# The impact of dyslipidemia on cardiovascular risk stratification of hypertensive patients and association of lipid profile with other cardiovascular risk factors: Results from the ICEBERG study 

Hipertansif hastalarda dislipideminin kardiyovasküler risk sınıflandırması üzerine etkisi ve lipid profilinin diğer kardiyovasküler risk faktörleriyle ilişkisi: ICEBERG çalışmasından sonuçlar

Giray Kabakcı, M.D., ${ }^{1}$ Nevres Koylan, M.D., ${ }^{2}$ Barış İlerigelen, M.D., ${ }^{3}$<br>Ömer Kozan, M.D., ${ }^{4}$ Kemalettin Büyüköztürk, M.D. ${ }^{2}$<br>Cardiology Departments of, ${ }^{1}$ Medicine Faculty of Hacettepe University, Ankara;<br>${ }^{2}$ Medicine Faculty of İstanbul University, İstanbul; ${ }^{3 i}$ istanbul University Cerrahpaşa School of Medicine, İstanbul; ${ }^{4}$ Medicine Faculty of Dokuz Eylül University, Izmir

Objectives: The ICEBERG study (Intensive/Initial Cardiovascular Examination regarding Blood pressure levels, Evaluation of Risk Groups) study focuses on the effect of dyslipidemia on cardiovascular risk evaluation and association of lipid profile with other risk factors.
Study design: The ICEBERG study consisted of two subprotocols: ICEBERG-1, conducted at 20 university hospitals (Referral group) and ICEBERG-2, conducted at 197 primary healthcare centers (Primary Care group). Each subprotocol had two patient profiles: patients previously diagnosed with essential hypertension and under medical treatment (Treated group), and patients with systolic blood pressure $\geq 130 \mathrm{mmHg}$ or diastolic blood pressure $\geq 85$ mmHg , with no antihypertensive treatment for at least three months before inclusion (Untreated group). Dyslipidemia was evaluated and cardiovascular risk stratification performed according to the ESC/ESH 2003 guidelines.
Results: A total of 1817 patients were analyzed. After incorporation of serum lipid values into cardiovascular risk stratification, the percentage of patients in "high" plus "very high" added risk groups increased to $55.2 \%$ ( $p<0.001$ ), $62.6 \%(p=0.25)$, and $60.7 \%(p<0.001)$ in Treated Referral, Untreated Referral, and Untreated Primary Care groups, respectively. The corresponding figures estimated only by medical history and physical examination were 51.2\%, $60.7 \%$, and $54.2 \%$, respectively. Serum lipid levels showed significant correlations with most risk factors.
Conclusion: Serum lipid levels are useful in stratifying hypertensive patients into cardiovascular risk groups more accurately, for appropriate antihypertensive treatment.
Key words: Cardiovascular diseases; comorbidity; dyslipidemias/epidemiology; hypertension/epidemiology.

Amaç: ICEBERG çalışması (Intensive/Initial Cardiovascular Examination regarding Blood pressure levels, Evaluation of Risk Groups) dislipideminin kardiyovasküler risk değerlendirmesi üzerine etkisi ve lipid profili ile diğer risk faktörleri arasındaki ilişki üzerinde odaklanmaktadır.
Çalışma planı: ICEBERG çalışması iki altgruptan oluşmaktadır. ICEBERG-1 20 üniversite hastanesinde (Refere grup), ICEBERG-2, 197 birinci basamak sağlık kuruluşunda (Primer Sağlık Kuruluşu grubu) yürütülmüştür. Her bir altgrupta iki hasta profili vardır: Daha önce esansiyel hipertansiyon tanısı konmuş ve tedavi altında olan hastalar (Tedavili grup) ve sistolik kan basıncı $\geq 130 \mathrm{mmHg}$ veya diyastolik kan basıncı $\geq 85 \mathrm{mmHg}$ olan ve en az üç aydır antihipertansif tedavi görmeyen hastalar (Tedavisiz grup). Bu hasta gruplarında dislipidemi değerlendirildi ve kardiyovasküler risk sınıflandırması ESC/ESH 2003 kılavuzuna göre yapıldı.
Bulgular: Çalışmada toplam 1817 hasta değerlendirildi. Hastaların serum lipid düzeyleri de göz önüne alınarak yapılan risk sınıflandırmasında "yüksek" ve "çok yüksek" risk grubundaki hastaların oranları Tedavili Refere grupta \%55.2'ye ( $p<0.001$ ), Tedavisiz Refere grupta \%62.6'ya ( $\mathrm{p}=0.25$ ), Tedavisiz Primer Sağlık Kuruluşu grubunda \%60.7'ye ( $p<0.001$ ) yükseldi. Bu değerler, sadece öykü ve fizik muayene ile yapılan risk sınıflandırmasında gruplarda sırasıyla \%51.2, \%60.7 ve \%54.2 idi. Serum lipid düzeyleri risk faktörlerinin birçoğu ile anlamlı korelasyon gösterdi.
Sonuç: Serum lipid düzeylerinin değerlendirilmesi, hastaların kardiyovasküler risk gruplarına daha hassas sınıflandırılmasında ve uygun antihipertansif tedavi için yararlıdır.
Anahtar sözcükler: Kardiyovasküler hastalık; komorbidite; dislipidemi/epidemiyoloji; hipertansiyon/epidemiyoloji.

