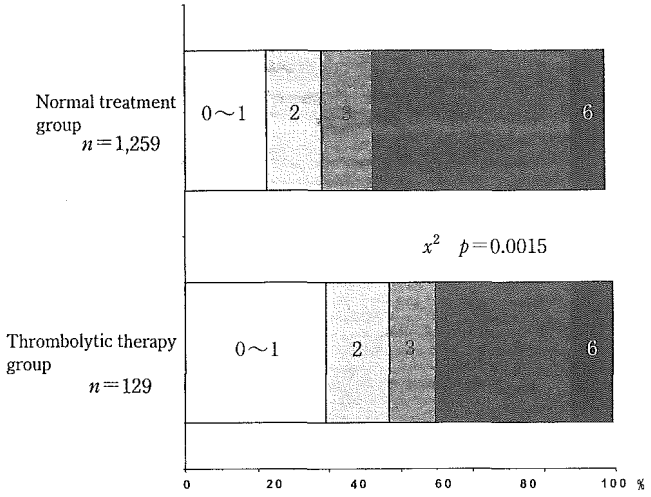

Fig. 3 The effects of thrombolytic therapy (tPA intravenous and intraarterial, and UK intraarterial and mega dose intravenous), and in brain infarction acute stage patients (Severity at admission : NIHSS 6-29) were compared with those of a conventional treatment group of the same severity. (JSSRS 2001)[4]

と思われる.

病型別実施頻度は **Fig. 5** で示すように心原性脳塞栓で約 8%と最も高く，アテローム血栓性梗塞でも 2%程度に施行されていることがわかる.

入院時，重症度別に血栓溶解療法の予後をみると，**Fig. 6** に示したように NIHSS 5-9 で mRS 0-1 頻度が 60%近くであるのみならず，NIHSS15-20 の重症例においても著効例が 25%と多く，非施行群との差が拡大していることがわかる.

脳卒中標準データベースの利点

ガイドラインとデータベースの関係については，前者は EBM に基づいた最適な治療法を提示するのが目的であるが，必ずしも結果に出ない．一方，後者はアウトカムアプローチで治療結果を提示するが，結果が悪くても改善策を提示できないという相互補完的なものであるとされている．すなわち，ガイドラインの検証にデータベースが必要となることを示唆している.

脳卒中標準データベースの利点としては，各施設における独立したデータベースとして標準化データが蓄積され，臨床統計（自己評価），臨床研究，情報開示に有用であること，共通部分を電子データで全国集計することにより日本の脳卒中診療の実態を迅速に把握可能であること，学会などの管理による準公的集計解析システムによ

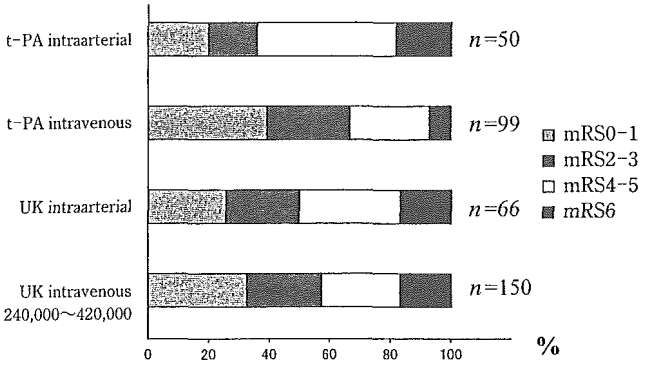

Fig. 4 Prognosis at hospital discharge for 365 patients who underwent thrombolytic therapy (modified Rankin scale)
(TIA, brain infarction : n=11,793, within 1 week of onset, JSSRS 2003)

