patients for 2 years, found that, although hsCRP levels measured 2 months after the index MI significantly predicted the risk of recurrent coronary events in crude analysis, the association was no longer significant after adjustment for ejection fraction and the
presence of pulmonary congestion (Harb et al., 2002). In this study, there was also almost no predictive value for LDL cholesterol. In a recent cross-sectional study of patients with stable coronary disease, hsCRP levels were measured in 118 persons with exercise-induced ischemia and 111 persons without such ischemia (Beattie et al., 2003).

Compared with those whose hsCRP levels were below 3.8 mg/L, individuals with levels of 3.8 mg/L or above were far more likely to have exercise-induced ischemia. Thus, hsCRP holds promise for improving clinical risk prediction in secondary prevention settings. However, given that patients with CVD are known to be at increased risk for additional events, hsCRP testing may have greater clinical utility in the primary prevention setting, where it may be used to guide targeted interventions. Further, before adopting hsCRP testing as a risk stratification tool among patients presenting with ACS or ischemic stroke or among those undergoing PCI, more data regarding the optimal timing of hsCRP assessment in relation to the onset of ischemic symptoms and appropriate cut point for defining “high” hsCRP levels are required. In the studies cited, the thresholds used to define an abnormal or elevated hsCRP level among patients with documented coronary disease range from 3 mg/L (Chew et al., 2001; de Winter et al., 2002) to 15.5 mg/L (Morrow et al., 1998). Using receiver operating characteristic curve analysis, the CAPTURE investigators found that a threshold of 10 mg/L maximized the predictive value of hsCRP in patients with unstable angina (Heeschen et al., 2000). It is likely that a gradient for the distribution of hsCRP levels exists across populations define by cardiovascular history, with the lowest distribution among healthy individuals, an intermediate range among patients with stable CAD, and the highest range among patients with ACS.

Nine risk factors were found to account for over 90% of the risk of first MI in a study of over 12,000 cases of MI: (Yusuf et al., 2004) dyslipidemia, smoking, hypertension, diabetes, abdominal obesity, depression and other psychosocial factors, low levels of physical activity, low levels of fruit and vegetable consumption, and low levels of alcohol consumption. Accumulating evidence indicates that obstructive sleep apnea should be added (Luthje and Andreas, 2008). All of these conditions have been reported to be associated with elevated hsCRP levels (Kushner et al., 2006). It is thus
reasonable to conclude that hsCRP predicts coronary events merely because it is associated with the major risk factors for atherosclerosis. This conclusion is supported by the recent report that increased hsCRP was largely attributable to conventional CHD risk factors in an Australian population study (Hung et al., 2008). Ramon et al., (2008) study showed that atherosclerotic burden, as reflected by the extent of angiographic CAD and CRP levels, predicts cardiac adverse events in patients with CAD. Michowitz et al., (2008) studied the predictive role of hsCRP in patients with diastolic heart failure. They concluded that hsCRP concentrations are elevated in patients with diastolic heart failure and correlate with disease severity.

The RR of hsCRP was found to be 2.09 (95 % CI 1.58 to 2.76). Based on part of these data, high-sensitivity assays for CRP have become available in standard clinical laboratories and that provide similar results in stored, fresh or frozen plasma. However, clinical application of CRP testing will depend not only on demonstration of independent predictive value, but also on demonstration that addition of inexpensive hsCRP testing to traditional screening methods improves cardiovascular risk prediction. Furthermore, application of hsCRP as a tool to assist clinical characteristics of hsCRP evaluation, and magnitude of risk of future coronary events that can be expected at each level of hsCRP. Infection and tissue injury if diagnosed in the early phase, can be treated accordingly by antibiotics or anti-inflammatory drugs.

4.5. Total cholesterol and low-density lipoprotein cholesterol

Cholesterol is a lipidic, waxy alcohol found in the cell membranes and transported in the blood plasma of all animals. Cholesterol is synthesized in virtually all cells, and significant amounts of it can be absorbed from the diet. Although cholesterol is essential for life, high levels in circulation are associated with atherosclerosis. According to the lipid hypothesis, abnormally high cholesterol levels (hypercholesterolemia), or, more correctly, higher concentrations of LDL cholesterol have been recognized as principle lipid risk factors (Durrington, 2003). A 2007 study pooling data on almost 9,00,000 subjects in 61 cohorts demonstrated that blood TC levels have an exponential effect on cardiovascular and total mortality, with the association more pronounced in
younger subjects. Still, because CVD is relatively rare in the younger population, the impact of high cholesterol on health is still larger in older people (Lewington et al., 2007).

Table 4.2 summarizes the biochemical parameters examined in serum samples of all patients divided according to the groups. All biochemical parameters are expressed with mean and standard deviation. Patients generally had moderate to high elevated levels of lipid risk factors or markers such as, TC, TG, LDL cholesterol, non-HDL cholesterol, lipid ratios (TC to HDL cholesterol, TG to HDL cholesterol, LDL cholesterol to HDL cholesterol, non-HDL cholesterol to HDL cholesterol) and low levels of HDL cholesterol in the test groups (group II and III) than the control (group I).

Risk of CVD increased significantly with increasing TC and LDL cholesterol. The percentage of hypercholesterolemia was higher in group III (44%) than group I (14%) and II (19%). The mean values of group I was found to be 165.3±29.9, in group II 170.2±33.7 and in group III 202.0±41.4. There was statistically significant difference between group III (p< 0.001) and group I and between group III (p< 0.001) and group II. There was no significant difference between group I and group II. The prevalence high – LDL cholesterolemia was higher in group III (50%) when compared with group I (10%) and II (17%). LDL cholesterol was higher in patients with CVD than the control. The mean values of group I was found to be 95.2±25.6, in group II 102.0±28.7 and in group III 137.4±41.9. There was statistically significant difference between group III (p< 0.001) and group I and between group III (p< 0.001) and group II. There was also a significant difference between group I and group II (p< 0.07) (Table 4.2).

Epidemiologic studies have consistently demonstrated a dose-response relation between TC level and CHD risk. The MRFIT screened >300,000 men and demonstrated a curvilinear relation between TC and age-adjusted CHD death rate; in MRFIT screeners with a TC level of ≥240 mg/dL, RR for CHD death was 3.4 compared with those with TC <182 mg/dL (Neaton and Wentworth, 1992). However, the influence of factors other than TC on CHD risk is clearly demonstrated by the findings of 25 years of follow-up in the Seven Countries Study (SCS) (Verschuren et al., 1995), in which a dose-response
relation was observed between TC and CHD mortality rate, yet at any given level of TC, CHD mortality rates varied by 4- to 5-folds.

The induction of hypercholesterolemia is a prerequisite for atherogenesis, and sometimes myocardial ischemia, in various experimental animals. In addition, certain species have hereditary forms of hypercholesterolemia and develop atherosclerosis spontaneously; a classical example is the WHHL rabbit, which carries the same molecular defect as human familial hypercholesterolemia. In contrast, low LDL cholesterol levels are well tolerated. LDL cholesterol as low as 25–60 mg/dL is physiologically sufficient (Brown and Goldstein, 1986). Animal species that do not develop atherosclerosis generally have LDL cholesterol levels below 80 mg/dL. The LDL cholesterol concentration in the newborn infant is approximately 30 mg/dL, indicating that such low levels are safe.

Moreover, persons who have extremely low levels of LDL cholesterol throughout life due to familial hypobetalipoproteinemia have documented longevity (Glueck et al., 1976). Epidemiological investigations of human populations incriminate high levels of LDL cholesterol as being atherogenic. In population studies, the serum TC is a good surrogate for LDL cholesterol levels. The FHS (Wilson et al., 1998), the MRFIT (Stamler et al., 1986), and the Lipid Research Clinics (LRC) trial (Lipid Research Clinics Program, 1984; Lipid Research Clinics Program, 1984) found a direct relationship between levels of LDL cholesterol (or TC) and the rate of new-onset CHD in men and women who were initially free of CHD. The same relation holds for recurrent coronary events in people with established CHD (Rossouw, 1990; Pekkanen et al., 1990; Wong et al., 1991). Any LDL cholesterol above 100 mg/dL appears to be atherogenic. The prevalence of elevated levels in large part accounts for the near universal development of coronary atherosclerosis in the United States and the high attendant risk for developing CHD over a lifetime - 49 percent for men and 32 percent for women (Lloyd-Jones et al., 1999).

Studies across different populations reveal that those with higher cholesterol levels have more atherosclerosis and CHD than do those having lower levels (McGill, 1968; Keys et al., 1980; Keys et al., 1984). People who migrate from regions where average
serum cholesterol in the general population is low to areas with high cholesterol levels show increases in their cholesterol levels as they acculturate. These higher levels in turn are accompanied by more CHD (Toor et al., 1960; Kagan et al., 1974). The positive relationship between serum cholesterol levels and the development of first or subsequent attacks of CHD is observed over a broad range of LDL cholesterol levels; the higher the level, the greater the risk (Stamler et al., 1986). Early prospective data suggested that the risk of CHD plateaued at lower cholesterol levels, but this apparent plateau has disappeared in larger studies (Stamler et al., 1986; Law et al., 1994; Law, 1999). Only in populations that maintain very low levels of serum cholesterol, e.g., TC <150 mg/dL (or LDL cholesterol <100 mg/dL) throughout life do we find a near-absence of clinical CHD (Keys et al., 1980; Grundy et al., 1990; People’s Republic of China-United States Cardiovascular and Cardiopulmonary Epidemiology Research Group, 1992; Law et al., 1994; Law et al., 1994).

Atherosclerosis generally can first be identified by gross pathological examination of coronary arteries in adolescence or early adulthood (McGill et al., 1997; 1998; 2000). The subsequent rate of atherogenesis is proportional to the severity of ambient risk factors including serum cholesterol levels. Moreover, the cholesterol level in young adulthood predicts development of CHD later in life. In three prospective studies with long-term follow-up (Anderson et al., 1987; Klag et al., 1993; Stamler et al., 2000), detection of elevated serum cholesterol in early adulthood predicted an increased incidence of CHD in middle age. The power of elevated LDL cholesterol to cause CHD is shown most clearly in persons with genetic forms of hypercholesterolemia (Brown and Goldstein, 1986). In these persons, advanced coronary atherosclerosis and premature CHD occur commonly even in the complete absence of other risk factors. These disorders provide the strongest evidence that LDL cholesterol is a powerful atherogenic lipoprotein. Since LDL cholesterol levels <100 mg/dL throughout life are associated with a very low risk for CHD in populations, they can be called optimal. Even when LDL cholesterol concentrations are near optimal (100–129 mg/dL), atherogenesis occurs; hence, such levels must also be called above optimal. At levels that are borderline high (130–159 mg/dL), atherogenesis proceeds at a significant rate, whereas at levels that are high (160–189 mg/dL) and very high (≥190 mg/dL) it is markedly accelerated. These
relationships are confirmed by the log-linear relationship between serum cholesterol levels and CHD risk observed in many populations (Law et al., 1994; Law, 1999).

The relation of elevated LDL cholesterol to the development of CHD must be viewed as a multi-step process beginning relatively early in life (Stary et al., 1992; Stary et al., 1994; Stary et al., 1995). The first stage of atherogenesis is the fatty streak, which consists largely of cholesterol-filled macrophages; most of the cholesterol in fatty streaks is derived from LDL cholesterol. The second stage consists of fibrous plaques in which a layer of scar tissue overlies a lipid rich core. Other risk factors contribute to plaque growth at this phase. The third stage is represented by the development of unstable plaques that are prone to rupture and formation of luminal thrombosis. Plaque rupture (or erosion) is responsible for most ACS (MI, unstable angina, and coronary death) (Libby, 1995; Libby et al., 1998; Fuster et al., 1999; Theroux and Fuster, 1998).

Elevated LDL cholesterol plays a role in the development of the mature coronary plaque, which is the substrate for the unstable plaque. Recent evidence also indicates that elevated LDL cholesterol contributes to plaque instability as well; conversely, LDL cholesterol lowering stabilizes plaques and reduces the likelihood of ACS. Clinical intervention with LDL cholesterol lowering therapy in patients with advanced coronary atherosclerosis (short-term risk reduction) thus aims to stabilize plaques and to prevent ACS (Brown et al., 1995; Brown and Zhao, 2000). In contrast, LDL cholesterol lowering earlier in life slows atherosclerotic plaque development, the foundation of the unstable plaque. This fact provides a rationale for long-term lowering of LDL cholesterol using both public health and clinical approaches.

4.6. Triglycerides

TG are formed from a single molecule of glycerol, combined with three fatty acids on each of the OH groups, and make up most of fats digested by humans. Ester bonds form between each fatty acid and the glycerol molecule. This is where the enzyme pancreatic lipase acts, hydrolysing the bond and 'releasing' the fatty acid. In TG form, lipids cannot be absorbed by the duodenum. Fatty acids, monoglycerides (one glycerol, one fatty acid) and some diglycerides are absorbed by the duodenum, once the TG have
been broken down. In the human body, high levels of TG in the bloodstream have been linked to atherosclerosis, and, by extension, the risk of heart disease and stroke.

In order to make a proper evaluation of lipid-related risk, HDL cholesterol, non-HDL cholesterol as well as TG levels and lipid ratios should also be considered as guidelines (Grundy et al., 2002; De Backer et al., 2003; Grundy et al., 2004). Hypertriglyceridemia was significantly higher in group III (53%) than the group I (33%) and II (38%). The mean values of group I was found to be 140.4±67.3, in group II 149.5±75.0 and in group III 175.6±86.2. There was statistically significant difference between group III (p< 0.003) and group I and between group III (p< 0.02) and group II. There was no significant difference between group I and group II (Table 4.2).

Taken as a whole, observational studies and analyses published during the past 5 years largely support TG as an independent risk factor for CHD. These studies have been conducted in populations across a wide spectrum of ages in a number of countries with quite different rates of CVD (Austin et al., 1998; Jeppesen et al., 1998; Howard et al., 1999; Avins and Neuhaus, 2000; Iso et al., 2001; Simons et al., 2001; Sharett et al., 2001). Most of these studies found that the magnitude of the risk associated with elevated TG levels seen in univariate analyses was attenuated, but not eliminated, by inclusion of HDL cholesterol into multivariate analyses.

Historically, elevated TG has predicted CHD events in univariate analysis, only to weaken after adjustment for other covariates, including plasma glucose and HDL cholesterol, to which it is strongly and inversely correlated (Criqui et al., 1993). Yet, even after adjustment for HDL cholesterol, detailed evaluation of population-based prospective studies has disclosed an independent effect of TG on CHD events (Sarwar et al., 2007). Coupled with the knowledge that combined hyperlipidemia (i.e., elevated LDL cholesterol and TG) promotes CHD to a significantly greater extent than either high LDL cholesterol or TG alone (Manninen et al., 1992), the present analysis was undertaken to test the hypothesis that low on-treatment levels of TG when added to low LDL cholesterol would be superior to low LDL cholesterol alone in reducing subsequent CHD events after an ACS.
Most studies also found that the RR of developing CHD associated with elevated TG to be higher in women than in men. Arguably, the most important study during this period consisted of meta-analyses of observational studies that assessed the role of various risk factors in men and in women (Austin et al., 1998). These meta-analyses involved 16 studies with a total of 46,413 men and five studies with a total of 10,664 women. The meta-analysis for men included studies conducted in the United States, Sweden, Finland, France, Germany, Italy, the United Kingdom, and Iceland. The meta-analysis for women included studies in the United States and Sweden. A major advantage of this study was its ability to demonstrate consistency of the association between elevated TG levels and risk of CHD across countries and genders.

All of the 16 studies in men showed increased univariate risks associated with elevated TG, of which the risks were statistically significant in 13. The univariate meta-analysis found a summary RR of 1.32 per 1-mmol increase in TG. Of note, the RR values were 2.49 in Scandinavian countries, 1.25 in other European countries, and 1.34 for studies in the United States. In a multivariate analysis that included HDL cholesterol, the summary RR was 1.14. All five of the studies of women showed significant results in univariate analysis. The univariate meta-analysis resulted in a summary RR of 1.76 per 1-mmol increase in TG. The RR values were 2.02 in Scandinavian countries and 1.71 for studies in the United States. In a multivariate analysis that included HDL cholesterol, the summary RR was 1.37.

A study by Iso et al., (2001) assessed the multivariate adjusted risk of CHD associated with higher non-fasting TG levels in 4,452 Japanese men and 6,616 Japanese women aged 40 to 69 years followed for 15.5 years; risks were adjusted based on age, BMI, cholesterol, hypertension status, smoking, glucose, and time since last meal. This population had mean cholesterol levels considerably lower than those in the United States. The multivariate adjusted risk associated with a 1-SD increase in TG (1.38 mmol) was 1.29 in men and 1.42 in women. Adjustment for HDL cholesterol levels only slightly attenuated the risks. Simons et al., (2001) reported on the risk of CHD for various lipids and other CHD risk factors entered into a multivariate analysis for 1,235 elderly men and 1,570 elderly women in Australia. For a 1-SD increase in TG (1.38 mmol), the
respective RRs 1.12 in a combined analysis of men and women aged 60 to 69 years, 1.14 in those aged 70 to 79 years, and 1.23 in those aged 80 years and above. The statistical significance of increases in TG was lost when HDL cholesterol was entered into the model.

Sharet et al., (2001) reported a 10-year follow-up of 5,434 men and 6,907 women aged 45 to 64 years in the ARIC study. Unlike the previously mentioned studies, this study did not find an impressive increase in risk associated with higher TG. For men, the univariate RR was 1.07 per 0.7-mmol increase in TG, which was attenuated to 1.01 when all other CHD risk factors were included in the model. For women, the authors reported a significantly increased risk of 1.29 per 0.7-mmol increase in TG in univariate analysis, but this was attenuated to a RR of 1.14 when all other CHD risk factors, including HDL, were included in the model. Jeppesen et al., (1998) reported on the risk of elevated TG in a group of 2,906 Danish men aged 53 to 74 years who were followed for 8 years. After adjusting for age, BMI, smoking, physical activity, hypertension, type 2 diabetes, LDL cholesterol, and HDL cholesterol, the authors found a RR of 1.5 for men in the middle tertile of TG compared with the lowest tertile and a RR of 2.2 for those in the highest tertile. The authors also stratified their analyses by tertiles of TG levels and tertiles of HDL cholesterol level. Within each tertile of HDL cholesterol level, a dose response relationship was seen of higher RRs of CHD at higher TG levels.

Howard et al., (1999) reported on the risks of lipid and other CVD risk factors in a 4-year follow-up of 1,846 American Indian men and 2,703 American Indian women. In univariate analysis, they found a RR of 1.08 in men and 1.58 in women. In multivariate analysis, which included as variables age, center, percent body fat, LDL cholesterol, HDL cholesterol, TG, hypertension, and diabetes, neither TG nor HDL cholesterol was significant in men. In contrast, TG, but not HDL cholesterol, was significant in women with a RR of 1.01 per 10-mg increase in TG. In contrast to these other studies, Avins and Neuhaus, (2000) assessed the contribution of TG to prediction of risk of CHD in three data sets: the MRFIT, the LRC Primary Prevention Trial (LRC-PPT), and the Lipid Research Clinics and Mortality Follow-up Study (LRC-MFS). In univariate analyses, they
found a hazard ratio of 1.15 in the MRFIT study, 1.60 in the LRC study, 1.63 in LRC-MFS men, and 2.62 in LRC-MFS women.

A meta-analysis of 21 population-based prospective studies involving a total of 65,863 men and 11,089 women found that each 89-mg/dL increase in TG level was associated with a 32% increase in CHD risk in men and a 76% increase in women (Abdel-Maksoud and Hokanson, 2002). The prevalence of hypertriglyceridemia is high. In the United States population-based NHANES III (Ford et al., 2002), 30.0% of 8,814 respondents (age ≥20 years) had serum TG levels ≥150 mg/dL. The prevalence of elevated TG levels was 42.8% among person's aged ≥50 years (Alexander et al., 2003).

4.7. High-density lipoprotein cholesterol

HDL cholesterol is one of the 5 major groups of lipoproteins, which enable lipids like cholesterol and TG to be transported within the water based blood stream. In healthy individuals, about thirty percent of blood cholesterol is carried by HDL cholesterol. It is hypothesized that HDL cholesterol can remove cholesterol from atheroma within arteries and transport it back to the liver for excretion or reutilization, which is the main reason why HDL-bound cholesterol is sometimes called "good cholesterol", or HDL cholesterol. A high level of HDL cholesterol seems to protect against CVD, and low HDL cholesterol levels (less than 40 mg/dL) increase the risk for heart disease. When measuring cholesterol, any contained in HDL particles is considered as protection to the body's cardiovascular health, in contrast to "bad" LDL cholesterol.

Low - HDLcholesterolemia was higher in group II (56%) and group III (65%) than group I (21%). The mean values of group I was found to be 42.1±8.3, in group II 38.4±6.5 and in group III 36.9±6.1. There was statistically significant difference between group II (p< 0.001) and group I and between group III (p< 0.001) and group I. There was also a significant difference between group II and group III (p< 0.09) (Table 4.2).

Strong epidemiological evidence links low levels of serum HDL cholesterol to increased CHD morbidity and mortality (Abbott et al., 1988; Gordon et al., 1989; Wilson
et al., 1998). High HDL cholesterol levels conversely convey reduced risk. Epidemiological data taken as a whole signify that a 1 percent decrease in HDL cholesterol is associated with a 2–3 percent increase in CHD risk (Gordon et al., 1989). Epidemiological studies consistently show low HDL cholesterol to be an independent risk factor for CHD. Its independent relationship holds after correction for other risk variables in multivariate analysis. In fact, in prospective studies (Wilson et al., 1980; Assmann et al., 1996), HDL cholesterol usually proves to be the lipid risk factor most highly correlated with CHD risk. ATP II specified low HDL cholesterol (<35 mg/dL) as one of several major risk factors used to modify the therapeutic goal for LDL cholesterol. The definition of low-HDL cholesterol was set to be the same for both men and women because of the view that a given level of HDL cholesterol would impart the same risk for men and women.

The mechanistic relationship between low HDL cholesterol levels and occurrence of CHD has not been fully elucidated. One theory holds that HDL cholesterol directly participates in the atherogenic process. Some research in laboratory animals backs a direct action. In genetically modified animals, high levels of HDL cholesterol appear to protect against atherogenesis (Rubin et al., 1991; Plump et al., 1994; Tangirala et al., 1999). In vitro, HDL cholesterol promotes efflux of cholesterol from foam cells in atherosclerotic lesions (reverse cholesterol transport) (Tall, 1998).

Recent studies indicate that the antioxidant and anti-inflammatory properties of HDL cholesterol also inhibit atherogenesis (van Lenten et al., 1995; Navab et al., 2000; Navab et al., 2000; Nofer et al., 2001; Barter et al., 2004). Further, some genetic forms of HDL cholesterol deficiency are accompanied by increased risk for CHD (Ng et al., 1995; Miller et al., 1998); others appear not to be (Romling et al., 1994; Takata et al., 1995; Miccoli et al., 1996). This latter finding raises the possibility that some subspecies of HDL cholesterol affect atherogenesis whereas others do not. Although there are conflicting data, multiple lines of evidence strongly intimate that HDL cholesterol plays a direct role in the atherogenic process. If so, it is a potential target for therapy. The direct role of HDL cholesterol in atherogenesis probably cannot fully account for the strong predictive
power of HDL cholesterol in epidemiological studies. A low HDL cholesterol level correlates with the presence of other atherogenic factors (Vega and Grundy, 1996).

In many persons, a low HDL cholesterol level correlates with elevations of serum TG and remnant lipoproteins (Schaefer et al., 1994; Phillips et al., 1981); in addition, low HDL cholesterol commonly shows linkage with small, dense LDL particles (Austin et al., 1990; Luc et al., 1997; Austin et al., 2000). The tight association among low HDL cholesterol, small LDL particles, and elevated TG has evoked the term lipid triad. Moreover, a low HDL cholesterol level can be a sign of insulin resistance and its associated metabolic risk factors (Vega and Grundy, 1996).

There are several factors that contribute to low HDL cholesterol levels that need to be identified in clinical practice (Heiss et al., 1980; Krauss, 1982; Stone, 1994). These include: elevated serum TG, overweight/obesity, physical inactivity, cigarette smoking, very high carbohydrate intakes (>60 percent of total energy intake), type 2 diabetes, certain drugs (beta-blockers, anabolic steroids, progestational agents) and genetic factors. In the general population, about 50 percent of the variability of serum HDL cholesterol levels derives from genetic factors (Cohen et al., 1994; Sviridov and Nestel, 2007); the other 50 percent presumably comes from the acquired factors listed above. Moreover, when a person has a genetic predisposition to reduced HDL cholesterol, acquired factors often drive HDL cholesterol to categorically low levels. Among these acquired factors, overweight and obesity appear to be most important (National Institutes of Health, 1998; National Institutes of Health, 1998; Brown et al., 2000). Part of the effect of overweight and obesity can be explained by their action to raise serum TG, which lowers HDL cholesterol levels, but they probably reduce HDL cholesterol through other mechanisms as well (Tato et al., 1995; Nie et al., 1998; Carr et al., 1999).

In ATP II (National Cholesterol Education Program, 1993; National Cholesterol Education Program, 1994), a low HDL cholesterol was defined as a level <35 mg/dL; the setting of this cut point was influenced by the concept that low HDL cholesterol is primarily a direct cause of atherosclerotic disease. More recently, the role of HDL cholesterol as an indicator of other risk correlates has been emphasized (Lamarche et al.,
This shift in perception requires a re-examination of the appropriate cutpoint for low HDL cholesterol. Clearly, low HDL cholesterol levels predict CHD at levels above 35 mg/dL (Wilson et al., 1998); this fact combined with the moderate reductions of HDL cholesterol caused by obesity and physical inactivity led the ATP III panel to recognize a somewhat higher HDL cholesterol level as a categorical risk factor.

The level <40 mg/dL was set as a low HDL cholesterol, both in men and women. Women typically have higher HDL cholesterol levels than men, and a cut point of <40 mg/dL will identify more men than women with low HDL cholesterol, i.e., approximately one-third of men and about one-fifth of women in the general population. Setting a different cut point for categorical low HDL cholesterol for men and women was rejected because it would make many women who are otherwise at low risk eligible for LDL cholesterol lowering drugs. On the other hand, as will be discussed subsequently, a higher level of HDL cholesterol (<50 mg/dL) is defined as a marginal risk factor in women, which will mandate more intensive lifestyle therapies (weight reduction and increased physical activity).

In prospective studies, including the FHS (Wilson et al., 1998), high HDL cholesterol is associated with reduced risk for CHD. In ATP II, this level (high HDL cholesterol) was also called a negative risk factor, and its presence evoked removal of one risk factor from the risk factor count used for setting treatment goals for LDL cholesterol. ATP III affirms the validity of this assignment.

4.8. Very low-density lipoprotein cholesterol

VLDL cholesterol is a type of lipoprotein made by the liver. VLDL cholesterol is one of the five major groups of lipoproteins, which enable fats and cholesterol to move within the water based solution of the blood stream. It is assembled in the liver from cholesterol and apolipoproteins. It is converted in the bloodstream to LDL cholesterol. VLDL particles have a diameter of 30-80 nm. VLDL cholesterol transports endogenous products (such as TG, phospholipids, cholesterol and cholesteryl esters) where chylomicrons transport exogenous (dietary) products.
VLDL cholesterol was higher in patients with CVD than the control (Table 4.2). The mean values of group I was found to be 28.2±13.7, in group II 29.8±14.9 and in group III 35.1±16.9. There was statistically significant difference between group III (p<0.004) and group I and between group III (p<0.02) and group II. There was no significant difference between group I and group II.

The most likely candidates for atherogenic triglyceride-rich lipoproteins (TGRLP) are remnant lipoproteins. These lipoproteins include small VLDL cholesterol and intermediate-density lipoproteins (IDL). They are cholesterol-enriched particles and have many of the properties of LDL cholesterol. Reviews of several independent lines of evidence support the atherogenicity of remnants (Havel, 1990; Grundy, 1998; Krauss, 1998). Specific evidence can be cited. In experimental animals, cholesterol-enriched remnants definitely cause atherosclerosis (Nordestgaard and Lewis, 1991). Genetic hyperlipidemias characterized by the accumulation of lipoprotein remnants commonly produce premature CHD and peripheral vascular disease in humans (Weisgraber et al., 1990; Mahley et al., 1991). In several clinical studies in which remnants were specifically identified, their elevations emerged as strong predictors of coronary atherosclerosis or CHD (Tatami et al., 1981; Steiner et al., 1987; Krauss et al., 1987; Phillips et al., 1993; Tomvall et al., 1993; Hodis et al., 1994; Koren et al., 1996; Thompson, 1998; Takeichi et al., 1999; Sacks et al., 2000; Karpe et al., 2001). This relation of remnants to CHD was also noted in several reviews (Grundy, 1998; Havel, 1990; Krauss, 1998). Finally, drug therapies that reduce remnant lipoproteins (fibrates, nicotinic acid, and statins) are accompanied by reduced risk for CHD.

Although a variety of methods have been developed to identify lipoprotein remnants, most are not applicable to clinical practice; the most readily available measure for clinical practice is VLDL cholesterol. Some cholesterol in VLDL cholesterol may reside in non-atherogenic TGRLP, but most of it apparently occurs in atherogenic remnants (Tatami et al., 1981; Kuchinskiene and Carlson, 1982; Miller and Small, 1983; Bjorkegren et al., 2000). Thus, VLDL cholesterol, as a marker for remnant lipoproteins, is a potential target of cholesterol-lowering therapy.
Atherogenic dyslipidemia and metabolic syndrome

A common form of dyslipidemia is characterized by three lipid abnormalities: elevated TG, small LDL particles or TC, and reduced HDL cholesterol (Brown and Zhao, 2000; Grundy, 1998; Krauss, 1998). Often the lipoprotein concentrations in this lipid triad are not categorically abnormal, but are only marginally deranged. More sophisticated methodology than that used in routine clinical practice can identify these multiple interrelated abnormalities. Still, in some persons, low HDL cholesterol levels can occur in the absence of other lipoprotein abnormalities. These persons are said to have isolated low HDL cholesterol. They are not common in the general population, however; more often, low HDL cholesterol occurs as a component of the lipid triad. Because of the common occurrence of the lipid triad, the relation of the lipid triad as a whole to CHD risk will be considered, and whether the entire triad is a target for therapy.

This syndrome has become increasingly common in the United States. It is characterized by a constellation of metabolic risk factors in one individual (Reaven, 1995; Grundy, 1999; Meigs, 2000). The root causes of the metabolic syndrome are overweight/obesity, physical inactivity, and genetic factors. The metabolic syndrome is closely associated with a generalized metabolic disorder called insulin resistance, in which tissue responsiveness to the normal action of insulin is impaired (Kolaczynski and Caro, 1998; Zimmet et al., 1999; Haffner, 1999). Some individuals are genetically predisposed to insulin resistance; in these persons, acquired factors (excess body fat and physical inactivity) elicit insulin resistance and the metabolic syndrome.

Atherogenic dyslipidemia and metabolic syndrome was more frequent among the patients with CVD. CVD patients with metabolic syndrome exhibited a more atherogenic lipid profile compared with controls. The prevalence of atherogenic dyslipidemia was significantly higher in group III (21%) than group I (1%) and II (5%). Metabolic syndrome was statistically significant difference between group I (3%) with group II (17%), group II and group III (32%) and group I and group III (Table 4.1.2).

The lipid triad occurs commonly in persons with premature CHD (Austin et al., 1988; Austin et al., 1990), hence the designation atherogenic lipoprotein phenotype or

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atherogenic dyslipidemia. Typical characteristics of persons with atherogenic dyslipidemia are obesity, abdominal obesity, insulin resistance, and physical inactivity (National Institutes of Health, 1998; National Institutes of Health, 1998). Many persons with type 2 diabetes have atherogenic dyslipidemia (Kreisberg, 1998; Verges, 1999; Durrington, 1999). In epidemiological studies in high-risk populations, the contributions of individual components of atherogenic dyslipidemia to CHD risk cannot reliably be dissected from the sum of lipid risk factors. Although there is evidence that each component of the lipid triad—low HDL cholesterol, small LDL, and remnant lipoproteins—is individually atherogenic, the relative quantitative contribution of each cannot be determined. For this reason, it is reasonable to view the lipid triad as a whole as a "risk factor."

Most persons with insulin resistance have abdominal obesity (Despres, 1993; Bjorntorp, 1997; Despres, 1998). The mechanistic connections between insulin resistance and metabolic risk factors are not fully understood and appear to be complex. Various risk factors have been included in the metabolic syndrome; the following list contains those factors that are generally accepted as being characteristic of this syndrome: abdominal obesity, atherogenic dyslipidemia, raised BP, insulin resistance ± glucose intolerance, prothrombotic state and proinflammatory state. Because of the high degree of association of these risk factors in persons with the metabolic syndrome, it has proven difficult to dissect the individual contributions of each factor to CHD risk. However, there is little doubt that this syndrome taken in aggregate enhances the risk for CHD at any given LDL cholesterol level.

From a population viewpoint, the increasing prevalence of the metabolic syndrome threatens to partially reverse the reduction in CHD risk that has resulted from a decline in serum LDL cholesterol levels in the United States population, which has occurred over the past three decades. The metabolic syndrome and its associated risk factors have emerged as a coequal partner to cigarette smoking as contributors to premature CHD (U.S. Department of Health and Human Services, 1996; Wilson et al., 1998; National Institutes of Health, 1998; National Institutes of Health, 1998; Assmann et al., 1998; Eckel and Krauss, 1998). In addition, the insulin resistance accompanying the
metabolic syndrome is one of the underlying causes of type 2 diabetes (Groop, 1999; Cavaghan et al., 2000). For these reasons, ATP III places increased emphasis on the metabolic syndrome as a risk enhancer.

There are two general approaches to the treatment of the metabolic syndrome. The first strategy modifies root causes, overweight/obesity and physical inactivity, and their closely associated condition, insulin resistance. Weight reduction (Su et al., 1995; Ahmad et al., 1997; Dengel et al., 1998) and increased physical activity (Devlin, 1992; Perseghin et al., 1996) both lower insulin resistance and indirectly mitigate the metabolic risk factors. The second approach directly treats the metabolic risk factors—atherogenic dyslipidemia, hypertension, the prothrombotic state, and underlying insulin resistance. At present, most success in clinical practice comes from pharmacological modification of the associated risk factors. However, the greatest potential for management of the syndrome lies in reversing its root causes. ATP III promotes this latter approach, which is a major new initiative for persons entering clinical cholesterol management.

