

Comparison of Various Lipid Variables as Predictors of Coronary Heart Disease in Japanese Men and Women With Type 2 Diabetes

Subanalysis of the Japan Diabetes Complications Study

HIROHITO SONE, MD, PHD, FACP¹
 SACHIKO TANAKA, PHD²
 SHIRO TANAKA, PHD³
 SATOSHI IIMURO, MD, PHD⁴
 SHUN ISHIBASHI, MD, PHD⁵
 SHINICHI OIKAWA, MD, PHD⁶
 HITOSHI SHIMANO, MD, PHD¹

SHIGEHIRO KATAYAMA, MD, PHD⁷
 YASUO OHASHI, PHD⁴
 YASUO AKANUMA, MD, PHD⁸
 NOBUHIRO YAMADA, MD, PHD¹
 ON BEHALF OF THE JAPAN DIABETES
 COMPLICATIONS STUDY GROUP*

OBJECTIVE—To determine the best lipid variable to predict coronary heart disease (CHD) in Japanese patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS—Eligible Japanese men and women (1,771) aged 40–70 years with type 2 diabetes from 59 institutes nationwide were followed for a planned 8-year period. The performance of eight conventional lipid variables, i.e., total cholesterol (TC), LDL-cholesterol (LDLC), HDL-cholesterol (HDLC), triglycerides (TGs), non-HDLC, TC/HDLC ratio, LDLC/HDLC ratio, and TG/HDLC ratio, as predictors of incident CHD were evaluated by four methods: hazard ratio (HR) per one SD increment by multivariate Cox analysis, χ^2 likelihood ratio test, area under the receiver operating characteristic curve (AUC), and tertile analysis.

RESULTS—Although all variables significantly predicted CHD events in men, non-HDLC (HR per one SD 1.78 [95% CI 1.43–2.21]; AUC 0.726) and TC/HDLC (HR 1.63 [1.36–1.95]; AUC 0.718) had the better predictive performances among the variables, including LDLC. In women, TGs (log-transformed; HR 1.72 [1.21–2.43]; AUC 0.708) were the best predictor according to results of tertile analysis (HR of the top tertile versus the bottom tertile 4.31 [1.53–12.16]). The associations with incident CHD were linear and continuous.

CONCLUSIONS—For Japanese diabetic men, non-HDLC and TC/HDLC were the best predictors, whereas TGs were most predictive for women. These findings, which included prominent sex differences, should be considered among clinical approaches to risk reduction among East Asians with diabetes.

Diabetes Care 35:1150–1157, 2012

From the ¹Department of Internal Medicine, Institute of Clinical Medicine, University of Tsukuba, Tsukuba, Japan; the ²EBM Research Center, Kyoto University, Kyoto, Japan; the ³Translational Research Center, Kyoto University, Kyoto, Japan; the ⁴Department of Biostatistics, University of Tokyo School of Medicine, Tokyo, Japan; the ⁵Department of Endocrinology and Metabolism, Jichi Medical College, Tochigi, Japan; the ⁶Third Department of Medicine, Nippon Medical School, Tokyo, Japan; the ⁷Fourth Department of Medicine, Saitama Medical School, Saitama, Japan; and the ⁸Institute for Adult Diseases, Asahi Life Foundation, Tokyo, Japan.

Corresponding author: Hirohito Sone, jdcstudy@md.tsukuba.ac.jp.

Received 27 July 2011 and accepted 6 January 2012.

DOI: 10.2337/dc11-1412

This article contains Supplementary Data online at <http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc11-1412/-/DC1>.

*A complete list of the members of the Japan Diabetes Complications Study Group can be found in the Supplementary Data online.

© 2012 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. See <http://creativecommons.org/licenses/by-nc-nd/3.0/> for details.

Type 2 diabetes is characterized by an excessive incidence of coronary heart disease (CHD), and serum lipid values are among the strongest predictors of CHD (1,2). Although serum LDL-cholesterol (LDLC) has been conventionally used as a therapeutic marker and/or target in many guidelines based on trials using statins (1,2), characteristic features of diabetic dyslipidemia, which are closely associated with insulin resistance, are elevated levels of triglycerides (TGs) and small, dense LDLC (independent of LDLC level) as well as decreased levels of HDL-cholesterol (HDLC) (1,2). The use of LDLC alone for assessment of cardiovascular risk would ignore these TG-rich lipoproteins (TRLs, i.e., VLDL and intermediate-density lipoprotein) and low HDLC, all of which affect the risk of a CHD event independently of LDLC (1–4). Moreover, LDLC values, as estimated by the Friedewald formula, become progressively less accurate as the TG level increases.

Based on this background, it has been established that other lipid parameters, typically non-HDLC (determined by subtracting the HDLC concentration from the total cholesterol [TC] concentration in plasma) or apolipoprotein B (apoB), both of which reflect TRLs and small, dense LDLC, can be considered better predictors of CHD than LDLC and have been introduced into some guidelines as a secondary target for therapy (5–7). Furthermore, the ratios of TC to HDLC (TC/HDLC), which has clinical significance equivalent to non-HDLC/HDLC, LDLC to HDLC (LDLC/HDLC), and TGs to HDLC (TG/HDLC) are also used for assessing cardiovascular risk (3,4). It should be mentioned that non-HDL/HDL is always one unit lower than TC/HDLC.

Despite these considerations, these fundamental lipid measures (TC, HDLC, and TGs) and their calculated indices (LDLC, non-HDLC, TC/HDLC, LDLC/HDLC, and TG/HDLC) have not been completely and directly compared as predictors of CHD by

multiple analytical methods in past prospective studies in diabetic subjects (8–19). Results obtained have been inconsistent, and only one study (19) analyzed men and women separately. Therefore, whether LDLC performs better than the other indices or, if not, which variable is the best predictor of a CHD event has not been fully determined in diabetic subjects. Furthermore, all previous examinations of the performance of lipid variables as predictors of CHD in diabetic subjects (8–19) were performed in Western countries or in Caucasians. It is uncertain whether their results can be extrapolated to East Asian diabetic subjects, who have substantially different profiles regarding CHD and its risk factors, including a much lower incidence of CHD and degree of obesity (20–22).