Dyslipidemia is characterized by elevated low-density lipoprotein (LDL) cholesterol and triglycerides (TG), and decreased high-density lipoprotein (HDL) cholesterol. There is considerable evidence that hypertension (HT), dyslipidemia, and other cardiovascular (CV) risk factors are linked epidemiologically, clinically, and metabolically. ${ }^{[1-5]}$

It is well known that high serum total and LDL cholesterol are particularly important risk factors for coronary artery disease. ${ }^{[6-8]}$ Many prospective and case-control studies have shown a positive association between serum TG and coronary artery disease risk and demonstrated the importance of fasting TG level as an independent risk factor ${ }^{[9,10]}$ A number of clinical trials including the Framingham Heart Study have shown that a low HDL cholesterol level predicts the risk for coronary artery disease independently of other risk factors. ${ }^{[11,12]}$ Each $1 \mathrm{mg} /$ dl decrease in HDL cholesterol has been shown to increase the risk for coronary artery disease by $2 \%$ and $3 \%$ in men and women, respectively. ${ }^{[13]}$ The Veterans Affairs HighDensity Lipoprotein Cholesterol Intervention Trial investigated the impact of fibrate therapy on CV risk and demonstrated that a $6 \%$ increase in HDL cholesterol was associated with a $22 \%$ decrease in coronary events. ${ }^{[14]}$

Individuals with high blood cholesterol levels have a higher prevalence of HT and those with high blood pressure have a higher prevalence of hypercholesterolemia. ${ }^{[15-17]}$ A recent epidemiologic study revealed that $56.5 \%$ of patients with HT also had concomitant dyslipidemia and the percentage of patients with HT and dyslipidemia in the total population was estimated to be $15 \%{ }^{[1]}$ The clustering of these two conditions is important, because individuals with coexisting HT and dyslipidemia are particularly likely to develop atherosclerosis. This interplay is now known to produce a marked increase in CV disease risk. ${ }^{[4,5]}$ The prevalence of stroke and peripheral arterial disease similarly increase among patients having both conditions. ${ }^{[15]}$

The "Intensive / Initial Cardiovascular Examination regarding Blood pressure levels: Evaluation of Risk Groups (ICEBERG)" study aimed to determine CV risk evaluation and stratification of subjects with high-normal or high blood pressure and also to evaluate the impact of different laboratory tests on patients' stratification. The objective of this article was to evaluate serum lipid profiles of the ICEBERG study population, impact of lipid profile on CV risk stratification, and the association of serum lipid levels with other CV risk factors.

## PATIENTS AND METHODS

Study design. ICEBERG is a healthcare organizationbased epidemiological study with two subprotocols. ICEBERG-1 was conducted at 20 referral hospitals (Referral group) and ICEBERG-2 was conducted at 197 primary healthcare centers (Primary Care group).

Study population and procedures. Both Referral and Primary Care groups consisted of two profiles of patients: risk profile A and B. Risk profile A consisted of patients who were under medical treatment for essential HT (Treated Patients). Risk profile B included patients diagnosed as having high-normal or high blood pressure [systolic blood pressure (SBP) $\geq 130 \mathrm{mmHg}$ or diastolic blood pressure (DBP) $\geq 85$ mmHg ] who had not received any anti-hypertensive medication for at least the three months before inclusion (Untreated Patients). Patients with secondary HT, pregnant patients and patients younger than 18 years of age were not included in the study. Signed informed consent was obtained from each patient who accepted to participate in the study. The study was approved by the Ethics Committee of Istanbul University, Istanbul School of Medicine.