There are no well-accepted criteria for the diagnosis of the metabolic syndrome. Nonetheless, many persons seen in clinical practice are readily recognized as having multiple metabolic risk factors. Most persons with the metabolic syndrome are overweight or obese; clinical studies have noted a high correlation between abdominal obesity and the risk factors characteristic of the metabolic syndrome (Bjorntorp, 1992; Despres, 1993; Bjorntorp, 1997). For example, closely associated with abdominal obesity is an elevation of serum TG (Bodkin et al., 1993; Julien et al., 1997; Mekki et al., 1999). The elevation can be either borderline high (150-199 mg/dL) or high (>200 mg/dL). A higher TG level is usually accompanied by lower HDL cholesterol concentrations (Phillips et al., 1981; Schaefer et al., 1988). HDL cholesterol levels <40 mg/dL occur commonly in men with insulin resistance (Karhapaa et al., 1994). Further, moderate (marginal) reductions of HDL cholesterol levels are observed commonly in women with the syndrome (Vanhala et al., 1997; Nilsson et al., 2000), thus for women, HDL cholesterol <50 mg/dL counts as one indicator in the diagnosis of the metabolic syndrome. A moderately strong association exists between insulin resistance and hypertension (Lind et al., 1995; Lender et al., 1997; Landsberg, 1999). Insulin resistance
also is associated with high-normal BP (Dyer et al., 1999; Falkner et al., 1999). Impaired fasting glucose (110–125 mg/dL) usually is an indicator of insulin resistance and is frequently accompanied by other metabolic risk factors (Haffner et al., 1996; Tripathy et al., 2000) measurement of fasting glucose in overweight and obese persons is a reasonable option (National Institutes of Health, 1998; National Institutes of Health, 1998). A portion of persons with impaired fasting glucose will eventually develop type 2 diabetes (Edelstein et al., 1997; Lindahl et al., 1999), which further enhances risk for CHD. Type 2 diabetes is the epitome of the metabolic syndrome. Other components of the metabolic syndrome (insulin resistance, proinflammatory state, and prothrombotic state) cannot be identified by routine clinical evaluation. However, in the presence of abdominal obesity, they often are present.

4.10. Non-High density lipoprotein cholesterol

Non–HDL cholesterol was higher in patients with CVD than the control (Table 4.2). The mean values of group I was found to be 123.3±27.1, in group II 131.8±31.5 and in group III 164.9±39.9. There was statistically significant difference between group II (p< 0.05) and group I and between group III (p< 0.001) and group I. There was also a significant difference between group II and group III (p< 0.001).

Non–HDL cholesterol offers the benefit of being an aggregate measure that includes the concentrations of all lipoproteins currently believed to contribute to atherosclerosis. By providing an inclusive measure of all atherogenic particles, there is a strong degree of biologic plausibility for the hypothesis that non–HDL cholesterol is a superior predictor of CVD. Not surprisingly, as TG increase, non–HDL cholesterol correlates with apo B much better than LDL cholesterol (Abate et al., 1993; Ballantyne et al., 2001). Several groups encouraged use of non–HDL cholesterol long before supporting longitudinal epidemiologic data was published (Garg and Grundy, 1990; Frost and Havel, 1998). The importance of the TG-rich lipoproteins included in the non–HDL cholesterol measure will likely increase as the population ages, becomes more obese, more insulin resistant, and more hyperglycemic (Brunzell et al., 2008). Insulin resistance, which increases with age and obesity, leads to a greater fatty acid flux to the liver with accompanied increased synthesis of VLDL cholesterol. Non–HDL cholesterol
is particularly elevated in patients with the metabolic syndrome and type 2 diabetes (Sniderman et al., 2001; Sattar et al., 2004). Non-HDL cholesterol also serves as an indirect marker for increased LDL atherogenicity. Small dense LDLs may be more atherogenic than larger buoyant LDLs. Insulin resistance, with its accompanying increases in TG and VLDL cholesterol enhances the exchange of cholesterol esters from LDL cholesterol for TG from VLDL cholesterol (Krauss and Siri, 2004). Subsequent lipolysis of TG from LDL cholesterol results in small dense LDL particles, which thus tend to co-occur in patients with elevated non-HDL cholesterol. This disassociation of LDL cholesterol and LDL particle number is addressed by including cholesterol in VLDL cholesterol.

Data from several population-based cohorts suggests that non-HDL cholesterol is superior to LDL cholesterol for the prediction of cardiovascular events. In 2001, (Cui et al., 2001) compared the predictive power of non-HDL cholesterol and LDL cholesterol in the 20-year follow-up of the Lipid Research Clinics Program Follow-up Study (LRCPRS). Among 2,406 men and 2,056 women with known coronary disease, there were 234 and 113 cardiovascular related deaths, respectively. Non-HDL cholesterol predicted mortality in both genders, whereas LDL did not show a significant correlation with cardiovascular death in women. A fixed 30 mg/dL increase in non-HDL cholesterol produced a 19% increase in mortality in men and a 11% increase in women, compared to 15% and 8%, respectively, for LDL cholesterol. In 2002, (Bittner et al., 2002) extended this finding to patients with known CHD undergoing revascularization. Among 1,514 patients enrolled in the Bypass Angioplasty Revascularization Investigation (BARI) trial, non-HDL cholesterol was a significant predictor of both nonfatal MI and angina pectoris, whereas LDL cholesterol and HDL cholesterol did not predict events during follow-up. In (Lu et al., 2003), examined CVD prediction amongst 4,549 patients with diabetes in the Strong Heart Study (SHS).

Hazard ratios for the upper tertile of non-HDL cholesterol were higher than those for LDL cholesterol and TG in both men and women and were higher than the ratio of TC to HDL cholesterol in women. The authors reported that the predictive power on non-HDL cholesterol persisted over wide ranges in TG values. In (Liu et al.,
supported these findings with a post-hoc analysis of diabetes patients in four large prospective studies: the Framingham Cohort Study (FCS), the Framingham Offspring Study (FOS), the LRPCFS, and the MRFIT. In a multivariate model, raised non-HDL cholesterol predicted increasing CHD risk, whereas increasing LDL cholesterol did not lead to greater risk. In 2005 (Ridker et al., 2005), conducted an important study comparing traditional lipid measures, non-HDL cholesterol, and specific apolipoproteins among the 15,632 initially healthy women of the WHS. These data indicated that the extreme quintiles of non-HDL cholesterol outperformed all of other single lipid measures, including apo A-I and was equivalent to the measure of apo B among healthy women. The upper quintile of LDL cholesterol was much less predictive.

Finally, two recent studies from the FCS confirm what has been learned about non-HDL cholesterol. First, Liu et al., (2006) found that after multivariate adjustment, there was no residual association between LDL cholesterol and risk for CHD after accounting for non-HDL cholesterol, whereas a strong positive and graded association between non-HDL cholesterol and risk for coronary disease after accounting for LDL remained. More recently, (Ingelsson et al., 2007) reported improved discrimination, better model calibration statistics, and a significant association between non-HDL cholesterol and CHD after adjusting for other risk factors. In their model, the association between LDL cholesterol and CHD was not significant. Non-HDL cholesterol also appears to be a superior predictor of subclinical atherosclerosis.

Recently, (Orakzai et al., 2008) studied 1,611 consecutive asymptomatic individuals (67% men; mean age 53 years) referred to a single electron beam tomography facility for coronary artery calcium (CAC) screening. Multivariate logistic regression was employed to test the association between baseline conventional lipid measures and the presence of CAC. In a model simultaneously controlling for increasing quartiles of all conventional lipid variables, only the association between non-HDL cholesterol and presence of CAC remained statistically significant. These results suggest that non-HDL cholesterol is the single best predictor of coronary atherosclerosis as measured by CAC. Kawamoto et al., (2005) found similar results using ultrasonography
to examine carotid atherosclerosis amongst elderly patients. Among 921 patients age 65 or older, the upper tertile of non-HDL cholesterol conferred an adjusted odds ratio of 2.99 for the presence of atherosclerosis, compared to an odds ratio of 2.69 for the upper tertile of LDL cholesterol.

Non-HDL cholesterol has the distinct advantage over LDL cholesterol in that it is equally accurate when measured on a fasting or nonfasting lipid panel. In contrast, routine measurement of LDL cholesterol is not accurate in a nonfasting specimen, as it is a calculated value that relies on the TG concentration according to the Freidewald equation (Friedewald et al., 1972). Although the Freidewald equation is reasonably accurate in patients with "normal" fasting TG values, it is not accurate in the nonfasting state. Because neither TC nor HDL cholesterol are acutely affected by fasting or feeding, non-HDL cholesterol remains accurate and useful as a measure of apo B containing particles in nonfasting specimens. In addition, calculated LDL values become increasingly inaccurate in the setting of elevated fasting TG, beginning as low as 100 mg/dL with marked differences beginning above 200 mg/dL (Mudd et al., 2007). Such mild to moderate hypertriglyceridemia is frequently seen in the increasingly common setting of metabolic syndrome or diabetes mellitus.

In contrast to LDL cholesterol, non-HDL cholesterol is robust from a laboratory measurement standpoint. Non-HDL cholesterol is based primarily on TC levels, a well-standardized, well-validated, and accurately calibrated parameter with little biological or laboratory variability. Although non-HDL cholesterol depends secondarily on HDL cholesterol, which has somewhat greater biological and laboratory imprecision, the impact of this additional imprecision is modest. First, the biological variability of HDL cholesterol is still relatively low, less than that of most other lipid parameters, such as TG. Second, HDL cholesterol levels are routinely much lower than TC, minimizing their contribution to the variability in non-HDL cholesterol measurement. A final advantage of non-HDL cholesterol is that it can be readily calculated from the values obtained on a routine lipid profile.
4.11. Lipid ratios

Lipid parameters can be combined into ratios that reflect the proportion of atherogenic to antiatherogenic lipids and lipoproteins. Proposed lipid ratios for CHD risk assessment include TC to HDL cholesterol, LDL cholesterol to HDL cholesterol, TG to HDL cholesterol, and apo B to apo A-I (Gotto et al., 2000; Gaziano et al., 1997; Castelli et al., 1983).

A United States case-control study that included 340 patients with no previous history of CHD who were discharged from the hospital after a confirmed MI reported that the TG to HDL cholesterol ratio was a powerful predictor of outcome, possibly because this ratio is so sensitive to the high-risk condition of concomitantly increased TG and decreased HDL cholesterol (Castelli et al., 1983). The association of TG to HDL cholesterol ratio with CHD risk in the present investigation confirmed previous reports that noted the combination of high TG and low HDL cholesterol (referred to as atherogenic dyslipidemia) (Dobiasova and Frohlich, 2001; Grundy, 2006) to be a powerful risk factor for CHD risk (Gaziano et al., 1997; Jeppesen et al., 2001; Barzi et al., 2005). There is evidence from 1 population study that a high TG to HDL cholesterol ratio might better predict CHD in men than conventional risk factors, such as hypertension, smoking, and physical activity (Gaziano et al., 1997).

However, the present investigation showed that, high TG to HDL cholesterol ratio was as strong a lipid predictor of CHD as the widely used TC to HDL cholesterol ratio. Thus, the ratio of TG to HDL cholesterol is likely to be the result of metabolic interactions, which may confer greater risk than the isolated factor in either (Lianqun et al., 2006). William et al., (2008) suggested that the TG to HDL cholesterol ratio was an imperfect surrogate for insulin resistance and its associated CHD risk, and it was only slightly better than the TC to HDL cholesterol ratio for this purpose. As a result of this interrelation between TG and HDL cholesterol, recent focus on high TG-low HDL cholesterol abnormality has grown considering risk assessment and drug therapy for CHD (Gaziano et al., 1997; Rizos and Mikhailidis, 2002).
In other studies, alternative ratios have been found to be the best predictors of risk. For example, in AFCAPS/TexCAPS, after adjustment for nonlipid risk factors, the apo B to apo A-I ratio was the best discriminator of baseline risk, and a value of ≥1.0 was associated with an increased risk for a first major coronary event of 38% (Gotto et al., 2000). In the Apolipoprotein-related Mortality Risk (AMORIS) study, apo B to apo A-I ratio and levels of apo B and apo A-I were strong predictors of fatal MI in multivariate analyses adjusted for age, TC, and TG (Walldius et al., 2001).

Perhaps the most widely used ratios are LDL cholesterol to HDL cholesterol and TC to HDL cholesterol. Retrospective analysis of the Helsinki Heart Study (HHS) revealed that LDL cholesterol to HDL cholesterol values >5 were associated with increased coronary risk (Manninen et al., 1992), whereas an analysis of 5-year data from the Program on the Surgical Control of the Hyperlipidemias (POSCH) study found that the highest hazard ratios were for LDL cholesterol to HDL cholesterol, with each 1-unit increment associated with a 1.2-fold increase in CHD risk (Buchwald et al., 2001). On the basis of observational data, the TC to HDL cholesterol ratio appears to be a better predictor of subsequent CHD (Gordon et al., 1989). Data from the FHS indicate that unlike LDL cholesterol, the TC to HDL cholesterol ratio maintains its predictive power in older patients (Castelli et al., 1992), possibly because this measure takes into account TG-rich lipoproteins.

The ability of the TC to HDL cholesterol ratio to predict development of CHD has been evaluated by statistical tests that compared this ratio with other lipid measures (Kinosian et al., 1994). In a logistic regression analysis, TC to HDL cholesterol was superior to TC alone or LDL cholesterol for identifying individuals at greater risk for subsequent CHD events in 2 general populations (FHS men and women) as well as a population of high-risk men from the LRC Coronary Primary Prevention Trial (LRC-CPPT). The TC to HDL cholesterol ratio was also superior to LDL cholesterol to HDL cholesterol in the LRC-CPPT cohort, an advantage that may be due to the inclusion of potentially atherogenic VLDL cholesterol (a surrogate for TG) in the numerator of the TC to HDL cholesterol ratio.
In addition, analysis of the association between TC to HDL cholesterol and 8-year CHD risk among Framingham men and women revealed a continuous increase in risk with increasing ratio (Kinosian et al., 1994). Some investigators (Hong et al., 1991; Castelli et al., 1992; Kinosian et al., 1995; Criqui and Golomb, 1998) propose that this “cholesterol ratio” is a simple approach for lipid risk assessment. This ratio reflects two powerful components of risk. A high TC is a marker for atherogenic lipoproteins, whereas low HDL cholesterol correlates with the multiple risk factors of the metabolic syndrome and probably imparts some independent risk. In fact, however, the TC to HDL cholesterol ratio is subsumed in the Framingham global risk equations that are the basis of the 10-year risk assessment used in ATP III. In this way, ATP III incorporates cholesterol ratios into risk assessment. If risk assessment is done using Framingham risk factors as continuous variables (e.g., by risk equations), then the ratio is essentially incorporated.

If risk assessment is made using TC and HDL cholesterol in graded, incremental steps, then the ratio is applied approximately. Regardless, ATP III does not define the TC to HDL cholesterol ratio as a specified lipid target of therapy. Instead, LDL cholesterol is retained as the primary target of lipid-lowering therapy. Nor is the TC to HDL cholesterol ratio recommended as a secondary target of therapy. Treatment of ratios will divert priority from specific lipoprotein fractions as targets of therapy. The non-HDL cholesterol to HDL cholesterol ratio would be expected to yield associations with CAD risk that are similar to those of the TC to HDL cholesterol and LDL cholesterol to HDL cholesterol ratios. However, few data are available at this time regarding the relation of the non-HDL cholesterol to HDL cholesterol ratio to CAD risk.

With regard to lipid ratios, the present study data (Table 4.4) are consistent with prior reports that the ratio of TC to HDL cholesterol, LDL cholesterol to HDL cholesterol, non-HDL cholesterol to HDL cholesterol, apo B to apo A-I (Castelli et al., 1983; Grover et al., 1995; Natarajan et al., 2003; Blake et al., 2002; Walldius et al., 2001; Jiang et al., 2004; Yusuf et al., 2004), TG to HDL cholesterol, (Dobiasova, 2004) and apo B to HDL cholesterol (Ridker et al., 2005) are strongly associated with incident cardiovascular events independently.
Table 4.4 Baseline mean levels of the various lipids and lipoproteins ratios

<table>
<thead>
<tr>
<th>Lipids and Lipoprotein Ratios</th>
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</thead>
<tbody>
<tr>
<td>TC to HDL cholesterol</td>
<td>4.0±0.8</td>
<td>4.9±4.2</td>
<td>5.6±1.2</td>
</tr>
<tr>
<td>LDL cholesterol to HDL cholesterol</td>
<td>2.4±0.8</td>
<td>2.6±0.8</td>
<td>3.8±1.2</td>
</tr>
<tr>
<td>TG to HDL cholesterol</td>
<td>3.4±1.7</td>
<td>4.0±2.0</td>
<td>4.8±2.5</td>
</tr>
<tr>
<td>Non-HDL cholesterol to HDL cholesterol</td>
<td>3.0±0.8</td>
<td>3.5±0.9</td>
<td>4.5±1.3</td>
</tr>
<tr>
<td>Apo B to Apo AI</td>
<td>0.8±0.4</td>
<td>1.1±0.1</td>
<td>1.3±0.2</td>
</tr>
<tr>
<td>Apo B to HDL cholesterol</td>
<td>1.2±0.4</td>
<td>2.0±0.6</td>
<td>2.3±0.5</td>
</tr>
</tbody>
</table>
However, it was also observed that the strength of association for the ratio of apo B to apo A-I was not superior in these data to the ratio of TC to HDL cholesterol. Thus, on the basis of the data in this study, as well as other nested case-control studies that have found the ratio of TC to HDL cholesterol to perform favorably (Stampfer et al., 1991; Shai et al., 2004). On the other hand, our data and those of several prior studies do suggest that the use of either the ratio of TC to HDL cholesterol or LDL cholesterol to HDL cholesterol is superior to the use of TC or LDL cholesterol alone.

Risk factors of CVD are often related to one another. Viz., hypertension is often associated with glucose intolerance and dyslipidemia. The pathogenesis of these disorders seems to have relation to the state of insulin resistance (Ferrannini and Natali, 1991; Reaven, 1991; Ferrari et al., 1991). Simple reduction of blood pressure or lowering of serum lipids alone may reduce the risk of CVD to some extent. However, in order to prevent the occurrence of CVD more effectively, comprehensive reductions of cardiovascular risks and improvement of insulin resistance should be considered. Therefore, it is of critical importance to understand the interrelationship of each risk factor.

The most significant finding of the present study (Table 4.5), however, is that the simultaneous assessment of hsCRP and blood lipids with its ratios may improve the prediction of future cardiovascular events compared to the measurement of only one of these markers. Patients with a combination of elevated levels of hsCRP and lipid profile showed the highest risk. However, the two factors together were superior to either factor alone in predicting risk.

The addition of hsCRP levels to standard cholesterol evaluation protocols improves clinicians' abilities to predict CVD risk (Ridker, 2003). In the PHS, hsCRP added to the predictive value of lipid parameters for determining future risk of MI (Ridker et al., 1998). Men with high levels of both hsCRP and TC had a 5.3 times greater RR of a future MI than did men with either high TC or high hsCRP levels alone (Ridker et al., 1998).
<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
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<tbody>
<tr>
<td><strong>Total cholesterol</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Low HsCRP/Low TC</td>
<td>57</td>
<td>53</td>
<td>14</td>
</tr>
<tr>
<td>Low HsCRP/High TC</td>
<td>5</td>
<td>7</td>
<td>15</td>
</tr>
<tr>
<td>High HsCRP/Low TC</td>
<td>29</td>
<td>28</td>
<td>39</td>
</tr>
<tr>
<td>High HsCRP/High TC</td>
<td>9</td>
<td>12</td>
<td>32</td>
</tr>
<tr>
<td><strong>Triglycerides</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low HsCRP/Low TG</td>
<td>42</td>
<td>39</td>
<td>9</td>
</tr>
<tr>
<td>Low HsCRP/High TG</td>
<td>20</td>
<td>20</td>
<td>16</td>
</tr>
<tr>
<td>High HsCRP/Low TG</td>
<td>23</td>
<td>37</td>
<td>38</td>
</tr>
<tr>
<td>High HsCRP/High TG</td>
<td>15</td>
<td>4</td>
<td>37</td>
</tr>
<tr>
<td><strong>HDL cholesterol</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low HsCRP/Low HDL cholesterol</td>
<td>58</td>
<td>54</td>
<td>14</td>
</tr>
<tr>
<td>Low HsCRP/High HDL cholesterol</td>
<td>4</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>High HsCRP/Low HDL cholesterol</td>
<td>33</td>
<td>32</td>
<td>37</td>
</tr>
<tr>
<td>High HsCRP/High HDL cholesterol</td>
<td>5</td>
<td>8</td>
<td>40</td>
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<tr>
<td><strong>LDL cholesterol</strong></td>
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<td></td>
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<tr>
<td>Low HsCRP/Low LDL cholesterol</td>
<td>30</td>
<td>34</td>
<td>22</td>
</tr>
<tr>
<td>Low HsCRP/High LDL cholesterol</td>
<td>30</td>
<td>24</td>
<td>5</td>
</tr>
<tr>
<td>High HsCRP/Low LDL cholesterol</td>
<td>21</td>
<td>23</td>
<td>47</td>
</tr>
<tr>
<td>High HsCRP/High LDL cholesterol</td>
<td>19</td>
<td>19</td>
<td>26</td>
</tr>
<tr>
<td><strong>Non-HDL cholesterol</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low HsCRP/Low HDL cholesterol</td>
<td>62</td>
<td>59</td>
<td>16</td>
</tr>
<tr>
<td>Low HsCRP/High HDL cholesterol</td>
<td>Nil</td>
<td>Nil</td>
<td>7</td>
</tr>
<tr>
<td>High HsCRP/Low HDL cholesterol</td>
<td>38</td>
<td>38</td>
<td>61</td>
</tr>
<tr>
<td>High HsCRP/High HDL cholesterol</td>
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<td>3</td>
<td>16</td>
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<tr>
<td><strong>Uric Acid</strong></td>
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<td></td>
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<tr>
<td>Low HsCRP/Low uric acid</td>
<td>60</td>
<td>44</td>
<td>12</td>
</tr>
<tr>
<td>Low HsCRP/High uric acid</td>
<td>2</td>
<td>15</td>
<td>11</td>
</tr>
<tr>
<td>High HsCRP/Low uric acid</td>
<td>38</td>
<td>34</td>
<td>63</td>
</tr>
<tr>
<td>High HsCRP/High uric acid</td>
<td>Nil</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td><strong>TC to HDL cholesterol ratio</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Low HsCRP/Low TC/HDL cholesterol</td>
<td>57</td>
<td>51</td>
<td>2</td>
</tr>
<tr>
<td>Low HsCRP/High TC/HDL cholesterol</td>
<td>4</td>
<td>8</td>
<td>20</td>
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<tr>
<td>High HsCRP/Low TC/HDL cholesterol</td>
<td>34</td>
<td>29</td>
<td>30</td>
</tr>
<tr>
<td>High HsCRP/High TC/HDL cholesterol</td>
<td>5</td>
<td>12</td>
<td>48</td>
</tr>
<tr>
<td><strong>TG to HDL cholesterol</strong></td>
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<tr>
<td>Low HsCRP/Low TG/HDL cholesterol</td>
<td>49</td>
<td>40</td>
<td>10</td>
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<tr>
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<td>12</td>
<td>17</td>
<td>39</td>
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<tr>
<td><strong>LDL cholesterol to HDL cholesterol</strong></td>
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<tr>
<td>Low HsCRP/Low LDL cholesterol/HDL cholesterol</td>
<td>58</td>
<td>55</td>
<td>13</td>
</tr>
<tr>
<td>Low HsCRP/High LDL cholesterol/HDL cholesterol</td>
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<td>37</td>
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<tr>
<td>High HsCRP/High LDL cholesterol/HDL cholesterol</td>
<td>7</td>
<td>8</td>
<td>38</td>
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The present findings suggest that this simple, multimarker approach might also be useful for risk assessment in clinically stable patients with CVD. The promising principle of a “multimarker” approach has recently been demonstrated in patients with an ACS, i.e., a simultaneous assessment of CRP (as a marker of inflammation) were associated with improved prognostic information in unstable patients (Sabatine et al., 2002). Both inflammation and lipid deposition are characteristic features of the atherosclerotic process. Modifying the risk factors or maintaining a healthy lifestyle, such as losing excess weight, not smoking, and taking regular exercise, can be a recommended way to reduce CRP and lipid profile levels and the risk of CVD.

4.12. Apolipoproteins

Apolipoproteins are the protein components of plasma lipoproteins and several different apolipoproteins have been identified. The major apolipoprotein of LDL cholesterol is apo B, is the chief protein component constituent of the atherogenic VLDL cholesterol, of IDL and of LDL particles, each particle including one apo B molecule.

Hence, plasma apo B levels reflect the total numbers of atherogenic particles. In humans, VLDL particles carry endogenously synthesized TG from the liver into plasma, where they undergo lipolysis to IDL by the action of lipoprotein lipase. IDL is lipolysed by hepatic lipase, converting to LDL cholesterol, or taken up by the liver via the LDL receptor. Apo B is also essential for the binding of LDL particles to the LDL receptor for cellular uptake and degradation of LDL particles. Apo A-I is the major apolipoprotein constituent of the antiatherogenic HDL cholesterol. Levels of apo A-I are strongly associated with those of HDL cholesterol. Apo A-I is critically involved in removing excess cholesterol from tissues and incorporating it into HDL for reverse transport, either directly or indirectly via LDL cholesterol to the liver. HDL also contains apo A-I, but its function and role in atherogenesis is unclear.

It is noteworthy that apo B, apo A-I and the apo B to apo A-I ratio reflect the status of the major atherogenic and anti-atherogenic pathways of lipoprotein metabolism. Accordingly, high apo B, high apo B to apo A-I ratio and low apo A-I levels in plasma indicate a high risk for CVD and vice versa. As with lipoprotein metabolism
in general, the levels of apo B and apo A-I are controlled by genetic, environmental and hormonal factors (Chan et al., 2004). Conditions that selectively elevate LDL cholesterol (e.g. familial hypercholesterolaemia) will increase apo B concentrations, and conditions which lower HDL cholesterol (e.g. type 2 diabetes) will lower apo A-I.

However, this is not always the rule. An important exception is hypertriglyceridaemia in the insulin resistant syndrome of central obesity, where LDL cholesterol levels are 'normal' yet apo B concentrations are elevated (Chan et al., 2004; Eckel et al., 2005). In this situation, the liver over secretes VLDL-apo B particles loaded with TG, which are then rapidly delipidated by hepatic lipase and converted to cholesterol-poor LDL, via a mechanism mediated by cholesteryl transfer protein, so that the plasma is rich in LDL apo B particles depleted of cholesterol.

Apo B was higher in patients with CVD than the control (Table 4.2). The mean values of group I was found to be 54.6±15.9, in group II 78.2±21.7 and in group III 64.5±14.3. There was statistically significant difference between group II (p< 0.001) and group I and between group III (p< 0.06) and group I. There was also a significant difference between group II and group III (p< 0.03). The mean values of apo A-I was in group I was found to be 72.0±40.6, in group II 77.0±17.1 and in group III 85.9±18.6. There was minor elevations found in the mean levels among all group and it was not statistically significant.

There were statistically significant difference among groups in the ratio between apo B to apo A-I and apo B to HDL cholesterol. The mean values of apo B to apo A-I was in group I was found to be 0.8±0.4, in group II 1.1±0.1 and in group III 1.3±0.2. The mean values of apo B to HDL cholesterol was in group I was found to be 1.2±0.4, in group II 2.0±0.6 and in group III 2.3±0.5. There was statistically significant in apo B to apo A-I ratio between group II (p< 0.004) and group I and between group III (p< 0.001) and group I. There was also a significant difference between group II and group III (p< 0.02). There was statistically significant in apo B to HDL cholesterol ratio between group II (p< 0.001) and group I and between group III (p< 0.001) and group I. There was no significant difference between group II and group III.
Various epidemiological studies that have shown that apolipoproteins are better predictors of cardiovascular risk than conventionally measured lipids, specifically LDL cholesterol and HDL cholesterol (Lamarche et al., 1996; Moss et al., 1999; Walldius et al., 2001; Talmud et al., 2002; Jiang et al., 2004; Shai et al., 2004; Yusuf et al., 2004; Ridker et al., 2005; Meisinger et al., 2005; St-Pierre et al., 2005). Quebec Cardiovascular Study was the first prospective study to demonstrate strongly that apo B was superior to cholesterol indices in predicting CHD risk (Lamarche et al., 1996). In a sample of 2,155 Canadian men followed for a period of 5 years for clinical signs of ischaemic heart disease (IHD), plasma apo B concentrations showed a strong association with onset of IHD (RR 1.4) independent of TG, HDL cholesterol, and TC to HDL cholesterol ratio. Stepwise logistic regression analysis also revealed that apo B was a stronger correlate of IHD than the TC to HDL cholesterol ratio. In the same study over 13 years of follow up, St-Pierre et al., (2005) recently reported that elevated plasma apo B levels remained an independent risk factor for IHD. This study also found that the association of high levels of apo B and an increased risk of IHD was more obvious in men with relatively low level of LDL cholesterol.

Thrombo Study (TS) investigated the predictive role of haemostatic and lipid variables on risk of recurrent coronary events in 1,045 MI patients with an average follow-up of 26 months (Moss et al., 1999). High apo B and low apo A-I levels were significant predictors of recurrent coronary events, independent of other lipid variables such as TC, LDL cholesterol and TG. The RRs for apo B and apo A-I were 1.82 and 0.54, respectively. In AMORIS, a total of 1,75,553 individuals from Sweden were recruited and followed for an average of 5.5 years (Wallidius et al., 2001). The relationships between fatal MI and apolipoproteins and other lipid measures were examined. In multivariate analyses (after adjusting for age, TC and TG), apo B, apo A-I and apo B to apo A-I ratio were all highly significant predictors of MI in both sexes. Apo B was also more significant than LDL cholesterol in prediction of risk of MI in both men and women. Receiver operating characteristics (ROC) analysis also showed that apo B had higher sensitivity and specificity than LDL cholesterol as a predictor variable in both sexes, especially in those with normal/low LDL cholesterol level. Similar findings were also observed in individuals aged 70 years or older.
Second Northwick Park Heart Study (NPHS II), included 2,508 healthy middle-aged United Kingdom men were recruited to examine the relative values of apo B and other lipid variables in predicting CHD risk over 6 years of follow-up (Talmud et al., 2002). In univariate analyses, the RRs for LDL cholesterol, apo B, apo A-I and apo B to apo A-I ratio were 2.67, 2.90, 0.52 and 3.58, respectively. Clearly, the apo B to apo A-I ratio conferred the highest RR of CHD. INTERHEART Study was a case-control observation study that assessed the relative importance of risk factors for CHD in 15,152 cases and 14,820 controls recruited from 52 countries worldwide (Yusuf et al., 2004). The ratio of apo B to apo A-I (OR 3.25) was the strongest risk factor in predicting MI, followed by current smoking (2.87), psychosocial factors (2.67), diabetes (2.37), hypertension (1.91) and abdominal obesity (1.62).

The apo B to apo A-I ratio is the most accurate summary index of the lipoprotein-related risk of vascular disease. Wallidus et al., (2004) demonstrated that the apo B to apo A-I ratio is superior to any of the cholesterol ratios as a summary index of the lipoprotein-related risk of vascular disease. The results of INTERHEART and AMORIS studies match up, almost data point for data point, providing striking quantitative confirmation. Finally, in both the INTERHEART and AMORIS studies, the influences of apo A-I and apo B were independent and equivalent. Independence and equivalence of LDL cholesterol and HDL cholesterol were also evident in the previous generations of cholesterol-based epidemiologic studies such as the Framingham Study and PROspective CARDiovascular Munster (PROCAM) study.

HPFS compared the predictive value of apo B with that of LDL cholesterol in 746 diabetic men followed-up for 6 years (Jiang et al., 2004). In both univariate and multivariate hazard models, the RR for apo B was higher than those for LDL cholesterol. The area under the ROC curve for the CVD-risk prediction model with apo B was larger than that for LDL cholesterol, indicating a better risk prediction for apo B than for LDL cholesterol. The predictive power of non-HDL cholesterol was as strong as that of apo B in these hazard models. However, the ratio of total to HDL cholesterol was the best predictor of CVD in this cohort of diabetic men. In NHS estimated the RR for lipids and apolipoproteins as predictors of CHD in 32,826 United States women over 8 years of
follow-up (Shai et al., 2004). The RRs for apo B, TG, LDL cholesterol, TC and HDL cholesterol were 1.8, 1.5, 1.4, 1.3 and 0.6, respectively, indicating that apo B levels were more strongly associated with increased CHD incidence than was LDL cholesterol. Under multivariate analysis, HDL cholesterol and its related ratios were the strongest contributors to predicting CHD. However, the study did not measure apo A-I, and could not therefore assess the predictive value of apo B to apo A-I.

In MONICA/KORA Augsburg Cohort Study after recruitment, 1,414 men and 1,436 women aged 35–64 years without a prior coronary event were followed-up for 13 years (Meisinger et al., 2005). Apo B and apo B to apo A-I ratio had predictive power similar to that of TC to HDL cholesterol in both sexes, after adjustment for age, smoking, alcohol, BMI, diabetes, and hypertension. In WHS included 15,632 initially healthy United States women aged 45 years or older over a 10-year period (Ridker et al., 2005). Under multivariate analysis, the RRs for LDL cholesterol (direct assay), non-HDL cholesterol, apo B and apo A-I were 1.62, 2.51, 2.50 and 0.57, respectively. Despite the authors concluding that non-HDL cholesterol and the ratio of TC to HDL cholesterol were as good as or better than apolipoprotein fractions in the prediction of future CVD events, apo B was in fact the single most significant lipid-related predictor of the occurrence of CVD events in the study. Hs-CRP was also a strong predictor of CVD, with RR of 2.98.

