Coronary Risk Factors in Angiographically Defined Patients with Chest Pain

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Coronary risk factors were assessed in 186 consecutive patients who received coronary angiography. The severity of coronary luminal narrowing was scored as the coronary sclerosis index (CSI). Patients were divided into normal coronary arteries (N, n = 72), coronary sclerosis without infarction (C, n = 73) and previous myocardial infarction (MI, n = 41). The CSI increased with age. A significant difference in serum triglycerides, HDL cholesterol and atherogenic index was observed between Groups C or MI and N. Multivariate analysis revealed that CSI had correlated with total- and HDL-cholesterol, uric acid and age in subjects under 55 years; and with age, blood sugar, factor H and HDL cholesterol in those of 55 years or over. When patients were classified by their total and LDL cholesterol level, a significantly different CSI was found between the desirable and high cholesterol levels in subjects under the age of 55, but it was not significant in those over 55. Therefore, disorders in lipid metabolism should be corrected in early middle age.

Key words: Coronary atherosclerosis, Myocardial infarction, Cholesterol, Uric acid, Lipoproteins, Age

The incidence of cardiac disease has recently increased to become the second leading cause of death in Japan. Changes in life style and eating habits may be responsible. Nevertheless, compared to Western countries, Japan has a relatively lower incidence of CHD.

A number of metabolic and psychosocial factors have been identified as coronary risk factors. Epidemiologic studies such as the Framingham Heart Study (1), Seven Countries Study (2), and Multiple Risk Factor Intervention Trial (3) have provided information on the association of coronary risk factors with the incidence or mortality of CHD over many years. An assessment of coronary risk factors in Japan was the goal of this study. Since the definitive diagnosis of CHD is based on coronary angiography, risk factors for CHD were analyzed in 186 patients who received coronary angiography to evaluate the cause of chest pain.

SUBJECTS AND METHODS

A total of 186 consecutive patients with chest pain, 122 males and 64 females, underwent coronary angiography. Evaluated at the time of admission were such risk factors as age, sex, body mass index [Kaup's index = $\text{body wt}/\text{ht}^2$], blood pressure, number of cigarettes smoked per day, levels of serum lipids and apo-lipoproteins, fasting blood sugar, uric acid and type A behavior. Serum lipids were estimated by enzymatic methods. Glucose and uric acid were measured by conventional methods after a 14-h fast. All medications were discontinued at least one week before the study. LDL cholesterol was determined by the equation of Friedewald et al (4). $\text{LDL cholesterol (mg/dl)} = \text{total cholesterol} - [\text{HDL cholesterol} + (1/5 \text{ triglyceride})]$. Apolipoproteins were determined by the immunodiffusion method.

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The assessment of Type A behavior and analysis of factor S (speed), factor J (job involvement) and factor H (hard driving and competitiveness) were done using a self-administered, computer-scored questionnaire using the Japanese edition of the Jenkins Activity Survey (JAS) (5). The hostility score was estimated using the scale developed by Cook and Medley (6). To exclude any influence of coronary spasms in the angiogram, nitroglycerin was injected into the coronary artery before the diagnostic angiography was performed. Coronary atherosclerosis was assessed and scored by three experts: 0 for no luminal narrowing, 1 for 25% of luminal cavity narrowing, 2 for 50%, 3 for 75%, 4 for 90%, 5 for 99%, and 6 for complete occlusion. The coronary sclerosis index (CSI) was calculated by multiplying the score by the number of coronary segments involved as classified according to AHA (7). Even though, there are some limitations since a computerized image analyzer was not available for this study, because the angiogram is a luminogram and the width of original arterial lumen is unknown, the least narrowed segment is often presumed to be normal.

Patients were divided into three groups: 72 normal coronary arteries (N), 73 apparent coronary sclerosis with at least 25% luminal narrowing in any segment and without a prior history or evidence of myocardial infarction (C), and 41 with evidence of

previous myocardial infarction (MI).

In addition, subjects were subdivided by their cholesterol level, using the classification of the National Cholesterol Education Program, and also by age: 55 years or older, and less than 55 years of age. Comparisons between the three groups were performed using a one-way analysis of variance followed by the Bonferroni test. Relationships between two variables were evaluated by the Statistical Analysis System. p value <0.05 was recognized as significant.

