Table 3 Correlation Between Laboratory Data and Thyroid Hormone Level in Normal Subjects

Thyroid state	TG††	FBG¶	HbA1c¶	TC‖	HDL‖	BMI	PR§	SBP‡	DBP‡
No. of subjects	3,084	2,976	2,976	2,726	2,726	3,130	3,057	2,355	2,355
TSH									
P	0.0015	NS	NS	0.015	0.0055	NS	NS	NS	NS
*	5.21	0.20	0.0090	1.83	−0.92	0.045	−0.10	−0.24	0.12
Normal thyroid									
fT3									
P	0.0043	NS	NS	NS	<0.0001	<0.0001	NS	NS	NS
*	12.16	0.15	−0.023	0.22	−4.01	1.06	0.12	1.75	0.64
fT4									
P	0.039	0.0006	0.030	0.0010	0.071	NS	<0.0001	0.002	0.023
*	18.00	6.03	0.14	13.09	3.16	0.43	4.83	7.06	2.95

*Correlation coefficient with each value.
P values are coefficient of correlation; p values are for comparisons with normal thyroid subjects after adjustment for appropriate confounding factors.
‡Without treatment for hypertension; §without treatment for arrhythmia; ¶without treatment for diabetes mellitus; ‖without treatment for hypertriglyceridemia; ‖without treatment for hyperlipidemia.
Abbreviations see in Table 1.

Table 4 Correlation Between Thyroid Status and IMT

	Normal thyroid	Hyperthyroidism	Hypothyroidism	Subclinical hyperthyroidism	Subclinical hypothyroidism	ANOVA p value
N	2,819	17	4	65	321	
IMT-max (mm)	1.30±0.55	1.21±0.63	1.73±0.97	1.25±0.53	1.40±0.58	0.048
Residual IMT-max*	0.002±0.491	−0.015±0.492	0.089±0.892	−0.052±0.467	−0.009±0.520	0.892
Residual IMT-max†	0.001±0.784	−0.046±0.506	0.094±0.855	−0.064±0.463	−0.001±0.510	0.786
N	2,818	17	4	65	320	
IMT-mean (mm)	0.821±0.13	0.79±0.13	0.93±0.09	0.83±0.13	0.83±0.13	0.042
Residual IMT-mean*	0.0004±0.105	−0.004±0.108	0.022±0.496	0.018±0.118	−0.008±0.112	0.581
Residual IMT-mean†	0.000±0.103	−0.301±0.103	0.014±0.035	0.014±0.111	−0.005±0.110	0.821

Values are mean±standard deviation.
*Aadjusted for age and sex; †adjusted by age, BMI, SBP, FBS, number of cigarettes/day, TG, TC and HDL.
IMT, intima–media thickness. Other abbreviations see in Tables 1,2.

thyroid dysfunction) and the prevalence of atherosclerotic vascular diseases, such as cerebral infarction, transient cerebral ischemic attack, cerebral stroke, acute myocardial infarction and angina pectoris (p=0.090, unpubl. data).

Discussion

In this large cross-sectional study of subclinical thyroid dysfunction in Japanese subjects, although the prevalence of SCH increased with age overall, the prevalence of SCH in elderly patients was lower than that reported in other studies, particularly in women: 18.8% for men older than 75 years and 12.7% for women older than 75 years. This finding differs from that of previous studies in which the prevalence of SCH was higher in elderly women than in elderly men[1,3,6] In the Colorado study, the prevalence of SCH was 16% in men older than 75 years and 21% in women older than 75 years[1] The differences in these trends might be due to different genetic, ethnic or environmental backgrounds of the subjects. On the other hand, the prevalence of subclinical hyperthyroidism was 2.13% in our study, which is similar to that in the Colorado study (2.1%)[1]

We found that the presence of SCH was associated with lower FBG levels and that subclinical hyperthyroidism was associated with higher FBG and HbA1c levels. Moreover, our results also indicate that thyroid hormone levels in normal subjects are significantly associated with various laboratory data, including FBG and HbA1c levels. Compared with normal subjects, serum thyroid hormone levels in subjects with SCH were lower and levels in subjects with subclinical hyperthyroidism were higher. Therefore, lower or higher levels of thyroid hormone (within the normal range) in subclinical thyroid dysfunction might influence glucose metabolism.

We did not observe any significant association between subclinical thyroid dysfunction and lipid metabolism, which was consistent with a previous US study[5] However, other studies in Norway and Australia have reported dyslipidemia in subjects with SCH[6,7] We examined whether higher TSH levels (>10μU/ml) in subjects with SCH were associated with lipid metabolism, but did not find any significant association between lipid metabolism and TSH levels >10μU/ml in subjects with SCH compared with normal subjects. Moreover, higher TSH levels did not show any association with FBG levels. These results might be related to aging, because hypofunction of the endocrine glands occurs with age. Serum lipid, FBG, and HbA1c levels were sustained in subjects with high TSH levels and SCH.

We did not observe any significant association between subclinical thyroid dysfunction and IMT, which suggests that subclinical thyroid dysfunction might not be related to an increased risk of atherosclerosis. Moreover, we did not find any significant association between SCH and previous history of arteriosclerotic vascular diseases. However, this result was not consistent with previous studies[8,10] possibly because of the size of our study population and different

surrogate markers for atherosclerosis.

The necessity for thyroid hormone replacements therapy for SCH is not supported by the present study results. The signs and symptoms of hypothyroidism are bradycardia, mild hypertension and hyperlipidemia, which might accelerate atherosclerosis in subjects with hypothyroidism![6] We examined the association between SCH and these symptoms or signs and did not observe an association between SCH and blood pressure or serum lipid levels. The association between lipid profile and SCH has been previously reported in Norway and Australia[6,7] and the different results might relate to differences in genetic background, life style and BMI. In the Tromsø study[7] the subjects were obese and those with SCH were even more obese than normal subjects. The difference in BMI between those and our investigations might induce different patterns of lipid metabolism. We did not observe any significant association between SCH and the symptoms or signs associated with hypothyroidism. Moreover, we did not find an association between SCH and IMT, as a surrogate marker for atherosclerosis, and did not find an association between SCN and past history of atherosclerotic disease. These results do not support the need for treatment of SCH in Japanese subjects. However, our investigation was a cross-sectional study, so the duration of SCH was not considered in the analysis. Our results do not completely deny that subjects with long-term SCH have increased risk of atherosclerosis.

In conclusion, we examined the association between subclinical thyroid dysfunction and various factors in a general population. We only found an association between glucose levels and subclinical thyroid dysfunction. The differences in serum glucose levels among the thyroid states (SCH, subclinical hyperthyroidism, and normal thyroid) were too small to lead to a recommendation for treatment of subclinical thyroid dysfunction and thus do not indicate a need for treatment of subclinical thyroid dysfunction in Japanese subjects.

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We have found that high concentration of mercaptoethanol (for example 10 mM) or long incubation times (for example 30 minutes) causes a decrease in immunostaining intensity, possibly due to loss of epitopes through excessive reduction (data not shown). In our laboratory, incubation of a 2 mm-thick gel for 10 minutes in 1 mM β-mercaptoethanol has proven adequate (Fig. 1). These conditions are suitable for VWF concentrations from 6 IU/dl to 250 IU/dl (data not shown). β-mercaptoethanol is a toxic and highly pungent reagent, therefore appropriate precautions should be taken when using it.

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Age- and gender-related differences of plasma prothrombin activity levels

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Dear Sir,

Advancing age is an important risk factor for venous or arterial thrombosis in both sexes (1–3). Moreover, gender is associated with differences in the prothrombotic state and in the progression of atherosclerosis that occurs with aging (4, 5). Prothrombin is one of the dominant factors influencing thrombin generation (6), and the prothrombin G20210A mutation accompanied by an increased level of prothrombin poses a risk factor for venous or arterial thrombosis (7, 8). However, gender differences in age-related changes in plasma prothrombin activity have not been investigated until now. In the present study, we measured prothrombin activity in 742 individuals derived from a general Japanese population which was supposed to be free of prothrombin G20210A mutation (9).

The study population was composed of samples randomly selected from the residents of Suita, a city located in the second largest urban area in Japan (the Suita Study) (4). All subjects had been visiting the National Cardiovascular Center every two years since 1989 for regular health checkups. Only subjects who provided written informed consent to have a blood examination were enrolled in this study. We excluded subjects treated with oral anticoagulant therapy. Finally, 742 subjects, aged 36 to 85 years (mean age: 64 years), were included in this study. Spearman correlation analysis was used to assess the association between aging and the level of prothrombin activity within a given gender. For comparison between the two gender groups, the Mann-Whitney U test was used. Differences with a value of $p<0.01$ for the Spearman correlation analysis and $p<0.05$ for the Mann-Whitney U test were considered to be significant. Statistical calculations were performed using SPSS version 12.0 (SPSS Inc, Chicago, IL, USA). Prothrombin activity was measured according to a published method (10) with a modification. Briefly, 200 µl of 20 mM Tris-HCl, 0.14 M NaCl, pH 7.5 buffer containing 1 mg/ml of bovine serum albumin (TBSA) was added to 50 µl of plasma anticoagulated with 0.13% sodium citrate. Then, diluted plasma was incubated for 150 seconds at 37°C, and we detected ΔA/min at 405 nm after adding 50 µl of the reagent containing 6 mM $CaCl_2$, 0.5 mM Boc-Val-Pro-Arg-pNA as a thrombin substrate, 500 pM carinactivase-1 as a thrombin activator, and TBSA. Calibration was performed with a standard-human-plasma (Dade Behring GmbH, Marburg, Germany). The coefficient of intra-assay variation for prothrombin activity assay was 2.0%.

