Impact of Increasing Diabetes on Coronary Artery Disease in the Past Decade

Hiroshi Takaishi¹, Takahiro Taniguchi¹, Yoshio Fujioka¹, Yuichi Ishikawa², and Mitsuhiro Yokoyama¹

¹ Division of Cardiovascular and Respiratory Medicine, Department of Internal Medicine, Kobe University Graduate School of Medicine, Hyogo, Japan.
² Faculty of Health Sciences, Kobe University School of Medicine, Hyogo, Japan.

We studied the coronary risk factors of hospitalized patients with coronary artery disease (CAD) in the Department of Cardiovascular Internal Medicine of Kobe University Hospital in 1993, 1996, 1999 and 2003, and examined trends in the factors over the past decade. The prevalences of diabetes mellitus (DM) (24.7%, 33.6%, 41.1% and 44.7%, respectively) and impaired glucose tolerance (IGT) (5.9%, 8.0%, 9.3% and 11.0%, respectively) steadily increased, whereas dyslipidemia (high total cholesterolemia, high triglyceridemia, or low high-density lipoproteinemia) and hypertension remained unchanged. We also revealed an increase in hemoglobin A1c levels (5.6%, 5.9%, 6.2% and 6.4%, respectively), in contrast to modest improvements in lipid levels and blood pressure levels. Additionally, patients with multi-vessel disease (MVD, stenosis in more than two major coronary vessels) significantly increased from 44.7% in 1993 to 58.8% in 2003 (p < 0.01). In 1993, DM and dyslipidemia were significant predictors for MVD (Odds Ratio: 2.72 and 2.68, respectively). On the other hand, in 2003, the significant predictor for MVD shifted to DM alone (Odds Ratio: 2.38). In conclusion, the prevalence rate of DM among CAD patients significantly increased in this decade, and the consequent increase in the prevalence of MVD should be recognized as the most important problem clinically. J Atheroscler Thromb, 2004; 11: 271–277.

Key word: Diabetes mellitus, Impaired glucose tolerance, Dyslipidemia, Coronary artery disease
Methods

Study patients
The study group consisted of CAD patients who were hospitalized and underwent coronary angiography in the Department of Cardiovascular Internal Medicine of Kobe University Hospital in 1993, 1996, 1999 and 2003. A diagnosis of CAD was established by the presence of significant coronary stenosis or a positive provocation test for vasospastic angina, documented by coronary angiography. We excluded re-hospitalized patients with recurrence and re-study in the same year, to eliminate duplication of data. Characteristics of the patients are shown in Table 1.

Coronary risk factors
We examined conventional coronary risk factors such as hypertension, glucose intolerance including DM and impaired fasting glucose (IGT), dyslipidemia, obesity, and smoking habit. Fasting blood samples were obtained on the day following admission and we measured fasting plasma glucose (FPG), glycated hemoglobin A1c (HbA1c), total cholesterol (TC), triglyceride (TG) and high-density lipoprotein cholesterol (HDLC). Low-density lipoprotein cholesterol (LDL-C) was calculated using Friedewald’s formula (TC – HDL-C – TG/5). In the case of admission from the emergency room, the fasting blood samples were obtained at least one week after the recovery. Hypertension was diagnosed in cases that had a history of medical treatment, a systolic blood pressure (SBP) ≥ 140 mmHg or a diastolic blood pressure ≥ 90 mmHg, according to the Japanese Society of Hypertension guidelines (8). Dyslipidemia was diagnosed in cases that had a history of medical treatment, high TC (≥ 220 mg/dl), high TG (≥ 150 mg/dl) or low HDL-C (< 40 mg/dl), according to the guideline of the Japan Atherosclerosis Society (JAS) (9). DM was diagnosed in cases that had a history of medical treatment, FPG ≥ 126 mg/dl or a DM pattern shown on the 75-g oral glucose tolerance test (OGTT), according to the guideline of the Japan Diabetes Society (JDS) (10). We routinely performed the 75-g OGTT for non-diabetic patients that had 100 ≤ FPG < 126 or HbA1c ≥ 5.9. IGT was indicated in cases that had an IGT pattern shown on the 75-g OGTT, according to the guideline of the JDS (10). Smoking history was taken as positive when the case had smoked for at least the past

Table 1. Comparison of coronary risk factors in the subjects with coronary artery disease in 1993, 1996, 1999 and 2000.

