Managing Dyslipidemia in Turkey: Suggested Guidelines
for a Population Characterized by Low Levels of High
Density Lipoprotein Cholesterol

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Abstract: Based on data from the Turkish Society of Cardiology and others, it is established that Turks have a high prevalence of coronary heart disease (CHD). Several risk factors are prominent in Turks: dyslipidemia, cigarette smoking, and hypertension. The dyslipidemia is unique in that very low levels of HDL-C and typically "normal" LDL-C levels characterize the Turkish population. The low HDL-C levels appear to be genetic in origin and are largely independent of high triglyceride levels (73% of Turkish men and 94% of women with HDL-C <40 mg/dl have triglyceride levels <150 mg/dl; only 15% of men and 3% of women with HDL-C <40 mg/dl have triglyceride levels >200 mg/dl). HDL-C levels are 10–15 mg/dl lower in Turks than seen in the United States or western Europe. Low HDL-C is a major risk factor; CHD risk increases 2–4% for every 1 mg/dl decrease in HDL-C levels. Existing treatment guidelines focus on plasma LDL-C levels and fail to take into account the continuous increase in CHD risk that occurs as HDL-C levels decrease. However, several studies show that patients with CHD or free of CHD but with multiple risk factors, who have low HDL-C and near optimal LDL-C, benefit very significantly from lipid-lowering therapy. Many of these patients with low HDL-C levels do not qualify for drug therapy based on existing guidelines. Therefore, we believe that unique guidelines must be developed to guide the treatment of low HDL-C Turkish patients. We suggest that treatment based on both the LDL-C level and the total cholesterol/HDL-C (TC/HDL-C) ratio is the best way to address treatment of patients with low HDL-C levels. The most effective drug treatment available presently in Turkey relies on lowering LDL-C levels to optimize the TC/HDL-C ratio. (Anadolu Kardiyl Derg, 2002; 4: 315-22)

Key Words: Plasma cholesterol, coronary heart disease, high density lipoproteins, triglycerides, statins

Abbreviations: coronary heart disease (CHD), high density lipoproteins cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), body mass index (BMI), Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), Veterans Affairs HDL Intervention Trial (VA HIT), Heart Protection Study (HPS)

Introduction

Atherosclerosis is a progressive disease process that causes heart attacks, strokes, and peripheral vascular disease. The onset of symptoms is modulated by age, gender, and three major modifiable risk factors—dyslipidemia, hypertension, and cigarette smoking—that account for about 85% of risk in excess of that associated with age (1). The prevalence and severity of the three major risk factors depends upon genetic traits and lifestyle habits that vary throughout the world. Because of this variability, treatments to control these risk factors may require modification to optimize risk reduction in specific countries or ethnic groups.

In Turkey, all three of the major risk factors have been linked to risk of developing coronary heart disease (CHD) (2-4). Cigarette smoking among men is more prevalent than in the United States, and is a major public health concern (2, 4, 5). Turks are also at risk because of dyslipidemia. In Turkey, however, the risk of premature vascular disease reflects an unusually high prevalence of low levels of high density lipoprotein cholesterol (HDL-C) (5), whereas in
western Europe and the United States it reflects high levels of low density lipoprotein cholesterol (LDL-C) (6). Treatment for managing dyslipidemia in Americans and western Europeans is based on threshold and goal levels of LDL-C (6, 7), which are the same irrespective of the HDL-C level. However, patients with low HDL-C levels (<40 mg/dl) are at risk and benefit from treatment even if their total cholesterol and LDL-C levels are “optimal” (8, 9). For these at-risk patients with low HDL-C levels and optimal LDL-C levels, existing guidelines delineate a complex approach. For low HDL-C patients with triglyceride levels >200 mg/dl, a secondary goal termed “non-HDL-C” is set at 30 mg/dl higher than the LDL-C goal. Non-HDL-C is calculated by subtracting the HDL-C level from the total cholesterol level (6). Drug treatment is then prescribed to achieve the non-HDL-C goal. If a patient with HDL-C <40 mg/dl has a fasting triglyceride level <200 mg/dl, drug treatment is not recommended except for therapy (niacin or fibrates) to raise HDL-C levels in patients with CHD or the equivalent.

This complex approach to the management of patients with low HDL-C levels has two potential problems. First, teaching physicians and patients about the validity of a treatment approach based on non-HDL-C levels is difficult. Second, it does not recommend statin therapy as a first-line drug treatment for low HDL-C patients irrespective of the pretreatment LDL-C level. Existing evidence demonstrates that statin therapy reduces morbidity and mortality from vascular disease in these patients (9).