RESULTS

The coronary sclerosis index was increased with age as shown in Fig. 1. The regression equation for the coronary sclerosis index with age was as follows: $CSI = 0.32 \text{ Age} - 11.54$ ($r = 0.318$, $p < 0.001$). CSI in Group MI was significantly higher than that of Group C. The mean and standard deviation of coronary risk factors in the three groups is shown in Table 1. Variables showing significant differences between Group C or Group MI and the normal individuals included age, serum triglycerides, HDL cholesterol, atherogenic index calculated as the ratio of LDL cholesterol and HDL cholesterol (LDL chol/HDL chol). The incidence of cigarette smoking was extremely high in the MI patients but not in Group C. Fasting blood sugar was high in Group C but not in the MI group. There were no apparent

Fig. 1. Coronary sclerosis index (CSI) was elevated with age as analyzed by the regression equation; $CSI = 0.32 \text{ Age} - 11.54$.

differences in body mass index, blood pressure, total cholesterol, LDL cholesterol, apolipoproteins, or behavioral test scores concerning type A behavior and related factors in the three groups. There were no apparent differences in the hostility score among the three groups (see Table 1).

To avoid the influence of a modification of life style on type A behavior assessment in the patients following an acute myocardial infarction, multiple regression analysis of coronary risk factors and CSI was performed on normal subjects and those in Group C, not the MI group.

As previously reported (8), metabolic factors, particularly lipid components, were critical as a risk for coronary disease in subjects under the age of 55. A total of 145 subjects belonging to Groups N and C were divided into two age groups: 63 subjects under 55 years of age and 82 subjects aged 55 years and older. Standard regression coefficients with a

CSI of F value more than 2 are shown in Table 2. Four factors, total cholesterol, uric acid, age, and HDL cholesterol, were significantly correlated with the coronary sclerosis index ($R=0.607$) in those under 55 years of age. Four factors, age, blood sugar, factor H and HDL cholesterol showed a correlation of $R=0.572$ in the group over 55 years of age. Considering all 145 subjects, age, blood sugar, factor S (speed), and uric acid were correlated with the coronary sclerosis index ($R=0.508$). To ascertain whether cholesterol was a "real" risk factor, subjects were divided into three groups according to serum cholesterol and LDL cholesterol level as proposed by the National Education Program (9).

An apparent difference of CSI was found between the low and high risk cholesterol level in the subjects under age 55 as shown in Table 3. Similar results in LDL cholesterol level were ob-

Table 1. Coronary risk factors in the subjects evaluated by coronary angiography.

	Group N	Group C	Group MI	p value ^A
number of subjects	72	73	41	
male/female	36/36	51/22	35/6	
age	53.0 ± 9.2	58.1 ± 7.5*	56.2 ± 7.5*	0.0011
Coronary sclerosis index	0.0 ± 0.0	7.7 ± 6.7**	14.3 ± 9.9**	0.0003
Body mass index (kg/cm ²)	22.5 ± 5.0	21.5 ± 7.5	23.1 ± 4.5	NS
Systolic pressure (mmHg)	124.4 ± 38.2	126.4 ± 40.6	128.4 ± 30.7	NS
Diastolic pressure (mmHg)	69.3 ± 23.4	70.7 ± 23.1	69.6 ± 15.4	NS
Cigarette (/day)	8.3 ± 15.1	10.8 ± 15.9	18.9 ± 23.7**	0.0088
Fasting blood sugar (mg/dl)	83.1 ± 38.0	102.5 ± 51.3*	94.6 ± 57.6	NS
Total cholesterol (mg/dl)	201.5 ± 39.4	214.7 ± 53.0	214.9 ± 43.3	NS
Triglyceride (mg/dl)	142.4 ± 74.4	175.2 ± 81.0*	192.4 ± 92.3**	0.0041
HDL cholesterol (mg/dl)	46.7 ± 16.5	36.3 ± 16.1**	34.8 ± 13.3**	0.0041
LDL cholesterol (mg/dl)	121.6 ± 46.2	133.4 ± 63.1	134.7 ± 54.6	NS
LDL chol/HDL chol	2.68 ± 1.25	3.42 ± 1.64**	3.83 ± 1.88**	0.005
apo A-I (mg/dl)	106.3 ± 56.6	104.5 ± 49.6	94.6 ± 52.9	NS
apo B (mg/dl)	77.8 ± 41.4	93.1 ± 45.4	92.3 ± 49.2	NS
apo C-II (mg/dl)	3.8 ± 2.8	4.9 ± 3.5	4.9 ± 3.3	NS
A-I/apo B	1.14 ± 0.68	0.98 ± 0.52	0.89 ± 0.56	NS
Uric acid (mg/dl)	5.5 ± 1.3	6.0 ± 1.6	6.2 ± 2.0*	0.0497
Behavioral study:				
Type A	0.99 ± 6.11	1.74 ± 6.37	-0.04 ± 5.17	NS
Factor S	-0.83 ± 6.60	0.73 ± 6.22	0.35 ± 6.32	NS
Factor J	-1.29 ± 4.15	-1.41 ± 5.18	-1.63 ± 3.54	NS
Factor H	2.03 ± 6.91	4.10 ± 7.46	1.38 ± 6.09	NS
Hostility score	153.7 ± 37.0	144.4 ± 21.9	152.5 ± 39.3	NS