The superiority of the apolipoprotein over the cholesterol ratios is based on better predictive performance of both the numerator (apo B) and the denominator (apo A-I). The pathophysiologic bases for the superiority of apo B over LDL cholesterol are clear. LDL cholesterol systematically underestimates LDL particle number whenever small, dense cholesterol ester-depleted particles predominate. Risk relates more closely to the LDL particle number than LDL cholesterol because it is the number of LDL particles that impinge on and penetrate the endothelium rather than the mass of cholesterol they transport that determines the extent of injury to the arterial wall. A meta-analysis of published data among healthy individuals recognized baseline levels of both apo A-I and B, and their ratio to be predictive of incidence of CHD onset (Thompson and Danesh, 2006).
The epidemiologic evidence regarding apo A-I versus HDL cholesterol has been mixed, although more recent studies using standardized methods for apo A-I have favored apo A-I over HDL cholesterol (Khuseyinova and Koenig, 2006; Barter and Rye, 2006). The plasma levels of apo A-I reflect the balance between production and clearance of apo A-I. Unfortunately, little is understood as to the determinants of either, although clearance appears to be influenced, at least in part, by multiple plasma transfer proteins and enzymes, all of which affect HDL composition.

These include phospholipid transfer protein, cholesterol ester transfer protein, lecithin-cholesterol acyltransferase (LCAT), hepatic lipase, and lipoprotein lipase (Lewis, 2006). Although not widely appreciated, HDL cholesterol and apo A-I do not always change to the same degree in response to metabolic challenge. As plasma TG increase, there is a steady and substantial decrease in HDL cholesterol, but little change in apo A-I. There is, therefore, a stoichiometric imbalance between apo A-I and HDL cholesterol in the response to TG (Tremblay et al., 2007).

The other factor to appreciate is technical. The laboratory determinations of apo B and apo A-I are standardized, can be done using automated techniques, and do not require fasting samples. Apo B can be measured more accurately than LDL cholesterol can be calculated. As well, the methods to measure apo A-I are now more robust than many of those to measure HDL cholesterol. Therefore, the laboratory provides another layer of advantage for apolipoproteins over lipids (Marcovina and Packard, 2006).

These conclusions are supported by the recent report that the measurement of apolipoproteins constitutes an acceptable alternative to the use of blood lipids in assessing prognosis for CHD patients (Michal Benderly et al., 2009). Although apo B may be a slightly more powerful predictor of CVD than non-HDL cholesterol, but it requires separate testing, therefore adding expense, and it is not universally available. Apo B and apo A-I was relatively carried out in a limited number of patients, of course, data from large, randomized, prospective trials are required to substantiate these findings.
4.13. Uric acid

Uric acid is the final product of purine nucleotides metabolism. In mammals uricase present in the liver converts urate into alantoin, substantially reducing uric acid plasma levels. Finally, uric acid is eliminated by the kidney (Wu et al., 1992). The relationship between uric acid and CVD has been known since the 19th century, after that many authors reported the classical association of gout, hypertension, obesity and CVD (Culleton et al., 1999; Choi et al., 2005). Further studies showed that most individuals had hyperuricemia, but not gout (Johnson et al., 2005) and reported its association with obesity, hypertension, dyslipidemia, kidney and CVD and more recently with the metabolic syndrome (Coutinho et al., 2007). Due to the strong association with cardiovascular risk factors it is possible that hyperuricemia is rather a risk marker than an independent risk factor for atherosclerosis (Ioachimescu et al., 2008). Several epidemiological studies have evaluated whether uric acid is an independent risk factor for CVD but the literature is still controversial (Culleton et al., 1999; Alderman et al., 1999; Liese et al., 1999; Moriaty et al., 2000; Niskanen et al., 2004; Hozawa et al., 2006; Krishnan et al., 2006; Bos et al., 2006).

The percentage of hyperuricemia was higher in group III (26%) and group II (21%) than group I (3%). The mean values of group I was found to be 4.5±1.0, in group II 5.4±1.4 and in group III 6.0±1.4 (Table 4.2). There was statistically significant difference between group II (p< 0.001) and group I and between group III (p< 0.001) and group I. There was no significant difference between group II and group III. The relationships between uric acid and inflammatory markers are shown in Table 4.5. The concentration of uric acid is positively correlated with hsCRP concentrations.

Due to their high prevalence’s, abdominal obesity and the metabolic syndrome are frequently associated with the prevalence of CVD (Grundy et al., 2005). Plasma uric acid is often elevated in subjects with the metabolic syndrome and large epidemiological studies show that its prevalence increases according to uric acid levels (Schmidt et al., 1996; Yoo et al., 2005). Onat et al., (2006) have quantitatively estimated the assigned risk to uric acid concentrations and the clustering of metabolic syndrome components in adult and elderly populations. For each increase in one standard deviation of uric acid
levels there was a 35% increment in the presence of the metabolic syndrome after adjustment for age, smoking, alcohol consumption, TC, diuretic use and CRP levels. A lower association was seen with abdominal obesity. These results in association with other studies (Tuttle et al., 2001; Chien et al., 2005) showed a clear and independent association of uric acid levels with the metabolic syndrome, this relationship occurring mainly in women. In males the association of uric acid levels and metabolic syndrome was weaker due to the strong link between central obesity and this entity (Onat et al., 2006). Regarding abdominal obesity, studies done in lean and obese Japanese men showed that visceral adiposity measured by computerized tomography was a strong contributor to elevated uric acid concentrations possibly due to reduction in the clearance of this substance (Takahashi et al., 1997; Ishizaka et al., 2005). In the Turkish Adult Risk Factor Study (TARFS) abdominal obesity was the most important determinant of uric acid concentration variability after adjustment for 13 variables, including the use of alcohol, diuretics, high BP, glucose regulation and gamma glutamyl transferase levels (Onat et al., 2006). These studies suggest that abdominal obesity is the main determinant of elevated plasma uric acid levels in the general population.

There is evidence that hypertension, which is usually associated with other components of metabolic syndrome may mediate the direct relationship between this entity and increased uric acid levels (Lin et al., 2004). The mechanisms underlying the increase in uric acid and its potential prognostic implications in patients with essential hypertension are still not completely known. Increased serum uric acid levels in asymptomatic and uncomplicated subjects with essential hypertension may reflect early renal vascular alterations, with reduction in cortical blood flow and depressed tubular secretion of urate caused by its reduced delivery to the tubular secretory sites (Verdecchia et al., 2000). In a recent analysis of the FHS, serum uric acid was an independent predictor of hypertension's presence and progression (Sundstrom et al., 2005).

Hypertriglyceridemia is a major abnormality of the metabolic syndrome and there is evidence that the association between uric acid concentrations and insulin resistance may be mediated by increased TG levels (Giacomello et al., 1997). An
independent relationship between hyperuricemia and TG was reported in the Coronary Artery Risk Development in Young Adults (CARDIA) study, in 4053 white and black men. In addition, there is evidence of a possible genetic association between hypertriglyceridaemia and hyperuricemia (Rathman et al., 1998).

In a white Brazilian male population (Desai et al., 2005), as well as in United States populations (Rathman et al., 1998; Sekby et al., 1990; Vourinen-Markkola et al., 1994; Lee et al., 1995), uric acid concentration was associated with abdominal obesity, increased TG levels, low levels of HDL cholesterol and the presence of metabolic syndrome diagnosed by the ATP III modified criteria (Grundy et al., 2005). The higher the number of metabolic syndrome components, the higher the serum uric acid concentrations. Desai et al., (2005) have also showed a linear and independent association between serum uric acid levels and the TG to HDL cholesterol ratio. This ratio has been directly correlated with insulin resistance in overweight subjects (McLaughlin et al., 2003) and with the risk of cardiovascular events (Jeppesen et al., 2001). Individuals with TG to HDL cholesterol ratio ≥3 had uric acid levels significantly higher than individuals with lower ratios. One possible explanation for these findings other than increased uric acid reabsorption due to insulin resistance (Messerli et al., 1980) is that the metabolic syndrome is associated with increased oxidative stress and uric acid has potent counteracting antioxidant effects (Nieto et al., 2000). In a subgroup of subjects evaluated in the ARIC study, carotid subclinical atherosclerosis was associated with an increased total serum antioxidant capacity. Serum antioxidant capacity was strongly related to uric acid levels. The elevation in uric acid plasma levels found in subjects with the metabolic syndrome could reflect a mechanism to neutralize the compensatory high oxidative stress associated with this entity (Tsouli et al., 2006).

As shown in the Table 4.5 a correlation of hsCRP, a marker of subclinical inflammation related to atherosclerosis, and serum uric acid levels has been described (Ruggiero et al., 2006; Frohlich et al., 2000). A significant independent association was found between uric acid and inflammatory markers, such as white blood cell count, blood neutrophil count, hsCRP, IL and TNF-α levels (Ruggiero et al., 2006). Moreover, there is a positive correlation between uric acid and inflammation in patients with
systolic heart failure (Leyva et al., 1998) independently of confounders like diuretic use, renal failure, insulin resistance or alcohol consumption. These data suggest that uric acid is not only a marker of the catabolic rate, but it may also be actively involved in the inflammatory process.

In the MONICA Augsburg study (Liese et al., 1999) that included 1,044 men, serum uric acid increase was an independent factor for all causes of death and possibly mortality from CVD. In the Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) study (Hoieggen et al., 2004), for each 0.16-mg/dL elevation of serum uric acid concentration there was, after adjustment for Framingham risk score, a hazard ratio of 1.013 for cardiovascular events in women. Data from the NHANES I (Lehto et al., 1998) suggest that for every 1.01 mg/dL increase in the uric acid level there is an increment of 48% in the risk of ischemic stroke in women. Similar results were found in 4,385 individuals who had participated in the Rotterdam study (Bos et al., 2006). In that study, after an average follow-up of 8.4 years high serum uric acid levels were associated with increased risk of MI and stroke; age- and sex-adjusted hazard ratios for highest versus lowest quintile of uric acid were 1.68 for CVD, 1.87 for MI, 1.57 for stroke, 1.77 for ischemic stroke, and 1.68 for hemorrhagic stroke. Adjustment for other vascular risk factors only slightly attenuated these associations. Associations were stronger in persons without hypertension than in those with hypertension.

Prospective data on 13,413 men and women, participants in the ARIC study (Hozawa et al., 2006) followed for 12.6 years showed an independent and positive relationship between uric acid and incidence of ischemic stroke in those individuals who did not use diuretics. Differently from the studies cited above data from 6763 patients of both Framingham and Framingham Offspring studies, uric acid levels were not independently associated with an increased risk of CHD, death from CVD or death from all causes after adjustment for risk factors and confounders (Culleton et al., 1999). Similarly in the ARIC study where 13,504 men and women were followed for up to 8 years (Moriarity et al., 2000) increased uric acid concentrations were not independently associated with an increased risk of CHD. More recently, Strasak et al., (2008), who followed 83,683 Austrian men for a median of 13.6 years, found a strong
relation between serum uric acid levels and risk factors for atherosclerosis. In their study the highest quintile of serum uric acid concentration (6.7 mg/dL) was significantly related to mortality from CHF and stroke; adjusted hazard ratios for the highest versus lowest quintiles of serum uric acid were 1.51 and 1.59, respectively.

The RR of hypercholesterolemia was found to be 3.14 (95 % CI 1.84 to 5.35). The RR of hypertriglyceridemia was found to be 1.60 (95 % CI 1.14 to 2.24). The RR of high LDL cholesterol was found to be 5.0 (95 % CI 2.69 to 9.29). The RR of HDL cholesterol was found to be 3.09 (95 % CI 2.06 to 4.64). The RR of uric acid was found to be 8.66 (95 % CI 2.71 to 27.71). From the studied parameter such as, high levels of TC, LDL cholesterol, TG, non-HDL cholesterol, lipid ratios, atherogenic dyslipidemia, metabolic syndrome, apo B, apo A-I, uric acid and low levels of HDL cholesterol were positively associated with CVD and it has been proven as risk factor or marker in CVD.

4.14. Electrophoresis

Lipoprotein electrophoresis was performed on serum from subjects suspected to CVD, who are exempted from the study population. Plate 4.1 shows the electrophoretic pattern of the study subjects. It is important in concern with the proposition that lipoprotein patterns might prove to be a valuable index of the presence of CVD, thus adding to the power of biochemical determinations of locate subject at risk of this disease.

4.15. Type A Personality

To understand the relationship between type A personality and CVD, type A behaviour patterns was assessed only in 50 patients (25 from group I and 25 from group III) by a self-administered questionnaire in patients from group I and group III, but not in group II. From the study it was noted that the percentage of type A personality was higher in group III (36%) than group I (16%). From the results it was understood, type A personality was a minor risk factor for CVD. The incidence of heart attacks and sudden death have been shown to increase significantly following the acute stress of natural disasters like hurricanes, earthquakes and tsunamis and as a consequence of any severe
Plate 4.1 Electrophoretic patterns of Lipoproteins

1, 2 Normal patients; 3-27 Suspected subjects
stressor that evokes "fight or flight' responses. CHD is also much more common in individuals subjected to chronic stress and recent research has focused on how to identify and prevent this growing problem, particularly with respect to job stress. In many instances, most persons create their own stress that contributes to coronary disease by smoking and other faulty lifestyles or because of dangerous traits like excess anger, hostility, aggressiveness, time urgency, inappropriate competitiveness and preoccupation with work. These are characteristic of Type A coronary prone behaviour, now recognized to be as significant a risk factor for heart attacks and coronary events as cigarette consumption, elevated cholesterol and BP. While Type A behaviour can also increase the likelihood of these standard risk factors, its strong correlation with CHD persists even when these influences have been excluded.

With respect to personality and Type A behavioural traits, Von Dusch, a 19th century German physician, first noted that excessive involvement in work appeared to be the hallmark of people who died from heart attacks. In 1959, a paper by Meyer (Mike) Friedman and Ray Rosenman appeared in the Journal of the American Medical Association entitled "Association of specific overt behaviour patterns with blood and cardiovascular findings: Blood cholesterol level, blood clotting time, incidence of arcus senilis and clinical coronary artery disease" (Friedman and Rosenman, 1959). As noted, psychiatrists and others interested in psychosomatic disorders had previously described certain personality characteristics in heart attack patients. However, it was not possible to prove that these had any causal relationship since such idiosyncrasies could have resulted from the illness rather than vice versa. Friedman and Rosenman, (1959) were the first to explain why specific behaviours could cause heart attacks and contribute to coronary artery disease. The term "Type A" was not mentioned in this initial paper but emerged the following year in an article describing how this type of "overt pattern behaviour A" could be detected by a "new psycho-physiological procedure" (Friedman et al., 1960). Rosenman was subsequently able to show the predictive value of this technique so that coronary prone patients could be identified and hopefully treated to prevent future problems.
Stroke

4.16. Non-modifiable risk factors

The patients were categorized under Group I, which included 29 males and 21 females with a mean age of 55.1±6.4 (randomly selected from control group), in Group IV included 30 males and 20 females with a mean age of 57.8±7.2 and in Group V included 35 males and 15 females with a mean age of 60.5±8.8. The mean age in group IV (p< 0.001) and group V (p< 0.001) was higher in patients than the control, with statistically significant differences. In all groups (I, IV and V) it was identified a predominantly male cohort 58%, 60% and 70% respectively. In many epidemiologic surveys, age remains one of the strongest predictors of disease. The risk of stroke increases in older. The percentage of the study population over 65 years was 6%, 18% and 40% in group I, IV and V respectively (Table 4.6).

4.16.1. Age, male sex and family history

The proportion of ischemic stroke was higher among men and women ≥70 years of age than among those 40 to 69 years of age. The higher proportion of ischemic stroke among older persons was reported from other studies (Suzuki et al., 1987; Lauria et al., 1995; Carolei et al., 1997; Kolominsky-Rabas et al., 1998; Lavados et al., 2005). For every 10 years you live, your risk of having a stroke increases. Men have 2 times more risk for stroke than women have. But more women die of stroke than of breast cancer. The risk for stroke is greater when heart attack, stroke, or TIA runs in your family (Jakicic, 2003).

4.17. Modifiable risk factors

Stroke risk factors, including smoking, obesity, hypertension and diabetes had a higher prevalence in the TIA or stroke groups than in control with a relatively high percentage of non-vegetarian (96%, 88% and 92% in group I, IV and V respectively) and physical inactivity (84%, 94% and 96% in group I, IV and V respectively). Smoking was reported in 24.7% of the study population. It was significantly higher in group V (36%) than group IV (16%) and group I (22). Of the participants, 6%, 8% and 20% (in group I, IV and V respectively) reported that they were current consumers of alcoholic beverage.
TABLE 4.6 Clinical characteristic of study patients (Stroke)

<table>
<thead>
<tr>
<th></th>
<th>Control (n=50)</th>
<th>Test group (Untreated) (n=50)</th>
<th>Test group (Treated) (n=50)</th>
</tr>
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<tbody>
<tr>
<td><strong>Non-modifiable risk factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>55.1±6.4</td>
<td>57.8±7.2</td>
<td>60.5±8.8</td>
</tr>
<tr>
<td>Elders ≥ 65 years (%)</td>
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<td>9</td>
<td>20</td>
</tr>
<tr>
<td>Sex M/F</td>
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<td>30/20</td>
<td>35/15</td>
</tr>
<tr>
<td>Family History (%)</td>
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<td>1</td>
<td>4</td>
</tr>
<tr>
<td><strong>Modifiable risk factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Food Habit – Veg/Non-Veg (%)</td>
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<td>12/88</td>
<td>8/92</td>
</tr>
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<td>Cigarette Smoking – Ever/Never (%)</td>
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<td>16/84</td>
<td>36/64</td>
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<tr>
<td>Alcohol Consumption – Ever/Never (%)</td>
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</tr>
<tr>
<td>BMI (%)</td>
<td>2</td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>Obesity (%)</td>
<td>2</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>Physical Activity – Low or Lack (%)</td>
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<td>96</td>
</tr>
<tr>
<td>Diabetes (%)</td>
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<td>38</td>
</tr>
<tr>
<td>Hypertension – SBP or DBP (%)</td>
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<td>38</td>
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<tr>
<td>Hypercholesterolemia (%)</td>
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</tr>
<tr>
<td>Atherogenic Dyslipidemia (%)</td>
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<td>6</td>
<td>14</td>
</tr>
<tr>
<td>Metabolic Syndrome (%)</td>
<td>6</td>
<td>16</td>
<td>34</td>
</tr>
<tr>
<td><strong>Treatment of study entry</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Hypoglycemic – Oral/Insulin</td>
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<td>15/1</td>
<td>15/3</td>
</tr>
<tr>
<td>ACE inhibitor (%)</td>
<td>32</td>
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</tr>
<tr>
<td>Antiplatelet Therapy (%)</td>
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</tr>
<tr>
<td>β - Blocker (%)</td>
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<td>Atorvastatin (%)</td>
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<tr>
<td>Other lipid lowering drugs (%)</td>
<td>2</td>
<td>16</td>
<td>Nil (0)</td>
</tr>
</tbody>
</table>
Obesity was found in 6% of the study population. It was significantly higher in group V (12%) and in group IV (4%) than group I (2%).

Of the people examined, 32% in group I, 38% in group IV and 54% in group V had BP levels of 140 or 90 or higher. The prevalence of hypertension was higher in group V than the other groups. The mean DBP was significantly higher in group V (\(p< 0.06\)) when compared with group I. There was no statistically significant difference between group I and group IV and group IV and group V. The mean SBP was significantly higher in group V (\(p< 0.001\)) than the group I and between group V (\(p< 0.02\)) than group IV. There was no difference between group I and group IV. The occurrence of hypertension was significantly higher in people aged 50 years and over in group I (93.8%), group IV (94.7%) and group V (88.9%). In all groups (I, IV and V) it was identified a predominantly male cohort 62.5%, 73.7% and 63% respectively.

History of diabetes was found in 30% of the study population. It was significantly higher for group V (38%) than for both group I (20%) and group IV (32%). The mean sugar level was significantly higher in group V (\(p< 0.09\)) when compared with group I. There was no statistically significant difference between group I and group IV and group IV and group V. In all groups (I, IV and V) it was identified a predominantly male cohort 60%, 68.8% and 73.7% respectively. The occurrence of diabetes was significantly higher in people aged 50 and over in group I (80%), group IV (87.5%) and group V (78.9%). Diabetic participants had a higher prevalence of stroke at baseline. Diabetic participants also had a higher prevalence of hypertension by history (Table 4.6).

**4.17.1. Cigarette smoking**

In the present study, it was found that smoking is an independent risk factor for stroke in men. Cigarette smoking has received attention as a risk factor for stroke (Shinton and Beevers, 1989; Surgeon General’s report, 1989). A number of studies have shown cigarette smoking to be an independent risk factor for stroke, after adjusting for age and hypertension, with RR ranging from 1.5 to 1.7 (Bonita et al., 1986; Colditz et al., 1988; Wolf et al., 1988; Donnan et al., 1989; Shinton and Beevers, 1989).
The epidemiological evidence suggests that smoking is causal because risk increases for smokers versus nonsmokers independently of other risk factors, because a dose-response relationship exists, and because risk decreases after smoking cessation.

The data from the Framingham study show that the risk of stroke increased as the number of cigarettes smoked increased (Wolf et al., 1988). Also, the meta-analysis (Shinton and Beevers, 1989) of the published data on the association between cigarette smoking and stroke demonstrated a significant dose-response relationship: the RR was 1.37 in people smoking fewer than 10 cigarettes a day and 1.82 in those who smoked more than 20. Both 12-year and 20-year follow-up studies of the HHP involving Japanese Americans living in Hawaii showed smoking to be a risk factor for cerebral infarction and for hemorrhagic stroke (Abbot et al., 1986; Goldberg et al., 1995). These findings reveal a recent trend among Japanese smokers, because the NIPPON DATA80 (Hirotsugu et al., 2004) was the first follow-up study for a representative Japanese population randomly selected throughout Japan. These findings combined with those of the present study have led to conclude that smoking is a risk factor for stroke.

4.17.2. Obesity

Excess weight increases the risk of stroke. People who have a stroke or heart disease often have excess body fat around their lower belly, or abdomen. This is sometimes called an “apple shape.” In the most recent guideline statements for healthcare professionals from the Stroke Council of the American Heart Association, obesity was categorized as a “less well documented or potentially modifiable risk factor (Goldstein et al., 2001).” Several studies have shown an association of obesity as defined by BMI with the risk of stroke. The HHP reported that BMI was associated with increased risk of thromboembolic stroke among nonsmoking men in older middle age (Abott et al., 1994).

In the FHS, an association between metropolitan relative weight and atherothrombotic stroke was found in women but not in men (Hubert et al., 1983). Obesity also can bring other risk factors with it, such as high BP, higher bad cholesterol,
and diabetes. Weight control and exercise improve your circulation and help reduce other risk factors (Jakicic, 2003).

4.17.3. Physical inactivity

It has been well established that physical activity plays an important role in preventing CHD and CVD in general (Berlin and Colditz, 1990; Powell et al., 1987; US Department of Health and Human Services, 1996). In 1999, Wannamethee and Shaper published a review, including five cohort studies, addressing the relationship between physical activity and stroke. They concluded that most of these studies had shown physical activity to be associated with a reduced risk of stroke and that moderate levels of physical activity may be sufficient to achieve a significant reduction in stroke risk (Wannamethee and Shaper, 1999).

The results of a meta-analysis indicate an association between physical activity and a lower risk of stroke. For occupational physical activity, being active was associated with a 43% and 23% lower risk of ischaemic stroke compared with respectively being inactive and being moderately active. Being moderately active at work was associated with a 36% lower risk of total stroke compared with being inactive at work. For leisure time physical activity, being active was associated with a 20-25% lower risk compared with being inactive. Being moderately active during leisure time was associated with a 15% lower risk on total stroke compared with being inactive during leisure time (Wendel et al., 2004). Exercise is important to help control weight, BP, cholesterol, and diabetes - all risk factors for stroke (Jakicic, 2003).

4.17.4. Hypertension

Most epidemiological studies have confirmed that BP is among most important single risk factors of stroke in all ethnic groups (World Health Organisation, 1971; Marmot et al., 1975; Kannel et al., 1976; Abu-Zeid et al., 1977; Callen et al., 1978; Kannel et al., 1978; Rabkin et al., 1978; Ueshima et al., 1980; MacMahon et al., 1990; Eastern Stroke and Coronary Heart Disease Collaborative Research Group, 1998; Lewington et al., 2002; Chobanian et al., 2003). There is good evidence that BP contributes to the development
of atherosclerosis and ischemic brain infarction. In general, 35-75 per cent of the stroke patients, depending on study material and methods, have been found to have elevated BP. The variation can mostly be explained by the different definitions of elevated BP. Hypertension has also been noted to be an important risk factor for recurrent stroke. The association between BP and stroke mortality is strong and direct, and the absolute risk of stroke mortality associated with high BP increases with age (Lewington et al., 2002).

4.17.5. Diabetes

In the MRFIT in 1973-75, 12-year mortality was determined for 5,163 men age 35-57 years who reported taking medication for diabetes and 3,24,815 men without a history of diabetes (Stamler et al., 1993). The risk of mortality from stroke was increased 2.8-fold among those with diabetes, even after adjusting for age, race, income, and cardiovascular risk factors. The risk of stroke mortality was greatest for nonhemorrhagic stroke (RR 3.8) than for subarachnoid (1.1) or intracranial hemorrhage (1.5) (Neaton et al., 1993). In the NHS, the risk of stroke and CVD was determined in 1,16,177 female registered nurses who were free of CHD, stroke, and cancer at baseline (Manson et al., 1991). There was an 8-year follow up during 1976-84. Sixteen nonfatal and eight fatal stroke cases were reported in the 1,483 women with diabetes, and 167 and 68 cases, respectively, among the nondiabetic women.

The age-adjusted risk of stroke for diabetic versus nondiabetic women was 4.1. The risk was similar for fatal (5.0) and nonfatal (3.8) strokes. The Copenhagen City Heart Study (CCHS) evaluated 3,015 men and 3,501 women age 55-84 years (Truelsen et al., 1994). There were 474 strokes over a 10-year period. Only 3% of men and 2% of women had a history of diabetes. The risk of stroke was greater for diabetes in the Copenhagen study than in the Framingham study, probably due to the restriction of diagnosis of diabetes to those with a reported clinical history, whereas the Framingham study included a casual blood glucose >150 mg/dl as part of the diagnosis for diabetes. McCall, (1992) has noted that a higher blood glucose level at hospital admission predicts a poorer prognosis after a stroke, irrespective of whether the patient is diabetic or not. Also, the degree of disability after the stroke may be worse among individuals with
elevated blood glucose at the time of the stroke. Animal models showed that hyperglycemia alone worsens the ischemic brain damage from a stroke.

4.17.6. Hypertension and diabetes

This study indicated that both hypertension and diabetes were independently associated with an increased risk of the incidence of stroke. BP was associated with the risk of stroke in a similar fashion both in diabetic and nondiabetic subjects. The highest risk of an incident stroke event was found among subjects who had both hypertension and diabetes. The analyses from another Finnish study (Lehto et al., 1996) and the UK Prospective Diabetes Study (UKPDS) (Davis et al., 1999) have demonstrated that hypertension or an increase in SBP were independently associated with an increased risk of stroke in the diabetic patients. Therefore, it may possible that the increased risk of stroke usually seen in hypertensive subjects may sometimes be related not only to the hypertension itself but also to diabetes. In the community of Rancho Bernardo, CA, 3,778 men and women who were age 50-79 years in 1972-74 were evaluated during the next 12 years for fatal and nonfatal stroke (Barrett-Connor and Khaw, 1988). The risk of stroke was significantly higher among diabetic men and women compared with those without diabetes. The risk of stroke among both diabetic and nondiabetic individuals increased substantially with higher SBP. For diabetic men and women, the risk of stroke among those with SBP ≥160 was about two times that of those with systolic BP <160.

Although subjects with hypertension are more likely to develop type 2 diabetes (Gress et al., 2000), and hypertension is very common in patients with type 2 diabetes (American Diabetes Association, 2003), two studies (Iso et al., 2004; Kissela et al., 2005) assessed the joint effect of hypertension and type 2 diabetes on the stroke risk in the general population. A Japanese study analyzed the relation between diabetes and the risk of ischemic stroke stratifying for the hypertension status and BMI (Iso et al., 2004) and found that the excess risk of ischemic stroke associated with diabetes was primarily observed in nonhypertensive subjects or those with high BMI but not in hypertensive subjects or subjects with low BMI. The Greater Cincinnati/Northern Kentucky Stroke Study (GCNKSS) determined the RR of ischemic stroke attributable to diabetes, hypertension, or both (Kissela et al., 2005). It indicated that the risk of stroke attributable
to a history of both diabetes and hypertension was substantially greater than for either condition alone, in keeping with the present study results. The RR for the incidence of hypertension and diabetes in the present study were found to be 1.68 (95% CI 1.04 to 2.72) and 1.40 (0.68 to 2.84) respectively.

From the studied parameter such as, age, male sex, family history, cigarette smoking, obesity, physical inactivity, hypertension and diabetes were positively associated with stroke. In particular age, male sex, cigarette smoking, physical inactivity, hypertension and diabetes are proven as risk factor in stroke.

In the present study with the exception of TG, all lipid levels and its ratios were strongly associated with subsequent risk of ischemic stroke. After additional adjustment for a large number of potential confounders, TC, LDL cholesterol, HDL cholesterol, the TC to HDL cholesterol ratio, LDL to HDL cholesterol ratio, non-HDL cholesterol and non-HDL cholesterol to HDL cholesterol ratio remained significantly associated with increased risk of ischemic stroke. The association between all lipid levels and risk of stroke were attenuated after adjustment for factors that affect lipid levels such as exercise (Sagiv and Goldbourt, 1994), alcohol consumption (Gaziano et al., 1993), smoking habits (Connelly et al., 1999), and BMI (Connelly et al., 1999). Since these behavioural factors are also risk factors for ischemic stroke (Kurth et al., 2006), the present study data may indicate that lipid levels are as part of the mechanism by which these factors may increase the risk of stroke.

4.18. Total cholesterol and low-density lipoprotein cholesterol

Table 4.7 summarizes the biochemical parameters examined in serum samples of all patients divided according to the groups. All biochemical parameters are expressed in mean and standard deviation. Patients generally had moderate to high elevated levels of lipid risk factors or markers such as, TC, LDL cholesterol, non-HDL cholesterol, lipid ratios (TC to HDL cholesterol, LDL cholesterol to HDL cholesterol Non-HDL cholesterol to HDL cholesterol), low levels of HDL cholesterol in the test groups than the control with exception of TG.
TABLE 4.7 Baseline mean levels of the biochemical parameters examined in serum samples of all patients

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group IV</th>
<th>Group V</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nonlipid risk factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (n = 20)</td>
<td>23.5±2.7</td>
<td>23.9±3.3</td>
<td>27.4±4.6</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>123±11.1</td>
<td>125±13.9</td>
<td>131.4±17.5</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>81.2±7.7</td>
<td>81.8±8.3</td>
<td>84.4±9.5</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>0.9±0.4</td>
<td>1.2±0.7</td>
<td>2.3±1.4</td>
</tr>
<tr>
<td>Glucose</td>
<td>114.7±21.8</td>
<td>115.7±30.6</td>
<td>125.3±33.5</td>
</tr>
<tr>
<td><strong>Lipid risk factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>166.1±30.8</td>
<td>170.8±30.2</td>
<td>184.7±32.1</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>137.6±71.4</td>
<td>151.2±76.1</td>
<td>156.1±74.8</td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol</td>
<td>40.1±6.8</td>
<td>40.9±8.4</td>
<td>37.0±5.0</td>
</tr>
<tr>
<td>Low-density lipoprotein cholesterol</td>
<td>98.9±26.9</td>
<td>99.6±24.4</td>
<td>115.3±28.9</td>
</tr>
<tr>
<td>Very Low-density lipoprotein cholesterol</td>
<td>27.8±14.7</td>
<td>30.3±15.2</td>
<td>31.8±17.2</td>
</tr>
<tr>
<td>Non-HDL cholesterol</td>
<td>126.2±28.1</td>
<td>125.4±23.2</td>
<td>147.9±33.4</td>
</tr>
<tr>
<td><strong>Ratios</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TC to HDL cholesterol</td>
<td>4.2±0.7</td>
<td>4.0±0.7</td>
<td>5.0±1.4</td>
</tr>
<tr>
<td>LDL cholesterol to HDL cholesterol</td>
<td>2.5±0.6</td>
<td>2.3±0.7</td>
<td>2.9±1.0</td>
</tr>
<tr>
<td>TG to HDL cholesterol</td>
<td>3.5±1.9</td>
<td>3.7±1.9</td>
<td>4.2±2.5</td>
</tr>
<tr>
<td>Non-HDL cholesterol to HDL cholesterol</td>
<td>3.2±0.7</td>
<td>3.2±0.8</td>
<td>3.9±1.2</td>
</tr>
</tbody>
</table>
Risk of stroke is increased significantly with increasing TC and LDL cholesterol. The percentage of hypercholesterolemia found to be higher in group V (34%) than group I (20%) and IV (22%). The mean values of group I was found to be 166.1±30.8, in group IV 170.8±30.2 and in group V 184.7±32.1. There was statistically significant difference between group V (p< 0.04) and group I and between group V (p< 0.02) and group IV. There was no significant difference between group I and group IV. The LDLcholesterolemia was higher in group V (22%) when compare with group I (14%) and IV (18%). LDL cholesterol was higher in patients with stroke than the control. The mean values of group I was found to be 98.9±26.9, in group IV 99.6±24.4 and in group V 115.3±28.9. There was statistically significant difference between group V (p< 0.003) and group I and between group V (p< 0.002) and group IV. There was no significant difference between group I and group IV.