In this analysis of data from a long-term follow-up of Japanese patients with type 2 diabetes, we compared eight conventional lipid variables, all of which are routinely measured or can be easily calculated in clinical care settings, as predictors of CHD events. To directly and quantitatively compare variables having different average values as well as variations in quantities and ratios, we used four different analytical methods to determine the best predictor of CHD. These were the multivariate-adjusted hazard ratio (HR) per one SD increment in the Cox hazard model, χ^2 likelihood ratio test, area under the receiver operating characteristic (ROC) curve (AUC), and tertile analysis.

RESEARCH DESIGN AND METHODS

Recruitment of patients

The present analysis was conducted as part of the Japan Diabetes Complications Study, a multicenter prospective study of the incidence of and risk factors for macro- and microvascular complications among 2,033 Japanese patients with type 2 diabetes aged 40–70 years with HbA_{1c} levels >6.5% who were registered from January 1995 to March 1996 from outpatient clinics in 59 university and general hospitals nationwide that specialize in diabetes care. For this analysis of macrovascular complications, of those 2,033 individuals, 940 men (mean age 57.8 ± 7.1 years) and 831 women (mean age 58.7 ± 6.8 years) were selected for the current study after consideration of the exclusion criteria prespecified in the study protocol (23). Excluded were patients with impaired glucose tolerance, a history of angina pectoris, myocardial

infarction, stroke, peripheral artery disease, familial hypercholesterolemia, type III hyperlipidemia (diagnosed by broad β band on electrophoresis), nephrotic syndrome (urine protein >3.5 g per day and serum total protein <6.0 mg/dL), and serum creatinine levels >1.3 mg/dL (120 μ mol/L). In the 8-year planned observation period, the median follow-up for the 1,771 patients was 7.86 years (final follow-up rate was 75%; 1,332/1,771 patients). The total person-years studied was 11,743 (6,106 for men and 5,637 for women). Diabetes and impaired glucose tolerance were diagnosed according to the Report of the Committee of the Japan Diabetes Society on the Classification and Diagnostic Criteria of Diabetes Mellitus, which is almost identical in terms of thresholds for glucose levels to those of the World Health Organization. The study protocol, which is in accordance with the Declaration of Helsinki and the Ethical Guidelines for Clinical/Epidemiological Studies of the Japanese Ministry of Health, Labor, and Welfare, received ethical approval from the institutional review boards of all participating institutes. All enrolled patients provided written informed consent.

Clinical and laboratory measurements

Patients were assessed yearly after the baseline evaluation. Mean values of at least two measurements each year were obtained for HbA_{1c}, fasting plasma glucose, and fasting serum lipids. HbA_{1c} assays were performed according to procedures outlined by the Laboratory Test Committee of the Japan Diabetes Society (JDS), which is known to be converted by the formula HbA_{1c} (JDS)(%) = HbA_{1c} (National Glycohemoglobin Standardization Program [NGSP])(%) – 0.4%. All other laboratory tests were performed at each participating institute. Serum LDLC was calculated using the Friedewald equation, except where TGs exceeded 400 mg/dL, in which case LDLC data were treated as “missing”. This was applicable to 20 subjects. All other measurements, including those for body weight, blood pressure, and a 12-lead electrocardiogram, were performed at least once yearly. A baseline dietary survey, which was validated and is widely used in Japan (24) and was comprised of food records and a food frequency questionnaire that included alcohol consumption, was undertaken. Information on cigarette smoking was collected using a self-administered questionnaire. Smoking status was classified into one

of three categories: current smokers, ex-smokers, and never smokers (25).

Outcome measures

The outcomes analyzed were a fatal or first nonfatal manifestation of CHD comprised of angina pectoris and myocardial infarction, both of which were diagnosed according to criteria defined by the Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA; World Health Organization) project. A patient with a first percutaneous coronary intervention or coronary artery bypass graft was also counted as having a CHD event. Information regarding primary outcome and other clinical variables for each subject was collected through an annual report that included detailed findings at the time of the event from each participating diabetologist who was providing care to those patients. The adjudication of end points was performed by central committees comprised of experts who were masked to risk factor status and was based on additional data such as a detailed history, sequential changes in electrocardiogram and serum cardiac biomarkers, and results of coronary angiography. The rate of concordance in diagnosis between participating diabetologists and committee experts was 93%.

Statistical analysis

All statistical analyses and data management were conducted at the central data center. Patient characteristics were described as mean ± SD, median and interquartile range, or percentage. We compared a CHD group with a no-CHD group by Student *t* test and Fisher exact test for numerical and categorical variables, respectively. Multivariate Cox regression analysis was used to calculate the adjusted HRs and 95% CIs for risk factors. The strength of associations of each lipid variable was assessed using the χ^2 likelihood ratio test, and the corresponding *P* values were estimated from the regression coefficient based on the Cox proportional hazards model. In addition, the relationships between tertiles of each baseline lipid variable and HR for CHD risks were assessed by the Cox proportional hazards model using the first tertile of each variable as the reference group. The discriminatory powers for CHD of the lipid variables were also compared by ROC curve analysis with application of various thresholds to the predicted probability obtained from the logistic regression model. The AUC was calculated by integrating the area between the ROC curve and the diagonal line where sensitivity

is equal to one specificity based on the trapezoidal rule. Multivariate-adjusted generalized additive models with a spline function of three degrees of freedom were used to explore potential nonlinear relationships. All *P* values are two sided and the significance level is 0.05. All statistical analyses were conducted using SAS packages version 9.2 (SAS Institute Inc., Cary, NC).

RESULTS

Baseline clinical variables according to occurrence of CHD events

Table 1 summarizes clinical baseline variables for men and women who had or had not experienced a CHD event during the follow-up period. In comparison with men without CHD, those with CHD had significantly higher levels of all lipid variables (but lower HDLC values) determined except for TGs, which was higher with borderline significance. Women with CHD had significantly higher systolic blood pressure and significantly higher levels of lipid variables with the exception of LDLC/HDLC, which was of borderline significance, and HDLC. In addition, women with, rather than without, CHD were significantly more likely to use an insulin sensitizer and agents for hypertension and dyslipidemia.