Significant difference between the subjects with normal coronary (Group N), with apparent coronary sclerosis (Group C) or previous myocardial infarction (Group MI), indicated as * $p < 0.05$, ** $p < 0.01$, p value^A based on F statistics.

Table 2. Multiple regression analysis of correlation of coronary risk factors and coronary sclerosis index.

Less than 55 years n = 63			55 years or above n = 82			Total n = 145		
	B	R ² increase		B	R ² increase		B	R ² increase
Cholesterol	0.387	(0.091)	Age	0.368	(0.134)	Age	0.380	(0.114)
Uric acid	0.260	(0.155)	Blood sugar	0.373	(0.105)	Blood sugar	0.275	(0.055)
Age	0.228	(0.050)	Factor H	0.250	(0.056)	Factor S	0.234	(0.056)
HDL chol	-0.268	(0.073)	HDL chol	-0.181	(0.033)	Uric acid	0.183	(0.033)
R =	0.607		R =	0.572		R =	0.508	

B: standard regression coefficient, R: multiple correlation coefficient

tained in subjects under 55 years. No apparent difference in the coronary sclerosis index was found in the serum cholesterol or LDL cholesterol level in those over 55 years of age.

DISCUSSION

Hypercholesterolemia is a major risk factor for coronary heart disease. While no apparent difference was found in the total cholesterol and LDL cholesterol levels in the three groups studied, the ratio of LDL cholesterol and HDL cholesterol showed a significant difference between Group C or MI and the normal individuals (Group N). The Multiple Risk Factor Intervention Trial constituted the largest cohort of 361,662 subjects with standardized serum cholesterol measurements and long-term mortality on follow-up. That trial revealed that the coronary risk rose progressively with an increase in cholesterol level, particularly values above 200 mg/dl. Recently, the National Cholesterol

Education Program (9) provided new guidelines for the treatment of high cholesterol levels in adults aged 20 years and over. The total cholesterol level was classified as follows: <200 mg/dl, desirable; 200 to 239 mg/dl, borderline high; $\geq$ 240 mg/dl, high. Regarding LDL cholesterol, <130 mg/dl has been classified as desirable, 139 to 159 mg/dl borderline high and $\geq$ 160 mg/dl, high risk. Following this classification the coronary sclerosis index was estimated in our study as shown in Table 3. A significantly higher coronary sclerosis index was found in the high risk cholesterol and LDL cholesterol group as compared to those the desirable cholesterol levels in the younger age group. No apparent difference in CSI by cholesterol and LDL cholesterol level was found in the older group. In contrast to our results, Castelli et al (10) reported that HDL cholesterol and total cholesterol levels were related to the development of CHD in both men and women aged 49 years and older. Hiasa et

Table 3. Coronary sclerosis index in the total and LDL cholesterol levels, and by age of less than 55 years and 55 years or above.

