

AAPI



**Clinical Implications:
Dyslipidemia in the
Asian Indian Population**

Clinical Implications: Dyslipidemia in the Asian Indian Population

Enas A. Enas, MD, FACC
Director of Coronary Artery Disease
in Asian Indians (CADI) Research

This monograph was adapted from material presented at the 20th Annual Convention of the American Association of Physicians of Indian Origin, Sheraton Chicago Hotel & Towers, Chicago, Ill, June 29, 2002.

Disclosure:

Doctor Enas A. Enas is a member of the speaker's bureau and/or a recipient of research support from the following companies: AstraZeneca Pharmaceuticals LP, Bristol Myers Squibb Company, Kos Pharmaceuticals, Inc, Merck & Co, Inc, Pfizer Inc, GlaxoSmithKline.

For additional information on Coronary Artery Disease among Asian Indians, please visit the CADI Research Foundation USA Website at <http://www.cadiresearch.com/>. CADI is a nonprofit tax-exempt organization dedicated to reducing the ravages of coronary artery disease among Asian Indians worldwide.



The opinions expressed in this document are those of the author and do not necessarily reflect those of the AAPI or the commercial supporter.

This Monograph may contain a discussion of therapies that are unapproved for use or are investigational, that involve ongoing research, or that utilize preliminary data.

Copyright © 2002 American Association of Physicians of Indian Origin, Oakbrook Terrace, Ill.
Strategic Edge Communications, Inc, 10 Madison Avenue, Lower Level, Morristown, NJ 07960

DYSLIPIDEMIA IN THE ASIAN INDIAN POPULATION: UNIQUE ASPECTS AND IMPLICATIONS FOR TREATMENT

INTRODUCTION

Heart disease and stroke are the principal components of cardiovascular disease, and are the first and third leading causes of death in the United States today. Decreasing morbidity and mortality from these diseases has been a major goal of the medical establishment and governmental health agencies. Only in the last half century have the underlying pathologies of these diseases been defined and the important role of risk factors identified.^{1,2}

Heart disease and stroke are usually due to atherosclerosis of large and medium sized arteries. Hypercholesterolemia is the most important factor in the pathogenesis of atherosclerosis. Hypertension, smoking, diabetes, obesity, physical inactivity, and atherogenic diets have all been identified as modifiable risk factors for heart disease. Age, male gender, and a family history of premature coronary heart disease (CHD) have been identified as nonmodifiable risk factors.³ Scientific data relative to atherosclerosis continues to evolve.

Since it is impossible for most physicians to keep up with the rapid changes occurring in all areas of medical practice, clinical practice guidelines are of tremendous value. These guidelines incorporate the latest scientific data relative to the pathophysiology, diagnostic approach, and therapeutic interventions for a particular disease.

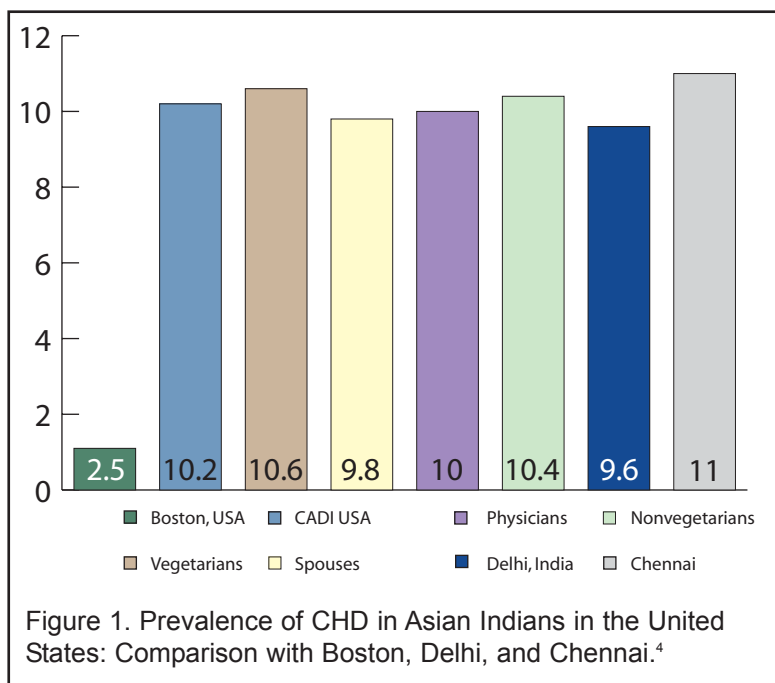
The National Cholesterol Education Program (NCEP) issued updated clinical practice guidelines on the prevention and management of high cholesterol in adults in 2001 entitled Adult Treatment Panel (ATP III).³ This was the third version of treatment guidelines for hypercholesterolemia; earlier versions were issued in 1988 and 1993. The NCEP is coordinated by the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH).

