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/m^2, 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} ≥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 ≥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 ~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/m^2, 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} ≥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 ≥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 ~4.3 mmol/L (170 mg/dL) became significant with HRs of ~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 ~6.3 became significant in both men and women but the HR was greater in women (~2.0) than in men (~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 LDLC 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 LDLC, 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.

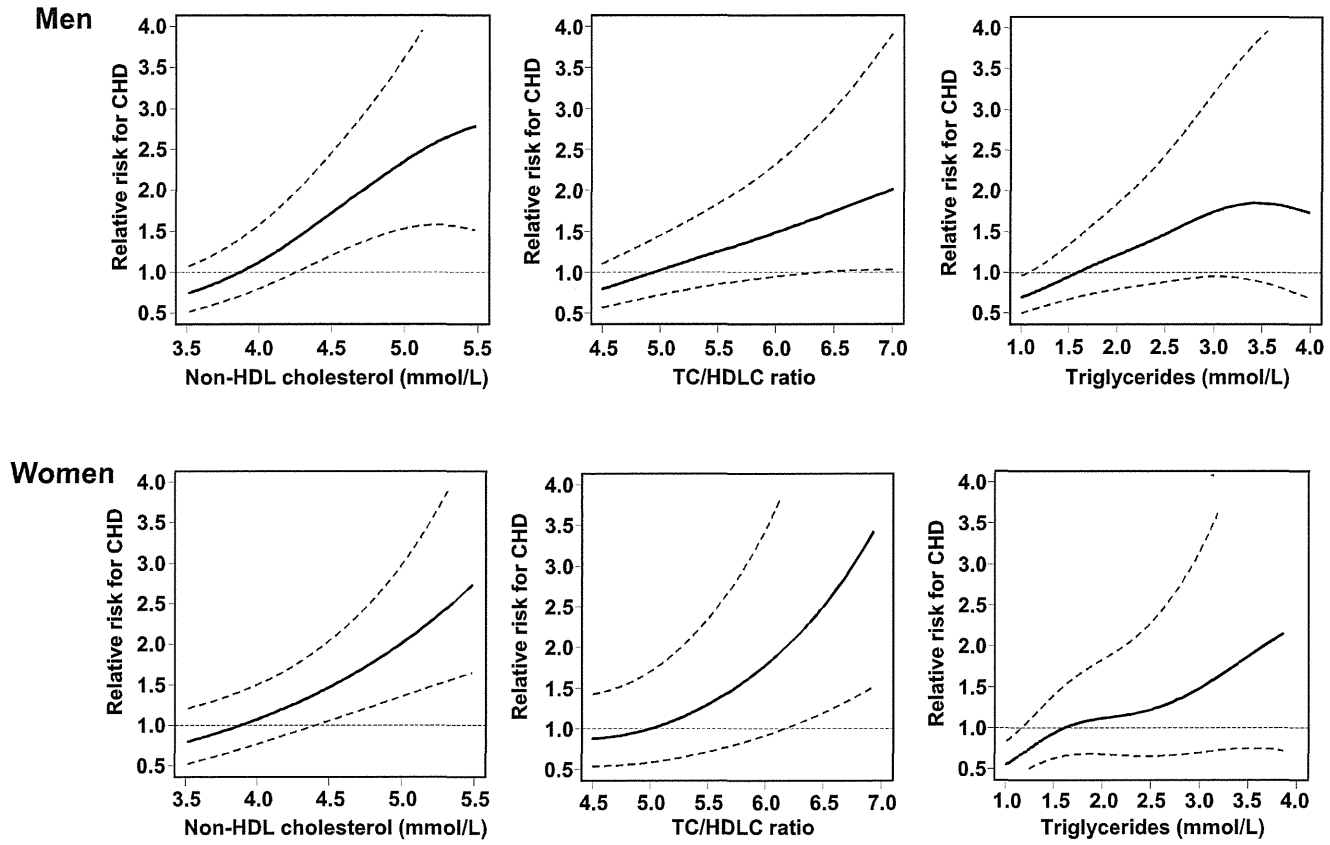

Figure 1—*Relative risk (solid line) and 95% CIs (broken line) of the incidence of CHD in relation to non-HDLC, TC/HDLC ratio, and TGs estimated by generalized additive models.*

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-HDLC 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-HDLC in clinical settings because there might be substantial discordance between apoB and non-HDLC 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-HDLC 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-HDLC 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.

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References

1. Mazzone T, Chait A, Plutzky J. Cardiovascular disease risk in type 2 diabetes mellitus: insights from mechanistic studies. Lancet 2008;371:1800–1809
2. Mooradian AD. Dyslipidemia in type 2 diabetes mellitus. Nat Clin Pract Endocrinol Metab 2009;5:150–159
3. Arsenault BJ, Boekholdt SM, Kastelein JJ. Lipid parameters for measuring risk of cardiovascular disease. Nat Rev Cardiol 2011;8:197–206
4. 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
5. 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
6. 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
7. 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
8. 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
9. 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
10. 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
11. 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
12. 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
13. 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
14. 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
15. 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
16. 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
17. 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
18. Eliasson B, Cederholm J, Eeg-Olofsson K, Svensson A-M, Zethelius B, Gudbjörnsdottir 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
19. 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
20. 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
21. 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
22. Chan JC, Malik V, Jia W, et al. Diabetes in Asia: epidemiology, risk factors, and pathophysiology. JAMA 2009;301:2129–2140
23. 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
24. Takahashi K, Yoshimura Y, Kaimoto T, Kunii D, Komatsu T, Yamamoto S. Validation of a food frequency questionnaire based on food groups for estimationg individual nutrient intake. Jpn J Nutr 2001;59:221–232 [in Japanese]
25. 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
26. 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
27. 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
28. 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
29. 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
30. 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
31. 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
32. 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. Wägner AM, Pérez A, Sánchez-Quesada JL, Ordóñez-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

Original Article

Carotid Artery Plaque and LDL-to-HDL Cholesterol Ratio Predict Atherosclerotic Status in Coronary Arteries in Asymptomatic Patients with Type 2 Diabetes Mellitus

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Aims: To investigate the clinical predictors of coronary atherosclerosis and to assess the utility of maximum-IMT for predicting coronary atherosclerosis in asymptomatic type 2 diabetic patients.
Methods: One hundred one Japanese patients with type 2 diabetes underwent computed tomography coronary angiography. Definitions of coronary artery stenosis and vulnerable coronary plaque were luminal narrowing of ≥50% and any coronary plaque with positive vessel remodeling and low attenuation, respectively. Carotid intima-media thickness (IMT) was assessed using B-mode ultrasound.
Results: Of the 101 patients, 40 had coronary artery stenosis without vulnerable coronary plaque, 7 had vulnerable coronary plaque without coronary artery stenosis, and 23 had coronary artery stenosis with vulnerable coronary plaque. Male sex ($p=0.031$), duration of diabetes ($p=0.024$), systolic blood pressure (SBP) ($p=0.039$), and the LDL/HDL ratio (LDL/HDL) ($p=0.013$) were independent predictors of coronary artery stenosis and the LDL/HDL ($p=0.042$) independently predicted vulnerable coronary plaque by logistic regression analyses. Areas under the curves in receiver operating characteristic curve analysis of the maximum-IMT, LDL/HDL, and these two parameters combined were 0.711 (95% CI 0.601-0.820), 0.618 (0.508-0.728), and 0.732 (0.632-0.831), respectively, for predicting coronary artery stenosis and 0.655 (0.537-0.773), 0.629 (0.504-0.754), and 0.710 (0.601-0.818), respectively, for predicting vulnerable coronary plaque.
Conclusions: Male sex, duration of diabetes, elevated SBP, and LDL/HDL were independent predictors of coronary artery stenosis. LDL/HDL was an independent predictor of vulnerable coronary plaque. Maximum-IMT predicted both coronary stenosis and vulnerable coronary plaque. Adding LDL/HDL improved the prediction of coronary artery stenosis and vulnerable coronary plaque.

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Key words; Coronary plaque, LDL-to-HDL cholesterol ratio, Computed tomography coronary angiography, Maximum carotid intima-media thickness

Introduction

Coronary artery disease (CAD) is a major cause of morbidity and mortality in patients with type 2 diabetes[1]. Although comprehensive and intensive management of multiple cardiovascular risk factors in type 2 diabetic patients is recommended to reduce the risk of cardiovascular events[2, 3], a considerable number of patients still develop CAD even under intensive management.

Acute coronary syndrome (ACS) is caused by disruption of an atherosclerotic plaque in two-thirds of those who experience it[4]. The characteristics of the

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culprit plaque responsible for ACS, designated as vulnerable coronary plaque, are large lipid cores, a thin fibrous cap, and positive vascular remodeling. Moreover, most lesions are not associated with significant coronary luminal stenosis before the event[5, 6]. Studies of asymptomatic type 2 diabetic patients revealed that silent myocardial ischemia existed irrespective of the number of traditional cardiovascular risk factors and was a cause of future cardiac events[7-10].