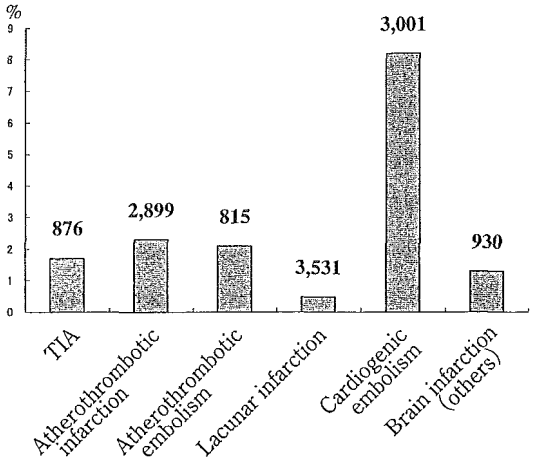

Fig. 5 Incidence of thrombolytic therapy according to subtype of brain infarction (admitted within 1 week)
n=12,052 (JSSRS 2003)

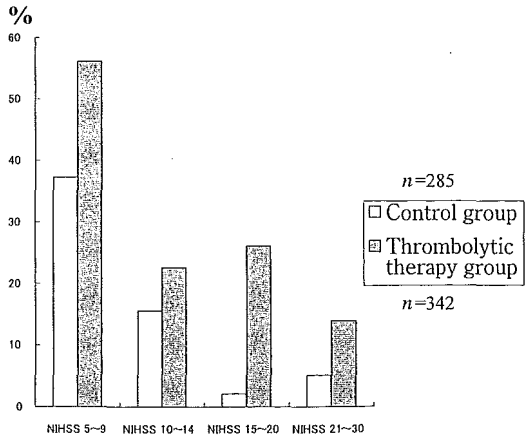

Fig. 6 Effects of thrombolytic therapy according to severity at admission (mRS 0-1 ratio)
Thrombolytic therapy group prognosis at discharge ; Control group prognosis at 3 months. Targets were subjects hospitalized within 3 hours of onset who were graded NIHSS 5-30 at admission (JSSRS 2003)

Table 2 Comparison of onset patterns of brain infarction and brain infarction type in Shenyang (China) investigated by stroke standard database

Pattern of onset and subtype of brain infarction in Shenyang (China) and Japan				
	Sudden complete	Acute onset	Onset during sleep	Stepwise progression
The First Hospital of Shenyang	2.5%	49.6%	12.8%	35.1%
China Medical University	2.4%	50.6%	3.6%	41.8%
Japan	34.2%	40.0%	10.3%	13.5%

Brain infarction types (%) in Shenyang (China) and Japan			
	The First Hospital of Shenyang	China Medical University	Japan
TIA	2.0	4.9	8.7
Atherothrombotic infarction	74.9	80.3	28.7
Lacunar infarction	18.5	12.1	28.0
Cardiogenic embolism	1.1	2.6	26.7
Brain infarction (others)	3.5	0	7.9

る指定病院群でのガイドライン実証研究や，大規模共同研究への応用が可能であること，臨床研修必修化に伴う研修医教育への活用，アウトカムアプローチによる医療の質の確保に貢献する可能性があること，将来的に共通の文化を持つアジアで，大規模共同研究を行う際にも役立つ可能性などが挙げられる．

中国の瀋陽の病院との共同研究による日中比較

著者らは，人口600万人の瀋陽第一病院（脳専門病院で神経内科，脳神経外科を重点配置）と，瀋陽にある中国医科大学神経内科（以下，中国医大）と同じデータベースを用いて脳卒中登録の共同研究を行っているので，データベースの利点の1つとしてその一部を紹介する（Table 2）[9]．

中国東北地方では，高血圧性脳出血が日本の30年前に匹敵するほど多く，脳神経外科ではもっぱら脳出血の手術を行っている．しかし，30年前の日本とは違ってゴマ油を多用するためか，アテローム血栓性梗塞の頻度が高いという結果であった．これに関しては診断技術の問題もある可能性を考え，MRIのある中国医大にも依頼して調査したが，やはり結果は同じであった．脳梗塞で最も大きな違いは心原性脳塞栓が瀋陽第一病院で1.1%，中国医大でも2.6%と日本の26.7%に比して圧倒的に少ないことであった．これについて危険因子を検討してみると，心房細動の頻度が約1/10と少なく，突発完成型発症の頻度が瀋陽第一病院2.5%と，日本の34.2%に比し明らかに少なかった．これらの事実は，瀋陽では心原性脳塞栓がきわめて少ないことを裏づけるものと思われる．実際に瀋陽第一病院で病棟を回っても，重症例が少ない印象を受けた．これは瀋陽の脳卒中患者の平均年齢が6歳程度若いことが関係しているかもしれない．心房細動は加齢と共に増加することはよく知られており，脳卒中データバンクでも同様の結果を得ている．