Treated Primary Care group patients were not analyzed in this article, since laboratory evaluations were not practical and not performed in this group because of its largest size ( $\mathrm{n}=8,496$ ).
Routine clinical evaluation. All patients were evaluated initially by medical history and a complete physical examination. At least two sitting blood pressure measurements were performed as described previously. ${ }^{[16]}$ In addition to demographic data and antihypertensive treatment history, data on hypertensive risk profile, concomitant diseases and target organ damage, waist circumference and body mass index measurements were collected as described in the "European Society of Cardiology Guidelines (2003)" ${ }^{[17]}$ and routine serum and urine analysis were performed.
Evaluation of the patients' lipid profile. The lipid profile of the patients was determined by measuring serum total cholesterol, HDL-cholesterol, LDL-cholesterol and TG levels. Dyslipidemia was diagnosed when serum total cholesterol and LDL-cholesterol levels were $>250 \mathrm{mg} / \mathrm{dl}$ and $>155 \mathrm{mg} / \mathrm{dl}$, respectively, and HDL-cholesterol level was $<40 \mathrm{mg} / \mathrm{dl}$ in men and $<48 \mathrm{mg} / \mathrm{dl}$ in women. ${ }^{[18]}$ In addition, apolipoprotein-A and -B levels were also measured as indicators of dyslipidemia. Evaluation of dyslipidemia was performed
in Treated and Untreated Referral groups and in Untreated Primary Care group.

## Stratification of patients by absolute CV risk factor.

Regarding overall absolute CV disease risk assessment, European Society of Cardiology Guidelines Committee classified patients into "low", "moderate", "high", and "very high" added risk groups. ${ }^{[17]}$ In the present study, target organ damage was assessed by the following approaches: 1) routine procedures [medical history, physical examination, electrocardiography (ECG), serum creatinine, and urine analysis]; 2) routine procedures along with subsequent reassessment by serum high sensitive C -reactive protein (hs-CRP) levels and urinary albumin excretion (plus echocardiography (ECHO) and carotid ultrasonography, in the untreated referral group). Patient stratification was performed separately and cumulatively using data on the following: 1) medical history plus physical examination including blood pressure measurements, 2) routine laboratory tests (fasting blood glucose, lipid profile, serum potassium, serum and urine creatinine, complete urine test), 3) presence of microalbuminuria, 4) high plasma hs-CRP levels, 5) electrocardiographic detection of left ventricular hypertrophy, 6) echocardiographic presence of left ventricular hypertrophy, and 7) detection of vascular end organ damage by carotid ultrasonography.

Statistical analysis. Descriptive data on demographic, physical and laboratory findings, risk factors, concomitant diseases, target organ damage, and blood pressure levels were expressed as mean and standard deviation and/or median for numeric variables and percent distributions for categorical ones.

Non-normally and normally distributed dependent variables between groups were compared using Kruskal-Wallis non-parametric ANOVA, MannWhitney U-test, chi-square test, and Fisher's exact test; and one-way ANOVA, Tukey HSD test and Student's $t$-test, respectively. Values of $\mathrm{p}<0.05$ were considered statistically significant.

## RESULTS

Study population profile. There were 765 patients ( $60.9 \%$ females; mean age $58 \pm 10$ years) in the Referral group, 164 patients ( $56.4 \%$ females; mean age $50 \pm 11$ years) in the Treated group, and 888 patients (54.9\% females; mean age $51 \pm 12$ years) in the Untreated Primary Care group.

The most common risk factors found in all the study groups were abdominal obesity ( $72.2 \%$ ), sedentary life style ( $62.8 \%$ ), age ( $>55$ for men, $>65$ for women) ( $30.4 \%$ ), and hs-CRP ( $\geq 1 \mathrm{mg} / \mathrm{dl}$ ) ( $85.2 \%$ ) and the most common concomitant diseases were heart disease $(22.0 \%$ ) and diabetes mellitus ( $20.4 \%$ ). Based

Table 1. Demographic features, physical examination findings, and risk factors in the study groups