Coronary computed tomography angiography (CCTA) was proposed as an alternative imaging modality to evaluate patients with known or suspected CAD[6, 11]. CCTA accurately identifies the presence of obstructive CAD and can evaluate the composition of coronary plaque[6, 12-14]. Compared with intravascular ultrasound, 64-slice CCTA is equally able to detect and evaluate coronary atherosclerotic plaque[15]. The characteristics of culprit lesions in ACS, as shown by CCTA, are positive vessel remodeling and low-attenuation plaque[6]. Moreover, patients having plaque with these characteristics were shown to be at higher risk for development of ACS over time than patients without such plaque characteristics[6]. The application of CCTA has been limited to patients at high CAD risk because of exposure to contrast media and radiation. Screening for CAD using CCTA is controversial in asymptomatic type 2 diabetic patients[2]; however, identifying the clinical predictors of vulnerable coronary plaque and coronary artery stenosis is important for appropriate management of these patients.

Carotid ultrasonography is useful to assess the extent of systemic atherosclerosis[16-18]. Increased carotid intima-media thickness (IMT), maximum-IMT in particular, is a strong predictor of future myocardial infarction[16]. Complex carotid plaque characterized by low echoicity, an irregular surface, and/or ulceration is also associated with future cardiovascular events[19, 20]. Although carotid IMT is a good predictor of future myocardial infarction[16] and the presence of coronary artery stenosis[21], the usefulness of maximum-IMT for predicting CAD is unclear in high risk but asymptomatic type 2 diabetic patients, because the participants in a previous study were limited to the patients at high risk of coronary heart disease or had previously diagnosed coronary heart disease[21]. Moreover, maximum-IMT has high sensitivity but low specificity for the detection of coronary artery stenosis in asymptomatic patients with type 2 diabetes[22, 23]. This would cause an overestimation of coronary artery stenosis; therefore, it is important to examine the predictability of maximum-IMT for CAD and examine whether the addition of other markers, such as the LDL-cholesterol (LDL-C)/HDL-cholesterol (HDL-C) ratio, which is one of the most important variables related to coronary atherosclerosis[24], to carotid IMT could improve the prediction of CAD.

Aim

To investigate the clinical predictors of coronary atherosclerosis and to assess the utility of maximum-IMT for predicting coronary atherosclerosis in asymptomatic type 2 diabetic patients.

Methods

Subjects

We retrospectively analyzed data on patients with type 2 diabetes who underwent CCTA at University of Tsukuba Hospital from April 2009 to March 2011. Because of complications associated with CCTA, such as renal failure, allergy, and radiation-related issues, we reserve its use for those patients at high risk for CAD in whom the risk/benefit ratio indicates its use. Reasons for performing CCTA were maximum-IMT ≥ 1.1 mm, ischemic change on electrocardiogram (ECG), positive exercise ECG test results, or left ventricular wall motion abnormality on echocardiography. In most healthy individuals, the maximum-IMT was reported not to exceed 1.1 mm in Japan[25]. ECG abnormalities such as Q waves, ST-T changes, or negative T waves, positive exercise ECG test results, and left ventricular wall motion abnormality on echocardiography suggest the presence of CAD. Exclusion criteria were chest symptoms, known CAD, type 1 diabetes mellitus, comorbid endocrine disorders, serum triglyceride (TG) level ≥ 400 mg/dL, and ventricular and supraventricular arrhythmias. All patients had undergone a structured interview, physical examination, and laboratory analysis. Hypertension was defined as systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg or current use of antihypertensive agents. Diabetic retinopathy was diagnosed by ophthalmologists. Urinary microalbumin excretion ≥ 30 mg/day indicated diabetic nephropathy. Glomerular filtration rate was estimated (eGFR) by an equation modified for the Japanese as previously described[26]. Diabetic neuropathy was defined by reduced bilateral ankle vibration sensation (<10 s) and/or reduced or absent bilateral Achilles tendon reflex and/or impairment of light touch; other causes of neuropathy were excluded. This study was approved by the institutional ethics committee and conducted according to the Helsinki Declaration.

Laboratory Analysis

Blood samples were collected the morning after an overnight fast. Plasma levels of glucose and serum levels of total cholesterol (TC), HDL-cholesterol (HDL-C), TG, and creatinine were determined by an automated analyzer (7700 clinical analyzer; Hitachi High-Technologies Corporation, Tokyo, Japan). Serum LDL-cholesterol (LDL-C) levels were calculated by the Friedewald equation when the plasma TG concentration did not exceed 400 mg/dL. HbA1c was measured by high-performance liquid chromatography (HLC-723G9; Tosoh Corporation, Tokyo, Japan). HbA1c values were converted from the Japanese Diabetes Society (JDS) values into National Glycohemoglobin Standardization Program (NGSP) equivalent values[27].

Assessment of CCTA

Coronary stenosis and vulnerable coronary plaque were assessed with a Philips Brilliance-64 scanner (Philips Medical Systems, Cleveland, OH, USA) with a 64×0.625-mm detector configuration. Scanning was performed at 120 kV and 600-1050 mA, 0.2 pitch, and with standard or sharp filters. 60 mL contrast agent (iopamidol 370 mg/mL; Schering AG, Berlin, Germany) was injected intravenously at a rate of 4 mL/s. When the signal density in the ascending aorta reached a predefined threshold of 100 Hounsfield units (HU), acquisition of CT data and an electrocardiogram trace were automatically started during a 7- to 9-s breath-hold. Patients whose heart rate was >70 beats/min were given oral metoprolol (20 mg) 1 h before the scan. Scans were analyzed using a Brilliance Workspace 3-D workstation (Philips Medical Systems). Each scan was analyzed independently by two experienced readers unaware of the patient's identity and clinical presentation. Luminal narrowing of 50% or more revealed by CCTA indicated coronary stenosis. Vulnerable coronary plaque was defined as positive vessel remodeling (remodeling index >1.10) and low-attenuation plaques (<50 HU) on CCTA[12, 28, 29]. Coronary artery lesions based on CCTA were categorized into four groups: 1) neither coronary artery stenosis nor vulnerable coronary plaque (stenosis [−]/vulnerability [−]); 2) coronary artery stenosis without vulnerable coronary plaque (stenosis [+]/vulnerability [−]); 3) vulnerable coronary plaque without coronary stenosis (stenosis [−]/vulnerability [+]); and 4) coronary artery stenosis with vulnerable coronary plaque (stenosis [+]/vulnerability [+]).

Assessment of Carotid Ultrasonography

B-mode examinations of the carotid arteries were performed by an ultrasound system with a 7.5/10-MHz linear-array transducer. Scanning of each common carotid artery (CCA) began just above the clavicle and then passed cephalically through the bifurcation as distally as possible. Carotid IMT was determined by the distance from the leading edge of the lumen-intima interface of the far wall to the leading edge of the media-adventitia interface of the near wall. Maximum-IMT was the greatest thickness measured on both sides of the CCA, bulbus and internal carotid artery, excluding the external carotid artery. Mean-IMT was measured for both CCAs, excluding the bulbus, and was defined as the average of 3 points that included the point of maximum-IMT and 2 points on either side (each point 1 cm distant from the point of maximum-IMT)[25]. The average mean-IMT for both sides was recorded. Carotid plaques were analyzed for their echogenic composition and surface characteristics and were considered to be complex carotid plaques if an irregular surface, a low echoic area, and/or ulceration were present[30].

Statistical Analysis

Categorical variables are expressed as numerals and percentages and were compared with the χ^2 test. Continuous variables are expressed as the mean ± SDs or median and interquartile range (IQR). Based on distribution, continuous variables were compared using unpaired Student's t test or the Mann-Whitney U test for two-group comparisons and ANOVA or Kruskal-Wallis tests for four-group comparisons. Logistic regression analyses identified variables related to coronary artery stenosis or vulnerable coronary plaque. Differences across tertiles of the maximum-IMT or the LDL/HDL ratio were analyzed with one-way ANOVA followed by the Bonferroni post hoc test. The ability of mean-IMT, maximum-IMT, LDL/HDL ratio, or a combination of those factors to predict coronary artery stenosis and vulnerable coronary plaque was examined by receiver operating characteristic (ROC) curve analyses. Area under the receiver operating characteristic curves (AUCs) and sensitivity, specificity, and positive and negative predictive values were calculated for detection of coronary artery stenosis and vulnerable coronary plaque. The effects of combinations of the maximum-IMT and LDL/HDL ratio for the presence of coronary plaque were assessed. All statistical analyses were performed by SPSS (version 15.0; Chicago, IL). Statistical significance was considered at $p<0.05$.

