後の生存確率（累積生存率と呼ばれる）は，オイラー乗数（自然対数の底）を $e=2.718\cdots$ として

$$\exp(-\lambda T)=e^{-\lambda T}$$

という指数関数となる．これを1から引いたものが累積発生率である．もし λT が十分小さければ，上の式は $1-\lambda T$ で，累積発生率は λT で近似できる（1年間に5％死亡するなら2年でほぼ10％死亡．しかし，50年で250％死亡するわけではない．なお，1年で5％の累積死亡に対応する λ は0.051293/年）．

疫学でよく用いられる相対危険 relative risk は累積発生率の比であるが，ハザードが時間によらずほぼ一定で λT が十分小さければ，これはハザードの比にほぼ一致する．欧米の臨床家が好むオッズ比は累積発生率を p とすると $p/(1-p)$ で表されるオッズの比であるが，累積発生率 p が小さければ相対危険にほぼ一致する．すなわち，ハザードが時間によらずほぼ一定でかつ十分小さければ

ハザード比＝相対危険＝オッズ比

となる．

9．カプラン・マイアー法

累積生存率を求める方法．Product-limit 法と原論文では呼ばれたが，論文著者の名をとって Kaplan-Meier 法と呼ばれる．人口動態統計など大規模データを扱う場合には，区間を区切って，その区間当初の集団数，区間中でのイベント（死亡）数・脱落数から区間内での発症確率を計算し，累積生存率を計算するが，カプラン・マイアー法ではイベントごとに発症確率を計算し，それを1から引き累積（掛け算）することで累積生存率を求める．したがって推定された累積生存率曲線は階段状となる．これを1から減ずれば累積発症率となる．打ち切りデータがなければ各時点での生存割合に一致する．

10．ログランク検定

累積生存率あるいはハザードの群間の違いを調べるために用いられる標準的な検定方法．3年あるいは5年といったある一定の時点での累積生存率を比較するのではなく，すべての時点にわたって一種の平均をとる方法である．累積生存率の比較のためにはほかにも一般化 Wilcoxon 検定などが存在するが，両群のハザード比が時点によらずほぼ一定の場合には，最も効率的（検出力が大きい）であることが知られている．

11．コックス回帰

比例ハザードモデルに基づく生存時間の回帰分析手法．提唱者 DR Cox にちなみ，このように呼ばれている．ハザードが対象者に依らない基準ハザードと（治療を含む）対象者の特性に依存する部分の積で表されると仮定するのが‘比例ハザード性’であり，通常は，後者に対数線形モデルを想定し，治療を含む予後因子・予測因子の効果を推定する．基準ハザードに対する前提なしで後者の推定を行えることが‘ミソ’であり，イベント発生の順序情報のみによる‘部分尤度’に基づく最尤法により検定・推定を行う．1972年の原論文は医学統計において最も引用された論文とされており，これらの功績で Cox 教授は Sir の称号を英女王から得ている．

実際の応用そして適切なデータの解釈においては，上記の比例ハザード性を実データから検証しておくことが重要とされているが，ブラックボックス的な応用事例には事欠かない．実際にハザードが比例的でない事例も数多い．がん治療における免疫治療の効果，治療効果が限定されるサブグループの存在，強い治癒的な治療による初期死亡例の増加などがその例である．

12．NNT

number-needed-to-treat の略．ある薬剤に予防効果があるとして，一人あるいは1イベントを救うために投与しなければならない必要対象者の数．無投与群での累積発生率を p_0，投与群での累積発生率を p_1 として

$$\mathrm{NNT}=\frac{1}{p_0-p_1}$$

で推定される．相対危険のみではなく，無投与群でのベースラインリスクに依存することに注意されたい．すなわちベースラインリスクが10倍となれば NNT は 1/10 となる．

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Japan Arteriosclerosis Longitudinal Study-Existing Cohorts Combine (JALS-ECC)

Rationale, Design, and Population Characteristics

Japan Arteriosclerosis Longitudinal Study (JALS) Group*

Background The Japan Arteriosclerosis Longitudinal Study-Existing Cohorts Combine (JALS-ECC) is a pooled study based on individual participant data from existing prospective cohort studies in Japan. Its purpose was to consider associations between risk factors and cardiovascular disease (CVD) outcomes, as well as differences between subgroups, defined by age, gender or geographical region, which could not be detected in the smaller samples.

Methods and Results Individual records for 66,691 participants in 21 cohort studies were pooled, accounting for a total of 575,628 person-years. From this data, there were 409 deaths attributed to stroke and 169 deaths attributed to coronary heart disease (CHD). Total stroke and CHD events were 1,478 and 178, respectively. Of the 1,424 total stroke events with a reported stroke subtype, 975 were classified as ischemic, 267 as hemorrhagic, and 178 as subarachnoid hemorrhage.

Conclusion The JALS-ECC collected data from existing cohort studies covering a diverse Japanese population, which has provided information about the effects of modifiable factors on the risks of the CVD. Such information should provide a reliable basis for establishing prevention strategies. (*Circ J* 2008; **72:** 1563–1568)

Key Words: Cohort study; Coronary heart disease; Meta-analysis; Stroke

Many of the epidemiological studies that have been conducted in Japan are internationally accepted as studies that have a unique perspective;[1–12] however, except for a few of them, the studies are either small in size or short in follow-up duration. Consequently, the small numbers of cardiovascular events recorded in individual studies have limited the strength of the evidence provided by any single study. Therefore, most studies cannot provide precise evidence about associations between risk factors and disease outcomes, nor can they reliably assess differences among subgroups defined by age, gender, or geographical region.

The Japan Arteriosclerosis Longitudinal Study (JALS) involves cohort studies conducted in Japan and consists of 2 different collaborative pooling projects based on individual participant data: the JALS with a common protocol, and the JALS with a meta-analysis of existing cohorts, which is called the Japan Arteriosclerosis Longitudinal Study-Existing Cohorts Combine (JALS-ECC).[13] The difference between these 2 studies is the method of standardizing measurements. Their common purpose is to clarify the following: (1) associations between risk factors and cardiovascular disease (CVD) outcomes; (2) risk factors and prevention strategies of CVDs nationwide; and (3) differences among subgroups defined by age, gender, or geographical region that cannot be detected from any single cohort study. The collaborating investigators expect that both studies, together with an assessment of homogeneity and heterogeneity among cohorts, will provide reliable evidence for an epidemiological hypothesis. The JALS-ECC is the precedent to the JALS and its principal aim is to propose a hypothesis and proper statistical methods for the JALS in progress by analyzing individual data. This paper describes the rationale, study design, and methods of the JALS-ECC.

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Methods

Study Design

Study Eligibility Cohort studies were eligible for inclusion if they satisfied the following criteria: (1) subjects were Japanese; (2) prospective cohort study; (3) at least 3,000 person-years of follow-up; (4) data included date of birth (or age), gender, height, weight, blood pressure, and total cholesterol recorded at baseline; and (5) data included date of death or the age at death (for death from stroke or coronary heart disease, at least) recorded during follow-up.

Principal Risk Factors The JALS group requested individual participants' data from the collaborating investigators: date of baseline survey, date of birth or age at baseline, gender, height, weight, history of CVDs, blood pressure (systolic and diastolic), total cholesterol, high-density lipoprotein-cholesterol (HDL-C), triglycerides, smoking and drinking habits. Data were requested not only from the baseline examination, but also from any subsequent examinations during follow-up in order to examine and control the effects of regression dilution bias.[14]

Principal Outcomes Individual participants' data were requested on the occurrence of any of the following out-

Table 1 Principal Outcomes in JALS-ECC

Events	ICD-9 codes	ICD-10 codes
Cardiovascular diseases		
Ischemic heart diseases	410	I21–I23
All cerebrovascular disease	430, 431, 433, 434, 436	I60, I61, I63, I64
Ischemic stroke	433, 434	I63
Hemorrhagic stroke	431	I61
Subarachnoid hemorrhage	430	I60
Total death		

JALS-ECC, Japan Arteriosclerosis Longitudinal Study-Existing Cohorts Combine; ICD-9, 9th Revision of the International Classification Diseases (–1994); ICD-10, 10th Revision of the International Classification Diseases (1995–).