Relationships between various lipid variables and CHD outcome

Multivariate-adjusted HRs per one SD, χ^2 values, and AUCs for CHD events for each lipid variable at baseline are shown in Table 2. In men, all lipid variables significantly predicted a CHD event with HRs per one SD ranging between 1.42 and 1.78. The largest HR value per one SD, χ^2 statistics, and AUCs were found for non-HDLc followed by TC/HDLC, which had findings very close to non-HDLc results.

In women, the largest HR per one SD was found for TGs (log-transformed) followed by non-HDLc and TC. These three indices had substantially larger χ^2 values and slightly larger AUCs than the other indices, whereas non-HDLc had the largest χ^2 value and TC had the largest AUC value (Table 2). Since subjects with elevated TGs are likely have higher glycemic or weight levels, we performed stratified analysis to categorize women according to values equal to or above or below the median of HbA_{1c} or BMI, which were 7.6% and 22.8 kg/m², respectively. As a result, a significantly larger multivariate-adjusted HR per one SD of log-transformed TGs

was observed only in those whose HbA_{1c} or BMI level was equal to or greater than the median, i.e., HbA_{1c} \geq 7.6%, HR 1.78 (95% CI 1.21–2.63), and *P* = 0.005 versus HbA_{1c} < 7.6%, 1.37 (0.76–2.47), and *P* = 0.27 (Supplementary Table 1); BMI \geq 22.8, 1.75 (1.17–2.62), and *P* = 0.008 versus BMI < 22.8, 1.51 (0.86–2.65), and *P* = 0.14 (Supplementary Table 2).

In the combined analysis of men and women, non-HDLc identified patients at greater risk of CHD than the other lipid variables and had an HR of 1.69 (95% CI 1.41–2.01), χ^2 statistic of 29.4 (*P* < 0.001), and AUC of 0.713 (95% CI 0.663–0.762) followed by TC/HDLC, for which results were 1.55 (1.33–1.81), 23.9 (*P* < 0.001), and 0.703 (0.651–0.754), respectively. These were better predictors than LDLc, for which results were 1.51 (1.26–1.80), 18.2 (*P* < 0.001), and 0.690 (0.641–0.738), respectively.

Table 3 shows HRs for CHD according to tertiles of lipid variables. In men, HRs were significantly elevated in the top compared with the bottom tertile (bottom compared with the top in case of HDLC) in all variables determined. Subjects in the top tertile of TC/HDLC and LDLc/HDLC had a four times or greater risk of CHD than those in the respective bottom tertile, followed by non-HDLc and LDLc, both of which had relatively high HRs of \sim 3.5 between extreme tertiles. In women, significantly elevated HRs in the top tertile compared with the bottom tertile were observed only for TGs, TG/HDLC ratio, and LDLc. Among those, the highest HR was noted for TGs, and was 4.31, which was considerably higher than that for the other lipid variables. Even subjects in the middle tertile for TGs, which indicated the normal level of 0.90–1.36 mmol/L, had a significantly higher risk of CHD than those in the bottom tertile. On the other hand, the HR for the TG/HDLC ratio was not higher than that for TGs alone either in men or women. If we again stratified women with values below and equal to or above the median for HbA_{1c} or BMI, which were 7.6% and 22.8 kg/m², respectively, significantly elevated HRs for TGs in the top tertile compared with the bottom tertile were observed only in those whose HbA_{1c} or BMI was at or greater than the median, i.e., HbA_{1c} \geq 7.6%, HR 6.74 (95% CI 1.43–31.67), and *P* = 0.016 versus HbA_{1c} < 7.6%, 2.95 (0.65–13.47), and *P* = 0.163 (Supplementary Table 3); BMI \geq 22.8, 3.95 (1.08–14.54), and *P* = 0.039 versus BMI < 22.8, 5.13

(0.90–29.30), and *P* = 0.066 (Supplementary Table 4).

Dynamic change in risk association of important lipid variables

To explore dynamic changes in risk association, including possible thresholds for lipid variables that were found to be good predictors, sex-stratified spline analysis was performed for non-HDLc, TC/HDLC, and TGs (Fig. 1). In each variable, the relationship was on a continuum, indicating difficulty in determining a clear cutoff value. When risks for men and women whose non-HDLc was 3.88 mmol/L (150 mg/dL) were set as a reference, risks of those with a non-HDLc value of \sim 4.3 mmol/L (170 mg/dL) became significant with HRs of \sim 1.5 in both men and women. When the TC/HDLC level of 5.0 was set for reference, risks in those whose TC/HDLC levels were \sim 6.3 became significant in both men and women but the HR was greater in women (\sim 2.0) than in men (\sim 1.5).

CONCLUSIONS—The current analysis of our Japanese subjects with type 2 diabetes revealed distinct sex differences in lipid variables that predict a CHD event. Although large sex differences in incidence and risk profiles (such as smoking) of CHD are well known, most previous studies on lipid variables as predictors of CHD (8–15,17,18) did not separately analyze men and women with diabetes. Our previous investigation to clarify risk factors (involving nonlipid parameters) for cardiovascular complications in Japanese diabetic subjects, which also analyzed men and women together, demonstrated that the serum TG level was a potent risk factor, unlike findings for Western diabetic subjects (23). Our current results further clarified that this effect of TGs was exclusively derived from its effect in women (23).