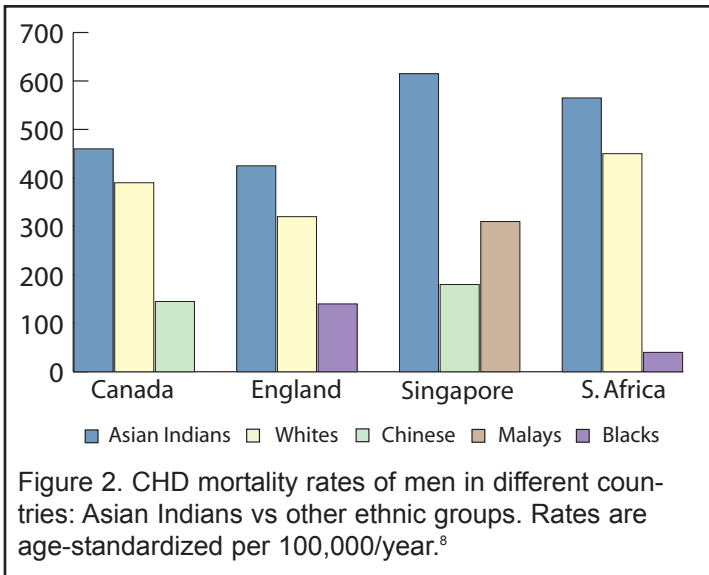
One of the problems with clinical practice guidelines, however, is they are based heavily on evidence from controlled trials. Randomized clinical trials have not been carried out to address many therapeutic questions pertaining to different racial and ethnic groups. This monograph will

review unique aspects of dyslipidemia in the Asian Indian population. Adjustments to NCEP ATP III Guidelines, based on the pattern of dyslipidemia seen in this population, will be outlined.

EPIDEMIOLOGY OF HEART DISEASE: ASIAN INDIANS VS OTHER POPULATIONS

Compared to the general population in the United States, the prevalence of CHD in Asian Indians is approximately 4 times higher (Figure 1). The higher prevalences are seen in Asian Indians living in the United States, as well as, in India. The rates are similar among vegetarians and non-vegetarians.^{4,5,6,7} CHD mortality rates obtained from studies in Canada, England, Singapore, and South Africa also document the differences between ethnic and racial groups.⁸ In these studies, CHD death rates were highest for Asian Indians, intermediate for whites, and lowest for Chinese and blacks (Figure 2). Women had a similar pattern to that of men. The death rates from CHD in the United States differ; the rates are highest in blacks, intermediate in whites, Hispanics and Native Americans, and lowest in Asians (Figure 3). The marked heterogeneity within the Asian American population masks the high rate of CHD among the Asian Indian subpopulation. It is worth pointing out that Asians in the United States comprise several ethnic groups including Chinese, with the lowest rates of CHD, and Asian Indians, with the highest rates of CHD.¹⁰

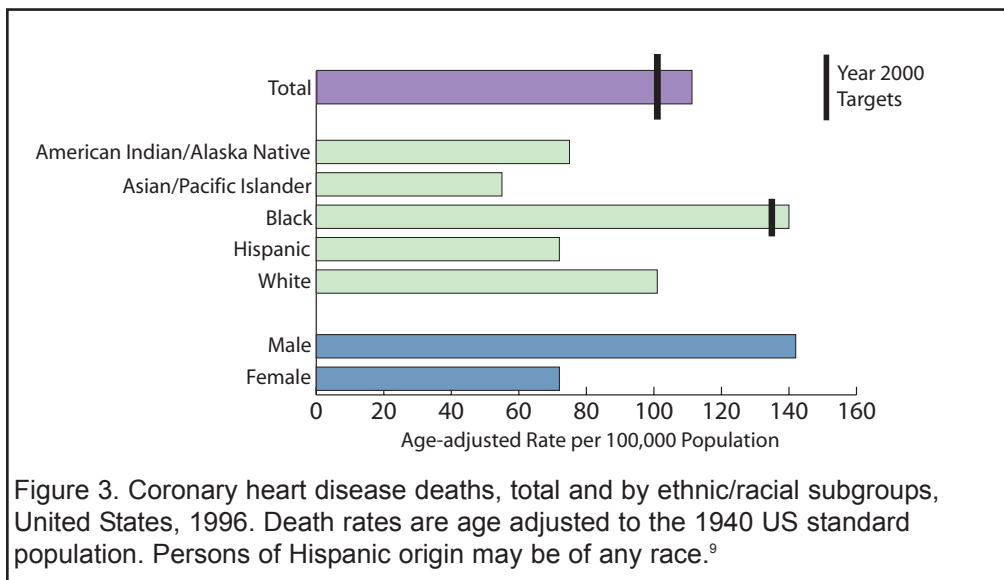




The relative rates of hospitalization from CHD also parallel the racial/ethnic differences seen in prevalence and mortality. In California, Asian Indians have the highest rate of hospitalization for CHD, and Chinese have the lowest rate. Intermediate rates were reported for whites, Japanese, and Filipinos.¹⁰ The racial/ethnic differences in susceptibility to CHD appear to have a genetic basis. It is essential physicians recognize the racial/ethnic differences and adjust lipid management strategies appropriately for each subpopulation.¹¹

HISTORICAL PERSPECTIVE

The creation in 1948 of the NHLBI at the National Institutes of Health (NIH), might be considered the advent of the contemporary study of atherosclerosis in the United States. The new institute reorganized the Framingham Heart Study in 1949, creating one of the first major efforts dedicated to the study of chronic disease. Based on Framingham Heart Study results



reported in 1961, the concept of risk factors for coronary heart disease was clearly established. Hypertension and hypercholesterolemia were initially identified as major contributors to cardiovascular disease. Smoking was identified as a risk factor for cardiovascular disease in the Surgeon General's report in 1964.⁷

While the crucial role of cholesterol in the development of atherosclerosis was recognized in the 1950s, it was not until 1988 that the NHLBI issued its first clinical practice guidelines under the auspices of the NCEP. The guidelines were updated in 1993, and the "Third Report of the NCEP Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults," also known as Adult Treatment Panel (ATP III), was issued in 2001.³

ASSESSING RISK: ATP III SUMMARY

Cholesterol is a lipid that is present in cell membranes and is the precursor for steroid hormones and bile acids. Cholesterol is found in the blood in distinct particles containing both lipids and proteins, and the particles are called lipoproteins. Lipoproteins found in humans are divided into classes according to their flotation constants or densities. Three major classes are found: low-density lipoproteins (LDL), high-density lipoproteins (HDL), and very-low-density lipoproteins (VLDL).