| Year | 1993 (n = 219) | 1996 (n = 238) | 1999 (n = 248) | 2003 (n = 277) | p |
|------|---------------|---------------|---------------|---------------|---|
| Male | n (%)         |               |               |               |   |
| Hypertension | n (%)         |               |               |               |   |
| Dyslipidemia | n (%)         |               |               |               |   |
| High TC | n (%)         |               |               |               |   |
| High TG | n (%)         |               |               |               |   |
| Low HDL-C | n (%)         |               |               |               |   |
| IGT | n (%)         |               |               |               |   |
| DM | n (%)         |               |               |               |   |
| Obesity | n (%)         |               |               |               |   |
| Smoking | n (%)         |               |               |               |   |
| Age (years old) | 61.0 ± 9.6     | 62.9 ± 9.1    | 63.9 ± 10.0   | 67.1 ± 10.1   | < 0.01 |
| SBP (mmHg) | 135.1 ± 18.8   | 132.0 ± 18.9  | 132.4 ± 19.5  | 130.1 ± 18.7  | 0.27 |
| TC (mg/dl) | 205.8 ± 41.3   | 183.7 ± 36.6  | 182.7 ± 34.9  | 176.8 ± 39.1  | < 0.01 |
| LDL-C (mg/dl) | 142.1 ± 43.0   | 115.7 ± 34.1  | 110.0 ± 29.9  | 108.8 ± 34.3  | < 0.01 |
| TG (mg/dl) | 144.5 ± 73.8   | 123.3 ± 63.7  | 125.6 ± 63.3  | 123.7 ± 70.3  | < 0.01 |
| HDLC (mg/dl) | 38.8 ± 19.2    | 43.6 ± 14.3   | 47.5 ± 13.9   | 43.8 ± 13.3   | < 0.01 |
| HbA1c (%) | 5.8 ± 1.6      | 5.9 ± 1.3     | 6.2 ± 1.3     | 6.4 ± 1.6     | < 0.01 |
| BMI (kg/m²) | 23.9 ± 3.2     | 23.6 ± 2.9    | 23.9 ± 3.6    | 23.9 ± 3.8    | 0.74 |

Values are the mean ± SD. TC: total cholesterol; TG: triglyceride; HDLC: high-density lipoprotein-cholesterol; high TC: ≥ 220 mg/dl; high TG: ≥ 150 mg/dl; low HDLC: < 40 mg/dl; IGT: impaired glucose tolerance; DM: diabetes mellitus; SBP: systolic blood pressure; LDL-C: low-density lipoprotein-cholesterol; HbA1c: glycated hemoglobin A1c; BMI: body mass index. Analysis was by chi-square test in upper panel and ANOVA in lower panel.
year. Obesity was diagnosed in cases that had body mass index (BMI) $\geq 25.0$ at the time of admission, according to the guideline of the Japan Society for the Study of Obesity (11).

**Acute coronary syndrome**

Acute coronary syndrome (ACS) (12, 13) was diagnosed in patients with either acute myocardial infarction (AMI) or unstable angina pectoris. AMI was diagnosed in patients who had typical symptoms, with either elevation of serum creatine kinase more than triple the upper normal limit, or electrocardiography findings of ST-T change following evolution of the Q wave. Non-Q wave infarction was diagnosed by typical ST segment and/or T wave changes associated with serum creatine kinase elevation. Unstable angina pectoris was diagnosed in patients hospitalized with worsening angina or new-onset angina at rest without creatine kinase elevations.

**Coronary angiography**

Coronary angiography was performed in patients with either ACS or possible ischemia, judged by results of exercise stress tests. Follow-up coronary angiography was routinely performed 6 months after therapy by percutaneous coronary intervention. Three experienced investigators carefully reviewed coronary angiograms and reported the severity of stenosis. Significant coronary stenosis was defined as $\geq 75\%$ stenosis. According to the number of vessels with significant stenosis, we determined 2-vessel disease (2VD) or 3-vessel disease (3VD). MVD was diagnosed by the presence of significant stenosis in more than two major coronary vessels. In cases without stenosis of coronary arteries, provocative tests to induce spasm were selectively performed by injecting intravenous ergonovine. Luminal narrowing $\geq 75\%$ with chest pain or ST-T changes were considered positive.