The association between TC and risk of ischemic stroke has been investigated in several prior observational studies, of which some found increased risk with increasing cholesterol levels (Iso et al., 1989; Benfante et al., 1994; Di Mascio et al., 1995; Koren-Morag et al., 2002; Tirschwell et al., 2004; Ebrahim et al., 2006) and some no clear associations (Leppala et al., 1999; Eastern Stroke and Coronary Heart Disease Collaborative Research Group, 1998; Bowman et al., 2003; Sacco et al., 2001). In a prospective study of over 7,87,000 Korean civil servants, TC was strongly associated with increased risk of ischemic stroke. For a 38.7 mg/dL increase of TC, the RR of ischemic stroke was 1.41 and TC levels of 160.1 mg/dL were significantly associated with stroke risk (Ebrahim et al., 2006). The Asia Pacific Cohort Studies Collaboration (APCSC) pooled data from 29 cohorts from the Asia-Pacific region and found a 25% increase in the risk of ischemic stroke for every 38.7 mg/dL increase in TC (Zhang et al., 2003). The Women's Pooling Project (WPP) pooled data from 8 cohort studies and found a 23% increase in the RR of ischemic stroke for every 38.7 mg/dL increase in TC among women aged <55 years (Horenstein et al., 2002).

In older age groups, however, there was no apparent association between TC and ischemic stroke. Other studies did not find association between TC and ischemic stroke risk (Eastern Stroke and Coronary Heart Disease Collaborative Research Group,
1998; Hart et al., 1999; Wannamethee et al., 2000; Bowman et al., 2003). This lack of association may be partly explained by evaluating only stroke mortality (Eastern Stroke and Coronary Heart Disease Collaborative Research Group, 1998; Hart et al., 1999; Wannamethee et al., 2000) and by controlling for markers of hypertension (Eastern Stroke and Coronary Heart Disease Collaborative Research Group, 1998; Wannamethee et al., 2000; Bowman et al., 2003), a potential biological mediator by which cholesterol increase ischemic stroke risk (Sesso et al., 2005).

The association between LDL cholesterol and risk of ischemic stroke has only been evaluated in few studies. A large study of over 11,000 patients with CHD showed a 14% increase in the RR of verified ischemic stroke or TIA per 40 mg/dL increase in LDL cholesterol (Koren-Morag et al., 2002). In contrast, a large cohort study of over 14,000 middle aged men and women found no consistent association between LDL cholesterol and ischemic stroke during 10 years of follow-up (Shahar et al., 2003).

Results of clinical trials of LDL cholesterol lowering with statins have demonstrated reduction in ischemic strokes. One study has found that statins may provide benefits for the long-term functional outcome when administered before the onset of cerebral ischemia (Marti-Fabregas et al., 2004). In the HPS, statins reduced 4.0% of the ischemic stroke (Heart Protection Study Collaborative Group, 2002). The ASCOT-LLA study found that statins reduced 27% of fatal and non-fatal stroke (Sever et al., 2003). Clinical trials with statins have possibly indicated a lipid mechanism to stroke, despite these HMG-CoA reductase inhibitors may have other effects such as interfering with platelet aggregation, antioxidative, improving blood flow to the ischemic brain (Vaughan and Delanty, 1999; Rosenson, 2000). In this study, LDL cholesterol was significantly associated with other ischemic stroke and the results might support the lipid mechanism to stroke.

In contrast to its established role in the pathogenesis of CHD, raised plasma cholesterol and LDL cholesterol are less well established as important risk factors for cerebrovascular disease (Postiglione and Napoli, 1995; Khaw, 1996; Oliver, 2000). The reasons are likely to be many. Nearly all CHD events are linked to coronary atheroma,
but less than half of strokes are due to large vessel atheroma. Non-atheromatous causes of strokes, such as cardiac arrhythmias leading to cerebral emboli, cardiomyopathies, or intracranial vessel diseases are responsible for most of the rest. Nevertheless, the majority of ischaemic strokes is caused by thromboemboli arising from atheromatous disease (outside the brain, either from the carotid arteries or the aortic arch), where hypercholesterolaemia is commonly present. The contention that cholesterol lowering is effective in reducing carotid atheroma is supported by ultrasound measurements of carotid artery intima-media thickness, independently shown to be a predictor of the occurrence of stroke (O’Leary et al., 1999). Such measurements indeed show that reductions of plasma LDL cholesterol by 25% or more prevented any detectable progress in carotid intimaimedia thickness and reduced the development of new lesions both in asymptomatic people and in patients <75 years old (Furberg et al., 1994; Krouse et al., 1995) — as for coronary atheroma. Thus, the reduction of CHD with cholesterol-lowering therapy would be still expected to be accompanied by some reduction in the incidence of stroke.

4.19. Triglycerides and very low-density lipoprotein cholesterol

Studies of TG level in relation to stroke or ischemic stroke either reported a positive association (Salonen et al., 1982; Lindenstrom et al., 1994; Hachinski et al., 1996;) or reported no association at all (Rhoads and Feinleib, 1983; Pedro-Botet et al., 1992; Haheim et al., 1993; Simons, 1998; Wannamethee et al., 2000).

Hypertriglycerideremia was significantly higher in group IV (38%) than the group V (34%) and group I (26%). The mean values in group I was found to be 137.6±71.4, in group IV 151.2±76.1 and in group V 156.1±74.8. There were no statistical significances in TG among all groups. The mean values of VLDL cholesterol in group I was found to be 27.8±14.7, in group IV 30.3±15.2 and in group V 31.8±17.2. There were no statistically significant in VLDL among all groups (Table 4.7).

In the Bezafibrate Infarction Prevention (BIP) study, after adjusted for traditional risk factors, TG > 200mg/dL were associated with an OR for ischemic stroke of 1.47 compared with lower TG levels (Tanne et al., 2001).
diagnostic angiography, Ballantyne et al., (1974) found no differences in TC or fasting TG when comparing patients with and without atheroma causing a >25% stenosis of the lumen of the internal carotid artery. However, in the group without atheroma, the investigators included patients with a 25% stenosis, thus narrowing the range of lesions investigated. Because angiography consistently underestimates extent of atherosclerotic arterial disease (Glagov et al., 1987; McPherson et al., 1987), choice of 25% stenosis as the discriminator between the two analysis groups probably misclassified some patients.

Rossner et al., (1978) found no significant correlation between TC and TG and the degree of carotid atherosclerosis in a study of stroke patients. Extent of atherosclerosis was dichotomized as "none or slight" and "moderate or severe," providing the opportunity for some misclassification. It is important to note that patients in this study were <55 years old since it has been shown that in younger individuals atherosclerosis is not as strongly linked to symptomatic disease as in older people (Hart and Miller, 1983). Some other studies also reported no association between TG and ischemic stroke (Pedro-Botet et al., 1992; Bowman et al., 2003).

4.20. High-density lipoprotein cholesterol

With regard to HDL cholesterol, several studies found a significant association between HDL cholesterol and ischemic stroke after adjustment for potential confounders (Leppala et al., 1999; Wannamethee et al., 2000; Sacco et al., 2001; Koren-Morag et al., 2002; Tirschwell et al., 2004). Low - HDL cholesterolemia was higher in group V (58%) and group I (40%) than group IV (34%). The mean values of group I was found to be 40.1±6.8, in group IV 40.9±8.4 and in group V 37.0±5.0 (Table 4.7). There was statistically significant difference between group V (p< 0.007) and group IV and between group V (p< 0.01) and group I. There was no significant difference between group I and group IV.

The inverse relationship between serum HDL cholesterol and stroke risk has strengthened in light of more recent epidemiological studies. Large cohort studies which have addressed this question included the British cohort (BS) (Wannamethee et al., 2000), the HHP (Curb et al., 2004), the ARIC study (Shahar et al., 2003), Oyabe study (OS)
(Soyama et al., 2003), Dubbo study (DS) (Simons, 1998), CCHS (Lindenstrom et al., 1994)
and the Israeli Ischemic Heart Disease Study (IIHDS) (Tanne et al., 1997). Although using
different HDL levels in comparison, most studies demonstrated a significant inverse
association (Lindenstrom et al., 1994; Simons, 1998; Tanne et al., 1997; Soyama et al.,
2003; Curb et al., 2004) and others demonstrated nonsignificant trends (Wannamethee et al.,
2000; Shahar et al., 2003; Curb et al., 2004) toward an inverse relationship of serum HDL
cholesterol and ischemic stroke risk. The populations studied included middle-aged and
elderly men and women from America, Australia, Europe, Hawaii, Israel and Japan.
When taken together it seems clear that higher baseline levels of serum HDL cholesterol
lower the risk of subsequent ischemic stroke. Case-control studies have also
demonstrated this inverse relationship (Sacco et al., 2001; Bowman et al., 2003). Low
serum HDL cholesterol levels may reflect a greater risk for atherosclerotic stroke, a
hypothesis supported by a few case-control studies. A study of 240 consecutive patients
with stroke or TIA demonstrated that low serum HDL cholesterol levels were more
frequently seen in the setting of atherosclerotic large-vessel disease relative to other
stroke subtypes, including small-vessel disease (Laloux et al., 2004).

In a large prospective cohort of 7,735 men, men in the top fifth percentile of HDL
cholesterol (>1.33 mmol/L) had a significant 40% reduction in risk of nonfatal stroke
when compared to the lowest fifth percentile (Wannamethee et al., 2000). A multiethnic
case-control study of elderly individuals showed significant associations between HDL
cholesterol and risk of ischemic stroke after confounder adjustment (Sacco et al., 2001).
Compared to participants with HDL cholesterol values of <35 mg/dL, participants with
>50 mg/dL had odds ratio of 0.31. The association was not modified by gender or
ethnicity. Overall, the published data strongly suggest that lower HDL cholesterol levels
are associated with increased risk of ischemic stroke.

In the NOrthern MAhhattan Stroke Study (NOMASS) of HDL cholesterol the
odds of having an atherosclerotic large vessel stroke was 0.20 in those with HDL
cholesterol concentrations ≥35 versus 0.60 for other stroke types (Sacco et al., 2001).
Similarly, the Group Health Cooperative study (GHCS) showed that odds of having a
large-vessel atherothrombotic stroke was reduced in the highest HDL cholesterol
quintile when compared with the lowest. The same association was not present for other stroke subtypes (Tirschwell et al., 2004). This association of HDL with atherosclerotic stroke is further strengthened by a study of carotid plaque progression (Johnsen et al., 2005). In 1952 subjects followed for 7 years, low HDL cholesterol was associated with a significant increase in carotid plaque volume by ultrasound.

The association of low HDL with increased plaque volume was strengthened when patients on cholesterol-lowering agents were excluded and may indicate an independent effect of HDL cholesterol. Few studies have compared serum HDL cholesterol against serum LDL cholesterol to determine relative contributions to stroke risk. In one study of the very old (aged ≥85 years) low serum HDL cholesterol was associated with an increased risk of stroke, CVD, and mortality whereas LDL cholesterol and TC had no association (Weverling et al., 2003). On the other side of the age spectrum, a study of young stroke patients demonstrated that low HDL cholesterol was the only serum lipid index associated with an increased risk of stroke (Albucher et al., 2000).

4.21. Atherogenic dyslipidemia and metabolic syndrome

Atherogenic dyslipidemia and metabolic syndrome was more frequent among the patients with stroke. Stroke patients with metabolic syndrome exhibited a more atherogenic lipid profile compared with controls. The prevalence of atherogenic dyslipidemia was significantly higher in group V (14%) than group I (2%) and IV (6%). Metabolic syndrome was statistically significant difference between group I (6%) and group IV (16%), group IV and group V (34%), group I and group V (Table 4.6).

The presence of metabolic syndrome has been associated with an increased risk of prevalent stroke in the existing literature. In the NHANES among 10,357 subjects (Ninomiya et al., 2004), the prevalence of metabolic syndrome was significantly higher in persons with a self-reported history of stroke (43.5%) than in subjects with no history of vascular disease (22.8%). Metabolic syndrome was independently associated with stroke history in all ethnic groups and in both sexes. The association between metabolic syndrome and stroke has been confirmed in other populations integrated by elderly
subjects, and the frequency of metabolic syndrome has been reported to be significantly higher in patients with a history of atherothrombotic or nonembolic ischemic stroke (Ninomiya et al., 2004; Milionis et al., 2005; Suk et al., 2003). This association supports the clinical use of the metabolic syndrome in the identification of subjects who are at an increased risk of experiencing a stroke. Long-term follow-up population-based studies have demonstrated that healthy individuals with the metabolic syndrome are at a markedly increased risk for major cardiovascular events, including stroke, and cardiovascular mortality (Isomaa et al., 2001; McNeill et al., 2005; Dekker et al., 2005). Adjusted risk ratios for incident ischemic stroke associated with metabolic syndrome in prospective studies range between 2.1 and 2.47, and a hazard ratio as high as 5.15 has been reported (Koren-Morag et al., 2005; Najarian et al., 2006; Chen et al., 2006; Kurl et al., 2006).

This predictive capacity appears not to be influenced by the metabolic syndrome definition used and shows no significant variation across the studied sex, age, or ethnic groups (Koren-Morag et al., 2005; Najarian et al., 2006). Moreover, the risk for incident ischemic stroke seems to augment with the increasing number of components of the metabolic syndrome, all of which have been individually associated with an increased risk for future cerebral ischemic events (Chen et al., 2006; Kurl et al., 2006).

4.22. Non-High density lipoprotein cholesterol

Non-HDL cholesterol was higher in patients with stroke than the control. The mean values of group I was found to be 126.2±28.1, in group IV 125.4±23.2 and in group V 147.9±33.4. There was statistically significant difference between group V (p< 0.001) and group I and between group V (p< 0.001) and group IV. There was no significant difference between group I and group I (Table 4.7).

The present study also analysed non-HDL cholesterol for ischemic stroke, which was proposed as a risk marker for CHD and as a secondary target of therapy (National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults, 2002). However, there were spare data about non-HDL cholesterol and stroke. In the SHS, increasing with non-HDL cholesterol the risk of
stroke had not increased significantly (Lu et al., 2003). The present study found that there was a significant increase of ischemic stroke with the increase of non-HDL cholesterol levels. Non-HDL cholesterol was the strongest statistical predictor of ischemic stroke followed by TC. This is in agreement with two recent studies that have identified non-HDL cholesterol as a strong predictor for CHD (Pischon et al., 2005) and overall CVD (Ridker et al., 2005). It has been previously shown in the WHS that non-HDL cholesterol is highly correlated with apolipoprotein B100, and both are of equally strength in prediction vascular events (Ridker et al., 2005). Another study found that the multivariable-adjusted hazard ratio of ischemic stroke was 2.45 for non-HDL cholesterol (Kurth et al., 2007). However, with regard to risk detection, non-HDL cholesterol may be preferred since it can be easily calculated by subtracting HDL cholesterol from TC.

Some studies have suggested that the association between lipid levels and ischemic stroke differs within the ischemic stroke subtypes (Benfante et al., 1994; Sacco et al., 2001; Tirschwell et al., 2004). In a health insurance-based case-control study, TC was stronger associated with ischemic strokes of the atherosclerotic and lacunar subtypes (Tirschwell et al., 2004). Furthermore, in that study (Tirschwell et al., 2004) and the previously mentioned case control study (Sacco et al., 2001), high HDL cholesterol levels were more strongly associated with the atherosclerotic subtype. In the WHS, TC appeared also to be more strongly associated with the atherosclerotic and lacunar ischemic stroke subtype (data not shown).

4.23. Lipid ratios

Although the TC to HDL cholesterol, TG to HDL cholesterol, LDL cholesterol to HDL cholesterol and non-HDL cholesterol to HDL cholesterol are a predictor of CVD, which contains both an atherogenic and an antiatherogenic lipid component (Stampfer et al., 1991; Kinosian et al., 1994; Criqui and Golomb, 1998), these various lipid ratios have not been as widely studied in association with stroke.

The mean values of TC to HDL cholesterol in group I was found to be 4.2±0.7, in group IV 4.0±0.7 and in group V 5.0±1.4. There was statistically significant difference between group V (p< 0.001) and group I and between group V (p< 0.001) and group IV.
There was no significant difference between group I and group IV. The mean values of LDL cholesterol to HDL cholesterol in group I was found to be 2.5±0.6, in group IV 2.3±0.7 and in group V 2.9±1.0. There was statistically significant difference between group V (p< 0.008) and group I and between group V (p< 0.001) and group IV. There was no significant difference between group I and group IV (Table 4.7).

The mean values of TG to HDL cholesterol in group I was found to be 3.5±1.9, in group IV 3.7±1.9 and in group V 4.2±2.5. There were no statistically significant among all groups. The mean values of non-HDL cholesterol to HDL cholesterol in group I was found to be 3.2±0.7, in group IV 3.2±0.8 and in group V 3.9±1.2. There was statistically significant difference between group V (p< 0.001) and group I and between group V (p< 0.001) and group IV. There was no significant difference between group I and group IV.

A prospective cohort study in women found that TC to HDL cholesterol ratio was significantly associated with increased risk of ischemic stroke (Kurth et al., 2007). Because the pathophysiology of ischemic stroke may be similar to that of CHD, a high TC to HDL cholesterol and LDL cholesterol to HDL cholesterol ratio may be an unrecognized risk factor for ischemic stroke. The present study results are consistent with the possibility of increased risk in those with the highest levels of TC to HDL cholesterol, LDL cholesterol to HDL cholesterol and non-HDL cholesterol to HDL cholesterol, but not TG to HDL cholesterol ratio.

### 4.24. High-sensitivity C-reactive protein

The patients with stroke or TIA had significant higher concentration of mean hsCRP levels between the group V (p<0.001) and group IV and group V (p<0.001) and group I. There was also a significant difference between group IV and group I (p< 0.01). The mean values of group I was found to be 0.9±0.4, in group IV 1.2±0.7 and in group V 2.3±1.4 (Table 4.7). Two cross-sectional studies (Ford and Giles, 2000; van Exel et al., 2002) indicated that a history of stroke was associated with raised plasma concentrations of hsCRP. NHANES III, a national probability survey of non-institutionalised United States individuals done between 1988 and 1994, reported that the odds ratio for stroke among participants age 40 years or older with hsCRP concentrations of at least 0.55
mg/dL compared with those with concentrations of 0.21 mg/dL or less was 1.71, 95% CI 1.11–2.64, after multivariate adjustment. The cross-sectional Leiden 85-Plus Study (van Exel et al., 2002) with 599 participants age 85 years at baseline showed that the adjusted odds ratio for a history of stroke was 2.11, 1.00–4.40, when individuals with the highest tertile of hsCRP concentration were compared to those with the lowest tertile.

Five prospective studies assessed the association between hsCRP and incidence of CVD in healthy adults. Ridker and colleagues, (1997) analysed data from the PHS by using a prospective, nested case-control design (543 cases of CVD and 543 controls from the study cohort; mean age 59 years), and indicated that the baseline concentration of hsCRP in apparently healthy men could predict the risk of first ischaemic stroke. The Framingham Study followed 591 men and 871 women (mean age 69.7 years) for 12–14 years and showed that raised plasma hsCRP concentrations independently predicted the risk of future ischaemic stroke and transient ischaemic attack (Rost et al., 2001). Curb and colleagues, (2003) examined the HHP cohort (259 cases of ischaemic stroke, mean age 55.8 years; 1,348 controls, mean age 58.1 years) by use of a prospective, nested case-control study with 20 years of follow-up, and suggested that high concentrations of hsCRP in middle adulthood was an important risk factor for thromboembolic stroke in healthy men. The CHS followed 5,417 individuals age 65 years or older for 10.2 years and showed that hsCRP was an independent risk factor for ischaemic stroke (Cao et al., 2003). However, the Health, Aging, and Body Composition (Health ABC) study did not find a significant association between hsCRP and risk of incident stroke, but their follow-up period of 3.6 years was relatively short (Cesari et al., 2003).

Four of these five prospective stroke studies (Ridker et al., 1997; Rost et al., 2001; Curb et al., 2003; Cao et al., 2003) had a long duration of follow-up (>8 years) and used the same format (RR) of stroke by comparing persons of highest vs lowest quartile of CRP) to report the association between hsCRP and incidence of stroke. Meta-analysis of these four studies showed that the overall RR for stroke when persons with the highest quartile of hsCRP concentration were compared to the lowest quartile was 1.68, 95% CI 1.40–2.01. The Health ABC Study which presented the RR for the comparison of the first versus the third tertile, rather than quartile, of hsCRP concentration was not included in
the meta-analysis. However, inclusion of the Health ABC Study did not essentially change the result. High concentrations of hsCRP have been shown to be associated with increased risk of developing cerebrovascular disease. However, ischaemic brain injury is characterised by acute local inflammation and raised CRP concentration (Beamer et al., 1998), as well as increases in other inflammatory cytokines (Fassbender et al., 1994). Moreover, raised concentrations of CRP have crucial prognostic implications in patients with acute ischaemic stroke (Di Napoli et al., 2001; Di Napoli and Papa, 2002). The major risk factors for stroke and CVD, such as smoking, diabetes, and hypertension, are associated with higher hsCRP levels (Mendall et al., 1996; Tracy et al., 1997). These relationships could potentially explain the associations that have been found between hsCRP level and stroke or mortality. In a recent prospective cohort study found that baseline serum hs-CRP level was an independent predictor for future ischemic stroke and all-cause mortality in an apparently healthy population (Shinji et al., 2008). It is interesting that these results were obtained in the Japanese population, which has a lower median hs-CRP level than Western populations (Makita et al., 2005; Nakamura et al., 2004). The RR of hypercholesterolemia was found to be 1.70 (95 % CI 0.86 to 3.34). The RR of hypertriglyceridemia was found to be 1.03 (95 % CI 0.71 to 2.39). The RR of high LDL cholesterolemia was found to be 1.57 (95 % CI 0.66 to 3.72). The RR of HDL cholesterol was found to be 1.45 (95 % CI 0.95 to 2.19). The RR of hsCRP was found to be 4.16 (95 % CI 1.87 to 9.27). RR for hsCRP was higher when compare with the lipid profile. Therefore, inclusion of the measurement of CRP as one of the strategies to assess stroke patients seems a reasonable approach for identifying high-risk individuals.

Some limitations should be considered when interpreting the findings of the present study. Firstly of all, population size was smaller. Secondly, ignoring the subtype of stroke all patients were considered as the complicated with stroke. This may have led to an over or under estimation of the impact of various risk factors by stroke subtype. Thirdly, although there is significant difference between the control and the test population in the lipid profile, but there is no abnormality found (the values are only in the upper normal limit). The findings should be confirmed with a larger, prospectively studied cohort.
A first aim for people with modifiable nonlipid risk factors is to alter them to reduce CHD risk. Risk reduction therapies consist of smoking cessation, control of hypertension, weight reduction, increased physical activity, and improved nutrition. Control of diabetic hyperglycemia will prevent microvascular complications, although clinical trials have not unequivocally demonstrated that improved glucose control lowers CHD events. Modification of blood pressure and lipids in people with diabetes, however, does reduce CHD risk. In addition, the recommendations for cholesterol management operationally take selected factors into account by setting lower thresholds for initiating treatment and lower goal levels for TC or LDL cholesterol for those at higher risk. A low HDL cholesterol (<40 mg/dL) also counts as a major risk factor for setting lower LDL goals, whereas a higher HDL cholesterol (≥60 mg/dL) takes away one other risk factor. Anti-inflammatory effects mediated via hsCRP have been advocated as a potential mechanism for early benefits of statin treatment.

**Cardiovascular disease and atorvastatin**

**4.25. High-sensitivity C-reactive protein and atorvastatin**

As shown in Table 4.8 and Fig. 4.1, the time course data indicated that mean hsCRP levels decreased from 1.9±0.7 mg/dL at the baseline to 1.2±0.4 mg/dL (p< 0.001) at the 3rd month, and 0.9±0.2 mg/dL (p< 0.001) at the end of the study (12th month) after administration of atorvastatin (10mg/day). However, the quantitative and proportional reduction was significantly higher in the atorvastatin group (group III) than group I (control) and a significant increase in group II (untreated) than the group I. After 3 and 12 months of treatment, hsCRP levels decreased by -36.8% and -25% respectively in group III (Table 4.8). There was a significant increase (p< 0.001) in the mean levels of hsCRP from 0.9±0.6 mg/dL to 1.1±0.4 mg/dL in the group II. Similar levels (1.0±0.3 mg/dL) were found at the end of the study (Fig. 4.1). Table 4.8 shows the percentage of increases in the levels of hsCRP in group II (22.2% and -9.1% for month 3 and 12 respectively). The mean levels of hsCRP in group I was found to be 0.8±0.3, 0.6±0.3 and 0.7±0.2 at the baseline, 3rd and 12th months respectively. There was no significant difference in the levels of hsCRP in the group I during the study period (Fig. 4.1).
Table 4.8 Changes in mean high-sensitivity C-reactive protein levels in group II and group III

<table>
<thead>
<tr>
<th>Time</th>
<th>Mean hsCRP</th>
<th>Group II</th>
<th>Group III</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean</td>
<td>Mean</td>
</tr>
<tr>
<td></td>
<td>Day 0</td>
<td>0.9±0.6</td>
<td>1.9±0.7</td>
</tr>
<tr>
<td></td>
<td>Month 3</td>
<td>1.1±0.4</td>
<td>1.2±0.4</td>
</tr>
<tr>
<td>Change</td>
<td>0.2</td>
<td>-0.7</td>
<td>-36.8%</td>
</tr>
<tr>
<td>(%)</td>
<td>22.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month 12</td>
<td>1.0±0.3</td>
<td>0.9±0.2</td>
<td></td>
</tr>
<tr>
<td>Change</td>
<td>-0.1</td>
<td>-0.3</td>
<td></td>
</tr>
<tr>
<td>(%)</td>
<td>-9.1%</td>
<td>-25%</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 4.1 Mean levels of high-sensitivity C-reactive protein in group I, II and III
The major primary prevention study that analyzed hsCRP data was the AFCAPS/TexCAPS (Downs et al., 1998; Ridker et al., 2001). The goal of this randomized, double blind, placebo-controlled trial was to evaluate hsCRP levels in 5,742 patients with either average TC or LDL cholesterol levels or below-average HDL cholesterol levels. Study participants included men or postmenopausal women age 45-73 years who did not have a history of uncontrolled hypertension, insulin-dependent diabetes, or secondary hyperlipidemia or were 150% of their ideal BMI based on their height. The median LDL cholesterol level and TC to HDL cholesterol ratio were 149.1 mg/dL and 5.96, respectively.

The median hsCRP was 0.16 mg/L. Patients were randomized to receive either placebo or lovastatin 20 mg daily for a 12-week run-in period, where they followed a Step I (low saturated fat, low cholesterol) diet. Lovastatin was increased to 40 mg at three months if the patient’s LDL cholesterol concentration exceeded 110 mg/dL. Patients were followed for 5.2 years. Patients’ hsCRP and LDL levels were divided into four quartiles. The primary endpoint was the occurrence of the first acute major coronary event (i.e., fatal or nonfatal MI, unstable angina, or sudden death from cardiac causes). Compared with placebo, lovastatin was associated with a 37% reduction in combined primary endpoints and a 14.8% reduction in hsCRP level (Downs et al., 1998; Ridker et al., 2001). A direct relationship between LDL cholesterol and hsCRP levels was not established, and change in lipid values was not associated with a change in hsCRP levels. With increasing quartiles, the RR of having a coronary event decreased significantly among patients receiving lovastatin versus placebo.

The original analysis found a 21% increase in risk for each escalating quartile. When the analysis was adjusted for age, sex, smoking status, hypertension, and family history, a 17% increase in risk was found with each quartile increase. Lovastatin reduced the risk of events in all patients with LDL cholesterol levels higher than the median, regardless of hsCRP levels. This reduction in risk with lovastatin was also seen in patients with hsCRP levels above the median and LDL cholesterol concentrations of ≤149.1 mg/dL. Such a reduction in risk of cardiovascular events with lovastatin was not observed in patients with LDL cholesterol and hsCRP levels below median values. After
examining results from this study, some researchers have inferred that the cardiovascular risk for patients with high hsCRP and low LDL cholesterol levels may be about the same as the risk for patients with high LDL cholesterol and low hsCRP levels (Ito et al., 2006).

A small study was conducted in a Texas hyperlipidemia clinic to determine if statins other than lovastatin would lower hsCRP levels (Jialal et al., 2001). Study participants included patients of age 18-70 years with LDL cholesterol concentrations of >130 mg/dL and TG concentrations of 200-600 mg/dL (n = 22). Patients were treated with simvastatin 20 mg, atorvastatin 10 mg, or pravastatin 40 mg daily. Levels of hsCRP and LDL cholesterol decreased significantly with all three statins. A decrease in TG levels was seen with simvastatin and atorvastatin only. This 12-week study did not measure cardiovascular endpoints, but the results may support the anti-inflammatory effect of the statins.

Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) demonstrated that lowering hsCRP levels in patients with coronary disease by intensive statin therapy resulted in reduced atherosclerotic lesion progression; in some patients there was even atheromatous regression, as measured by intravascular ultrasonography. These findings suggest that to maximize the benefit of statin therapy, physicians may need to monitor hsCRP levels in addition to LDL cholesterol levels for secondary prevention of CVD. JUPITER will clarify whether such monitoring could also be beneficial for primary prevention.

Because inflammation is an integral part of the underlying pathophysiology of atherosclerosis and hsCRP is a useful clinical marker of this inflammatory process, an important unresolved question is whether hsCRP screening combined with traditional lipid screening would provide an improved strategy for statin use in primary prevention of CVD. The JUPITER trial was designed to answer this question. Several factors governed the design. First, statin therapy has been repeatedly demonstrated to lower the risk of CVD events. Secondly, several studies have now shown statins to have a greater impact on lowering CVD risk in individuals with higher levels of inflammation
(Ridker et al., 1998; Ridker et al., 2001). As already noted, for example, investigators in the CARE trial of secondary prevention found that the benefit of pravastatin was greater among subjects with elevated hsCRP levels (Ridker et al., 1998). Similarly, in the AFCAPS/TexCAPS of primary prevention with lovastatin, the event reduction among those with low LDL cholesterol but high hsCRP was virtually identical to that seen in patients with high LDL cholesterol (Ridker et al., 2001). Thirdly, more than half of CVD events occur in individuals with LDL cholesterol levels that current guidelines do not consider eligible for therapy. And finally, because of the hsCRP-lowering effects of statins, treating individuals with high hsCRP levels but normal LDL cholesterol levels may extend the benefit of prophylactic statins.

The results of the JUPITER trial is eagerly anticipated (Ito et al., 2006). JUPITER is being conducted to determine whether rosuvastatin 20 will reduce the risk of major cardiovascular events in patients with low LDL cholesterol concentrations (<130 mg/dL) who are at high vascular risk and have hsCRP concentrations of \( \geq 2 \) mg/L. Trial results could provide an evidence base for the use of hsCRP in addition to LDL cholesterol to guide statin therapy in primary prevention. Because of its potential impact on public health, this trial represents an extremely important step in understanding the links among inflammation, statin therapy, and CVD prevention—knowledge that could lead to substantial alterations in our approach to cardiovascular prophylaxis and treatment.

The success seen with statins in primary cardiovascular risk reduction led to the evaluation of statins in patients with existing CVD. The CARE study found that cholesterol-lowering therapy was beneficial in most patients with coronary disease who had average cholesterol levels (Sacks et al., 1996). The CARE study included 4,159 patients who had a history of MI and TC concentrations of <240 mg/dL (mean ± S.D., 209±17 mg/dL) and LDL cholesterol concentrations of 115–174 mg/dL (mean ± S.D., 139±15 mg/dL). Patients received either 40 mg of pravastatin daily or placebo. The primary outcome measure of a fatal coronary event or a nonfatal MI occurred in 10.2% of the pravastatin treated group and 13.2% of patients in the placebo group. Patients receiving pravastatin had a 24% lower risk of the primary endpoint compared with

153
patients in the placebo group. A significantly greater incidence of coronary artery bypass graft (CABG) surgery and angioplasty was seen in patients receiving placebo.

The conclusions of the CARE study were further explored by Ridker et al., (1998) to evaluate whether hsCRP and SAA levels were associated with recurrent coronary events. Prerandomization blood samples were evaluated from 391 patients enrolled in the CARE study who suffered recurrent nonfatal MI or a fatal coronary event. These samples were matched in a nested, case-controlled fashion with patients who did not have a second vascular event. Of note, it was not designated as to whether or not they received pravastatin or placebo. The serum levels of both inflammatory markers were higher in patients with recurrent events than in patients without recurrent events. However, the difference between the two groups was not considered significant.

Patients in the highest hsCRP quintile (>0.66 mg/L) had a 75% higher RR of cardiovascular events than patients in the lowest hsCRP quintile (<0.12 mg/L). Ridker et al., (1998) also evaluated 708 participants from the CARE study who had hsCRP and SAA values above or below the 90th percentile (hsCRP concentration of >0.99 mg/L). Patients with hsCRP levels exceeding the 90th percentile were classified as having inflammation, and those with hsCRP levels below the 90th percentile were considered to be without inflammation.

These groups were further divided by whether they received pravastatin. Regardless of inflammation status, patients in the pravastatin-treatment group had a 28% reduced risk of recurrent MI or coronary death compared with patients in the placebo group. Among patients with inflammation, pravastatin prevented twice as many coronary events than did placebo (54% versus 25%, respectively). The authors concluded that there was an association between pravastatin’s ability to reduce inflammation and prevent recurrent coronary events.

To examine the long-term effects of pravastatin on hsCRP levels, Ridker et al., (1999) selected the 477 participants in the CARE study who remained free of recurrent cardiovascular events and had available five-year blood samples. It was noted that hsCRP levels continued to increase in patients who received placebo but decreased in
patients treated with pravastatin. Since these results were adjusted for several factors, including lipid levels, the investigators concluded that the reduction seen in hsCRP levels in the pravastatin-treated group was related to the nonantihyperlipidemic effects of the drug.

Cannon et al., (2004) conducted a randomized, double blind, double-dummy trial to compare the degree of LDL cholesterol lowering with 40 mg of pravastatin (moderate therapy) versus 80 mg of atorvastatin (intensive therapy). This study, the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22), included 4,162 patients who had been hospitalized for ACS within the 10 days preceding study enrollment. Study participants had a TC level of ≤240 mg/dL within 24 hours of enrollment or as an outpatient within the previous six months or had a TC concentration of ≤200 mg/dL with lipid-lowering therapy. The primary outcome measure was the time from randomization until the first occurrence of one of the following events: death from any cause, MI, documented unstable angina, hospitalization, revascularization with either PCI or CABG surgery (performed at least 30 days after study randomization), or stroke.

