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High-Density Lipoprotein-Cholesterol and Ischemic Heart Disease Risk in Korean Men With Cardiac Risk
— A Prospective Cohort Study —

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Background: Although many epidemiological studies have suggested that a decreased level of high-density lipoprotein-cholesterol (HDL-C) is a risk factor for heart disease; this relationship remains uncertain in relation to triglycerides (TG). This study examined the effects of serum TG and HDL-C on the incidence of ischemic heart disease (IHD) in Korean men.
Methods and Results: A 14-year prospective cohort study was carried out with 29,171 Korean men who received insurance from the National Health Insurance Corporation and underwent a second screening for their cardiovascular risks. The main outcome measures were incidence of IHD. During 379,539 person-years of follow-up, 1,634 IHD (227 fatal IHD) events occurred. In the age-adjusted models, men in the lowest level of HDL-C (<30 mg/dl) showed a higher risk [hazard ratio (HR) 1.57; 95% confidence interval (CI) 1.26–1.95] when compared with men with the highest concentration (HDL-C ≥60 g/dl), defined as the reference group. When TG were included in the multivariate adjusted Cox model, the relationship of HDL-C with IHD was weakened but remained (HR 1.38; 95%CI 1.10–1.73). The results were similar for TG in the multivariate model including HDL-C.
Conclusions: These findings indicate that elevated TG and reduced HDL-C are independent risk factors for IHD risk in Korean men with cardiovascular risks. (*Circ J* 2009; **73:** 1296–1301)

Key Words: High-density lipoprotein-cholesterol; Ischemic heart disease; Myocardial infarction; Triglyceride

Results of several prospective cohort studies have suggested a positive association between triglycerides (TG) and the risk of ischemic heart disease (IHD).[1–8] However, control for concomitant variations in high-density lipoprotein-cholesterol (HDL-C) attenuated the relationship in some prospective studies.[3,5,7,8] As reduced HDL-C concentrations have also been consistently associated with an increased risk of IHD, it has been suggested that the relationship of TG to IHD may be mediated by a negative correlation between TG and HDL-C.[10,11] However, most of these studies have been published in Western countries and recently, interest has shifted focus to populations in Asian countries that have been undergoing rapid economic development and Westernization.

Synergism among common factors such as TG and HDL-C would have substantial public health and clinical relevance because it would place some individuals at extremely high risk. The precise relationship between TG, HDL-C and IHD or myocardial infarction (MI) remains unclear and controversial in Asian populations because of severely limited data. To date no studies pertaining to the relationship between TG, HDL-C and IHD or MI have been published in Korea, so in this large prospective study of 29,171 Korean men, we specifically examined it with the aim of assessing whether TG and HDL-C are independent risk factors.

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Methods

Study Participants

In Korea, employees of the government and teachers in private schools participate in the Korea Medical Insurance Corporation (KMIC), now part of the National Health Insurance Corporation (NHIC). Of the entire Korean population, 1,213,594 people were insured by the KMIC and all are required to participate in biennial medical examinations.[12,13] Subsequently, the biennial primary examination for the insured was completed in 1992 (95% participation) and 1994 (94%), 37% (1993) and 24% (1995) of the insured workers' dependents completed biennial medical examinations. The subjects who presented with cardiac risk factors at the primary medical examination were required to undergo a secondary medical examination that included specific tests for TG and HDL-C. The cardiac risk factors included a total cholesterol (TC) >250 mg/dl, abnormal ECG, abnormal blood pressure (BP; systolic BP >140 mmHg or diastolic BP >90 mmHg), or abnormal eye fundus examination. Subjects with cardiac risk factors comprised approximately 10% of the total group. Nevertheless, most of the participants in the secondary examination were otherwise healthy and had values within the normal range in terms of body mass index and systolic BP (**Table 1**). We are currently using these