LDL cholesterol contains cholesterol and a single protein or apolipoprotein, apoB-100. LDL constitutes about 60% to 70% of total serum cholesterol. LDL is the major atherogenic lipoprotein, and is the primary target for cholesterol lowering therapy. The ATP III classification of total cholesterol and LDL cholesterol serum levels are listed in Table 1.

HDL contains cholesterol and apo AI and apo AII apolipoproteins. HDL constitutes, about 20% to 30% of total serum cholesterol. HDL is thought to protect against the development of atherosclerosis. The ATP III Classifications of HDL Cholesterol serum levels are listed in Table 2.

Triglycerides are transported in the blood as chylomicrons following absorption from the small intestine, or as a component of VLDL if synthesized by the liver. The

Table 1. ATP III Classification of Total Cholesterol and LDL Cholesterol.³

Total Cholesterol (mg/dL)		LDL Cholesterol (mg/dL)	
<200	Desirable	<100	Optimal
200-239	Borderline High	100-129	Near Optimal/Above Optimal
≥240	High	130-159	Borderline High
		160-189	High
		≥240	Very high

ATP III classification of serum triglycerides is listed in Table 3. VLDL is triglyceride-rich lipoprotein and constitutes about 10% to 15% of total serum cholesterol. VLDL has several apolipoproteins, including apo B100, apo CI, apo CII, apo CIII and apo E. VLDL is a precursor of LDL. Some forms of VLDL are actually partially degraded lipoproteins called VLDL remnants. VLDL remnants appear to promote atherosclerosis, similar to LDL. Since both VLDL remnants and LDL are atherogenic, they may be combined to estimate risk prediction. The sum of VLDL + LDL is called non-HDL cholesterol.

Table 2. ATP III Classification of HDL Cholesterol.³

Serum HDL Cholesterol (mg/dL)	
<40	Low HDL Cholesterol
≥60	High HDL Cholesterol

Lipoprotein(a) [Lp(a)] has been categorized as an emerging lipid risk factor by ATP III. Lp(a) represents a class of LDL particles that have as a protein moiety apolipoprotein B-100 linked to another protein moiety, apolipoprotein(a). Lp(a) is structurally similar to plasminogen, but has no thrombolytic activity. Several studies report a strong association between Lp(a) levels and CHD risk. Lp(a) measurement is a useful addition to the major risk factors for identifying persons at still higher risk than those revealed by LDL, HDL, and triglyceride levels.¹² An elevated Lp(a) level presents the option to raise a person's risk to a higher level and to target the person for a more aggressive treatment. The optimal level of Lp(a) should be no greater than 20 mg/dL.^{11,13,14}

ATP III has classified homocysteine as an emerging non-lipid risk factor. While the link between homocysteine and CHD is not well understood, some hold that the association is strong enough to make it a direct target of therapy.¹⁵ Measurement of homocysteine remains an option in selected cases, such as in someone with a strong family history of

premature CHD, yet who is an otherwise low-risk patient. The optimal level of homocysteine should be no greater than 10 mol/L.¹¹

The first step in risk management is risk assessment by measurement of LDL cholesterol as part of lipoprotein analysis, and identification of accompanying risk factors. Major risk factors identified by ATP III are listed in Table 4.³ The category of highest risk consists of CHD and CHD risk equivalents. CHD risk equivalents carry a risk for major coronary events equal to that of established CHD. CHD risk equivalents include:

- ◆ Other forms of atherosclerotic disease
- ◆ Diabetes
- ◆ Multiple risk factors that confer a 10-year risk >20%

Risk status in persons without clinically apparent CHD or other clinical forms of atherosclerotic disease is determined by counting the risk factors. For those with 2 or more risk factors, 10-year risk assessment is carried out using the Framingham scoring system to identify individuals whose short-term risk warrants consideration of intensive treatment. Separate Framingham point scores have been developed for men and for women. The scoring system is included in the ATP III Executive Summary.³ Table 5 lists the LDL goal based on risk category assessment.

Table 3. ATP III Classification of Serum Triglycerides.³

Serum Triglycerides (mg/dL)	
<150	Normal
150-199	Borderline High
200-499	High
≥500	Very High

ASSESSING RISK IN ASIAN INDIANS

The common pattern of dyslipidemia seen in Asian Indians when compared to the lipid profile of white Americans is listed in Table 6.^{16,17,18,19} Asian Indians tend to have higher levels of triglycerides, lower HDL levels, and higher levels of Lp(a). In addition, the higher CHD risk in this population may be related to a higher

Table 4. ATP III Nonlipid Risk Factors for CHD.³

Modifiable Risk Factors	Nonmodifiable Risk Factors
Hypertension	Age
Cigarette Smoking	Male Gender
Thrombogenic/Hemostatic State	Family History of Premature CHD
Diabetes	
Obesity	
Physical Inactivity	
Atherogenic Diet	