|  | Referral Groups |  |  |  |  |  | Primary Care Group <br> Untreated ( $\mathrm{n}=888$ ) |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  | Treated ( $\mathrm{n}=765$ ) |  |  | Untreated ( $\mathrm{n}=164$ ) |  |  |  |  |  |
|  | n | \% | Mean $\pm$ SD | n | \% | Mean $\pm$ SD | n | \% | Mean $\pm$ SD |
| Age (years) | $58 \pm 10$ |  |  | $50 \pm 11$ |  |  |  |  | $51 \pm 12$ |
| Gender (F/M) |  |  |  |  |  |  |  |  |  |
| Females | 464/762 | 60.9 |  | 92/163 | 56.4 |  | 485/883 | 54.9 |  |
| Males | 298/762 | 39.1 |  | 71/163 | 43.6 |  | 398/883 | 45.1 |  |
| Physical findings |  |  |  |  |  |  |  |  |  |
| Systolic blood pressure ( mmHg ) | $142.5 \pm 21.1$ |  |  |  |  | 154.6 $\pm 18.4$ |  |  | $158.0 \pm 19.9$ |
| Diastolic blood pressure ( mmHg ) | $86.1 \pm 11.1$ |  |  |  |  | $93.9 \pm 10.6$ |  |  | $96.3 \pm 10.7$ |
| Body mass index (kg/m²) | $29.3 \pm 4.9$ |  |  |  |  | $28.4 \pm 4.4$ |  |  | $29.1 \pm 4.9$ |
| Waist circumference (cm) |  |  |  |  |  |  |  |  |  |
| Males |  |  | $99.3 \pm 11.9$ |  |  | 99.9さ14.0 |  |  | $99.5 \pm 12.5$ |
| Females |  |  | $99.0 \pm 14.3$ |  |  | $93.2 \pm 12.5$ |  |  | $98.5 \pm 14.0$ |
| Risk factors or concomitant diseases |  |  |  |  |  |  |  |  |  |
| Age (>55 for men; >65 for women) | 307/764 | 40.2 |  | 42/164 | 25.6 |  | 198/871 | 22.7 |  |
| Smoking | 118/765 | 15.4 |  | 33/164 | 20.1 |  | 212/887 | 23.9 |  |
| Alcohol consumption | 57/765 | 7.5 |  | 17/164 | 10.4 |  | 108/888 | 12.2 |  |
| Sedentary life style | 470/765 | 61.4 |  | 98/164 | 59.8 |  | 574/888 | 64.6 |  |
| High-sensitivity CRP ( $\geq 1 \mathrm{mg} / \mathrm{dl}$ ) | 649/747 | 86.9 |  | 133/156 | 85.3 |  | 679/814 | 83.4 |  |
| Abdominal obesity | 561/753 | 74.5 |  | 100/163 | 61.4 |  | 557/770 | 72.3 |  |
| Heart disease | 290/765 | 37.9 |  | 34/164 | 20.7 |  | 75/888 | 8.5 |  |
| Diabetes mellitus | 169/743 | 22.8 |  | 25/160 | 15.6 |  | 167/872 | 19.2 |  |
| Renal disease | 69/765 | 9.0 |  | 9/164 | 5.5 |  | 53/888 | 6.0 |  |



Figure 1. Distribution of patients in study groups into different (A) grades of hypertension and (B) into CV risk groups according to existing risk factors before additional tests. Distribution between the groups showed significantly different patterns for both panels ( $\mathrm{p}<0.001$, by Kruskal-Wallis test). Group comparisons were as follows: (A) $\mathrm{p}<0.001$ for Treated Referral Group vs other groups; $\mathrm{p}=0.001$ for Untreated Referral vs Untreated Primary Care groups; (B) $\mathrm{p}<0.001$ for Treated Referral vs Untreated Primary Care groups, and for Treated Primary Care vs Untreated Referral groups; and $\mathrm{p}=0.06$ for Treated vs Untreated Referral groups by Mann-Whitney U-test.
on laboratory findings (i.e. slight increase in serum creatinine, presence of proteinuria), $9.0 \%, 5.5 \%$, and $6.0 \%$ of Treated Referral, Untreated Referral, and Untreated Primary Care patients had renal disease, respectively. Table 1 summarizes the major characteristics of the study groups.

## Blood pressure measurements and severity of HT.

 The patients were stratified into different degrees of increased blood pressure according to the "European Society of Cardiology Guidelines (2003)" ${ }^{[17]}$ (Fig. 1a). The patients were stratified into high-normal (SBP 130139 mmHg and/or DBP $85-89 \mathrm{mmHg}$ ), grade 1 (mild)HT (SBP 140-159 mmHg and/or DBP 90-99 mmHg), grade 2 (moderate) HT (SBP 160-179 mmHg and/or DBP 100-109 mmHg), grade 3 (severe) HT (SBP $\geq 180$ mmHg and/or DBP $\geq 110 \mathrm{mmHg}$ ), and isolated systolic HT (SBP $\geq 140 \mathrm{mmHg}$ and DBP $<90 \mathrm{mmHg}$ ).

The distribution of patients to blood pressure groups differed significantly among the subgroups ( $\mathrm{p}<0.001$ ). There were significant differences between treated and untreated patients in both Referral and Primary Care groups (p values $<0.001$ ). As could be expected, the percentage of patients with grade 3 HT was smallest in the Treated Referral group.