The mean ± SD of prothrombin activity level in men and women was 110.2 ± 17.0 (range: 54.5–158.5%) and 120.4 ± 17.4 (range: 57.5–194.4%), respectively. Figure 1 shows the age-related distribution (36–85 years) of prothrombin activity in 348 men (Fig. 1A) and 394 women (Fig. 1B). As a whole, a linear decrease of prothrombin activity level with age was observed in

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men (r=-0.34, p<0.0001), but not in women (r=-0.04, p=0.47). When prothrombin activity level was analyzed in 10-year age groups, significant decreases were observed in the men aged 46–55 years and 56–65 years (p<0.0001), aged 56–65 years and 76–85 years (p<0.05), and in the women aged 66–75 years and 76–85 years (p<0.0001). Levels of prothrombin activity were decreased in both sexes in the oldest age group (aged 76–85 years). With regards to gender-related change, the prothrombin activity level in the age group of 56–65 years, 66–75 years, and 76–85 years was significantly lower in men than in women.

In the present study, we showed the age-related decrease in the plasma prothrombin activity of men and gender-related change in the plasma prothrombin activity. These results contribute to the understanding of age-related hypercoagulability and to the practical institution of anticoagulant therapy in older patients. It has been established that thrombin generation increases with age in both sexes, evidenced by plasma prothrombin fragment F1+2 levels produced by the cleavage of prothrombin by factor Xa (11, 12). Age-related hypercoagulability does not likely stem from the prothrombin activity, because the prothrombin activity of men showed the age-related decrease, but it may result from some other mechanisms including decreased levels of anticoagulant proteins such as protein C and S (11, 13). We presented here the gender-related change of significantly lower prothrombin activity levels in men in the age of 56–85 years than in women. Men tend to develop thrombotic events including recurrent venous thrombosis (14), but this tendency was not related to the plasma level of prothrombin activity. Our work sheds further light on the point that, when considering relative hypercoagulability, gender-adjustment is necessary for the comparison of prothrombin activity levels.

With regards to anticoagulant therapy, the plasma levels of vitamin K-dependent coagulation factors decrease with increasing intensity of anticoagulation therapy (15). At the same time, the risks of major haemorrhage increase according to the intensity of anticoagulation therapy, especially in patients older than 80 years (16). Given our current study results, the markedly decreased prothrombin level in the age group of 76–85 years, especially in men, provides a potential mechanistic explanation for the increased rate of major haemorrhage observed in elderly patients receiving anticoagulant therapy.

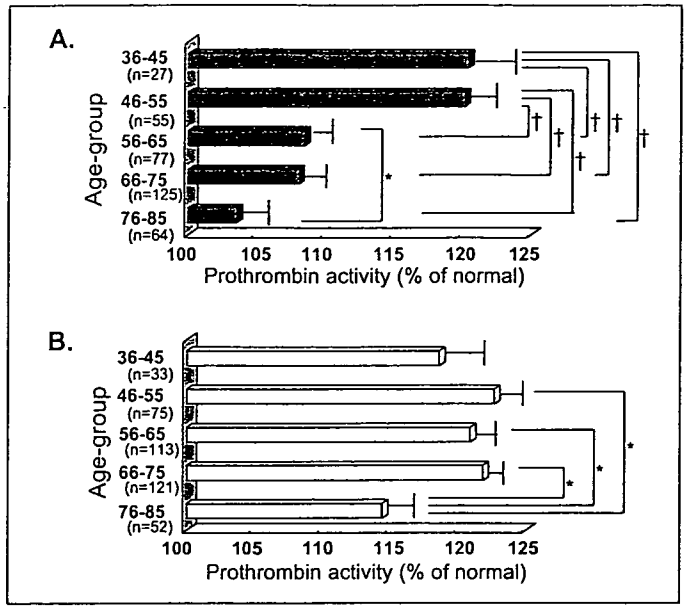

Figure 1: Age-related changes of plasma prothrombin activity levels according to gender (A: men, B: women). Populations aged from 36 to 85 years old were divided into five age groups by gender. Data are expressed as the mean ± SEM. *: P<0.05, †: P<0.0001, compared between two age groups of the same gender.

In conclusion, there are significant age- and gender-related differences in plasma prothrombin activity levels. In particular, the prothrombin activity level in men in the age group of 76–85 years was lower than that of any other age group in either gender.

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吹田市基本健診での生活習慣とメタボリックシンドロームに関する研究

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目的　都市住民のメタボリックシンドローム（Mets）有病率とMets定義病態に関連する生活習慣の特徴を性・年齢ごとに評価した。

方法　平成16年度吹田市基本健康診査受診者のうち問診票で有効回答が得られた30～89歳の26,522人の男女を対象とした。MetsはUS National Cholesterol Education Program: Adult Treatment Panel Ⅲの基準を改変して診断した。Mets有病率，Mets有病者での構成因子の有病率を求め，さらにMetsと関連する生活習慣の検討を行った。

結果　30～89歳でのMetsの有病率は，男性19.4%，女性10.7%であった。Mets有病者のうち，若年群では肥満の有病率が高く（30歳代：男性82%，女性90%），高齢群では血圧高値の有病率が高い傾向にあった（80歳代：男性99%，女性98%）。生活習慣では，「他の人より食べる量が多い」「早食いである」「睡眠が不規則である」「立位・歩行時間が1時間未満である」は，男女ともすべての年代でMetsと関連していた。4項目のいずれにも該当しない対象者と1項目該当の対象者のMetsの多変量調整オッズ比は1.29～2.17の値をとり，2個では1.66～4.60，3個では3.13～5.09で，4個すべてに該当する対象者では5.36であった。

結論　Metsの構成因子は年齢により異なっていたが，過食・早食い・不規則な睡眠・運動不足はすべての年代でMetsとの関連がみられ，これらを多く満たす人ほどMetsのリスクが高かったことから，これら4つの項目はMetsの予防・改善の保健指導の項目となりうる生活習慣と考えられた。

キーワード　メタボリックシンドローム，有病率，生活習慣

Ⅰ はじめに

メタボリックシンドローム（Metabolic Syndrome: 以下，Mets）は，肥満，高血糖，脂質代謝異常，血圧高値などの循環器疾患危険因子が集積しやすく，循環器疾患やⅡ型糖尿病を予防する上で目標を定めやすい病態として公衆衛生・予防医学の分野でも注目されている[1]。前向きコホート研究では，Metsの循環器疾患・Ⅱ型糖尿病に対するリスクがこれまでに確認されてきた[2)-8)]。Metsの原因については，遺伝要因と近年の生活習慣における近代化・欧米化といった環境要因の両面の関与が指摘されており，特にアジア人は欧米化した生活習慣によってMetsになりやすい遺伝要因を有していることが知られている[9)10)]。わが国でも，戦後より脂肪摂取量の増加や労働の機械化・交通網の発達による運動量の減少など生活習慣が著しく変化しており，肥満や代謝性疾患の増加も顕著で，Mets有病率の上昇が指摘されている[11)]。しかし，Mets有病率と関連する生活習慣をわ

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が国の都市住民で検討した報告はみられない。

Metsの診断基準はこれまでにいくつか提唱されてきた。代表的なものには，1999年に世界保健機構（WHO）から提唱されたインスリン抵抗性を必須項目とするもの[12]，2001年にUS National Cholesterol Education Program: Adult Treatment Panel Ⅲ（NCEP ATP Ⅲ）の一部として提唱された循環器疾患の予防に焦点をおいたものがあるが[13]，これらに対し，診断基準が複数存在することに対する多岐にわたる評価や診断基準の見直しの必要性も指摘された[14]。2005年に国際糖尿病連合（IDF）から提唱された基準では，ウエスト周囲径による腹部肥満が必須項目とされ，また，従来の項目以外のものも今後研究されるべき項目として考慮されている[15]。2005年に日本内科学会が日本肥満学会・糖尿病学会・動脈硬化学会などの8学会と合同で提唱した日本人のための基準でも，IDFの基準と同様にウエスト周囲径による腹部肥満が必須項目とされている[16]。今後，これらの新しい診断基準を用いた研究が望まれるが，その一方，わが国の過去の健診の多くはウエスト周囲径を項目に含んでいないのが現状である。身長・体重は健診で広く一般に測定され，そこから算出されるBody Mass Index（BMI）は肥満の診断に日常的に使用されている。過去の研究においてNCEP ATP Ⅲの基準のウエスト周囲径による腹部肥満をBMIによる肥満に改変した基準が用いられているが[17]，NCEP ATP Ⅲの基準によると腹部肥満は必須項目ではなく1つの構成因子であり，改変による影響は比較的少ないと思われる。すでに行われた健診のデータを用いてMetsの研究を行う場合には，改変されたNCEP ATP Ⅲの基準を用いるのが現実的な方法と思われる。

著者らは，都市住民を対象に改変したNCEP ATP Ⅲの診断基準を用い，Metsとその構成因子の有病率，Metsに関連する生活習慣を分析し，Metsの予防・改善に役立てることを目的として本研究を行った。

表1　対象者の性・年代別分布

	総数	30歳代	40歳代	50歳代	60歳代	70歳代	80歳代
総数	26 522	2 649	2 697	4 290	9 378	6 055	1 453
男性	8 652	418	504	840	3 649	2 679	562
女性	17 870	2 231	2 193	3 450	5 729	3 376	891

Ⅱ 方　法

（1） 研究の対象

平成16年度吹田市基本健康診査の受診予定者全員（100,885人）にあらかじめ生活習慣問診票を送付し，受診者が記入した問診票は健診の際に医師によって再点検した。健診受診者中の，61,879人の血液検査が同一施設で行われ，このうち30～89歳であり，かつ問診票で有効回答が得られた26,522人（男性8,652人，女性17,870人）を本研究の対象とした。対象者の性・年齢別分布を表1に示す。