Table 1. Characteristics of study participants according to the combination of coronary artery stenosis and vulnerable coronary plaque

Coronary artery stenosis	(−)	(+)	(−)	(+)	*p* value
Vulnerable coronary plaque	(−)	(−)	(+)	(+)	
	n=31	*n*=40	*n*=7	*n*=23	
Age (years)	60±10	63±10	56±10	65±10	0.093
Male/female	12/19	30/10	5/2	16/7	0.012
BMI (kg/m^2)	25.9±6.0	26.1±5.4	27.7±3.6	26.0±4.4	0.870
Duration of diabetes (years)	7.0 (1.0-12.0)	8.5 (2.0-19.5)	9.0 (6.0-15.0)	12.0 (7.0-20.0)	0.081
Hypertension, n (%)	15 (48)	33 (83)	3 (43)	18 (78)	0.006
Systolic blood pressure (mmHg)	133±19	140±20	131±11	133±17	0.310
Diastolic blood pressure (mmHg)	77±11	80±10	76±8	73±13	0.090
Current smoking, n (%)	8 (26)	11 (28)	4 (57)	9 (39)	0.320
Family history of CAD, n (%)	5 (16)	8 (20)	2 (29)	6 (26)	0.784
Retinopathy, n (%)	5 (16)	20 (50)	2 (29)	10 (43)	0.025
Nephropathy, n (%)	10 (32)	20 (50)	2 (29)	8 (35)	0.378
Neuropathy, n (%)	15 (48)	23 (58)	2 (29)	15 (65)	0.311
HbA1c (%)	10.0±2.2	10.1±1.9	10.2±2.3	9.4±1.7	0.535
Fasting plasma glucose (mmol/L)	9.8±3.5	9.1±2.6	9.3±4.0	8.6±2.0	0.477
Total cholesterol (mmol/L)	5.04±1.13	4.89±1.13	4.73±0.97	5.21±1.54	0.724
LDL cholesterol (mmol/L)	2.98±0.77	3.00±0.96	2.84±0.93	3.39±1.33	0.367
HDL cholesterol (mmol/L)	1.37±0.57	1.19±0.40	1.11±0.13	1.05±0.23	0.054
LDL/HDL ratio	2.4±0.8	2.7±1.0	2.7±1.1	3.4±1.6	0.011
Triglycerides (mmol/L)	1.53±0.58	1.55±0.72	1.71±0.52	1.66±0.68	0.818
White cell count (×10^9/L)	6.0±1.8	7.1±2.2	7.3±1.7	7.0±1.8	0.143
eGFR (mL/min/1.73 m^2)	89±28	91±33	79±22	81±18	0.552
Medications, n (%)					
Insulin treatment	7 (23)	8 (20)	2 (29)	5 (22)	0.965
Sulfonylurea	18 (59)	19 (48)	3 (43)	12 (52)	0.800
Glinides	2 (6)	3 (8)	1 (14)	1 (4)	0.836
Metformin	11 (35)	14 (35)	4 (57)	11 (48)	0.547
Thiazolidinedione	2 (6)	6 (15)	1 (14)	4 (17)	0.630
α-Glucosidase inhibitor	7 (23)	5 (13)	3 (43)	8 (35)	0.117
Incretin-related therapies	4 (13)	7 (18)	0 (0)	1 (4)	0.330
Statin	8 (26)	12 (30)	4 (57)	12 (52)	0.111
Any antihypertensive agent	6 (19)	19 (48)	3 (43)	15 (65)	0.007
ACEI or ARB	6 (19)	17 (42)	3 (43)	13 (57)	0.041
Ca blocker	4 (13)	18 (45)	1 (14)	13 (57)	0.003
β blocker	1 (3)	4 (10)	0 (0)	2 (9)	0.598
Mean-IMT of common carotid artery (mm)	1.0 (0.8-1.3)	1.0 (0.9-1.2)	0.9 (0.8-0.9)	1.1 (0.9-1.4)	0.146
Maximum-IMT of carotid artery (mm)	1.6 (1.3-2.6)	2.4 (2.0-3.0)	2.3 (1.1-3.1)	2.6 (2.2-3.6)	0.001
Complex carotid plaque, n (%)	7 (22)	12 (30)	1 (14)	14 (61)	0.013

Data are the mean±SD or median (interquartile range). BMI, body mass index; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; hypertension, systolic blood pressure ≥140 and/or diastolic blood pressure ≥90 or treatment; LDL/HDL ratio, LDL-to-HDL cholesterol ratio; IMT, intima-media thickness; ACEI, angiotensin-converting-enzyme inhibitor; ARB: angiotensin II receptor blocker

Results

Characteristics of Subjects

Initially, 124 patients were enrolled; however, 18 patients were excluded because they had type 1 diabetes (*n*=3), known CAD (*n*=4), comorbid endocrine disorders (*n*=7), or hypertriglyceridemia (*n*=1), or were in a poor general condition (*n*=3). An additional 5 patients were excluded due to motion artifacts and/or clip artifacts, leaving 101 patients for analysis. Of the subject group, 97 had a maximum-IMT ≥1.1 mm, 31 had ischemic changes on the ECG, 24 had a

Table 2. Characteristics of study participants according to coronary artery stenosis or vulnerable coronary plaque

	all	Coronary artery stenosis		*p* value	Vulnerable coronary plaque		*p* value
		(−)	(+)		(−)	(+)	
	n=101	*n*=38	*n*=63		*n*=71	*n*=30	
Age (years)	62±10	59±10	64±10	0.032	61±10	63±11	0.417
Male/female	63/38	17/21	46/17	0.004	42/29	21/9	0.304
BMI (kg/m^2)	26.1±5.2	26.2±5.6	26.0±5.1	0.848	26.0±5.6	26.4±4.3	0.740
Duration of diabetes (years)	9.0 (2.5-15.0)	8.5 (1.8-12.3)	10.0 (4.0-20.0)	0.053	8.0 (2.0-13.0)	10.5 (6.8-20.0)	0.039
Hypertension, n (%)	69 (68)	18 (47)	51 (81)	<0.001	48 (68)	21 (70)	0.813
Systolic blood pressure (mmHg)	136±19	133±18	138±19	0.228	137±20	133±15	0.257
Diastolic blood pressure (mmHg)	77±11	77±10	77±12	0.772	78±10	73±12	0.029
Current smoking, n (%)	32 (32)	12 (32)	20 (32)	0.986	19 (27)	13 (43)	0.102
Family history of CAD, n (%)	21 (21)	7 (18)	14 (22)	0.648	13 (19)	8 (27)	0.344
Retinopathy, n (%)	37 (37)	7 (18)	30 (48)	0.003	25 (35)	12 (40)	0.648
Nephropathy, n (%)	40 (40)	12 (32)	28 (44)	0.200	30 (42)	10 (33)	0.402
Neuropathy, n (%)	55 (54)	17 (45)	38 (60)	0.128	38 (54)	17 (57)	0.772
HbA1c (%)	9.9±2.0	10.1±2.2	9.9±1.9	0.678	10.1±2.1	9.6±1.9	0.271
Fasting plasma glucose (mmol/L)	9.2±2.9	9.8±3.5	8.9±2.4	0.158	9.4±3.0	8.8±2.6	0.332
Total cholesterol (mmol/L)	5.00±1.21	4.99±1.10	5.00±1.29	0.937	4.96±1.12	5.10±1.43	0.611
LDL cholesterol (mmol/L)	3.07±1.01	2.42±0.86	3.14±1.12	0.368	2.99±0.88	3.26±1.25	0.214
HDL cholesterol (mmol/L)	1.21±0.43	1.32±0.53	1.14±0.35	0.042	1.27±0.49	1.07±0.21	0.005
LDL/HDL ratio	2.8±1.2	2.4±0.9	3.0±1.3	0.013	2.6±0.9	3.3±1.6	0.029
Triglycerides (mmol/L)	1.58±0.65	1.56±0.56	1.59±0.70	0.835	1.54±0.66	1.67±0.64	0.347
White cell count (×10^9/L)	6.8±2.0	6.3±1.8	7.1±2.1	0.066	6.7±2.1	7.1±1.8	0.348
eGFR (mL/min/1.73 m^2)	87±28	87±27	88±29	0.984	90±31	81±19	0.105
Medications, n (%)							
Insulin treatment	22 (22)	9 (24)	13 (21)	0.719	15 (21)	7 (23)	0.806
Sulfonylurea	52 (51)	21 (55)	31 (49)	0.555	37 (52)	15 (50)	0.846
Glinides	7 (7)	3 (9)	4 (6)	0.767	5 (7)	2 (7)	0.946
Metformin	40 (40)	15 (40)	25 (40)	0.983	25 (35)	15 (50)	0.165
Thiazolidinedione	13 (13)	3 (8)	10 (16)	0.246	8 (11)	5 (17)	0.459
α-Glucosidase inhibitor	23 (23)	10 (26)	13 (21)	0.510	12 (17)	11 (37)	0.030
Incretin-related therapies	12 (12)	4 (11)	8 (13)	0.744	11 (16)	1 (3)	0.084
Statin use	36 (36)	12 (32)	24 (38)	0.508	20 (28)	16 (53)	0.016
Any antihypertensive agent	43 (43)	9 (24)	34 (54)	0.003	25 (35)	18 (60)	0.021
ACEI or ARB	39 (39)	9 (24)	30 (48)	0.017	23 (32)	16 (53)	0.048
Ca blocker	36 (36)	5 (13)	31 (49)	<0.001	22 (31)	14 (47)	0.133
β blocker	7 (7)	1 (3)	6 (10)	0.186	5 (7)	2 (7)	0.946
Mean-IMT of common carotid artery (mm)	1.0 (0.8-1.4)	0.9 (0.8-1.2)	1.1 (0.9-1.4)	0.173	1.1 (0.8-1.2)	1.0 (0.9-1.4)	0.489
Maximum-IMT of carotid artery (mm)	2.3 (1.6-3.1)	1.6 (1.2-2.7)	2.4 (2.1-3.2)	<0.001	2.1 (1.5-2.8)	2.6 (2.1-3.7)	0.014
Complex carotid plaque, n (%)	34 (34)	8 (21)	26 (41)	0.037	19 (27)	15 (50)	0.024