In our Japanese men with diabetes, non-HDLc and TC/HDLC, which are calculated from TC and HDLC, were the two best predictors of CHD and were superior to LDLc. These results confirmed the validity in Japanese diabetic men of the previously reported superiority of non-HDLc (9–11,13) or TC/HDLC (or non-HDLc/HDLC) (9,10,12,17,18) over LDLc as CHD predictors among Western diabetic populations. Also supported is that lipoproteins other than LDL, such as VLDL and chylomicron remnants, provide predictive power in addition to that of LDLc and could

Table 1—Patient characteristics at baseline

| | Men | | | Women | | |
|---|----------------------|---------------------|-----------|----------------------|---------------------|------------|
| | No-CHD | CHD | P | No-CHD | CHD | P |
| n | 870 | 70 | | 786 | 45 | |
| Age (years) | 57.9 ± 7.1 | 60.0 ± 6.3 | 0.027 | 58.8 ± 6.8 | 59.9 ± 6.7 | 0.28 |
| Diabetes duration (years) | 11.4 ± 7.6 | 12.2 ± 7.7 | 0.35 | 10.2 ± 6.6 | 11.2 ± 4.9 | 0.053 |
| BMI (kg/m ²) | 22.8 ± 2.7 | 22.7 ± 2.4 | 0.90 | 23.2 ± 3.4 | 24.2 ± 3.1 | 0.060 |
| Blood pressure (mmHg) | 131 ± 16/ 77 ± 10 | 134 ± 16/ 79 ± 9 | 0.40/0.19 | 132 ± 17/ 76 ± 10 | 139 ± 15/ 78 ± 8 | 0.004/0.16 |
| Fasting plasma glucose (mmol/L) | 8.5 ± 2.6 | 8.4 ± 3.4 | 0.33 | 8.6 ± 2.8 | 9.2 ± 3.1 | 0.23 |
| HbA _{1c} (%) | 7.7 ± 1.2 | 8.0 ± 1.5 | 0.17 | 8.1 ± 1.4 | 8.2 ± 1.3 | 0.36 |
| Serum lipid variables | | | | | | |
| TC (mmol/L) | 5.00 ± 0.89 | 5.37 ± 0.77 | <0.001 | 5.38 ± 0.86 | 5.81 ± 0.93 | 0.004 |
| HDLC (mmol/L) | 1.36 ± 0.42 | 1.25 ± 0.38 | 0.008 | 1.49 ± 0.46 | 1.43 ± 0.49 | 0.29 |
| TGs (mmol/L)* | 1.19 (0.82) | 1.35 (0.91) | 0.076 | 1.10 (0.81) | 1.45 (0.51) | <0.001 |
| LDLC (mmol/L) | 2.99 ± 0.84 | 3.40 ± 0.81 | <0.001 | 3.31 ± 0.79 | 3.64 ± 0.79 | 0.014 |
| Non-HDLC (mmol/L) | 3.64 ± 0.92 | 4.12 ± 0.85 | <0.001 | 3.88 ± 0.89 | 4.39 ± 0.97 | 0.002 |
| TC/HDLC ratio | 3.97 ± 1.30 | 4.63 ± 1.36 | <0.001 | 3.89 ± 1.19 | 4.49 ± 1.59 | 0.023 |
| LDLC/HDLC ratio | 2.41 ± 1.07 | 2.96 ± 1.07 | <0.001 | 2.43 ± 0.95 | 2.91 ± 1.34 | 0.056 |
| Therapeutic measures | | | | | | |
| Diabetes | | | | | | |
| Diet only (%) | 21 | 17 | 0.54 | 16 | 9 | 0.29 |
| Insulin (%) | 20 | 23 | 0.65 | 23 | 33 | 0.15 |
| Sulfonylureas (%) | 55 | 61 | 0.32 | 60 | 60 | 1.00 |
| α-Glucosidase inhibitors (%) | 21 | 21 | 0.88 | 20 | 20 | 1.00 |
| Biguanides (%) | 6 | 2 | 0.72 | 5 | 4 | 1.00 |
| Insulin sensitizer (%) | 2 | 1 | 1.00 | 2 | 9 | 0.014 |
| Others | | | | | | |
| Antihypertensive agents (%) | 21 | 21 | 0.88 | 30 | 58 | <0.001 |
| Agents for dyslipidemia (%) | 14 | 16 | 0.72 | 34 | 53 | 0.010 |
| Diet | | | | | | |
| Energy intake (kJ/day)* | 1,776 (567) | 1,703 (508) | 0.82 | 1,597 (491) | 1,568 (394) | 0.94 |
| Fat intake (g/day)* | 53 (22) | 53 (17) | 0.45 | 50 (21) | 49 (16) | 0.94 |
| Exercise (kJ/day)* | 140 (302) | 145 (264) | 0.73 | 118 (229) | 95 (254) | 0.35 |
| Current/past smoker (%) | 44/39 | 54/36 | 0.20 | 9/6 | 7/5 | 1.00 |
| Alcohol intake: never, three drinks or less, more than three drinks (%)** | 40/48/12 | 45/46/9 | 0.61 | 87/13/0 | 87/13/0 | 1.00 |

Data are mean ± SD or *median (interquartile range). **One drink is equivalent to 12.6 g of ethanol based on the U.S. Department of Agriculture definition.

explain part of the residual cardiovascular risk characterized by the LDL-C level alone (3,4). It also has been suggested that non-HDLC is superior as a predictor to LDL-C because non-HDLC is an indirect estimate of LDL particle number, and LDL particle number relates more closely to risk than LDL-C (6). Although studies have attempted to determine whether non-HDLC or TC/HDLC best identifies patients at greater risk of CHD, the statistical differences between the two were relatively small (10,12). For example, in the UK Prospective Diabetes Study (12), although TC/HDLC was a significantly stronger predictor of CHD than non-HDLC, HRs per one SD increment for those two variables were very close (1.36 and 1.35, respectively), and differences in results of ROC analysis were not

clinically important, which was supported by the results of another study (10).

Although our results for men were quite close to those in Western studies that analyzed men and women together, our findings in female subjects differed from those findings or results in Japanese men with diabetes. Among our female subjects, TGs, TC, and non-HDLC were the best predictors of CHD risk as assessed by HRs for one SD increment, χ^2 statistics, or AUCs. However, tertile analysis indicated that TGs were the best variable examined, and that it was a significant predictor beginning at values as low as 0.90 mmol/L. That value was lower than reported in Western countries (14,17) but was close to the optimal upper limit in the newest U.S. guidelines (4).