Table 2. The serum lipid profile of patients in the study groups (Mean $\pm$ SD)



Figure 2. The percentages of the study patients having elevated serum total and LDL-cholesterol levels and a reduced HDL-cholesterol level according to medical history and measured serum lipid values.

Evaluation of dyslipidemia according to serum lipid profile. Table 2 summarizes the lipid profile of patients in all the study groups. Serum total cholesterol, LDL-cholesterol, and HDL-cholesterol levels revealed that dyslipidemia was present in $45.8 \%$ ( $41.8 \%$ males, $48.5 \%$ females) of the Treated Referral, 42.5\% ( $40.3 \%$ males, $44.6 \%$ females) of the Untreated Referral, and $47.6 \%$ ( $43.1 \%$ males, $51.4 \%$ females) of the Untreated Primary Care patients. The percentages of patients having dyslipidemia according to history in these groups were $39.9 \%$ ( $35.2 \%$ males, 43.1\% females), $18.9 \%$ ( $19.7 \%$ males, $18.5 \%$ females) and $19.4 \%$ ( $17.8 \%$ males, $20.6 \%$ females), respectively. Thus, dyslipidemia was diagnosed in a total of $65.0 \%$ of the Treated patients (Referral) and $54.6 \%$ of the Untreated patients (both Referral and Primary Care). Figure 2 shows the percentages of patients having elevated total cholesterol and LDL-cholesterol levels and a reduced HDL-cholesterol level according to both history and measured values. Overall, of patients (29.2\%) with dyslipidemia according to history, $20.6 \%$ had elevated total cholesterol, $9.2 \%$ had elevated LDL-cholesterol, and 6.8\% had reduced HDL-cholesterol levels.

Among all patients, $5.9 \%$ ( $6.5 \%$ males, $5.5 \%$ females) were currently using antilipidemic drugs. The distribution of patients using antilipidemic drugs was as follows: $12.5 \%$ in Treated Referral, $0.6 \%$ in Untreated Referral, and $2.1 \%$ in Untreated Primary Care groups.
The association between serum lipid profile and other CV risk factors. Serum total cholesterol levels were correlated with systolic and diastolic blood pressures, obesity parameters (i.e. body mass index and waist circumference), and microalbuminuria in Treated Referral patients (Table 3). On the other
hand, total serum cholesterol level was correlated only with systolic pressure in Untreated patients. LDL-cholesterol levels showed a positive correlation with systolic and diastolic blood pressures and obesity parameters in Treated Referral patients, but no correlation was observed in Untreated patients (Table 3). In both Treated and Untreated patients, HDL-cholesterol levels showed negative correlations with waist circumference and hs-CRP levels as well as with ECG and ECHO parameters (Sokolow index and left ventricular mass index, respectively) as indicators of left ventricular hypertrophy (Table 3). Serum TG levels were positively correlated with almost all other CV risk factors in Treated patients, whereas in Untreated patients, only obesity parameters and hs-CRP levels were correlated with TG levels (Table 3).

The impact of serum lipid profile on CV risk stratification. The patients in the study groups were stratified into CV risk groups according to the "European Society of Cardiology Guidelines (2003) ${ }^{[17]}$ regarding existing risk factors in history and concomitant diseases before additional tests (Fig. 1b). There were significant differences between the subgroups in this respect ( $\mathrm{p}<0.001$ ). The rate of patients with "high" plus "very high" added risk was significantly higher in Untreated groups compared to the Treated group ( $\mathrm{p}<0.001$ ).

The rates of patients in "high" plus "very high" added risk groups assessed by medical history and physical examination were $51.2 \%, 60.7 \%$, and $54.2 \%$ in Treated Referral, Untreated Referral, and Untreated Primary Care patients, respectively. Following evaluation of serum lipid levels, a stepwise restratification was made and the corresponding rates increased to $55.2 \% ~(\mathrm{p}<0.001), 62.6 \% ~(\mathrm{p}=0.25)$, and to $60.7 \%$ ( $\mathrm{p}<0.001$ ), respectively (Fig. 3). When all risk groups