（2） 診断基準

NCEP ATP Ⅲ基準の5項目（高血糖［血糖≧110mg/dlまたは治療中］，血圧高値［血圧≧130/85mmHgまたは治療中］，高中性脂肪血症［中性脂肪≧150 mg/dl］，低HDLコレステロール血症［HDLコレステロール　男性40 mg/dl未満・女性50mg/dl未満］，肥満［BMI≧25kg/m^2］）のうち，3項目以上を満たした場合，Metsと診断した[13]。Metsの構成因子とMetsの有病率を性・年代別に求めた。また，Mets対象者についてのMetsの構成因子の有病率を性・年代別に求めた。問診票での食事・運動・睡眠などの30項目の生活習慣のうち，30～49歳・50～69歳・70～89歳のすべての年代で男女共通してMetsと関連する項目を，ロジスティック回帰モデルを用いて年齢調整して求めた。さらに，それらの生活習慣に1つも該当しない対象者とそれらの生活習慣の組み合わせに該当する対象者のMetsの多変量調整オッズ比を，ロジスティック回帰モデルを用いて性・年齢・飲酒・喫煙を調整して求めた。有意水準は$p<0.05$とし，解析にはSPSS ver11.0を用いた。

Ⅲ 結　果

Metsの構成因子とMetsの性・年代別有病率を図1に示す。高血糖あるいは血圧高値の有病率は，男女とも年代と共に上昇傾向にあった。高中性脂肪血症では，男性は40歳代から年代と共に低下傾向，女性は上昇傾向にあった。低HDLコレステロール血症では，男性は年代による大きな変化はなく，女性は年代と共に上昇傾向にあった。肥満では，男性は年代と共に低下傾向，女性は上昇傾向にあった。Metsの有病率は，男性は60歳代で最も高く，女性は年代と共に上昇傾向にあった。30～89歳でのMetsの有病率は，男性19.4%，女性10.7%であった。

Mets有病者のMets構成因子有病率を性・

図1　メタボリックシンドローム（Mets）の構成因子（5項目）とMetsの有病率

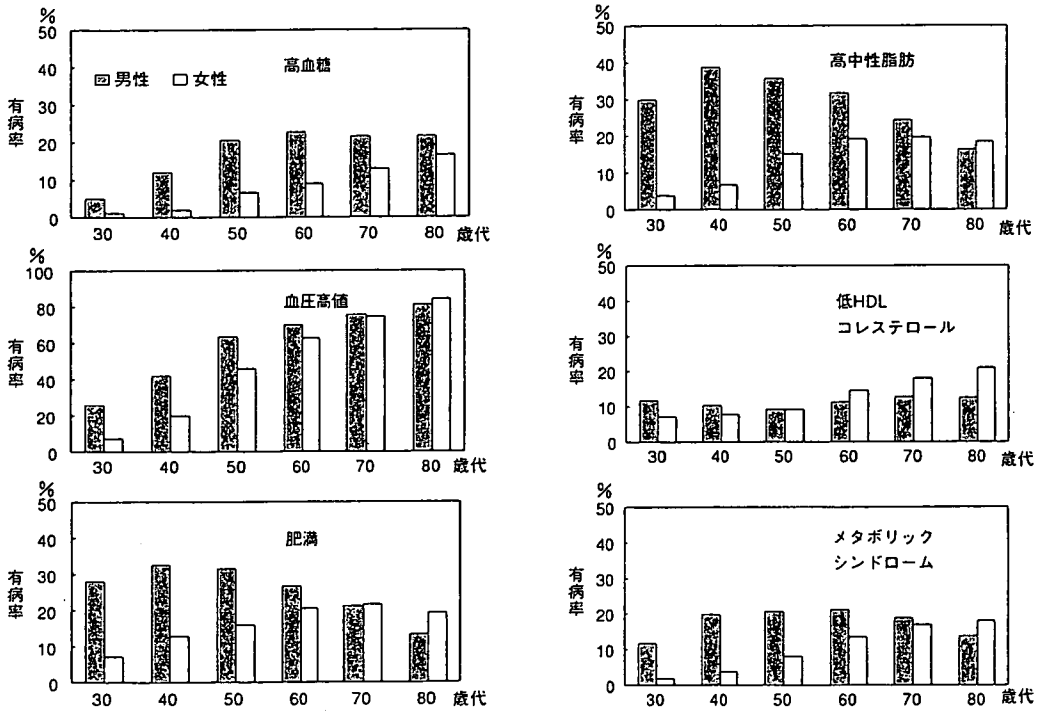


図2　メタボリックシンドローム（Mets）有病者でのMets構成因子（5項目）有病率

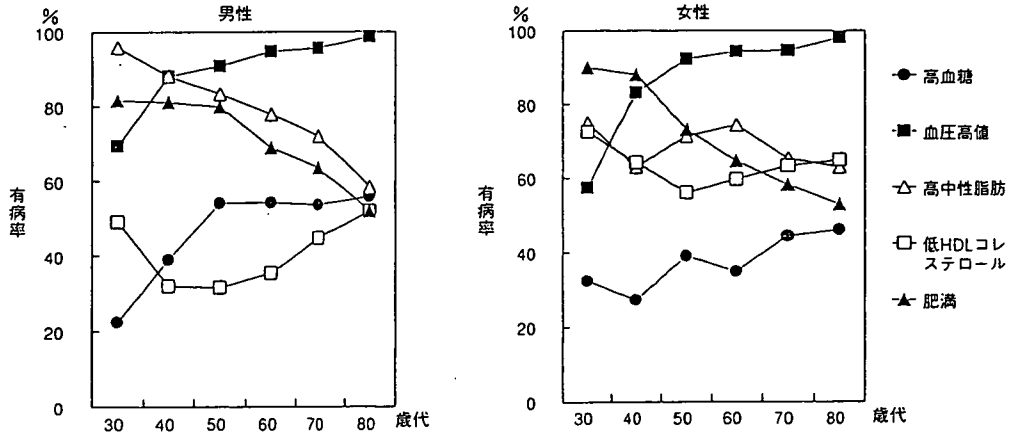


表2　生活習慣の性・年代別割合

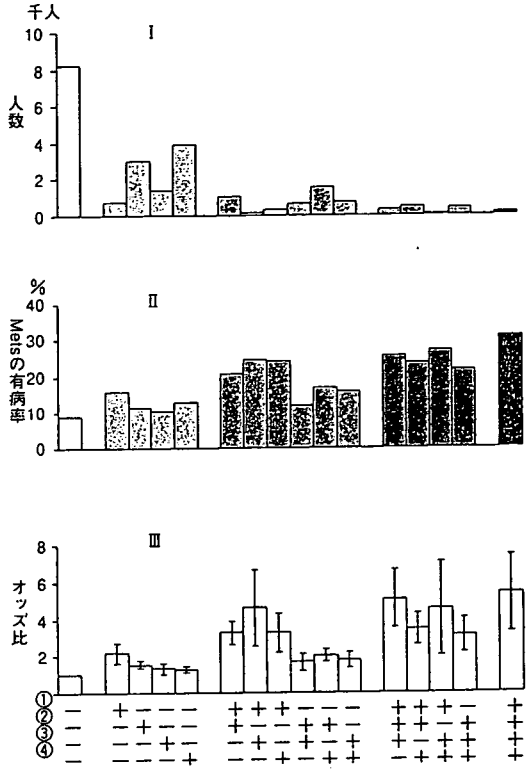
（単位　%）

	総数	30～49歳	50～69	70～89
男性				
他の人より食べる量が多い	15.2	26.7	16.2	10.5
早食いである	35.4	53.9	39.0	24.9
睡眠が不規則である	15.8	31.7	14.4	13.2
立位・歩行時間が1時間未満である	23.4	23.8	20.1	28.1
女性				
他の人より食べる量が多い	14.2	15.5	15.0	11.0
早食いである	32.5	37.1	34.6	23.1
睡眠が不規則である	18.5	20.9	17.5	18.1
立位・歩行時間が1時間未満である	17.2	13.2	14.6	28.3

年代別にグラフ化する（図2）。男性では，血圧高値・高血糖の有病率は年代と共に上昇傾向，肥満・高中性脂肪血症は低下傾向にあった。女性では，血圧高値・高血糖の有病率は年代と共に上昇傾向，肥満は低下傾向にあった。男女ともに共通した傾向として，若年群では肥満の有病率が高く（30歳代：男性82%，女性90%），高齢群では血圧高値の有病率が高いという傾向がみられた（80歳代：男性99%，女性98%）。

生活習慣とMetsの関連の検討では，「他の人より食べる量が多い」「早食いである」「睡眠が不規則である」「立位・歩行時間が1時間未満である」の4項目が，30～49歳，50～69歳，70～89歳のすべての年代で男女ともにMetsと関連していた。この4項目の生活習慣の性・年代別割合を表2に示す。また，この4項目の組み合わせに該当する対象者の分布を図3（Ⅰ）に，それらの対象者でのMetsの有病率を同（Ⅱ）に，4項目のいずれにも該当しない対象者を基準とした4項目の組み合わせ別によるMetsの多変量調整オッズ比を同（Ⅲ）に示す。1個該当する対象者のMetsの多変量調整オッズ比（95%信頼区間）は1.29（1.14-1.46）から2.17（1.74-2.70）の値をとり，2個では1.66（1.28-2.14）から4.60（3.16-6.69），3個では3.13（2.41-4.06）から5.09（3.90-6.66），4個すべてに該当する対象者では5.36（3.85-7.45）であり，該当する生活習慣の個数が多いほどMetsの多変量調整オッズ比が高い傾向がみられた。

図3　メタボリックシンドローム（Mets）と関連のある生活習慣（4項目）の組み合わせ別による対象者人数（Ⅰ），Mets有病率（Ⅱ），Metsの多変量調整オッズ比（Ⅲ）



注　1）生活習慣：①他の人より食べる量が多い，②早食いである，③睡眠が不規則である，④立位・歩行時間が1時間未満である。また，「+」はその生活習慣に該当することを，「−」は該当しないことを示す。
2）Ⅲのグラフ内の縦棒は，95%信頼区間を示す。