海外での脳卒中データバンクの動向

ドイツではt-PA治療の管理のため，20の脳卒中センターが共同でデータバンクを構築し，German Stroke data bankとして中央での3カ月および1年後の，電話による予後追跡調査を実施している．このデータバンクで6,234例の脳梗塞を解析したところ，そのうち4%にt-PA治療が行われていたが脳出血は8.8%と少なく，3カ月後のmRS 0-1は35%であった．このようなシステムを用いれば，短期間に精度の高いphaseIVの臨床試験に相当する結果を得ることができると述べている[10]．このシステムはドイツ厚生省がサポートする水平型データバンクで，主要な脳卒中センターの大半が参加した臨床的脳卒中ネットワークとして，将来的に遺伝子研究，画像，Stroke Unitなどを加味したpermanent infrastructureを目指すとしている．

カナダでも同様に，厚生省その他による基金を基に大規模な脳卒中ネットワークシステムを構築している．このシステムでは，発症2週間以内の入院例を対象に6カ月後の予後を中央で調査し集計している．わが国と異なりnurse coordinatorが同意をとり管理し，Webで入力し電送する仕組みで，医師は診断，治療以外はあまり関与しないシステムのようである．昨年度で7,500名登録したが予後調査同意は3,400名のみであり，単なる追跡といえども同意取得の難しさを表している．今後は同意を得なくてもよい方法を検討するという．調査結果では虚血性脳卒中が73.4%で2時間以内入院がその24%であり，4,107例中t-PA治療は9%に行われたという．また

2時間以内入院例では17%とかなりの頻度で実施されたとしている．さらに最近では電子カルテ対応の院内版データベースも開発しているとの学会報告もあった．

米国ではかつてNIHで行っていた脳卒中データバンクは中止となったが，最近t-PA治療の調査を目的としたデータベースが構築されている[5]．WAVE1として数州規模でweb site登録方式により3カ月間に6,000例を登録し，虚血性脳卒中が80%を占め，3時間以内入院が22%，t-PA治療実施例が4.6%（60分以内入院では58.6%）であったと報告している．その後のWAVE 2では，159病院で21,259例の登録を行い解析しているとの報告があった．登録病院の例として954床のDuke大学病院では，年間705名の脳卒中患者が登録されたとしている．

脳卒中データベースの条件として，1）目標を明示，2）病院の仕事中に入力可能，3）発症率をみる疫学研究は不可，4）単純である（複雑かつ学術研究目的は不可），5）急性期脳卒中のモニタリングを目的とする，6）すべての脳卒中を含めるべき，7）全国レベルで登録するべきことを，同じ29th International Stroke Conferenceの脳卒中データバンクシンポジウムでBroderick JPが述べていたが，まさに同感であった．

地域脳卒中診療拠点病院構想

厚生労働省は，癌に関してはすでに2001年8月に一般病院を中心とする地域癌診療拠点病院の指定要件を発表し，すでに全国で承認を行っている．その条件は，診療体制として専門的医療体制，緩和ケア，病診連携が実施されていること，専門看護師，MSW，診療録管理士などがそろっており，医療施設としては集中治療室，放射線治療施設などがあり，医療機器としては高度な医療機器が整備されていることを挙げている．また，院内癌登録システム（全国共通データベースに登録）の整備を挙げている（現在，すべての癌の共通データベースが開発中であるが，まだ完成には至っていないようである）．研修体制としては，地域および院内医療従事者の研修を実施すること，情報提供体制としてホームページへの地域癌診療情報公開，医療機関からの相談に対応し情報提供を行うこと，癌情報の収集および提供（5年生存率など）を行うことなどを条件としている．

