Original Article

Current Trends in Lifestyle-Related Disease Management by General Practitioners: A Report from the "Heart Care Network" Groups

The Heart Care Network Groups

Aims: In Japan, it is believed that guidelines for lifestyle-related disease are used in routine clinical practice, however, there are few reports on the actual rate of healthcare conducted in accordance with these guidelines by general practitioners and on their usefulness in preventing cardiovascular events. Therefore, the Heart Care Network (HCN) groups were organized mainly by general practitioners treating lifestyle diseases in 62 areas of Japan.

Methods: The HCN has collected data on lifestyle diseases in high-risk patients in routine practices and investigated management conditions, guideline target achievement rates and medication. Additionally, the incidence of cardiovascular events was assessed.

Results: We analyzed 14,064 cases. The lipid profile, blood pressure, glycemic control were significantly improved over the 3 years. The incidence of cardiovascular events were significantly reduced by the achievement of target LDL cholesterol, systolic blood pressure and hemoglobin A1c and even after adjustment for age, gender, history of myocardial infarction, the reduction of these lifestyle-related parameters remains significant.

Conclusion: These results revealed the current trends in the healthcare activities of general practitioners, the management conditions for lifestyle diseases in CHD high-risk patients and their effects on reducing cardiovascular events.

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Key words; Coronary heart disease, Hypertension, Hyperlipidemia, Diabetes mellitus

Introduction

In the past several years, the number of deaths due to coronary heart disease (CHD) has leveled off in Japan but is still the second-ranking cause of death¹⁾. Attention is focused on the strict management of "lifestyle diseases", such as hyperlipidemia, hypertension and diabetes mellitus as risk factors of CHD. To elucidate CHD risk factors, many epidemiological surveys have been performed to date. In the USA, epidemiological data have been published from studies on local residents and people undergoing health checks in the Framingham Heart Study^{2,3)}, whereas in Japan similar data were collected in the Hisayama Study⁴⁾ and NIPPON DATA⁵⁾. These studies and many others conclusively demonstrated that hyperlipidemia, hypertension and diabetes mellitus are independent risk factors for

cardiovascular disease⁶⁾. It has been reported that the risk for onset of cardiovascular events in patients with 4 risk factors, high BMI, hypertension, hyperglycemia, and hypercholesterolemia, was 31.3 times higher than in those with no risk factors⁷⁾, suggesting that combined multiple risk factors synergistically increase the overall cardiovascular risk⁸⁾.

In Japan, management targets for hypertension, hyperlipidemia and diabetes mellitus have been set in the Japanese Society of Hypertension Guidelines for the Management of Hypertension⁹⁾, Japan Atherosclerosis Society Guidelines for Diagnosis and Treatment of Atherosclerotic Cardiovascular Diseases¹⁰⁾, and the Treatment Guide for Diabetes¹¹⁾, respectively, based on data from Japan and overseas.

Although it is believed that these guidelines are used in routine clinical practice in Japan, there are few reports on the actual rate of healthcare conducted in accordance with these guidelines by general practitioners and on their usefulness in preventing cardiovascular events.

Under these circumstances, the Heart Care Network (HCN) research groups were organized mainly

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by the local core hospital and 10 to 20 collaborating general practitioners who were treating lifestyle diseases in 62 local areas of Japan between 2000 and 2005 (see appendix). The HCN has collected data on lifestyle diseases in CHD high-risk patients in routine practices and investigated management conditions, guideline target achievement rates and medication conditions via research groups in each region.

In the present study, we compiled and reanalyzed HCN data from each region about 14,000 cases nationwide. From the results, it was possible to examine the healthcare activities of general practitioners, the management conditions for lifestyle diseases in CHD high-risk patients and their effects on reducing cardiovascular events.