Ⅳ 考　察

本研究では，都市住民の検討により，Metsの構成因子が年代によって異なり，若年群では肥満の割合が，高齢群では血圧高値の割合が高かった。このことは，年齢や性によってMetsの病態が異なることを示しており，予防や治療にあたって個々の構成因子の対象が基本になることを示している。

「他の人より食べる量が多い」「早食いである」「睡眠が不規則である」「立位・歩行時間が1時間未満である」は，すべての性・年齢でMetsとの関連がみられ，該当する数が多いほどMetsのリスクが高いことが明らかになった。

「過食」「運動不足」とMetsの関連は過去の研究でも示されたが[16)19)]，「早食いである」「睡眠が不規則である」とMetsの関連についての報告は著者らの知る限りこれまでにない。

「早食いである」とMetsの関連の機序は，過去の疫学研究結果，すなわち炭水化物の吸収を遅延させるアカルボースの投与により循環器疾患発症のリスクが半減したこと[20)]，摂取後の血糖上昇度の指標であるグリセミック・インデックス（GI値）が高い食品を摂取していた群は心筋梗塞のリスクが高かったこと[21)]，糖負荷後血糖の高い群は死亡のリスクが高かったことからも推察される[22)]。これらにより，急激な血糖上昇は循環器疾患のリスクを高める可能性が示唆され，また本研究の結果と合わせて，「早食いである」による急激な血糖上昇はMetsを経て循環器疾患発症につながる可能性が示唆される。一方，「早食いである」によって摂食のシグナルが脳の満腹中枢に伝わる前に多量摂取してしまうという機序も考えられる[23)]。本研究のデータで，「他の人より食べる量が多い」人の62%が「早食いである」であったことから，両者は同時に起こりやすい行動様式であると考えられる。

「睡眠が不規則である」とMetsの関連の機序は明らかでない。本研究のデータで「他の人より食べる量が多い」「立位・歩行時間が1時間未満である」「現在飲酒・喫煙」のいずれでもない対象者について「睡眠が不規則である」とMetsの構成因子の関連を検討した結果でも，女性で「睡眠が不規則である」と肥満の関連がみられた。

本研究で挙げられた4項目の生活習慣は，すべての性・年代でMetsとの関連がみられたことから，Metsは年齢によって構成因子が異なる病態である一方で，Metsに共通した要因はこれらの生活習慣に起因するものと考えられる。そのため，年齢の幅広い集団を対象とした保健指導でこれらの項目が有用となる可能性が考えられる。また，これらの項目に該当する数が多いほどMetsの割合が高いことから，これらのリスクを減らす指導がMetsの予防・改善につながるものと思われるが，その有用性は今後保健指導の場で検証される必要がある。

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Circ J 2007; **71:** 1335–1347

Unstable Angina and Non-ST Elevation Acute Coronary Syndrome

—— Epidemiology and Current Management in Japan (Japan Multicenter Investigation for Cardiovascular Disease-D (JMIC-D) Committee) ——

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Background A multicenter study was conducted to assess the current medical management of unstable angina (UA) and non-ST-elevation acute coronary syndrome in Japan.
Methods and Results This study presents the results of a nationwide questionnaire survey of 770 sites and a case report investigation performed at 20 sites. The questionnaire survey revealed that the number of acute myocardial infarction (AMI) patients treated annually was 1.56-fold greater than the number of UA patients. Non-ST-elevation AMI accounted for 17% of all patients with AMI. Analysis of case reports for 885 UA patients showed extensive use of invasive treatment. In the UA patients, the cumulative incidence of a composite endpoint (all-cause mortality, AMI, and urgent coronary revascularization) was 2% at 1 month and 9% at 6 months. Stratified analysis with respect to the composite endpoint through 6 months showed a significantly lower incidence in patients treated with a calcium-channel blocker than in patients not treated with a calcium-channel blocker.
Conclusions In Japan, fewer patients are hospitalized annually for treatment of UA than for AMI. The largest percentage of UA patients had Braunwald class III disease. Non-ST-elevation AMI is managed in Japan according to the principle of early invasive treatment, resembling the treatment for ST-elevation AMI. The outcome of treatment is better for Japanese UA patients than for Japanese AMI patients. (*Circ J* 2007; **71:** 1335–1347)

Key Words: Acute coronary syndromes; Epidemiology; Non-ST elevation; Unstable angina

According to the Population and Vital Statistics of Japan for 2003, heart disease is the second leading cause of death, and ischemic heart disease, including acute myocardial infarction (AMI), is the most frequent cause of cardiac death[1] If the aging of society continues, mortality from ischemic heart disease will increase further, so more effort should be made to improve treatment.

In 2002, the Japanese Circulation Society established guidelines for the diagnosis and treatment of acute coronary syndrome (ACS), but most of the clinical data used as the basis for the guidelines was gathered overseas[2] Because of differences in the pathophysiology of ACS between Japanese and Caucasians[3] the Japanese ACS guideline should be based on data obtained from Japanese patients.

Several multicenter studies on the treatment of AMI have already been conducted in Japan[4] but there have been few studies of unstable angina (UA). According to recent recommendations for treatment of ACS made by the Japanese Circulation Society, as well as the relevant American and European societies, the treatment of individual patients should not be based on diagnoses such as AMI or UA, but on whether ST changes are found on admission[2,5] In Japan, none of the multicenter studies has compared baseline characteristics, treatment, and outcomes in patients with ST-elevation and non-ST-elevation ACS, except for a few single-center studies[6,7]

Accordingly, we launched the Japan Multicenter Investigation for Cardiovascular Disease-D (JMIC-D) to investigate the number of patients with UA and non-ST-elevation ACS and the current management practices for both disease manifestations in Japan, with the aim of using the results to optimize specific therapeutic recommendations.

Methods

This study comprised a questionnaire survey (study 1) and a case report investigation (study 2). The questionnaire survey was designed to investigate the number of hospitalized patients with UA or AMI, and the treatment policies for these conditions at the participating sites. The case report investigation was designed to obtain detailed treatment and outcome data for individual patients. All statistical tests were 2-sided with an α=0.05 significance level. Between-group comparisons were tested using chi-square tests or Fisher's exact test where appropriate. In this study,

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2. Sendai Cardiovascular Center	*Shunsuke Tanino (Moved to Tanino Naika Junkannki Clinic)*
3. Jichi Medical School Omiya Medical Center	*Muneyasu Saito (Changes to Saitama kinen Hosipital)*
4. Sekishinkai Sayama Hospital	*Masami Sakurada (Moved to Tokorozawa Heart Clinic)*
5. Nippon Medical School Hospital	*Teruo Takano, Keiji Tanaka*
6. Nippon Medical School Chiba Hokusoh Hospital	*Kyouichi Mizuno*
7. Yokohama Rosai Hospital	*Kenichi Katoh*
8. Yokohama City University Medical Center	*Kazuo Kimura*
9. Toyohashi Heart Center	*Shigenori Ito (Moved to Moriyama Municipal Hospital, City of Nagoya)*
10. Nagoya Daini Red Cross Hospital	*Haruo Hirayama*
11. National Cardiovascular Center	*Hiroshi Nonogi*
12. Kansai Rosai Hospital	*Shinsuke Nanto*
13. Osaka Police Hospital	*Kazuhisa Kodama, Atsushi Hirayama*
14. Osaka City Central Hospital	*Kazuo Haze*
15. Sakurabashi Watanabe Hospital	*Kenshi Fujii*
16. Osaka Koseinenkin Hospital	*Tatsuya Sasaki*
17. Matsushita Memorial Hospital	*Hiroki Sugihara*
18. Wakayama Medical University	*Yoshiaki Tomobuchi*
19. Kobe City General Hospital	*Shigefumi Morioka*
20. Kumamoto Chuo Hospital	*Shuichi Oshima*

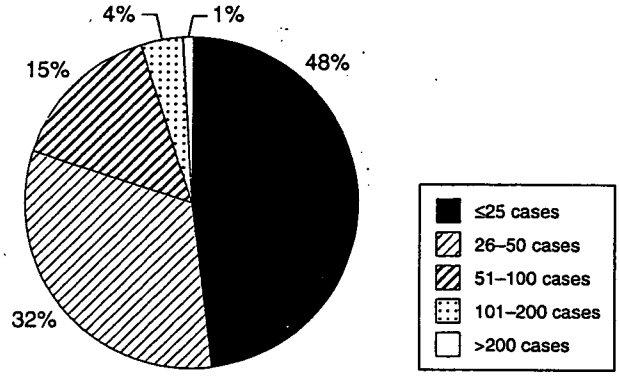


Fig 1. Approximate number of unstable angina (UA) patients hospitalized in 2000 at 582 cardiovascular care sites.

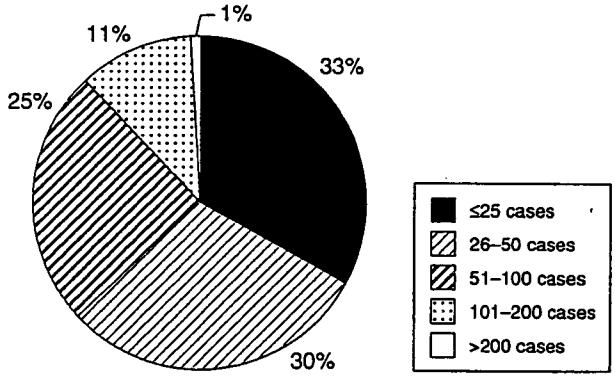


Fig 2. Approximate number of acute myocardial infarction (AMI) patients treated in 2000 at 580 cardiovascular care sites.