	desirable	borderline	high risk	p value ^A
serum cholesterol	less than 199mg/dl	200–239mg/dl	more than 240mg/dl	
aged less than 55	2.05 $\pm$ 3.94 (n = 40)	2.42 $\pm$ 5.19 (n = 12)	7.36 $\pm$ 6.91 (n = 11) ^{a,b)}	0.0072
55 years or above	6.27 $\pm$ 8.42 (n = 30)	5.31 $\pm$ 6.99 (n = 29)	4.69 $\pm$ 5.54 (n = 23)	NS
LDL cholesterol	less than 129mg/dl	130–159mg/dl	more than 160mg/dl	
aged less than 55	2.03 $\pm$ 4.36 (n = 33)	3.29 $\pm$ 5.07 (n = 17)	5.67 $\pm$ 6.87 (n = 13)	NS
55 years or above	5.82 $\pm$ 8.73 (n = 36)	5.15 $\pm$ 6.54 (n = 22)	5.08 $\pm$ 5.47 (n = 24)	NS

a) significant difference between desirable level group and high risk level group

b) difference between borderline group and of high risk group (p < 0.1)

p value^A based on F statistics.

al (11) reported the cholesterol level was more associated with CHD defined by coronary angiography in aged patients.

We believe that a high cholesterol level is a pertinent risk factor for coronary sclerosis progression in people under the age of 55. In other words, reduction of hypercholesterolemia should be considered in younger patients to reduce the risk of CHD. A low HDL cholesterol level was found in the CHD groups. HDL is involved in the reversal of cholesterol transport from peripheral tissues such as the arteries to the liver. A low HDL cholesterol level indicates suppression of this reverse transport and promotes the development and progression of coronary sclerosis (12), as observed in this study.

No apparent difference in apo A-I was observed among the three groups studied. Several authors (13, 14) have reported that apolipoproteins are a more sensitive indicator of CHD than serum lipids. Our study revealed that serum lipids are a more appropriate indicator of CHD, particularly in people under the age of 55. A correlation between the level of triglyceride and that of HDL cholesterol was found in the present study. Sakuma et al (15) demonstrated that the conversion from HDL₃ to HDL₂ was impaired in hypertriglyceridemia. Further studies on the metabolism of HDL are required. As seen in the results of multiple regression analysis, the blood sugar level independently contributed to the CSI. The prevailing evidence that CHD is a common sequela of impaired glucose tolerance would be borne out by our study.

A possible association between elevated serum uric acid and coronary heart disease has been noted in several studies (16, 17). Other reports have failed to confirm this finding, or noted that the use of diuretics was the probable cause of the hyperuricemia. In this study, the administration of diuretics was discontinued at least one week before the blood studies to eliminate any influence on uric acid. Persky et al (16) reported that uric acid and the prevalence of ECG abnormalities and mortality appear to be secondary associations between uric acid and other risk factors in men. However, the association could not be explained by other risk factors for women. Kannel (17) from the results of the Framingham Study, reported that uric acid values were correlated with serum cholesterol,

glucose tolerance, weight, and blood pressure. Kannel concluded that elevated serum uric acid and gout were associated with the derangement of other major cardiovascular risk factors making it difficult to evaluate the influence of elevated serum uric acid level on CHD risk. In the present study, multivariate analysis indicated a moderate independent effect of uric acid, taking the associated greater burden of coronary sclerosis into account. The serum uric acid value was correlated with serum triglyceride ($r=0.386$) which showed an inverse correlation ($r=-0.348$) with HDL. Further studies are indicated to clarify the role of uric acid on atherogenesis.

A significantly higher serum triglyceride level was found in the CHD and MI groups vs. the normal subjects in this study, although the role of hypertriglyceridemia on atherosclerosis is controversial (18, 19). Eisenberg (20) stated that, in hypertriglyceridemia, both LDL and HDL contained a subnormal amount of cholesterol and did not clear as much cholesterol from the plasma as normal lipoproteins, and that excess cholesterol was present in VLDL. Such VLDL particles did not complete the VLDL $\rightarrow$ LDL conversion pathway and were cleared instead by alternate routes (macrophages or smooth muscle cells) which were potentially atherogenic. In this study, we observed an inverse correlation between HDL cholesterol and serum triglyceride. The association between HDL and triglyceride appears to be the central issue in the pathogenesis of atherosclerosis (21).

Considering a high serum uric acid level as a coronary risk factor, uric acid may be independent of triglyceride and HDL. A history of cigarette smoking was significantly linked to myocardial infarction in this study. In the Framingham Study, similar results were reported by Kannel et al (22) that the impact of cigarette smoking is greatest for occlusive arterial disease. Recent studies indicate that the elevated fibrinogen level and platelet activation, and altered hemostatic function caused by smoking can contribute to thrombus formation as a major cause of acute myocardial infarction (23).