Table 1. General Characteristics by HDL-C Level in Korean Men

Characteristic	Total (n=29,171)	HDL-C (mg/dl) <30 (n=1,471)	30–39 (n=5,607)	40–39 (n=9,840)	50–59 (n=6,122)	≥60 (n=6,131)
Age, years (mean)	45.3	45.3	45.4	45.4	45.5	45.6
BMI, kg/m^2 (mean)	24.2	24.7	24.6	24.4	24.2	24.0
Systolic blood pressure, mmHg (mean)	129.4	130.7	130.5	130.3	130.6	131.3
Total serum cholesterol, mg/dl (mean)	257.5	263.1	257.3	254.3	256.8	262.0
TG, mg/dl (mean)	242.9	318.9	271.1	231.9	223.8	238.7
Overweight, n (%)	37.6	45.0	41.4	38.0	35.6	33.8
Any alcohol drinking (%)	80.2	76.3	77.2	79.3	81.2	84.2
Physical activity† (%)	29.4	28.5	27.3	29.4	29.9	31.0
Hypertension (%)	50.6	50.7	51.2	49.7	50.4	51.8
Diabetes (%)	10.4	10.6	11.3	9.4	10.3	11.3
Smoking status (%)						
Never smoked	18.7	15.5	16.8	18.6	20.4	19.8
Former smoker	19.6	17.3	17.6	19.3	20.8	21.5
Current smoker	61.7	67.3	65.6	62.1	58.8	58.7

Overweight was defined as BMI ≥25 kg/m^2.
†Physical activity was assessed by the question, "Do you exercise regularly?"
HDL-C, high-density lipoprotein-cholesterol; BMI, body mass index; TG, triglycerides.

secondary examinees as the study population for a prospective cohort study of TG, HDL-C and IHD or MI risk.

This cohort study with a follow-up of up to 13 years (average 12.73 year, SD 2.63 year), includes 65,568 Korean men aged from 30 to 95 years of age who received health insurance from the NHIC and who completed secondary medical evaluations from 1992 to 1995. Among 65,568 participants, 37,238 participants had their serum levels of HDL-C and TG measured.

We excluded 1,044 subjects (1.59%) with incomplete data for body mass index and alcohol intake, as well as 2,672 subjects (4.08%) who reported a history of any form of cancer, respiratory disease, liver disease, or cardiovascular disease, and 3,627 (5.53%) women were excluded. The final sample size was 29,171 subjects.

Data Collection

The NHIC biennial examinations are conducted in a standardized fashion by medical staff at local hospitals or places of employment. In the 1992 to 2005 questionnaires, participants were asked to describe their smoking habit, including the number of cigarettes smoked per day and the duration of cigarette smoking in years, together with other health habits including alcohol consumption. The completed questionnaires were reviewed and edited by trained staff and then entered into an electronic database. The data were further edited in the creation of the analysis files.

The primary medical examination included measurement of weight, height, BP, serum TC, and fasting serum glucose. The secondary medical examination included serum levels of TG and HDL-C. BP was measured in the seated position by a registered nurse or technician using a standard mercury sphygmomanometer or automatic manometer. A fasting serum specimen was drawn and analyzed for TC, TG and HDL-C glucose. Each hospital that conducted the examinations had internal and external quality control procedures directed by the Korean Association of Laboratory Quality Control.

Using data collected in the examination, the participants were classified as "current" smokers if they reported smoking currently for at least 1 year, "never-smokers" if they had never smoked, or "ex-smokers" if they had smoked but had quit for at least 1 month by the time of interview. Current smokers were further classified according to the average number of cigarettes smoked per day (1–9, 10–19 or ≥20 cigarettes per day) and duration of smoking (1–10, 20–19, 20–29, or ≥30 years).

Body mass index was calculated as weight in kilograms divided by height in meters squared. Hypertension was defined as a systolic BP of at least 140 mmHg or a diastolic BP of at least 90 mmHg. Using the National Cholesterol Education Program guidelines,[14] serum TC level was classified as desirable (<200 mg/dl), borderline to high (200–239 mg/dl), or high (≥240 mg/dl). Using diagnostic criteria from the National Diabetes Data Group, diabetes was defined as a fasting serum glucose level ≥126 mg/dl or history of treatment.

The follow-up period was up to 14 years, from January 1, 1993 to December 31, 2006. The exact dates of completion of the survey form were not recorded. Consequently, follow-up accrual began on January 1 of the calendar year following the year in which the survey form was completed. Persons who completed a survey but died within the calendar year of the survey were excluded.