Methods

Subjects

The subjects were adult (≥ 20 years old) patients with a history of myocardial infarction or with ≥ 2 lifestyle related diseases, such as hyperlipidemia, hypertension, and diabetes mellitus, who visited any of the 799 medical clinics or institutions participating in HCN research groups in 62 regions nationwide. Each clinic or institution tried to recruit at least 20 patients. The criteria for each disease on registration were as follows: for hyperlipidemia, LDL-cholesterol (LDL-C) ≥ 140 mg/dL or total cholesterol (TC) ≥ 220 mg/dL; hypertension, systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg; and diabetes mellitus, random blood glucose ≥ 200 mg/dL or fasting blood glucose (FBG) ≥ 126 mg/dL according to the Japanese guidelines for hypertension, hyperlipidemia and diabetes mellitus⁹⁻¹¹. In addition, patients who were already receiving treatment for these diseases could be registered regardless of satisfying these criteria. The exclusion criteria were as follows: (1) the presence of known untreated neoplasms; (2) type I diabetes mellitus; (3) the presence of secondary hypertension; and (4) severe chronic pulmonary disease. Data of patients whose survey data could be obtained at least twice, i.e., those followed for ≥ 1 year were used for the analysis. Informed consent was obtained from all patients to participate in this study, which complied with the Declaration of Helsinki and proceeded according to the ethics policies of the involved clinic of institutions.

Data Collection

The survey items were height, body weight, chest x-ray findings (cardiothoracic ratio $\geq 50\%$ or not), findings of fasting blood test such as TC, HDL-C, tri-

glycerides (TG), LDL-C (calculated using the Friedewald formula or measured value in cases with triglycerides (TG) > 400 mg/dL), blood glucose, HbA1c, blood pressure measured in a seated position after 15 minutes rest on three separate occasions within 3 months prior to survey (average values of three measurements), medications, and incidence of cardiovascular events, including death associated with CHD, stroke, cardiogenic shock, sudden death, in addition to non-fatal myocardial infarction and stroke. Changes in healthcare activities (medications and status of application of lifestyle improvement program) and management conditions for CHD risk factors, such as hyperlipidemia, hypertension, diabetes mellitus, obesity, smoking (smokers were defined as smoking at the time of the survey), and alcohol consumption (drinkers were defined as drinking ≥ 3 times per week and drinking ≥ 1 unit of alcohol each time), were surveyed once a year, 4 times in total: at registration for the 3-year survey, and during the first, second, and third years of the survey, respectively. Guideline target achievement was determined by whether the mean of each value (LDL-C, SBP, HbA1c) obtained in each survey satisfied the guideline target level.

Statistical Analysis

Statistical analysis was performed using 1-way repeated measure analysis of variance (ANOVA) for changes in each of the measured values, and the chi-square test for the guideline target achievement rate. Kaplan-Meier estimation and the log-rank test were used for the onset of cardiovascular events. Cox proportional hazard models adjusting for age, gender and history of myocardial infarction were also used for multivariate analysis. In these survival analyses, cases without any events were censored at the date of the last survey.

The level of statistical significance was $< 5\%$. Values of blood pressure and age are expressed as the mean $\pm$ SD.

Results

Patient Characteristics

Of 15,055 registered patients, 14,064 patients (6,198 men and 7,866 women) whose survey data could be obtained at least twice were analyzed (mean number of recruited patients in each clinic or institution was 17.6 patients/institution). There were no significant differences in all characteristics between 14,064 patients and the residual 911 patients. The mean follow-up period was 960.7 days (range, 1–1095 days).

Table 1. Patient characteristics

Parameter	Value
No. of registered patients subjected to analysis	14,064
Mean age, years	66.8 ± 10.2
History of myocardial infarction, n (%)	2,003 (14)
Abnormal cardiothoracic ratio, n (%)	3,542 (25)
Hyperlipidemia, n (%)	11,684 (83)
TC, mg/dL	214.9 ± 36.5
TG, mg/dL	163.0 ± 119.3
HDL-C, mg/dL	55.2 ± 15.3
LDL-C, mg/dL	128.8 ± 32.7
Hypertension, n (%)	12,402 (88)
SBP, mmHg	142.6 ± 16.7
DBP, mmHg	80.1 ± 14.9
Diabetes mellitus, n (%)	7,166 (51)
Fasting blood glucose, mg/dL	121.2 ± 42.7
HbA1c, %	6.62 ± 1.48
Obesity [BMI, ≥25 kg/m ²], n (%)	5,839 (42)
BMI, kg/m ²	24.7 ± 3.5
Smoking, n (%)	2,087 (15)
Alcohol consumption, n (%)	4,756 (34)