The Turkish Population Is Characterized by Low HDL-C Levels

Two major studies of cardiovascular disease risk factors in Turkey have shown that Turks have relatively low levels of total cholesterol and LDL-C (5, 10). The average total cholesterol levels are 150–200 mg/dl, reflecting the variability in LDL-C levels associated with the amount of saturated fat consumed in different areas of the country (Table 1) (5). Nevertheless, the levels of HDL-C are lower in every region of Turkey than in populations of western European origin (Table 2) (5). The mean HDL-C level of men in Turkey is 36 mg/dl, or 10 mg/dl lower than in American men (11). In Turkish women, the mean HDL-C level is 42 mg/dl, or 14 mg/dl lower than in American women (12). These differences are strikingly important because observational studies suggest that CHD risk increases by 2–4% for every 1 mg/dl decrease in HDL-C (13). These very low HDL-C levels impact vascular disease risk in Turkey. Despite the much lower total cholesterol and LDL-C levels in Turks, estimates of CHD morbidity and mortality in the Turkish population are similar to those in the United States (2-4, 10). In addition, HDL-C levels are independent predictors of CHD risk in Turks (10).

Why Do Turks Have Low HDL-C?

Plasma levels of HDL-C are modulated by both lifestyle and genetic factors. The lifestyle factors that commonly affect HDL-C levels include physical activity, obesity, cigarette smoking, ethanol consumption, and the proportion of calories consumed as carbohydrates (14-21). These factors are associated with variability in HDL-C levels in the Turkish population, but they do not account for the disparity in HDL-C levels between the Turkish population and western European/United States populations (5, 22, 23). Several lines of evidence suggest that the low HDL-C levels of Turks are of genetic origin.
First, the HDL-C levels of adults in Turkey are similar despite substantial regional differences in the type of dietary fat that is consumed (5). The average HDL-C values of populations consuming diets enriched in monounsaturated fat (the Ayvalık region) are similar to those of populations consuming diets high in saturated fat (Trabzon, Kayseri, Adana) (Table 2). Additional evidence that low HDL-C levels are not related to lifestyle comes from studies of Turks living outside of Turkey (Table 3) (22, 24). The average HDL-C levels of Turks in Germany and the United States are identical to those of Turks residing in Turkey. The data from Turks living in San Francisco are of particular interest. Although most of these individuals have typical American lifestyles (including diets), their HDL-C levels are not different from those of Turks in Germany or Turkey. Furthermore, the non-Turkish spouses of Turks residing in San Francisco have the higher HDL-C levels typical of western European populations (22).

HDL are a heterogeneous class of lipoproteins, and specific subclasses have been characterized. With the exception of some well-characterized rare disorders (25-28), most individuals with the low HDL-C levels associated with increased CHD risk have lower levels of one specific subfraction of HDL. This subfraction, known as HDL<sub>2</sub>, or LpAI, is reduced in Turks with low HDL-C, (Table 2). The HDL<sub>2</sub> (isolated by ultracentrifugation) and LpAI (characterized by electroimmunoassay) are in essence the same class of lipoprotein isolated by two different techniques (29). LpAI contains apolipoprotein AI, unlike the LpAI/AII subclass of HDL, which contains both apolipoproteins AI and AII. We have shown that Turkish men and women with reduced HDL-C levels have LpAI levels that are ~20–25% lower than non-Turkish individuals with higher HDL-C levels (23). The concentration of the LpAI subclass of HDL is directly associated with protection from CHD (30).

The reduction in LpAI or HDL<sub>2</sub> levels in populations with low HDL-C levels is often associated with increased activity of hepatic lipase, an enzyme that has a major role in HDL catabolism (31). In Turks with low HDL-C, the plasma activity of hepatic lipase is 25–30% higher than in controls of western European origin, who typically have higher HDL-C levels (Table 4) (22).

Interestingly, we have recently shown that HDL-C levels are not low in prepubescent Turkish children (32), but are similar to those of prepubescent children in different populations around the world (33-37). However, in Turks, HDL-C levels decrease considerably during adolescence, especially in those of higher socioeconomic status. This profound decrease in HDL-C—20 mg/dl in males and 13 mg/dl in females—may reflect alterations in androgen/estrogen balance in Turks at puberty and a modulation of hepatic lipase affecting HDL-C levels.

### Does Hypertriglyceridemia Account for Reduced HDL-C Levels in Turks?

In some populations, such as South Asians (38), low HDL-C is associated with hypertriglyceridemia due to insulin resistance (38-44). However, adjustment for triglycerides and body mass index (BMI) by analysis of covariance suggests that HDL-C levels in Turks are independent of the effects of hypertriglyceridemia and BMI on HDL-C (22). Furthermore, Table 3: Mean HDL-C levels (mg/dl) of Turks residing in Turkey, Germany and San Francisco.