Although the role of TGs in CHD is known to be influenced by ethnicity,

especially in Asians (26), the specific reasons why TGs were a leading predictor of CHD in Japanese diabetic women but not in men have yet to be clarified. However, our results in women are similar to those in other studies of East Asian diabetic subjects (27–29), which showed that TGs had stronger associations with cardiovascular morbidity (27,29) and mortality (28) than LDL-C, although these studies were either cross-sectional (27,29) or relatively small-scale and short-term (28). In particular, a cross-sectional study in Hong Kong (27) revealed that TGs were strongly associated with ischemic heart disease in women but not in men with type 2 diabetes. A meta-analysis of cohort studies in Asian-Pacific general populations also revealed that TGs were the best predictor of CHD death among single lipid variables, although

Table 2—Multivariate-adjusted HRs per one SD increment with 95% CI, χ^2 (likelihood ratio test) statistics, and the AUC

| | Men | | | Women | | |
|-----------------------|---------------------|--------------------|------------------------|---------------------|--------------------|------------------------|
| | HR (95% CI) | χ^2 (P value) | AUC (95% CI) | HR (95% CI) | χ^2 (P value) | AUC (95% CI) |
| TC | 1.57 (1.25–1.99) | 13.4 (<0.001) | 0.697 (0.636–0.758) | 1.58 (1.20–2.06) | 9.6 (0.002) | 0.721 (0.644–0.798) |
| LDLC | 1.59 (1.28–1.98) | 14.8 (<0.001) | 0.694 (0.629–0.758) | 1.41 (1.06–1.86) | 5.3 (0.021) | 0.705 (0.626–0.784) |
| HDLC | 1.47 (1.09–1.98) | 6.9 (0.009) | 0.669 (0.604–0.734) | 1.03 (0.72–1.48) | 0.03 (0.85) | 0.667 (0.577–0.756) |
| TGs (log-transformed) | 1.42 (1.08–1.85) | 6.4 (0.011) | 0.664 (0.595–0.733) | 1.72 (1.21–2.43) | 9.2 (0.002) | 0.708 (0.630–0.786) |
| Non-HDLC | 1.78 (1.43–2.21) | 22.0 (<0.001) | 0.726 (0.664–0.787) | 1.60 (1.21–2.12) | 9.7 (0.002) | 0.715 (0.634–0.796) |
| TC/HDLC ratio | 1.63 (1.36–1.95) | 19.7 (<0.001) | 0.718 (0.656–0.780) | 1.48 (1.11–1.95) | 6.8 (0.009) | 0.696 (0.609–0.782) |
| LDLC/HDLC ratio | 1.52 (1.29–1.79) | 16.1 (<0.001) | 0.709 (0.646–0.772) | 1.44 (1.09–1.91) | 6.2 (0.013) | 0.695 (0.608–0.781) |
| TG/HDLC ratio | 1.49 (1.20–1.85) | 10.4 (0.001) | 0.680 (0.615–0.746) | 1.36 (1.01–1.85) | 3.4 (0.066) | 0.683 (0.597–0.769) |

Each lipid variable for CHD events at baseline adjusted by age, diabetes duration, BMI, systolic blood pressure, HbA_{1c}, smoking, and alcohol intake.

men and women were not separately analyzed (30). Interestingly, in our female subjects, TC was a better predictor than LDLC by all four analytical methods, suggesting that TLRs involving remnant or small, dense LDL strongly affect the etiology of CHD in this population.

It is well known that the serum level of TGs, which is closely associated with insulin resistance, is influenced by a number of metabolic factors, typically including glycemic and weight status. Insulin

resistance is believed to contribute to the atherogenic dyslipidemia seen in diabetes by increasing the hepatic secretion of VLDL and other apoB-containing lipoprotein particles as a result of increased free fatty acid flux to the liver (31). This raises the long-standing debate as to whether the association of the TG level to CHD is a direct effect of the TRLs themselves or is a biomarker of accompanying disorders (32). Our results in stratified, multivariate-adjusted analysis suggested

that at least the serum level of TGs is a significant and independent predictor in women whose HbA_{1c} or BMI was equal to or above the median. Although the precise mechanisms of these phenomena cannot be derived from epidemiological observations, improving glycemic and weight status could be beneficial to avoid the harmful influence of hypertriglyceridemia. Conversely, HDLC was not a significant predictor of CHD in women although it was moderately predictive in

Table 3—HRs with 95% CIs for each lipid variable according to tertiles

| | Men | | | Women | | |
|-------------------|-----------|------------------|---------|-----------|-------------------|-------|
| | Ranges | HR (95% CI) | P | Ranges | HR (95% CI) | P |
| TC (mmol/L) | 4.63–5.40 | 1.81 (0.95–3.44) | 0.069 | 5.02–5.69 | 1.23 (0.45–3.38) | 0.687 |
| | 5.41– | 2.98 (1.61–5.51) | 0.001 | 5.70– | 2.23 (0.90–5.56) | 0.084 |
| LDLC (mmol/L) | 2.66–3.33 | 1.81 (0.93–3.52) | 0.081 | 2.97–3.62 | 2.31 (0.82–6.54) | 0.114 |
| | 3.34– | 3.45 (1.83–6.48) | 0.0001 | 3.63– | 3.02 (1.12–8.12) | 0.029 |
| HDLC (mmol/L) | 1.14–1.40 | 1.74 (0.82–3.67) | 0.147 | 1.27–1.55 | 0.83 (0.38–1.84) | 0.652 |
| | –1.13 | 2.48 (1.23–5.00) | 0.011 | –1.26 | 1.31 (0.61–2.79) | 0.487 |
| TGs (mmol/L) | 0.94–1.48 | 1.09 (0.55–2.13) | 0.810 | 0.90–1.36 | 3.35 (1.21–9.23) | 0.020 |
| | 1.49– | 2.01 (1.07–3.78) | 0.031 | 1.37– | 4.31 (1.53–12.16) | 0.006 |
| Non-HDLC (mmol/L) | 3.25–3.98 | 1.42 (0.70–2.86) | 0.328 | 3.49–4.19 | 1.14 (0.44–2.94) | 0.791 |
| | 3.99– | 3.67 (1.97–6.83) | <0.0001 | 4.20– | 2.02 (0.84–4.86) | 0.118 |
| TC/HDLC ratio | 3.4–4.3 | 1.95 (0.91–4.19) | 0.088 | 3.3–4.2 | 1.17 (0.50–2.73) | 0.724 |
| | 4.4– | 4.13 (2.05–8.33) | <0.0001 | 4.3– | 1.50 (0.67–3.35) | 0.329 |
| LDLC/HDLC ratio | 1.9–2.7 | 1.66 (0.78–3.53) | 0.185 | 2.0–2.7 | 1.11 (0.48–2.58) | 0.810 |
| | 2.8– | 4.11 (2.09–8.08) | <0.0001 | 2.8– | 1.57 (0.71–3.48) | 0.265 |
| TG/HDLC ratio | 0.70–1.26 | 1.38 (0.66–2.90) | 0.399 | 0.56–1.05 | 2.60 (1.04–6.46) | 0.041 |
| | 1.27– | 2.86 (1.44–5.69) | 0.003 | 1.06– | 3.27 (1.30–8.25) | 0.012 |