Data are the mean±SD or median (interquartile range). BMI, body mass index; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; hypertension, systolic blood pressure ≥140 and/or diastolic blood pressure ≥90 or treatment; LDL/HDL ratio, LDL-to-HDL cholesterol ratio; IMT, intima-media thickness; ACEI, angiotensin-converting-enzyme inhibitor; ARB: angiotensin II receptor blocker

Table 3. Logistic regression models for variables associated with the presence of coronary artery disease and vulnerable coronary plaque

	B	SE	OR (95% CI)	*p* value
For coronary stenosis				
Age	0.056	0.033	1.06 (0.99-1.13)	0.091
Male sex	1.203	0.558	3.33 (1.12-9.95)	0.031
BMI	0.001	0.057	1.00 (0.90-1.12)	0.990
SBP	0.032	0.015	1.03 (1.00-1.06)	0.039
Duration of diabetes	0.074	0.033	1.08 (1.01-1.15)	0.024
Current smoking	−0.623	0.614	0.54 (0.16-1.79)	0.311
Family history of CAD	0.459	0.652	1.58 (0.44-5.68)	0.482
HbA1c	0.071	0.145	1.07 (0.81-1.43)	0.626
Maximum-IMT	0.358	0.373	1.43 (0.69-2.97)	0.338
LDL/HDL ratio	0.866	0.348	2.38 (1.20-4.71)	0.013
Complex carotid plaque	0.562	0.652	1.75 (0.49-6.30)	0.389
For vulnerable coronary plaque				
Age	0.003	0.031	1.00 (0.94-1.07)	0.920
Male sex	0.041	0.553	1.04 (0.35-3.08)	0.940
BMI	0.053	0.055	1.05 (0.95-1.18)	0.343
SBP	−0.012	0.016	0.99 (0.96-1.02)	0.446
Duration of diabetes	0.040	0.028	1.04 (0.98-1.10)	0.156
Current smoking	0.631	0.549	1.88 (0.64-5.52)	0.251
Family history of CAD	0.533	0.601	1.70 (0.52-5.54)	0.375
HbA1c	−0.164	0.148	0.85 (0.63-1.13)	0.267
Maximum-IMT	0.417	0.347	1.52 (0.77-2.99)	0.230
LDL/HDL ratio	0.464	0.229	1.59 (1.02-2.49)	0.042
Complex carotid plaque	0.579	0.583	1.79 (0.57-5.59)	0.320

BMI, body mass index; CAD, coronary artery disease; hypertension, SBP ≥140 and/or DBP ≥90 or treatment; LDL/HDL ratio, LDL-to-HDL cholesterol ratio; maximum-IMT, maximum carotid intima-media thickness

positive exercise ECG test, and 31 had a left ventricular wall motion abnormality on echocardiography. Some patients had two or more of these conditions. There were 15 patients with cerebrovascular disease and 5 patients with peripheral arterial disease. **Table 1** shows the baseline characteristics of study subjects according to the category of coronary artery lesion. Sex, hypertension, retinopathy, LDL/HDL ratio, use of any antihypertensive agent, maximum-IMT, and complex carotid plaque differed significantly among the following four groups: stenosis (−)/vulnerability (−), stenosis (+)/vulnerability (−), stenosis (−)/vulnerability (+), and stenosis (+)/vulnerability (+). As shown in **Table 2**, compared with the stenosis (−) group, the stenosis (+) group included more individuals who were older, male, had hypertension, had retinopathy, were taking any antihypertensive agent or who had complex carotid plaque, lower HDL-C levels, a higher LDL/HDL ratio, and higher maximum-IMT values; differences between the stenosis (+) and stenosis (−) groups were significant. In the vulnerable coronary artery (+) group compared with the vulnerability (−) group, the duration of diabetes was higher, values for the LDL/HDL ratio and maximum-IMT were higher, and the percentages of those with complex carotid plaque and who used statins were higher; these differences were significant; however, DBP and HDL-C were significantly lower in the vulnerable coronary artery (+) group than in the vulnerability (−) group (**Table 2**). Logistic regression analyses showed that male sex (odds ratio [OR] 3.33 [95% confidence interval 1.12-9.95], $p=0.031$); duration of diabetes (OR 1.08 [1.05-1.15], $p=0.024$); SBP (OR 1.03 [1.00-1.06], $p=0.039$); and LDL/HDL ratio (2.38 [1.20-4.71], $p=0.013$) independently predicted the presence of coronary artery stenosis after adjustments for age, body mass index (BMI), current smoking, family history of CAD, HbA1c, maximum-IMT, and complex carotid plaque (**Table 3**). The LDL/HDL ratio (OR 1.59 [1.02-2.49], $p=0.042$) independently predicted vulnerable coronary plaque adjusted by age, sex, BMI, SBP, duration of diabetes, current smoking, family

history of CAD, HbA1c, maximum-IMT, and complex carotid plaque (**Table 3**).

Combined Effects on Coronary Artery Lesions According to the Maximum-IMT and the LDL/HDL Ratio

Table 4 and **Fig. 1A** show combinations of the effects of the maximum-IMT and LDL/HDL ratio on coronary artery stenosis. According to the results of tertile analysis of maximum-IMT, 12 patients (34%) in the lowest tertile (T1), 26 (81%) in the middle tertile (T2), and 25 (74%) in the highest tertile (T3) had coronary artery stenosis ($p=0.001$). Analysis using the variance post-hoc test revealed a statistically significant difference between the T1 group and each of the other 2 groups in the maximum-IMT category regarding coronary artery stenosis ($p<0.001$ and $p=0.001$, respectively). In the LDL/HDL ratio category, 18 patients (55%) in T1, 20 (61%) in T2, and 25 (71%) in T3 had coronary artery stenosis ($p=0.352$). There was no significant difference in the frequency of coronary artery stenosis associated with an increase in the LDL/HDL ratio for each tertile of the maximum-IMT ($p=0.949$ for T1, $p=0.531$ for T2, and $p=0.512$ for T3). Increasing frequency of coronary stenosis was observed in the T2 and T3 categories of the maximum-IMT compared with the T1 category of the maximum-IMT for each category of the LDL/HDL ratio. Statistical significance was observed among the tertiles of the maximum-IMT in the T3 of the LDL/HDL ratio ($p=0.001$). There were, however, no significant differences in T1 and T2 of the LDL/HDL ratio ($p=0.166$ and $p=0.135$, respectively).

Table 4 and **Fig. 1B** show combinations of the effects on vulnerable coronary plaque according to the maximum-IMT and the LDL/HDL ratio. According to the results of tertile analysis of the maximum-IMT, 6 patients (17%) in T1, 11 (34%) in T2, and 13 (38%) in T3 had vulnerable coronary plaque. In the LDL/HDL ratio category, 7 patients (21%) in T1, 8 (24%) in T2, and 15 (43%) in T3 had vulnerable coronary plaque. Analysis of variance revealed no significant difference among the tertiles of maximum-IMT or LDL/HDL ($p=0.352$ and $p=0.107$, respectively). There was a difference in the frequency of vulnerable coronary plaque associated with increases in the LDL/HDL ratio for each category of the maximum-IMT. The frequency of vulnerable coronary plaque associated with increases in the LDL/HDL ratio was observed in the T1 and T3 categories of the maximum-IMT. According to tertile analysis of the LDL/HDL ratio in the T1 category of maximum-IMT, the LDL/HDL ratio was associated with improved prediction of vulnerable coronary plaque but without statistical significance ($p=0.078$). Increasing frequency of vulnerable coronary plaque was observed in the T2 and T3 categories of the maximum-IMT compared with the T1 category of the maximum-IMT for either T1 or T2 category of the LDL/HDL ratio; however, these relationships were not observed in the T3 category of the LDL/HDL ratio.