UA was defined according to the Braunwald Classification with creatine kinase (CK) and CK-MB isozyme values not greater than twice the respective upper limits of normal; a diagnosis of AMI was made if the CK and CK-MB values exceeded twice the upper limits of normal and the time from onset to admission was within 24 h.

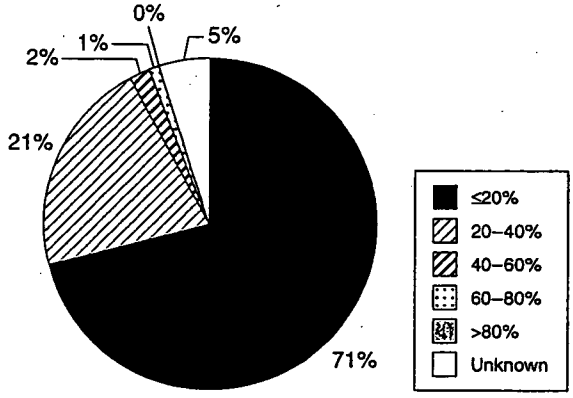


Fig 3. Approximate percentage of patients with non-ST elevation acute myocardial infarction (AMI) among all AMI patients at 574 responding sites.

Study 1: Questionnaire Survey

A questionnaire composed of the 8 questions listed below was sent to the 770 sites certified for cardiovascular care by the Japanese Circulation Society. To increase the response rate and to avoid null answers, multiple choice responses to the questions were set, as shown in parentheses below.

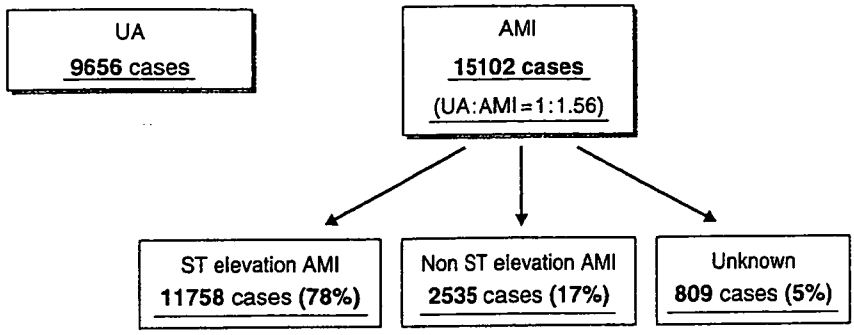
UA (1) Approximate number of hospitalized UA patients during the year from January to December 2000 (≤25; 26–50; 51–100; 101–200; >200).

(2) Treatment with heparin immediately after hospital arrival, excluding bolus administration for coronary angiography and/or revascularization (for all patients apart from those with contraindications; only for refractory patients not responding to appropriate antianginal treatment or for severe cases; not used in principle).

(3) Timing of coronary angiography (immediately after arrival at hospital; after stabilization by drug treatment; not performed if stabilized by drug treatment; no definite policy).

(4) Use of heparin after percutaneous coronary intervention (PCI) (not used in principle; for some patients; for all patients in principle).

AMI (1) Approximate number of hospitalized AMI patients during the year from January to December 2000



Number of sites sent the additional questionnaire: 387

Number of responding sites: 217 (response rate: 56.1%)

Fig4. Number and ratio of unstable angina (UA) and acute myocardial infarction (AMI) patients: results from the additional questionnaires.

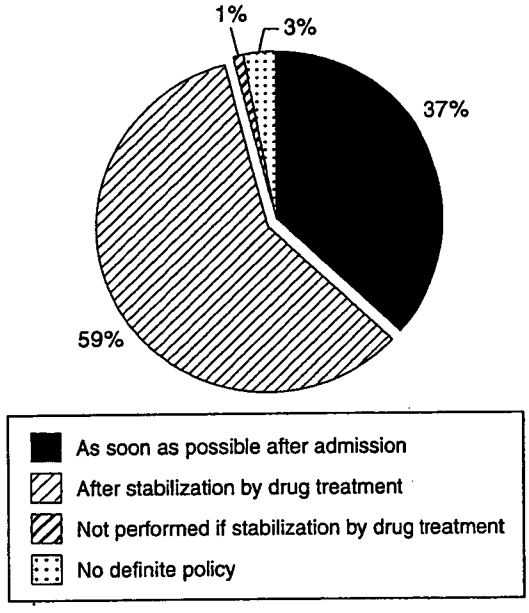


Fig5. Timing of coronary angiography for unstable angina (UA) patients. Number of responding sites: 574.

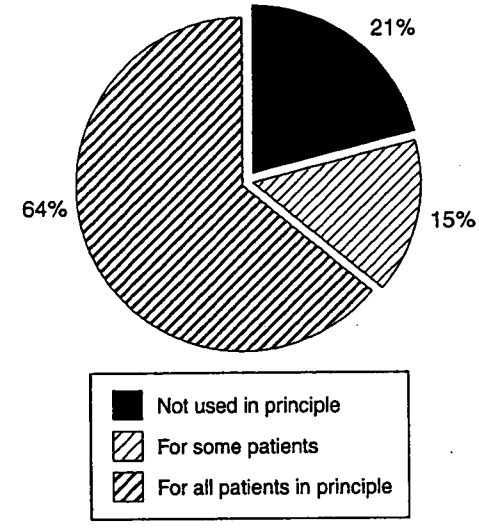


Fig7. Use of Heparin after percutaneous coronary intervention (PCI). Number of responding sites: 521.

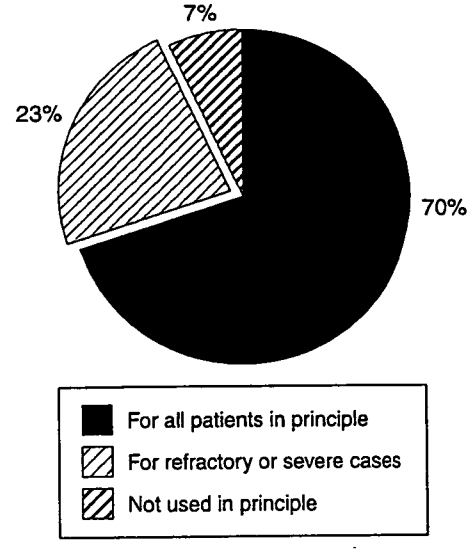


Fig6. Treatment with heparin immediately after admission. Number of responding sites: 582.

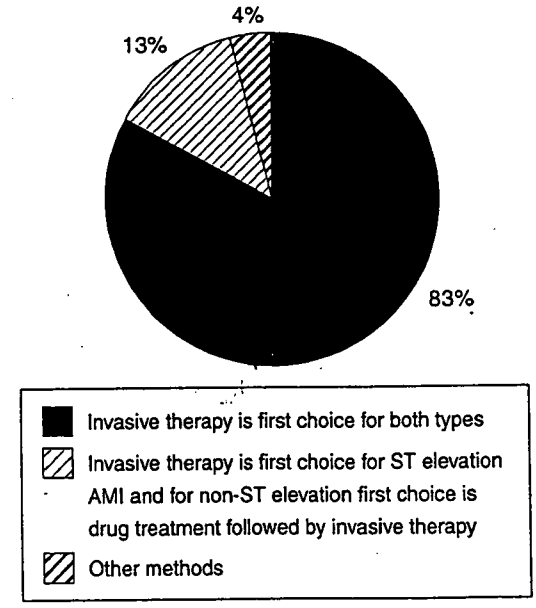


Fig8. Treatment principles for ST elevation and non-ST elevation acute myocardial infarction (AMI) at 576 responding sites.

Table 2 Baseline Characteristics of Patients With UA

Sex	
M	652 (74%)
F	233 (26%)
Age (years)	
Median	67 (Max: 93 Min: 27)
Mean±SD	66.2±10.8
Concomitant disease	
Hypertension	
Yes	514 (58%)
No	371 (42%)
Diabetes	
Yes	328 (37%)
No	557 (63%)
Hyperlipidemia	
Yes	373 (42%)
No	512 (58%)
Cerebrovascular disease	
Yes	75 (8%)
No	810 (92%)
Renal disease	
Yes	81 (9%)
No	804 (91%)
Liver disease	
Yes	24 (3%)
No	861 (97%)
Previous disease	
MI	
Yes	221 (25%)
No	664 (75%)
History of PTCA, stent	
Yes	198 (22%)
No	684 (77%)
Unknown	3 (0.3%)
History of CABG	
Yes	39 (4%)
No	845 (95%)
Unknown	1 (0.1%)
Time from onset to admission (h)	
Median	15.75 (Max: 1,258 Min: 0)
Mean±SD	70.11±140.8
Duration of hospitalization (days)	
Median	12 (Max: 259 Min: 0)
Mean±SD	18.35±22.10
Braunwald class	
I	225 (25%)
II	112 (13%)
III	548 (62%)
A	87 (10%)
B	775 (88%)
C	23 (3%)
ECG abnormality on admission	
ST deviation	
No change	376 (42%)
Elevation	130 (15%)
Depression	364 (41%)
Elevation + Depression	4 (0.5%)
Unknown	11 (1%)

UA, unstable angina; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass graft.

Table 3 Baseline Characteristics of Patients With AMI

Sex	
M	727 (78%)
F	210 (22%)
Age (years)	
Median	66 (Max: 96 Min: 28)
Mean±SD	65.2±12.2
Concomitant disease	
Hypertension	
Yes	512 (55%)
No	425 (45%)
Diabetes	
Yes	312 (33%)
No	625 (67%)
Hyperlipidemia	
Yes	349 (37%)
No	588 (63%)
Cerebrovasculer disease	
Yes	68 (7%)
No	869 (93%)
Renal disease	
Yes	63 (7%)
No	874 (93%)
Liver disease	
Yes	16 (2%)
No	921 (98%)
Previous disease	
MI	
Yes	149 (16%)
No	785 (84%)
Unknown	3 (0.3%)
History of PTCA, stent	
Yes	97 (10%)
No	838 (89%)
Unknown	2 (0.2%)
History of CABG	
Yes	25 (3%)
No	911 (97%)
Unknown	1 (0.1%)
Time from onset to admission (h)	
Median	3.0 (Max: 29 Min: 0)
Mean±SD	5.35±5.75
Duration of hospitalization (days)	
Median	21 (Max: 257 Min: 0)
Mean±SD	25.53±22.24
ECG abnormality on admission	
Elevation	782 (83%)
ST deviation	
Non elevation	133 (14%)
No change	34
Depression	99
Elevation + Depression	15 (2%)
Unknown	7 (1%)

AMI, acute MI. Other abbreviations as in Table 2.