HRs with 95% CIs for each lipid variable according to tertiles (HRs for the lowest tertile as a reference are shown except for HDLC where the top tertile is the reference) for CHD risk analyzed by Cox multivariate models adjusted by age, sex, diabetes duration, BMI, HbA_{1c}, systolic blood pressure, smoking status, and alcohol intake.

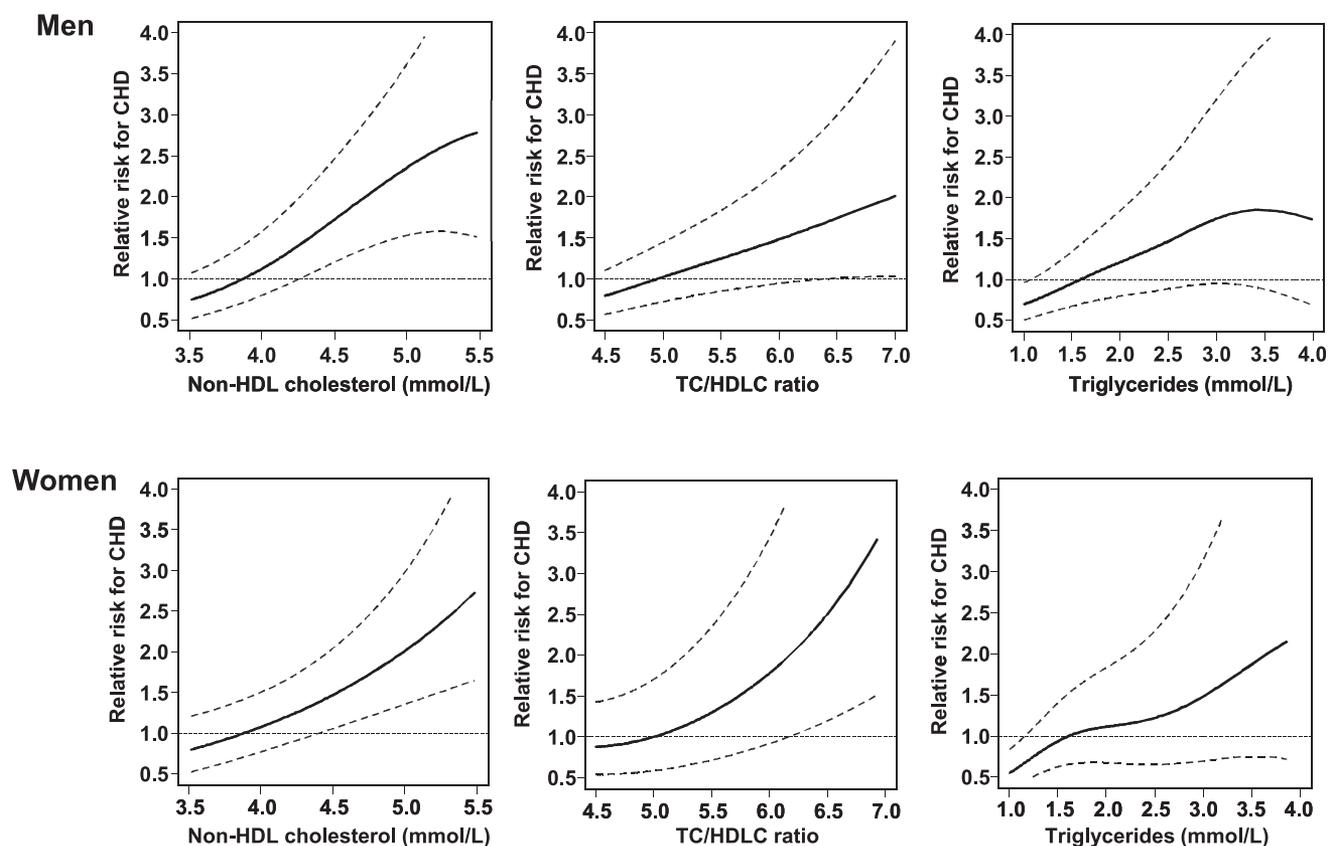


Figure 1—Relative risk (solid line) and 95% CIs (broken line) of the incidence of CHD in relation to non-HDL, TC/HDLC ratio, and TGs estimated by generalized additive models.

men. The serum level of HDLC is naturally higher in East Asians than in Western populations, especially women (33,34), as in our cohort. Therefore, it is possible that the clinical impact of low HDLC was not apparent and, instead, that of TGs was enhanced in East Asians. Accordingly, TG/HDLC did not add useful information to that provided by TGs alone either in men or women. TG/HDLC was also reportedly not superior to non-HDL in Spanish patients with type 2 diabetes (35).