TC, total cholesterol; TG, triglycerides; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index

Patient characteristics are shown in **Table 1**. They included 2,003 patients (14%) with a history of myocardial infarction, 11,684 (83%) with hyperlipidemia, 12,402 (88%) with hypertension, and 7,166 (51%) with diabetes mellitus. Those with multiple lifestyle diseases included 6,123 (44%) with hyperlipidemia and hypertension, 1,830 (13%) with diabetes mellitus and hypertension, and 1,130 (8%) with hyperlipidemia and diabetes mellitus. All 3 diseases were present in 4,131 (29%), and 1,828 (13%) also had obesity (defined as BMI ≥25 kg/m²; **Fig. 1**).

Time-Course of Changes in Coronary Risk Factors

1) Obesity, Smoking, and Alcohol Consumption

Over the 3-year survey period, the percentage of patients with obesity remained at 43%; that of smokers decreased from 15% to 13%, and that of those drinking alcohol changed from 35% to 34%. Hence no major changes were observed overall.

The percentage of patients offered guidance to stop smoking for smokers and diet and exercise therapy for all registered patients showed no significant change over 3 years.

2) Lipids

Fig. 2 shows changes of mean LDL-C values and

Fig. 1. Concomitant risk factors. **Fig. 2.** Changes in 3-year mean values and guideline target achievement rates for LDL-C.

guideline target achievement rates over 3 years. In all patients, LDL-C showed a significant ($p < 0.0001$) decrease from 128.8 ± 32.7 to 120.0 ± 29.2 mg/dL. The achievement rate for LDL-C target set in the Guidelines for Diagnosis and Treatment of Atherosclerotic Cardiovascular Diseases⁹⁾ (<140 mg/dL for patients with two risk factors, <120 mg/dL for patients with three or four risk factors or diabetes, <100 mg/dL for patients with myocardial infarction) showed a significant ($p < 0.0001$) increase from 45.0% to 57.1%. Both mean TC and TG showed significant ($p < 0.0001$) decreases from 214.9 ± 36.5 to 204.1 ± 33.1 mg/dL and 163.0 ± 119.3 to 147.6 ± 92.1 mg/dL over 3 years, respectively, while HDL-cholesterol (HDL-C) showed a significant increase from 55.2 ± 15.3 to 56.2 ± 15.6 mg/dL ($p < 0.0001$). The achievement rate for the therapeutic target values (TC <220 mg/dL for patients with two risk factors, <200 mg/dL for patients with three or four risk factors or diabetes, <180 mg/dL for patients with myocardial infarction, TG <150 mg/dL, HDL-C ≥40 mg/dL) also showed significant ($p <$

Fig. 3. Changes in 3-year mean values and guideline target achievement rates for SBP.

0.0001) improvement from 38.0% to 51.4% for TC, 57.3% to 63.4% for TG, 86.7% to 87.9% for HDL-C, respectively.

3) Blood Pressure

Significant decreases were observed over 3 years for both SBP (from 142.6 ± 15.7 to 137.5 ± 14.3 mmHg) and DBP (from 80.1 ± 10.8 to 77.1 ± 8.7 mmHg; both $p < 0.0001$). The achievement rate for the therapeutic target values of the Japanese Society of Hypertension: Guidelines for the management of hypertension (JSH 2004) ($<130/85$ mmHg for young or middle age adults, $<140/90$ mmHg for elderly, $<130/80$ mmHg for patients with diabetes) also showed significant improvement from 24.7% to 34.0% for SBP and from 57.2% to 68.1% for DBP (both $p < 0.0001$). Changes of mean SBP values and guideline target achievement rates are shown in **Fig. 3**.

4) Blood Glucose

Mean FBG significantly ($p < 0.0001$) fell from 121.2 ± 42.7 to 116.7 ± 37.3 mg/dL and the guideline target achievement rate significantly ($p < 0.0001$) increased from 69.6% to 74.6%. Mean HbA1c values also improved from 6.62% to 6.50% ($p < 0.0001$). The achievement rate for the therapeutic target values of the Treatment Guide for Diabetes ($<6.50\%$) also showed significant improvement from 52.8% to 56.3%. Changes of mean HbA1c and guideline target achievement rates over 3 years are shown in **Fig. 4**.