Risk Category	LDL Goal mg/dL
CHD and CHD Risk Equivalents	<100
Multiple (2+) Risk Factors	<130
0 to 1 Risk Factor	<160

prevalence of the metabolic syndrome, insulin resistance, and diabetes. The metabolic syndrome has become increasingly common in the United States, and is common in the Asian Indian population in the United States. The metabolic syndrome is thought to be associated with genetic factors, overweight/obesity, and physical inactivity. The syndrome is characterized by abdominal obesity, atherogenic dyslipidemia, elevated blood pressure, insulin resistance glucose intolerance, prothrombotic state, and proinflammatory state.³ Table 7 lists risk factors that are associated with the metabolic syndrome.^{3,11}

Lipid	Relative Serum Concentrations
TC	Similar
LDL	Similar
Small Dense LDL	Similar
Triglycerides	Higher
HDL	Lower
Lp(a)	Higher

Based on known ethnic differences in risk prediction, the Framingham model accurately predicts the CHD risk among whites and blacks living in the United States. For Americans of Japanese and Hispanic descent and for Native Americans, the Framingham model overestimates CHD risk. For Asian Indians, the Framingham model may underestimate the CHD risk by greater than 100%.^{11,17,20,22,23} Total cholesterol levels and LDL levels are correlated with extent and severity of CHD in Asian Indians as in whites. But at any given total cholesterol or LDL level, Asian Indians have a greater CHD risk than whites.^{11,24} Therefore, Asian Indians with dyslipidemia should be treated as aggressively as if they had a CHD risk equivalent—similar to the treatment of patients with diabetes or heart disease. Thus, while a total cholesterol level of <200 mg/dL is desirable according to the Framingham model for those with 0 to 1 risk factor, the goal for the Asian Indian population should be <160 mg/dL. An LDL level of <160 mg/dL is appropriate for

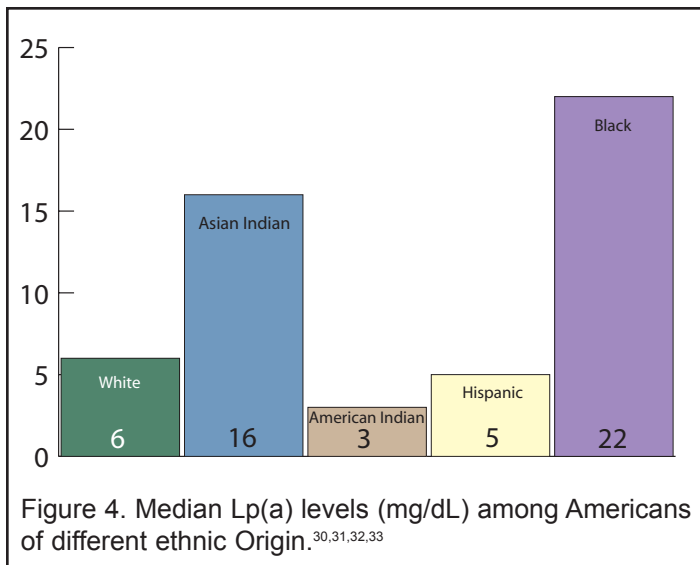
most Americans with 0 to 1 risk factor, but a level of <100 mg/dL is optimal for Asian Indians.²⁵

HDL levels of 60 mg/dL are considered optimal in both whites and Asian Indians. HDL levels are considered low when they drop below 40 mg/dL. However, most experts consider a level <50 mg/dL to be low in women. In fact, HDL levels <50 mg/dL are used as one of the diagnostic criteria for the diagnosis of metabolic syndrome in women by the ATP III. A study of Asian Indians living in the United States found that 54% of men had an HDL level below 40 mg/dL, and 68% of women had levels below 50 mg/dL.^{4,19}

The acceptable “normal” level of triglycerides was decreased from <200 mg/dL in the ATP II report to <150 mg/dL in the ATP III classification. In the United States, 43% of Asian Indian males and 24% of Asian Indian females have levels that exceed 150 mg/dL.^{4,19} The CHD risk among Asian Indians is at least 2-fold higher than other populations, even when adjusted for all conventional risk factors and the various components of the metabolic syndrome.^{11,17,20,22,23}

Lipoprotein(a) is still considered an emerging risk factor in the US population at large, but appears to be a major risk factor in Asian Indians.^{5,26-29} A high level of Lp(a) is the most prevalent dislipidemia in patients with premature CHD. Lp(a) levels are governed almost exclusively by race, ethnicity, and genetics, unlike other lipids, where the levels are influenced by age, gender, diet, and other environmental factors.³⁰⁻³³ Although Lp(a) levels >30 mg/dL are generally considered the threshold at which high risk of premature CHD increases rapidly, levels below 20 mg/dL are considered optimum, particularly in Asian Indians.^{14,28} Studies of Asian Indians in North America found that 25% to 50% of sampled populations have levels >30 mg/dL. High levels

Risk Factor	Defining Level
Abdominal Obesity	Waist Circumference
Men (Whites)	>102 cm (>40 in)
(Asian Indian)	>90 cm (>36 in)
Women (Whites)	>88 cm (>35 in)
(Asian Indian)	>80 cm (>32 in)
Triglycerides	≥150 mg/dL
HDL Cholesterol	
Men	>40 mg/dL
Women	>50 mg/dL
Blood Pressure	≥130/85 mmHg
Fasting Glucose	110-125 mg/dL



of Lp(a) were also reported for Asian Indians living in Canada, Singapore, the United Kingdom, and India.²⁷ Lp(a) levels among people of different ethnicities in the United States are given in Figure 4.