同様な構想は，日本における死因の第3位でかつ発生頻度，有病率において，三大成人病の中でトップの脳卒中でも検討されるべきものと思われる．その理由として，近い将来に超急性期脳梗塞に対するt-PAの保険適応承認の可能性があり，脳梗塞の専門的治療（血栓溶解療法など）が普及する可能性があり，その場合には脳卒中専門医による迅速な診断，治療が必要となることが挙げられる．このためには脳卒中拠点診療病院で急性期治療を行う体制，すなわち，1時間以内に搬送し，血栓溶解療法が実施できる救急システムなどを整備する必要がある．地域癌診療拠点病院の指定要件に沿って脳卒中における条件を考えてみると，診療体制として脳卒中専門医による医療体制，病診連携がなされていること，専門看護師，MSW，診療録管理士などがそろっており，医療施設として24時間救急対応で集中治療室，脳卒中ケアユニット（またはチーム）があり，医療機器としてはCT（24時間稼働），MRI，SPECT，血管撮影装置などが整備されていること，院内脳卒中登録システム（脳卒中標準データベース）が稼働し（可能ならJSSRS脳卒中データバンクへ登録），情報提供体制としてホームページへの脳卒中診療成績の公開，地域脳卒中診療情報公開，医療機関からの相談に対応し情報提供を行うこと，研修体制として地域および院内医療従事者の研修を実施することなどが挙げられる．ただし，地域癌診療拠点病院と異なるのは，脳卒中は癌と異なり一刻を争う救急疾患，すなわちbrain attackであることである．したがって，地域癌診療拠点病院のように二次医療圏に1カ所といった指定ではなく，条件を満たす病院をできるだけ多く指定する必要がある．予算措置などなくても，この指定により脳卒中救急病院が国民に明示されることによって地域の救急搬送システムの効率化が図られ，病診連携が促進されることにつながると思われる．

おわりに

脳卒中データバンクによる解析で脳卒中の現状が明らかになりつつあるが，t-PAが認可された時には，open prospective studyとして急性期脳梗塞の連続例の登録を行う必要がある．すでに米国，ドイツ，カナダではこのような目的でデータバンクをスタートさせている．わが国でもすでに標準になりつつある脳卒中データバンクをさらに普及させ，t-PA治療を実施する施設では必須化して大規模なデータ蓄積を行っていく必要がある．これにより，よりよい適応，投与法などを明らかにして，本当の意味での日本人のための脳卒中ガイドラインを作っていくことが重要である．

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要　旨

脳卒中標準データベースの有用性

小林　祥泰

Japan Standard Stroke Registry Study（JSSRS）group では，日本人のための EBM を確立するための infrastructure として，国際標準指標を用いた全国レベルで継続性のある脳卒中急性期患者データバンクを構築しつつある．虚血性脳卒中では保険適応はないが，超急性期血栓溶解療法が行われた例についての解析を行い，その有用性を示唆する結果を得ている．脳出血でも，選択された例においては手術の有効性が示唆された．本システムは急性期脳卒中を扱う中核病院の臨床データベースとしても継続的に機能するものであり，各施設における脳卒中診療の正確な把握，全国標準の集計が容易となり，医療情報開示，インフォームド・コンセントなどに必要な資料作成にも大きな威力を発揮する．

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α-Glucosidase inhibitor reduces the progression of carotid intima-media thickness