Table 2 Baseline Characteristics of the Population in the JALS-ECC, 1985–2005

Regions	Cohort name	Cohort size, n	Follow-up mortality, start-end (year)	Follow-up (months)		Follow-up morbidity, start-end (year)	Follow-up (months)		Female (%)	Age (years)					
										Male			Female		
				Mean	SD		Mean	SD		Mean	SD	Min-Max	Mean	SD	Min-Max
Community-based															
Hokkaido	Tannno/ Soubetsu	2,066	1991–1999	66.1	30.1	1991–1999	66.1	30.1	56.1	60.5	10.9	25–91	59.8	10.5	22–83
Akita 1		6,484	1988–2003	167.4	36.4	1988–2000	141.7	27.2	64.9	58.5	11.9	27–93	56.8	11.2	22–94
Akita 2	Ikawa	2,595	1985–1999	128.8	29.5	1985–1999	128.8	29.5	56.4	56.1	10.9	40–88	56.1	10.7	40–88
Iwate	Ohasama	3,114	1990–2001	125.5	26.6	1990–2001	125.5	26.6	60.9	57.9	12.9	26–89	57.0	11.8	34–87
Ibaraki	Kyowa	4,479	1985–1999	120.6	30.7	1985–1999	120.6	30.7	57.2	54.7	9.4	40–83	54.9	9.6	40–83
Niigata	Tokamachi	8,480	1993–2003	93.8	31.5	1993–2003	93.8	31.5	66.9	59.5	12.8	28–92	57.3	12.0	29–93
Toyama	Oyabe	5,197	1988–1998	119.5	20.3	1988–1998	119.5	20.3	68.8	58.8	11.7	23–89	56.0	11.1	22–89
Wakayama		1,365	1989–1999	114.9	29.7	–	–	–	54.5	59.8	9.5	40–80	60.5	9.9	40–80
Osaka	Yao, Minami-takayasu	3,855	1985–1998	114.7	42.7	1985–1998	114.7	42.7	65.2	56.1	11.1	40–84	52.9	10.7	40–87
Shiga 1	Shigaraki	2,934	1992–2004	115.0	28.0	1992–2001	87.2	21.9	58.9	56.5	13.7	29–88	56.6	14.1	29–94
Shiga 2		1,138	1999–2002	35.2	6.0	1999–2002	35.2	6.0	58.5	72.7	6.5	60–93	74.7	7.6	45–99
Hiroshima	Hiroshima	2,222	1992–2001	70.9	22.0	1992–2000	43.5	23.3	71.3	70.6	8.0	60–93	72.8	7.8	60–96
Kochi	Kaboku	779	1992–2003	108.6	37.7	–	–	–	60.3	77.4	5.5	64–94	76.1	5.1	64–92
Ehime	Ohzu	5,301	1996–2003	66.1	12.6	1996–2003	66.1	12.6	66.1	62.3	12.6	22–95	58.0	14.1	20–94
Fukuoka 1	Hisayama	757	1990–2000	118.4	19.5	1990–2000	118.4	19.5	60.5	61.0	10.3	42–87	60.7	10.1	42–91
Fukuoka 2	Tanushimaru	1,920	1999–2003	44.9	3.7	1999–2003	44.9	3.7	58.6	63.5	10.9	40–94	62.0	11.0	40–95
Kumamoto		2,465	1999–2003	50.7	2.9	1999–2003	50.7	2.9	30.0	47.1	4.2	40–55	46.8	4.3	40–55
Work-site based															
Tokyo		801	1995–2001	69.4	7.3	1995–2001	69.4	7.3	25.5	50.5	7.9	35–67	51.1	6.5	36–68
Toyama		7,057	1990–2002	126.4	37.7	1990–2002	126.4	37.7	37.7	38.0	9.9	18–65	36.3	10.2	18–64
Aichi		2,810	1997–2001	31.8	10.6	1997–2001	31.8	10.6	0.0	51.0	6.7	34–70	–	–	–
Osaka		872	1985–2005	127.1	49.6	1985–2005	127.1	49.6	12.4	41.0	12.1	20–70	32.6	12.3	19–63
Total		66,691	1985–2005	99.9	49.0	1985–2005	93.4	45.1	55.5	54.2	13.8	18–95	56.3	13.5	18–99

Abbreviation see in Table 1.

comes: nonfatal stroke, nonfatal myocardial infarction (MI), cause-specific cardiovascular death, and all-cause mortality (Table 1). Details of the diagnostic criteria used for the definition of major cardiovascular events and data on the completeness of follow-up were also collected. All outcomes were classified, after recoding when necessary, according to the 9th revision of the International Classification of Diseases until the end of 1994, and according to the 10th revision of the International Classification of Diseases from the beginning of 1995.[15] For any study that did not use this classification system, events were re-coded by the Coordinating Center staff members.

Data Management

All data were submitted electronically from collaborating investigators, and were checked by staff at the JALS Coordinating Center. The reports of completeness and consistency were referred back to the collaborating investigators for review and confirmation. When data queries arose, the Collaborating Center staff members and collaborating investigators discussed and resolved the problems. The process of the correction was kept on record and it was checked periodically in the Coordinating Center.

The data provided for inclusion in the JALS-ECC are held in strict confidence by the Coordinating Center. The data from each cohort study remain the property of the principal investigators of that study and will not be used for any presentation or publication without the permission of the Steering Committee. Permission to submit each cohort's data to the JALS Coordinating Center was obtained from each institute's ethical review board.

Statistical Analysis Plan

Collected individual follow-up data will be expanded into person-year type data, taking age changes into account. The expanded data will then be aggregated by gender, cohort, and age category. All analyses will be done by gender. Hazard ratios of risk factors and their confidence intervals will be calculated using the Poisson regression model for each event. Potential confounding factors and effect modifiers will included in the model. Heterogeneity in the effect of risk factors among cohorts will be assessed using the

Table 3 Number of Fatal Events in Each Study, JALS-ECC 1985–2005

Study	n	Total						Male						Female					
		All	Stroke				CHD	All	Stroke				CHD	All	Stroke				CHD
			Total	Isch	Hemo	SAH			Total	Isch	Hemo	SAH			Total	Isch	Hemo	SAH	
Community-based																			
Hokkaido	2,066	138	20	5	8	7	13	82	10	4	6	0	5	56	10	1	2	7	8
Akita 1	6,484	1,120	–	–	–	–	–	595	–	–	–	–	–	525	–	–	–	–	–
Akita 2	2,595	379	21	11	5	3	2	219	8	5	1	1	1	160	13	6	4	2	1
Iwate	3,114	384	57	27	18	12	21	241	37	20	13	4	16	143	20	7	5	8	5
Ibaraki	4,479	402	39	20	11	6	31	244	20	13	5	1	17	158	19	7	6	5	14
Niigata	8,480	424	44	14	16	13	5	238	21	9	7	5	3	186	23	5	9	8	2
Toyama	5,197	479	69	38	16	14	27	264	35	23	7	5	16	215	34	15	9	9	11
Wakayama	1,357	198	15	9	4	1	11	117	6	4	2	0	5	81	9	5	2	1	6
Osaka	3,855	283	25	16	2	7	6	166	14	11	1	2	6	117	11	5	1	5	0
Shiga 1	2,934	281	–	–	–	–	–	171	–	–	–	–	–	110	–	–	–	–	–
Shiga 2	1,135	90	13	11	2	0	1	46	7	7	0	0	1	44	6	4	2	0	0
Hiroshima	2,222	467	48	29	15	3	21	175	15	9	5	1	8	292	33	20	10	2	13
Kochi	776	301	31	11	7	4	26	157	8	1	3	0	12	144	23	10	4	4	14
Ehime	5,300	189	–	–	–	–	–	114	–	–	–	–	–	75	–	–	–	–	–
Fukuoka 1	757	88	12	4	4	4	1	53	5	3	0	2	1	35	7	1	4	2	0
Fukuoka 2	1,920	38	5	3	1	1	–	20	4	3	1	0	0	18	1	0	0	1	0
Kumamoto	2,465	1	–	–	–	–	–	1	0	0	0	0	0	0	0	0	0	0	0
Work-site based																			
Tokyo	801	4	0	0	0	0	0	4	0	0	0	0	0	0	0	0	0	0	0
Toyama	7,057	105	7	1	4	2	3	85	7	1	4	2	3	20	0	0	0	0	0
Aichi	2,810	7	2	0	0	2	0	7	2	0	0	2	0	0	0	0	0	0	0
Osaka	872	15	1	0	1	0	1	14	1	0	1	0	1	1	0	0	0	0	0
Total	66,676	5,393	409	199	114	79	169	3,013	200	113	56	25	95	2,380	209	86	58	54	74

All, all-cause mortality; Isch, ischemic stroke; Hemo, hemorrhagic stroke; SAH, subarachnoid; CHD, coronary heart disease; –, no data available. Other abbreviation see in Table 1.

Table 4 Number of Nonfatal Events in Each Study, JALS-ECC 1985–2005

Study	n	Total					Male					Female				
		Stroke				CHD	Stroke				CHD	Stroke				CHD
		Total	Isch	Hemo	SAH		Total	Isch	Hemo	SAH		Total	Isch	Hemo	SAH	
Community-based																
Hokkaido	2,066	75	59	7	9	75	41	34	6	1	10	34	25	1	8	5
Akita 1	6,484	280	185	55	40	280	138	103	27	8	–	142	82	28	32	–
Akita 2	2,595	106	67	24	15	106	56	38	11	7	9	50	29	13	8	6
Iwate	3,114	210	151	40	18	210	107	83	18	5	–	103	68	22	13	–
Ibaraki	4,479	125	69	32	24	125	62	43	11	8	30	63	26	21	16	17
Niigata	8,480	–	–	–	–	–	–	–	–	–	19	–	–	–	–	11
Toyama	5,197	143	90	30	22	143	69	51	12	6	–	74	39	18	16	–
Wakayama	1,357	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Osaka	3,855	66	36	17	13	66	35	19	13	3	15	31	17	4	10	7
Shiga 1	2,934	71	54	10	7	71	32	27	1	4	10	39	27	9	3	4
Shiga 2	1,135	3	3	0	0	3	2	2	0	0	–	1	1	0	0	–
Hiroshima	2,222	77	64	8	2	77	23	20	3	0	6	54	44	5	2	6
Kochi	776	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Ehime	5,300	95	76	13	5	95	52	48	3	1	7	43	28	10	4	3
Fukuoka 1	757	45	29	11	5	45	14	9	3	2	8	31	20	8	3	7
Fukuoka 2	1,920	24	18	4	2	24	18	14	3	1	6	6	4	1	1	1
Kumamoto	2,465	3	2	1	0	3	3	2	1	0	3	0	0	0	0	0
Work-site based																
Tokyo	801	1	1	0	0	1	2	1	1	0	3	0	0	0	0	1
Toyama	7,057	86	61	14	13	86	65	44	12	10	16	21	17	2	3	2
Aichi	2,810	9	7	0	2	9	9	7	0	2	12	0	0	0	0	0
Osaka	872	5	3	1	1	5	5	3	1	1	6	0	0	0	0	0
Total	66,676	1,424	975	267	178	230	733	548	126	59	160	692	427	142	119	70

Abbreviations see in Tables 1,3.

mixed-effect Poisson regression model. The effects of regression dilution will be assessed and adjusted by proposed methods using repeat measurements of risk factors data. All analyses will be done using SAS version 9.13 (SAS Institute Inc, Cary, NC, USA) and PROC GENMOD will be used for the Poisson regression.