The primary outcome measure occurred in 26.3% of patients receiving moderate therapy and 22.4% of patients receiving intensive therapy. The median LDL cholesterol levels reached in the moderate and intensive therapy groups were 96 and 62 mg/dL, respectively. The median baseline hsCRP level in both the pravastatin and atorvastatin groups dropped from 12.3 to 2.1 mg/L (in the pravastatin group) and to 1.3 mg/L (in the atorvastatin group) by the end of the study. The authors concluded that intensive statin therapy with atorvastatin 80 mg was more effective in protecting against death or major cardiovascular events than moderate therapy with pravastatin 40 mg. Ridker and colleagues, (2005) conducted a study that included 3,745 patients from the PROVE IT-TIMI 22 trial. The patients selected had to be free of recurrent events and have 30-day follow-up laboratory data. Both LDL cholesterol and hsCRP levels were reduced by statin therapy at 30 days, and only a small correlation was found between the achieved LDL cholesterol and hsCRP values.
A similar level of correlation was observed in patients with subsequent recurrent coronary events. Less than 3% of the variance in achieved CRP levels was explained by the variance achieved in LDL cholesterol level. Patients in whom statin therapy resulted in LDL cholesterol levels of <70 mg/dL had lower age-adjusted rates of recurrent MI or death from coronary causes, and patients with a hsCRP concentration of <2 mg/L had 2.8 versus 3.9 events per 100 person-years. Data were separated into quartiles based on achievement of the LDL cholesterol or hsCRP goal. It was concluded that, regardless of the goal, LDL cholesterol (<70 mg/dL) was achieved, patients with low hsCRP levels after statin therapy may have better clinical outcomes, compared with patients with higher hsCRP levels. Over 80% of patients who achieved optimum targets were receiving atorvastatin 80 mg. No difference regarding clinical endpoints was seen between treatment with atorvastatin 80 mg and pravastatin 40 mg once patients met LDL cholesterol and hsCRP targets.

The benefit of statin use in the secondary prevention of fatal and nonfatal coronary events has been shown, but few studies have examined the effects of statin use in physical atherosclerosis. Nissen et al., (2004) randomized 654 patients to receive moderate therapy (pravastatin 40 mg daily) or intensive therapy (atorvastatin 80 mg daily). A total of 502 patients had evaluable intravascular ultrasound examinations. The primary outcome measure was the percentage of change in atheroma volume compared with baseline. The results showed that the progression rate was lower in the atorvastatin group compared with the pravastatin hsCRP group. There was also benefit in the atorvastatin group regarding the change in total atheroma volume and the percentage atheroma volume. The authors found a significant benefit in intensive therapy compared with moderate therapy in the reduction of progression of coronary atherosclerosis.

In the 502 patients with evaluable ultrasounds, (Nissen et al., 2005) further examined the relationship between the reductions in LDL cholesterol and hsCRP levels and the rate of disease progression measured by ultrasonography. In this evaluation, they found a slower rate of progression in the intensive therapy group compared with patients receiving moderate therapy. However, a weak but significant correlation between the percent reductions in LDL cholesterol and hsCRP levels was found. There
was not a significant correlation in the individual pravastatin- and atorvastatin-treatment groups. For primary prevention of cardiovascular events, evaluating hsCRP levels in patients with average or below-average cholesterol levels may be of benefit in limited clinical circumstances. In AFCAPS/TexCAPS, with the exception of the group with LDL cholesterol and hsCRP levels less than the median values, the number needed to treat in each quartile to derive a risk-reduction benefit varied widely (range, 35-86 patients).

Several recent studies also confirmed the anti-inflammatory effects of atorvastatin. The anti-inflammatory potential of HMG CoA reductase inhibitors, as reflected by modulation of hsCRP, might be beneficial in the treatment of patients with multiple sclerosis. Betteridge et al., (2007) studies the effects of rosuvastatin compared with atorvastatin in achieving a combined target of LDL cholesterol <70 mg/dl and hsCRP <2 mg/L in 509 patients with type 2 diabetes mellitus. HsCRP was effectively decreased in patients with type 2 diabetes receiving rosuvastatin or atorvastatin, whereas rosuvastatin decreased LDL cholesterol significantly more than atorvastatin.

Qu et al., (2008) compare the short-term effect of treatment with atorvastatin and rosuvastatin on levels of serum lipids, inflammatory markers and adiponectin in patients with hypercholesterolemia. Atorvastatin and rosuvastatin both lowered levels of hsCRP, MMP-9, PAI-1, TC, and LDL cholesterol from baseline values. Sellner et al., (2008) evaluated serum levels of hsCRP in relapsing-remitting metabolic syndrome patients receiving interferon-beta (INF-β) and atorvastatin as add-on therapy. The study shows that INF-β treatment is associated with increased serum levels of hsCRP in metabolic syndrome patients. In contrast, when atorvastatin is added to INF-β, hsCRP serum levels decrease to the normal range, indicating an anti-inflammatory action of atorvastatin in metabolic syndrome.

Gupta et al., (2008) evaluate the effect of a lower dose (20 mg) of atorvastatin on hsCRP concentrations in patients with ACS. The decrease in hsCRP was significantly greater in the subgroups of smoking, hypertension and past history of CVD with atorvastatin. The use of a lower dose of atorvastatin can offer an attractive approach for early treatment of patients with ACS. Comparative Atorvastatin Pleiotropic effects
The decrease in hsCRP was largely independent of baseline LDL cholesterol and change in LDL cholesterol. In these patients with documented CAD, evidence of low-grade inflammation, and normal range lipid profiles, the effects of atorvastatin on changes in hsCRP were dose dependent, with the high dose (80 mg) being associated with significantly greater reductions in hsCRP concentrations. Both doses were associated with a significant and progressive decline in hsCRP largely independent of changes in LDL cholesterol, HDL cholesterol, and TG (Bonnet et al., 2008).

Ray et al., (2009) compare the prognostic utility of apo B to A-I, TC to HDL cholesterol ratio, non-HDL cholesterol, or hsCRP as predictors of clinical risk among patients receiving statin therapy after ACS. On-treatment apo B to A-I, TC to HDL cholesterol, and non-HDL cholesterol offered similar prognostic information to LDL cholesterol. However, the addition of hsCRP to lipid-based measurements significantly improved risk prediction. On treatment CRP measurement may therefore offer additive prognostic information to lipids in ACS patients.

Montecucco et al., (2009) have recently shown that hsCRP induces chemokine secretion and adhesion molecule up-regulation in human primary monocytes cultured in adherence. Given the increasing evidence on direct immunomodulatory properties of statins, Montecucco et al., (2009) investigated their possible anti-inflammatory role on CRP-treated human monocytes. Statins inhibited CRP-induced chemokine secretion, ICAM-1 up-regulation and migration in human adherent monocytes, through the inhibition of HMG-CoA reductase-ERK 1/2 pathway. This pathway could represent a very promising target to reduce hsCRP induced activities in monocyte-mediated diseases, such as atherosclerosis (Montecucco et al., 2009). HsCRP serum levels decrease to the normal range, indicating an anti-inflammatory action of atorvastatin.
4.26. Total cholesterol, low-density lipoprotein cholesterol and atorvastatin

As shown in Table 4.9 and Fig. 4.2, the data indicated that mean TC levels decreased from 201.9±38.6 mg/dL at the baseline to 169.2±27.4 mg/dL (p< 0.001) at the 3rd month, and 161.8±20.8 mg/dL (p< 0.08) at the end of the study (12th month) after administration of atorvastatin. After 3 and 12 months of treatment, TC levels decreased by -16.3% and -4.4% respectively in group III (Table 4.9). There was a significant increase (p< 0.001) in the mean levels of TC from 167.8±29.5 mg/dL at the baseline to 184.5±28.9 mg/dL at the 3rd month in the group II. There was a significant decrease (p< 0.001) found between the 3rd month and the 12th month in group II (patients were advised to take other lipid lowering (e.g. fibrate) drugs by the doctor) (Table 4.10 and Fig. 4.2). The mean levels of TC in group I was found to be 165.0±30.0, 167.2±35.7 and 162.9±25.8 at the baseline, 3rd and 12th months respectively. There was no significant difference in the levels of TC in the group I during the study period (Fig. 4.2).

In Table 4.9 and Fig. 4.3, the information indicated that mean LDL cholesterol levels decreased from 143.1±46.6 mg/dL at the baseline to 99.0±23.6 mg/dL (p< 0.001) at the 3rd month, and 90.1±19.9 mg/dL (p< 0.003) at the end of the study (12th month) after administration of atorvastatin. After 3 and 12 months of treatment, LDL cholesterol levels decreased by -44.1% and -9.0% respectively in group III (Table 4.9). There was a significant increase (p< 0.02) in the mean levels of LDL cholesterol from 101.2±25.9 mg/dL at the baseline to 110.5±25.5 mg/dL at the 3rd month in the group II. There was a significant decrease (p< 0.007) found between the 3rd month and the 12th month in group II (Table 4.10 and Fig. 4.3). The mean levels of LDL cholesterol in group I was found to be 97.0±30.0, 94.0±25.4 and 89.2±29.1 at the baseline, 3rd and 12th months respectively. There was no significant difference in the levels of LDL cholesterol in the group I during the study period (Fig. 4.3).

In meta-analyses it was found that, for every 10% reduction in TC, there was a 10% to 11% decrease in the risk for all-cause mortality and a 13% to 15% decrease in the risk for CHD related mortality (Gould et al., 1995; 1998).
Table 4.9 Changes in mean total cholesterol and low-density lipoprotein cholesterol levels in patients after atorvastatin therapy

<table>
<thead>
<tr>
<th>Time</th>
<th>Group III</th>
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<tr>
<td></td>
<td>TC</td>
<td>LDL cholesterol</td>
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</tr>
<tr>
<td></td>
<td>201.9±38.6</td>
<td>143.1±46.6</td>
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<td>169.2±27.4</td>
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</tr>
<tr>
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</tr>
<tr>
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<td>Change</td>
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<tr>
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Table 4.10 Changes in mean total cholesterol and low-density lipoprotein cholesterol levels in untreated patients

<table>
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<th>Time</th>
<th>Group II</th>
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<tbody>
<tr>
<td></td>
<td>TC</td>
<td>LDL cholesterol</td>
<td></td>
</tr>
<tr>
<td></td>
<td>167.8±29.5</td>
<td>101.2±25.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>184.5±28.9</td>
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<td></td>
</tr>
<tr>
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<tr>
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<tr>
<td>Change</td>
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<td>Month 12</td>
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</tr>
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<td>Change</td>
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</tr>
<tr>
<td>(%)</td>
<td>-7.3%</td>
<td>-9.2%</td>
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Fig. 4.2 Mean levels of total cholesterol in group I, II and III

Fig. 4.3 Mean levels of low-density lipoprotein cholesterol in group I, II and III
Number of studies involving statin regimens that were more intensive and/or reduced TC to either lower absolute levels (Cannon et al., 2004; Nissen et al., 2004; de Lemos et al., 2004; LaRosa et al., 2005; Baigent et al., 2005; Pedersen et al., 2005). Given recent AHA statistics (Thorn et al., 2006) that CVD was identified as a contributing or underlying cause of >1.4 million deaths in 2002, long-term cholesterol lowering treatment that reduces TC by 19-38 mg/dL could prevent significant numbers of CHD-related deaths each year. A reduction of TC by 19-38 mg/dL would represent a reduction of -9% to 19% for the average American adult, who has a TC concentration of 203 mg/dL according to the NHANES (Ford et al., 2003).

Many guidelines for the use of lipid lowering drugs recommend target levels of LDL cholesterol in addition to plasma TC targets. High serum concentrations of LDL cholesterol are now well established as a risk factor for CHD and LDL cholesterol reduction forms a central component of CVD risk management guidelines (Smith et al., 2006; Grundy et al., 2004; De Backer et al., 2003). The efficacy of statins in lowering LDL cholesterol and their beneficial effects on cardiovascular events have been demonstrated in a large number of clinical outcomes trials (Scandinavian Simvastatin Survival Study Investigators, 1994; Sacks et al., 1996; Cholesterol and Recurrent Events Trial Investigators, 1998; MRC/BHF Heart Protection Study, 2002; Sever et al., 2003; Cannon et al., 2004) and statins are now recognized as the first-line treatment for dyslipidemia (De Backer et al., 2003; Grundy et al., 2004; Smith et al., 2006).

Early placebo-controlled clinical trials of statins were performed primarily in patients with or at high risk of CHD who were statin naive (Scandinavian Simvastatin Survival Study Investigators, 1994; Sacks et al., 1996; Cholesterol and Recurrent Events Trial Investigators, 1998). Outcomes of these trials supported decisions by the NCEP ATP and other bodies to specify cholesterol goals for high-risk patients (Executive Summary of The Third Report of The National Cholesterol Education Program Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults, 2001; De Backer et al., 2003). However, later trials enrolled patients with a variety of risk factors and, due to improvements in CVD management, included greater proportions of patients who were already receiving some form of treatment for their CHD, such as
antihypertensive and lipid-lowering medications (MRC/BHF Heart Protection Study, 2002; Shepherd et al., 2002; ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group, 2002; Sever et al., 2003; Cannon et al., 2004).

Recommendations in CVD management guidelines (De Backer et al., 2003; Grundy et al., 2004; Smith et al., 2006) are based largely on results of large clinical outcomes trials. The most recent update of the NCEP ATP III guidelines appeared in 2004 (Smith et al., 2006), following publication of five large statin trials (MRC/BHF Heart Protection Study, 2002; Shepherd et al., 2002; ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group, 2002; Sever et al., 2003; Cannon et al., 2004). One of the new recommendations in the NCEP ATP III update was the option of an LDL cholesterol goal of <70 mg/dL (beyond the existing goal of <100 mg/dL) for patients at very high risk of CVD and the guidelines also indicated that the majority of patients would require intensive LDL cholesterol-lowering therapy to achieve this goal (Grundy et al., 2004).

The HPS and the PROVE IT-TIMI 22 study (Cannon et al., 2004) were cited to support the addition of this optional goal. A secondary analysis of HPS demonstrated that lowering LDL cholesterol in patients without particularly elevated LDL cholesterol at the baseline (<116 mg/dL) to levels <77 mg/dL was associated with a significant 21% reduction in risk of major vascular events. A similar 22% proportional risk reduction was also observed in patients with baseline LDL cholesterol <100 mg/dL, suggesting that there was no known threshold below which lowering LDL cholesterol would not safely reduce risk of CVD (MRC/BHF Heart Protection Study, 2002). In the PROVE IT-TIMI 22 study, reducing LDL cholesterol with intensive atorvastatin 80 mg therapy, from a median of 106 mg/dL at the baseline to 62 mg/dL at end of study, reduced risk of the primary endpoint by 16% vs LDL cholesterol-lowering with more moderate pravastatin 40 mg therapy to a median of 95 mg/dL, levels consistent with the traditional goal of 100 mg/dL (Cannon et al., 2004). These results indicated that intensive lipid-lowering therapy may be required to lower LDL cholesterol to well below goal.

The NCEP ATP III update also supported, for the first time, use of lipid-lowering drugs in moderately high-risk patients without clinically overt CHD (who are reaching
the existing LDL cholesterol goal of <130 mg/dL) to achieve a new optional LDL cholesterol goal of <100 mg/dL (Grundy et al., 2004) and cited the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial—Lipid-Lowering Trial (ALLHAT-LLT) (ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group, 2002) and the ASCOT-LLA (Sever et al., 2003) in support of this recommendation, because both trials included patients who were at least predominantly without CHD and who were at moderately high CHD risk. The lipid-lowering arm of ASCOT included hypertensive patients without CHD but with three or more additional CHD risk factors and was stopped early after a median follow-up of 3.3 years because of a significant 36% reduction in risk of the primary endpoint (nonfatal MI and fatal CHD) with atorvastatin 10 mg vs placebo, at which point patients receiving atorvastatin therapy had attained a mean LDL cholesterol of 90 mg/dL (Sever et al., 2003). In ALLHAT-LLT, pravastatin 40 mg did not reduce all-cause mortality vs usual care, perhaps due to the high rate of open-label statin use in the usual care group, but the trial did demonstrate a 27% reduction in the composite endpoint of CHD death and nonfatal MI in African Americans with pravastatin vs usual care (ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group, 2002), supporting the NCEP ATP III recommendation that goals should not be modified on the basis of ethnicity (Grundy et al., 2004).

In addition to providing support for revisions to LDL cholesterol goals, the results of new clinical trials were cited as evidence for the benefits of statin therapy in older patients and in patients with diabetes. The PROSPER trial demonstrated a 15% reduction in risk of major cardiovascular events with statin therapy vs placebo in older patients aged 70 to 82 years with or without a history of CVD (Shepherd et al., 2002). Benefit of statin therapy in older patients was also supported by HPS, which included almost 6,000 patients aged 70 or older and observed that this older population experienced a similar reduction in risk of major cardiovascular events with statin therapy vs placebo (28% risk reduction) to the overall HPS population (24% risk reduction) (MRC/BHF Heart Protection Study, 2002). Consequently, the NCEP ATP III update recognized the benefit of statins in older, high-risk patients and the possible need for intensive statin therapy in older persons with established CVD (Grundy et al., 2004).
In addition to benefits in older patients, the HPS trial also demonstrated benefits in patients with diabetes (Collins et al., 2003) and included 5,963 patients with diabetes, of whom just over half had CHD. Treatment with simvastatin 40 mg was associated with a 22% reduction in risk of major vascular events vs placebo in patients with diabetes, which was similar to the 24% reduction observed in the overall HPS population (Collins et al., 2003). On the basis of the HPS results, the NCEP ATP III update assigned patients with CHD and diabetes to the new category of patients at very high risk of CVD, the category to which the new optional LDL cholesterol goal of <70 mg/dL applies (Grundy et al., 2004). Patients with ACS are also placed in this very high-risk category, with supporting evidence from the PROVE IT-TIMI 22 trial (Cannon et al., 2004) and the earlier MIRACL study (Schwartz et al., 2001).

Since the NCEP ATP III update in 2004, four large clinical outcomes trials investigating the benefit of statin treatment on cardiovascular events have reported: the TNT study (LaRosa et al., 2005), the Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) study (Pedersen et al., 2005), the Collaborative Atorvastatin Diabetes Study (CARDS) (Colhoun et al., 2004), and the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study (Amarenco et al., 2006). Both TNT (LaRosa et al., 2005) and IDEAL (Pedersen et al., 2005) demonstrated increased clinical benefit of intensive over less-intensive statin treatment in patients with prior CHD. The TNT study compared the incremental benefit of treatment with atorvastatin 80 mg over atorvastatin 10 mg in 10,001 patients with clinically evident CHD. After a median of 4.9 years, patients treated with atorvastatin 80 mg achieved a mean LDL cholesterol of 77 mg/dL and benefited from a 22% reduction in risk of the composite primary endpoint (death from CHD, nonfatal non-procedure-related MI, resuscitation after cardiac arrest, and fatal or nonfatal stroke) compared with patients randomized to atorvastatin 10 mg, who achieved a mean LDL cholesterol of 101 mg/dL (LaRosa et al., 2005). IDEAL investigated whether intensive lipid-lowering (atorvastatin 80 mg) produced increased clinical benefit relative to a more moderate regimen (simvastatin 20 mg) in 8,888 patients with a previous MI. Initial analysis of IDEAL revealed that patients treated with atorvastatin 80 mg achieved a mean LDL cholesterol of 81 mg/dL and benefited from a nonsignificant 11% RR reduction in the composite primary endpoint of
major coronary events (coronary death, hospitalization for nonfatal acute MI, or cardiac arrest with resuscitation) (Pedersen et al., 2005). However, post-hoc cox regression analysis showed a significant 13% RR reduction in the primary endpoint with atorvastatin 80 mg vs simvastatin 20 to 40 mg (Pedersen et al., 2005). After publication of these trials, the AHA/American College of Cardiology guidelines for secondary prevention of CHD were updated to advise that the LDL cholesterol goal should be <100 mg/dL for all patients with CHD and other clinical forms of atherosclerotic disease and, in addition, it is reasonable to treat LDL cholesterol <70 mg/dL in such patients (Smith et al., 2006). It remains to be seen whether the next NCEP ATP guidelines will also include this option for all patients with CHD.

CARDS demonstrated the benefit of statin therapy for prevention of CVD endpoints in patients with type 2 diabetes plus other risk factors, but who did not have elevated LDL cholesterol (Colhoun et al., 2004). CARDS randomized 2,838 patients with type 2 diabetes but no prior CVD to atorvastatin 10 mg or placebo. After a median 3.9-year follow-up, patients randomized to atorvastatin 10 mg experienced a 37% reduction in risk of major cardiovascular events (acute CHD, coronary revascularization procedures, and stroke) vs placebo (Colhoun et al., 2004). This prompted the CARDS investigators to suggest that patients with type 2 diabetes should be treated according to their high-risk status rather than their LDL cholesterol level. NCEP ATP III recognizes diabetes as a CHD risk equivalent and current guidelines set an LDL cholesterol goal of <100 mg/dL for most patients with diabetes, with the option of a goal of <70 mg/dL in patients with diabetes and CHD (Grundy et al., 2004). However, NCEP ATP III guidelines state that diabetes patients of young age or without other CHD risk factors can be considered to be at only moderately high CHD risk and recommends that for these patients lipid-lowering therapy is not initiated unless LDL cholesterol levels are ≥130 mg/dL (Grundy et al., 2004).

Based on results of CARDS (Colhoun et al., 2004) and HPS (MRC/BHF Heart Protection Study, 2002) the American Diabetes Association (ADA) has set an LDL cholesterol goal of <100 mg/dL for all individuals with diabetes who do not have existing CHD, including younger patients younger than 40 years of age with additional

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cardiovascular risk factors, and an optional goal of <70 mg/dL for patients with diabetes and CHD Standards of medical care in diabetes 2007. It remains to be seen whether CARDS will have an impact on NCEP ATP guidelines for CHD management in diabetes patients.

The SPARCL study was the first, large-scale, prospective trial to evaluate the effect of intensive statin therapy on risk of recurrent stroke in patients with prior stroke or TIA but no CHD (Amarenco et al., 2006). SPARCL randomized 4,731 patients with recent stroke or TIA (1-6 months prior to randomization) to atorvastatin 80 mg or placebo. After a median follow-up of 4.9 years, atorvastatin 80 mg was associated with a 16% reduction in risk of fatal or nonfatal stroke compared with placebo. Furthermore, treatment with atorvastatin 80 mg was associated with reductions in risk for a number of secondary endpoints, including any coronary event (42% risk reduction) and revascularizations (45% risk reduction), suggesting multiple benefits of atorvastatin treatment in this patient population (Amarenco et al., 2006). Results of SPARCL support initiation of high-dose statin treatment soon after a stroke or TIA and support inclusion of other forms of atherosclerotic disease as a CHD risk equivalent in the NCEP ATP III guidelines (Grundy et al., 2004).

It has been suggested that clinical manifestations of coronary atherosclerosis are changing. Results from recent trials indicate that rates of hard CHD events—MI and coronary death— have fallen substantially below those predicted by Framingham risk scoring (Sever et al., 2003; LaRosa et al., 2005; Arad et al., 2005; Arad et al., 2005; Grundy 2005). Reasons for this change may include healthy volunteer effects, prevention of MI through angioplasty or thrombolysis in patients with ACS, institution of preventative therapy in earlier stages of CVD, and improved treatment of atherosclerotic CVD to prevent death. As a consequence, clinical trials basing their power calculations on the assumption of cardiovascular risk as assessed by traditional risk scoring methods may underestimate the required power to detect significant effects of treatment on these hard outcomes. Other forms of CVD are now thought to predominate and total CVD rate, which also includes revascularization and stroke, may be a more appropriate focus for endpoints in future clinical studies. In particular, it seems important to include stroke
among outcomes because of recent evidence that lipid-lowering therapies affect stroke outcomes similarly to coronary outcomes (Amarenco et al., 2006).

Results of recent clinical trials appear to support these observations. The primary endpoint in IDEAL was the occurrence of a major coronary event, essentially a measure of hard CHD events. In IDEAL, in patients receiving atorvastatin 80 mg, the reduction in risk of the primary endpoint did not reach significance vs simvastatin 20 mg in the initial analysis (11% risk reduction); however, for the more inclusive composite secondary endpoint of major cardiovascular events, which included stroke, reduction in risk did reach significance (13% risk reduction) (Pedersen et al., 2005). In TNT, treatment with atorvastatin 80 mg was associated with a significant 22% reduction in risk of the primary endpoint (major cardiovascular events), which included stroke, vs atorvastatin 10 mg (LaRosa et al., 2005). Like TNT, PROVE IT-TIMI 22 used a large composite primary endpoint and demonstrated that atorvastatin 80 mg was associated with a significant 16% reduction in risk of the primary endpoint vs pravastatin 40 mg (Cannon et al., 2004). Thus, in future trials, more inclusive endpoints may have to be used to demonstrate statistically significant benefits of CVD therapy.

Secondary prevention clinical trials frequently demonstrate significance for their secondary endpoints, particularly large composite endpoints. The TNT trial recruited patients with CHD and showed that, compared with atorvastatin 10 mg, treatment with atorvastatin 80 mg was associated with significant reductions in the risk of several composite secondary endpoints (LaRosa et al., 2005). For less-inclusive secondary endpoints, such as PAD and all-cause mortality, TNT failed to demonstrate significance. In IDEAL, atorvastatin 80 mg significantly reduced the risk of several composite secondary endpoints, relative to simvastatin therapy, as well as a number of the individual components of these endpoints, such as nonfatal MI, revascularization, and PAD (Pedersen et al., 2005).

PROVE IT-TIMI 22 likewise achieved significance for its secondary endpoints, including the composite endpoint of death, MI, or urgent revascularization, as well as the individual endpoints of revascularization and recurrent unstable angina. However,
significant reductions were not observed for the composite secondary endpoint of death due to CHD, MI, or revascularization, the individual endpoint of death from any cause, and the composite endpoint of death or MI (Cannon et al., 2004). Primary prevention trials have also demonstrated significance for their secondary endpoints. In ASCOT-LLA, reductions were observed with atorvastatin 10 mg vs placebo for four secondary endpoints: total cardiovascular events, including revascularization procedures (21% risk reduction), total coronary events (29% risk reduction), the primary endpoint excluding silent MI (38% risk reduction), and fatal and nonfatal stroke (27% risk reduction). There was also a non significant reduction in all cause mortality.

Of the tertiary endpoints, there was a significant 41% reduction in the incidence of chronic stable angina; however, other tertiary endpoints, including silent MI, unstable angina, peripheral artery disease, and development of life-threatening arrhythmias, diabetes mellitus, and renal impairment did not achieve significance (Sever et al., 2003). In CARDS, atorvastatin 10 mg was associated with a 32% reduction in risk of acute cardiovascular events vs placebo. Reduction in all-cause mortality did not achieve significance; however, CARDS was terminated 2 years early because the prespecified early stopping rule for efficacy was met, which reduced the power of the study to detect hard endpoints, such as changes in mortality (Colhoun et al., 2004).

Both PROVE IT-TIMI 22 (Cannon et al., 2004) and HPS (MRC/BHF Heart Protection Study, 2002) demonstrated that patients benefited from use of statin therapy to lower LDL cholesterol levels to well below the NCEP ATP III goal of <100 mg/dL (Grundy et al., 2004), the cardiovascular benefit of statin therapy was demonstrated in comparison with placebo and may not reflect the situation of the general patient population, of which greater numbers are now receiving lipid-lowering medication (MRC/BHF Heart Protection Study, 2002). PROVE IT-TIMI 22 enrolled patients with ACS, who may benefit more from intensive lipid-lowering therapy than lower risk patients (Cannon et al., 2004). Therefore, results of HPS and PROVE IT-TIMI 22 must be interpreted with caution, as they may not extrapolate to the modern patient population or to other risk groups. In addition, the NCEP ATP III guidelines recognized the need
for additional data before recommending the optional goal of <70 mg/dL to a broader range of patients (Grundy et al., 2004).

Since the NCEP ATP III update, the TNT study has provided direct evidence that, in patients with CHD, reducing LDL cholesterol to 77 mg/dL with atorvastatin 80 mg reduced the risk of a major cardiovascular event over and above any risk reduction in patients achieving the recommended LDL cholesterol goal of 100 mg/dL with atorvastatin 10 mg (LaRosa et al., 2005). In addition, IDEAL demonstrated improved clinical outcomes in patients with a previous MI who received atorvastatin 80 mg and achieved a mean LDL cholesterol of 81 mg/dL vs patients who received more moderate statin therapy and achieved a mean LDL cholesterol of 104 mg/dL (Pedersen et al., 2005). In TNT and IDEAL, intensive atorvastatin therapy was associated with a similar safety profile to moderate statin therapy, demonstrating that high-dose statin therapy provides increased clinical benefit with few increased safety concerns (LaRosa et al., 2005; Pedersen et al., 2005). In addition, both studies indicate that intensive statin therapy may be required to achieve aggressive LDL cholesterol goals (LaRosa et al., 2005; Pedersen et al., 2005) and, therefore, highlight the value of titrating treatment until patients reach goal. Although most patients should be able to reach LDL cholesterol goal with statin therapy, some patients may require additional treatment, and both the AHA and NCEP ATP III guidelines advocate addition of niacin or fibrate to statin therapy in patients who fail to reach goals with statin therapy alone (Grundy et al., 2004; Smith et al., 2006). It is clear from comparative analysis that the relationship between LDL cholesterol and event rates is consistent, even at low LDL cholesterol levels. There is, therefore, direct evidence to support the increased benefits of achieving LDL cholesterol goals well below the current <100 mg/dL target. It is likely that these data will be reflected in subsequent revisions of the NCEP ATP guidelines.

Several studies have demonstrated that the lipid-lowering benefits of statins are often evident within a few months (Schwartz et al., 2001; Sever et al., 2003; Colhoun et al., 2004), and reductions in clinical endpoints are usually apparent after 1 to 2 years (MRC/BHF Heart Protection Study, 2002; Colhoun et al., 2005; Sever et al., 2005). This compares favorably with nonstatin lipid-lowering trials in which the benefits for clinical
outcomes can take as long as 5 years or more to manifest (The Lipid Research Clinics Coronary Primary Prevention Trial results II, 1984; Canner et al., 1986).

The early benefit of statin treatment in preventing CVD outcomes has been demonstrated in two primary prevention trials. In CARDS, post-hoc analysis revealed an apparent reduction in CHD events after only 6 months, with the maximum treatment effect on the primary endpoint occurring after 12 months, and significance achieved at 18 months (Colhoun et al., 2005). In ASCOT-LLA, reductions in CHD events were apparent for atorvastatin 10 mg vs placebo after 30 days, and were significant after 90 days (Sever et al., 2005). The early benefit of statin treatment on outcomes is particularly evident in patients with ACS, who are at very high risk of CVD, and is highlighted by results of two recent atorvastatin trials. In MIRACL, after only 4 months, patients receiving atorvastatin 80 mg experienced a 16% RR reduction in the composite primary endpoint (death, nonfatal acute MI, cardiac arrest with resuscitation, recurrent symptomatic myocardial ischemia requiring hospitalization) compared with those receiving placebo (Schwartz et al., 2001). Similarly, in PROVE IT-TIMI 22, atorvastatin 80 mg provided a 14% reduction in risk of the primary endpoint after 6 months relative to pravastatin 40 mg (Cannon et al., 2004).

The A to Z trial compared the effect of early intensive statin treatment with more moderate statin therapy in patients with ACS. In A to Z, patients were randomized to either simvastatin 40 mg for 1 month followed by simvastatin 80 mg until trial completion or placebo for 4 months followed by simvastatin 20 mg (de Lemos et al., 2004). The A to Z trial did not show a significant benefit of intensive over moderate statin treatment for reducing the composite primary endpoints of cardiovascular death, nonfatal MI, readmission for ACS, and stroke (de Lemos et al., 2004).

4.27. Triglycerides and atorvastatin

However, several lines of evidence support TG as a biomarker of CHD risk owing to the role of TG-rich lipoproteins in atherothrombosis. Following the hydrolysis of exogenously derived chylomicrons or endogenously secreted VLDL cholesterol, cholesterol-enriched remnant by-products enter the sub-endothelial space. In
hypertriglyceridemic states, remnants accumulate, resulting in a proinflammatory and oxidative milieu that may enhance adhesion molecule expression, foam cell formation, and smooth muscle cell toxicity (Yu and Cooper, 2001). Indirectly, high levels of TG may also be associated with hypertriglyceridemic HDL particles, which are thought to be less efficient in reverse cholesterol transport (Greene et al., 2001; Skeggs et al., 2002), as well as an increased proportion of small, dense LDL particles which may be more susceptible to oxidative modification (Steinberg et al., 1989; Austin et al., 1990).

Table 4.11 and Fig. 4.4, show that mean TG levels decreased from 167.1± 63.2 mg/dL at the baseline to 148.5±40.5 mg/dL (p< 0.06) at the 3rd month, and 149.5± 38.9 mg/dL at the end of the study (12th month) after administration of atorvastatin. After 3 months of treatment, TG levels decreased by -11.1 % and similar mean levels were maintained after 12 months of treatment in group III (Table 4.11). There was an increased in the mean levels of TG from 138.1±60.3 mg/dL at the baseline to 153.1±73.1 mg/dL at the 3rd month in the group II. There was a decreased in the mean levels as 140.0±43.7 mg/dL was found from 3rd month and 12th month in group II. Both increased and decreased mean levels between time course is clinically insignificant (Fig. 4.4). The mean levels of TG in group I was found to be 139.7±57.6, 151.3±74.2 and 155.2±47.6 at 0, 3rd and 12th months respectively. There was no significant difference in the levels of TG in the group I during the study period (Fig. 4.4).