**Statistical analysis**

Continuous variables were expressed with the mean ± standard deviation (SD) and analyzed using one-way fractional ANOVA with post-hoc test using the Bonferroni correction. Categorical data were presented as the frequency and analyzed using the chi-square test. Chi-square test or logistic regression was used to estimate the odds ratio and 95% confidence intervals for ACS and MVD. Probability values of less than 0.05 were considered significant. All data were analyzed using the Statview software version 4.0.

**Results**

**Patient characteristics**

We studied the clinical characteristics of CAD patients hospitalized in 1993, 1996, 1999 and 2003 (Table 1). There was no significant change in gender. Over 70% of the CAD patients were male in each year. Among the prevalence of categorized risk factors, DM was the only factor with significant elevation. The prevalence of hypertension, dyslipidemia (high TC, high TG, and low HDL-C), IGT, and obesity was not altered. In contrast, current smoking significantly decreased, to less than 50%. On comparison of the levels of risk factors among CAD patients, age and HbA1c increased steadily and significantly. HDL-C also increased. TC and LDL-C, and triglyceride steadily improved. SBP and body mass index were not altered.

**Coronary risk factors in ACS in 1993 and 2003**

We compared coronary risk factors in ACS between 1993 and 2003. The prevalence of IGT and DM increased and that of current smokers decreased in the past decade (IGT: 5.9% in 1993 to 11.0% in 2003, DM: 24.6% in 1993 to 46.8% in 2003). Smoking: 66.7% in 1993 to 48.6% in 2003 (Table 2). In logistic regression analysis for predictors of ACS, neither DM nor IGT had significant odds ratio for ACS in 1993 and 2003 (Table 2). In this study, the recent increase in the prevalence of DM seemed not to be associated with the frequency of ACS.

**Influence of DM on MVD in 1993 and 2003**

Next, we compared the number of vessels with significant stenosis in the coronary arteries. Each population rate of 2VD, 3VD, and MVD in 2003 was significantly higher than those in 1993 (30.3%, 28.4%, 58.8% versus 25.6%, 19.2%, 44.7%, respectively, $p < 0.01$) (Fig. 1). In 1993, there was a linear trend between DM and the number of vessels with significant stenosis and between dyslipidemia, especially low HDL-C, and the number of vessels with significant stenosis (Table 3). DM and dyslipidemia had significantly high odds ratio for MVD, indicating that these were important predictors for MVD (Table 4). In 2003, we also found a significant linear trend between the prevalence of DM and the number of vessels with significant stenosis, but dyslipidemia had no significance in MVD (Tables 3 and 4), although dyslipidemia still had the highest prevalence.

**Discussion**

Since the marked by increasing population of DM patients in Japan has come into focus, we compared coronary risk factors among CAD inpatients in 1993, 1996, 1999 and 2003 at our hospital, and examined the recent trend of DM among CAD patients over the past decade and its influence on the clinical characteristics of CAD in this study. The prevalence of glucose intolerance including IGT and DM significantly increased from 30.6% in 1993 to 55.6% in 2003 ($p < 0.01$), and HbA1c levels among CAD inpatients correspondingly increased, although the
Table 2. Predictor in categorized risk factors for acute coronary syndrome.

|   | 1993 (n = 69) | 2003 (n = 109) |
|---|---------------|-----------------|
|   | n (%) OR 95% CI | n (%) OR 95% CI |
| ACS | 69 (55.1) 0.67 0.37–1.20 0.12 | 109 (63.3) 0.93 0.57–1.54 0.79 |
| Hypertension | 38 (55.1) | 69 (63.3) |
| Dyslipidemia | 44 (63.8) 0.96 0.53–1.74 0.90 | 71 (65.1) 1.15 0.70–1.90 0.59 |
| High TC | 23 (33.3) 0.92 0.50–1.67 0.77 | 27 (24.8) 0.64 0.37–1.10 0.11 |
| High TG | 22 (31.8) 1.13 0.61–2.09 0.70 | 27 (24.8) 1.17 0.66–2.06 0.60 |
| Low HDL-C | 27 (39.1) 1.05 0.58–1.88 0.87 | 50 (45.9) 1.45 0.89–2.37 0.14 |
| IGT | 4 (6.8) 0.96 0.29–3.25 0.95 | 12 (11.0) 1.03 0.48–2.24 0.94 |
| DM | 17 (24.6) 1.00 0.51–1.93 0.99 | 51 (46.8) 1.14 0.70–1.86 0.59 |
| Obesity | 22 (31.8) 0.86 0.46–1.66 0.68 | 40 (36.7) 1.33 0.68–1.87 0.14 |
| Smoking | 46 (66.7) 1.50 0.92–2.44 0.10 | 53 (48.6) 1.50 0.92–2.44 0.10 |