Table 3. Correlations between serum lipid profile parameters and other cardiovascular risk factors

|  | Treated (Referral) |  | Untreated (Referral and Primary Care) |  |
| :---: | :---: | :---: | :---: | :---: |
|  | r | $p$ | r | $p$ |
| Total cholesterol |  |  |  |  |
| Systolic blood pressure | 0.124 | <0.001 | 0.073 | 0.019 |
| Diastolic blood pressure | 0.123 | <0.001 | 0.037 | 0.240 |
| Body mass index | 0.048 | 0.001 | 0.037 | 0.244 |
| Waist circumference | 0.030 | 0.047 | 0.053 | 0.109 |
| Microalbuminuria (qualitative) | 0.043 | 0.006 | .- | .- |
| LDL-cholesterol |  |  |  |  |
| Systolic blood pressure | 0.074 | <0.001 | 0.042 | 0.179 |
| Diastolic blood pressure | 0.071 | <0.001 | 0.034 | 0.284 |
| Body mass index | 0.042 | 0.012 | 0.041 | 0.194 |
| Waist circumference | 0.045 | 0.010 | 0.064 | 0.053 |
| HDL-cholesterol |  |  |  |  |
| Waist circumference | -0.038 | 0.027 | -0.119 | <0.001 |
| Microalbuminuria (qualitative) | -0.073 | <0.001 | .- | .- |
| Microalbuminuria (quantitative) | -0.104 | 0.005 | -0.025 | 0.425 |
| High sensitivity C-reactive protein | -0.088 | 0.001 | -0.128 | <0.001 |
| Sokolow index | -0.121 | 0.002 | -0.052 | 0.156 |
| Left ventricular mass index | .- | .- | -0.254 | 0.002 |
| Triglyceride |  |  |  |  |
| Systolic blood pressure | 0.062 | <0.001 | 0.020 | 0.533 |
| Diastolic blood pressure | 0.070 | <0.001 | 0.023 | 0.454 |
| Body mass index | 0.075 | <0.001 | 0.110 | <0.001 |
| Waist circumference | 0.093 | <0.001 | 0.159 | <0.001 |
| Microalbuminuria (qualitative) | 0.079 | <0.001 | .- | .- |
| Microalbuminuria (quantitative) | 0.120 | 0.001 | 0.057 | 0.076 |
| High sensitivity C-reactive protein | 0.047 | 0.075 | 0.114 | <0.001 |

are considered after including lipid profile data to medical history, shifts to upper risk groups were found as $5.5 \%, 3.7 \%$, and $9.3 \%$ in the three study groups, respectively.

## DISCUSSION

Cardiovascular disease is one of the leading causes of death and loss of productivity worldwide. Patients with multiple CV risk factors are at much greater risk for CV disease-related events than those with a single factor. Abnormalities in plasma lipoprotein metabolism play a central role in the pathogenesis of atherosclerosis, and arterial HT with elevated systolic or diastolic blood pressure is positively and independently associated with coronary heart disease. ${ }^{[19,20]}$ Data from the Framingham Study demonstrated that HT tended to occur in association with other atherogenic risk factors (e.g. $78 \%$ of hypertensive men and $82 \%$ of hypertensive women had multiple CV risk factors). ${ }^{[21]}$

This report presents the data of ICEBERG study which has been conducted in patients having high-nor$\mathrm{mal} /$ high blood pressure levels with or without hyper-
tensive treatment, and focuses on the evaluation of dyslipidemia as a CV risk factor. The diagnosis of dyslipidemia was based on the patients' medical history and measured serum lipid profile levels. The data revealed that a total of $65.0 \%$ of the treated and $54.6 \%$ of the untreated patients had dyslipidemia. In all study groups, the majority of the patients had a reduced HDL-cholesterol level. This finding is in accordance with the data of the TEKHARF cohort of 2001/02, which revealed low HDL-cholesterol levels in $64 \%$ of men and $35.5 \%$ of women. ${ }^{[22]}$ Elevated LDL-cholesterol and triglyceride levels were in the second and third place among indications of impaired lipid status, respectively. Of all the patients, only $5.9 \%$ were currently using antilipidemic drugs. Finding of similar percentages of patients with dyslipidemia in both Treated and Untreated Referral groups may implicate inadequate management and/or poor patient compliance to therapy.

Indeed, many patients have both HT and dyslipidemia. ${ }^{[1]}$ The risk for CV disease associated with the presence of both HT and dyslipidemia has been demonstrated to be greater than that associated with


Figure 3. The percentages of the study patients in "high" plus "very high" added risk groups according to medical history and physical examination (HPE), and to HPE plus serum lipid profile. ${ }^{*} \mathrm{p}<0.001$ (McNemar test).

HT or dyslipidemia alone. ${ }^{[23]}$ Gaziano et al. ${ }^{[24]}$ noted a potential interaction between elevated cholesterol levels and HT in the development of myocardial infarction. Thus, the need to quantify a person's overall CV risk is of great importance.