Friedman (24) defined a coronary-prone behavior pattern or life style characterized by extreme competitiveness, striving for achievement, aggressiveness, haste, impatience, restlessness, hyperalertness,

explosiveness of speech, tension of facial musculature, and feeling of being under time constraints and under the challenge of responsibility as the type A behavior pattern. Those with the opposite pattern of behavior, relaxed, unhurried, mellow, satisfied, were designated as type B individuals. Several studies of type A behavior have utilized a self-administered, computer-scored questionnaire for determining the presence and intensity of the behavior pattern. This questionnaire, the Jenkins Activity Survey, was standardized and validated against clinical judgments of type A behavior. The test provides continuous scores on type A dimension and on three of its major behavioral components as determined by factor analysis: speed and impatience, job involvement, and hard-driving conscientiousness. This JAS in the Japanese edition was also validated for the assessment of type A behavior in Japanese as reported in a telephone company study in Nagoya (25). An association of type A behavior and coronary disease has emerged from retrospective evaluations of the Western Collaborative Group Study (26), Framingham Heart Study (29) and also from coronary angiographic studies (27, 28). In the present investigation, type A score did not differ among the three groups. Williams et al (30) reported a relationship between the hostility score and CHD. We did not find a significant relationship between the hostility score and CSI. Multivariate regression coefficient analysis between coronary risk factors and CSI revealed that only factor S had significance in subjects in groups C and N. Since the experience of severe chest pain or fear of death due to acute myocardial infarction may provoke a modification of life style and behavior, subjects with myocardial infarction were excluded from this study of the analysis of type A behavior. The contribution of type A behavior to coronary sclerosis was minimal in this study; only factor H or factor S was associated with CSI. The difference in the contribution of type A behavior to coronary sclerosis in this study to reports from western countries may be depend upon the differences in social influences. Ragland and Brand (31) reported that the mortality rate from CHD was significantly higher among type A patients than type B patients. They also stated that patients with CHD and type A behavior were not at increased risk for CHD mortality.

The results of the present study lead us to conclude the following: 1) coronary sclerosis progresses linearly with age, and 2) serum lipid disorders such as elevated LDL cholesterol or diminished HDL cholesterol are pertinent risk factors for the progression of coronary sclerosis in people under the age of 55. While an elevated serum uric acid level appears to be a moderate independent risk factor for coronary sclerosis, the mechanism for its role in atherogenesis is obscure and further studies are necessary. Cigarette smokers are at high risk for myocardial infarction. Type A behavior as measured by JAS may not indicate a risk for CHD among Japanese, but the hard-driving and speed-impatience components of the type A behavior pattern are predictors of CHD as reported by Lutz et al (32).

Abbreviations used; CSI: Coronary sclerosis index, N: Normal coronary, C: Coronary sclerosis without infarction, MI: Myocardial infarction, HDL: High density lipoprotein, LDL: Low density lipoprotein, CHD: Coronary heart disease

REFERENCES

- 1) Kannel WB, Eaker ED. Psychosocial and other features of coronary heart disease: Insights from the Framingham Study. *Am Heart J* **112**: 1066, 1986.
- 2) Keys A. Coronary heart disease in seven countries. *Circulation* **41** Suppl. 1: 1, 1970.
- 3) Martin MJ, Hulley SB, Browner WS, et al. Serum cholesterol, blood pressure, and mortality: Implications from a cohort of 361,662 men. *Lancet* **II**: 933, 1986.
- 4) Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma without of the preparative ultracentrifuge. *Clin Chem* **19**: 499, 1972.
- 5) Jenkins CD, Rosenman RH, Zyzanski SJ. Prediction of clinical coronary heart disease by a test for the coronary-prone behavior pattern. *Psychosom Med* **33**: 193, 1971.
- 6) Cook W, Medley D. Proposed hostility and pharisaic-virtue scales for the MMPI. *J Appl Psychol* **38**: 414, 1954.
- 7) AHA Committee Report. A reporting system on patients evaluated for coronary artery disease. *Circulation* **51**: 5, 1975.
- 8) Fujinami T, Sakuma N, Hayashi K, et al. Coronary heart disease and hyperlipidemia. *Cardioangiology* **25**: 55, 1989 (in Japanese).
- 9) The Expert Panel. Report of the National Cholesterol Education Program Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults. *Arch Intern Med* **148**: 36, 1988.
- 10) Castelli WP, Garrison RJ, Wilson PWF, et al. Incidence