ACS: acute coronary syndrome, OR: odds ratio, CI: confidence interval, TC: Total cholesterol, TG: Triglyceride, HDL-C: high-density lipoprotein-cholesterol, high TC: ≥ 220 mg/dl, high TG: ≥ 150 mg/dl, low HDL-C: < 40 mg/dl, IGT: impaired glucose tolerance, DM: diabetes mellitus. Analysis was chi-square test.

Comparing lipid profiles of CAD inpatients over the past decade, a decrease in TC and LDL-C and an increase in HDL-C emerged. In this study, the rate of patients taking HMG-CoA reductase inhibitors (statins) among CAD inpatients increased from 15% in 1993 to 33% in 2003 (data not shown). Although the prevalence of dyslipidemia among CAD inpatients remained constant and high, these results suggested that appropriate treatment, including statins and fibrates, at least, for the prevention of the worsening of dyslipidemia was provided over the past decade. The prevalence of hypertension and the SBP level also did not change in these years. Dyslipidemia and hypertension should be well managed by diet, exer-

Fig. 1. Comparison of prevalence of multi-vessel disease (MVD) among the patients with coronary artery disease (CAD) in 1993 and 2003. 2VD: 2-vessel disease, 3VD: 3-vessel disease. MVD was diagnosed by the presence of significant stenosis in more than two major coronary vessels. * p < 0.01, analysis was by chi-square test.
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A steady decrease in the current smoking rate among CAD inpatients over the past decade was observed. Against the background of recent educational activities for smoking-related disease such as CAD and cancer, the smoking rate in the Japanese, especially in adult men, has been decreasing. Our findings may follow this trend. Recent findings confirmed CAD as a major outcome of the metabolic syndrome, which is clinically recognized as obesity, elevated blood pressure, elevated triglycerides, reduced HDL-C and glucose intolerance (14). In our study, cases with more than three of these metabolic abnormalities increased from 18.7% in 1993 to 26.7% in 2003 (data not shown). Although the increasing prevalence of obesity and BMI level was not significant during this decade, we should be cautious of the increase in the prevalence of the metabolic syndrome.

ACS is an urgent state in which the coronary arteries are sub-occluded or occluded with thrombus following the breakdown of unstable atheromatous plaque and erosion (12, 13). Recent reports have revealed that DM patients have a higher rate of acute myocardial infarction (7, 15, 16), and the National Cardiovascular Center recently revealed that the prevalence of DM and IGT among inpatients with ACS reached 46% and 18%, respectively. Hence, we investigated whether DM is associated with the frequency of ACS. The prevalence of DM in the ACS group significantly increased over the past decade and reached 46.8% in 2003, although the odds ratio of DM for ACS was not significant in 1993 or 2003 (Table 2). We could not provide conclusive evidence that DM is directly contributive to the increased frequency of ACS. On the other hand, DM had a high odds ratio for MVD, suggesting that DM is associated with severe progression in CAD. Several studies have already reported that DM accelerated coronary atherosclerosis (3–6), and easily induced MVD (17–20). In 1993, DM and dyslipidemia were important predictors for MVD (Table 4). However, in 2003, important predictors for MVD shifted to DM alone, and dyslipidemia was not a significant predictor for MVD (Table 4), although dyslipidemia still had the highest prevalence in CAD (Table 1).