The multiplicative effects of elevated Lp(a) are significant. Modestly elevated Lp(a) levels of 20 mg/dL to 30 mg/dL are associated with a 2- to 3-fold higher risk of MI or restenosis following coronary angioplasty and bypass surgery.^{13,34,35} This risk increases 10-fold when an Lp(a) level >50 mg/dL occurs in persons with high cholesterol levels. The risk of MI is 100-fold higher when Lp(a) levels >55 mg/dL are accompanied by low HDL and a high ratio of total cholesterol to HDL.³⁶⁻³⁸

When combined with concomitant elevation of triglycerides, and LDL, and decreases in HDL concentrations, the pathophysiological effects of elevated Lp(a) are exponentially increased.³⁸ This “deadly lipid quartet,” commonly present in Asian Indians, usually results from affluent lifestyles led by immigrants, as well as those living in urban areas in India.³⁹ The high rates of CHD in Asian Indians are due to a combination of genetic predisposition and lifestyle factors. Metabolic abnormalities seem to have a synergistic effect on the development of CHD in genetically susceptible individuals, such as those with elevated levels of Lp(a).

PREVENTION OF CHD IN ASIAN INDIANS

As discussed earlier, in treating dyslipidemia, Asian Indian ethnicity should be considered a CHD risk equivalent, with an LDL goal of <100 mg/dL.⁴⁰ Table 8 lists an approach to the patient for evaluating risk for CHD and for implementing therapy if necessary.

The optimal level of risk factors for Asian Indians is listed in Table 9. This chart includes desirable goals for blood lipids and non-lipid risk factors. Note also that the optimum waist size for Asians, including Asian Indians, has been adjusted downward according to the recommendations of the World Health Organization (WHO).⁴¹ This takes into account the cut point at which metabolic abnormalities increase rapidly.

The most important aspect of preventing CHD is identifying individuals at high risk of developing CHD at an early age. Since Lp(a) is fully expressed in the first year of life, tracking Lp(a) from childhood may be a better option than focusing on other dyslipidemias that are not expressed until later life.³⁹ This is particularly true of those with a family history of premature CHD.

Modification of lifestyle, such as increasing physical activity and decreasing consumption of calories—particularly saturated fat—should begin early in life. Avoiding abdominal obesity is as important, if not more important, than avoiding total obesity. Consumption of all types of tobacco products should be eliminated. Appropriate drug therapy should be considered for all lipid abnormalities and risk factor abnormalities, which do not respond to lifestyle adjustment.⁴²⁻⁴⁴

COMBINATION DRUG THERAPY FOR CORRECTING DYSLIPIDEMIA IN ASIAN INDIANS

Prospective studies in Asian populations have shown that the positive relationship between CHD risk and blood total cholesterol continues down to at least 115 mg/dL without any evidence of a threshold.²⁵ The Heart Protection Study has recently confirmed the safety and benefits of lowering LDL to as low as 65 mg/dL.⁴⁵ In most patients with hypercholesterolemia,

Table 8. Approach to the Patient with Hyperlipidemia for Evaluating Risk for CHD and for Implementing Therapy.

- ◆ Rule out secondary dyslipidemia (Diabetes, hypothyroidism, obstructive liver disease, chronic renal failure, drug-induced)
- ◆ Perform risk assessment
- ◆ Encourage smoking cessation
- ◆ Control hypertension and diabetes
- ◆ Implement therapeutic lifestyle changes (improved diet, weight loss, increased physical activity)
- ◆ Achieve LDL-cholesterol goal with statin therapy
- ◆ Achieve other lipid (HDL, triglycerides, Lp[a]) and non-lipid (homocysteine) goals with niacin or Niaspan.
- ◆ Monitor response and adherence to therapy every 4 to 6 months

Risk Factor	Male	Female
Cholesterol (mg/dL)	<150	<150
LDL (mg/dL)	<100	<100
HDL (mg/dL)	>40	>50
Triglyceride (mg/dL)	<150	<150
Lp(a) (mg/dL)	<20	<20
Homocysteine (μmol/L)	<10	<10
Blood Pressure (mm Hg)	<120/80	<120/80
Fasting Glucose (mg/dL)	<110	<110
Waist Size (cm/in)	<90/36	<80/32

HMG-CoA reductase inhibitors, commonly referred to as “statins,” are the drugs of choice because they reduce LDL cholesterol most effectively. Bile acid sequestrants (cholestyramine; colestipol [Colestid]), nicotinic acid (crystalline, timed-release preparations, extended-release nicotinic acid [Niaspan]), and fibric acid derivatives (gemfibrozil [Lopid]); fenofibrate (Tricor) are alternative therapies. Statins can reduce LDL levels by 30% to 60%.²⁵

A summary of statins approved for use in the United States is given in Table 10. The marked reduction in mortality, coronary events, and stroke has been documented in 8 landmark clinical trials using statins.⁴⁶ The beneficial effects of statins on clinical events may involve both lipid and non-lipid mechanisms.

The challenge for the physician is to use statins early, in sufficient doses, and for extended periods of time. Those who wait for susceptible individuals to develop symptoms before deciding to treat should not forget the fact that a sudden death may be the first symptom of CHD in up to a third of the cases.