<table>
<thead>
<tr>
<th></th>
<th>Americans in USA</th>
<th>Germans in Germany</th>
<th>Turks in Turkey</th>
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<th>Turks in San Francisco</th>
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<tbody>
<tr>
<td>Men</td>
<td>47</td>
<td>47</td>
<td>37</td>
<td>38</td>
<td>37</td>
</tr>
<tr>
<td>Women</td>
<td>56</td>
<td>60</td>
<td>43</td>
<td>45</td>
<td>46</td>
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Table 4: Hepatic lipase activity is increased in Turks with low HDL levels.

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<thead>
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<th>Non-Turkish (White Americans)</th>
<th>Turkish (Istanbul)</th>
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<tbody>
<tr>
<td></td>
<td>Men (n = 31)</td>
<td>Women (n = 29)</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>45 ± 11&lt;sup&gt;c&lt;/sup&gt;</td>
<td>58 ± 15&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hepatic lipase (mmol/l/l)</td>
<td>38 ± 14&lt;sup&gt;f&lt;/sup&gt;</td>
<td>26 ± 8&lt;sup&gt;e&lt;/sup&gt;</td>
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<sup>*p < 0.001; †p < 0.01.</sup>
Turks have substantially lower HDL-C levels for any given value of triglyceride than do the Framingham study subjects (persons of western European origin) (Figure 1). At low triglyceride levels (<100 mg/dl), the HDL-C levels are ~15–20 mg/dl lower in Turkish men and ~10–15 mg/dl lower in Turkish women than in Framingham subjects. Thus, low HDL-C levels at low triglyceride levels distinguish the Turks from other populations and further suggest that an independent factor, (6) which is most likely genetic, is modulating HDL-C levels. These results clearly distinguish Turks from South Asians, who are characterized by low HDL-C associated with hypertriglyceridemia and insulin resistance (38). Turks have low HDL-C levels at all triglyceride levels.

Current Guidelines for Managing Patients with Low HDL-C Levels:

Current guidelines for managing patients with low HDL-C levels focus on absolute values of LDL-C as thresholds for initiating treatment and as goals of therapy (6, 7). These LDL-C-based guidelines fail to take into account the continuous increase in CHD risk that occurs as HDL-C values decline (45). However, individuals with total cholesterol and LDL-C levels below the goal values indicated by treatment guidelines can still be at risk if their HDL-C levels are <40 mg/dl (8).

Data from clinical trials show that patients with low HDL-C levels (<40 mg/dl) benefit from cholesterol-lowering therapy even if their total cholesterol and LDL-C levels do not exceed the threshold values.

Figure 1. Comparison of HDL-C levels versus triglycerides. Data are shown separately for women (upper panel) and men (lower panel) from the United States Framingham study (52) and from Turkey (adapted from reference 5). Turkish men and women have lower HDL-C levels at all triglyceride levels.
for initiating drug treatment. The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) was a study of low HDL-C patients with an average LDL-C of 156 mg/dl, which is below the threshold value of 160 mg/dl for initiating hypolipidemic drug therapy in most patients with multiple CHD risk factors but no history of CHD (46). The patients were also at risk because of age (men ≥ 45 years; women ≥ 55 years). The two-thirds of the participants who had baseline levels of HDL-C <40 mg/dl benefited from treatment. The goal of treatment was to reduce LDL-C levels with lovastatin to a value of 110 mg/dl, which is well below the value of 130 mg/dl used as the LDL-C treatment target for a person without CHD (6).

Two studies of patients with existing vascular disease and low HDL-C levels also suggest that lipid-lowering therapy benefits CHD patients with pretreatment LDL-C levels below the threshold values for initiating treatment. In the Veterans Affairs HDL Intervention Trial (VA HIT), the average pretreatment HDL-C level was 32 mg/dl and the average pretreatment LDL-C level was 111 mg/dl, which is in the optional range (100–129 mg/dl) for initiating drug therapy of dyslipidemic CHD patients. Insulin resistance was highly prevalent among these patients: 25% had type 2 diabetes mellitus, 57% were hypertensive, and the average BMI was 29 kg/m2 (47). Treatment of these patients with gemfibrozil, 0.6 g twice daily, reduced the incidence of fatal and nonfatal CHD events by 22%, suggesting that hypolipidemic drug treatment of high-risk patients with LDL-C levels that are near optimal (100–130 mg/dl) is beneficial and should be mandated therapy instead of optional therapy.