In this study, we included vasospastic angina patients among those studied. Recent evidence has shown that increase in triglyceride and remnant levels and hyperinsulinemia are significantly related to the develop-

### Table 3. Comparison of categorized coronary risk factors divided by number of vessels affected.

| Year | Vessels | Hypertension | Dyslipidemia | High TC | High TG | Low HDL-C | DM | Obesity | Smoking |
|------|---------|--------------|--------------|--------|--------|-----------|-----|---------|---------|
| 1993 | 1 vessel| 63 (66.3)    | 56 (58.9)    | 31 (32.6) | 27 (28.4) | 29 (30.5) | 7 (7.4) | 18 (18.9) | 65 (68.4) |
|      | 2 vessels| 34 (60.7)    | 40 (71.4)    | 21 (37.5) | 19 (33.9) | 23 (41.1) | 3 (5.4) | 17 (30.4) | 34 (60.7) |
|      | 3 vessels| 25 (59.5)    | 35 (83.3)    | 18 (42.9) | 17 (40.5) | 26 (61.9) | 2 (4.8) | 17 (40.5) | 23 (54.8) |
|      | p        | 0.67         | 0.02         | 0.50    | 0.37    | < 0.01    | 0.80  | 0.03    | 0.28    |
| 2003 | 1 vessel| 60 (63.2)    | 61 (64.2)    | 39 (36.8) | 21 (22.1) | 37 (38.9) | 7 (7.4) | 18 (18.9) | 65 (68.4) |
|      | 2 vessels| 54 (64.3)    | 47 (56.0)    | 22 (26.2) | 17 (20.2) | 32 (38.1) | 3 (5.4) | 17 (30.4) | 34 (60.7) |
|      | 3 vessels| 53 (67.1)    | 56 (70.9)    | 20 (25.3) | 21 (26.6) | 37 (46.8) | 2 (4.8) | 17 (40.5) | 23 (54.8) |
|      | p        | 0.86         | 0.27         | 0.17    | 0.61    | 0.46      | 0.26  | < 0.01  | 0.95    |

TC: total cholesterol, TG: triglyceride, HDL-C: high-density lipoprotein-cholesterol, high TC: ≥ 220 mg/dl, high TG: ≥ 150 mg/dl, low HDL-C: < 40 mg/dl, IGT: impaired glucose tolerance, DM: Diabetes mellitus. Analysis was by chi-square test.
Development of vasospastic angina (21, 22). We examined whether the recent increase in glucose intolerance has affected the frequency of vasospastic angina. Interestingly, we found that vasospastic angina decreased from 11.8% in 1993 to 6.9% in 2003 (p = 0.07) (data not shown). Sueda et al. recently reported that the frequency of vasospastic angina has been decreasing in Japan, possibly due to the widespread use of calcium antagonists (23). Our findings might be compatible with those of their report.

The whole number of coronary angiographies rapidly increased from 357 in 1993 to 759 in 2003, and the whole number of CAD patients hospitalized for coronary angiography also increased from 238 in 1993 to 384 in 2003 at our hospital. This number of CAD patients also included some patients who were re-hospitalized in the same year, especially in cases of DM patients who tended to be re-hospitalized with recurrence, or for re-treatment. To determine the exact trend of coronary risk factors among CAD inpatients, we excluded the re-hospitalized patients with recurrence, for re-treatment or for re-study, as described in “Study Patients”.

Table 4. Predictor in categorized risk factors for multi-vessel disease.

|         | 1993 | 2003 |
|---------|------|------|
| MVD (n = 98) |      |      |
| Hypertension | 59 (60.2) | 107 (65.6) |
| Dyslipidemia | 75 (76.5) | 103 (63.2) |
| High TC | 39 (39.8) | 42 (25.8) |
| High TG | 36 (36.7) | 38 (23.3) |
| Low HDL-C | 49 (50.0) | 69 (42.3) |
| IGT | 5 (5.1) | 15 (9.2) |
| DM | 34 (34.7) | 87 (53.4) |
| Obesity | 31 (31.6) | 58 (35.6) |
| Smoking | 57 (58.2) | 68 (41.7) |

OR: odds ratio, CI: confidence interval, TC: total cholesterol, TG: triglyceride, HDL-C: high-density lipoprotein-cholesterol, high TC: ≥ 220 mg/dl, high TG: ≥ 150 mg/dl, low HDL-C: < 40 mg/dl, IGT: impaired glucose tolerance, DM: diabetes mellitus. Multi-vessel disease (MVD) was diagnosed by the presence of significant stenosis in more than two major coronary vessels. Analysis was by chi-square test.

In conclusion, the profile of CAD inpatients changed and the importance of DM among coronary risk factors grew in a single center investigation. The consequent increase in the prevalence of MVD should be recognized as the most important problem clinically. A further prospective multi-center survey is needed to investigate the influence of the increasing population with DM on CAD.

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