5) Use of Therapeutic Drugs

The prescription rates for antihyperlipidemic drugs showed no major changes over 3 years; a drug prescription rate of about 75% was maintained throughout this period. The most common drug class prescribed was

Fig. 4. Changes in 3-year mean values and guideline target achievement rates for HbA1c.

HMG-CoA reductase inhibitor (statin) (**Fig. 5a**).

Prescription figures for antihypertensive drugs revealed that about half the patients were prescribed calcium channel blockers (CCBs) throughout the survey period, whereas angiotensin II receptor blockers (ARBs) showed an increase from 22.4% to 35.8% and diuretics increased from 9.2% to 12.5% in 3 years. As a result, the mean number of drugs prescribed/patient increased from 1.45 to 1.62 (**Fig. 5b**). Analysis of the concomitant use of antihypertensive drugs at the time of registration showed concomitant angiotensin-converting enzyme (ACE) inhibitors and CCBs was the most common combination (22% of patients on concomitant medication) and concomitant ARBs and CCBs was the second (20% of patients on concomitant medication). In the third year, ACE inhibitors plus CCBs dropped to 16% and were replaced by ARB plus CCB as the most common combination at 30%.

Among antidiabetic drugs, prescription rates for insulin, biguanides, and anti-insulin resistance drugs increased over 3 years and, as a result, the mean number of drugs prescribed/patient increased from 0.96 to 1.15 (**Fig. 5c**).

6) Cardiovascular Events

The incidence of all cardiovascular events during the 3-year survey period was 15.1/1,000 persons/year. By disease, the incidence rate/1,000 persons/year was 4.4 for fatal and nonfatal myocardial infarction, and 7.8 for fatal and non-fatal stroke.

Over 3 years, the incidence of cardiovascular events was significantly lower in patients who achieved target values of LDL-C, SBP, and HbA1c than in those who did not (**Fig. 6a-c**). In multivariate analysis, the Cox proportional hazard model adjusting for age, gender, and history of myocardial infarction showed a sig-

Fig. 5. Prescriptions of drugs and changes over time.

- a) Antihyperlipidemic drugs
 b) Antihypertensive drugs
 CCB, calcium channel blockers; ACE, angiotensin converting enzyme;
 ARBs, angiotensin II receptor blockers
 c) Antidiabetic drugs
 α-GIs, alpha-glucosidase inhibitors

Fig. 6. Effect of guideline target achievement rates on cardiovascular events.

- a) LDL-C: Significantly higher event-free survival was observed in achieved group (Log-rank test, $p=0.0001$)
 b) SBP: Significantly higher event-free survival was observed in achieved group (Log-rank test, $p=0.0148$)
 c) HbA1c: Significantly higher event-free survival was observed in achieved group (Log-rank test, $p=0.0006$)
 LDL-C, LDL cholesterol; SBP, systolic blood pressure

Table 2. Results of multivariate analysis

	HR	95%CI	<i>p</i>
LDL-C			
Not achieved	1.00	Reference	
Achieved	0.77	0.64–0.93	0.0066
SBP			
Not achieved	1.00	Reference	
Achieved	0.58	0.47–0.71	<0.0001
HbA1c			
Not achieved	1.00	Reference	
Achieved	0.62	0.51–0.75	<0.0001

HRs and CIs were adjusted by age, gender, smoking, alcohol consumption, history of myocardial infarction.

HR, hazard ratio; CI, confidence interval; LDL-C, LDL cholesterol; SBP, systolic blood pressure

nificantly lower risk for cardiovascular events in patients who achieved target values of LDL-C, SBP, and HbA1c than in those who did not (**Table 2**).

Discussion

In this study, we demonstrated significant associations between the achievement of target values in the guidelines for each disease and cardiovascular events at high risk of CHD under the routine care of general practitioners. Furthermore, we investigated the clinical healthcare activities of general practitioners, mainly by analyzing patterns of drug prescriptions. Based on the results, several effects and problems related to routine healthcare in Japan became apparent.