	Atorvastatin Lipitor®	Simvastatin Zocor®	Lovastatin Mevacor®	Fluvastatin Lescol®	Pravastatin Pravachol®
Dose Range, [mg/day]	10-80	5-80	10-80	20-80	10-40
Effect on Lipid Levels (%)					
Total Cholesterol	↓25-45	↓20-40	↓17-34	↓15-21	↓11-28
LDL	↓41-61	↓23-47	↓24-40	↓19-31	↓17-35
HDL	↓3-12	↑5-21	↑7-9	↑2-10	↑4-8
Triglycerides	↓27-46	↓10-46	↓10-19	↓1-12	↓11-24

While statins are the therapeutic cornerstone for reducing major coronary events, they primarily affect LDL. Triglycerides are only modestly decreased, and HDL is only modestly elevated. Statins have little or no effect on Lp(a). When goal levels of LDL are achieved, but HDL is abnormally low, triglycerides abnormally high, and/or Lp(a) abnormally high, a second lipid-lowering compound from a different class should be added to the regimen. While ATP III recommends treating other lipid risk factors only if the LDL goal is not achieved, HDL, triglycerides, Lp(a) and the TC/HDL ratio should also be evaluated along with LDL in the Asian Indian patient. Physicians should also check homocysteine levels.¹¹

Treatment	Mean Percent Change from Baseline				
	N	LDL-C	HDL-C	TG	Lp(a)
Placebo [†]	44	-1	+5	-6	-5
Niaspan 500 mg qhs	87	-3	+10	-5	-3
Niaspan 1000 mg qhs		-9	+15	-11	-12
Niaspan 1500 mg qhs		-14	+22	-28	-20
Niaspan 2000 mg qhs		-17	+26	-35	-24

*Dosages were titrated at monthly intervals.
[†]Placebo data are after 24 weeks of placebo therapy.⁴⁷

A patient’s response to therapy should be checked about 6 weeks after starting drug therapy. If the goal for each of the lipid levels—LDL, HDL, triglycerides, Lp(a), and the TC/HDL ratio—has not been achieved, the next appropriate step should be undertaken. This may include increasing the dose of the statin or adding a second agent, such as a bile acid sequestrant, a fibric acid derivative, or nicotinic acid. Nicotinic acid is preferable if a second agent is added, since it has a greater beneficial effect on HDL, triglycerides, and the TC/HDL ratio than do the compounds in the other 2 classes. Only nicotinic acid lowers Lp(a).

A recently introduced once-daily extended-release formulation of nicotinic acid (Niaspan) retains the traditional efficacy of immediate-release niacin on serum lipids and lipoproteins, but is associated with fewer

Table 12. Lipid Response to Comparative Dose-escalation, 28-week Study of Advicor*, Niaspan† and Lovastatin‡.

Treatment and Dose	Mean Percent Change from Baseline				
	N	LDL-C	HDL-C	TG	Lp(a)
Advicor 2000mg/40mg	42	-42	+30	-44	-22
Niaspan† 2000 mg	41	-14	+24	-31	-32
Lovastatin‡ 40 mg qhs	53	-32	+6	-20	0

*Advicor was started at a dose of 1000 mg/20 mg, which was increased at 4 week intervals to a maximum of 2000 mg/40 mg.
†Niaspan monotherapy was titrated at week intervals from 500 mg to 200 mg.
‡The lovastatin monotherapy group received 20 mg for 12 weeks, and then 40 mg for the remaining 16 weeks.⁴⁹

episodes of flushing than with the crystalline preparation. Hepatotoxicity, which was a problem with earlier sustained-release preparations, does not appear to be a problem with Niaspan. Niaspan reduces both triglycerides and Lp(a) levels by up to 35% and 24%, respectively, and selectively increases the cardioprotective sub-fraction of HDL by up to 26% (Table 11). LDL is decreased by up to 17%. The dose should be initiated at 500 mg and gradually increased at 4-week intervals to 2000 mg daily to reduce flushing.⁴⁷ Taking dosages at bedtime and taking aspirin or non-steroidal anti-inflammatory drugs 30 minutes prior to Niaspan reduces the frequency and severity of flushing episodes.

A new single entity formulation of Niaspan in combination with lovastatin was recently approved for marketing.⁴⁸ This formulation, known as Advicor, is available in tablets containing 500/20, 750/20, or 1000/20 mg niacin/mg lovastatin. The enhanced activity of Advicor combination therapy compared to lovastatin and Niaspan monotherapy is shown in Table 12. A study comparing Advicor 1000 mg/40 mg, atorvastatin 20 mg, and simvastatin 20 mg confirmed the enhanced effect of the statin/Niaspan combination therapy compared to statin alone on HDL, TG, and Lp(a)

Table 13. Lipid Response to a Comparative Study of Advicor (Combination Niaspan/Lovastatin) vs Monotherapy with Atorvastatin and Simvastatin.*

Treatment and Dose	Mean Percent Change from Baseline			
	LDL-C	HDL-C	TG	Lp(a)
Advicor 2000mg/40mg	-42	+19	-32	-20
Atorvastatin 20 mg Simvastatin 20 mg	-45	+3	-23	+3
20 mg	-35	+8	-6	-1

*The LDL response to all three arms was similar; the HDL, triglyceride, and Lp(a) response to combination therapy was much greater than with monotherapy.⁵⁰

levels (Table 13).

The best way to initiate therapy is to use Advicor 500/20 and gradually increase the dose up to 2000/40 to optimize the levels of the various lipoproteins. The safety and benefits of using Niaspan to treat diabetic dyslipidemia has been well documented.⁵¹ It is important to stress that sustained-release (as opposed to extended-release) niacin preparations are not approved for the treatment of dyslipidemia and should not be used, especially in combination with statins.