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Abstract

Objective: An open randomized prospective study was performed to elucidate the effect of an α-glucosidase inhibitor, voglibose, on the progression of atherosclerosis in subjects with type 2 diabetes.
Research design and methods: Voglibose at a dose of 0.4–0.6 mg/day was added on 51 subjects out of 101 type 2 diabetic patients being treated with diet, sulphonylurea (SU) or insulin injections, and the average (AveIMT) and maximum intima-media thickness (MaxIMT) of their carotid arteries were examined for 3 years.
Results: Irrespective of the differences in treatments, addition of voglibose reduced the progression of AveIMT and MaxIMT to -0.024 ± 0.047 (±S.D.) and -0.021 ± 0.144 mm/year, respectively. Without voglibose, diabetic patients showed significant ($P < 0.0001$) progression of AveIMT and MaxIMT (0.056 ± 0.046 and 0.098 ± 0.122 mm/year, respectively). The administration of voglibose resulted in a significant reduction of hemoglobin A1c (HbA1c), total cholesterol and triglyceride concentrations, as well as an increase in HDL cholesterol concentration. Multivariate regression analysis showed that administration of voglibose independently reduced the progression of AveIMT by 0.069 mm/year ($P < 0.0001$).
Conclusions: These results suggest that voglibose reduces the progression of IMT and may be a candidate for an anti-atherosclerotic drug for type 2 diabetic patients.

Keywords: Intima-media thickness; α-Glucosidase inhibitor; Postprandial hyperglycemia

Abbreviations: IMT, intima-media thickness; AveIMT, average IMT; MaxIMT, maximum IMT; HbA1c, hemoglobin A1c; SU, sulphonylurea.

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1. Introduction

In westernized countries, more than half of the subjects with type 2 diabetes die from coronary heart disease [1]. Another large portion of the patients suffer from cerebral infarction and peripheral vascular disease, mainly due to markedly advanced atherosclerosis. The UK prospective diabetes study [2] and Finnish studies [3] have shown an association of the glycated hemoglobin A1c (HbA1c) level with the risk for coronary heart disease in type 2 diabetic patients. However, no study has yielded results to support strict glycemic control or hypoglycemic agents leading to significant reduction in mortality and morbidity from coronary heart disease in patients with type 2 diabetes.

As a subclinical and clinical index of atherosclerosis in diabetic patients, the intima-medial thickness (IMT) of the carotid artery has been used [4–15]. We have shown that several anti-platelet drugs may attenuate or inhibit the progression of carotid IMT [11,12], which would otherwise progress significantly [13] in type 2 diabetic patients treated with oral administration of sulphonylurea (SU) or subcutaneous insulin injections. There have been a few reports showing a potent effect of some thiazoligines in regressing carotid artery wall thickening [14–15]. Recently, STOP-NIDDM study has clearly shown that acarbose attenuates the progression of the IMT mean [16] and reduced the incidence of coronary heart disease in subjects with impaired glucose tolerance [17]. However, there have been no reports on the effect of the other α-glucosidase inhibitor, voglibose. The present open randomized prospective study was performed to clarify whether long-term voglibose administration could affect IMT progression of the carotid artery in subjects with type 2 diabetes.

2. Materials and methods

Ultrasonographic scanning of the carotid arteries was performed using an echotomographic system (EUB-450, Hitachi Medico, Tokyo, Japan) with an electrical linear transducer (midfrequency of 7.5 MHz). The axial resolution of this system was at least 0.3 mm. Scanning of the extracranial common carotid artery, carotid bulb, and internal carotid artery in the neck was performed bilaterally from three different longitudinal projections (i.e., anterior-oblique, lateral, and posterior-oblique), as well as the transverse projection, as we have reported previously [6–8]. All images were photographed. The scanning session lasted an average of 30 min. The detection limit of this echo system using 7.5 MHz is 0.1 mm.