In a recent retrospective cohort study aiming to estimate the prevalence of concurrent HT and dyslipidemia among a veteran population and to compare the prevalence of CV disease among groups with isolated versus concurrent HT and dyslipidemia, it was found that $57.8 \%$ of all patients had HT or dyslipidemia and that nearly one-third (30.7\%) of all patients had both. ${ }^{[15]}$ Moreover, patients with these two conditions were found to have 3 to 4 times higher prevalence of myocardial infarction than those with either condition alone, and 2 to 3 times higher prevalence of coronary artery disease, peripheral arterial disease, and cerebrovascular disease. ${ }^{[15]}$

Estimates from the National Health and Nutrition Examination Survey III found that the prevalence of HT was $32.8 \%$ and the rate of LDL-cholesterol above $130 \mathrm{mg} / \mathrm{dl}$ was $49 \%$ for men and $43 \%$ for women. ${ }^{[25]}$ Johnson et al. ${ }^{[15]}$ reported prevalences of HT and dyslipidemia as $52.1 \%$ and $36.3 \%$, respectively, in their study population.

In the current study, correlation analyses demonstrated statistically significant relationships between serum lipid profile and other major CV risk factors. Impairment in the lipid profile was mostly correlated with elevated blood pressure levels (systolic and/or diastolic) and with obesity parameters (body mass
index and/or waist circumference). Significant correlations of reduced HDL-cholesterol with microalbuminuria, hs-CRP, and left ventricular hypertrophy parameters are of particular importance. Although correlation coefficients ( r values) are relatively low and statistical significance might be influenced by large sample size, our observations are in accordance with the findings of Castelli and Anderson ${ }^{[26]}$ who noted that blood pressure and serum cholesterol were strongly correlated among hypertensive patients and recommended early treatment for hypercholesterolemia in patients with HT.

Another important finding of our study was that, when two sets of data (lipid profile data and routine clinical evaluation data obtained from medical history and physical examination) were incorporated into CV risk stratification, we observed marked upward shifts to "high and very high added risk" groups in all the study groups. This effect was also evident when all risk groups were considered. These observations suggest that incorporation of serum lipid data into screening will be useful for a more factual risk stratification of patients with high-normal and high blood pressure levels at both Referral and Primary Health Care settings.

Recent studies have suggested that substantial reductions in the risk of coronary heart disease, stroke, and death can be achieved by targeting HT and dyslipidemia. ${ }^{[27,28]}$ For instance, it is estimated that $79 \%$ of ischemic heart disease events and $69 \%$ of strokes may be prevented if LDL-cholesterol level is decreased by 70 $\mathrm{mg} / \mathrm{dl}$ and diastolic pressure by 11 mmHg . ${ }^{[27]}$

In conclusion, an important fraction of ICEBERG patients with high-normal and high blood pressure levels, either under antihypertensive therapy or not was found to have dyslipidemia. The serum lipid profile of these patients correlated significantly with other major CV risk factors. These observations taken together with the data demonstrating the importance of dyslipidemia in patients' risk stratification imply that patients with high blood pressure and impaired lipid profile are at high risk and should be the target of aggressive primary preventive strategies to reduce the burden of HT and subsequent CV disease.

## Acknowledgments

We would like to acknowledge the collaboration and commitment of all local investigators and their staff, without whom the present study would not have been possible.

ICEBERG-1 trial was performed in cardiology departments of Akdeniz University, Ankara Numune

Hospital, Ankara University, Atatürk Research and Education Hospital, Çukurova University, Dokuz Eylül University, Ege University, Erciyes University, Gazi University, Hacettepe University, İstanbul University Cerrahpaşa Medical Faculty, İstanbul University İstanbul Medical Faculty, Kadir Has University, Kocaeli University, Mersin University, Ondokuz Mayıs University, Trakya University, Yüksek İhtisas Hospital, and nephrology department of Hacettepe University.

Statistical analyses of the data were performed by Omega-CRO.