The Heart Protection Study (HPS), a trial of 20,536 high-risk patients in the United Kingdom, included patients with total cholesterol and LDL-C levels that did not meet threshold values for initiating drug therapy (9, 48). Patients received a fixed dose of simvastatin (40 mg daily) or a placebo for 5 years. About 17% had baseline LDL-C levels <100 mg/dl (average, 97 mg/dl). Treatment of these patients reduced the average LDL-C to ~65 mg/dl, and their risk of a CHD event or stroke was 24% lower than in similar patients who received a placebo (9). These results indicate that drug treatment should be considered for high-risk patients irrespective of pretreatment LDL-C levels. In the 35% of HPS subjects with baseline HDL-C <35 mg/dl, treatment reduced the risk of a CHD event by 29% (9).

Since these trials suggest that high-risk patients with pretreatment levels of LDL-C that are “at goal” benefit from lipid-lowering therapy, how should similar patients (patients with low total cholesterol, low LDL-C, and low HDL-C levels) be evaluated for treatment? This is the typical patient that we see in Turkey: normal LDL-C and very low HDL-C.

Suggested Guidelines for Managing Patients with Low HDL-C Levels

Existing guidelines do not mandate therapy for patients with low HDL-C levels who do not have levels of LDL-C that qualify for initiation of drug therapy. How should these patients be managed? Data from clinical trials and observational studies support the use of the total cholesterol/HDL-C ratio (TC/HDL-C) as an indicator of subsequent vascular disease risk irrespective of absolute values of total cholesterol, LDL-C, or HDL-C (45, 49). Risk is lowest when the TC/HDL-C ratio is below 3.5 (45). Here we suggest that this should be a goal of therapy in addition to LDL-C <100 mg/dl for high-risk patients (Table 5). According to this criterion, over 90% of Turkish CHD (or CHD equivalent) patients would be candidates for drug therapy, compared with only 58% according to National Cholesterol Education Program guidelines (unpublished data).

AFCAPS/TexCAPS provides guidelines for patients with no history of vascular disease who have low HDL-C levels and LDL-C levels that do not require tre-

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<th>Risk category</th>
<th>Goals</th>
<th>Lifestyle changes initiated for</th>
<th>Drug therapy initiated for</th>
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<tr>
<td></td>
<td>LDL-C</td>
<td>TC/HDL-C</td>
<td>LDL-C</td>
</tr>
<tr>
<td>CHD or equivalent</td>
<td>&lt;100 and</td>
<td>&lt;3.5</td>
<td>≥100 or</td>
</tr>
<tr>
<td>2+ risk factors</td>
<td>130 and</td>
<td>4.5</td>
<td>≥130 or</td>
</tr>
<tr>
<td>0-1 risk factor</td>
<td>160 and</td>
<td>5.5</td>
<td>≥160 or</td>
</tr>
</tbody>
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CHD: Coronary heart disease, HDL-C: High density lipoprotein cholesterol, LDL-C: Low density lipoprotein cholesterol, TC: Total cholesterol
treatment based on current guidelines (49). In that study, the pretreatment TC/HDL-C ratio was the best predictor of subsequent risk, and entry into the study required a TC/HDL-C $\geq 6.0$ (50). The AFCAPS/TexCAPS cohort was also at high risk because of age (men $\geq 45$ years; women $\geq 55$ years). Based on this trial, it seems prudent to recommend drug treatment for individuals at risk because of age and low HDL-C ($<40$ mg/dl) if their LDL-C level exceeds 130 mg/dl or if the TC/HDL-C ratio is $\geq 6.0$ (Table 5). The treatment goals for individuals with two or more risk factors are LDL-C $<130$ mg/dl and TC/HDL-C $<4.5$. For lower risk (0–1 risk factor), drug therapy is initiated for LDL-C $160$ mg/dl or TC/HDL-C $\geq 7.0$. The goals for this group are LDL-C $<160$ mg/dl and TC/HDL-C $<5.5$.

The question as to when to start drug therapy in those qualifying for such treatment is a worthwhile consideration. In patients with CHD or the equivalent, most would agree that drug therapy should begin immediately. Likewise, lifestyle changes should be instituted in all patients at risk of CHD. However, for low HDL-C patients without CHD, it may be reasonable to defer drug therapy until age $\geq 45$ years in men and $\geq 55$ years in women. Although this may not be ideal (atherosclerosis can begin in adolescence), it may be more practical at the present time.

**Conclusion:** Patients with low HDL-C levels are at high risk of developing vascular disease even if their total cholesterol and LDL-C levels are below the threshold values for initiating treatment according to current guidelines. Since there is substantial clinical trial evidence that these patients benefit from lipid-lowering therapy, new approaches are required to treat them. We suggest that treatment based on both the LDL-C level and the TC/HDL-C ratio is one way of addressing the treatment issues of patients with low HDL-C levels.

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