(≤25; 26–50; 51–100; 101–200; >200).

(2) Approximate percentage of patients with ST-elevation AMI among all AMI patients (≥80%; 60–80%; 40–60%; 20–40%; ≤20%; unknown).

(3) Treatment principles (first-line treatment) for ST-elevation and non-ST-elevation AMI (invasive therapy is first choice for both types; invasive therapy is first choice for ST-elevation and for non-ST-elevation first choice is drug treatment followed by invasive therapy; other methods).

Study 2: Case Report Investigation

Twenty sites (Table 1) were randomly selected from among those participating in the questionnaire survey (study 1) and were requested to submit case reports for 50 consecutive patients treated for UA and 50 treated for AMI after January 2000. A case report was to include the following information.

Demographic Data and Clinical Profile Sex, age, concomitant disease, previous disease, time from onset to admission, Braunwald classification (only for UA patients), and ECG findings. Hypertension, hyperlipidemia, diabetic, kidney disease, and liver disease that were concomitant diseases were diagnosed by individual investigator based on the diagnostic standard of each site.

Treatment Findings of coronary angiography, details

Table 4 Details of Treatment of Patients With UA

Coronary Angiography	
Yes	*810 (92%)*
No	*75 (8%)*
Time from admission to angiography (h)	
Median	*28.4 (Max: 333 Min: 0)*
Mean±SD	*58.02±68.44*
Coronary vessel with significant stenosis before intervention	
0 vessel	*78*
1 vessel	*360*
2 vessels	*217*
3 vessels	*170*
LMT	*59*
Unknown	*4*
Culprit vessel	
LMT	*43*
LAD	*424*
LCX	*178*
RCA	*229*
Graft or other	*13*
Stenosis of culprit vessel before intervention	
100%	*85*
99%	*229*
90%	*339*
75%	*73*
50%	*6*
25%	*5*
0%	*59*
Unknown	*14*
TIMI flow past the culprit lesion before intervention	
0	*73*
1	*39*
2	*142*
3	*505*
Unknown	*56*
Revascularization	
Yes	*647 (73%)*
No	*238 (27%)*
Interventional procedure	
PTCA	*519 (80%)*
Stent	*406 (63%)*
ICT	*13 (2%)*
IVCT	*5 (1%)*
CABG	*101 (16%)*
Other	*31 (5%)*
Time from admission to revascularization (h)	
Median	*57 (Max: 5,857.25 Min: 0)*
Mean±SD	*144.97±296.28*
Stenosis after intervention	
100%	*5*
99%	*2*
90%	*4*
75%	*1*
50%	*30*
25%	*214*
0%	*280*
Unknown	*111*
TIMI Flow after intervention	
0	*11*
1	*1*
2	*3*
3	*508*
Unknown	*124*
Treatment with continuous heparin infusion	
Yes	*606 (68%)*
No	*279 (32%)*
Max daily dosage (units)	
Median	*12,000 (Max: 38,400 Min: 480)*
Mean±SD	*12,692±4,236*
Duration (days)	
Median	*3 (Max: 43 Min: 1)*
Mean±SD	*4.31±3.51*
Treatment with antiplatelet medication after admission	
Yes	*842 (95%)*
No	*43 (5%)*
ASA alone	*286*
Ticlopidine alone	*14*
ASA + Ticlopidine	*349*
ASA + Other	*61*
Ticlopidine + Other	*3*
Other alone	*16*
ASA + Ticlopidine + Other	*99*
Unknown	*14*

LMT, left main trunk; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; RCA, right coronary artery; TIMI, Thrombolysis In Myocardial Infarction; ICT, intracoronary thrombolysis; IVCT, intravenous thrombolysis; ASA, acetylsalicylic acid. Other abbreviations as in Table 2.

Table 5 Details of Treatment of Patients With AMI

Coronary angiography	
Yes	*917 (98%)*
No	*20 (2%)*
Time from admission to reperfusion therapy (h)	
Median	*1.0 (Max: 1,426.5 Min: 0)*
Mean±SD	*15.6±81.1*
Coronary vessel with significant stenosis before reperfusion	
0 vessel	*10 (1%)*
1 vessel	*481 (52%)*
2 vessels	*253 (28%)*
3 vessels	*161 (18%)*
LMT	*33 (4%)*
Unknown	*1 (0.1%)*
Culprit vessel	
LMT	*22 (3%)*
LAD	*436 (51%)*
LCX	*163 (19%)*
RCA	*321 (38%)*
Graft or other	*9 (1%)*
Unknown	*70 (7%)*
Stenosis of culprit vessel before reperfusion	
100%	*496*
99%	*229*
90%	*107*
75%	*13*
50%	*3*
25%	*5*
0%	*0*
Unknown	*64*
TIMI flow past the culprit lesion before reperfusion	
0	*479*
1	*89*
2	*140*
3	*136*
Unknown	*73*
Reperfusion therapy	
Yes	*855 (91%)*
No	*82 (9%)*
Reperfusion therapy modality	
PTCA	*765 (89%)*
Stent	*558 (65%)*
ICT	*72 (8%)*
IVCT	*62 (7%)*
CABG	*36 (4%)*
Other	*59 (7%)*
Time from admission to reperfusion (h)	
Median	*1.5 (Max: 2,798.75 Min: −22.5)*
Mean±SD	*27.76±163.44*
Stenosis after reperfusion therapy	
100%	*15 (1.8%)*
99%	*11 (1.3%)*
90%	*5 (0.6%)*
75%	*15 (1.8%)*
50%	*81 (9.5%)*
25%	*317 (37.1%)*
0%	*362 (42.3%)*
Unknown	*49 (5.7%)*
TIMI flow after reperfusion therapy	
0	*20 (2%)*
1	*13 (2%)*
2	*45 (5%)*
3	*703 (82%)*
Unknown	*74 (8%)*
Treatment with continuous heparin infusion	
Yes	*766 (82%)*
No	*170 (18%)*
Unknown	*1 (0.1%)*
Max daily dosage (units)	
Median	*14,400 (Max: 80,000 Min: 480)*
Mean±SD	*14,051±5,304*
Duration (days)	
Median	*4 (Max: 212 Min: 1)*
Mean±SD	*5.09±8.71*
Treatment with antiplatelet medication after admission	
Yes	*905 (97%)*
No	*32 (3%)*
ASA alone	*218*
Ticlopidine alone	*11*
ASA + Ticlopidine	*394*
ASA + Other	*71*
Ticlopidine + Other	*2*
Other alone	*2*
ASA + Ticlopidine + Other	*190*
Unknown	*17*

Abbreviations as in Tables 2–4.

Table 6 Clinical Outcomes in Patients Presenting With UA

Cardiac events	
During the first month	
Yes	*21 (2%)*
No	*806 (91%)*
Unknown	*58 (7%)*
Time from admission to event (days)	
Mean±SD	*9.7±7.9*
Details of events	
Death	*9*
MI	*6*
Urgent (re-) PCI	*4*
Urgent (re-) CABG	*2*
During the initial 6 months	
Yes	*78 (9%)*
No	*749 (85%)*
Unknown	*58 (7%)*
Time from admission to event (days)	
Mean±SD	*85.2±76.5*
Details of events	
Death	*22*
MI	*18*
Urgent (re-) PCI	*34*
Urgent (re-) CABG	*4*
Major bleeding	
During hospitalization	
Yes	*37 (4%)*
No	*848 (96%)*
Time from admission to event (days)	
Mean±SD	*6.9±7.6*
Details of bleeding	
Intracranial hemorrhage	*0*
Spontaneous or puncture site, etc	*8*
Need for blood transfusion	*23*
Hematoma with need for surgery	*1*
Other	*5*

PCI, percutaneous coronary intervention. Other abbreviations as in Table 2.

Table 7 Clinical Outcomes in Patients Presenting With AMI

Cardiac events	
During the first month	
Yes	*77 (8%)*
No	*807 (86%)*
Unknown	*53 (6%)*
Time from admission to event (days)	
Mean±SD	*8.9±8.6*
Details of events	
Death	*58*
Re-infarction	*2*
Post infarction angina	*8*
Urgent (re-) PCI	*7*
Urgent (re-) CABG	*2*
During the initial 6 months	
Yes	*132 (14%)*
No	*752 (80%)*
Unknown	*53 (6%)*
Time from admission to event (days)	
Mean±SD	*48.8±57.9*
Details of events	
Death	*77*
Re-infarction	*12*
Post infarction angina	*27*
Urgent (re-) PCI	*25*
Urgent (re-) CABG	*7*
Major Bleeding	
During hospitalization	
Yes	*81 (9%)*
No	*856 (91%)*
Time from admission to event (days)	
Mean±SD	*5.5±9.7*
Details of bleeding	
Intracranial	*3 (0.3%)*
Spontaneous or puncture site, etc	*33 (3.5%)*
Need for blood transfusion	*35 (3.7%)*
Hematoma with need for surgery	*5 (0.5%)*
Other	*15 (1.6%)*

Abbreviations as in Tables 2,3,6.

of revascularization, use of heparin, use of oral antiplatelet drugs, use of antianginal drugs (only for UA patients).