The observed reductions in TG levels with statins range from 7% to 30% (Downs et al., 1998; The Long-Term Intervention with Pravastatin in Ischaemic Disease Study Group, 1998; Jones et al., 1998). In a pooled analysis of 7 double-blind studies of similar design in which 2,689 patients with TG levels <400 mg/dL were treated with lovastatin, pravastatin, or simvastatin (Stein et al., 1998), statin therapy had no significant effect on TG levels in patients with baseline TG levels <150 mg/dL. In patients with baseline TG levels >250 mg/dL, significant dose-dependent reductions in TG levels ranged from 22% to 45% (Stein et al., 1998). Thus, the statins' effectiveness in reducing TG levels is associated with the TG level at the baseline. Statins are also effective in lowering non-HDL cholesterol, and the more potent statins (eg, atorvastatin) reduce concentrations of TG-rich lipoproteins, including atherogenic remnant particles (Stein et al., 2001).
Table 4.11 Changes in mean triglycerides levels in group II and group III

<table>
<thead>
<tr>
<th>Time</th>
<th>Triglyceride</th>
<th>Group II</th>
<th>Group III</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>138.1±60.3</td>
<td>167.1±63.2</td>
</tr>
<tr>
<td>Day 0</td>
<td>153.1±73.1</td>
<td>148.5±40.5</td>
<td></td>
</tr>
<tr>
<td>Month 3</td>
<td>15</td>
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<td></td>
</tr>
<tr>
<td>Change (%)</td>
<td>10.9%</td>
<td>-11.1%</td>
<td></td>
</tr>
<tr>
<td>Month 12</td>
<td>140.0±43.7</td>
<td>149.5±38.9</td>
<td></td>
</tr>
<tr>
<td>Change (%)</td>
<td>-13.1</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-8.6%</td>
<td>0.7</td>
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Fig. 4.4 Mean levels of triglycerides in group I, II and III
The fact that plasma TG correlates with atherogenic remnants (Imke et al., 2005), coupled with the excess risk of CHD with combined elevation of LDL cholesterol and TG (Schaefer, 1994), supports the notion that low on-treatment LDL cholesterol and TG may improve CHD risk beyond low LDL cholesterol alone. The 1.6% reduction in risk associated with each 10-mg/dl decrement in on-treatment TG that is independent of the reduction in risk associated with decreases in LDL cholesterol or non-HDL cholesterol is noteworthy because it includes adjustment of other closely aligned TG covariates (e.g., diabetes, hypertension, obesity, and HDL cholesterol). Moreover, the 2.3% lower incidence of recurrent CHD events associated with each 10% lower TG concentration (after adjustment for high LDL cholesterol and low HDL cholesterol) raises the possibility that additional reduction in CHD risk may be attained through efforts aimed at lowering both LDL cholesterol and TG compared with lowering LDL cholesterol alone.

Accordingly, if a combined strategy of low LDL cholesterol and low TG proves to be more effective in reducing CHD events than intensive LDL cholesterol lowering alone, then additional strategies might be considered after ACS, including replacement of saturated and trans fats with mono- and polyunsaturated fats (Sacks and Katan, 2002), especially derivatives such as omega-3 fatty acids that are cardioprotective and at high doses possess TG-lowering properties (Harris and Bulchandani, 2006; Yokoyama et al., 2007), or the addition of niacin- or fibrate-based therapy, which is currently under investigation for CHD event rate reduction beyond LDL cholesterol lowering (Brown and Boden, 2007; Action to Control Cardiovascular Risk in Diabetes Study Group, 2007).

In the PROVE IT-TIMI 22 trial, the most noteworthy finding was the reduced risk of CHD with low on-treatment TG (<150 mg/dl) that was independent of the level of LDL cholesterol. For each 10-mg/dl decline in on treatment TG, was observed a 1.6% lower risk of the composite end point (p < 0.001) after adjustment for LDL cholesterol and other covariates. Moreover, the combination of low LDL cholesterol (<70 mg/dl) and low TG (<150 mg/dl) was associated with the lowest event rates compared with higher LDL cholesterol, higher TG, or both (Michael et al., 2008). PROVE IT-TIMI 22 trial, observations on the relationship between lower event rates with reduced on treatment
TG are consistent with 2 recent studies. They include a large Chinese Prospective Study (CPS) that found TG to be predictive of CHD mortality, even in the setting of low TC (He et al., 2004), and the PROCAM stratified by HDL cholesterol, which identified a higher CHD risk with high TG (>150 mg/dl) in subjects at all levels of LDL cholesterol (Assmann, 2001). Taken together, aiming for low on-treatment levels of LDL cholesterol and TG may be particularly effective after ACS where residual CHD risk remains elevated despite recent diagnostic and therapeutic advancements (Giugliano and Braunwald, 2006).

The PROVE IT-TIMI 22 trial (Cannon et al., 2004) and the HPS (Heart Protection Study Collaborative Group, 2002) served as the impetus for the NCEP optional recommended LDL cholesterol target of <70 mg/dl (Grundy et al., 2004). Whereas lowering LDL cholesterol to <70 mg/dl has been recommended, the impact of low on-treatment TG beyond achieved LDL cholesterol <70 mg/dl has been less well defined. For example, although TG levels <150 mg/dl are defined as normal, the NCEP does not recommend TG lowering as a primary target of therapy. Rather, non-HDL cholesterol has become a secondary target when TG levels exceed 200 mg/dl (Grundy et al., 2002).

Previously, the combination of LDL cholesterol <70 mg/dl and hsCRP <2 mg/l was shown to be associated with statistically significant reductions in recurrent MI or vascular death compared with higher levels of LDL cholesterol and hsCRP (Ridker et al., 2005). Moreover, in the PROVE IT-TIMI 22 trial, high hsCRP was also found to be associated with each of the factors comprising the metabolic syndrome (Ray et al., 2005). Michael et al., (2008) study shows that there was a 41% lower risk of CHD events between 30 days after ACS and the 2-year follow-up with attainment of LDL cholesterol <70 mg/dl, hsCRP <2 mg/l, and TG <150 mg/dl compared with higher levels in all 3 parameters after adjustment for other covariates.

Mechanistically, if elevated TG represents in part a prothrombotic state (Simpson et al., 1983; Chan et al., 1997), then low on-treatment levels of LDL cholesterol, hsCRP, and TG may be a consideration in ACS patients, owing to the intimate linkage between lipids, inflammation, and thrombosis (Ray and Cannon, 2004). This may justify
consideration of other therapies (Fazio and Linton, 2004; Giannini et al., 2004; Brown, 2005; Gelfand and Cannon, 2006; Harris and Bulchandani, 2006; Yokoyama et al., 2007; Brown and Boden, 2007) if future clinical trials demonstrate clinical benefit beyond LDL cholesterol lowering.

The guidelines issued by the NCEP ATP III (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001) identify low HDL cholesterol level as an important risk factor for CVD and as a criterion for the initiation of lifestyle changes, and use of therapeutic agents. Nevertheless, treatment emphasis remains firmly on reduction of LDL cholesterol, primarily using statins, which very effectively reduce circulating levels of atherogenic LDL cholesterol via upregulation of LDL receptors. The clinical success of statins confirms the epidemiological evidence and points to elevated LDL cholesterol as a direct cause of atherosclerosis progression (Baigent et al., 2005). However, statins also increase HDL cholesterol, measured as HDL cholesterol or apo A-I, and, based on the strong epidemiologic evidence, it is possible that this action may independently contribute to their benefits.

4.28. High-density lipoprotein cholesterol and atorvastatin

Table 4.12 and Fig. 4.5, show that mean HDL cholesterol levels increased from 37.4±6.1 mg/dL at the baseline to 42.2±7.6 mg/dL (p< 0.001) at the 3rd month, and 42.1±4.2 mg/dL at the end of the study (12th month) after administration of atorvastatin. After 3 months of treatment, HDL cholesterol levels increased by 12.8% and similar mean levels were maintained after 12 months of treatment in group III (Table 4.12). There was a significant (p< 0.003) increase in the mean levels of HDL cholesterol from 39.2±6.3 mg/dL at the baseline to 44.4±8.8 mg/dL at the 3rd month in the group II. There was a significant (p< 0.007) decrease in the mean levels as 41.7±6.1 mg/dL was found from the 3rd month and 12th month in group II (Fig. 4.5). The mean levels of HDL cholesterol in group I was found to be 40.3±5.9, 45.0±9.8 and 43.0±8.8 at the baseline, 3rd and 12th months respectively. There was a significant (p< 0.04) difference in the levels of HDL cholesterol in the group I between baseline and 3rd month, and no significant difference between the 3rd and 12th month (Fig. 4.5).
Table 4.12 Changes in mean high-density lipoprotein cholesterol levels in group II and group III

<table>
<thead>
<tr>
<th>Time</th>
<th>Mean HDL cholesterol</th>
<th>Group II</th>
<th>Group III</th>
</tr>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0</td>
<td>39.2±6.3</td>
<td>37.4±6.1</td>
<td></td>
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<tr>
<td>Month 3</td>
<td>44.4±8.8</td>
<td>42.2±7.6</td>
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</tr>
<tr>
<td>Change (%)</td>
<td>5.2</td>
<td>4.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>13.3 %</td>
<td>12.8%</td>
<td></td>
</tr>
<tr>
<td>Month 12</td>
<td>41.7±6.1</td>
<td>42.1±4.2</td>
<td></td>
</tr>
<tr>
<td>Change (%)</td>
<td>-2.7</td>
<td>-0.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-6.1%</td>
<td>-0.2</td>
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Fig. 4.5 Mean levels of high-density lipoprotein cholesterol in group I, II and III
Table 4.13 and Fig. 4.6, show that mean VLDL cholesterol levels decreased from 34.8±15.3 mg/dL at the baseline to 28.3±9.1 mg/dL (p< 0.004) at the 3rd month, and 29.6±7.8 mg/dL at the end of the study (12th month) after administration of atorvastatin. After 3 months of treatment, VLDL cholesterol levels increased by -18.7% and similar mean levels were maintained after 12 months of treatment in group III (Table 4.13). There was an increased in the mean levels of VLDL cholesterol from 27.4±12.0 mg/dL at the baseline to 30.7±14.5 mg/dL at the 3rd month in the group II. There was a decreased in the mean levels as 27.9±8.7 mg/dL was found from the 3rd month and the 12th month in group II. Both increased and decreased mean levels between time course is clinically insignificant (Fig. 4.6). The mean levels of VLDL cholesterol in group I was found to be 28.5±12.5, 30.2±14.8 and 30.1±8.9 at the baseline 3rd and 12th months respectively. There was no significant difference in the levels of VLDL cholesterol in the group I between baseline, 3rd and 12th month (Fig. 4.6).

From the combined data from four large prospective studies, (Gordon et al., 1989) estimated that an increment of 1 mg/dl in HDL cholesterol is associated with a 2-3% lower risk of CHD. Thus, a relatively modest statin-mediated effect on HDL cholesterol, for example, an increase of 10% that is possible with statins (Barter et al., 2006), might provide important protection from CVD in addition to the undoubted benefits of LDL cholesterol reduction. However, extrapolation from epidemiology to putative benefits of drug therapy requires caution. Support for the concept of HDL-raising by drugs comes from prospective trials of fibrates and of nicotinic acid, two drug types with substantial effects on HDL cholesterol and VLDL cholesterol metabolism (Manninen et al., 1988; Rubins et al., 1999; The Coronary Drug Project Research Group 1975; Brown, 2001), and also from early clinical work with infusions of apo A-I in liposomes where dramatic reductions in coronary atheroma have been observed (Nissen et al., 2003). In contrast, recent trials of torcetrapib, an inhibitor of cholesteryl ester transfer protein (CETP) that induces substantial increases in HDL cholesterol and apo A-I failed to show any benefit on atherosclerosis (Nissen et al., 2007; Kastelein et al., 2007; Bots et al., 2007). It is possible that the plasma concentrations of HDL cholesterol or apo A-I may not always reflect the protective activity of the HDL system. It is important to consider both the magnitude of effect on HDL cholesterol level and the mechanism by which it is achieved.
Table 4.13 Changes in mean very low-density lipoprotein cholesterol levels in group II and group III

<table>
<thead>
<tr>
<th>Time</th>
<th>Mean VLDL cholesterol</th>
<th>Group II</th>
<th>Group III</th>
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<td></td>
<td></td>
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<tr>
<td>Day 0</td>
<td>27.4±12.0</td>
<td>34.8±15.3</td>
<td></td>
</tr>
<tr>
<td>Month 3</td>
<td>30.7±14.5</td>
<td>28.3±9.1</td>
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<td>Change (%)</td>
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<td>12.0%</td>
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<td>Month 12</td>
<td>27.9±8.7</td>
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<td></td>
</tr>
<tr>
<td>Change (%)</td>
<td>-2.8</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-9.1%</td>
<td>4.6%</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 4.6 Mean levels of very low-density lipoprotein cholesterol in group I, II and III
Two explanations have been proposed for the effects of statins on HDL cholesterol. In cell experiments, inhibition of HMG-CoA reductase by statins was shown to increase peroxisome-proliferator receptor activator-alpha (PPARα) activity and, like fibrates, to elevate the hepatic synthesis of apo A-I (Martin et al., 2001). Such an effect would be expected to increase the formation of HDL cholesterol precursor particles. A second explanation revolves around the metabolic relationship between HDL cholesterol and TG-rich atherogenic lipoproteins. Guerin et al., (2000) showed that atorvastatin reduced circulating levels of CETP, and also importantly the rate of CETP-mediated CE transfer from HDL cholesterol to VLDL cholesterol secondary to reduction in the latter. Statins, however, are not known to be direct inhibitors of CETP.

With statins, elevations in HDL cholesterol range between 3% and 15%. These are relatively modest increases compared with agents such as nicotinic acid, fibrates, and the recently developed CETP inhibitors. However, given the widespread use of statins and the putative benefit of HDL cholesterol elevation, it is important to thoroughly assess this aspect of statin action. Most clinical trials of statins were designed with LDL cholesterol as the primary endpoint and conducted in patients with hypercholesterolemia, excluding those with very high TG. Usually the study populations had normal HDL cholesterol levels on average and were treated for at least 6 weeks. In the placebo-controlled trial of (Hunninghake et al., 1990), a study was made of the rate of change of lipoprotein parameters in response to a range of doses of pravastatin.

Patients were randomized following dietary stabilization and then treated for 12 weeks. In the pravastatin groups, HDL cholesterol increased from the baseline, reached maximal levels at 4 weeks and remained steady thereafter, whilst in the placebo group it was almost unchanged. At week 12, pravastatin had increased HDL cholesterol by 6-7% from the baseline, compared with 1% for placebo. The observed time course of the HDL cholesterol increases with pravastatin paralleled the reductions in both LDL cholesterol and TG, suggesting a mechanistic relationship between the changes. A treatment period of =6 weeks appears adequate for assessing the effects of statins on HDL cholesterol.
Statin-induced effects on HDL cholesterol are relatively small compared with those of LDL cholesterol and, as a result, most clinical trials of statins are underpowered with respect to HDL cholesterol parameters. To allow comparison between trials, data relating to errors of the estimates for changes in HDL cholesterol and apo A-I have been converted to 95% confidence intervals. The findings from the four largest placebo-controlled statin trials, which measured both HDL cholesterol and apo A-I and reported the errors of the estimates of change. All four trials were in patients with primary hypercholesterolemia with TG levels <450 mg/dl. Patients were randomized in a parallel design following a dietary lead period =2 weeks.

In two of the studies (Davidson et al., 2002, Bays et al., 2004), the errors of estimates are reported only for the pooled 10-80 mg simvastatin dose groups. It is apparent that the percentage changes in HDL cholesterol in the statin-treated groups are consistently greater than placebo; the lack of overlap in the 95% confidence limits suggests real drug responses. A similarly large study of pravastatin 20 mg (The Pravastatin Multinational Study Group for Cardiac Risk patients, 1993) found a 7% increase in HDL cholesterol compared with placebo. Over the four trials the magnitude of effect on apo A-I was consistently less than on HDL cholesterol, and not statistically different from placebo in two of them. This suggests that statins change HDL cholesterol to a more cholesterol-rich form.

Eight other smaller placebo-controlled trials (n=106) in hypercholesterolemic patients of duration =6 months also fitted our selection criteria (Capurso et al., 1992; Pravastatin Multicenter Study Group II 1993; Frederiksen et al., 1993 Wiklund et al., 1993; Haffner et al., 1995; Bak et al., 1998; de Jongh et al., 2002; Rosenson and Bays 2003). In 14 of the 15 statin dose groups comprising these studies, the mean change in HDL cholesterol was numerically greater than in the corresponding placebo group. This was also the case for apo A-I in all nine groups in which it was measured. However, differences vs. placebo were not always significant, perhaps reflecting smaller group sizes. Similar findings were reported in a 12-week study in patients of African-American descent, where the HDL cholesterol response to pravastatin was numerically greater but not significantly different from placebo (Jacobson et al., 1995).
It is important to consider whether statin-induced changes in HDL cholesterol, like those in LDL cholesterol, can be maintained over the long term. Keech et al., (1994) measured the effects of simvastatin 20 and 40 mg over 3 years in patients considered to be at risk of CHD. Although this study did not include a dietary lead-in period, changes from the baseline in the placebo group were minor. In the combined simvastatin groups, significant increases in HDL cholesterol of 8–10% vs. placebo were maintained over 3 years while increases in apo A-I were also significant vs. placebo (5% measured up to 2 years only). HDL cholesterol and occasionally also apo A-I have been monitored in large-scale placebo controlled studies employing atherosclerosis progression or cardiovascular event endpoints, conducted for ≥2 years. In general, the study populations were more inclusive than in shorter-term studies. In all but one trial, there was a positive effect on HDL cholesterol (range, 1.5–10%) relative to placebo. The apo A-I responses when measured were lower and relatively variable. Data from these longer-term trials are consistent with those of shorter lipid endpoint studies bearing in mind that compliance often decreases as the duration of the study increases.

The relatively large sample sizes in outcomes studies provide opportunities to identify factors contributing to the HDL cholesterol response and thereby deduction as to possible mechanisms. In the untreated population, there is a well-established inverse curvilinear relationship between plasma levels of TG and HDL cholesterol, with most variation in HDL cholesterol being apparent at TG levels <220 mg/dl (Lamarche et al., 1996). This reflects in part the action of CETP since high VLDL-TG levels facilitate the two-way transfer of TG and cholesteryl ester between VLDL cholesterol and HDL cholesterol. In a follow-up to the WOSCOPS (Shepherd et al., 1995, Streja et al., 2002) analyzed data from those participants in the active group who were fully compliant (about half). Mean percent change in the pravastatin group decreased across quintiles of baseline HDL cholesterol, such that the absolute increment remained relatively constant. Independent contributors to statin induced change in HDL cholesterol were alcohol intake, BMI, and reduction in plasma TG, all of which have influence on plasma CETP levels and/or activity. Most likely the reduction in cholesteryl ester transfer from HDL cholesterol that results in elevation of HDL cholesterol is governed by the degree of reduction in VLDL cholesterol. The effect of statin would be to shift the patient's
position on the population curve relating HDL cholesterol to TG levels. Such a mechanism involving CETP would be consistent with alteration of the particle size distribution of HDL cholesterol towards larger, relatively cholesterol rich particles that are characteristic of healthy low-risk populations manifesting the ideal profile of low TG and high HDL cholesterol. Such statin-induced changes in subpopulations of HDL cholesterol have been consistently demonstrated in the studies of (Asztalos et al., 2000; Asztalos, 2004; Asztalos et al., 2005; Asztalos et al., 2007).

Hepatic lipase is another factor with a key role in TG and lipoprotein metabolism. Increased hepatic lipase due to a common polymorphism (-514 C.T) is associated with lower levels of the larger HDL particles as well as greater numbers of small dense (more atherogenic LDL cholesterol) (Kuusi et al., 1980; Zambon et al., 1993; Watson et al., 1994; Zambon et al., 2001; LaRosa et al., 2005). In an intervention trial with combination lipid-lowering therapy including lovastatin (Zambon et al., 2001), subjects homozygous for this allele had the highest hepatic lipase activity, lowest HDL particles and the most angiographic improvement compared to those heterozygous or lacking the allele. In summary, data from placebo-controlled trials in hypercholesterolemic subjects confirm that statins cause definite increases in HDL cholesterol; the mechanism most likely involves reduced transfer of cholesteryl ester from HDL cholesterol to VLDL cholesterol but other factors such as hepatic lipase and other statin-induced effects may also contribute. The data also suggest that statin effects on HDL cholesterol and apo A-I are maintained over time and that a treatment period of 6 weeks is sufficient to assess and compare different statins in this respect. Comparative effects of statins on HDL cholesterol at recommended starting doses In clinical practice, most patients remain on the statin dose first prescribed (EUROASPIRE II Study Group, 2001) so it is appropriate to first compare the effects on HDL cholesterol of statins when used at their recommended starting doses: atorvastatin 10 or 20 mg, pravastatin 20 or 40 mg, rosuvastatin 5 or 10 mg, and simvastatin 20 or 40 mg.

Blasetto et al., (2003) reported data from five individual trials prospectively designed for pooling into two sets (1) (Davidson et al., 2002; Olssen et al., 2002; Schwartz et al., 2004) and (2) (Paoletti et al., 2001, Brown et al., 2002). All trials were of parallel

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design with treatment duration =6 weeks, measured both HDL cholesterol and apo A-I and reported the errors of the estimates of percentage change. Eligible patients included those with hypercholesterolemia, a relatively normal HDL cholesterol level, TG <400 mg/dl, with or without high risk, manifest CHD or type 2 diabetes. Between the statins there is a tendency for rosuvastatin to have the greatest effect on both HDL cholesterol and apo A-I. Mean percent changes in HDL cholesterol from baseline across the trials weighted by patient numbers were as follows: rosuvastatin 8.5%, pravastatin 6.5%, simvastatin 6.4%, atorvastatin 5.5%. In some but not all trials, significant differences have been reported in the HDL cholesterol response to the starting doses of rosuvastatin and atorvastatin. For example, in the largest study (Schuster et al., 2004), the effect of rosuvastatin 10 mg on HDL cholesterol (9.2%) was significantly greater than either atorvastatin 10 mg (6.8%, p<0.01) or 20 mg (5.7%, p<0.0001).

Apo A-I responses show similar trends between statins but are generally lower than for HDL cholesterol, with greater variability. Two further large trials compared atorvastatin and simvastatin (Olsson et al., 2003, Barter and O’Brien 2000 - data not shown). Olsson et al., (2003) (n=535 per group) reported notably lower HDL cholesterol responses than in the trials described above although the effect of simvastatin on HDL cholesterol (3.3%) was significantly greater than for atorvastatin (-0.1%). The same was true of apo A-I (0.8% vs. -1.8%). However, no difference was apparent between these statins in the study of Barter and O’Brien (2000).

Moreover, Insull et al., (2007) compared atorvastatin 10 mg, rosuvastatin 10 mg, and simvastatin 20 mg and found that all increased HDL cholesterol to similar extents (6–7%). In 17 of these (Malini et al., 1991; Farmer et al., 1992; The European Study Group, 1992; Lambrecht and Malini, 1993; Steinhagen-Thiessen, 1994; Weir et al., 1996; Bertolini et al., 1997; Hunninghake et al., 1998; Barter and O’Brien 2000; Duvovne et al., 2000; Saunders et al., 2000; Wu et al., 2002; Bays et al., 2003; Schwartz et al., 2004; Ferdinand et al., 2006; Lloret et al., 2006). As in the case of (Olsson et al. 2003), statin trials occasionally provide unexpectedly low or high HDL cholesterol responses. Milionis et al., (2006) reported only a modest increase in HDL cholesterol with rosuvastatin 10 mg (3.3%) and a fall of 1.6% with atorvastatin 20 mg. Negative HDL cholesterol responses to
pravastatin have been reported (Rosenson and Bays, 2003) as well as atypically low responses to starting doses of simvastatin (Haffner et al., 1995; Simsons, 1998; de Farnier et al., 2000; Jongh et al., 2002; Milionis et al., 2004). In contrast, unexpected relatively large increases in HDL cholesterol have occasionally been reported for pravastatin 10–40 mg (McPherson et al., 1992; The Lovastatin Pravastatin Stud Group 1993; Jacotot et al., 1995), simvastatin (Deslypere, 1989; Pietro et al., 1989; Simsons, 1998; Illingworth et al., 2001), and atorvastatin (7.3–9.0%) (Brown et al., 1998; Illingworth et al., 2001).

Data from placebo-controlled trials of long duration suggest that the effects of statins on HDL cholesterol are maintained over time. However, the relatively attenuated HDL cholesterol effect of high dose atorvastatin has been observed in long-term studies. In a double-blind comparison of atorvastatin 80 mg and pravastatin 40 mg (Nissen et al., 2004), the percentage increases in HDL cholesterol from baseline at 18 months were 2.9% and 5.6% respectively. An absolute difference in HDL cholesterol levels of 1.2–1.9 mg/dl between the groups treated with simvastatin 20 mg or atorvastatin 80 mg (in favor of the former) was reported to be maintained over 4 years in the study of (Pedersen et al., 2005), although the difference diminished in the fifth year of observation. Similarly, in ACS patients, there was a difference of 1.6% in HDL cholesterol levels between pravastatin 40 mg and atorvastatin 80 mg over a 2-year period, (Cannon et al., 2004). However, there was no difference in this respect between 10 mg and 80 mg of atorvastatin over 5 years (LaRosa et al., 2005).

Statin treatment reduces coronary events in patients with low HDL cholesterol levels (Pedersen et al., 1998; Sacks et al., 2000; Gotto et al., 2000). Moreover, HDL cholesterol levels continued to predict cardiovascular risk even when LDL cholesterol was reduced to very low levels by atorvastatin (Barter et al., 2007). However, the respective contribution made by statin induced increases in HDL cholesterol to cardiovascular benefit is not always apparent from clinical trial data. This may be due to considerable inter-individual differences (depending in turn on the particular combination of risk factors and genetic predisposition) in the degree to which a change in HDL cholesterol impacts upon disease progression and perhaps most importantly to the overwhelming positive effect of reductions in LDL cholesterol. In the outcome
studies mentioned above in which statins were compared, the differences in HDL cholesterol responses due to pravastatin in (Cannon et al., 2004) and simvastatin in (Pedersen et al., 2005) did not outweigh the superior LDL cholesterol reductions due to atorvastatin 80 mg. The potential contributions made to outcomes by statin-induced changes in HDL cholesterol are best discerned in the large scale such as in the Pravastatin Pooling Project (PPP), which combined data from three large trials of pravastatin 40 mg (Sacks et al., 2000).

As expected, baseline LDL cholesterol and HDL cholesterol levels, analyzed in quintiles, were strongly predictive (positively and negatively, respectively) of events in the placebo group. In the treated group, the slope of the line-relating baseline LDL cholesterol to risk was markedly reduced, indicating the statin had markedly ameliorated LDL-associated risk. In contrast, the slope of the HDL cholesterol line was only slightly reduced indicating a rather modest effect on the HDL cholesterol associated risk. This might be expected given that the effect of the statin on LDL cholesterol was greater (-25% to -28%) than that on HDL cholesterol (5%). Post hoc analysis of data from the 4S by Cox Proportional Hazard suggested an independent benefit of the simvastatin effect on HDL cholesterol, a reduction in risk of 0.8% for each 1% increase (Scandinavian Simvastatin Survival Study 1994, Pedersen et al., 1998).

The application of other statistical models also found significant or marginally significant independent benefit arising from the increases in HDL cholesterol. In an additional post hoc analysis of the 4S study, (Ballantyne et al., 2001) found that the subgroup defined as having HDL cholesterol in the lowest and TG in the highest quartile had the most substantial event reduction.

In order to address this issue with respect to progression or regression of coronary atherosclerosis, (Nicholls et al., 2007) combined data from four trials that used intravascular ultrasound to measure atheroma volume. In multivariate analyses, as expected, the on-treatment LDL cholesterol was correlated with the atheroma parameters, but the change in HDL cholesterol (but not the on-treatment value) also made a strong independent contribution. Notably, participants who showed lesion
regression manifested not only low on-treatment LDL cholesterol but also an HDL cholesterol increase greater than the overall mean of 7.5%. There are some weaknesses in this post hoc analysis. For example in two of the pooled trials, statin therapy was unrandomized background treatment, all four trials were open-label and there were no placebo groups. Thus, while an association between change in HDL cholesterol and reduced atherosclerosis progression was apparent, a direct, HDL cholesterol mediated causal effect of statins cannot be directly inferred.

With statins, the impact of reduction in the apo B containing lipoproteins on atherosclerosis and cardiovascular events is sure to be greater than that due to any changes in HDL cholesterol levels. Nevertheless, given the strength and independence of the epidemiologic relationships, it is reasonable to expect that statin-induced elevations in HDL cholesterol make an independent contribution to benefit. It would be difficult to conceive a clinical outcomes trial that would provide absolute verification of this hypothesis. It would be necessary to compare statins in such a way that LDL cholesterol levels were the same between groups (and equivalent in terms of other potential ‘pleiotropic’ effects), allowing only HDL cholesterol responses to differ.

However, as noted earlier, statins increase HDL cholesterol parameters and lower TG, altering the HDL cholesterol subpopulations in a way consistent with clinical benefit. The evidence related above lends some support to this hypothesis. Moreover, it is reasonable to expect that the degree of HDL cholesterol associated benefit of statins is proportional to the change in HDL cholesterol levels. It is important therefore to assess statins not only in terms of their capacity to reduce LDL cholesterol and VLDL cholesterol but also their respective abilities to raise levels of HDL cholesterol.

4.29. Non-HDL cholesterol and atorvastatin

Clinical trials of cholesterol-lowering therapy have not specifically identified non-HDL cholesterol (independent of LDL) as a target of therapy; thus, it has been difficult to isolate the impact of lowering non-HDL cholesterol per se on CHD risk. However, the same statement could be made about LDL itself. For example, it has been
widely assumed from primary and secondary prevention trials of statin therapy that risk reduction is a response to LDL cholesterol lowering.

In Table 4.14 and Fig. 4.7, the information indicated that mean non-HDL cholesterol levels decreased from 163.9±38.3 mg/dL at the baseline to 129.3±32.3 mg/dL (p< 0.001) at the 3rd month, and 120.8±19.8 mg/dL (p< 0.08) at the end of the study (12th month) after administration of atorvastatin. After 3 and 12 months of treatment, non-HDL cholesterol levels decreased by -24.6% and -5.8% respectively in group III (Table 4.14). There was a significant increase (p< 0.009) in the mean levels of non-HDL cholesterol from 128.6±26.8 mg/dL at the baseline to 140.1±28.4 mg/dL at the 3rd month in the group II. There was a significant decrease (128.1±21.3, p< 0.006) found between 3rd month and 12th month in group II (Table 4.14 and Fig. 4.7). The mean levels of non-HDL cholesterol in group I was found to be 124.9±28.1, 122.2±30.5 and 116.5±35.1 at the baseline 3rd and 12th months respectively. There was no significant difference in the levels of non-HDL cholesterol in the group I during the study period (Fig. 4.7).

Of interest, however, the percentage reductions of LDL cholesterol and VLDL cholesterol on statin therapy are similar (Vega and Gundy, 1990). Consequently, it is not possible to differentiate risk reduction due to LDL lowering from non-HDL cholesterol lowering. Most clinical trials have not specifically included persons with hypertriglyceridemia; thus it can be assumed that lowering of VLDL cholesterol was a minor contributor to risk reduction in statin trials.

However, in clinical practice, the situation may be different; when TG are high, a significant fraction of non-HDL cholesterol is contained in VLDL cholesterol. Here LDL cholesterol may not be the only significant lipid risk factor. Consequently, when TG are high, non-HDL cholesterol (including VLDL cholesterol) can serve as a secondary target of therapy. A “normal” VLDL cholesterol can be defined as that present when TG are <150 mg/dL; this value typically is ≤30 mg/dL (Lipid Research Clinics Program Epidemiology Committee, 1979). Conversely, when TG levels are >150 mg/dL, VLDL cholesterol usually is >30 mg/dL. Thus, a reasonable goal for non-HDL cholesterol is one that is 30 mg/dL higher than the LDL-cholesterol goal.

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Table 4.14 Changes in mean non-HDL cholesterol levels in group II and group III

<table>
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<th>Mean non-HDL cholesterol</th>
<th>Group II</th>
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</tr>
<tr>
<td>Month 12</td>
<td>128.1±21.3</td>
<td>-8.6%</td>
<td>-21.1%</td>
</tr>
<tr>
<td>Change (%)</td>
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</table>

Fig. 4.7 Mean levels of non-HDL cholesterol in group I, II and III
A specific goal of therapy for serum TG is not identified in ATP III for two reasons: (a) triglyceride levels have more day-to-day variability than non-HDL-cholesterol levels and thus are less reliable, and (b) non-HDL cholesterol as a target allows more flexibility in choice of therapies to reduce atherogenic lipoproteins contained in the combined LDL+VLDL fraction.

Reduction of non-HDL cholesterol can be accomplished with intensification of statin therapy, use of a statin with greater LDL cholesterol lowering efficacy, or the addition of a fibrate or niacin specifically to enhance VLDL reduction (Executive Summary of The Third Report of The National Cholesterol Education Program Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults, 2001; Betteridge and Gibson, 2004).

Overall, statins have a greater ability than other lipid-lowering drugs to beneficially affect the entire range of atherogenic lipoproteins, including the atherogenic components of non-HDL cholesterol (Sniderman et al., 2001; Executive Summary of The Third Report of The National Cholesterol Education Program Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults, 2001; Chapman and Caslake, 2004).

Statins slow the secretion of VLDL cholesterol from the liver and attenuate the subsequent formation of IDL and LDL cholesterol. They also increase the clearance of IDL and LDL cholesterol from plasma (Sniderman et al., 2001; Chapman and Caslake, 2004). Generally, statins lower non-HDL cholesterol and LDL cholesterol by similar percentages (Grundy et al., 2004). More efficacious statins can also adequately lower TG, especially in combination with aggressive therapeutic lifestyle changes, including weight reduction and increased physical activity (Executive Summary of The Third Report of The National Cholesterol Education Program Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults, 2001).

Three non-outcomes studies investigated intensive lipid lowering in patients with diabetes with varying dose levels of rosuvastatin. In A Randomized Double-blind Study to Compare Rosuvastatin and Atorvastatin in Patients with Type 2 Diabetes, 509
patients were treated with either statin at 10 and 20 mg/day for 8 weeks at each dosage. By 16 weeks, mean LDL cholesterol and non-HDL cholesterol reductions with rosvustatin were 57.4 and 50.6%, respectively, compared with 46 and 41.5% with atorvastatin (Betteridge and Gibson, 2004).