Outcomes

The principal outcome variables were death from IHD (International Classification of Diseases, 10th Revision [ICD-10] codes I20–I25) and MI (ICD-10) codes I21) alone. Outcomes were ascertained from the diagnosis stated on hospital discharge summaries and from causes of death on death certificates. In Korea, professionally trained and certified medical chart recorders' abstract the charts and assign a discharge diagnosis in a standardized fashion using World Health Organization codes for common diseases such as IHD and MI. Follow-up was initiated according to the time of the earliest event.

Statistical Analysis

The HDL-C level was categorized as follows: <30, 30–39, 40–49, 50–59, and ≥60 mg/dl. Bivariate analyses provided information about the relationship between HDL-C and related factors such as age, body mass index, systolic BP, serum TC, alcohol consumption, and smoking status. In order to assess the independent effects of TG and HDL-C on IHD events, Cox proportional hazard models were used.

Table 2. HDL-C and TG Levels and Ischemic Heart Disease Risk in Korean Men

	Age-adjusted*			Age, life-style and BMI adjusted*	Multivariate adjusted‡
	n	Rate†	HR (95%CI)	HR (95%CI)	HR (95%CI)
HDL-C, mg/dl					
<30	107	566	1.57 (1.26–1.95)	1.44 (1.15–1.80)	1.38 (1.10–1.73)
30–39	366	503	1.37 (1.18–1.60)	1.29 (1.10–1.50)	1.25 (1.07–1.46)
40–49	559	435	1.18 (1.02–1.36)	1.14 (0.99–1.32)	1.14 (0.98–1.31)
50–59	308	385	1.04 (0.88–1.22)	1.03 (0.88–1.21)	1.03 (0.88–1.21)
≥60	294	370	1.00	1.00	1.00
TG, mg/dl					
<100	158	497	1.00	1.00	1.00
100–149	366	639	1.04 (0.85–1.27)	1.03 (0.84–1.26)	1.05 (0.86–1.29)
150–199	422	690	1.20 (0.98–1.47)	1.16 (0.95–1.42)	1.15 (0.94–1.41)
200–249	317	532	1.28 (1.04–1.58)	1.23 (0.99–1.52)	1.22 (0.99–1.51)
≥250	723	669	1.40 (1.16–1.69)	1.36 (1.12–1.65)	1.33 (1.10–1.61)

*Separate models for HDL-C and TG levels.
†Incidence rate per 100,000 person year.
‡Adjusted for age, smoking status, alcohol drinking, exercise and BMI. Model with HDL-C was adjusted for TG and model with TG was adjusted for HDL-C.
HR, hazard ratio; CI, confidence interval. Other abbreviations see in Table 1.

Table 3. HDL-C and TG Levels and Myocardial Infarction Risk in Korean Men

	Age-adjusted*			Age, life-style and BMI adjusted*	Multivariate adjusted‡
	n	Rate†	HR (95%CI)	HR (95%CI)	HR (95%CI)
HDL-C, mg/dl					
<30	52	271	1.61 (1.17–2.21)	1.42 (1.03–1.96)	1.34 (0.97–1.85)
30–39	162	220	1.28 (1.02–1.61)	1.16 (0.92–1.46)	1.11 (0.88–1.40)
40–49	230	177	1.03 (0.83–1.27)	0.98 (0.79–1.21)	0.97 (0.78–1.40)
50–59	112	138	0.80 (0.63–1.03)	0.80 (0.62–1.02)	0.80 (0.62–1.02)
≥60	138	172	1.00	1.00	1.00
TG, mg/dl					
<100	59	180	1.00	1.00	1.00
100–149	145	209	1.15 (0.85–1.56)	1.11 (0.82–1.51)	1.11 (0.80–1.54)
150–199	160	224	1.30 (0.96–1.75)	1.15 (0.92–1.69)	1.18 (0.85–1.63)
200–249	128	239	1.46 (1.07–1.98)	1.37 (1.00–1.87)	1.40 (1.08–1.96)
≥250	307	252	1.61 (1.22–2.13)	1.57 (1.18–2.08)	1.51 (1.12–2.05)

*Separate models for HDL-C and TG levels.
†Incidence rate per 100,000 person year.
‡Adjusted for age, smoking status, alcohol drinking, exercise and BMI. Model with HDL-C was adjusted for TG and model with TG was adjusted for HDL-C.
Abbreviations see in Tables 1,2.