This investigation has several strengths, including the nationwide sampling from nearly 60 institutes. We also used four different analytical methods and analyzed men and women separately, which was not done in past studies. Nevertheless, some limitations of our study deserve consideration. Variability in laboratory measurements could be present among participating hospitals (36). However, such an influence is virtually negligible because laboratory testing in Japan is well standardized. In fact, a nationwide precision control survey (37) demonstrated that coefficients of variation of tests of TC, HDLC, and TGs were <5%. Only baseline data were used

for this analysis; therefore, therapeutic management during the follow-up period could have influenced results. Baseline proportions of women receiving therapy with insulin sensitizers or agents for hypertension or dyslipidemia were higher in the CHD group than in the no-CHD group, probably because of treatment selection bias. The large difference in the proportion of subjects taking agents for dyslipidemia (mainly statins) between men and women also might have influenced the results.

That we did not measure apolipoproteins in this study was another limitation. Although some studies of subjects with (14,15) and without (38,39) diabetes have provided relatively small support for replacement of conventional variables with measurements of apolipoproteins, recent meta-analysis (7) demonstrated that the use of apoB, a measure of the number of atherogenic lipid particles, could be more beneficial to prevent cardiovascular events than that of non-HDL in clinical settings because there might be substantial discordance between apoB and non-HDL levels depending on

individual differences in composition of the apoB lipoproteins. In addition, apoB is a better predictor of cardiovascular risk especially when cholesterol-enriched remnants or cholesterol-enriched LDL is present; therefore, apoB is not necessarily interchangeable with non-HDL for evaluation of individual patients in clinical settings (40). Finally, in this analysis, we did not use detailed dietary data, including data on saturated fat, carbohydrates, and the ratio of energy requirements to ingested calories, which could influence serum lipid profiles. This should be clarified in a future study.

In conclusion, the present analysis shows that for Japanese subjects with diabetes, non-HDL and TC/HDLC for men and TGs for women were the best predictors of CHD. These findings should be considered in the clinical approach to risk reduction among East Asians with diabetes, and using these variables as management markers for dyslipidemia among this population has potential value.

Acknowledgments—This study was supported by grants from the Ministry of Health,

Labor, and Welfare. The funder had no role in the design and conduct of the study.

No potential conflicts of interest relevant to this article were reported.

H.So., Sa.T., Sh.T., S.Ii., S.Is., S.O., H.Sh., S.K., Y.O., Y.A., and N.Y. researched data, contributed to the discussion, and wrote and edited the manuscript. H.So. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

The authors thank all the patients, staff, and diabetologists all over Japan for their long-standing collaboration in this study. The authors also thank Satomi Fukuya and Yasuko Maruyama (University of Tsukuba) for their excellent secretarial assistance.