Results

Individual records for 66,691 participants in 21 cohort studies were included in this study, with 82.7% of the participants from community-based cohorts and 17.3% from work-site based cohorts (Table 2). The mean follow-up

JALS のデザイン論文の訂正です。Total CHD のイベント数に誤りがありました。

Table 4. Number of Non-fatal events in each study, JALS-ECC, 1985-2005

Study	n	Total					Male					Female				
		Stroke				CHD	Stroke				CHD	Stroke				CHD
		Total	Isch	Hemo	SAH		Total	Isch	Hemo	SAH		Total	Isch	Hemo	SAH	
Community based																
Hokkaido	2,066	75	59	7	9	15	41	34	6	1	10	34	25	1	8	5
Akita1	6,484	280	185	55	40	-	138	103	27	8	-	142	82	28	32	-
Akita2	2,595	106	67	24	15	15	56	38	11	7	9	50	29	13	8	6
Iwate	3,114	210	151	40	18	-	107	83	18	5	-	103	68	22	13	-
Ibaraki	4,479	125	69	32	24	47	62	43	11	8	30	63	26	21	16	17
Niigata	8,480	-	-	-	-	30	-	-	-	-	19	-	-	-	-	11
Toyama	5,197	143	90	30	22	-	69	51	12	6	-	74	39	18	16	-
Wakayama	1,357	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Osaka	3,855	66	36	17	13	22	35	19	13	3	15	31	17	4	10	7
Shiga1	2,934	71	54	10	7	14	32	27	1	4	10	39	27	9	3	4
Shiga2	1,135	3	3	0	0	-	2	2	0	0	-	1	1	0	0	-
Hiroshima	2,222	77	64	8	2	12	23	20	3	0	6	54	44	5	2	6
Kochi	776	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Ehime	5,300	95	76	13	5	10	52	48	3	1	7	43	28	10	4	3
Fukuoka1	757	45	29	11	5	15	14	9	3	2	8	31	20	8	3	7
Fukuoka2	1,920	24	18	4	2	7	18	14	3	1	6	6	4	1	1	1
Kumamoto	2,465	3	2	1	0	3	3	2	1	0	3	0	0	0	0	0
Work-site based																
Tokyo	801	1	1	0	0	4	2	1	1	0	3	0	0	0	0	1
Toyama	7,057	86	61	14	13	18	65	44	12	10	16	21	17	2	3	2
Aichi	2,810	9	7	0	2	12	9	7	0	2	12	0	0	0	0	0
Osaka	872	5	3	1	1	6	5	3	1	1	6	0	0	0	0	0
Total	66,676	1,424	975	267	178	230	733	548	126	59	160	692	427	142	119	70

Abbreviations see in Tables 1, 3.

Table 5 Baseline Summary Statistics for Studies Included in JALS-ECC 1985–2005

Cohort	Blood pressure				Device	Total cholesterol (mg/dl)		HDL-C (mg/dl)		LQC	Triglyceride (mg/dl)		Blood glucose (mg/dl)			
	SBP		DBP										Fasting		Casual	
	Mean	SD	Mean	SD		Mean	SD	Mean	SD		Mean	SD	Mean	SD	Mean	SD
Community-based																
Hokkaido	132.7	21.5	77.9	10.6	SP	193.3	33.1	54.3	13.9	CDC	134.0	92.3	93.4	20.8	–	–
Akita 1	132.6	18.9	78.4	11.0	SP	188.0	35.5	–	–	–	119.0*	73.1	–	–	106.7*	23.5
Akita 2	134.7	19.6	81.4	11.2	SP	188.8	32.3	59.6	14.1	CDC	132.0	86.1	119.6	29.4	135.3	44.1
Iwate	130.4	16.9	73.4	11.2	OC	195.8	36.7	51.7*	13.8	CDC	–	–	–	–	–	–
Ibaraki	136.7	19.7	81.5	11.7	SP	194.7	37.0	58.1*	13.9	CDC	157.4	106.8	124.5	36.3	130.6	42.1
Niigata	127.1	18.5	73.3	10.8	SP	197.0	35.5	56.6	14.3	OTH	138.0	94.6	–	–	–	–
Toyama	126.5	19.9	75.5	11.2	RZ	194.0	36.2	47.1	11.7	OTH	128.6	79.4	–	–	–	–
Wakayama	–	–	–	–		197.9*	34.4	50.4*	13.2	–	114.4*	71.5	–	–	–	–
Osaka	132.2	20.2	79.7	11.7	SP	203.7	35.7	60.3*	13.4	CDC	138.4	89.9	108.0	23.1	130.6	38.5
Shiga 1	132.0	19.7	78.0	11.8	SP	193.2	34.7	56.1	14.2	CDC	131.8	86.9	–	–	107.7	34.1
Shiga 2	145.4*	18.4	77.3*	10.2	OC	193.9*	35.4	48.6*	12.6	CDC	105.6*	54.5	–	–	–	–
Hiroshima	136.1	21.5	78.1	11.4	SP	215.3	38.3	52.5	14.6	CDC	149.7	85.0	–	–	112.9	41.7
Kochi	143.7	22.4	78.8	12.1	OC	191.8	36.4	49.2	14.4	CDC	119.4	61.7	–	–	112.0	30.0
Ehime	129.9	18.7	76.2	10.9	SP	205.6	38.0	59.7	15.8	CDC	120.5	76.0	95.8	19.0	105.9	29.9
Fukuoka 1	133.0	21.5	77.9	10.6	SP	209.5	37.7	52.5	11.8	OTH	115.8	88.1	98.0	20.5	107.1	21.7
Fukuoka 2	133.6	20.8	78.8	11.6	SP	199.8	34.6	55.8	14.0	–	113.7	83.4	97.8	20.1	–	–
Kumamoto	126.8	17.2	79.9	11.3	SP	207.1	36.4	57.4	15.0	CDC	145.3	139.7	103.5	23.5	–	–
Work-site based																
Tokyo	124.5	17.4	81.8	11.7	OC	244.6	18.7	55.2	17.1	OTH	–	–	–	–	–	–
Toyama	118.5	14.6	71.0	11.8	SP	190.5	35.3	53.3	13.1	OTH	103.5	64.4	92.7	13.1	–	–
Aichi	129.4	19.0	79.2	12.0	SP	206.9	33.7	53.5	13.7	OTH	132.2	92.8	97.6	20.6	–	–
Osaka	121.4	17.8	74.8	12.6	SP	186.6	31.3	58.5*	11.7	CDC	147.5	89.3	100.0	14.8	111.1	27.3

**Data available for less than 50% of all of participants.*
SBP, systolic blood pressure; DBP, diastolic blood pressure; Device, measuring device; HDL-C, high-density lipoprotein-cholesterol; LQC, lipids quality control; SP, sphygmomanometers; CDC, CDC CRMLN; OC, automatic device cuff-oscillometric; RZ, random-zero sphygmomanometers; OTH, other quality control program. Other abbreviations see in Tables 1,3.

Table 6 Data on Smoking and Drinking Habits, JALS-ECC 1985–2005

Cohort	Smoking habit				Drinking habit				
	Current /Non	Current /Ex/Non	No. per day (cont.)	No. per day <20,≥20	Current /Non	Current /Ex/Non	No. per day (cont.)	No. per day <1,1–2,2–3, ≥3*	Conversion to ethanol
Community-based									
Hokkaido	○	○	–	–	○	○	–	–	–
Akita 1	○	–	○	○	○	–	○	○	▲
Akita 2	○	○	○	○	○	○	○	○	○
Iwate	○	○	–	–	○	○	–	–	–
Ibaraki	○	○	○	○	○	○	○	○	○
Niigata	○	○	–	–	○	–		–	–
Toyama	○	–	○	○	○	–	○	○	▲
Wakayama	○	○	○	○	○	○	○	○	○
Osaka	○	○	○	○	○	○	○	○	○
Shiga 1	○	○	○	○	○	○	○	○	○
Shiga 2	○	○	–	○	○	–	–	–	–
Hiroshima	○	–	○	○	–	–	–	–	–
Kochi	○	○	–	○	○	–	–	○**	▲
Ehime	○	○	–	○	○	○	–	○	○
Fukuoka 1	○	○	–	○	○	○	○	○	○
Fukuoka 2	○	○	–	○	○	○	–	○	▲
Kumamoto	○	○	○	○	○	○	○	○	○
Work-site based									
Tokyo	○	○	○	○	○	○	○	○	○
Toyama	○	○	–	○	○	○	○	○	○
Aichi	○	○	○	○	○	–	–	○	▲
Osaka	○	○	○	○	○	○	○	○	▲

**Units of "gou" (traditional Japanese unit of measurement, by volume, corresponding to 23 g of ethanol), 1 gou 180 ml of sake; **<3, ≥3 ("gou"/day).*
▲=Data on frequency per week (or month) not available.
cont., continuous. Other abbreviations see in Tables 1,3.

period was 93.4 months. During a total of 575,628 person-years, there were 409 deaths attributed to stroke and 169 deaths attributed to CHDs; total stroke and CHD events were 1,478 and 230, respectively (Table 3). Of the 1,424 total stroke events with reported stroke subtype information, 975 were classified as ischemic, 267 as hemorrhagic and 178 as subarachnoid hemorrhage (Table 4).

Table 5 is a summary of the data on exposures. Data for baseline height, weight, and blood pressures were available for all participants, and for total cholesterol, HDL-C, and

triglycerides from 95.5%, 67.2%, and 76.5% participants, respectively. Blood pressure was measured in each cohort using standard or random-zero sphygmomanometers and automatic devices based on the cuff-oscillometric method.

Table 6 shows the current smoking and drinking habits of the cohorts. All cohort studies included current cigarette smoking status. Eighteen studies additionally recorded "non-smoker" or "ex-smoker" for non-smokers, and 16 studies recorded the number of cigarettes smoked per day. Twenty studies asked about current drinking status and 12 studies additionally recorded "non-drinker" or "ex-drinker" for non-drinkers.

Discussion

The JALS-ECC is a meta-analysis of 21 prospective cohort studies that had enrolled a total of 66,691 subjects. It is the largest study in Japan investigating the morbidity and mortality of CVD as the study outcomes.