Atorvastatin therapy modifies all of the components of the lipid triad. Taken together, the present study with various clinical trials support a beneficial effect of atorvastatin that favorably modifies atherogenic dyslipidemia and major coronary events.

4.30. Apolipoproteins and atorvastatin

Mean baseline apo B level in group I was 62.0±23.8 mg/dL, and 61.2±18.5 mg/dL at the 3rd month. There was no significant difference between the baseline and the 3rd month. Mean value of apo B in group II was 77.1±17.1 mg/dL, and 54.6±16.0 mg/dL at the 3rd month. There was a significant (p< 0.005) decreased was found in group II between the baseline and the 3rd month. In statin treated patients who had baseline apo B levels were 64.4±14.3 mg/dL, and 58.3±12.0 mg/dL at the 3rd month and there was a clinical significant (p< 0.001) decreased in group III between the baseline and the 3rd month (Fig. 4.8). Mean baseline apo A-I level in group I was 54.6±16.0 mg/dL, and 52.3±13.6 mg/dL at the 3rd month. Mean value of in apo A-I group II was 78.2±21.7 mg/dL, and 79.6±19.8 mg/dL at the 3rd month. In statin treated patients who had baseline apo A-I levels were 85.9±18.6 mg/dL, and 87.0±15.2 mg/dL at the 3rd month and there was no clinical significant among the groups (Fig. 4.9).

Although clinical evidence clearly demonstrates that apo B and apo A-I are significantly associated with CAD risk, they have not been generally accepted as therapeutic targets by the various bodies providing lipid-regulating guidelines (Executive Summary of The Third Report of The National Cholesterol Education Program Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults, 2001; Haffner, 2003; Ballantyne et al., 2005). However, a target apo B level of <90 mg/dl for patients with CAD or at high risk of CAD has been suggested by the Canadian Cardiovascular Society (CCS) (Collins-Nakai and Dagenais, 1999).
Fig. 4.8 Mean levels of apolipoprotein B in group I, II and III

Fig. 4.9 Mean levels of apolipoprotein A-I in group I, II and III
Based on the known strong positive relationship between non-HDL cholesterol and apo B, a target level for apo B has been proposed by Grundy as an updated revision of the NCEP ATPIII guidelines (Grundy, 2002). Regarding cut-off values for apo A-I, Wallius et al., (2004) defined cutoff apo A-I levels of 115mg/dl for males, and 125mg/dl for females, corresponding to apo B to apo A-I ratios of 0.9 and 0.8, respectively. Results from several major statin trials have also demonstrated the superiority of apo B and apo A-I over cholesterol indices as predictors of treatment benefits on cardiovascular outcomes (Pedersen et al., 1998; Roeters et al., 2000; Gotto et al., 2000; Simes et al., 2002). AFCAPS/TexCAPS was a primary prevention study of the effect of lovastatin in reducing the occurrence of coronary events in 6,605 asymptomatic individuals with average LDL cholesterol and below-average HDL cholesterol (Gotto et al., 2000). Although levels of LDL cholesterol, HDL cholesterol and apo B at entry were significant predictors of a first acute major coronary event, only on-treatment apo B and apo B to apo A-I ratio were predictive of subsequent risk. In the LIPID Trial relationships of baseline and on-study lipids with subsequent CHD events were examined in 9,014 CHD patients after treatment with pravastatin for 1 year (Simes et al., 2002). Baseline apo B and apo A-I were stronger predictors of CHD events than LDL cholesterol and HDL cholesterol. The adjusted RR for apo B, apo A-I, LDL cholesterol and HDL cholesterol were 2.07, 0.41, 1.28 and 0.52, respectively. The unadjusted on treatment concentrations of apo B and apo A-I were predictive of a subsequent coronary event (RR 1.49 and 0.61 respectively).

In the 4S, lipoprotein changes and reduction in the incidence of major CHD events were examined in 4,444 CHD patients randomized to receive simvastatin or placebo over a median follow-up of 5 years (Pedersen et al., 1998). Baseline apo B was significant predictor of CHD for patients in the placebo and treatment groups, but LDL cholesterol only predicted CHD risk for patients in the placebo group. The on-treatment concentrations of LDL cholesterol and apo B were both predictive of major coronary events after 1 year of treatment. The risk reductions (%) for each additional 1% lipid reduction for LDL cholesterol and apo B were 1.7% and 1.1%, respectively. The Leiden Heart Study (LHS), 848 patients (675 men, 173 women) with angiographically-proven CAD who received effective statin treatment (Roeters et al., 2000). In univariate analysis,
the RR for on-treatment LDL cholesterol, HDL cholesterol, apo B and apo A-I were 1.16, 0.37, 3.21 and 0.20, suggesting that apo B and apo A-I were superior to LDL cholesterol for predicting vascular events.

Under multivariate analysis, on-treatment apo B and apo A-I were the only significant predictors for subsequent MI and all-cause mortality, after adjusting for TC, TG, gender, diabetes, age and smoking. The RR for apo B and apo A-I were 7.94 and 0.29, respectively. These data show that changes in plasma apo B levels in response to treatment with a statin may be better predictors of clinical benefit than changes in LDL cholesterol.

Apo B and apo A-I was comparatively carried out in small sample size. Hence the efficacy of a therapeutic regimen based on apo B or apo B to apo A-I in decreasing CVD events requires to be formally investigated.

4.31. Lipids, lipoproteins ratios and atorvastatin

4.31.1. TC to HDL cholesterol ratio

As shown in Fig. 4.10, the data indicated that mean TC to HDL cholesterol levels decreased from 5.5±1.4 at the baseline to 4.1±1.0 (p< 0.001) at the 3rd month, and 3.8±0.6 (p< 0.01) at the end of the study after administration of atorvastatin. There were no significant differences in the mean levels of TC to HDL cholesterol between the baseline to the 3rd month and between 3rd month to 12th month. The mean value at the baseline was 4.3±0.7 and 4.3±1.1 at the 3rd month in the group II. A similar level was found 12th month (4.2±0.7). The mean levels of TC to HDL cholesterol in group I was found to be 4.6±0.7, 3.9±0.7 and 4.0±1.2 at the baseline, 3rd and 12th months respectively. There was no significant difference in the levels of TC to HDL cholesterol in the group I during the study period.

4.31.2. LDL cholesterol to HDL cholesterol ratio

As shown in Fig. 4.11, the data indicated that mean LDL cholesterol to HDL cholesterol levels decreased from 4.0±1.4 at the baseline to 2.4±0.8 (p< 0.001) at the 3rd month, and 2.1±0.6 (p< 0.03) at the end of the study after administration of atorvastatin.
Fig. 4.10 Mean levels of TC to HDL cholesterol ratio in group I, II and III

Fig. 4.11 Mean levels of LDL cholesterol to HDL cholesterol ratio in group I, II and III
There were no significant differences in the mean levels of LDL cholesterol to HDL cholesterol between the baseline to the 3rd month and between the 3rd month to 12th month. The mean value at the baseline was 2.6±0.7 and 2.6±1.0 at the 3rd month in the group II. Similar level was found 12th month (2.5±0.7). The mean levels of LDL cholesterol to HDL cholesterol in group I was found to be 2.7±1.0, 2.1±0.6 and 2.4±1.3 at the baseline, 3rd and 12th months respectively. There was a significant (p< 0.01) difference in the levels of LDL cholesterol to HDL cholesterol at the baseline to the 3rd month and there was no significant difference between the 3rd month to 12th month in the group I during the study period.

4.3.1.3. TG to HDL cholesterol ratio

As shown in Fig. 4.12, the data indicated that mean TG to HDL cholesterol levels decreased from 4.5±2.1 at the baseline to 3.5±1.1 (p< 0.002) at the 3rd month, and similar level was maintained at the 12th month. The mean value was 3.5±1.0 at the end of the study after administration of atorvastatin. There were no significant differences in the mean levels of TG to HDL cholesterol between the baseline to 3rd month and between the 3rd month to 12th month. The mean value at the baseline was 3.6±1.6 and 3.5±1.7 at the 3rd month in the group II. Similar level was found 12th month (3.4±1.0). The mean levels of TG to HDL cholesterol in group I was found to be 3.3±1.5, 3.2±1.2 and 3.7±1.2 at the baseline, 3rd and 12th months respectively. There was no significant difference in the levels of TG to HDL cholesterol at the baseline to the 3rd month and there was a significant (p< 0.09) difference between the 3rd month to 12th month in the group I during the study period.

4.3.1.4. Non-HDL cholesterol to HDL cholesterol ratio

As shown in Fig. 4.13, the data indicated that mean non-HDL cholesterol to HDL cholesterol levels decreased from 4.5±1.4 at the baseline to 3.1±1.0 (p< 0.001) at the 3rd month, and similar level was maintained at the 12th month. The mean value was 2.9±0.6 at the end of the study after administration of atorvastatin. There were no significant differences in the mean levels of non-HDL cholesterol to HDL cholesterol between the baseline to 3rd month and between the 3rd month to 12th month.
Fig. 4.12 Mean levels of TG to HDL cholesterol ratio in group I, II and III

Fig. 4.13 Mean levels of non-HDL to HDL cholesterol ratio in group I, II and III
The mean value was 3.5±0.9, 3.3±1.1 and 3.1±0.7 at the baseline, 3rd month and 12th month in the group II. The mean levels of non-HDL cholesterol to HDL cholesterol in group I was found to be 3.2±0.7, 2.8±0.7 and 3.0±1.3 at the baseline, 3rd and 12th months respectively. There was a significant (p< 0.06) difference in the levels of non-HDL cholesterol to HDL cholesterol at the baseline to the 3rd month and there was no significant difference between the 3rd month to 12th month in the group I during the study period.

4.31.5. Apo B to apo A-I

Mean baseline apo B to apo A-I ratio in group I was 1.2±0.4, and 1.2±0.3 at the 3rd month. There was no significant difference between the baseline and the 3rd month. Mean value of apo B to apo A-I ratio in group II was 1.0±0.2, and 0.9±0.2 at the 3rd month. There was a significant (p< 0.005) decreased was found in group II between the baseline and the 3rd month. In statin treated patients who had baseline apo B to apo A-I ratio were 0.8±0.2, and 0.7±0.1 at the 3rd month and there was a clinical significant (p< 0.01) decreased in group III between the baseline and the 3rd month (Fig. 4.14).

4.31.6. Apo B to HDL cholesterol

Mean baseline apo B to HDL cholesterol ratio in group I was 1.5±0.7, and 1.4±0.5 at the 3rd month. There was no significant difference between the baseline and the 3rd month. Mean value of apo B to HDL cholesterol ratio in group II was 2.0±0.6, and 1.6±0.6 at the 3rd month. There was a significant (p< 0.008) decreased was found in group II between the baseline and the 3rd month. In statin treated patients who had baseline apo B to HDL cholesterol ratio 1.7±0.5, and 1.4±0.4 at the 3rd month and there was a clinical significant (p< 0.01) decreased in group III between the baseline and the 3rd month (Fig. 4.15).

For each ratio (TC to HDL cholesterol, LDL cholesterol to HDL cholesterol, TG to HDL cholesterol, non-HDL cholesterol to HDL cholesterol, apo B to apo A-I and apo B to HDL cholesterol), the decrease from baseline was significantly larger in patients receiving atorvastatin compared to untreated groups (I and II).
Fig. 4.14 Mean levels of apolipoprotein B to A-I ratio in group I, II and III

Fig. 4.15 Mean levels of apolipoprotein B to HDL cholesterol ratio in group I, II and III
By combining measures of atherogenic and antiatherogenic lipids or lipoproteins, lipid ratios provide a risk measure that is independent of absolute values of the individual lipid measures. Many studies have demonstrated the strong predictive ability of TC to HDL cholesterol, apo B to apo A-I, and other lipid ratios for CAD (Assmann and Schulte, 1992; Castelli et al., 1992; Kinosian et al., 1994; Pedersen et al., 1998; Gotto et al., 2000; Buchwald et al., 2001; Walldius et al., 2001; Yusuf et al., 2004; Sniderman et al., 2003; Manninen et al., 1992; Kinosian et al., 1995; Criqui and Golomb, 1998; Ballantyne and Hoogeveen, 2003), including analyses of on-treatment ratios in statin clinical end point trials. The current analysis shows that a low dose of atorvastatin (10 mg/day) produced large reductions in lipid ratios, comparable in magnitude to reductions associated with clinical benefit in cardiovascular prevention trials.

In the secondary-prevention 4S in hypercholesterolemic patients, both baseline and on-treatment TC to HDL cholesterol ratios were significant predictors of major coronary events (Pedersen et al., 1998). On-treatment values were highly significant predictors of risk, with each unit decrement in ratio associated with a 17.6% risk reduction and each 1% reduction associated with a 1.3% risk reduction. Overall, simvastatin 20–40 mg treatment resulted in a 34% risk reduction in major coronary events in the context of a 39% reduction in TC to HDL cholesterol ratio. In the AFCAPS/TexCAPS, performed in patients with average TC and low HDL cholesterol, baseline and 1-year on-treatment apo B to apo A-I ratios, and percent change from baseline at 1 year were significant predictors of a first acute major coronary event (Gotto et al., 2000). In the lovastatin group, the apo B to apo A-I ratio was reduced from 0.97 to 0.73 at 1 year, representing a 23.9% reduction in risk. Overall, lovastatin 20–40 mg therapy was associated with a 37% reduction in risk for acute major coronary events.

Data from 5 trials showed that rosuvastatin 10 mg reduced the TC to HDL cholesterol ratio by 38%, the LDL cholesterol to HDL cholesterol ratio by 51%, the non-HDL cholesterol to HDL cholesterol ratio by 47%, and the apo B to apo A-I ratio by 40% from baseline. Rosuvastatin 10 mg treatment resulted in significantly greater reductions versus atorvastatin in TC to HDL cholesterol (38% vs 30%), LDL cholesterol to HDL cholesterol (51% vs 39%), non-HDL cholesterol to HDL cholesterol (47% vs 37%), and

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apo B to apo A-I (40% vs 31%) ratios. The reductions observed with rosuvastatin 10 mg versus simvastatin and pravastatin were as follows: 39% versus 29% and 23% for TC to HDL cholesterol; 52% versus 39% and 30% for LDL cholesterol to HDL cholesterol; 48% versus 36% and 28% for non-HDL cholesterol to HDL cholesterol; and 40% versus 30% and 23% for apo B to apo A-I ratios (Raphael et al., 2005).

It is therefore important to include an evaluation and comparison of the effects of statin treatment on lipid ratios in lipid-lowering trials.

4.32. Uric acid and atorvastatin

Mean baseline uric acid level in group I was 4.3 mg/dL, and this increased to 4.4 mg/dL on the 3rd month and to 4.7 mg/dL at the end of the study. There were a significant increased found between baseline to 3rd month (p< 0.08) and between 3rd month to 12th month (p< 0.09). There was a significant increased (p< 0.04) in the mean levels of uric acid from 5.3 mg/dL at the baseline to 5.6 mg/dL at the 3rd month in the group II. The mean value of uric acid at the 12th month was 5.4 mg/dL and it was clinically insignificant. Nevertheless, in statin treated patients who had baseline uric acid level 5.5 mg/dL, decreased as 4.9 mg/dL at the 3rd month and thereafter 4.4 mg/dL at the end of the study period. Uric acid levels were reduced by 10.9% (p< 0.001) at the 3rd month and 10.2% at 12th (p< 0.001) month (Fig. 4.16). In the current study, atorvastatin treatment resulted in a significant decrease in serum uric acid levels, implying a peliotropic action related to the particular drug itself and not a class effect. It is noteworthy that uric acid reduction was independent of changes in lipidemic parameters.

Atorvastatin can reduce insulin resistance in dyslipidemic patients with non-insulin-dependent diabetes (Paolisso et al., 2000). However, it is unlikely that an atorvastatin-mediated increase in insulin sensitivity had a role in decreasing urate synthesis because this atorvastatin effect on uric acid is small, and it is unlikely that the majority of the patients had insulin resistance (Vasilios et al., 2004). In addition, the effect of statin treatment on patients with diabetes (Athyros et al., 2003) was similar to that in patients without diabetes. It has been suggested that dyslipidemia per se
Fig. 4.16 Mean levels of uric acid in group I, II and III
represents a significant aggravating factor for renal dysfunction in patients with diabetes (Gin et al., 2000) and hypertension (Manttari et al., 1995); in GREek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) Study, 20% of patients had diabetes and 40% had hypertension (Athyros et al., 2002). High serum cholesterol levels seem to have a similar action on glomerular mesangial cells and endothelial cells (Gin et al., 2000). This appears to be analogous to the process of atherosclerosis because mesangial cells possess binding sites for LDL cholesterol and oxidized LDL (Elisaf et al., 2002).

Clinical and experimental studies have shown the role of lipids in decline in renal function (Guijarro et al., 1995). In the structured-care group, a reduction in uric acid (and adjusted creatinine) levels was seen as early as treatment week 6. This may be caused by a direct effect of atorvastatin on renal function (possibly because of increased renal blood flow induced by improved endothelial function) (Huggins et al., 2000). Moreover, in patients who discontinued atorvastatin therapy (n=17) because of personal reasons or side effects, uric acid, creatinine, and creatinine clearance values returned to previous levels within 4 weeks, although these patients continued taking their other medication and followed the same diet. In these patients, changes in these parameters were similar to those in the no-statin patients in the usual-care group. The decrease in uric acid and creatinine levels gradually became more evident after treatment week 6. There are 3 possible explanations for that. First, the effect of atorvastatin on uric acid level may be dose dependent (Vasilios et al., 2004). Second, a time-dependent improvement in lipid profile during the atorvastatin titration period may represent a gradual reduction in the lipid contribution to glomerulosclerosis (O'Donnell et al., 1993). Third, patients receiving structured care had fewer CHD recurrent events during the study, thus preserving cardiac performance and renal blood flow (Vasilios et al., 2004).

The beneficial effect of uric acid level reduction on clinical outcome might be a reflection of the improvement in renal function, even within normal range, because uric acid level changes are closely linked to changes in creatinine levels and creatinine clearance. Renal and IHD may progress in parallel. Creatinine level is a predictor of CHD risk in some studies, (Elisaf et al., 2002; Athyros et al., 2003) and uric acid levels also predict CHD risk (Fang and Aldeman, 2000; Bickel et al., 2002). Whether uric acid levels,
in turn, mediate some of the vascular event risk associated with impaired renal function remains to be established. In the usual-care group, 14% of patients were on long-term treatment with other hypolipidemics (12%, statins; 2%, fibrates). Those on statin therapy had a nonsignificant decrease (2.5%) in uric acid levels. This could be attributed to several causes. The decrease in uric acid levels might be an effect of certain statins.

Previous studies showed no change in uric acid levels with simvastatin (Steinmetz et al., 1996), pravastatin (Tsalamandris et al., 1994), lovastatin (Gardner et al., 1996), fluvastatin (Locsey et al., 1997) or rouvastatin (Milionis et al., 2006). Furthermore, statin doses in the usual-care group were low, and only 3% of patients in this group reached the NCEP LDL cholesterol target. However, the reduction in uric acid levels was significant in patients administered atorvastatin in the usual-care group. This might be related to the greater improvement in renal function, with greater LDL cholesterol (Vasilios et al., 2004). These results may be in favour of a preferable choice of atorvastatin for the treatment of hyperlipidemic patients with elevated levels of uric acid.

**Stroke and atorvastatin**

4.33. Total cholesterol, low-density lipoprotein cholesterol and atorvastatin

Historically, the etiological link between hypercholesterolemia and stroke has been less clear than for CHD. The lack of association between TC levels and stroke in most epidemiological and observational studies has been a source of controversy. In fact, a meta-analysis of 45 prospective studies that included 4,50,000 subjects with 13,000 incident strokes among them found no association between TC level and stroke (Prospective Studies Collaboration, 1995).

Mean baseline TC level in group I was 165.0±30.0 mg/dL, and 167.2±35.8 mg/dL at the 3rd month. There was no significant difference between the baseline and the 3rd month. Mean value of TC in group IV was 163.7±23.6 mg/dL, and 175.0±19.0 mg/dL at the 3rd month. There was a significant (p< 0.02) increased was found in group IV between the baseline and the 3rd month. In statin treated patients who had baseline TC
levels were 191.5±33.5 mg/dL, and 165.2±28.1 mg/dL at the 3rd month and there was a clinical significant (p< 0.001) decreased in group V between the baseline and the 3rd month (Table 4.15 and Fig. 4.17).

Mean baseline LDL cholesterol level in group I was 97.0±30.1 mg/dL, and 94.0±25.4 mg/dL at the 3rd month. There was no significant difference between the baseline and the 3rd month. Mean value of LDL cholesterol in group IV was 94.2±18.4 mg/dL, and 97.8±16.2 mg/dL at the 3rd month. There was no significant difference between the baseline and the 3rd month. In statin treated patients who had baseline LDL cholesterol levels were 120.3±29.3 mg/dL, and 95.0±24.0 mg/dL at the 3rd month and there was a clinical significant (p< 0.001) decreased in group V between the baseline and the 3rd month (Table 4.16 and Fig. 4.18).

The unexpected finding of a reduced incidence of stroke in the first major statin trials conducted in patients with known CHD raised new expectations. In the 4S trial (Scandinavian Simvastatin Survival Study, 1994) of 4,444 patients with CHD and high serum TC levels, there was a significant reduction in strokes (30%) after 5 years in the simvastatin group as compared to the placebo group, although the number of deaths due to cerebrovascular disease was similar. The CARE and the LIPID (Byington et al., 2001) studies confirmed the efficacy of statins in reducing the incidence of strokes in patients with CHD and TC levels within the normal range or moderately elevated levels. In the CARE trial, the pravastatin group had a 31% lower incidence of all strokes, although the incidence of fatal strokes, as in the 4S study, was about the same as in the control group. In the LIPID study, pravastatin significantly reduced the incidence of strokes by 19%.

These results were confirmed in other trials with atorvastatin. The MIRACL study showed that atorvastatin, initiated 24–96 h after an ACS, reduced recurrent ischemic events; remarkably and significantly, there were 50% fewer strokes in the atorvastatin group than in the placebo group (Waters et al., 2002). Likewise, in the GRACE study, atorvastatin, in comparison to “usual” care, reduced the risk of stroke (relative risk reduction (RRR) 0.53) (Athyros et al., 2002).
Table 4.15 Changes in mean total cholesterol and low-density lipoprotein cholesterol levels in patients after atorvastatin therapy

<table>
<thead>
<tr>
<th>Time</th>
<th>Group V</th>
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<tr>
<td></td>
<td></td>
<td>TC</td>
<td>LDL cholesterol</td>
</tr>
<tr>
<td>Day 0</td>
<td>191.5±33.5</td>
<td>120.3±29.3</td>
<td></td>
</tr>
<tr>
<td>Month 3</td>
<td>165.2±28.1</td>
<td>95.0±24.0</td>
<td></td>
</tr>
<tr>
<td>Change (%)</td>
<td>- 26.3%</td>
<td>- 25.3%</td>
<td></td>
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<tr>
<td></td>
<td>- 13.7%</td>
<td>- 21.0%</td>
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Table 4.16 Changes in mean total cholesterol and low-density lipoprotein cholesterol levels in untreated patients

<table>
<thead>
<tr>
<th>Time</th>
<th>Group IV</th>
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<tbody>
<tr>
<td></td>
<td>TC</td>
<td>LDL cholesterol</td>
<td></td>
</tr>
<tr>
<td>Day 0</td>
<td>163.7±23.6</td>
<td>94.2±18.4</td>
<td></td>
</tr>
<tr>
<td>Month 3</td>
<td>175.0±19.0</td>
<td>97.8±16.2</td>
<td></td>
</tr>
<tr>
<td>Change (%)</td>
<td>11.3</td>
<td>3.6</td>
<td></td>
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<tr>
<td></td>
<td>6.9%</td>
<td>3.8%</td>
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Fig. 4.17 Mean levels of total cholesterol in group I, IV and V

Fig. 4.18 Mean levels of low-density lipoprotein cholesterol in group I, IV and V
Given the preceding trials demonstrating a highly significant benefit of statins in patients with coronary disease and hypercholesterolemia, the TNT investigators aimed to assess the efficacy of high-dose statins in CHD patients with already low cholesterol levels (LaRosa et al., 2005). A total of 10,001 patients with coronary disease and LDL cholesterol levels less than 130 mg/dL were randomly assigned to 80 or 10 mg of atorvastatin. The primary end point was a major cardiovascular event, which included stroke.

Mean LDL cholesterol levels were 77 mg/dL in the 80-mg arm and 101 mg/dL in the 10-mg arm (LaRosa et al., 2005). After a median follow-up of 4.9 years, there was a 2.2% absolute and 22% RRR in the primary outcome measure of a major cardiovascular event (LaRosa et al., 2005). Subgroup analysis revealed a significant reduction in cerebrovascular events and stroke (Waters et al., 2006). The extent of cholesterol lowering had a direct effect on stroke risk, as each 1-mg/dL reduction in LDL cholesterol correlated with a 0.5% RRR in stroke (Waters et al., 2006).

By the late 1990s, many trials had demonstrated the overwhelming efficacy of statins in preventing cardiovascular and cerebrovascular events in patients with pre-existing coronary disease. In contrast, the role of these agents in patients without prior CVD was unclear. The WOSCOP study randomized 6,595 men with hypercholesterolemia and no history of MI to pravastatin, 40 mg/d, or placebo (Shepherd et al., 1995). After 4.9 years of follow-up, the incidence of coronary events and deaths from any cause were reduced 31% and 22%, respectively (Shepherd et al., 1995). Subgroup analysis revealed a nonsignificant reduction in stroke rate of 11% (Shepherd et al., 1995).

In the CARDS, 2,838 patients with type 2 diabetes and at least one other vascular risk factor were randomized to atorvastatin, 10 mg/d, or placebo (Colhoun et al., 2004). Patients had no documented history of CVD and had an LDL cholesterol concentration of 4.14 mmol/L or lower. The study was terminated 2 years earlier than planned because the prespecified early stopping rule for efficacy had been met. With a median follow-up of 3.9 years, CARDS demonstrated a 37% rate reduction in the primary end
point of a major cardiovascular event (including stroke) (Colhoun et al., 2004). Assessed independently, the stroke rate was reduced by an impressive 48% (Colhoun et al., 2004). The ASCOT study examined 19,342 patients with hypertension and at least three other cardiovascular risk factors (Sever et al., 2003). Of this group, 10,305 patients with non-fasting TC concentrations of 6.5 mmol/L or less were randomly assigned to atorvastatin, 10 mg, or placebo. The lipid-lowering arm was stopped 2 years early because atorvastatin led to highly evident efficacy in the primary outcome of nonfatal MI and fatal CHD. Stroke risk was significantly reduced by 27% (Sever et al., 2003).

In contrast to ASCOT, the ALLHAT-LLT did not find a statistically significant difference in cardiovascular events, including stroke (The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group, 2002). A subgroup of 10,355 high-risk hypertensive patients with an LDL cholesterol concentration of 120 to 189 mg/dL, or 100 to 129 mg/dL with coexisting CHD and a TG concentration of less than 350 mg/dL, were randomly assigned to pravastatin, 40 mg/d, or usual care. No statistically significant difference in cardiovascular end points, including stroke (4.07% in the pravastatin group and 4.5% in the usual care group), were found (The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group, 2002). Of note, reductions in LDL cholesterol were small, and the baseline demographics of ALLHAT patients were different than those in ASCOT, with a greater proportion of older, female, African American, and CHD (14%) patients (The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group, 2002).

The HPS enrolled 20,536 high-risk vascular patients with CHD, diabetes, PVD, or a combination of these, and randomized them to 40 mg of simvastatin daily or placebo (Heart Protection Study Collaborative Group, 2002). There was a 24% reduction in major vascular events (Heart Protection Study Collaborative Group, 2002). Strokes were also significantly reduced by 25%, with 444 strokes in the simvastatin group and 585 in the placebo group (Heart Protection Study Collaborative Group, 2002). The reduction in strokes was mainly due to a 30% reduction in ischemic events, with no significant change in hemorrhagic stroke incidence. Amarenco et al., (2004) conducted an important meta-analysis of all randomized statin trials published before August 2003. They found
a 21% RRR for stroke, with no heterogeneity between trials. This systematic review of over 90,000 patients also demonstrated a nonsignificant reduction of 9% for fatal strokes, with no increase in hemorrhagic strokes (Amarenco et al., 2004). Statin effects were closely linked to degree of LDL cholesterol reduction. Each 10% reduction in LDL cholesterol was estimated to reduce the risk of all stroke types by 15.6% (Amarenco et al., 2004). The authors deduced that LDL cholesterol reduction accounted for 34% to 80% of the observed benefit, with the remainder being related to possible pleiotropic effects (Amarenco et al., 2004).

However, a more recent meta-analysis of over 1,20,000 patients who have taken part in randomized trials evaluating statin therapy was unable to demonstrate statins' cholesterol-lowering effects to have a protective role in stroke (O'Regan et al., 2008). The authors blamed restricted variance of the independent variables across trials. They also hypothesized that statins' pleiotropic effects may be more protective in ischemic stroke prevention than LDL cholesterol reduction alone.

HPS was the first large, randomized trial to allow analysis of recurrent strokes. Subgroup analysis of 3,280 patients with prior cerebrovascular disease did not show any significant reduction in the incidence of stroke (169 strokes in the simvastatin group and 170 in the placebo group) (Collins et al., 2004). Reasons for the negative results include late enrollment at a time when stroke risk is low (on average 4.3 years after their most recent TIA or stroke) and insufficient power (Collins et al., 2004). Regardless, these patients still did benefit from statin use because a highly significant reduction in coronary events occurred.

The SPARCL study was the first and is currently the only clinical trial designed to study the effect of statin treatment on secondary stroke prevention (Amarenco et al., 2006). SPARCL was a prospective, multicenter, double-blind, randomized, placebo-controlled trial that compared the effects of 80 mg/d of atorvastatin versus placebo in 4,731 patients who had suffered a stroke or TIA 1 to 6 months before entry, had LDL cholesterol levels of 100 to 190 mg/dL, and had no history of CHD or atrial fibrillation (Amarenco et al., 2006). The primary end point was a fatal or nonfatal stroke. Mean
duration of follow-up was 4.9 years. During the trial’s course, mean LDL cholesterol went from 132.7 to 72.9 mg/dL in the atorvastatin group and 133.7 to 128.5 mg/dL in the placebo group (Amarenco et al., 2006).

A primary end point occurred in 265 (11.2%) patients in the atorvastatin arm and 311 (13.1%) patients in the placebo arm, resulting in a 16.0% RRR of nonfatal or fatal stroke (Amarenco et al., 2006). The number needed to treat to prevent one stroke in 5 years was 46 (Amarenco et al., 2006). Analysis of secondary end points revealed significant reductions in combined risk of stroke or TIA (23%), major cardiovascular events, any coronary events, and revascularization procedures (Amarenco et al., 2006). The surprisingly impressive reductions in coronary events strongly support the NCEP ATP III recommendation that ischemic stroke be considered a coronary equivalent (Amarenco et al., 2006). No significant difference in mortality or serious adverse events occurred. Interestingly, the SPARCL results may actually underestimate atorvastatin’s benefit in secondary stroke prevention because there was considerable open-label use of statins during the trial (25% of placebo patients and 11% of atorvastatin patients), resulting in only a 78% net difference in statin use between the two groups (Amarenco et al., 2006).

Post hoc analysis demonstrated that 27.9% of patients had a greater than 50% reduction in LDL cholesterol concentration (Amarenco et al., 2007). Compared to patients who had no change or an increase in LDL cholesterol, these patients had a 31% decreased risk of nonfatal and fatal stroke. In addition, compared with LDL cholesterol ≥100 mg/dL, achieving LDL cholesterol less than 70 mg/dL was associated with a 28% risk reduction of stroke (Amarenco et al., 2007). These observations strongly suggest that statin use primarily achieves a reduced risk of ischemic stroke via its cholesterol lowering properties.

4.34. **Triglycerides, high-density lipoprotein cholesterol, very low-density lipoprotein cholesterol non-HDL cholesterol, lipid ratios and atorvastatin**

The ATP and ADA guidelines recommend that dyslipidemic therapy be geared at achieving target LDL cholesterol goals in persons with low HDL cholesterol levels and
that serum HDL cholesterol levels are a secondary target (Executive Summary of The Third Report of The National Cholesterol Education Program Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults, 2001; Dyslipidemia management in adults with diabetes, 2004). The Expert Group on HDL cholesterol, a working group reporting on low HDL cholesterol levels, advised additional treatment with a fibrate or niacin in persons with diabetes, the metabolic syndrome, or HDL cholesterol levels <40 mg/dL (Gotto and Brinton, 2004). The importance of raising HDL cholesterol in reducing cardiovascular and stroke risk has also been highlighted in recent reviews (Brewer, 2004; Ashen and Blumenthal, 2005).

Mean baseline TG level in group I was 139.7±57.6 mg/dL, and 151.3±74.2 mg/dL at the 3rd month. Mean value of TG in group IV was 153.3±69.2 mg/dL, and 160.2±70.3 mg/dL at the 3rd month. In statin treated patients who had baseline TG levels were 157.1±87.4 mg/dL, and 149.6±56.2 mg/dL at the 3rd month. There was no significant difference between the baseline and the 3rd month in all groups (Fig. 4.19).

Mean baseline VLDL cholesterol level in group I was 28.5±12.5 mg/dL, and 30.2±14.8 mg/dL at the 3rd month. Mean value of VLDL cholesterol in group IV was 31.0±13.4 mg/dL, and 31.9±13.5 mg/dL at the 3rd month. In statin treated patients who had baseline VLDL cholesterol levels were 32.5±20.1 mg/dL, and 29.7±11.5 mg/dL at the 3rd month. There was no significant difference between the baseline and the 3rd month in all groups (Fig. 4.20).