Predictive Value of Mean-IMT, Maximum-IMT, and LDL/HDL Ratio

Fig. 2A shows the AUCs for prediction of coronary artery stenosis. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of variables for maximum-IMT are provided in **Table 5**. A maximum-IMT ≥1.7 mm predicted coronary artery stenosis with a sensitivity of 0.89, specificity of 0.55, PPV of 0.77, and NPV of 0.75 (AUC 0.711 [0.601-0.820]; $p<0.001$). An LDL/HDL ratio ≥3.0 predicted coronary artery stenosis with sensitivity of 0.40, specificity of 0.74, PPV of 0.71, and NPV of 0.42 (AUC 0.618 [0.508-0.728]; $p=0.048$). The combination of the maximum-IMT and LDL/HDL ratio improved these values (AUC 0.732 [0.632-0.831]; $p<0.001$). The combination of maximum-IMT ≥1.8 and LDL/HDL ratio ≥2.5 had sensitivity of 0.52, specificity of 0.87, PPV of 0.87, and NPV of 0.52; however, mean-IMT of CCA did not significantly discriminate the presence of coronary artery stenosis (AUC 0.581 [0.465-0.697]; $p=0.176$).

Fig. 2B shows the AUCs for the prediction of vulnerable coronary plaque. Sensitivities, specificities, PPVs, and NPVs of each parameter were as follows (**Table 5**): maximum-IMT ≥2.1 mm had sensitivity of 0.80, specificity of 0.45, PPV of 0.38, and NPV of 0.84 (AUC 0.655 [0.537-0.773], $p=0.014$) and an LDL/HDL ratio ≥3.0 had sensitivity of 0.50, specificity of 0.72, PPV of 0.43, and NPV of 0.77 (AUC 0.629 [0.504-0.754], $p=0.042$). These values were improved by the combination of the maximum-IMT and the LDL/HDL ratio (AUC 0.710 [0.601-0.818]; $p=0.001$). The combination of maximum-IMT ≥2.3 mm or LDL/HDL ratio ≥3.0 had sensitivity of 0.90, specificity of 0.44, PPV of 0.40, and NPV of 0.91; however, mean-IMT of CCA did not significantly discriminate the presence of vulnerable coronary plaque (AUC 0.543 [0.419-0.668]; $p=0.492$).

Discussion

This study had three major findings. First, male sex, duration of diabetes, elevated SBP, and the LDL/HDL ratio were independently associated with the

Table 4. Frequency of coronary plaque according to the tertile of Maximum-IMT and LDL/HDL-C ratio

	Maximum-IMT(mm)				
	Total	T1 (<2.0)	T2 (2.0-2.6)	T3 (≥2.7)	*p* for tertile of maximum-IMT
For coronary artery stenosis					
LDL/HDL ratio					
Total		12/35 (34)	26/32 (81)**	25/34 (74)*	0.001
T1 (<2.17)	18/33 (55)	5/14 (36)	6/8 (75)	7/11 (64)	0.166
T2 (2.17-3.06)	20/33 (61)	4/11 (36)	9/12 (75)	7/10 (70)	0.135
T3 (>3.06)	25/35 (71)	3/10 (30)	11/12 (92)*	11/13 (85)*	0.001
p for tertile of LDL/HDL ratio	0.352	0.949	0.531	0.512	
For vulnerable coronary plaque					
LDL/HDL ratio					
Total		6/35 (17)	11/32 (34)	13/34 (38)	0.352
T1 (<2.17)	7/33 (21)	1/14 (7)	3/8 (38)	3/11 (27)	0.220
T2 (2.17-3.06)	8/33 (24)	1/11 (9)	3/12 (25)	4/10 (40)	0.274
T3 (>3.06)	15/35 (43)	4/10 (40)	5/12 (42)	6/13 (46)	0.956
p for tertile of LDL/HDL ratio	0.107	0.078	0.698	0.654	

Data are expressed as n/N (%). *$p<0.01$ and **$p<0.001$ vs. T1 in maximum-IMT. IMT, intima-media thickness; LDL/HDL ratio, LDL-to-HDL cholesterol ratio

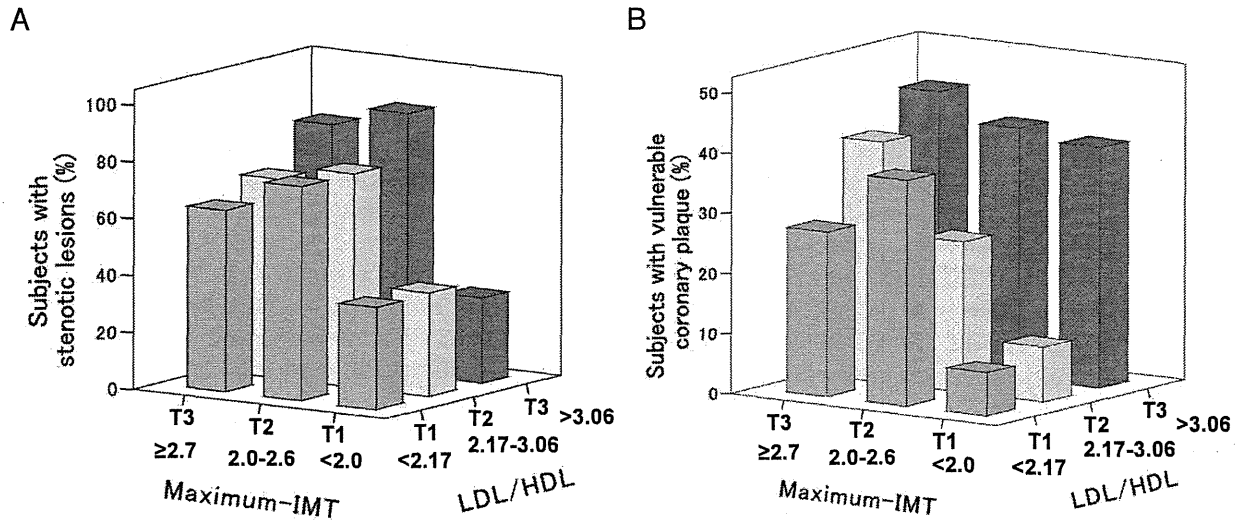

Fig. 1. A: Presence of coronary artery stenosis in different maximum-IMT categories according to 3 categories of the LDL-to-HDL cholesterol (LDL/HDL) ratio (tertile, T). In the T1 group in the maximum-IMT category, 34% of subjects had coronary artery stenosis whereas in the T2 and T3 groups, 81% and 74% of subjects, respectively, had coronary artery stenosis. In the T1 group in the LDL/HDL ratio category, 55% of subjects had coronary artery stenosis whereas in the T2 and T3 groups, 61% and 71% of subjects, respectively, had coronary artery stenosis.
B: Presence of vulnerable coronary plaque for different maximum-IMT categories according to 3 categories of LDL/HDL ratio (tertile, T). In the T1 group in the maximum-IMT category, 17% of subjects had vulnerable coronary plaque whereas in the T2 and T3 groups, 34% and 38% of subjects, respectively, had vulnerable coronary plaque. In the T1 group in LDL/HDL ratio category, 21% of subjects had vulnerable coronary plaque, whereas in the T2 and T3 groups, 24% and 43% of subjects, respectively, had vulnerable coronary plaque.