First, substantial improvements were found in management conditions for hypertension, hyperlipidemia, and diabetes mellitus over the 3-year investigation period. This appears to be due to the healthcare activities of physicians with the introduction of potent drugs such as statins and CCBs, ACE inhibitors and ARBs. On the other hand, no major changes in obesity and smoking were observed that indicated difficulties in changing a patient's lifestyle, such as diet, exercise, and smoking habits.

Target achievement rates among patients taking antihyperlipidemic agents in the Japan Lipid Assessment Program (J-LAP)¹²⁾ were 53.1% for TC and 63.4 for LDL-C, whereas we observed slightly lower rates of 51.4% and 57.1%, respectively. This difference was probably because the subjects in the present study had ≥ 2 CHD risk factors or were secondary prevention cases, which made them more severe cases than those included in J-LAP and therefore more difficult to treat. It is also possible that the participating

physicians did not change the treatment target based on the patients' disease state. In the 3 years of the survey, although approximately 60% of patients were prescribed statins, in about 1 in 4 patients, antihyperlipidemic drugs, including statins, were not prescribed. Furthermore, among hypertensive patients, about half did not receive drug treatment and of those who did, about half achieved blood pressure target values; that is, only 1 in 4 patients with hypertension received sufficient antihypertensive treatment, a problem called the "one-half rule"¹³⁾.

For hypertension, major changes were seen for drug prescriptions and this appeared to contribute to the increase in the guideline target achievement rate. Among prescriptions, the percentage of ARB showed a marked increase of about 1.6-fold over 3 years; however, prescriptions of ACE inhibitors decreased. This is considered to be caused by several ARBs that have been launched during those years and recent evidence in favor of their inhibitory effects against new-onset diabetes, a renal protective effect^{14, 15)}. For diuretics, there is concern about metabolic adverse reactions¹⁶⁾ and hence the prescription frequency in Japan had been rather low¹⁷⁾; however, in HCN we observed a slightly increased prescription rate of these medications over 3 years. The participants in HCN were possibly in the process of reconsidering diuretics based on recommendations for prescription of these agents by the Japan Society of Hypertension and other academic societies made under the influence of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)¹⁸⁾ and other studies. This survey showed that patients achieving the SBP guideline target value accounted for only 34.0% even in the third year. It is necessary to introduce more aggressive antihypertensive therapy for better blood pressure management in the future.

Among anti-diabetic drugs, a notable increase in biguanides prescriptions was observed. Since deaths caused by lactic acidosis were reported in the 1970s, biguanides have been largely avoided; however, in recent years several misunderstandings have been resolved and a possible reason in the increased use of these drugs might be the rising incidence in Japan of type 2 diabetes mellitus associated with obesity, which often responds well to these drugs¹⁹⁾.

The most noteworthy result of this survey was that we could confirm that patients who did not achieve guideline target values for hyperlipidemia, hypertension, and diabetes mellitus experienced significantly more events than those achieving the targets. Currently, various diagnosis and treatment guidelines are applied by general practitioners in Japan, but

there are few epidemiological data showing any connection between the achievement of target values and inhibition of cardiovascular events. Therefore, our nationwide HCN data are valuable since they verify the appropriateness of guideline treatment target values and the beneficial effect of their attainment in routine healthcare by general practitioners.

This research was an observational cohort study under routine healthcare; it did not specify what interventions, such as medication or patient guidance, were to be used during the survey period. For this reason, the research allows only limited evaluation of the efficacy of specific treatment methods. However, since the treatments given are analyzed by the research groups in each region every year, the participating physicians have gained increased awareness of the management of lifestyle diseases during the survey period. Therefore this research can be notionally considered a cohort study wherein the test intervention was physicians' awareness. The organization of HCN research groups has deepened discussions and promoted reform of the awareness of physicians, leading to increased guideline achievement rates. This implies that scientific societies and guideline committees should make efforts to undertake activities to promote their guidelines and follow the status of subsequent clinical application. The present data also reconfirm the importance of activities of small-sized, regional hospital-clinic cooperative research groups such as HCN.

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Appendix

a) The nationwide-network organization of "HCN research groups"

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