Mean baseline HDL cholesterol level in group I was 40.3±5.9 mg/dL, and 45.0±9.8 mg/dL at the 3rd month. There was a significant difference (p< 0.04) between the baseline and the 3rd month. Mean value of HDL cholesterol in group IV was 42.3±8.2 mg/dL, and 45.6±8.6 mg/dL at the 3rd month. There was no significant difference was found in group IV between the baseline and the 3rd month. In statin treated patients who had baseline HDL cholesterol levels were 37.6±5.8 mg/dL, and 42.0±8.6 mg/dL at the 3rd month and there was a clinical significant (p< 0.002) decreased in group V between the baseline and the 3rd month (Table 4.17 and Fig. 4.21).
Fig. 4.19 Mean levels of triglycerides in group I, IV and V

Fig. 4.20 Mean levels of very low-density lipoprotein cholesterol in group I, IV and V
Table 4.17 Changes in mean high-density lipoprotein cholesterol levels in group IV and group V

<table>
<thead>
<tr>
<th>Time</th>
<th>Mean HDL cholesterol</th>
<th>Group IV</th>
<th>Group V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 0, Month 3</td>
<td>42.3±8.2</td>
<td>45.6±8.6</td>
<td>37.6±5.8</td>
</tr>
<tr>
<td>Change (%)</td>
<td>3.3</td>
<td>7.8%</td>
<td>11.7%</td>
</tr>
</tbody>
</table>

High-density lipoprotein cholesterol

![Bar chart showing mean levels of high-density lipoprotein cholesterol in group I, IV, and V](image)

Fig. 4.21 Mean levels of high-density lipoprotein cholesterol in group I, IV, and V
Mean baseline non-HDL cholesterol level in group I was 124.9±28.1 mg/dL, and 122.2±30.5 mg/dL at the 3rd month. There was no significant difference between the baseline and the 3rd month. Mean value of non-HDL cholesterol in group IV was 124.2±16.9 mg/dL, and 130.0±18.9 mg/dL at the 3rd month. There was no significant difference was found in group IV between the baseline and the 3rd month. In statin treated patients who had baseline non-HDL cholesterol levels were 156.6±39.0 mg/dL, and 121.8±28.3 mg/dL at the 3rd month and there was a clinical significant (p< 0.001) decreased in group V between the baseline and the 3rd month (Table 4.18 and Fig. 4.22).

Mean baseline TC to HDL cholesterol level in group I was 4.2±0.8, and 3.9±0.7 at the 3rd month. Mean value of TC to HDL cholesterol in group IV was 4.0±0.9, and 3.9±0.7 at the 3rd month. In statin treated patients who had baseline TC to HDL cholesterol levels were 5.5±1.5, and 4.9±5.2 at the 3rd month. There was no significant difference between the baseline and the 3rd month (Fig. 4.23).

Mean baseline LDL cholesterol to HDL cholesterol level in group I was 2.7±1.0, and 2.1±0.6 at the 3rd month. There was a significant difference (p< 0.01) between the baseline and the 3rd month. Mean value of LDL cholesterol to HDL cholesterol in group IV was 2.3±0.7, and 2.2±0.6 at the 3rd month. There was no significant difference between the baseline and the 3rd month. In statin treated patients who had baseline LDL cholesterol to HDL cholesterol levels were 3.2±1.0, and 2.3±0.7 at the 3rd month and there was a clinical significant (p< 0.001) decreased in group V between the baseline and the 3rd month (Fig. 4.24).

Mean baseline TG to HDL cholesterol level in group I was 3.3±1.5, and 3.2±1.2 at the 3rd month. Mean value of TG to HDL cholesterol in group IV was 3.7±2.1, and 3.6±1.7 at the 3rd month. In statin treated patients who had baseline TG to HDL cholesterol levels were 4.3±2.8, and 3.6±1.5 at the 3rd month. There was no significant difference between the baseline and the 3rd month (Fig. 4.25).

Mean baseline non-HDL cholesterol to HDL cholesterol level in group I was 3.2±0.7, and 2.8±0.7 at the 3rd month. There was a significant difference (p< 0.06) between the baseline and the 3rd month. Mean value of non-HDL cholesterol to HDL cholesterol
Table 4.18 Changes in mean non-HDL cholesterol levels in group IV and group V

<table>
<thead>
<tr>
<th>Time</th>
<th>Mean non-HDL cholesterol</th>
<th></th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Group IV</td>
<td>Group V</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0</td>
<td>124.2±16.9</td>
<td>156.6±38.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month 3</td>
<td>130.0±18.9</td>
<td>121.8±28.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change (%)</td>
<td>5.8</td>
<td>-34.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.6%</td>
<td>-22.2%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fig. 4.22 Mean levels of non-HDL cholesterol in group I, IV and V
Fig. 4.23 Mean levels of TC to HDL cholesterol ratio in group I, IV and V

Fig. 4.24 Mean levels of LDL cholesterol to HDL cholesterol ratio in group I, IV and V
in group IV was 3.1±0.9, and 2.9±0.7 at the 3rd month. There was no significant difference between the baseline and the 3rd month. In statin treated patients who had baseline non-HDL cholesterol to HDL cholesterol levels were 4.2±1.4, and 3.0±0.7 at the 3rd month and there was a clinical significant (p< 0.001) decreased in group V between the baseline and the 3rd month (Fig. 4.26).

As discussed earlier statin therapy had no significant effect on TG levels in patients with baseline TG levels <150 mg/dL. Raising serum HDL cholesterol can decrease cardiovascular risk by 5.5% for each 1 mg/dL increment in baseline HDL cholesterol (Gordon et al., 1986). There are various pharmacological and nonpharmacological means to increase serum HDL cholesterol (Fleming, 2002). Lifestyle-associated improvement in HDL cholesterol appears to be greatest in persons with the highest baseline HDL cholesterol levels (≥60 mg/dL) (Williams, 2004). Many of these lifestyle modifications have been shown to reduce overall stroke risk, but it is unclear what effect they will have in patients with low-HDL at the highest risk of CVD.

Statins have been shown to reduce the risk of ischemic stroke by about 20% in multiple large studies (Amarenco et al., 2004). Each 10% reduction in LDL cholesterol is estimated to reduce the risk of stroke by 15.6% (Amarenco et al., 2004). The effects of statin therapy on HDL cholesterol vary based on the particular agent and dose used (Jones et al., 2003), for example, high-dose rosuvastatin increased HDL cholesterol by 14% (Nissen et al., 2006) whereas high-dose atorvastatin increased HDL cholesterol by less than 3% (Jones et al., 2003). A study of in-hospital initiation of statin in stroke patients found no significant effect on HDL cholesterol at 3 months from statin initiation (Sanossian et al., 2006). The effect of statins may vary among patients, with those with low HDL cholesterol and elevated TG more likely to benefit from statin therapy (Amarenco et al., 2004).

4.35. Anti-inflammatory action of atrovastatin

In a meta-analysis of 14 randomized trials of statins (Amarenco et al., 2004), the most important finding was that the greater the between group differences in LDL cholesterol reduction, the greater the reduction in stroke risk. This suggested that LDL
Fig. 4.25 Mean levels of TG to HDL cholesterol ratio in group I, IV and V

Fig. 4.26 Mean levels of non-HDL to HDL cholesterol ratio in group I, IV and V
cholesterol reduction was probably the main mechanism whereby statins reduced stroke events. However, LDL cholesterol reduction could only explain between 30% and 80% of the variance of stroke risk reduction, leaving room for other additional causes. These cholesterol-independent actions may provide additional cardiovascular benefits. Thus, an array of proposed "pleiotropic" effects has been suggested.

The beneficial effects of statins on CHD and cerebrovascular disease have been linked to their anti-inflammatory effects. Statins decrease the expression of adhesion molecules (e.g., ICAM-1, VCAM-1, E-selectin, and LFA-1) and inflammatory mediators (e.g., hsCRP, CD40, IL-1β, IL-6, and TNF-α).

Statins affect the leukocyte adhesion cascade by both TC dependent and cholesterol-independent mechanisms. Among the cholesterol-independent mechanisms, lovastatin can directly bind to the L (lovastatin) site in the inserted domain of the integrin, LFA1. The binding of lovastatin induces conformational changes in LFA-1 and inhibits the interaction of LFA-1 and ICAM-1 by an allosteric mechanism (Weitz-Schmidt et al., 2001), thus contributing to the effects of statins on cell adhesion, invasion, and inflammation. Similarly, simvastatin also inhibits LFA-1 by binding to the L site. These effects are cholesterol-independent, because they can be reversed by adding GGPP or mevalonate. NF-kB, which is activated by Rho proteins, plays an important role in the transcriptional regulation of cytokines, chemokines, and adhesion molecules as well as the inflammatory promoter hsCRP. Under inflammatory conditions, hsCRP upregulates ICAM-1 and VCAM-1 in endothelial cells.

Statins suppress hsCRP at the transcriptional level, resulting in the subsequent suppression of ICAM-1 and VCAM-1. These molecules promote leukocyte recruitment into vascular walls, an important process in the initiation and development of atherosclerosis. Therefore, the beneficial effects of statins on CHD/cerebrovascular disease may be due to suppression of hsCRP expression. Also, it should point out that levels of hsCRP and modulation of these levels by statins did not significantly correlate with those of LDL cholesterol levels (Veillard and Mach, 2002; Ehrenstein et al., 2005).
Mean baseline hsCRP level in group I was 0.8±0.3 mg/dL, and 0.6±0.3 mg/dL at the 3rd month. There was no significant difference between the baseline and the 3rd month. Mean value of hsCRP in group IV was 1.3±0.7 mg/dL, and 1.1±0.6 mg/dL at the 3rd month. There was a significant (p< 0.01) decreases was found in group IV between the baseline and the 3rd month. In statin treated patients who had baseline hsCRP levels were 1.8±0.6 mg/dL, and 1.1±0.4 mg/dL at the 3rd month and there was a clinical significant (p< 0.001) decreased in group V between the baseline and the 3rd month (Table 4.19 and Fig. 4.27).

Observational data suggest that statins (Di Napoli and Papa, 2001) and angiotensin-converting enzyme inhibitors (Di Napoli and Papa, 2003) are probably more effective in the presence of high hsCRP concentrations and that the efficacy of antiplatelet therapy (Di Napoli and Papa, 2002) in secondary prevention appears to be directly related to the levels of inflammatory markers. These observations suggest that individuals with higher hsCRP concentrations might benefit from more aggressive medical therapy. The use of biochemical markers for guiding therapy might not be a controversial issue in the future, and there is no doubt that hsCRP possesses suitable characteristics for this purpose. However, additional well designed epidemiological studies are needed to validate these findings. Whereas high hsCRP may be of value in targeting aggressive treatment in patients with risk factors but no overt clinical manifestations of cerebrovascular disease - i.e., primary prevention - a case cannot be made at present for changing secondary prevention.

Several pharmacological agents proven to reduce vascular risk influence hsCRP concentrations. Of these, the statin drugs are the most important, and studies with pravastatin, lovastatin, cerivastatin, simvastatin, atorvastatin, and rosvastatin have all shown that, on average, median hsCRP concentrations decline by 15% to 40% as early as 6 weeks after initiation of therapy (Gotto, 202). Although the data for other lipid-lowering agents are less robust, fibrates appear to act in a similar manner (Gervois et al., 2004; Kleemann et al., 2004), and niacin and gemfibrozil have also been reported to reduce hsCRP concentration (Rizos and Mikhailidis, 2002). Whether lowering hsCRP concentrations represents a useful pharmacological goal in itself is unclear.
Table 4.19 Changes in mean high-sensitivity C-reactive protein levels in group IV and group V

<table>
<thead>
<tr>
<th>Time</th>
<th>Mean hsCRP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group IV</td>
</tr>
<tr>
<td>Day 0</td>
<td>1.3±0.7</td>
</tr>
<tr>
<td>Month 3</td>
<td>1.1±0.6</td>
</tr>
<tr>
<td>Change</td>
<td>0.2</td>
</tr>
<tr>
<td>(%)</td>
<td>15.4%</td>
</tr>
</tbody>
</table>

Fig. 4.27 Mean levels of high-sensitivity C-reactive protein in group I, IV and V
Evidence from animal studies in MI and ischemic stroke has shown that hsCRP exacerbates ischemic injury in the acute phase, through complement binding (Lagrand et al., 1997; Vila et al., 2000; Di Napoli, 2001; Baidoshvili et al., 2002; Nijmeijer et al., 2003), but the extent to which this mechanism is pathophysiologically relevant in the chronic inflammatory response to atherosclerosis is uncertain.

Statins lowered hsCRP independent of cholesterol parameters in the AFCAPS/TEXCAPS (Ridker et al., 2001) and appeared to be more effective in reducing cardiovascular endpoints in primary or secondary prevention studies of lipid-lowering in individuals with higher hsCRP concentrations (Ridker et al., 1998; Ridker et al., 2001). It remains unclear whether hsCRP is simply a marker of treatment effect on systemic atherosclerosis, or represents a therapeutic target. Results from the HPS indicated that efficacy of statins for protection of individuals at high risk from either cardiovascular or cerebrovascular events was not greater in those with raised cholesterol, suggesting the likelihood of an alternate protective action (Heart Protection Study Collaborative Group, 2002). Because cerebrovascular endpoints have not been studied as a primary goal of trials to date, further trials in primary and secondary prevention are required. A large randomized clinical trial (JUPITER) has already been initiated to evaluate the effects of statin (rosuvastatin) therapy in primary prevention of stroke as part of a combined vascular end-point in individuals with LDL cholesterol concentration <3.36 mmol/L who are judged to be at high vascular risk on the basis of a hsCRP concentration ≥2 mg/L (Ridker, 2003).

Whereas strategies involving hsCRP screening for the primary and secondary prevention of CHD among middle-aged subjects have apparently proven to be relatively cost-effective and, in some cases, cost-saving (Ess and Szucs, 2001; Blake et al., 2003), consistent data in stroke and elderly patients are scant (Di Napoli and Papa, 2003). Additional well designed epidemiological studies are needed to define the potential role of hsCRP -based screening in primary prevention of stroke. It is important that these issues be fully resolved in such prospective studies before hsCRP screening becomes accepted practice.
Finally, the results of statin trials like the HPS have provided support for treatment strategies based on global cardiovascular risk. Both stroke and CHD share common risk factors and pathophysiologies, and CHD is a significant cause of morbidity and mortality. Thus, among patients who have had a first stroke, the risk of MI or of a fatal cardiovascular event is high, and the relative importance of mortality due to cardiac problems increases as one survives long after a stroke (Dhamoon et al., 2006). Therefore, the ability to rank stroke patients based on risk of future cardiovascular events should allow more effective, targeted, and cost effective treatment (Dhamoon et al., 2006; Amarenco and Tonkin, 2004). Further studies are needed to definitively clarify the role of statin therapy in preventing recurrent strokes.

4.36. Safety profile

Several recent clinical trials have shown that patients treated with high doses of atorvastatin have better outcomes than patients treated with placebo (Schwartz et al., 2001), usual are (Koren et al., 2004), lower doses of pravastatin (Taylor et al., 2002; Nissen et al., 2004; Cannon et al., 2004), or lower doses of atorvastatin (LaRosa et al., 2005). Nearing completion are 2 other large-scale randomized trials comparing either atorvastatin or simvastatin 80 mg/day with lower doses of these statins (MacMahon et al., 2000; Pedersen et al., 2004). High-dose statins lower LDL cholesterol and hsCRP levels to a greater degree than low-dose statins do; thus, it is reasonable to expect that higher doses of more potent statins would be most effective in preventing cardiovascular events.

High-dose statins are not commonly prescribed in clinical practice. Reasons for this include the higher cost of higher doses and the nonlinear relation of statin dose to lowering of LDL cholesterol, whereby doubling the dose produces a decrease in LDL cholesterol of only approximately 6% (Knopp, 1999). Additionally, most patients can achieve NCEP LDL cholesterol target levels without maximum doses of the more potent statins. The main reason that many physicians prescribe higher doses only occasionally may be related to safety concerns. Cerivastatin, the most potent statin on a milligram-for-milligram basis, was withdrawn from the market in 2001 because it caused rhabdomyolysis 10 times more frequently than did other statins (Furberg and Pitt, 2001).
The 80-mg dose of rosuvastatin (Jones et al., 2003) and the 160-mg dose of simvastatin (Davidson et al., 1997) were tested clinically but were abandoned because of unacceptably high rates of adverse effects.

4.36.1. Risks of statins

In epidemiologic studies, very low blood cholesterol levels are associated with increases in noncardiac mortality and in a variety of noncardiac diseases (Jacobs et al., 1992). When statins were first studied clinically in the 1980s, the list of potential adverse effects included sleep disturbances, violent death, decreased mental acuity, depression, hemorrhagic stroke, cataracts, cancer, hepatic dysfunction, and myopathy. Subsequently, well-designed studies have shown that statins do not disturb sleep (Eckernas et al., 1993; Harrison and Ashton 1994; Keech et al., 1996), impair cognitive function, (Harrison and Ashton 1994; Gengo et al., 1995) or cause cataracts (Laties et al., 1991; Schlienger et al., 2001). Rates of violent death and hemorrhagic stroke are not increased in statin-treated patients compared with control subjects in large, randomized trials. The risks of statins that still remain are elevations of hepatic enzymes, myopathy, and possibly cancer.

4.37. Serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, bilirubin and atorvastatin

Mean baseline SGOT levels in group I were 24.7±3.4 U/L, 26.2±3.5 U/L at the 3rd month and this was increased to 25.2±4.7 U/L at the end of the study. There were no significant differences found between baseline to 3rd month and between 3rd month to 12th month. Mean value of SGOT in group II were 26.6±4.7 U/L, 26.7±5.8 U/L at the 3rd month and this was increased to 30.2±9.1 U/L at the end of the study. There was no significant difference found between baseline to 3rd month and a significant (p< 0.07) increase was found between 3rd month to 12th month. Nevertheless, in statin treated (group III) patients who had baseline SGOT level 26.2±7.2 U/L increased as 28.4±10.6 U/L at the 3rd month and thereafter 29.4±6.0 U/L at the end of the study period. There were no significant differences found between baseline to 3rd month and between 3rd month to 12th month (Fig. 4.28).
Mean baseline SGPT levels in group 1 were 26.0±5.3 U/L, and this was increased to 27.3±5.8 U/L at the 3rd month and this was decreased 26.0±4.8 U/L at the end of the study. There were no significant differences found between baseline to 3rd month and between 3rd month to 12th month. Mean value of SGPT in group II was 26.6±6.0 U/L, and this was increased to 29.3±6.1 U/L at the 3rd month and thereafter increased to 31.3±10.0 U/L at the end of the study. There was a significant (p< 0.07) difference found between baseline to 3rd month and no significant difference was found between 3rd month to 12th month. Nevertheless, in statin treated patients who had baseline SGPT level 28.3±7.0 U/L increased as 30.3±11.3 U/L at the 3rd month and thereafter 31.0±4.5 U/L at the end of the study period. There were no significant differences found between baseline to 3rd month and between 3rd month to 12th month (Fig. 4.29).

Mean baseline bilirubin level in group I was 1.1±0.2 mg/dL, and 1.1±0.2 mg/dL at the 3rd month. Mean value of bilirubin in group II was 1.1±0.3 mg/dL, and 1.1±0.2 mg/dL at the 3rd month. In statin treated patients who had baseline bilirubin level 1.0±0.2 mg/dL, and 1.1±0.2 mg/dL at the 3rd month and there was no clinical significant among the groups (Fig. 4.30). Table 4.20 (Fig. 4.31) and Table 4.21 (Fig. 4.32) shows the mean levels of SGOT and SGPT in patients with stroke. There were no significant changes among the groups.

The effect on transaminases seems to be dependent on statin dose, and effects on other liver enzymes and bilirubin emerge with higher doses (Ballantyne et al., 2003; Illingworth et al., 2001). High doses of lovastatin caused hepatic necrosis in rabbit models, and early clinical studies of lovastatin revealed frequent, but minor, elevations of hepatic enzyme concentrations (Tolman, 2002). The United States Food and Drug Administration (FDA) therefore approved this first statin with the recommendation that "liver function tests be performed before initiation of treatment, at 6 and 12 weeks after initiation of treatment or elevation in dose, and periodically thereafter (eg, semiannually).” If an increase in SGOT OR SGPT concentrations >3 times the upper limit of normal (ULN) persisted, then discontinuation of therapy was recommended (Tolman, 2002). The "Warnings" section of the product information is similar for the other statins.
Fig. 4.28 Mean levels of serum glutamic oxaloacetic transaminase in group I, II and III

Fig. 4.29 Mean levels of serum glutamic pyruvic transaminase in group I, II and III
Fig. 4.30 Mean levels of bilirubin in group I, II and III
Table 4.20 Changes in mean serum glutamic oxaloacetic transaminase levels in group I, IV and V

<table>
<thead>
<tr>
<th>Time</th>
<th>Mean SGOT (U/L)</th>
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<tbody>
<tr>
<td></td>
<td>Group I</td>
<td>Group IV</td>
<td>Group V</td>
</tr>
<tr>
<td>Baseline</td>
<td>24.7±4.6</td>
<td>25.0±5.2</td>
<td>26.0±7.6</td>
</tr>
<tr>
<td>Month 3</td>
<td>26.2±3.4</td>
<td>25.4±4.2</td>
<td>29.4±13.2</td>
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Table 4.21 Changes in mean serum glutamic pyruvic transaminase levels in group I, IV and V

<table>
<thead>
<tr>
<th>Time</th>
<th>Mean SGPT (U/L)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group I</td>
<td>Group IV</td>
<td>Group V</td>
</tr>
<tr>
<td>Baseline</td>
<td>26.0±5.3</td>
<td>25.2±5.1</td>
<td>28.2±7.0</td>
</tr>
<tr>
<td>Month 3</td>
<td>27.3±5.8</td>
<td>25.0±4.0</td>
<td>30.2±13.6</td>
</tr>
</tbody>
</table>
Fig. 4.31 Mean levels of serum glutamic oxaloacetic transaminase in group I, IV and V

Fig. 4.32 Mean levels of serum glutamic pyruvic transaminase in group I, IV and V
Monitoring of hepatic enzymes in large, randomized, clinical trials has provided a wealth of data that are relevant to clinical practice. In the AFCAPS/TexCAPS, SGOT and SGPT concentrations were measured every 6 weeks for the first year and then semiannually for the remaining 4 years of the trial. Among the 3,242 patients who were randomized to receive lovastatin, 36% had an elevated enzyme level on ≥1 occasion, but so did 30% of the 3,248 patients in the placebo arm (Downs et al., 2001). However, consecutive elevations that were >3 times the ULN occurred in only 0.6% of lovastatin and 0.3% of placebo patients, a nonsignificant difference (Downs et al., 2001). Of the 18 patients treated with lovastatin who had confirmed SGOT or SGPT elevations >3 times the ULN, the abnormality resolved with continued treatment or did not recur with rechallenge in 14 patients; 3 patients had an alternative diagnosis and only 1 had a positive rechallenge. These findings indicate that isolated minor elevations in SGOT or SGPT are not a cause for alarm or a reason to discontinue treatment in most cases. In the HPS in which 20,536 subjects were treated with simvastatin 40 mg or placebo for 5 years, there was no significant excess of SGOT or SGPT elevation in simvastatin patients compared with controls. Only 9 patients in the simvastatin group and 4 patients in the placebo group had persistent elevations >4 times the ULN (Heart Protection Study Collaborative Group, 2002). Similarly, no significant differences in the rates of hepatic enzyme elevations were reported in the pravastatin trials: CARE, LIPID, or WOSCOPS (Sacks et al., 1996; The Long-Term Intervention with Pravastatin in Ischaemic Disease Study Group, 1998; Shepherd et al., 1995).

In the ASCOT-LLA study, in which 10,305 patients were treated with atorvastatin 10 mg or placebo for 3.3 years, no significant differences was noted in SGOT or SGPT elevations between the 2 treatment groups (Sever et al., 2003). In a summary report on safety in the first 44 atorvastatin trials sponsored by Pfizer Inc., 0.5% of 9,416 atorvastatin-treated patients had persistent SGOT or SGPT elevations that were 3 times the ULN compared with 0.3% of placebo-treated patients (Newman et al., 2003). The rate of these enzyme elevations at the 10-mg (0.13%) and 20-mg (0.12%) atorvastatin doses was actually lower than the placebo rate (0.28%). The cause of minor hepatic enzyme abnormalities in patients receiving statins is unknown (Tolman, 2002). Minor elevations do not presage liver failure and, in most cases, resolve spontaneously with
continued treatment (Tolman, 2002). Acute liver failure did not occur in any of the 35,000 patients randomized to statin therapy in the 9 long-term trials in which adverse events were reported (Scandinavian Simvastatin Survival Study Group, 1994; Shepherd et al., 1995; Sacks et al., 1996; The Long-Term Intervention with Pravastatin in Ischaemic Disease Study Group, 1998; Downs et al., 1998; Shepherd et al., 2002; Heart Protection Study Collaborative Group 2002; Sever et al., 2003; Colhoun et al., 2004). Isolated cases have occurred, but whether they are more frequent than the expected rate of idiopathic acute liver failure in the general population is unclear (Tolman, 2002). In any case, periodic monitoring of SGPT and SGOT is unlikely to prevent the exceedingly rare case of acute liver failure. Fractionated bilirubin levels are recommended to rule out hepatic injury.

4.38. Creatinine phosphokinase and atorvastatin

Mean baseline CPK levels in group I were 145.5±30.7 U/L, and 145.0±29.2 U/L at the 3rd month. There was no significant difference found between baseline to 3rd month. Mean value of CPK in group II were 146.5±37.3 U/L, and this was increased to 149.6±33.8 U/L at the 3rd month and this increase was not clinical significant. In statin treated patients who had baseline CPK level 149.3±33.8 U/L, and 149.5±31.1 U/L at the 3rd month and this increase was not clinical significant (Fig. 4.33).

The most serious risk associated with statins is myositis with rhabdomyolysis, as highlighted by the withdrawal of cerivastatin from the market worldwide in August 2001 because of ≥52 deaths caused by this complication (Furberg and Pitt, 2001). According to data reported to the FDA, the risk of fatal rhabdomyolysis is 3.16 per million prescriptions of cerivastatin (Staffa et al., 2002). This is much higher than the rates for other statins: 0.19 per million prescriptions for lovastatin, 0.12 for simvastatin, 0.04 for pravastatin and atorvastatin, and 0 for fluvastatin (Staffa et al., 2002). The risk of rhabdomyolysis is increased by factors that increase the serum concentration of statins. These include small body size, advanced age, renal or hepatic dysfunction, diabetes mellitus, and hypothyroidism (Iribarren et al., 1995).
Fig. 4.33 Mean levels of creatine phosphokinase in group I, II and III
Drugs that interfere with the metabolism of statins are the most important risk factor for rhabdomyolysis. These include the fibric acid derivatives, niacin, cyclosporine,azole antifungals, macrolide antibiotics, protease inhibitors, nefazodone, verapamil, diltiazem, amiodarone, and large quantities of grapefruit juice (Thompson et al., 2003). The mechanism by which statins induce muscle injury is unknown, but recent studies have focused on the small GTP-binding proteins, Ras, Rac, and Rho (Thompson et al., 2003). These proteins promote cell maintenance and growth and attenuate apoptosis (Thompson et al., 2003). By blocking the HMG-CoA reductase enzyme, statins decrease levels of the mevalonate metabolites, farnesyl pyrophosphate and geranylgeranyl pyrophosphate, thus reducing prenylation of Ras, Rac, and Rho (Thompson et al., 2003). Serious muscle problems have been uncommon in the statin trials. In the 44 atorvastatin trials reported by Newman and colleagues, (Newman et al., 2003) none of the 9,416 atorvastatin-treated patients had rhabdomyolysis, and only 1 had an elevation in CPK >10 times the ULN; 0.4% of patients stopped taking the drug because of myalgia. In ASCOT, 1 of 5,168 atorvastatin-treated patients had rhabdomyolysis (Sever et al., 2003).

Thompson and colleagues, (2003), among 83,858 patients randomly assigned to a statin or placebo in previous large statin trials, 49 cases of myositis and 7 cases of rhabdomyolysis were reported in the statin groups compared with 44 and 5 cases, respectively, in the placebo groups. In the HPS trial, persistent CPK elevations >4 times the ULN were observed in only 7 simvastatin-treated patients and 1 patient in the placebo group. Only 49 of 10,269 patients who were randomized to statin therapy discontinued treatment because of muscle symptoms compared with 50 of 10,267 control patients. However, muscle complaints were common: 33% of patients in both the simvastatin and placebo groups reported unexplained muscle pain or weakness during 1 of the 3 first-year or subsequent semiannual visits (Heart Protection Study Collaborative Group, 2002). Muscle complaints also appear to be very common in patients treated with statins in clinical practice. Some patients will have elevated blood levels of CPK, but most will not. CPK measurements may not be helpful in the assessment of muscle symptoms because CPK concentrations are often elevated in the absence of a statin. For example, a study found 29% of patients receiving placebo had ≥1 CPK elevation during a 48-week treatment period (Bradford et al., 1991). However,
muscle biopsies have documented statin-associated myopathy in a few patients with normal CPK levels (Phillips et al., 2002).

4.39. Urea, creatinine and atorvastatin

Mean baseline urea level in group I was 30.1±9.0 mg/dL, and this decreased by 28.8±6.4 mg/dL at the 3rd month and 29.0±7.5 mg/dL at the end of the study. There were no significant differences found between baseline to 3rd month and between 3rd month to 12th month. The mean levels of urea 25.5±6.1 mg/dL at baseline to 26.1±6.1 mg/dL at the 3rd month in the group II. The mean value of urea at the 12th month was 25.3±5.9 mg/dL and it was clinically insignificant. However, in statin treated patients who had baseline urea level 29.7±7.7 mg/dL decreased as 27.9±6.3 mg/dL at the 3rd month and thereafter 28.1±5.0 mg/dL at the end of the study period. Urea level was significant (p< 0.02) difference between baseline and 3rd month and there was no significant difference between 3rd month and 12th (Fig. 4.34).

Mean baseline creatinine level in group I was 0.9±0.1 mg/dL, and this increased by 0.9±0.2 mg/dL at the 3rd month and decreased 0.9±0.2 mg/dL at the end of the study. There were no significant differences found between baseline to 3rd month and between 3rd month to 12th month. The mean levels of creatinine 1.0±0.2 mg/dL at baseline to 1.0±0.2 mg/dL at the 3rd month in the group II. The mean value of creatinine at the 12th month was 1.0±0.3 mg/dL and it was clinically insignificant. However, in statin treated patients who had baseline creatinine level 1.0±0.2 mg/dL decreased as 0.9±0.1 mg/dL at the 3rd month and thereafter 0.9±0.1 mg/dL at the end of the study period. Creatinine level was significant (p< 0.001) difference between baseline and 3rd month and there was no significant difference between 3rd month and 12th (Fig. 4.35). Table 4.22 (Fig. 4.36) and Table 4.23 (Fig. 4.37) shows the mean levels of urea and creatinine in patients with stroke. There were no significant changes among the groups.

According to a recent report by the National Lipid Association (NLA) Statin Safety Task Force (SSTF), statins do not appear to be associated with renal failure or insufficiency without concomitant rhabdomyolysis (Kasiske et al., 2006). The FDA AERS database reports 0.3-0.9 cases per one million statin prescriptions (Davidson et al., 2006).
Fig. 4.34 Mean levels of urea in group I, II and III

Fig. 4.35 Mean levels of creatinine in group I, II and III
Table 4.22 Changes in mean urea levels in group I, IV and V

<table>
<thead>
<tr>
<th>Time</th>
<th>Mean urea (U/L)</th>
<th>Group I</th>
<th>Group IV</th>
<th>Group V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>30.1±9.0</td>
<td>26.1±6.1</td>
<td>26.5±10.2</td>
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</tr>
<tr>
<td>Month 3</td>
<td>28.8±6.4</td>
<td>24.6±5.2</td>
<td>28.0±11.3</td>
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</tr>
</tbody>
</table>

Table 4.23 Changes in mean creatinine levels in group I, IV and V

<table>
<thead>
<tr>
<th>Time</th>
<th>Mean creatinine (U/L)</th>
<th>Group I</th>
<th>Group IV</th>
<th>Group V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>0.9±0.1</td>
<td>1.0±0.2</td>
<td>1.0±0.2</td>
<td></td>
</tr>
<tr>
<td>Month 3</td>
<td>1.0±0.2</td>
<td>1.2±0.2</td>
<td>1.2±0.3</td>
<td></td>
</tr>
</tbody>
</table>
Fig. 4.36 Mean levels of urea in group I, IV and V

Fig. 4.37 Mean levels of creatinine in group I, IV and V
In general, routine measurements of serum creatinine and proteinuria are not necessary for patients on statins. Pre-treatment baseline creatinine levels may be helpful in identifying patients with underlying renal disease who may be at risk for higher muscle toxicity on statin therapy. If creatinine levels are noted to increase while on statin therapy, an adjustment in statin dosing may be required. Discontinuation of the drug is generally not necessary. Similarly, if proteinuria is detected, discontinuing statin therapy is not necessary, while dose adjustments may be reasonable. Any perturbation of renal indices should warrant further investigation of other non-statin related causes. In patients with chronic kidney disease, statin therapy may be initiated with close attention to dose adjustments in moderate to severe renal disease (McKenney et al., 2006).

Results of a large meta-analysis of 44 clinical trials with atorvastatin indicate that the proportion of patients who withdrew from studies because of treatment-related adverse events was 3% for atorvastatin recipients, 4% for patients treated with other statins and 1% for those who received placebo (Downs et al., 1998). Additional data from the United States FDA adverse event reporting system (Ridker, 2003) and a large postmarketing analysis (Alsheikh-Ali and Karas, 2007) suggest that atorvastatin has a tolerability profile similar to those of other commonly used statins.

In the present study, there were no notable differences in the types of adverse events reported between the untreated (group I, II and IV) and the atorvastatin group (III and V), and there were no abnormalities observed in liver function (SGOT, SGPT and bilirubin levels), muscle enzyme (CPK levels) and kidney (urea and creatinine). The SGOT and SGPT levels slightly increased, but this small increment was considered clinically insignificant and measuring liver enzymes once together with CRP, lipid profile after starting three months of therapy is probably sufficient for the patients.

Compliance with atorvastatin therapy was very good for CVD patients and stroke patients, and no adverse reactions to atorvastatin treatment were observed.