In each model, age, smoking, body mass index, alcohol drinking, and exercise were controlled to delineate the independent effects of TG and HDL-C. An interaction term of TG level (high/low) and HDL-C level (high/low) was added to the model to examine their interaction.

Results

Participant Characteristics

Table 1 shows the baseline clinical characteristics according to the 5 categories of HDL-C level at baseline for the whole study population. The mean TG and HDL-C levels were 242.9 (165.3) and 51.0 (22.8) m/dl, respectively. The body mass index and prevalence rate of current smoking decreased with increasing levels of HDL-C.

HDL-C and TG Levels and IHD Events

During the 379,539 person-years of follow-up, 1,634 IHD events (227 fatal IHD) and 694 MI (191 fatal) occurred. **Table 2** presents the hazard ratio (HR) for IHD across categories of HDL-C and TG. In the age-adjusted models, men in the lowest level of HDL-C (HDL <30 mg/dl) showed a higher HR (HR 1.57, 95% confidence interval (CI) 1.26–1.95) when compared with men with the highest concentration (HDL ≥60 mg/dl), defined as the reference group. When TG were included in the multivariate adjusted Cox model, the relationship of HDL-C with IHD was attenuated, but remained (HR 1.38, 95%CI 1.10–1.73). Likewise, in the age adjusted models, men in the highest levels of TG (≥250 mg/dl) showed a higher HR (HR 1.40, 95%CI 1.16–1.69) when compared with men with the lowest concentration (TG <100 mg/dl), defined as the reference group. When HDL-C was included in the multivariate adjusted Cox model, the relationship of TG with IHD was attenuated, but remained (HR 1.33, 95%CI 1.10–1.61).

Table 3 presents the HR for MI across categories of HDL-C and TG. The relationships between HDL-C and TG and MI were similar to those in IHD. Adjustment for TG level weakened the relationship between HDL-C and MI; however, adjustment for HDL-C level did not alter the relationship between TG and MI. Life-table curves showed an increase of both IHD and MI events among men in the

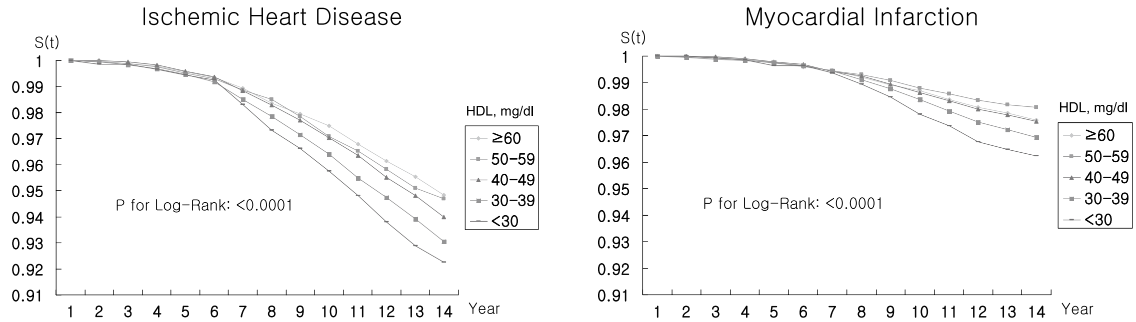

Figure 1. Life-table curves by categories of high-density lipoprotein (HDL)-cholesterol: 14-year ischemic heart disease and myocardial infarction in Korean men.