Outcome All-cause death, AMI, and urgent coronary revascularization during the first 6 months, as well as in-hospital major bleeding events.

In this study, information about medical treatment with nicorandil, ACE inhibitors, ARBs and statins, and information of device usage (thrombectomy or distal protection) was not included.

Prior to initiation, the protocol and conduct of the study were approved by the ethical committee or institutional review board of each participating site.

Results

Study 1: Questionnaire Survey

Of the 770 sites, 584 responded to the questionnaire (response rate of 76%).

Number of Patients No more than 25 patients with UA were hospitalized annually at 274 of the 582 sites (48%). The annual number of UA patients was 26–50 at 186 sites (32%), 51–100 at 90 sites (15%), and greater than 100 at 32 sites (5%) (Fig 1).

The annual number of AMI patients was no greater than 25 at 194 of the 580 sites (33%), 26–50 at 175 sites (30%), 51–100 at 146 sites (25%), and greater than 100 at 65 sites (12%). In general there were fewer UA patients than AMI patients at each site (Fig 2).

Fig 3 shows the percentage of non-ST-elevation patients among all those with AMI. Non-ST-elevation AMI accounted for not more than 20% of all cases of AMI at 409 of the 574 sites (71%).

To obtain a more accurate estimate of the number of UA patients relative to AMI patients, another questionnaire was sent to the 389 sites that reported treating more than 25 AMI patients per year. Of these, 217 (56.1%) responded to the additional questionnaire. The total annual number of UA and AMI patients at the 217 sites was 9,656 and 15,102, respectively, a ratio of 1:1.56. Among the 15,102 AMI patients, 2,535 (17%) were diagnosed as non-ST-elevation AMI (Fig 4).

Treatment Provided (1) Timing of coronary angiography–"after stabilization by drug treatment" was the most frequent response chosen by 341 of the 574 sites (59%). Patients underwent coronary angiography as soon as possible after arrival at 211 sites (37%) (Fig 5).

(2) Use of heparin–Heparin was administered immediately after arrival at hospital to all patients without contraindications at 411 of the 582 sites (70%). The next most frequent choice was "only refractory patients not responding to appropriate antianginal treatment or for severe cases", the management selected by 133 sites (23%) (Fig 6).

After PCI, heparin was used in principle at 333 of the 521 sites (64%), but was not usually administered at 112 sites (21%) (Fig 7).

(3) Treatment of ST-elevation and non-ST-elevation

Table 8 Stratified Analysis of Cardiac Events According to Baseline Characteristics in UA

	Cardiac events during initial 6 months (incidence)	χ^2 test p value	Details of events (cases)			
			Death	MI	u-PCI	u-CABG
Sex, age						
M	8.4% (51/609)	0.0821	12	13	24	2
F	12.4% (27/218)		10	5	10	2
<65 years	7.7% (29/376)	0.1225	5	8	16	0
≥65 years	10.9% (49/451)		17	10	18	4
Previous disease						
MI						
No	8.3% (51/616)	0.0527	8	17	24	2
Yes	12.8% (27/211)		14	1	10	2
History of PTCA, stent, etc						
No	9.2% (59/638)	0.8758	18	16	22	3
Yes	9.6% (18/187)		3	2	12	1
History of CABG						
No	9.4% (74/787)	0.8588	20	18	32	4
Yes	10.3% (4/39)		2	0	2	0
Concomitant disease						
Any of below						
No	5.1% (5/98)	0.1183	1	1	3	0
Yes	10.0% (73/729)		21	17	31	4
Hypertension						
No	8.6% (29/339)	0.4720	11	5	12	1
Yes	10.0% (49/488)		11	13	22	3
Diabetes						
No	8.0% (42/524)	0.0668	12	8	18	4
Yes	11.9% (36/303)		10	10	16	0
Hyperlipidemia						
No	10.2% (48/469)	0.3659	16	8	24	0
Yes	8.4% (30/358)		6	10	10	4
Cerebrovascular disease						
No	9.0% (68/754)	0.1914	19	15	30	4
Yes	13.7% (10/73)		3	3	4	0
Renal disease						
No	7.7% (58/752)	<0.0001	12	15	28	3
Yes	26.7% (20/75)		10	3	6	1
Liver disease						
No	9.4% (76/806)	0.9883	21	17	34	4
Yes	9.5% (2/21)		1	1	0	0
ECG abnormality on admission						
ST change						
No	6.7% (24/356)	0.0331	3	8	12	1
Yes	11.1% (51/460)		18	10	20	3
T wave inversion						
No	7.6% (34/446)	0.0935	10	10	12	2
Yes	11.0% (41/372)		11	8	20	2
Braunwald class						
I/II/III						
I	6.2% (13/211)		2	5	4	2
II	8.7% (9/104)	0.1304	1	2	6	0
III	10.9% (56/512)		19	11	24	2
A/B/C						
A	13.9% (11/79)		6	0	5	0
B	8.7% (63/725)	0.1327	15	16	28	4
C	17.4% (4/23)		1	2	1	0

u-PCI, urgent PCI; u-CABG, urgent CABG. Other abbreviations as in Tables 2,6.

AMI–most of the sites (83%; 477/576) used invasive therapy as first-line treatment of AMI of both types (Fig 8).

Study 2: Case Report Investigation

The 20 randomly selected sites submitted case reports on 885 UA patients and 937 AMI patients.

Baseline characteristics of the UA patients were similar to those of the AMI patients with respect to sex, age, and concomitant disease. The median time from symptom onset to admission of the UA patients was 15.25 h, substantially longer than for the AMI patients. Among the UA patients, 62% were classified as Braunwald Class III. Among the AMI patients, 17% were diagnosed as non-ST-elevation AMI (Tables 2,3).

Among the UA patients, 92% underwent coronary angiography and 73% underwent coronary revascularization: percutaneous transluminal coronary angioplasty in 80%, coronary stenting in 63%, and CABG in 16%. The median time from admission to revascularization was 57 h for the UA patients, much longer than the 1.5 h for the AMI patients. A lower percentage of UA patients (68%) than AMI patients (82%) received continuous infusion of heparin (Tables 4,5).

Cardiac events occurred in 21 UA patients (2.0%) during

Table 9 Stratified Analysis of Cardiac Events According to Treatment of UA

	Cardiac events during initial 6 months (incidence)	χ^2 test p value	Details of events (cases)			
			Death	MI	u-PCI	u-CABG
Antianginal treatment						
Nitrates (po)						
No	9.3% (41/441)	0.8874	14	11	13	3
Yes	9.6% (37/386)		8	7	21	1
Nitrates (iv)						
No	8.6% (32/370)	0.4882	3	8	20	1
Yes	10.1% (46/457)		19	10	14	3
Nitrates (td)						
No	9.4% (64/678)	0.9869	18	16	27	3
Yes	9.4% (14/149)		4	2	7	1
Ca blocker (po)						
No	12.2% (52/425)	0.0046	19	11	21	1
Yes	6.5% (26/402)		3	7	13	3
Ca blocker (iv)						
No	9.6% (76/795)	0.5299	20	18	34	4
Yes	6.3% (2/32)		2	0	0	0
β-blocker						
No	9.1% (54/596)	0.5573	15	17	22	0
Yes	10.4% (24/231)		7	1	12	4
Heparin						
No	10.2% (26/255)	0.6155	6	6	14	0
Yes	9.1% (52/572)		16	12	20	4
Coronary angiography						
No	16.4% (11/67)	0.0413	6	1	2	2
Yes	8.8% (67/760)		16	17	32	2
Revascularization						
No	9.3% (19/204)	0.9470	9	4	3	3
Yes	9.5% (59/623)		13	14	31	1
PTCA						
No	9.4% (12/127)	0.9926	5	2	5	0
Yes	9.5% (47/496)		8	12	26	1
Stent						
No	10.0% (23/231)	0.7503	8	3	12	0
Yes	9.2% (36/392)		5	11	19	1
CABG						
No	9.7% (51/524)	0.6067	9	13	28	1
Yes	8.1% (8/99)		4	1	3	0
Time from admission (h)						
To coronary angiography						
<6	11.7% (23/196)	0.1032	7	4	12	0
≥6	7.9% (44/558)		9	13	20	2
To revascularization						
<6	11.1% (14/126)	0.4866	2	2	10	0
≥6	9.1% (44/485)		11	12	20	1
No. coronary vessels with significant stenosis						
0	0.0% (0/59)		0	0	0	0
1	7.8% (27/344)		3	9	14	1
2	11.1% (23/207)	0.0683	8	6	9	0
3	11.1% (18/162)		6	2	8	2
LMT	12.5% (2/16)		0	0	2	0
Stenosis (%) of culprit vessel before revascularization						
0	0.0% (0/41)		0	0	0	0
25	0.0% (0/4)		0	0	0	0
50	0.0% (0/6)		0	0	0	0
75	10.1% (7/69)	0.0244	2	1	4	0
90	7.6% (25/330)		5	6	14	0
99	8.9% (19/213)		5	7	6	1
100	18.1% (15/83)		4	3	7	1
Stenosis (%) of culprit vessel after revascularization						
0	4.8% (13/270)		2	5	5	1
25	11.9% (24/202)		4	7	13	0
50	23.3% (7/30)		1	0	6	0
75	0.0% (0/1)	<0.0001	0	0	0	0
90	50.0% (2/4)		1	0	1	0
99	50.0% (1/2)		1	0	0	0
100	60.0% (3/5)		0	0	3	0
TIMI flow grade past the culprit lesion before revascularization						
0	20.0% (14/70)		3	3	7	1
1	18.4% (7/38)	0.0002	1	2	4	0
2	8.4% (11/131)		3	4	3	1
3	6.1% (29/474)		6	8	15	0

TIMI flow grade past the culprit lesion after revascularization					
0	*27.3% (3/11)*	*0.1856*	*0*	*3*	*0*
1	*0.0% (0/1)*		*0*	*0*	*0*
2	*0.0% (0/3)*		*0*	*0*	*0*
3	*8.8% (43/488)*		*13*	*22*	*1*

Abbreviations as in Tables 2,6,8.