Pooling projects of epidemiological studies of CVD, namely the Asia Pacific Cohort Studies Collaboration (APCSC)[16] and the Prospective Studies Collaboration (PSC), have been published previously.[17] Those studies reported the association between risk factors and CVD in the Asian and Pacific populations. The APCSC also revealed the homogeneity in relative risks, although the absolute risk for stroke and the absolute risk for CHD in the Asian population were different.[18–24] Those differences could be attributed to lifestyle differences, such as nutrition and physical activity; however, the APCSC did not look at those parameters. Lifestyle differences could also account for the differences seen in absolute risks in domestic CVD epidemiological studies in Japan. The difference in absolute risk of stroke and the absolute risk of CHD between urban vs rural areas and northern vs southern areas has been reported.[3,6,12,25–27] In addition, previous Japanese studies did not focus attention on geographical differences, with most large-scale studies lumping many areas together as 1 cohort or conducting studies in 1 area,[1,2,28,29] whereas JALS covers a diverse Japanese population and, as such, should enable an in-depth analysis of the differences among subgroups defined by age, gender, or geographical area.

To assure the accuracy and precision of combining data from various cohort studies for this project, consistency in the definitions of outcome and measurement of risk factors was required. Most studies used the standard definitions for CHDs based on the criteria from the Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) study.[30] For example, MI was defined according to clinical features, characteristic electrocardiogram changes, and marked elevations in blood levels of cardiac enzymes. Most studies also reported stroke diagnoses based on typical clinical features and characteristic changes on computed tomography and/or magnetic resonance imaging brain scans using either the criteria from the MONICA study[30] or the WHO.[31] Studies that used definitions other than these have their definitions reported elsewhere.[12,32]

Most laboratories that measured lipids participated in some type of quality control program, such as the US Cholesterol Reference Method Laboratory Network (CRMLN) of the Centers for Disease Control and Prevention (CDC).[33] It seems reasonable to integrate this data and correlate lipid measurements with outcomes, but the present JALS-ECC study did not conduct a strict standardization of lipids measurements and outcomes. Conversely, data on smoking and drinking habits, and medical history were based on self-reported or administered questionnaires, making it difficult to combine data and determine objective outcomes, which is a limitation of this study.

In conclusion, the JALS-ECC project succeeded in collecting valuable data from existing cohort reports, which provided information about the effects of modifiable factors on the risks of the CVD. Such information should provide a reliable basis for establishing prevention strategies.

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Appendix 1

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Hokkaido (Tanno/Soubetsu): K Shimamoto, S Saitoh, S Takagi; *Akita 1*: K Suzuki, K Sato; *Akita (Ikawa)*: S Sato, H Imano, M Kiyama, K Maeda, Y Ishikawa, A Kitamura, T Shimamoto; *Iwate (Ohasama)*: Y Imai, T Ohkubo, M Kikuya, H Metoki, K Asayama, J Hashimoto, R Inoue; *Iwate (Iwate-KENCO)*: A Okayama, K Sakata, M Nakamura, A Ogawa, T Tago, T Akaba, Y Terayama; *Iwate (Higashiyama)*: M Nakamura, F Tanaka, M Nagano, K Sato, M Ogawa, T Segawa; *Miyagi (Tsurugaya district, Sendai City)*: I Tsuji, K Ohmori-Matsuda, S Kuriyama, N Nakaya, A Hozawa; *Ibaraki (Kyowa)*: H Iso, T Tanigawa, K Yamagishi, R Cui, A Ikeda, H Noda; *Chiba (Kamogawa City)*: S Mizushima, S Ichinohe, R Yanagibori, K Amano; *Tokyo (Itabashi)*: T Suzuki, H Yoshida, Y Shimizu, H Iwasa; *Gunma (Kusatsu Town)*: S Shinkai, Y Fujiwara, H Amano; *Niigata (Sado)*: T Momotsu, K Suzuki, K Sanpei, K Taneda, N Tanabe; *Niigata (Nagaoka City (Yoita district))*: S Shinkai, Y Fujiwara, H Amano; Mie *(Taiki Town (Kisei district))*: M Tsushima, C Maruyama, T Maruyama, T Nakamori, S Nakano; *Shiga (Takashima)*: Y Kita, H Ueshima, Y Nakamura, K Matsui, S Tamaki, H Sugihara; *Wakayama (Hidakagawa (Miyama and Nakatsu))*: K Sakata, N Nishio, A Saika; *Osaka (Minamitakayasu district, Yao City)*, A Kitamura, T Okada, M Kiyama, T Ohira, S Sato, T Shimamoto; *Osaka (Minoo City)*: T Shiraishi, N Nakanishi; *Hiroshima (Hiroshima)*: M Yamada, S Fujiwara, F Kasagi, Y Mimori; *Ehime (Ozu City and Hassei-district, Ikata Town)*: K Okada, M Konishi, I Saito, K Watanabe, S Hitsumoto; *Kochi (Kahoku)*: M Nishinaga, K Okumiya, J Takata; *Ehime (Imabari)*: T Miki, Y Tabara, K Kohara, J Nagura; *Fukuoka (Hisayama)*: Y Kiyohara, H Arima, K Yonemoto, T Ninomiya, Y Doi, M Kubo; *Fukuoka (Kasuya)*: J Hayashi; *Saga (Nishiarita)*: M Kitakaze; *Kumamoto 2*: H Soejima, H Ogawa, H Kawano, S Koshi, I Katayama, T Marubayashi; *Okinawa (Ishigaki)*: J Hayashi; *Tokyo Worker 1*: T Kushiro, A Takahashi; *Tokyo Worker 2*: A Yamashina, H Tomiyama; *Nagoya Worker*: H Toyoshima, K Tamakoshi, H Yatsuya, K Wada, R Otsuka; *Toyama Worker*: H Nakagawa, K Miura, Y Morikawa, M Ishizaki, T Kido; Y Naruse; *Ehime Worker*: T Miki, Y Tabara, K Kohara, J Nagura; *Kyoto Worker*: K Takeda; *Osaka Worker*: Y Naito, T Ohira, S Sato, A Kitamura, T Shimamoto; *Kumamoto Worker*: H Kawano, H Soejima, S Nakayama, H Fujii, I Koba
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Practical Risk Prediction Tools for Coronary Heart Disease in Mild to Moderate Hypercholesterolemia in Japan

— Originated From the MEGA Study Data —

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Background A simple and practical risk prediction tool for coronary heart disease (CHD) to determine the specific risk level in each patient that fits the true clinical practice setting is needed and would be valuable in Japan.

Methods and Results A 5-year risk prediction score and chart for CHD based on the MEGA study data was developed in the present study. The MEGA risk prediction score and chart were constructed based on the coefficient of each risk factor. The risk factors included in these risk prediction tools were: treatment (diet, diet plus pravastatin), sex, age, baseline high-density lipoprotein-cholesterol, baseline low-density lipoprotein-cholesterol, glucose abnormality (diabetes and impaired fasting glucose), hypertension, and smoking. The MEGA risk prediction score comprised the risk score for each risk factor, and it can predict 5-year risk for CHD with 5 levels of risk, based on the total risk score. The MEGA risk prediction chart more accurately predicts risk, by reflecting the accumulation of risk factors and using an 8-color visual chart.

Conclusions The MEGA risk prediction score and chart, developed from the MEGA study data, more easily and accurately assesses the 5-year CHD risk in mild to moderate hypercholesterolemic patients in the usual clinical practice setting in Japan. (*Circ J* 2008; **72:** 1569–1575)

Key Words: Coronary artery disease; Follow-up studies; Hypercholesterolemia; Risk factors; Statin

Coronary heart disease (CHD) represents one of the main causes of death in the USA and Europe[1] and is the second most frequent cause of death in Japan[2] CHD risk increases remarkably with the accumulation of risk factors[3–5] Data from some epidemiological studies and clinical trials have identified several risk factors for CHD[6,7] and some risk prediction scores for CHD were developed using risk factor analysis from these data. The Framingham risk model is a typical one[8] However, it is well known that the estimated incidence of CHD by the Framingham prediction model is not consistent with the actual incidence in different populations. Therefore, different prediction scores have been developed in several countries[9–12] In 2006, the Health Risk Evaluation Chart,[13] a risk chart corresponding to the Framingham CHD risk score, was developed based on the Nippon Data 80,[14] which used a 19-year follow-up study of data of the Japanese general population.

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Thus, despite the different risk prediction tools available in several countries, it remains unclear whether these tools accurately predict risk in patients with hypercholesterolemia treated by diet with or without a statin. Regarding risk prediction for the population receiving lipid-lowering pharmacotherapy, the CHD predicted value obtained from the Framingham risk model was compared with the observed CHD incidence in a substudy of WOSCOPS,[15] conducted to confirm the efficacy of pravastatin to prevent the first onset of ischemic heart disease. The observed incidence of CHD was similar to the predicted CHD risk using the Framingham risk model in the placebo group, whereas in the pravastatin group the observed CHD incidence was lower than the predicted CHD risk, indicating that the Framingham risk model does not accurately apply to patients receiving pravastatin.[16]

The MEGA study is a large-scale clinical study conducted to evaluate the efficacy of pravastatin treatment to decrease the risk of cardiovascular events in patients with mild to moderate hypercholesterolemia without a past history of ischemic heart disease and/or stroke[17,18] This report shows that 2 different 5-year CHD incidence risk prediction tools, a risk prediction score and chart, developed from the MEGA study data is accurate and efficient for clinical application.