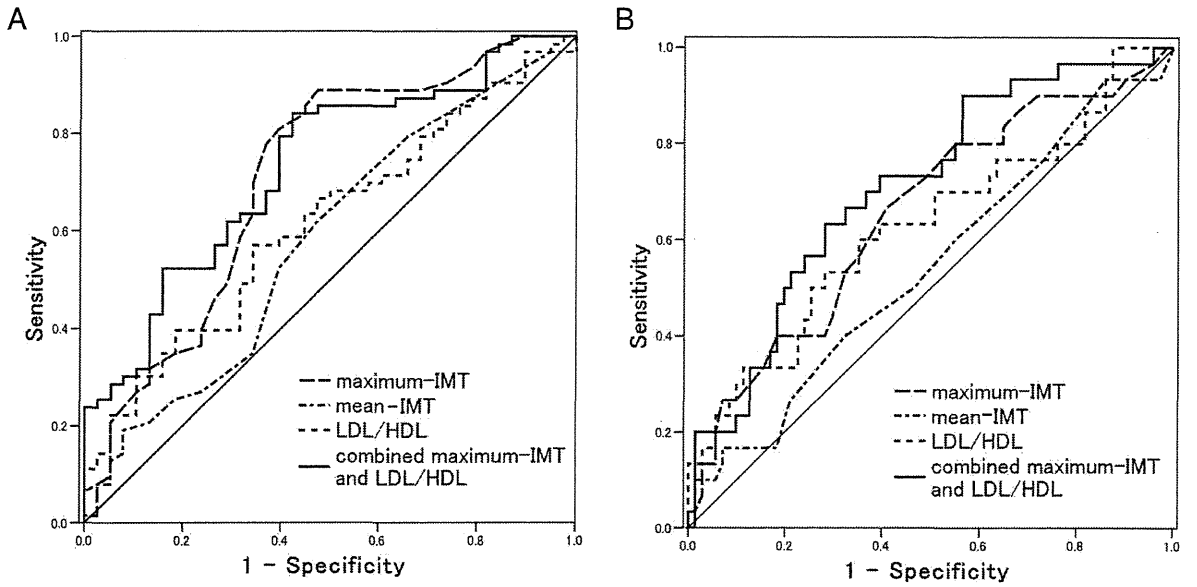

Fig. 2. A: Comparison among the AUCs of the mean-IMT, maximum-IMT, LDL-to-HDL cholesterol (LDL/HDL) ratio, and the combination of maximum-IMT and LDL/HDL ratio for the presence of coronary artery stenosis (A) and for the presence of vulnerable coronary plaque (B). A: The AUCs (95% confidence interval), cut-off values, sensitivities, and specificities were as follows: maximum-IMT 0.711 (0.601-0.820), 1.7mm, 0.89, and 0.55; LDL/HDL ratio 0.618 (0.508-0.728), 3.0, 0.40, and 0.74; and the combination of maximum-IMT and the LDL/HDL ratio 0.732 (0.632-0.831), 1.8 mm and 2.5, 0.52, and 0.87. B: The AUCs, cut-off values, sensitivities, and specificities were as follows: maximum-IMT 0.655 (0.537-0.773), 2.1 mm, 0.80, and 0.45; LDL/HDL ratio 0.629 (0.504-0.754), 3.0, 0.40, and 0.74; and the combination of maximum-IMT and LDL/HDL ratio 0.710 (0.601-0.818), 2.3 mm or 3.0, 0.90, and 0.44.

presence of coronary artery stenosis whereas the LDL/HDL ratio was independently associated with the presence of vulnerable coronary plaque. Second, maximum-IMT values predicted both coronary artery stenosis and vulnerable coronary plaque. Third, the combination of maximum-IMT and the LDL/HDL ratio had greater predictive value than each parameter alone, as shown by the AUC for predicting both coronary artery stenosis and vulnerable coronary plaque. To our knowledge, this is the first investigation of clinical predictors of vulnerable coronary plaque in high risk but asymptomatic patients with type 2 diabetes.

High LDL-C, low HDL-C, elevated blood pressure, hyperglycemia, smoking, and diabetic retinopathy are independent risk factors for CAD in type 2 diabetes[31, 32]. The TC/HDL ratio and LDL/HDL ratio were reported to be better predictors of future cardiovascular disease than single lipid parameters (TC, LDL-C, and HDL-C)[33]. Traditional risk factors were shown to have distinct effects on plaque stability: stable plaque was associated with age and hypertension in men and with elevated glycosylated hemoglobin and hypertension in women; plaque erosion with smoking in both sexes; and plaque rupture with elevated levels of serum TC in both sexes and with smoking and elevated TC/HDL ratio in men[4, 34]. Subjects with lower HDL-C were at high risk of cardiovascular disease regardless of whether statins were used[35]. These findings are consistent with our results; therefore, our results appear highly plausible, given the findings in those previous epidemiological and pathological studies.

Our finding of lower DBP in the vulnerability (+) group than in the vulnerability (−) group is probably due to a greater proportion of anti-hypertensive drug use in the former than the latter group. The higher rate of statin use in the vulnerability (+) than in the vulnerability (−) group reflects poorer control of LDL-C.

Carotid IMT is strongly predictive of future cardiovascular events[36] and is associated with the presence of coronary atherosclerotic plaque evident by coronary angiography[21]. Increased maximum-IMT was shown to be associated with the presence of coronary artery stenosis as assessed by CCTA in asymptomatic patients with type 2 diabetes[22, 23]. The maximum-IMT, which includes the CCA, bulbus, and internal carotid artery, was reported to have superior

Table 5. Sensitivity, specificity, PPV and NPV for identification of individuals with stenotic lesions at different maximum-IMT or LDL/HDL thresholds

	For coronary artery stenosis (n=63)				For vulnerable coronary plaque (n=30)			
	Sensitivity	Specificity	PPV	NPV	Sensitivity	Specificity	PPV	NPV
Maximum-IMT (mm)								
1.2	0.97	0.18	0.66	0.78	0.93	0.10	0.30	0.78
1.3	0.94	0.24	0.67	0.69	0.90	0.13	0.30	0.75
1.4	0.90	0.29	0.68	0.65	0.90	0.18	0.32	0.81
1.5	0.89	0.34	0.69	0.65	0.90	0.23	0.33	0.84
1.6	0.89	0.45	0.73	0.71	0.90	0.28	0.35	0.87
1.7	0.89	0.55	0.77	0.75	0.87	0.32	0.35	0.85
1.8	0.86	0.58	0.77	0.71	0.83	0.35	0.35	0.83
1.9	0.84	0.58	0.77	0.69	0.80	0.35	0.34	0.81
2.0	0.81	0.63	0.78	0.67	0.80	0.41	0.36	0.83
2.1	0.78	0.66	0.79	0.64	0.80	0.45	0.38	0.84
LDL/HDL								
2.0	0.75	0.34	0.65	0.45	0.77	0.31	0.32	0.76
2.5	0.59	0.61	0.71	0.47	0.63	0.54	0.37	0.78
3.0	0.40	0.74	0.71	0.42	0.50	0.72	0.43	0.77
3.5	0.29	0.89	0.82	0.43	0.33	0.83	0.45	0.75
4.0	0.16	0.95	0.93	0.40	0.23	0.93	0.58	0.74

PPV, positive predictive value; NPV, negative predictive value; LDL/HDL ratio, LDL-to-HDL cholesterol ratio; Maximum-IMT, maximum carotid intima-media thickness

predictive value than the mean-IMT of the CCA for a cardiovascular event or coronary artery stenosis[16, 23]. Moreover, the relationship of CAD with characteristics of carotid plaque has been indicated. Complex carotid plaque was associated with complex coronary plaque[19]. Echolucent carotid plaque, a component of complex carotid plaque, was reported to be lipid-and macrophage-rich[37] and to predict future coronary events in stable CAD[19]. An irregular surface of carotid plaque was associated with vascular events[38]. Our data are consistent with these findings.

Interestingly, we found that the maximum-IMT had moderate predictive value not only for coronary artery stenosis but also for vulnerable coronary plaque in asymptomatic patients with type 2 diabetes. On the other hand, the LDL/HDL ratio could predict vulnerable coronary plaque but not coronary artery stenosis, especially in T1 of the maximum-IMT category. These data indicate that maximum-IMT is a useful predictor of both coronary artery stenosis and vulnerable coronary plaque and that the LDL/HDL ratio is a useful predictor of vulnerable coronary plaque in patients categorized as being in T1 of the maximum-IMT. Our data also suggest that the maximum-IMT has a threshold for the prediction of coronary artery stenosis because the prevalence of coronary artery stenosis clearly increased between T1 and T2 and was similar between T2 and T3 in the maximum-IMT category; however, we could not exclude the presence of coronary artery stenosis in the lowest maximum-IMT category because its prevalence was 34% in this group.

Kasami *et al.* showed that the cut-off level of maximum-IMT for predicting the presence of coronary artery stenosis was 1.90 mm with sensitivity of 0.93 and specificity of 0.55 in type 2 diabetic patients without a history of CAD[23]. A similar result was reported by Irie *et al.*: the maximum-IMT cut-off level was 1.55 mm with sensitivity of 0.90 and specificity of 0.46 in asymptomatic patients with type 2 diabetes[22]. Our result is comparable to these results, indicating that maximum-IMT is useful in screening for coronary artery stenosis.

We showed that the AUC of the combination of maximum-IMT and LDL/HDL ratio for predicting the presence of coronary artery stenosis was greater than the maximum-IMT alone; however, the maximum-IMT alone had higher sensitivity than the combined maximum-IMT and LDL/HDL ratio, which had higher specificity than the maximum-IMT. Therefore, the maximum-IMT alone is useful to rule out

coronary artery stenosis and the combination of maximum-IMT and LDL/HDL ratio is of use in ruling it in.

Our cut-off level of maximum-IMT for predicting vulnerable coronary plaque was 2.1 mm, which is plausible because maximum-IMT of the carotid artery ≥ 1.9 mm was shown to be associated with myocardial infarction[39]. Moreover, the maximum-IMT is superior to the LDL/HDL ratio for this purpose. Combining the two significantly improved the AUC for predicting the presence of vulnerable coronary plaque compared with the maximum-IMT alone. The combination of maximum-IMT ≥ 1.7 mm or LDL/HDL ratio ≥ 3.0 could predict vulnerable coronary plaque with sensitivity of 0.97 and specificity of 0.27. Prediction of the stenosis (−)/vulnerability (+) group is important, because angiographic encroachment of the lumen was reported as < 50% in ACS[5, 6], and patients who could not be included in that group cannot be identified using routine cardiac examinations. Five of the 7 patients in the stenosis (−)/vulnerability (+) group were detected using the combination of maximum-IMT ≥ 1.7 mm or LDL/HDL ratio ≥ 3.0 (data not shown).