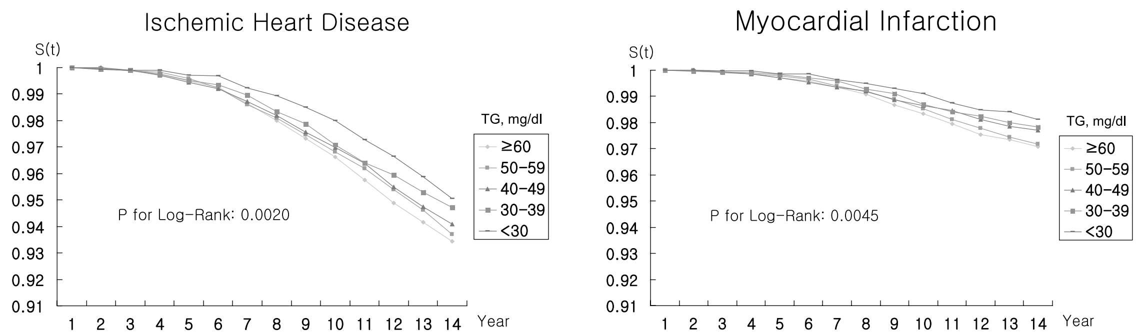

Figure 2. Life-table curves by categories of triglyceride (TG): 14-year ischemic heart disease and myocardial infarction in Korean men.

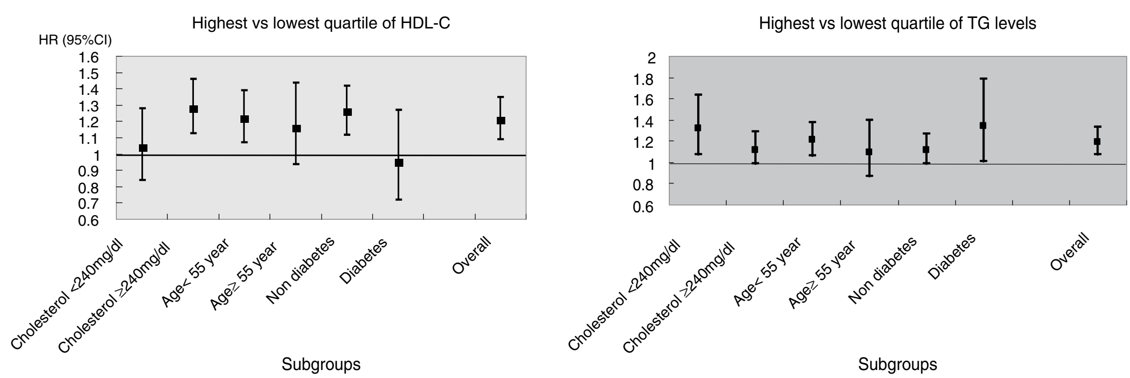

Figure 3. Hazards ratio (HR) (95% confidence interval (CI)) comparing within subgroups for risk of ischemic heart disease between individuals belonging to highest vs lowest quartile of high-density lipoprotein-cholesterol (HDL-C) or triglyceride (TG) levels. Patient analyses were adjusted by age, smoking status, alcohol drinking, body mass index, and TG in the HDL-C analysis or HDL-C in the TG analysis. Number of subjects in subgroup with total cholesterol <240 mg/dl was 10,033 and 19,138 were in the total cholesterol ≥240 mg/dl group. The number of subjects in subgroup age <55 years was 5,006 and 24,165 were in age ≥55 years group. There were 26,140 in the nondiabetes group and 3,031 were in the diabetes group. Overall subject number was 29,171.

lowest category of HDL-C (**Figure 1**). Likewise, the life-table curve showed an increase of both IHD and MI events among men in the highest category of TG level (**Figure 2**).

Figure 3 shows the HR comparison within subgroup risk of IHD between individuals belonging to the highest vs the lowest quartile of HDL-C or TG level. There was no evidence for an interaction between HDL-C and age, diabetes or TC for IHD risk. Likewise, there was no evidence for an interaction between TG and age, diabetes or TC for IHD risk. We could not find any interaction between TG and HDL-C. In terms of the HRs among the subgroups, HDL-C was an important marker in those whose TC level was >240 mg/dl, whereas the TG level was important when TC <240 mg/dl. Both HDL-C and TG had significantly higher HRs in those aged less than 55 years when compared with subjects aged over 55 years. In subjects without diabetes, HDL-C had significantly higher HRs than TG, but in subjects with diabetes, only TG had a significant HR. However, the overall HR for IHD was above 1.0 in both HDL-C and TG.