ATP III did not recommend hormone replacement therapy in post-menopausal women with dyslipidemia.³ While estrogen replacement therapy can lower Lp(a) levels by up to 50% in post-menopausal women, this therapy should only be used in specialized cases until the current controversy of estrogen replacement therapy in general is resolved.⁵²

It has been reported that folic acid and vitamins B₆ and B₁₂ play a role in the metabolism of homocysteine.^{3,15} Treatment with folic acid can return plasma homocysteine concentrations to normal. Trials are under way to determine whether folic acid will prevent progression or possibly even induce the regression of atherosclerotic lesions.²⁰

SUMMARY

A wealth of knowledge has evolved over the past half-century linking atherosclerotic changes to CHD and stroke. During the same time, risk factors for atherosclerosis have been identified. Blood lipid abnormalities have been identified as primary risk factors. While lifestyle changes can prevent or slow the development of atherosclerosis, pharmacological intervention is frequently required. The NCEP has updated the treatment recommendations for dyslipidemia in 2001. These guidelines, however, do not address the specific concerns of certain subpopulations in the United States, such as Asian Indians.

The consequences of atherosclerosis in the Asian Indian population tend to be more severe and develop earlier in life. While total cholesterol and LDL cholesterol levels are similar to whites, HDL levels are lower, triglyceride levels are higher, and Lp(a) levels are higher. Combination therapy with a statin and extended-release nicotinic acid (Niaspan) may better correct the lipid abnormalities seen in the Asian Indian population.

REFERENCES

1. Braunwald E. Shattuck Lecture—Cardiovascular medicine at the turn of the millennium: Triumphs, concerns, and opportunities. *New Engl J Med.* 1997;337:1360-1369.
2. *Morbidity and Mortality: 2002 Chart Book on Cardiovascular, Lung, and Blood Diseases.* National Institutes of Health, National Heart, Lung, and Blood Institute, 2002.
3. NCEP III. Executive summary of the third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). *JAMA.* 2001;285:2486-2497.
4. Enas EA, Garg A, Davidson MA, et al. Coronary heart disease and its risk factors in first-generation immigrant Asian Indians to the United States of America. *Indian Heart J.* 1996;48:343-353.
5. Enas EA, Mehta J. Malignant coronary artery disease in young Asian Indians: thoughts on pathogenesis, prevention, and treatment. *Clin Cardiol.* 1995;18:131-135.
6. Enas EA, Yusuf S, Mehta J. Prevalence of coronary artery disease in Asian Indians. *Am J Cardiol.* 1992;70:945-949.
7. Mohan V, Deepa R, Shanthi Rani S, et al. Prevalence of coronary artery disease and its relationship to lipids in a selected population in South India. The Chennai Urban Population Study (CUPS No. 5). *J Am Coll Cardiol.* 2001;38:682-687.
8. Enas EA, Yusuf S, Mehta J. Meeting of International Working Group on coronary artery disease in South Asians. *Indian Heart J.* 1996;48:727-732.
9. Healthy People 2000, Heart Disease and Stroke Progress Review. Centers for Disease Control and Prevention, National Center for Health Statistics. 1996.
10. Klatsky AL, Tekawa I, Armstrong MA, et al. The risk of hospitalization for ischemic heart disease among Asian Americans in northern California. *Am J Public Health.* 1994;84:1672-1675.
11. Enas EA. <http://www.cadiresearch.com/illustrated.htm>. Accessed 2002.
12. Enas EA. Why is there an epidemic of malignant CAD in young Indians? *Asian J Clin Cardiol.* 1998;1:43-59.
13. von Eckardstein A, Schulte H, Cullen P, et al. Lipoprotein(a) further increases the risk of coronary events in men with high global cardiovascular risk. *J Am Coll Cardiol.* 2001;37:434-439.
14. Hoogeveen RC, Gambhir JK, Gambhir DS, et al. Evaluation of Lp(a) and other independent risk factors for CHD in Asian Indians and their USA counterparts. *J Lipid Res.* 2001;42:631-638.
15. Boushey CJ, Beresford SA, Omenn GS, et al. A quantitative assessment of plasma homocysteine as a risk factor for vascular disease: Probable benefits of increasing folic acid intakes. *JAMA.* 1995;274:1049-1057.
16. Gupta R, Gupta VP, Sarna M, et al. Prevalence of coronary heart disease and risk factors in an urban Indian population: Jaipur Heart Watch-2. *Indian Heart J.* 2002;54:59-66.
17. Anand S, Yusuf S, Vuksan V, et al. Differences in risk factors, atherosclerosis, and cardiovascular disease between ethnic groups in Canada: the study of health assessment and risk in ethnic groups (SHARE). *Lancet.* 2000;356:279-284.
18. Haffner SM, D'Agostino R Jr, Goff D, et al. LDL size in African Americans, Hispanics, and non-Hispanic whites: the insulin resistance atherosclerosis study. *Arterioscler Thromb Vasc Biol.* 1999;19:2234-2240.
19. Enas EA, Jacob S. Coronary artery disease in Indians in the USA. In: Sethi K, ed. *Coronary artery disease in Indians—a global perspective.* Mumbai: Cardiological Society of India, 1998:32-43.
20. Grundy SM. Obesity, metabolic syndrome, and coronary atherosclerosis. *Circulation.* 2002;105:2696-2698.
21. D'Agostino RB Sr, Grundy S, Sullivan LM, Wilson P. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. *JAMA.* 2001;286:180-187.
22. Forouhi N, McKeigue P. How far can risk factors account for excess coronary mortality in South Asians? *Can J Cardiol.* 1997;13(Suppl B):47B.
23. Miller GJ, Beckles GL, Maude GH, et al. Ethnicity and other characteristics predictive of coronary heart disease in a developing community: principal results of the St James Survey, Trinidad. *Int J Epidemiol.* 1989;18:808-817.
24. Hughes LO, Wojciechowski AP, Raftery EB. Relationship between plasma cholesterol and coronary artery disease in Asians. *Atherosclerosis.* 1990;83:15-20.
25. Enas EA, Senthilkumar A, Mathai A. Statins in the prevention and treatment of coronary artery disease: closing the knowledge and treatment gap. *Asian J Clin Card.* 2002;5:8-45.
26. Enas EA, Dhawan J, Petkar S. Coronary artery disease in Asian Indians: lessons learned so far and the role of Lp(a). *Indian Heart J.* 1997;49:25-34.