Methods

The MEGA study, a prospective randomized open-label study, was conducted from February 1994 to March 2004. A total of 8,214 patients with hypercholesterolemia (total cholesterol (TC) 220–270 mg/dl) and no history of ischemic

Table 1 Baseline Characteristics of Study Patients in the MEGA Study

	Diet group	*Diet plus pravastatin group*
No. of patients	*3,966*	*3,866*
Age (years)	*58.4±7.2*	*58.2±7.3*
Women	*2,718 (69%)*	*2,638 (68%)*
BMI (kg/m²)	*23.8±3.0*	*23.8±3.1*
SBP (mmHg)	*132.4±16.8*	*132.0±16.8*
DBP (mmHg)	*78.8±10.2*	*78.4±10.4*
*HT**	*1,664 (42%)*	*1,613 (42%)*
*Glucose abnormality***	*828 (21%)*	*804 (21%)*
Current/past smoker	*791 (20%)*	*823 (21%)*
TC (mg/dl)	*242.6±12.2*	*242.6±12.1*
TG (mg/dl)†	*127.5 (37.0–1,322.5)*	*127.4 (34.5–1,010.0)*
HDL-C (mg/dl)	*57.5±15.1*	*57.5±15.0*
LDL-C (mg/dl)	*156.5±17.6*	*156.6±17.5*
Lipoprotein(a) (mg/dl)	*24.7±25.2*	*24.7±25.6*

**Reported by physicians. **Documented diabetes and it also included the patients who had fasting glucose equal or greater than 110 mg/dl (impaired fasting glcose). †Data are median (interquartile range). All data are mean±SD or number (%) unless otherwise indicated.*

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HT, hypertension; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol.

heart disease or stroke were enrolled. They comprised men of 40–70 years of age and post-menopausal women up to 70 years of age. The patients were assigned either to diet alone (diet group) or diet in combination with pravastatin treatment (10–20 mg/day, approved dose in Japan; diet plus pravastatin group). The mean follow-up period was 5.3 years. The primary endpoint was CHD (fatal and non-fatal myocardial infarction, angina pectoris, cardiac/sudden death, and angioplasty). Secondary endpoints were stroke, all cardiovascular disease, and total mortality. Major exclusion criteria included familial hypercholesterolemia, a history of cardiovascular disease, a current diagnosis of malignancy, and secondary hyperlipidemia.

Patients were evaluated, including the onset of endpoints, by the attending physician at 1, 3 and 6 months after the start of follow-up and every 6 months thereafter.

For each event, the diagnosis was made by the attending physician (including data from electrocardiogram and myocardial scintigraphy as needed) and reported in detail. Electrocardiography was performed annually. Information on individual patients was entered in the case report forms by their attending physicians and reported to the central Data Center. The Endpoint Committee evaluated each event in a blinded manner according to the criteria we reported previously[17] Throughout the study period, TC, high-density lipoprotein-cholesterol (HDL-C), triglycerides (TG), and lipoprotein(a) [Lp(a)] concentrations were centrally measured at the same laboratory using methods standardized by the Centers for Disease Control and Prevention (CDC; Atlanta, GA). Low-density lipoprotein-cholesterol (LDL-C) concentration was estimated by the Friedewald formula[19] The intention-to-treat analysis comprised 7,832 patients. Details of the design of MEGA study and the main results were reported previously[17]

To construct the risk prediction tools, 7,760 of the 7,832 patients were evaluated using explanatory variables (72 of the 7,832 patients were excluded because of missing explanatory variables). To determine the explanatory variables, a univariate analysis was performed and then the significant factors were incorporated into the multivariate analysis model. For the risk factors determined by this multivariate model, $p<0.20$ served as the criterion for backward elimination of variables. The factors included in the tools were: treatment group (diet group, diet plus pravastatin group), sex (male, female), age (≤54, 55–59, 60–64, ≥65 years), baseline HDL-C (<40, 40–<60, ≥60 mg/dl), baseline LDL-C (<140, 140–<160, ≥160 mg/dl), glucose abnormality and hypertension (none, hypertension and normal fasting blood glucose concentration, glucose abnormality and normal blood pressure, glucose abnormality and hypertension), and smoking habit (non-smoker [including ex-smoker], smokers). Although baseline LDL-C was not identified as a risk factor for CHD in the present study, it was included in the MEGA risk tools because it was included in other risk prediction models. Because abnormality in glucose tolerance was included in glucose abnormality as a risk factor in the Guidelines for Arteriosclerosis 2007[20] patients with a fasting blood glucose concentration ≥110 mg/dl were included as diabetics in the present study.

To construct the MEGA risk prediction score, each risk score was established as an integer, taking into consideration the coefficient of each explanatory variable. The total risk score of each patient was calculated as a sum of the risk scores, and classified into 5 risk levels based on population quintiles for both treatment groups. The 5-year predicted value by each risk level was estimated from the Cox proportional hazard model to be used as the mean value of the predicted value at 5 years for each patient, and calculated for each treatment group[21] To confirm the precision of the MEGA risk prediction model, we visually compared the estimated value to the observed value, and we plotted the receiver operating characteristic (ROC) curve using the development of CHD as the endpoint, and predictability was compared using the area under the ROC curve.

Further, we developed a simple, 5-year risk prediction chart based on the coefficient of each explanatory variable. The MEGA 5-year risk assessment chart for CHD displays the lipid parameters (HDL-C, LDL-C) by age on the y-axis and the characteristics associated with CHD risk (sex, smoking, hypertension, glucose abnormality) on the x-axis. In constructing the chart, the 2 categories of HDL-C (<40, 40–<60 mg/dl) and LDL-C (140–<160, ≥160 mg/dl) were integrated because the risk scores were set to the same degree. The 5-year CHD risk of each cell was estimated by the Cox proportional hazard model, and 8 levels of risk defined (each with its own color). The layout of the chart optimizes

Table 2 The β-Coefficients and HRs of the Multivariable Cox Proportional Hazard Model for 5-Year Risk of Coronary Heart Disease

	β	HR	95%CI
Groups			
Diet group	*0*	*1.00*	–
Diet plus pravastatin group	*−0.350*	*0.70*	*0.50–0.99*
Sex			
Women	*0*	*1.00*	–
Men	*0.784*	*2.19*	*1.49–3.21*
Age			
<55	*0*	*1.00*	–
55–59	*0.231*	*1.26*	*0.72–2.19*
60–64	*0.566*	*1.76*	*1.07–2.89*
≥65	*0.932*	*2.54*	*1.58–4.08*
HDL-C (mg/dl)			
≥60	*0*	*1.00*	–
40–<60	*0.714*	*2.04*	*1.29–3.24*
<40	*0.683*	*1.98*	*1.05–3.74*
LDL-C (mg/dl)			
<140	*0*	*1.00*	–
140–<160	*0.230*	*1.26*	*0.72–2.19*
≥160	*0.274*	*1.32*	*0.76–2.29*
HT, glucose abnormality***			
No	*0*	*1.00*	–
HT and normal fasting glucose†	*1.125*	*3.08*	*1.71–5.55*
Glucose abnormality and normal BP††	*1.646*	*5.19*	*2.88–9.35*
Glucose abnormality and HT	*1.992*	*7.33*	*4.12–13.04*
Current smoker			
No	*0*	*1.00*	–
Yes	*0.409*	*1.51*	*0.99–2.28*

**Documented. **Documented diabetes and it also included the patients who had fasting glucose equal or greater than 110 mg/dl (impaired fasting glcose). †Normal fasting glucose was defined as patients meet following criteria; reported as non-diabetes by physicians and fasting plasma glucose less than 110 mg/dL. ††Normal BP was defind as patients reported as non-HT by physicians. HR, hazard ratio; CI, confidence interval; BP, blood pressure. Other abbreviations see in Table 1.*

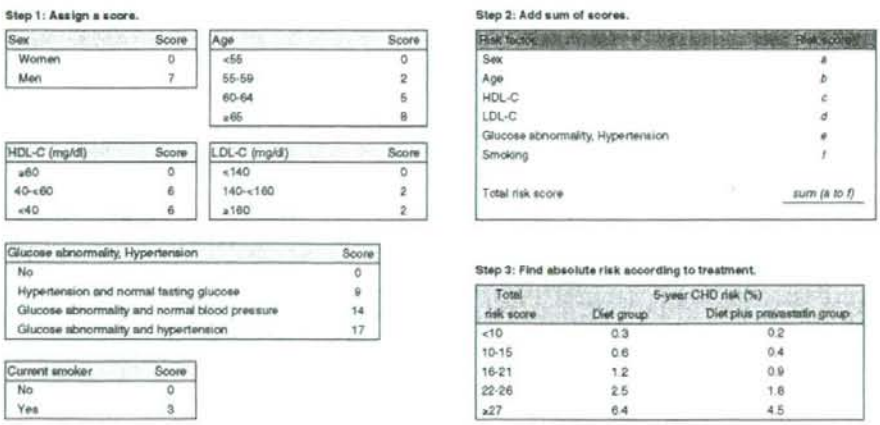

Fig 1. Simplified calculation form for estimating the 5-year risk of coronary heart disease (CHD) incidence in the diet group and diet plus pravastatin group. HDL-C, high-density lipoprotein-cholesterol: LDL-C, low-density lipoprotein-cholesterol.

the visual expression of the person's risk level from low to high with an 8-color gradation from the lower-left to the upper-right. For statistical analyses, the SAS software (release 8.2, SAS Institute, Cary, NC, USA) was used.