Clinical Implications

Several cardiovascular risk scores have been proposed[40]. Although useful for predicting future cardiovascular events, their value is not high for predicting the presence of coronary artery stenosis[41]. Lee *et al.* showed that three cardiovascular risk scores (Framingham risk score, systematic coronary risk evaluation, and Chinese multi-provincial cohort study) predicted the presence of coronary artery stenosis detected by CCTA with a sensitivity of 0.61-0.70 and specificity of 0.55-0.66[41]. The current and previous studies showed that maximum-IMT can predict the presence of coronary artery stenosis with sensitivity of 0.84-0.93 and specificity of 0.46-0.57[22, 23]. Maximum-IMT appears superior to risk scores in screening for obstructive CAD. Moreover, we could predict the status of the coronary atherosclerotic burden with two simple measures: maximum-IMT and LDL/HDL ratio. This suggests that carotid ultrasonography is a worthwhile tool to predict the atherosclerotic status of coronary arteries.

Study Limitations

This study has limitations. First, it was cross-sectional with a relatively small number of subjects, all of which were Japanese. The number of patients was too small to assess clinically useful cut-off values. Our participants had poor glycemic and lipid control, and, although they were asymptomatic, they were at high risk for cardiovascular disease. We reserve the use of CCTA for those patients at high risk for CAD in view of the risk/benefit ratio for CCTA. Under most circumstances we could not ethically perform CCTA in patients with maximum-IMT < 1.1 mm for comparison with those with maximum-IMT ≥ 1.1 mm. In addition, because of our criteria for the performance of CCTA, we could not identify enough patients with good glycemic and lipid control for comparison with those with poor glycemic and lipid control. These issues could have introduced selection bias. However, our data regarding the cut-off values of maximum-IMT for the prediction of coronary artery stenosis are thought to be similar to those of previous studies[22, 23]; thus, we consider that our results could be applicable to patients with type 2 diabetes at low to moderate risk. Second, the clinical significance of vulnerable coronary plaque detected by CCTA has not been fully established. CCTA has failed to characterize lesions at risk of plaque erosion, which could be responsible for one-third of ACS[42]. Prospective studies are needed on the association between vulnerable plaque assessed by CCTA and development of future CAD. Third, methods for measuring IMT are not standardized[36]. Finally, IMT measurements were performed by two expert sonographers as routine clinical examinations, which allows for intra-sonographer differences. Our results should be confirmed in prospective studies with an appropriate sample size and subjects from various ethnic groups.

Conclusion

Male sex, duration of diabetes, elevated SBP, and the LDL/HDL were independent predictors of coronary artery stenosis and the LDL/HDL was an independent predictor of vulnerable coronary plaque. Maximum-IMT predicts both coronary stenosis and vulnerable coronary plaque and adding the LDL/HDL improved the prediction of coronary artery stenosis and vulnerable coronary plaques in asymptomatic patients with type 2 diabetes.

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K.F. developed the study design, researched the data, contributed to discussions, wrote the manuscript, and reviewed and edited the manuscript. H. Su. planned and supervised this research, researched the data, contributed to discussions, wrote the manuscript, and reviewed and edited the manuscript. A.S. researched the data, contributed to discussions, wrote the manuscript, and reviewed and edited the manuscript. S.K., Y.H., and K.S. developed the study

design, researched the data, contributed to discussions, and reviewed and edited the manuscript. H.I., K.K., S.Y., and A.T. researched the data, contributed to discussions, and reviewed and edited the manuscript. N.Y., H. So., and H. Sh. developed the study design, contributed to discussions, and reviewed and edited the manuscript.

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References

1) International Diabetes Federation: IDF Diabetes Atlas, fourth edition. Available from http://www.idf.org/diabetesatlas/. Accessed 1 November 2011
2) Bax JJ, Young LH, Frye RL, Bonow RO, Steinberg HO, Barrett EJ: Screening for coronary artery disease in patients with diabetes. Diabetes Care, 2007; 30: 2729-2736
3) Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O: Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med, 2003; 348: 383-393
4) Burke AP, Farb A, Malcom GT, Liang YH, Smialek J, Virmani R: Coronary risk factors and plaque morphology in men with coronary disease who died suddenly. N Engl J Med, 1997; 336: 1276-1282
5) Falk E, Shah PK, Fuster V: Coronary plaque disruption. Circulation, 1995; 92: 657-671
6) Motoyama S, Sarai M, Harigaya H, Anno H, Inoue K, Hara T, Naruse H, Ishii J, Hishida H, Wong ND, Virmani R, Kondo T, Ozaki Y, Narula J: Computed tomographic angiography characteristics of atherosclerotic plaques subsequently resulting in acute coronary syndrome. J Am Coll Cardiol, 2009; 54: 49-57
7) Giri S, Shaw LJ, Murthy DR, Travin MI, Miller DD, Hachamovitch R, Borges-Neto S, Berman DS, Waters DD, Heller GV: Impact of diabetes on the risk stratification using stress single-photon emission computed tomography myocardial perfusion imaging in patients with symptoms suggestive of coronary artery disease. Circulation, 2002; 105: 32-40
8) Kato M, Matsumoto N, Nakano Y, Suzuki Y, Yoda S, Sato Y, Kasama S, Nagao K, Hirayama A: Combined Assessment of Myocardial Perfusion and Function by ECG-Gated Myocardial Perfusion Single-Photon Emission Computed Tomography for the Prediction of Future Cardiac Events in Patients With Type 2 Diabetes Mellitus. Circ J, 2011; 75: 376-382
9) Rajagopalan N, Miller TD, Hodge DO, Frye RL, Gibbons RJ: Identifying high-risk asymptomatic diabetic patients who are candidates for screening stress single-photon emission computed tomography imaging. J Am Coll Cardiol, 2005; 45: 43-49
10) Wackers FJ, Young LH, Inzucchi SE, Chyun DA, Davey JA, Barrett EJ, Taillefer R, Wittlin SD, Heller GV, Filipchuk N, Engel S, Ratner RE, Iskandrian AE: Detection of silent myocardial ischemia in asymptomatic diabetic subjects: the DIAD study. Diabetes Care, 2004; 27: 1954-1961
11) Hulten EA, Carbonaro S, Petrillo SP, Mitchell JD, Villines TC: Prognostic value of cardiac computed tomography angiography: a systematic review and meta-analysis. J Am Coll Cardiol, 2011; 57: 1237-1247
12) Motoyama S, Kondo T, Sarai M, Sugiura A, Harigaya H, Sato T, Inoue K, Okumura M, Ishii J, Anno H, Virmani R, Ozaki Y, Hishida H, Narula J: Multislice computed tomographic characteristics of coronary lesions in acute coronary syndromes. J Am Coll Cardiol, 2007; 50: 319-326
13) Miller JM, Rochitte CE, Dewey M, Arbab-Zadeh A, Niinuma H, Gottlieb I, Paul N, Clouse ME, Shapiro EP, Hoe J, Lardo AC, Bush DE, de Roos A, Cox C, Brinker J, Lima JA: Diagnostic performance of coronary angiography by 64-row CT. N Engl J Med, 2008; 359: 2324-2336
14) Scholte AJ, Schuijf JD, Kharagjitsingh AV, Jukema JW, Pundziute G, van der Wall EE, Bax JJ: Prevalence of coronary artery disease and plaque morphology assessed by multi-slice computed tomography coronary angiography and calcium scoring in asymptomatic patients with type 2 diabetes. Heart, 2008; 94: 290-295
15) Sun J, Zhang Z, Lu B, Yu W, Yang Y, Zhou Y, Wang Y, Fan Z: Identification and quantification of coronary atherosclerotic plaques: a comparison of 64-MDCT and intravascular ultrasound. Am J Roentgenol, 2008; 190: 748-754
16) Iglesias del Sol A, Bots ML, Grobbee DE, Hofman A, Witteman JC: Carotid intima-media thickness at different sites: relation to incident myocardial infarction; The Rotterdam Study. Eur Heart J, 2002; 23: 934-940
17) Yamasaki Y, Kodama M, Nishizawa H, Sakamoto K, Matsuhisa M, Kajimoto Y, Kosugi K, Shimizu Y, Kawamori R, Hori M: Carotid intima-media thickness in Japanese type 2 diabetic subjects: predictors of progression and relationship with incident coronary heart disease. Diabetes Care, 2000; 23: 1310-1315
18) Tanaka S, Honda M, Wu B, Kazumi T: Clinical features of normal weight Japanese patients with type 2 diabetes who had formerly been obese. J Atheroscler Thromb, 2011; 18: 115-121
19) Honda O, Sugiyama S, Kugiyama K, Fukushima H, Nakamura S, Koide S, Kojima S, Hirai N, Kawano H, Soejima H, Sakamoto T, Yoshimura M, Ogawa H: Echolucent carotid plaques predict future coronary events in patients with coronary artery disease. J Am Coll Cardiol, 2004; 43: 1177-1184
20) Johnsen SH, Mathiesen EB, Joakimsen O, Stensland E, Wilsgaard T, Lochen ML, Njolstad I, Arnesen E: Carotid atherosclerosis is a stronger predictor of myocardial infarction in women than in men: a 6-year follow-up study of 6226 persons: the Tromso Study. Stroke, 2007; 38: 2873-