27. Enas EA. Lipoprotein(a) is an important genetic risk factor for coronary artery disease in Asian Indians. *Am J Cardiol.* 2001;88:201-202.
28. Gupta R, Kastia S, Rastogi S, et al. Lipoprotein(a) in coronary heart disease: A case-control study. *Indian Heart J.* 2000;52:407-410.
29. Gambhir JK, Kaur H, Gambhir DS, et al. Lipoprotein(a) as an independent risk factor for coronary artery disease in patients below 40 years of age. *Indian Heart J.* 2000;52:411-415.
30. Wang W, Hu D, Lee ET, et al. Lipoprotein(a) in American Indians is low and not independently associated with cardiovascular disease. The Strong Heart Study. *Ann Epidemiol.* 2002;12:107-114.
31. Howard BV, Le NA, Belcher JD, et al. Concentrations of Lp(a) in black and white young adults: relations to risk factors for cardiovascular disease. *Ann Epidemiol.* 1994;4:341-350.
32. Anand S, Enas EA, Pogue J, et al. Elevated lipoprotein(a) levels in South Asians in North America. *Metabolism.* 1998;47:182-184.
33. Haffner SM, Gruber KK, Morales PA, et al. Lipoprotein(a) concentrations in Mexican Americans and non-Hispanic whites: The San Antonio Heart Study. *Am J Epidemiol.* 1992;136:1060-1068.
34. Desmarais R L, Sarembock IJ, Ayers CR, et al. Elevated serum lipoprotein(a) is a risk factor for clinical recurrence after coronary balloon angioplasty. *Circulation.* 1995;91:1403-1409.
35. Hoff HF, Beck GJ, Skibinski CI, et al. Serum Lp(a) level as a predictor of vein graft stenosis after coronary artery bypass surgery in patients. *Circulation.* 1988;77:1238-1244.
36. Enas EA, Mehta JL. Lipoprotein(a): An important risk factor in coronary artery disease. *J Am Coll Cardiol.* 1998;32:1132-1134.
37. Solymoss BC, Marcil M, Wesolowska E, et al. Relation of coronary artery disease in women <60 years of age to the combined elevation of serum lipoprotein(a) and total cholesterol to high-density cholesterol ratio. *Am J Cardiol.* 1993;72:1215-1219.
38. Hopkins PN, Wu LL, Hunt SC, et al. Lipoprotein(a) interactions with lipid and nonlipid risk factors in early familial coronary artery disease. *Arterioscler Thromb Vasc Biol.* 1997;17:2783-2792.
39. Enas EA. Coronary artery disease epidemic in Indians: a cause for alarm and call for action. *J Indian Med Assoc.* 2000;98:694-702.
40. Enas EA. Avoiding premature coronary deaths in British Asians: guidelines for pharmacologic intervention are needed. *BMJ.* 1996;312:376.
41. Redefining obesity and its treatment: the Asia-Pacific perspective 2000: International Diabetes Institute in Australia and WHO. Available at: http://www.diabetes.com.au/research/report_obesity.htm. Accessed June 7, 2002.
42. Enas EA. Arresting and reversing the epidemic of CAD among Indians. In: Kumar A, ed. *Current Perspectives in Cardiology.* Chennai: Cardiological Society of India, 2000:109-128.
43. Enas EA, Senthilkumar A. Conquering the epidemic of coronary artery disease among Indians: crucial role of cardiologists. *Cardiology Today.* 2001;5:282-294.
44. Enas EA. High rates of CAD in Asian Indians in the United States despite intense modification of lifestyle: What next? *Current Science.* 1998;74:1081-1086.
45. HPS. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: A randomised placebo-controlled trial. *Lancet.* 2002;360:7-22.
46. Mathew M, Gogtay JA. Role of Statins in Dyslipidaemia. *Asian J Clin Cardiol.* 2000;3:33-42.
47. Niaspan (niacin extended-release tablets) Product Information. Miami, FL: Kos Pharmaceuticals Inc.; 2002.
48. Kashyap ML, McGovern ME, Berra K, et al. Long-term safety and efficacy of a "once-daily" niacin/lovastatin formulation for patients with dyslipidemia. *Am J Cardiol.* 2002;89:672-678.
49. Advicor (niacin extended-release and lovastatin tablets) Product Information. Miami, FL: Kos Pharmaceuticals Inc.; 2002.
50. Bays HE, McGovern ME, Simmons PD. Lipoprotein effects of a new dual component drug (extended-release niacin/lovastatin) compared to starting doses of atorvastatin and simvastatin. *J Am Coll Cardiol.* 2002;39(suppl A):245A.
51. Grundy SM, Vega GL, McGovern ME, et al. Efficacy, safety, and tolerability of once-daily niacin for the treatment of dyslipidemia associated with type 2 diabetes: results of the assessment of diabetes control and evaluation of the efficacy of niaspan trial. *Arch Intern Med.* 2002; 162:1568-1576.
52. WHI. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA.* 2002;288:321-333.

Supported by an educational grant from

Kos Pharmaceuticals, Inc.

Created by:



STRATEGICEDGE COMMUNICATIONS, INC.