Table 10 Stratified Analysis of Cardiac Events by Treatment With Calcium-Channel Blockers in Patients With UA

	Incidence of cardiac events during initial 6 months		*χ^2 test p value*
	Treated	*Not treated*	
Diltiazem	*8.44% (13/154)*	*9.66% (65/673)*	*0.6412*
Amlodipine	*5.88% (8/136)*	*10.13% (70/691)*	*0.1213*
Nifedipine	*8.11% (6/74)*	*9.56% (72/753)*	*0.6831*

Abbreviation as in Table 2.

Table 11 Stratified Analysis of Cardiac Events by the Timing of Initial Calcium-Channel Blocker Treatment in Patients With UA

Incidence of cardiac events during initial 6 months		*χ^2 test p value*
Before onset of UA	*After admission*	
7.47% (13/174)	*6.96% (11/157)*	*0.8706*

Abbreviation as in Table 2.

Table 12 Stratified Analysis of Cardiac Events According to Baseline Characteristics in AMI

	Cardiac events during initial 6 months (incidence)	*χ^2 test p value*	*Details of events (cases)*				
			Death	*MI*	*PIA*	*u-PCI*	*u-CABG*
Sex, age							
M	*13.1% (90/688)*	*0.0038*	*50*	*7*	*18*	*13*	*2*
F	*21.4% (42/196)*		*27*	*4*	*8*	*2*	*1*
<65 years	*9.3% (41/442)*	*<0.0001*	*18*	*4*	*10*	*9*	*0*
≥65 years	*20.6% (91/441)*		*59*	*7*	*16*	*6*	*3*
Infarct region							
Infarct region							
Anterior	*16.7% (71/425)*		*46*	*7*	*10*	*6*	*2*
Inferior	*13.2% (43/326)*		*21*	*3*	*11*	*7*	*1*
Lateral	*12.0% (9/75)*	*0.6351*	*7*	*0*	*1*	*1*	*0*
Posterior	*16.7% (8/48)*		*2*	*1*	*4*	*1*	*0*
Other	*11.1% (1/9)*		*1*	*0*	*0*	*0*	*0*
Time from onset to admission							
Time from onset to admission (h)							
<6	*13.6% (89/655)*	*0.0545*	*52*	*8*	*21*	*7*	*1*
≥6	*18.9% (43/228)*		*25*	*3*	*5*	*8*	*2*
<12	*15.1% (117/773)*	*0.6799*	*64*	*10*	*25*	*15*	*3*
≥12	*13.6% (15/110)*		*13*	*1*	*1*	*0*	*0*
Previous disease							
Angina							
No	*11.6% (64/550)*	*0.0005*	*41*	*5*	*12*	*5*	*1*
Yes	*20.2% (67/332)*		*35*	*6*	*14*	*10*	*2*
MI							
No	*13.2% (98/740)*	*0.0019*	*55*	*8*	*22*	*11*	*2*
Yes	*23.4% (33/141)*		*21*	*3*	*4*	*4*	*1*
History of PCI							
No	*14.3% (113/791)*	*0.1628*	*67*	*9*	*23*	*11*	*3*
Yes	*19.8% (18/91)*		*9*	*2*	*3*	*4*	*0*
History of CABG							
No	*14.7% (126/858)*	*0.4612*	*72*	*10*	*26*	*15*	*3*
Yes	*20.0% (5/25)*		*4*	*1*	*0*	*0*	*0*
Concomitant disease							
Any disease below							
No	*8.4% (11/131)*	*0.0230*	*6*	*0*	*3*	*2*	*0*
Yes	*16.1% (121/753)*		*71*	*11*	*23*	*13*	*3*
Hypertension							
No	*12.2% (49/402)*	*0.0366*	*29*	*5*	*9*	*6*	*0*
Yes	*17.2% (83/482)*		*48*	*6*	*17*	*9*	*3*
Diabetes							
No	*13.3% (79/592)*	*0.0593*	*46*	*3*	*21*	*6*	*3*
Yes	*18.2% (53/292)*		*31*	*8*	*5*	*9*	*0*
Hyperlipidemia							
No	*16.3% (90/552)*	*0.1399*	*58*	*6*	*16*	*9*	*1*
Yes	*12.7% (42/332)*		*19*	*5*	*10*	*6*	*2*
Cerebrovascular disease							
No	*14.5% (119/820)*	*0.2099*	*65*	*10*	*26*	*15*	*3*
Yes	*20.3% (13/64)*		*12*	*1*	*0*	*0*	*0*

Hyperuricemia							
No	*14.4% (121/839)*	*0.0661*	*75*	*8*	*23*	*12*	*3*
Yes	*24.4% (11/45)*		*2*	*3*	*3*	*3*	*0*
Renal disease							
No	*14.0% (115/824)*	*0.0026*	*66*	*8*	*24*	*14*	*3*
Yes	*28.3% (17/60)*		*11*	*3*	*2*	*1*	*0*
Liver disease							
No	*15.1% (131/869)*	*0.3650*	*76*	*11*	*26*	*15*	*3*
Yes	*6.7% (1/15)*		*1*	*0*	*0*	*0*	*0*
Acute heart failure on admission							
No/Yes							
No	*9.2% (57/620)*	*0.0000*	*18*	*7*	*20*	*11*	*1*
Yes	*28.4% (74/261)*		*59*	*4*	*5*	*4*	*2*
Killip class							
1	*8.9% (41/463)*	*<0.0001*	*15*	*3*	*15*	*7*	*1*
2	*16.5% (15/91)*		*11*	*0*	*2*	*2*	*0*
3	*37.1% (13/35)*		*9*	*1*	*3*	*0*	*0*
4	*57.7% (41/71)*		*37*	*3*	*0*	*0*	*1*
Forrester class							
1	*9.0% (23/255)*	*<0.0001*	*9*	*2*	*8*	*4*	*0*
2	*19.3% (17/88)*		*11*	*1*	*1*	*3*	*1*
3	*18.9% (10/53)*		*6*	*1*	*3*	*0*	*0*
4	*43.3% (26/60)*		*22*	*1*	*2*	*0*	*1*
ECG abnormality on admission							
ST change							
No	*6.3% (2/32)*	*0.1290*	*0*	*1*	*0*	*1*	*0*
Elevation	*14.0% (103/736)*		*60*	*8*	*21*	*11*	*3*
Depression	*19.8% (19/96)*		*11*	*2*	*4*	*2*	*0*
CLBBB							
No	*14.5% (124/856)*	*0.0396*	*72*	*8*	*26*	*15*	*3*
Yes	*28.6% (8/28)*		*5*	*3*	*0*	*0*	*0*
Abnormal Q wave							
No	*14.0% (80/571)*	*0.2900*	*42*	*8*	*19*	*9*	*2*
Yes	*16.7% (52/312)*		*35*	*3*	*7*	*6*	*1*
CK, CK-MB							
CK max							
<3,000	*13.6% (74/544)*	*0.2792*	*32*	*9*	*21*	*11*	*1*
≥3,000	*16.3% (54/332)*		*42*	*2*	*5*	*4*	*1*
CK-MB max							
<250	*12.6% (57/452)*	*0.4479*	*22*	*9*	*19*	*5*	*2*
≥250	*14.5% (45/310)*		*36*	*0*	*3*	*6*	*0*

PIA, post infarction angina; CLBBB, complete left bundle branch block; CK, creatine kinase. Other abbreviations as in Tables 2,3,6,8.

the first month and in 78 patients (9.0%) during the initial 6 months. During hospitalization, 37 UA patients (4.0%) experienced severe hemorrhagic events. Both cardiac events and severe hemorrhagic events were less frequent in the UA patients than in the AMI patients (Tables 6,7).

Events Stratified by Clinical Profile and Treatment

Table 8 shows the 6-month incidence of cardiac events stratified by baseline characteristics of the UA patients. The incidence of cardiac events was significantly higher in patients with renal disease than in those without renal disease. Cardiac events were more frequent in women, patients with a history of myocardial infarction (MI), and patients with diabetes. The incidence of cardiac events was significantly higher in patients with ST segment changes on admission than in those without such changes. It was also higher, but not significantly so, in patients with T-wave inversion than in those without T-wave inversion. The incidence of cardiac events tended to increase with the severity of Braunwald classification.

Table 9 shows the 6-month incidence of cardiac events in UA patients stratified by treatment. With regard to antianginal therapy, the incidence of cardiac events was significantly lower in those treated with an oral calcium-channel blocker than in those not so treated. The incidence of cardiac events was also significantly lower in those undergoing coronary angiography after arrival at hospital than in those not undergoing it. Neither use of heparin nor revascularization was significantly associated with the incidence of cardiac events. Cardiac events did not occur in any of the patients without significant stenosis on initial coronary angiography. The outcome was worse in patients with significant stenosis persisting after revascularization than in those without.

Because oral calcium-channel blockers are suggested to reduce the risk of cardiac events in UA patients, the effects of the most commonly used drugs of this class (eg, diltiazem, amlodipine, and nifedipine) were evaluated. The incidence of cardiac events was lower in patients taking amlodipine than in those not taking it (Table 10).

The relationship of the timing of treatment with calcium-channel blockers to the risk of cardiac events was evaluated and the incidence of cardiac events was lower in patients who started treatment with a calcium blocker after admission than in those who were continuously treated before the onset of UA, although the difference was not significant (Table 11).

Tables 12 and 13 summarize the 6-month incidence of cardiac events in AMI patients stratified by clinical profile and by treatment, respectively. Clinical factors that were associated with a significantly higher incidence of cardiac events were female sex, age ≥65 years, a history of angina