2880
21) Kablak-Ziembicka A, Tracz W, Przewlocki T, Pieniazek P, Sokolowski A, Konieczynska M: Association of increased carotid intima-media thickness with the extent of coronary artery disease. Heart, 2004; 90: 1286-1290
22) Irie Y, Sakamoto K, Kubo F, Okusu T, Katura T, Yamamoto Y, Umayahara Y, Katakami N, Kaneto H, Kashiyama T, Ueda Y, Kosugi K: Association of coronary artery stenosis with carotid atherosclerosis in asymptomatic type 2 diabetic patients. J Atheroscler Thromb, 2011; 18: 337-344
23) Kasami R, Kaneto H, Katakami N, Sumitsuji S, Yamasaki K, Kuroda T, Tachibana K, Yasuda T, Kuroda A, Matsuoka TA, Matsuhisa M, Shimomura I: Relationship Between Carotid Intima-Media Thickness and the Presence and Extent of Coronary Stenosis in Type 2 Diabetic Patients With Carotid Atherosclerosis but Without History of Coronary Artery Disease. Diabetes Care, 2011; 34: 468-470
24) Kimura T, Itoh T, Fusazaki T, Matsui H, Sugawara S, Ogino Y, Endo H, Kobayashi K, Nakamura M: Low-density lipoprotein-cholesterol/high-density lipoprotein-cholesterol ratio predicts lipid-rich coronary plaque in patients with coronary artery disease--integrated-backscatter intravascular ultrasound study. Circ J, 2010; 74: 1392-1398
25) Kawamori R, Yamasaki Y, Matsushima H, Nishizawa H, Nao K, Hougaku H, Maeda H, Handa N, Matsumoto M, Kamada T: Prevalence of carotid atherosclerosis in diabetic patients. Ultrasound high-resolution B-mode imaging on carotid arteries. Diabetes Care, 1992; 15: 1290-1294
26) Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, Yamagata K, Tomino Y, Yokoyama H, Hishida A: Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis, 2009; 53: 982-992
27) Kashiwagi A, Kasuga M, Araki E, Oka Y, Hanafusa T, Ito H, Tominaga M, Oikawa S, Noda M, Takahiko Kawamura T, Tokio Sanke T, Namba M, Hashiramoto M, Sasahara T, Nishio Y, Kuwa K, Ueki K, Takei I, Umemoto M, Murakami M, Yamakado M, Yatomi Y, Ohashi H: International clinical harmonization of glycated hemoglobin in Japan: From Japan Diabetes Society to National Glycohemoglobin Standardization Program values. Diabetology International, 2012; 3: 8-10
28) Uetani T, Amano T, Kunimura A, Kumagai S, Ando H, Yokoi K, Yoshida T, Kato B, Kato M, Marui N, Nanki M, Matsubara T, Ishii H, Izawa H, Murohara T: The association between plaque characterization by CT angiography and post-procedural myocardial infarction in patients with elective stent implantation. JACC Cardiovasc Imaging, 2010; 3: 19-28
29) Komatsu S, Hirayama A, Omori Y, Ueda Y, Mizote I, Fujisawa Y, Kiyomoto M, Higashide T, Kodama K: Detection of coronary plaque by computed tomography with a novel plaque analysis system, 'Plaque Map', and comparison with intravascular ultrasound and angioscopy. Circ J, 2005; 69: 72-77
30) Triposkiadis F, Sitafidis G, Kostoulas J, Skoularigis J, Zintzaras E, Fezoulidis I: Carotid plaque composition in stable and unstable coronary artery disease. Am Heart J, 2005; 150: 782-789
31) Turner RC, Millns H, Neil HA, Stratton IM, Manley SE, Matthews DR, Holman RR: Risk factors for coronary artery disease in noninsulin dependent diabetes mellitus: United Kingdom prospective diabetes study (UKPDS: 23). BMJ, 1998; 316: 823-828
32) Kramer CK, Rodrigues TC, Canani LH, Gross JL, Azevedo MJ: Diabetic retinopathy predicts all-cause mortality and cardiovascular events in both type 1 and 2 diabetes: meta-analysis of observational studies. Diabetes Care, 2011; 34: 1238-1244
33) Ingelsson E, Schaefer EJ, Contois JH, McNamara JR, Sullivan L, Keyes MJ, Pencina MJ, Schoonmaker C, Wilson PW, D'Agostino RB, Vasan RS: Clinical utility of different lipid measures for prediction of coronary heart disease in men and women. JAMA, 2007; 298: 776-785
34) Burke AP, Farb A, Malcom GT, Liang Y, Smialek J, Virmani R: Effect of risk factors on the mechanism of acute thrombosis and sudden coronary death in women. Circulation, 1998; 97: 2110-2116
35) Jafri H, Alsheikh-Ali AA, Karas RH: Meta-analysis: statin therapy does not alter the association between low levels of high-density lipoprotein cholesterol and increased cardiovascular risk. Ann Intern Med, 2010; 153: 800-808
36) Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M: Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. Circulation, 2007; 115: 459-467
37) Gronholdt ML, Nordestgaard BG, Bentzon J, Wiebe BM, Zhou J, Falk E, Sillesen H: Macrophages are associated with lipid-rich carotid artery plaques, echolucency on B-mode imaging, and elevated plasma lipid levels. J Vasc Surg, 2002; 35: 137-145
38) Prabhakaran S, Rundek T, Ramas R, Elkind MS, Paik MC, Boden-Albala B, Sacco RL: Carotid plaque surface irregularity predicts ischemic stroke: the northern Manhattan study. Stroke, 2006; 37: 2696-2701
39) Rundek T, Arif H, Boden-Albala B, Elkind MS, Paik MC, Sacco RL: Carotid plaque, a subclinical precursor of vascular events: the Northern Manhattan Study. Neurology, 2008; 70: 1200-1207
40) Chamnan P, Simmons RK, Sharp SJ, Griffin SJ, Wareham NJ: Cardiovascular risk assessment scores for people with diabetes: a systematic review. Diabetologia, 2009; 52: 2001-2014
41) Lee BC, Lee WJ, Hsu HC, Chien KL, Shih TT, Chen MF: Using clinical cardiovascular risk scores to predict coronary artery plaque severity and stenosis detected by CT coronary angiography in asymptomatic Chinese subjects. Int J Cardiovasc Imaging, 2011; 27: 669-678
42) Ozaki Y, Okumura M, Ismail TF, Motoyama S, Naruse H, Hattori K, Kawai H, Sarai M, Takagi Y, Ishii J, Anno H, Virmani R, Serruys PW, Narula J: Coronary CT angiographic characteristics of culprit lesions in acute coronary syndromes not related to plaque rupture as defined by optical coherence tomography and angioscopy. Eur Heart J, 2011; 32: 2814-2823

Special Report

Background to Discuss Guidelines for Control of Plasma HDL-Cholesterol in Japan*

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A decrease in high density lipoprotein-cholesterol (HDL-C) is a strong risk factor for atherosclerotic disorders in Japan, probably more important than an increase in low density lipoprotein-cholesterol (LDL-C). While there are rational grounds for the argument that elevation of HDL-C leads to decreased risk, there has as yet been no direct evidence of such an effect. If elevation of HDL-C decreases the risk, this effect is expected throughout the normal range of HDL-C or perhaps even higher than that. Simulation based on epidemiological data indicated that it may eventually reduce the incidence of ischemic heart disease by 60-70% in Japan. In the risk management guideline, "low" HDL-C is presently defined as 40 mg/dL or below. While there is no evidence that strongly urges a change in this definition, the results of epidemiological studies support "The higher the HDL-C level, the lower the risk," even in the "normal range". Elevation of the HDL-C level may reduce the risk, probably at least up to 70 mg/dL; however, there are no supportive data for this effect still being obtained over 80 mg/dL. Patients with homozygous CETP deficiency should be followed-up while controlling other risk factors, so as not to dismiss the possibility of a risk increase with an extremely elevated HDL-C level.

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Key words; HDL, LDL, Guidelines, NNT, Prevention

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Clinical Relevance of HDL-C Management

Numbers of epidemiological studies have established that the risk of coronary artery disease increases as plasma HDL-C decreases, and decreases as it increases. In addition, many experimental approaches