Results

During the 5-year follow-up, 138 CHD events were observed in the MEGA study. The baseline characteristics of the study population are shown in Table 1. The coefficient of each risk factor for CHD obtained from the Cox proportional hazard model and hazard ratio are shown in Table 2, and the 5-year risk prediction processes using the MEGA risk prediction score for CHD are summarized in Fig 1. A proportionally higher risk score was found for glucose abnormality alone (risk score 14), hypertension alone (risk

Table 3 Baseline Characteristics in Each Risk Level

	Total risk score				
	<10	10–<16	16–<22	22–<27	27–
Risk level	1	2	3	4	5
No. of patients	1,434	1,517	1,719	1,414	1,676
Age (years)	55.22±5.70	57.17±6.87	58.52±7.52	60.26±7.10	60.20±7.24
Women	1,336 (93.2%)	1,162 (76.6%)	1,238 (72.0%)	986 (69.7%)	607 (36.2%)
BMI (kg/m²)	22.62±2.83	23.57±2.90	23.89±3.08	24.40±3.14	24.55±3.07
SBP (mmHg)	123.78±14.87	129.11±15.36	133.63±16.69	135.97±16.45	137.40±16.71
DBP (mmHg)	74.68±9.57	77.19±9.88	79.49±10.18	80.49±9.93	80.66±10.51
HT*	38 (2.6%)	320 (21.1%)	893 (51.9%)	961 (68.0%)	1,033 (61.6%)
Glucose abnormality**	0 (0.0%)	19 (1.3%)	251 (14.6%)	516 (36.5%)	1,395 (83.2%)
Current smoker	38 (2.6%)	123 (8.1%)	333 (19.4%)	156 (11.0%)	511 (30.5%)
TC (mg/dl)	242.80±12.30	242.69±11.86	243.62±12.00	241.97±12.03	241.78±12.14
LDL-C (mg/dl)	151.04±17.81	157.33±17.40	157.39±16.89	157.50±17.23	159.21±17.16
HDL-C (mg/dl)	69.77±14.45	58.57±14.01	58.06±14.52	53.56±12.86	49.44±10.59
TG (mg/dl)†	98.5 (37.5–519.0)	120.3 (37.0–675.7)	126.0 (34.5–656.0)	142.3 (42.0–486.5)	152.7 (43.0–775.0)
Lipoprotein(a) (mg/dl)	27.03±27.82	25.76±26.85	25.02±25.53	24.33±24.83	22.16±22.75

*Reported by physicians. **Documented diabetes and it also included the patients who had fasting glucose equal or greater than 110 mg/dl (impaired fasting glucose). †Data are median (interquartile range). All data are mean±SD or number (%) unless otherwise indicated. The 72 patients were excluded from this analysis because of missing data of the risk factors for coronary heart disease.

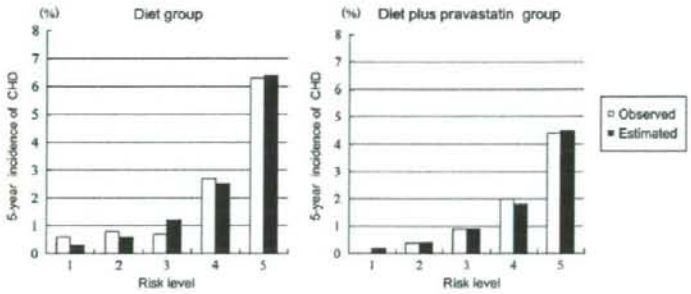

Fig 2. Comparison between the observed and estimated 5-year incidence of coronary heart disease (CHD) for the diet group and the diet plus pravastatin group.

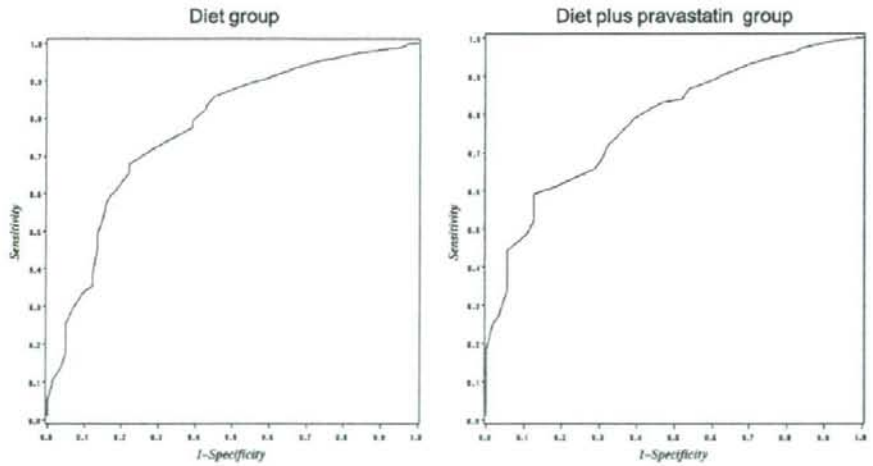

Fig 3. Receiver operating characteristic curves for the diet group and diet plus pravastatin group.

score 9) and their combination (risk score 17) compared to the scores for men (risk score 7), age ≥65 years (risk score 8), and low HDL-C (risk score 6).

Notably, the risk scores for a high LDL-C (risk score 2) and smoking (risk score 3) were lower than those for the other risk factors. The risk quintiles were determined by the intrinsic cut-off points of 10, 16, 22 and 27.

Table 3 shows patients' background factors as classified by risk level. Mean age tended to be higher for the higher risk levels. There were more women than men in the lower

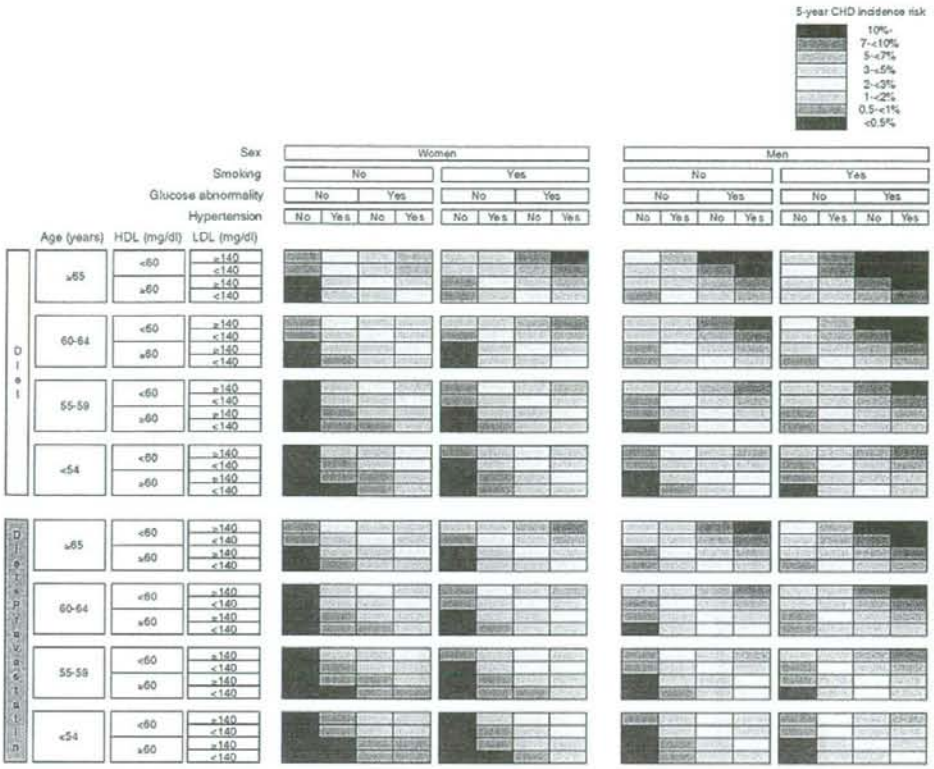

Fig 4. Risk assessment chart for 5-year risk of coronary heart disease (CHD) incidence, including sex, age, high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL)-cholesterol, glucose abnormality (including impaired fasting glucose), hypertension, and smoking.

risk levels. Body mass index increased (ranging from 0.26 to 0.91) for each increase of 1 risk level. Prevalence of glucose abnormality (documented diabetes and high fasting blood sugar concentration), hypertension, and smoking habit were greater in the higher risk levels, whereas TC concentration was similar across risk levels. LDL-C concentrations were similar for the 4 highest levels of risk and were somewhat lower for the lowest risk level. HDL-C concentrations were higher at the lower levels of risk and tended to decrease as the level of risk increased. TG tended to increase slightly as the risk levels increased, whereas concentrations of Lp(a) tended to decrease slightly as the risk levels increased.

The specificity of the MEGA risk assessment was validated with good concordance between the 5-year predicted values and the observed incidence. The range of the 5-year predicted values was similar for the predicted values (ranging from 0.3% to 6.4% diet group, 0.2% to 4.5% diet plus pravastatin group) and the observed values (0.6% to 6.3% diet group, 0 to 4.4% diet plus pravastatin group, Fig 2). The area under the curve (AUC) for the ROC curves was 0.774 for the diet group and 0.784 for the diet plus pravastatin group (Fig 3).

The MEGA risk prediction chart was constructed as shown in Fig 4. It depicts the increasing risk with its 8-color grading, according to the combination of risk factors in men and women in each treatment group. The 5-year predicted risk was higher in the diet group than in the diet plus pravastatin group. A 5-year CHD risk ≥10% was found for men >65 years old and men 60–64 years old who were smokers and diabetic in the diet group (red cells), and for women >65 years old who were smokers and had glucose abnormality plus hypertension. When all the risk factors were present, the highest predicted risk was estimated at 21% for men and at 10% for women <65 years old in the diet group (data not shown).

Discussion

The MEGA risk prediction score and MEGA risk prediction chart reported here are CHD risk assessment tools developed using MEGA study data. The MEGA risk score easily predicts 5 grades of 5-year CHD risk, and even greater accuracy of risk prediction is achieved with the MEGA risk chart with 8 grades of risk, in mild to moderate hypercholesterolemia without a history of cardiovascular disease. The risk factors included in the MEGA risk prediction tools have been well known as CHD risk factors[6,7,22] The accumulation of these risk factors is associated with a higher CHD risk;[14] and the MEGA risk tools are consistent with these findings.

The MEGA Study included patients with hypercholester-

olemia who were 40 to 70 years old (postmenopausal women <70 years) with a TC concentration of 220–270 mg/dl and no past history of cardiovascular disease. These patients were recruited from outpatient clinics, therefore, the MEGA risk tools are useful to predict the likelihood of developing CHD over 5 years in typical people with mild to moderate hypercholesterolemia with no history of cardiovascular disease. A key characteristic of the MEGA risk tools is that it is possible to assess risk in people treated with diet alone and in people receiving pharmacotherapy. Notably, the Framingham risk score did not predict risk accurately in patients treated with pravastatin in a WOSCOPS substudy[16]

Interestingly, an exponential increase in the predicted value was found as the risk levels increased. A near doubling in the 5-year predicted value from risk level 1 to risk level 2 was found with the MEGA risk prediction score. An even greater increase in predicted value was seen when risk was increased from level 4 to level 5.