- of coronary heart disease and lipoprotein cholesterol levels. The Framingham Study. *J Am Med Assoc* **256**: 2835, 1986.11.
- 11) Hiasa Y, Nosaka H, Ito Y, et al. Multivariate analysis of risk factors of ischemic heart disease. A coronary arteriographic approach. *Heart* **13**: 679, 1981 (in Japanese).
 - 12) Eisenberg S. High density lipoprotein metabolism. *J Lipid Res* **25**: 1017, 1984.
 - 13) Thompson C. Apoproteins: Determinants of lipoprotein metabolism and incidences of coronary risk. *Br Heart J* **51**: 585, 1984.
 - 14) Bruzell JD, Sniderman AD, Albers JJ, et al. Apoproteins B and A-I and coronary artery disease in humans. *Atherosclerosis* **4**: 49, 1984.
 - 15) Sakuma N, Lin C, Matsumoto Y, et al. Changes of HDL subfraction concentration and particle size by intralipid in vivo. *Atherosclerosis* **74**: 91, 1988.
 - 16) Persky VW, Dyer AR, Idris-Soven E, et al. Uric acid: A risk factor for coronary heart disease? *Circulation* **59**: 969, 1979.
 - 17) Kannel WB. Metabolic risk factors for coronary heart disease in women: Perspective from the Framingham Study. *Am Heart J* **114**: 413, 1987.
 - 18) Barbir M, Wile D, Trayner I, et al. High prevalence of hypertriglyceridaemia and apolipo protein abnormalities in coronary artery disease. *Br Heart J* **60**: 397, 1988.
 - 19) Castelli WP. The triglyceride issue; A view from Framingham. *Am Heart J* **112**: 432, 1986.
 - 20) Eisenberg S. Lipoprotein abnormalities in hypertriglyceridemia: Significance in atherosclerosis. *Am Heart J* **113**: 555, 1987.
 - 21) Nikkilä EA, Taskinen M-R, Sane T. Plasma high-density lipoprotein concentration and subfraction distribution in relation to triglyceride metabolism. *Am Heart J* **113**: 543, 1987.
 - 22) Kannel WB, McGee DL, Castelli WP. Latest perspective on cigarette smoking and cardiovascular disease: The Framingham Study. *J Cardiac Rehabil* **4**: 267, 1984.
 - 23) FitzGerald GA, Oates JA, Nowak J. Cigarette smoking and hemostatic function. *Am Heart J* **115**: 267, 1988.
 - 24) Friedman M, Rosenman RH, Straus R, et al. The relationship of behavior pattern A to the state of the coronary vasculature: A study of fifty-one autopsy subjects. *Am J Med* **44**: 525, 1968.
 - 25) Hayano J, Takeuchi S, Yoshida S, et al. Type A behavior pattern in Japanese employees: Cross-cultural comparison of major factors in Jenkins Activity Survey (JAS) responses. *J Behav Med* **12**: 219, 1989.
 - 26) Rosenman RH, Brand RJ, Sholtz RI, et al. Multivariate prediction of coronary heart disease during 8.5 year follow-up in the Western Collaborative Group Study. *Am J Cardiol* **37**: 903, 1976.
 - 27) Blumenthal JA, Williams RB, Kong Y, et al. Type A behavior pattern and coronary atherosclerosis. *Circulation* **58**: 634, 1978.
 - 28) Williams RB, Barefoot JC, Heney TL, et al. Type A behavior and angiographically documented coronary atherosclerosis in a sample of 2,289 patients. *Psychosom Med* **50**: 139, 1988.
 - 29) Kannel WB, Eaker ED. Psychosocial and other features of coronary heart disease: Insights from the Framingham Study. *Am Heart J* **112**: 1066, 1986.
 - 30) Williams RB Jr, Haney TL, Lee KL, et al. Type A behavior hostility and coronary atherosclerosis. *Psychosom Med* **42**: 539, 1980.
 - 31) Ragland DR, Brand RJ. Type A behavior and mortality from coronary heart disease. *N Engl J Med* **318**: 65, 1988.
 - 32) Lutz DJ, Holmes DS, Cramer RE. Hard-driving and speed-impatience components of the type A behavior pattern as predictors of physiological arousal, subjective arousal and challenge seeking. *J Psychosom Res* **31**: 713, 1987.
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