Discussion

In Korea, this is the first prospective analysis of the association between HDL-C, TG and IHD events. The results for a large sample of Korean men suggest that reduced HDL-C and increased TG levels are an independent risk factor for both IHD and MI.

Several prospective epidemiological studies have investigated reduced HDL-C levels as a significant risk factor for IHD,[1–8] but with inconsistent results. Although most previous studies have shown a positive association between HDL-C and IHD in general,[15,16] reliable information about subgroup analysis with a large sample size is scarce. Even in the case of studies that have reported a positive association between HDL-C and a particular group, the results have been criticized because of small sample sizes and short periods of observation.

The Asian Pacific Cohort Collaboration Study has reported that HDL-C is associated with coronary heart disease (CHD); however, there was no evidence of an interaction between TG level and age, sex or diabetes status for fatal CHD.[8] In Iso et al's study,[7] the relationship between TG and CHD was observed similarly for persons with TC levels lower vs higher than the median for men and women combined; however, the interaction term was not statistically significant. The present findings support the results of those studies. Both of them,[7,8] as well as our own, comprised basically of healthy subjects, and this similarity in approach may explain, in part, the similar results obtained.

As reduced HDL-C concentration has consistently been reported to be associated with an increased risk of IHD, it has been suggested that the relationship of TG to IHD may be mediated by a negative correlation between TG and HDL-C.[2,6] In most studies, the positive relationship between TG level and IHD risk persisted after adjustment for possible confounders, but disappeared after HDL-C was included in the multivariate model.[6]

The present results are robust evidence that serum HDL-C levels are associated with the risk of developing IHD, independent of other major measurable risk factors. The association was attenuated after adjusting for TG, suggesting that the relationship of serum TG level to IHD may be mediated, at least to a certain extent, by the negative correlation between the TG and HDL-C levels. However, the relationship of HDL-C to TG is not linear,[2] so the risk of IHD among subjects with elevated TG levels may differ according to the etiology of the hypertriglyceridemic state. In an attempt to determine whether or not TG and HDL-C are independent risk factors for IHD, we divided the study participants into 5 groups according to TG or HDL-C level. The associations between TG and IHD, and HDL-C and IHD were significant in the lower HDL-C group and the higher TG group. However, in the multivariate adjusted model for MI risk, HDL-C showed no significant relationship in the lower quintiles, though TG showed relationships even in the multivariate adjusted model.

There are many other well-known cardiovascular risk factors, including smoking, exercise and obesity, and there have been efforts to improve these behavioral factors. The high-risk group with combined risk factors is also important.[17] Lipid levels are also a well-known risk factor and are used as treatment targets and goals. So far, we have found that there are relatively fewer reports of TG and HDL-C, which may be because HDL-C is not a modifiable risk factor. However, recent new treatments to improve HDL-C have been introduced[18,19] and further reports on the risk of HDL-C are therefore required. More cohort studies to clarify the relationship between TG, HDL-C and IHD are needed because the anti-atherogenic effect of HDL-C elevation by cholesteryl ester transfer protein inhibition is controversial.

Study Limitations

A potential limitation of our study is the relatively brief duration of follow-up and our reliance on discharge data and death certificates. We believe; however, that the large size of the cohort (approximately 30,000 participants) provided sufficient statistical power to overcome that limitation. Reliance on diagnoses from death certificates may introduce both random and systematic errors. Random error would tend to diminish the study's power to detect associations, and systematic error could alter the distribution of events and perhaps the risk factor–disease relationships if the errors were related to exposure status. However, the consistency of our findings (ie, the significant relationships between HDL-C and IHD events) tend to suggest that major systematic errors related to the coding of death from either IHD or MI events were unlikely. The conclusion of the study should be limited to the special population who met the selection criterion, such as those who undergo a secondary health examination because of abnormal findings of cardiovascular risk factors in the first examination.

In conclusion, this prospective study provides strong evidence that HDL-C and TG are both independent risk factors for IHD, and that TG is an independent risk factor for MI.

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