## REFERENCES

1. Eaton CB, Feldman HA, Assaf AR, McPhillips JB, Hume AL, Lasater TM, et al. Prevalence of hypertension, dyslipidemia, and dyslipidemic hypertension. J Fam Pract 1994;38:17-23.
2. Thomas F, Rudnichi A, Bacri AM, Bean K, Guize L, Benetos A. Cardiovascular mortality in hypertensive men according to presence of associated risk factors. Hypertension 2001;37:1256-61.
3. O’Meara JG, Kardia SL, Armon JJ, Brown CA, Boerwinkle E, Turner ST. Ethnic and sex differences in the prevalence, treatment, and control of dyslipidemia among hypertensive adults in the GENOA study. Arch Intern Med 2004;164:1313-8.
4. Thomas F, Bean K, Guize L, Quentzel S, Argyriadis P, Benetos A. Combined effects of systolic blood pressure and serum cholesterol on cardiovascular mortality in young ( $<55$ years) men and women. Eur Heart J 2002;23:528-35.
5. Liao D, Mo J, Duan Y, Lin HM, Darnell M, Qian Z. The joint effect of hypertension and elevated LDLcholesterol on CHD is beyond additive. [Abstract] Eur Heart J 2004;25(Suppl 1):235.
6. Gould AL, Rossouw JE, Santanello NC, Heyse JF, Furberg CD. Cholesterol reduction yields clinical benefit: impact of statin trials. Circulation 1998;97:946-52.
7. Ballantyne CM. Low-density lipoproteins and risk for coronary artery disease. Am J Cardiol 1998;82:3Q-12Q.
8. Brown BG, Zhao XQ, Bardsley J, Albers JJ. Secondary prevention of heart disease amongst patients with lipid abnormalities: practice and trends in the United States. J Intern Med 1997;241:283-94.
9. Austin MA. Plasma triglyceride and coronary heart disease. Arterioscler Thromb 1991;11:2-14.
10. Hokanson JE, Austin MA. Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a metaanalysis of population-based prospective studies. J Cardiovasc Risk 1996;3:213-9.
11. Castelli WP, Garrison RJ, Wilson PW, Abbott RD, Kalousdian S, Kannel WB. Incidence of coronary
heart disease and lipoprotein cholesterol levels. The Framingham Study. JAMA 1986;256:2835-8.
12. Kwiterovich PO Jr. The antiatherogenic role of highdensity lipoprotein cholesterol. Am J Cardiol 1998; 82:13Q-21Q.
13. Gordon DJ, Probstfield JL, Garrison RJ, Neaton JD, Castelli WP, Knoke JD, et al. High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. Circulation 1989;79:8-15.
14. Rubins HB, Robins SJ, Collins D, Fye CL, Anderson JW, Elam MB, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. N Engl J Med 1999;341:410-8.
15. Johnson ML, Pietz K, Battleman DS, Beyth RJ. Prevalence of comorbid hypertension and dyslipidemia and associated cardiovascular disease. Am J Manag Care 2004;10:926-32.
16. O'Brien E, Asmar R, Beilin L, Imai Y, Mallion JM, Mancia G, et al. European Society of Hypertension recommendations for conventional, ambulatory and home blood pressure measurement. J Hypertens 2003;21:821-48.
17. European Society of Hypertension-European Society of Cardiology Guidelines Committee. 2003 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. J Hypertens 2003;21:1011-53.
18. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. 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;285:2486-97.
19. Shurtleff D. Some characteristics related to incidence of cardiovascular disease and death, Framingham study, 16-year follow-up. In: Kannel WB, Gordon T, editors. The Framingham Study: an epidemiologic investigation of cardiovascular disease. Section 26, Washington, DC: National Heart, Lung \& Blood Institute; NIH publication No. HE 20-3002. Government Printing Office; 1970.
20. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group. JAMA 1991;265:3255-64.
21. Kannel WB. Fifty years of Framingham Study contributions to understanding hypertension. J Hum Hypertens 2000;14:83-90.
22. Onat A, Hergenc G, Uzunlar B, Ceyhan K, Uyarel H, Yazici M, et al. Determinants of HDL-cholesterol and its prediction of coronary disease among Turks. [Article in Turkish] Türk Kardiyol Dern Arş 2003;31:5-13.
23. Borghi C. Interactions between hypercholesterolemia and hypertension: implications for therapy. Curr Opin

Nephrol Hypertens 2002;11:489-96.
24. Gaziano JM, Sesso HD, Breslow JL, Hennekens CH, Buring JE. Relation between systemic hypertension and blood lipids on the risk of myocardial infarction. Am J Cardiol 1999;84:768-73.
25. American Heart Association. Heart Disease and Stroke Statistics: 2004 Update. Dallas: American Heart Association; 2003.
26. Castelli WP, Anderson K. A population at risk.

Prevalence of high cholesterol levels in hypertensive patients in the Framingham Study. Am J Med 1986; 80:23-32.
27. Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than $80 \%$. BMJ 2003;326:1419-23.
28. Wong ND, Pio JR, Franklin SS, L'Italien GJ, Kamath TV, Williams GR. Preventing coronary events by optimal control of blood pressure and lipids in patients with the metabolic syndrome. Am J Cardiol 2003;91:1421-6.