The IMT was measured as the distance from the leading edge of the first echogenic line to the leading edge of the second echogenic line, as defined by Pignoli and coworkers [4,5,10]. The first line represents the lumen–intimal interface, and the second line is produced by the collagen-containing upper layer of the tunia adventitia. At each longitudinal projection, the site of the greatest thickness, including a plaque lesion, was sought along the near and far arterial walls from the common carotid artery to the internal carotid artery. Three determinations of IMT were conducted, at the site of the greatest thickness and at two other points, 1 cm upstream and 1 cm downstream from this site. These three determinations were averaged. The greatest value among the six averaged IMTs (three from the left and three from right) was used as the representative IMT value (AveIMT) for each individual. The greatest thickness among the six longitudinal projections was used as MaxIMT. All scans were conducted by physicians (R.H.-O. and M.H.) who were unaware of the clinical characteristics of the subjects. Determination of IMTs using photographs was performed by another physician (N.K.). The reproducibility of the IMT measurement was examined by conducting another scan 1 week later on eight participants. The mean difference in IMT between these two determinations was 0.01 mm, and the standard deviation was 0.04 mm, demonstrating good reproducibility for repeated measurements, as described previously [6]. The threshold of AveIMT for normal subjects was less than 1.1 mm [5,7,8].

A total of 103 subjects with type 2 diabetes were recruited from among the outpatients of Osaka University Hospital and Osaka Police Hospital. The determination of type 2 diabetes was based on the World Health Organization criteria. Each patient who fulfilled the following inclusion criteria was considered for the study: (1) no episodes of ketoacidosis and absence of ketonuria, (2) diagnosis of diabetes after 30 years of age, (3) insulin therapy (if any) started after

duration of diabetes for at least 5 years, (4) absence of overt diabetic nephropathy or other renal tract disease, and (5) absence of active diabetic proliferative retinopathy. The patients with recent event of acute coronary disease, brain stroke, and arteriosclerosis obliterans (ASO) within 3 months at the baseline examination were excluded. Patients who had advanced AveIMT (>0.8 mm for –49 years old, >0.9 mm for 50–59 years old, >1.0 mm for 60–69 years old, >1.1 mm for 70– years old, respectively) at the baseline examination were enrolled in this study. Written consent was obtained from every subject after a full explanation of the study. The study was also approved by the Ethics Committees of Osaka University and Osaka Police Hospital. Patient characteristics at the baseline examination and after the follow-up period are shown in Table 1.

The subjects were randomly separated into two groups of those administered or not administered with the α-glucosidase inhibitor, voglibose along the prefixed assignment. Voglibose was administered (0.4–0.6 mg/day) to 53 of 103 subjects with type 2 diabetes being treated with diet alone (n = 22), or sulphonylurea (n = 61) or insulin (n = 20). After oral administration of voglibose, two subjects who showed side effects (bowel discomfort) were advised to terminate drug administration and were excluded from this study. Carotid artery intima-media thickness was examined with and without voglibose administration for the follow-up period of 3.3 ± 0.2 years, as well as other clinical parameters such as hemoglobin A1c concentration, lipid profiles, blood pressure, and body mass index. During the follow-up period, consistent therapy for diabetes was performed.

Table 1
Patient characteristics

Parameter	Without α-glucosidase			With α-glucosidase			
	Before		After	Before		After	
	Mean ± S.D.	p1	Mean ± S.D.	Mean ± S.D.	p2	Mean ± S.D.	p3
Gender (female/male)	20/30			25/26			
Age (years)	60.4 ± 9.6			58.6 ± 7.5			
Duration (years)	12.7 ± 7.2		22.9 ± 2.91	13.1 ± 8.2			
BMI (kg/m^2)	22.7 ± 2.92		8.1 ± 1.6	23.0 ± 3.67		23.0 ± 3.55	
HbA1c (%)	8.4 ± 1.4		5.43 ± 0.88	8.2 ± 1.3	0.0002	7.6 ± 0.9	
T-Chol (mmol/l)	5.69 ± 1.17		1.37 ± 0.56	5.63 ± 0.93	0.0038	5.29 ± 0.90	
TG (mmol/l)	1.72 ± 1.20		1.43 ± 0.42	1.82 ± 1.17	0.0185	1.53 ± 0.73	
HDL-Chol (mmol/l)	1.42 ± 0.36		139 ± 17	1.47 ± 0.43	0.0130	1.55 ± 0.51	
sBP (mmHg)	133 ± 13	0.0135	78 ± 9.3	138 ± 16		137 ± 17	
dBP (mmHg)	75 ± 8.4			79 ± 8.7		76 ± 9.0	
Diabetes treatment[a]	10/30/10			11/30/10			
Hypolipidemic drug[b]	4/9/15			2/11/14			
Hypotensive drug[c]	1/14/15			0/15/16			
Current smoker[d]	7			8			
AveIMT (mm)	1.31 ± 0.38	0.0078	1.49 ± 0.43	1.40 ± 0.40	0.0013	1.33 ± 0.41	
MaxIMT (mm)	1.75 ± 0.67	<0.0001	2.06 ± 0.74	1.92 ± 0.81		1.88 ± 0.80	
dAveIMT (mm/year)			0.056 ± 0.046			−0.024 ± 0.047	<0.0001
dMaxIMT (mm/year)			0.098 ± 0.122			−0.021 ± 0.144	<0.0001