Notably, little difference was seen between the estimated and observed incidence of CHD in both treatment groups with the MEGA risk score. This is consistent with what would be expected, when considering the association between the distribution of cases with risk factors and the increasing CHD risk across risk levels (Table 2).

The AUC of the ROC curve plotted in terms of total risk score for each treatment group was higher than 0.77 in both treatment groups. In a study reported previously, the AUC was 0.76 for the prediction of the main cardiovascular events (fatal and non-fatal myocardial infarction, coronary insufficiency [prolonged angina with documented electrocardiographic changes], heart failure, and stroke) using the Framingham risk model[23] Thus, the correspondence between these AUC values indicate the CHD risk predicted by the MEGA risk prediction score has a precision similar to that by the Framingham risk model.

A lower 5-year predicted risk was obtained with the MEGA risk prediction score than with the Framingham risk model. For the diet only treatment group, the predicted risk was one-sixth lower in the low-risk level and two-thirds lower in the high-risk level with the MEGA risk score compared with the Framingham model. A simple comparison of the 2 prediction models might not be possible because the Framingham model was developed based on a general population without left ventricular hypertrophy (LVH), whereas the MEGA Study included patients with LVH. Further, it has been reported that the Framingham risk model is not applicable in different populations[24,25] Thus, the MEGA risk score might be superior in its accuracy for determining CHD risk in patients with moderate hypercholesterolemia, such as Japanese patients.

The MEGA risk prediction chart provides even greater accuracy because of the incorporation of multiple risk factors. The 8 levels of risk predicted are color-coded, with the 5-year risk increasing from the bottom-left to upper-right of the chart, according to sex and age in combination with lipid factors and smoking, glucose abnormality, and hypertension. Concordance between the MEGA risk score and the MEGA risk chart is validated by the use of the same analysis model for both, with a different β coefficiency used for the risk chart to account for it having 1 less category of HDL-C and LDL-C than the risk score.

In the present study, 2 types of risk prediction tools were developed that apply to each treatment group. As noted previously, the Framingham risk model has been shown to underestimate the risk in patients who are treated with a statin. A substudy of WOSCOPS, a primary prevention study similar to our study, calculated CHD risk using the Framingham risk model and compared the observed incidence using time course changes in mean concentrations of serum cholesterol and HDL-C[15] In the placebo group the observed incidence and predicted risk were similar, whereas in the pravastatin group the observed incidence was lower than the predicted risk. Thus, the efficacy of pravastatin to reduce CHD risk is not sufficiently explained by changes in serum lipid concentrations, based on the Framingham risk model. It seems, therefore, that CHD risk should be calculated separately based on treatment or not with a statin.

There are a few limitations to our analyses. First, the MEGA risk prediction tools are applicable to patients with mild to moderate hypercholesterolemia (TC 220–270 mg/dl). Notably, however, 70% of the estimated 20 million ambulatory patients with hypercholesterolemia in Japan fall within this range. Second, the MEGA prediction tools are applicable to treated patients only, including diet treatment, as it is based on data from patients treated in the MEGA study. The predicted CHD risk for untreated persons using the MEGA risk tools is likely to be lower than the actual risk. Third, these risk prediction tools are based on data in Japanese patients, although it is feasible to consider using these tools in people with a similar profile.

We believe the MEGA risk prediction tools are valuable for use in usual clinical practice, with greater ease and accuracy to predict the 5-year CHD risk in patients with mild to moderate hypercholesterolemic patients, such as Japanese patients. Moreover, these are highly useful as educational tools for high-risk patients.

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Pravastatin reduces the risk for cardiovascular disease in Japanese hypercholesterolemic patients with impaired fasting glucose or diabetes: Diabetes subanalysis of the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) Study

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Abstract

Diabetes mellitus (DM) is a major risk factor for cardiovascular disease (CVD) in patients with no history of CVD. Evidence for the effect of statins on CVD in the diabetic population in low-risk populations (e.g., Japanese) is limited. We evaluated the effect of pravastatin on risk reduction of CVD related to baseline glucose status in a primary prevention setting. The Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) Study, in patients with mild-to-moderate hypercholesterolemia (220–270 mg/dL), showed that low-dose pravastatin significantly reduced the risk for CVD by 26%. This exploratory subanalyses examined the efficacy of diet plus pravastatin on CVD in 2210 patients with abnormal fasting glucose (AFG, including 1746 patients with DM and 464 patients with impaired fasting glucose (IFG) at 5 years in the MEGA Study. CVD was threefold higher in AFG patients (threefold higher in DM, and twofold higher in IFG) compared with normal fasting glucose (NFG) patients in the diet group. Diet plus pravastatin treatment significantly reduced the risk of CVD by 32% (hazard ratio 0.68, 95% CI 0.48–0.96, number needed to treat, 42) in the AFG group compared with the diet alone group, and no significant interaction between AFG and NFG (interaction $P = 0.85$) was found. Safety problems were not observed during long-term treatment with pravastatin. In conclusion, pravastatin reduces the risk of CVD in subjects with hypercholesterolemia and abnormal fasting glucose in the primary prevention setting in Japan.

Keywords: Diabetes mellitus; Hypercholesterolemia; Prevention; Coronary disease; Stroke

1. Introduction

Accumulated evidence has demonstrated that reduction of cholesterol decreases the risk of cardiovascular disease (CVD) [1–5]. These studies also demonstrated the benefit of lipid-lowering therapy in patients with diabetes mellitus (DM) [5–9]. Despite convincing data obtained from studies conducted in Western countries with a high incidence of CVD, the evidence in low-risk populations, such as Japanese, is scarce, and the effect of cholesterol reduction in DM unresolved. Worldwide epidemiologic data indicate that Japanese individuals have a lower risk for CVD, including the lowest

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risk level in coronary heart disease (CHD) and equivalent risk levels of stroke compared with most Western countries [10]. The incidence of CVD is proportionally higher in diabetic patients with hypercholesterolemia, even in low-risk Japanese subjects [11]. The prevalence of DM is rapidly increasing in Japan. Impaired insulin secretion, rather than insulin sensitivity, is a major cause of glucose intolerance in Japanese subjects [12]. This is in contrast with Western populations, where there is a strong relation between glucose intolerance and insulin resistance [13]. The relationship between body weight and developing DM is different in Japanese subjects compared with Western subjects. Fat deposition in Japanese subjects is different to that in Western subjects [14]. Thus, the burden of DM and CVD and its pathological conditions are different in Japanese and Western populations. Therefore, we carried out a detailed evaluation to determine if a treatment strategy similar to that used in Western countries was beneficial in Japanese subjects. In addition, previous reports have provided evidence of a beneficial effect on glycemic control and new-onset DM with pravastatin [9,15], thus we determined if this effect in Japanese individuals was observed.

The Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) Study [16,17] was conducted in Japan. It was the first study to evaluate the effect of pravastatin on CVD in an Asian population. The risk reductions achieved in the MEGA Study were similar to those in Western studies in high-risk populations, despite the low approved dose of pravastatin used in the MEGA Study. The principal results of the MEGA Study, reported in 2006, showed that small-to-moderate changes in lipid profiles significantly reduced the relative risk for CHD by 33% ($P=0.01$) and CVD by 26% ($P=0.01$) with diet plus pravastatin (diet + pravastatin) compared with diet alone [17]. The objective of this subanalysis of the MEGA Study was to evaluate the effect of diet + pravastatin therapy on CVD in hypercholesterolemic patients without previous CHD or stroke stratified by baseline glucose status.

2. Methods

2.1. Enrollment and follow-up

The details of the MEGA Study have been described elsewhere [16,17]. A total of 8214 men and postmenopausal women aged 40–70 years with hypercholesterolemia whose total cholesterol (TC) levels were 220–270 mg/dL, who did not have a history of CHD and stroke, and who provided written informed consent, were enrolled. The enrollment period was February 1994 to March 1999; follow-up ended in March 2004.

Eligible patients were randomly assigned to the National Cholesterol Education Program (NCEP) step I diet [18] alone (diet alone group) or to the step I diet + pravastatin (diet + pravastatin group). Major exclusion criteria included familial hypercholesterolemia, a history of CVD, current diagnosis of malignancy, and secondary hyperlipidemia. The dose of pravastatin was 10–20 mg daily (approved dose in Japan). Patients in both groups were counseled to follow the NCEP step I diet throughout the study period. Treatment in the diet + pravastatin group was initiated at pravastatin 10 mg/day. During follow-up, pravastatin dose could be adjusted by the treating physician, with titration upwards to 20 mg/day if TC level did not decrease to ≤220 mg/dL, in compliance with the approved Japanese dose. Patients in each group with a TC of >270 mg/dL, even after enhancement of assigned treatment, could be switched to other aggressive treatments, including statin therapy. Concomitant treatment for complications was not restricted in either group.

Patients were evaluated by their attending physicians at 1, 3, and 6 months after the start of follow-up, and every 6 months thereafter. Health checks at each clinic visit included biochemical tests and assessment of patient compliance with dosing instructions. For each event, detailed information was obtained from physicians and evaluated by the Endpoint Committee under blinding according to established criteria [16]. Throughout the study period, levels of TC, high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), and lipoprotein (a) were measured at the same laboratory using methods standardized by the Centers for Disease Control and Prevention (CDC; Atlanta, GA, USA). Low-density lipoprotein cholesterol (LDL-C) level was estimated by the Friedewald formula [19]. Follow-up was initially scheduled for 5 years but based on recommendation from the Data and Safety Monitoring Committee, the study was continued to increase the number of events. Hence, patients who provided written consent at 5 years to continue the study were followed-up until the end of March 2004.