References

- Mazzone T, Chait A, Plutzky J. Cardiovascular disease risk in type 2 diabetes mellitus: insights from mechanistic studies. *Lancet* 2008;371:1800–1809
- Mooradian AD. Dyslipidemia in type 2 diabetes mellitus. *Nat Clin Pract Endocrinol Metab* 2009;5:150–159
- Arsenault BJ, Boekholdt SM, Kastelein JJ. Lipid parameters for measuring risk of cardiovascular disease. *Nat Rev Cardiol* 2011;8:197–206
- Miller M, Stone NJ, Ballantyne C, et al.; American Heart Association Clinical Lipidology, Thrombosis, and Prevention Committee of the Council on Nutrition, Physical Activity, and Metabolism; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular Nursing; Council on the Kidney in Cardiovascular Disease. Triglycerides and cardiovascular disease: a scientific statement from the American Heart Association. *Circulation* 2011;123:2292–2333
- Ramjee V, Sperling LS, Jacobson TA. Non-high-density lipoprotein cholesterol versus apolipoprotein B in cardiovascular risk stratification: do the math. *J Am Coll Cardiol* 2011;58:457–463
- Sniderman A, McQueen M, Contois J, Williams K, Furberg CD. Why is non-high-density lipoprotein cholesterol a better marker of the risk of vascular disease than low-density lipoprotein cholesterol? *J Clin Lipidol* 2010;4:152–155
- Sniderman AD, Williams K, Contois JH, et al. A meta-analysis of low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, and apolipoprotein B as markers of cardiovascular risk. *Circ Cardiovasc Qual Outcomes* 2011;4:337–345
- Bos G, Dekker JM, Nijpels G, et al.; Hoorn Study. A combination of high concentrations of serum triglyceride and non-high-density-lipoprotein-cholesterol is a risk factor for cardiovascular disease in subjects with abnormal glucose metabolism—the Hoorn Study. *Diabetologia* 2003;46:910–916
- Lu W, Resnick HE, Jablonski KA, et al. Non-HDL cholesterol as a predictor of cardiovascular disease in type 2 diabetes: the strong heart study. *Diabetes Care* 2003;26:16–23
- Jiang R, Schulze MB, Li T, et al. Non-HDL cholesterol and apolipoprotein B predict cardiovascular disease events among men with type 2 diabetes. *Diabetes Care* 2004;27:1991–1997
- Schulze MB, Shai I, Manson JE, et al. Joint role of non-HDL cholesterol and glycated haemoglobin in predicting future coronary heart disease events among women with type 2 diabetes. *Diabetologia* 2004;47:2129–2136
- Holman RR, Coleman RL, Shine BS, Stevens RJ. Non-HDL cholesterol is less informative than the total-to-HDL cholesterol ratio in predicting cardiovascular risk in type 2 diabetes. *Diabetes Care* 2005;28:1796–1797
- Liu J, Sempos C, Donahue RP, Dorn J, Trevisan M, Grundy SM. Joint distribution of non-HDL and LDL cholesterol and coronary heart disease risk prediction among individuals with and without diabetes. *Diabetes Care* 2005;28:1916–1921
- Bruno G, Merletti F, Biggeri A, et al. Effect of age on the association of non-high-density-lipoprotein cholesterol and apolipoprotein B with cardiovascular mortality in a Mediterranean population with type 2 diabetes: the Casale Monferrato Study. *Diabetologia* 2006;49:937–944
- Charlton-Menys V, Betteridge DJ, Colhoun H, et al. Apolipoproteins, cardiovascular risk and statin response in type 2 diabetes: the Collaborative Atorvastatin Diabetes Study (CARDS). *Diabetologia* 2009;52:218–225
- van Hateren KJ, Landman GW, Kleefstra N, et al. The lipid profile and mortality risk in elderly type 2 diabetic patients: a ten-year follow-up study (ZODIAC-13). *PLoS ONE* 2009;4:e8464
- Taskinen MR, Barter PJ, Ehnholm C, et al.; FIELD study investigators. Ability of traditional lipid ratios and apolipoprotein ratios to predict cardiovascular risk in people with type 2 diabetes. *Diabetologia* 2010;53:1846–1855
- Eliasson B, Cederholm J, Eeg-Olofsson K, Svensson A-M, Zethelius B, Gudbjörnsdóttir S; National Diabetes Register. Clinical usefulness of different lipid measures for prediction of coronary heart disease in type 2 diabetes: a report from the Swedish National Diabetes Register. *Diabetes Care* 2011;34:2095–2100
- Tohidi M, Hatami M, Hadaegh F, Safarkhani M, Harati H, Azizi F. Lipid measures for prediction of incident cardiovascular disease in diabetic and non-diabetic adults: results of the 8.6 years follow-up of a population based cohort study. *Lipids Health Dis* 2010;9:6
- Lee ET, Keen H, Bennett PH, Fuller JH, Lu M. Follow-up of the WHO multinational study of vascular disease in diabetes: general description and morbidity. *Diabetologia* 2001;44(Suppl. 2):S3–S13
- Sone H, Ito H, Ohashi Y, Akanuma Y, Yamada N; Japan Diabetes Complication Study Group. Obesity and type 2 diabetes in Japanese patients. *Lancet* 2003;361:85
- Chan JC, Malik V, Jia W, et al. Diabetes in Asia: epidemiology, risk factors, and pathophysiology. *JAMA* 2009;301:2129–2140
- Sone H, Tanaka S, Tanaka S, et al.; Japan Diabetes Complications Study Group. Serum level of triglycerides is a potent risk factor comparable to LDL cholesterol for coronary heart disease in Japanese patients with type 2 diabetes: subanalysis of the Japan Diabetes Complications Study (JDCS). *J Clin Endocrinol Metab* 2011;96:3448–3456
- Takahashi K, Yoshimura Y, Kaimoto T, Kunii D, Komatsu T, Yamamoto S. Validation of a food frequency questionnaire based on food groups for estimating individual nutrient intake. *Jpn J Nutr* 2001;59:221–232 [in Japanese]
- Saito K, Sone H, Kawai K, et al. Risk imparted by various parameters of smoking in Japanese men with type 2 diabetes on their development of microalbuminuria: analysis from the Tsukuba Kawai Diabetes Registry. *Diabetes Care* 2007;30:1286–1288
- Godsland IF, Johnston DG, Chaturvedi N. Mechanisms of disease: lessons from ethnicity in the role of triglyceride metabolism in ischemic heart disease. *Nat Clin Pract Endocrinol Metab* 2007;3:530–538
- Ko GT, Chan JC, Chow CC, et al. Triglyceride, albuminuria and blood pressure are the major associations of non-fatal cardiovascular disease in Chinese type 2 diabetes. *Acta Diabetol* 2003;40:80–84
- Chan WB, Tong PC, Chow CC, et al. Triglyceride predicts cardiovascular mortality and its relationship with glycaemia and obesity in Chinese type 2 diabetic patients. *Diabetes Metab Res Rev* 2005;21:183–188
- Tseng CH, Tseng CP, Chong CK, Cheng JC, Tai TY. Independent association between triglycerides and coronary artery disease in Taiwanese type 2 diabetic patients. *Int J Cardiol* 2006;111:80–85
- Barzi F, Patel A, Woodward M, et al.; Asia Pacific Cohort Studies Collaboration. A comparison of lipid variables as predictors of cardiovascular disease in the Asia Pacific region. *Ann Epidemiol* 2005;15:405–413
- Bitzur R, Cohen H, Kamari Y, Shaish A, Harats D. Triglycerides and HDL cholesterol: stars or second leads in diabetes? *Diabetes Care* 2009;32(Suppl. 2):S373–S377
- Goldberg IJ, Eckel RH, McPherson R. Triglycerides and heart disease: still a

- hypothesis? *Arterioscler Thromb Vasc Biol* 2011;31:1716–1725
33. Zhang L, Qiao Q, Tuomilehto J, et al. Blood lipid levels in relation to glucose status in seven populations of Asian origin without a prior history of diabetes: the DECODA study. *Diabetes Metab Res Rev* 2009;25:549–557
 34. Zhang L, Qiao Q, Tuomilehto J, et al.; DECODE Study Group. Blood lipid levels in relation to glucose status in European men and women without a prior history of diabetes: the DECODE study. *Diabetes Res Clin Pract* 2008;82:364–377
 35. Wagner AM, Perez A, Sanchez-Quesada JL, Ordonez-Llanos J. Triglyceride-to-HDL cholesterol ratio in the dyslipidemic classification of type 2 diabetes. *Diabetes Care* 2005;28:1798–1800
 36. Contois JH, Warnick GR, Sniderman AD. Reliability of low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, and apolipoprotein B measurement. *J Clin Lipidol* 2011;5:264–272
 37. Japan Medical Association. Report of nationwide quality control survey of laboratory tests 1997 [in Japanese]. Japan Medical Association, Tokyo, Japan
 38. Ingelsson E, Schaefer EJ, Contois JH, et al. Clinical utility of different lipid measures for prediction of coronary heart disease in men and women. *JAMA* 2007;298:776–785
 39. Ridker PM, Rifai N, Cook NR, Bradwin G, Buring JE. Non-HDL cholesterol, apolipoproteins A-I and B100, standard lipid measures, lipid ratios, and CRP as risk factors for cardiovascular disease in women. *JAMA* 2005;294:326–333
 40. Sniderman AD, Williams K, McQueen MJ, Furberg CD. When is equal not equal? *J Clin Lipidol* 2010;4:83–88