Data are shown as means ± S.D. p1: before vs. after without α-glucosidase; p2: before vs. after with α-glucosidase; p3: without vs. with α-glucosidase.

[a] Numbers of subjects with diabetes treatment are shown as diet/sulphonyl urea/insulin treatment.

[b] Numbers of subjects with hypolipidemic drug are shown as clofibrates/probucol/HMG-CoA reductase inhibitors.

[c] Numbers of subjects with hypotensive drugs are shown as beta-blockers/Ca-channel blockers/angiotensin-converting enzyme inhibitors.

[d] Number of current smokers at the termination of follow-up period.

Anti-hypertensive drugs (diuretics, beta-blockers, alpha-blockers, Ca-channel blockers, and angiotensin-converting enzyme inhibitors) were given to 52 of the patients. Anti-hyperlipidemic drugs were given to 48 of the patients (clofibrates to 6 subjects, probucol to 20 subjects, HMG-CoA reductase inhibitors to 29 subjects). The administration of these drugs remained constant during the follow-up period. None of the patients received anti-platelet drugs, insulin sensitizers (troglitazone or pioglitazone), or biguanides during the follow-up period. No patient showed any onset of coronary heart disease, cerebro-vascular disease, or ASO during the follow-up period.

Patients' smoking status was classified as never having smoked, former smoker (ceased smoking for at least 3 years), or current smoker. In this study, current smokers at the termination of follow-up period were analysed as a group, and compared with those who had never smoked and former smoker. Blood pressure was measured with a mercury sphygmomanometer. After a supine rest of 5 min, three measurements in the sitting position were conducted and the mean value was used. At the baseline determination, blood was withdrawn for analyses of serum total cholesterol and high-density lipoprotein cholesterol, serum triglycerides, plasma glucose, and hemoglobin A1c levels by standard laboratory techniques.

The annual changes in AveIMT and MaxIMT per year (mm/year) were calculated with the following equations

$$\text{Annual change in AveIMT} = \frac{\text{Last AveIMT} - \text{Initial AveIMT}}{\text{Follow-up period}}$$

$$\text{Annual change in MaxIMT} = \frac{\text{Last MaxIMT} - \text{Initial MaxIMT}}{\text{Follow-up period}}$$

Data were presented as means ± S.D. The laboratory data were compared by Student's and paired *t*-tests or one-way analysis of variance. These statistical analyses were carried out using the HALBAU (Gendai Sugaku-sha, Kyoto, Japan) statistical package on a personal computer.

3. Results

Baseline AveIMT (1.31 ± 0.38 versus 1.40 ± 0.40 mm) and MaxIMT (1.75 ± 0.67 versus 1.92 ± 0.81 mm) showed no significant differences among the groups with and without voglibose administration. Both groups had fairly controlled hemoglobin A1c levels (8.3 ± 1.3%), total cholesterol concentrations (5.66 ± 1.05 mmol/l), and systolic blood pressure (136 ± 15 mmHg) at the baseline examination. Annual changes in AveIMT of diabetic patients without voglibose administration showed a significantly ($P = 0.00267$) linear relationship with the mean