2.2. Endpoints

The primary composite endpoint of the MEGA Study was the first occurrence of CHD, comprising fatal and non-fatal myocardial infarction, cardiac and sudden death, coronary revascularization procedure, and angina. Secondary endpoints included stroke, cerebral infarction (CI), intracranial hemorrhage, CHD + CI, CI + transient ischemic attack (TIA), all cardiovascular events (CVD), and total mortality. Analysis primarily focused on CVD because there were sufficient events, and CHD, stroke, CI (component of CVD), and total mortality were also evaluated.

2.3. Statistical analyses

In the main MEGA Study results, the observed risk reduction for stroke was different between the initially planned 5-year follow-up and the entire follow-up period that included the extended follow-up [17]. This difference was attributed to the observation that consent to participate in the extended follow-up was obtained more frequently from patients who were in the diet + pravastatin group than in the diet alone

group at 5 years [20]. The present analysis used 5-year data to reduce potential bias from the high drop-in rate for statin use in patients in the diet group caused by the additional follow-up period. In the present subanalysis, patients enrolled in the MEGA Study were retrospectively recategorized according to baseline single fasting plasma glucose (FPG) status. They were stratified to three groups: (1) diabetes, based on physician's clinical diagnosis or an FPG of ≥126 mg/dL; (2) impaired fasting glucose, for an FPG of 110–125 mg/dL; and (3) normal fasting glucose (NFG), for an FPG of <110 mg/dL or no history of DM. The abnormal fasting glucose (AFG) group comprised the DM and IFG groups. Results for subjects without FPG were classified as NFG. Statistical analyses by fasting glucose subgroups were done according to the intention-to-treat principle. Time-to-event curves were estimated by the Kaplan–Meier method at 5 years. Event rates were compared between the diet group and diet + pravastatin group. Hazard ratios (HR) and 95% confidence intervals (95% CI) were estimated by the Cox proportional hazards model adjusted by sex and age. The effect of taking pravastatin adjuvant to diet therapy was compared between the AFG and NFG groups using the Cox interaction model.

3. Results

3.1. Clinical characteristics

Of the 7832 patients analyzed in the intention-to-treat main analysis of the MEGA Study, 1746 were classified as DM, 464 as IFG, and 5622 as NFG (Table 1). At baseline, mean age was approximately 58 years old in each group. The NFG group had a significantly lower proportion of men, current smokers, and obesity compared with DM and IFG groups. In the DM group, 65% of patients took insulin or oral hypoglycemic agents. Approximately 12%–16% of the entire study cohort took a renin–angiotensin system (RAS) inhibitor for hypertension, and the proportion of patients on a RAS inhibitor was significantly higher in the DM and IFG groups than in the NFG group.

Patients assigned to diet therapy alone and diet + pravastatin therapy were well balanced at baseline for each glucose status (Table 2a). HDL-C level was lower, and TG level higher, in the DM and IFG groups than in the NFG group (Table 2a). HbA1c levels were 6.9%, 5.4%–5.5% and 5.2% in the DM, IFG, and NFG groups, respectively.

3.2. Efficacy

3.2.1. Changes in lipid profiles by glucose metabolism status

During the 5-year follow-up of the entire study population, mean TC and LDL-C levels were significantly reduced by 11.5% and 17.9%, respectively, in the diet + pravastatin group compared with reductions of 2.0% and 2.9%, respectively, in the diet alone group. HDL-C increased by 5.5% in the diet + pravastatin group vs. 2.9% in the diet alone group. No significant difference was found between the diet alone group and diet + pravastatin group at baseline for each glucose status. Baseline HDL-C was significantly lower, and TG significantly higher, in DM and IFG than NFG. No difference was found in TC or LDL-C among the DM, IFG, and NFG groups. Baseline FPG and HbA1c were significantly higher in the DM and IFG groups compared with NFG. After follow-up, the difference between the diet group and diet + pravastatin group was similar for each change in lipid parameters in the DM, IFG, and NFG groups (Table 2a, b). No significant difference was found in the change in FPG and HbA1c between diet group and diet + pravastatin group among DM, IFG, and NFG.

3.2.2. Endpoints

The incidence of CVD was threefold higher in AFG (threefold higher in DM and twofold higher in IFG) compared with NFG in the diet alone group (Table 3). CHD and stroke (com-

Table 1
Baseline characteristics according to glucose status, RAS, renin–angiotensin system; DM, diabetes mellitus; IFG, impaired fasting glucose; NFG, normal fasting glucose

Characteristic	DM (n = 1746)	IFG (n = 464)	NFG (n = 5622)	P-value
Mean age (years)	59 ± 7	58 ± 7	58 ± 7	0.01
Age ≥ 65 years (%)	24	25	23	0.47
Women (%)	58	62	72	<0.001
Current smoker (%)	20	16	14	<0.001
Hypertension (%)	42	55	41	<0.001
Obesity (BMI ≥ 25 (%))	37	41	30	<0.001
Mean BMI (kg/m^2)	24.2 ± 3.4	24.4 ± 3.0	23.7 ± 3.0	<0.001
Drug use (%)				
Insulin	9	0	0	<0.001
Sulfonylurea	33	0	0	<0.001
γ-glucosidase inhibitor	16	0	0	<0.001
Thiazolidinedione	4	0	0	<0.001
Other oral hypoglycemic	3	0	0	<0.001
RAS inhibitor	14	16	12	<0.001

Table 2
Laboratory data at baseline (a) and follow-up period (b) by glucose status

Parameter	DM		IFG		NFG		Total	
	Diet ($n=893$)	Diet + pravastatin ($n=853$)	Diet ($n=224$)	Diet + pravastatin ($n=240$)	Diet ($n=2849$)	Diet + pravastatin ($n=2773$)	Diet ($n=3966$)	Diet + pravastatin ($n=3866$)
a. Baseline								
Total cholesterol (mg/L)	242.0 ± 12.6	242.2 ± 12.0	242.4 ± 11.9	243.5 ± 12.1	242.8 ± 12.0	242.7 ± 12.0	242.6 ± 12.1	242.6 ± 12.0
LDL-C (mg/L)	156.6 ± 18.8	157.8 ± 17.4	154.9 ± 17.9	157.5 ± 15.7	156.7 ± 16.8	156.3 ± 17.8	156.5 ± 17.3	156.7 ± 17.6
HDL-C (mg/L)[a]	54.7 ± 15.1	54.8 ± 13.7	56.2 ± 16.0	55.4 ± 12.6	58.5 ± 14.9	58.6 ± 15.2	57.5 ± 15.1	57.5 ± 14.8
Triglycerides (mg/L)[a]	140.0 (101.3–195.0)	135.0 (101.3–184.0)	145.8 (115.3–198.0)	140.0 (106.3–194.8)	123.3 (92.0–171.5)	124.3 (93.0–173.0)	127.5 (95.0–179.0)	127.4 (95.7–176.5)
FPG (mg/L)[a]	141.7 ± 40.5	143.0 ± 44.5	114.9 ± 4.2	114.9 ± 4.2	93.6 ± 8.3	94.2 ± 8.3	108.2 ± 30.6	108.7 ± 31.9
HbA1c (%)[a]	6.9 ± 1.3	6.9 ± 1.3	5.4 ± 0.5	5.5 ± 0.5	5.2 ± 0.4	5.2 ± 0.5	5.9 ± 1.2	5.9 ± 1.2
b. Follow-up								
Total cholesterol (mg/L)	235.3 ± 19.5	212.3 ± 19.4	236.1 ± 15.9	214.4 ± 16.8	238.4 ± 16.0	215.1 ± 18.2	237.5 ± 16.9	214.4 ± 18.4
[% change, %]	[−2.7]	[−12.2*]	[−2.5]	[−11.8*]	[−1.7]	[−11.3*]	[−2.0]	[−11.5*]
LDL-C (mg/L)	149.0 ± 20.5	127.2 ± 19.0	148.8 ± 18.7	128.2 ± 17.0	152.0 ± 18.2	128.3 ± 19.4	151.1 ± 18.8	128.0 ± 19.2
[% change, %]	[−4.2]	[−19.0*]	[−3.3]	[−18.0*]	[−2.5]	[−17.5*]	[−2.9]	[−17.9*]
HDL-C (mg/L)	56.2 ± 14.5	57.4 ± 14.1	55.9 ± 14.7	58.2 ± 12.2	59.6 ± 14.3	61.1 ± 14.5	58.6 ± 14.5	60.1 ± 14.4
[% change, %]	[3.6]	[5.4*]	[2.1]	[6.2*]	[2.8]	[5.5*]	[2.9]	[5.5*]
Triglycerides (mg/L)	135.1 (102.0–182.7)	122.3 (95.0–167.6)	146.3 (113.8–188.5)	125.9 (100.2–161.6)	121.3 (93.2–162.2)	116.4 (88.5–155.0)	125.3 (95.9–168.3)	118.5 (90.4–157.8)
[% change, %]	[0.9]	[−2.3*]	[1.6]	[−5.4*]	[1.4]	[−3.2*]	[1.3]	[−3.2*]
FPG (mg/L)	144.5 ± 38.6	146.6 ± 36.8	109.0 ± 12.3	109.9 ± 13.2	97.2 ± 11.9	97.8 ± 12.0	109.8 ± 30.0	110.8 ± 29.7
[% change, %]	[4.8]	[6.8]	[−5.0]	[−4.4]	[3.1]	[3.3]	[3.0]	[3.7]
HbA1c (%)	6.9 ± 1.2	7.0 ± 1.2	5.5 ± 0.6	5.5 ± 0.6	5.2 ± 0.5	5.3 ± 0.5	5.8 ± 1.1	5.8 ± 1.1
[% change, %]	[2.2]	[2.7]	[2.2]	[1.1]	[0.1]	[0.6]	[1.2]	[1.6]

The values for follow-up data were averaged for the follow-up periods. The percentage change was calculated against baseline. All data (except triglycerides) were mean ± S.D.; triglycerides, median (interquartile range).

[a] The values for combined diet alone and diet + pravastatin groups were significantly different ($P<0.001$) among DM, IFG, and NFG.

* $P<0.05$ against diet group.