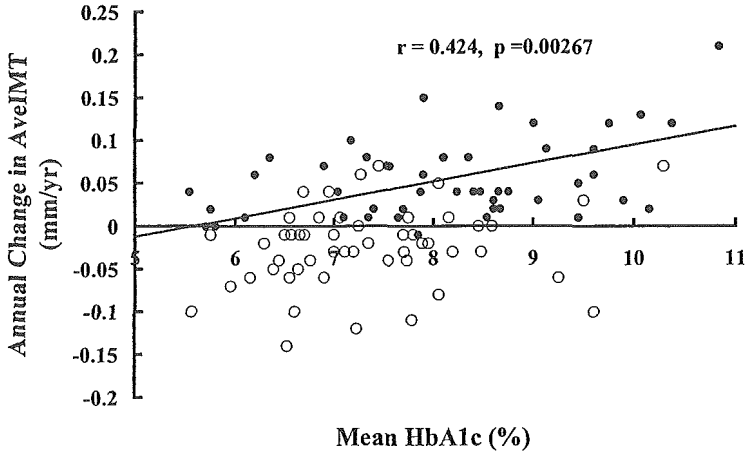

Fig. 1. Relationship between annual change in AveIMT and mean hemoglobin A1c levels during the follow-up period with (open circles) and without (closed circles) voglibose administration.

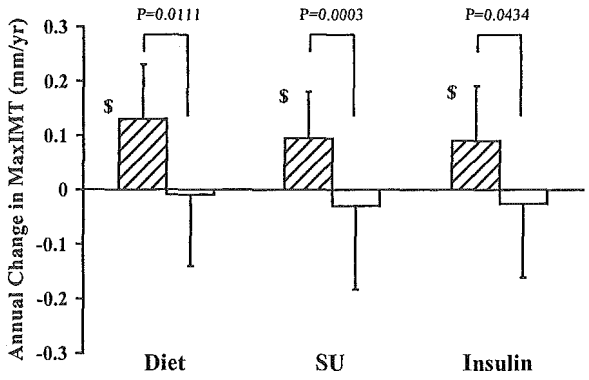

Fig. 2. Annual change in MaxIMT during the follow-up period with (open bar) and without (shaded bar) voglibose in type 2 diabetic subjects under treatment with diet alone, sulphonylurea (SU), or insulin injections. Data are shown as mean ± S.D. $ indicates a significant change from the baseline examination by paired *t*-test.

hemoglobin A1c levels during the follow-up period. On the contrary, annual changes in AveIMT of diabetic patients with voglibose administration showed a lower value than those without voglibose administration, but showed no significant relationship with the mean hemoglobin A1c during the follow-up period (Fig. 1).

With the continuation of the treatment with diet alone (n = 10), sulphonylurea (n = 30) or insulin injections (n = 10), AveIMT (0.064 ± 0.054, 0.052 ± 0.031, 0.060 ± 0.029 mm/year, respectively), and MaxIMT (0.130 ± 0.100, 0.094 ± 0.086, 0.090 ± 0.102 mm/year, respectively; Fig. 2) significantly (P < 0.01) increased by 0.056 ± 0.046 and 0.098 ± 0.122 mm/year, respectively, on a group basis. On the other hand, voglibose administration to the diabetic subjects treated with diet alone (n = 11), SU (n = 30), or insulin injections (n = 10) slowed AveIMT increase (−0.015 ± 0.042, −0.023 ± 0.047, −0.024 ± 0.042 mm/year, respectively) and MaxIMT increase (−0.009 ± 0.131, −0.030 ± 0.153, −0.026 ± 0.135 mm/year, respectively; Fig. 2). The administration of voglibose resulted in annual reduction of AveIMT (−0.024 ± 0.047 mm/year) (Fig. 1) and MaxIMT (−0.021 ± 0.144 mm/year) and significant (P = 0.0002) reduction of hemoglobin A1c levels in diabetic subjects from 8.2 ± 1.3 to 7.6 ± 0.9% on a group basis. Plasma total cholesterol and triglyceride concentrations showed significant reductions, and plasma HDL cholesterol concentration showed a significant increase after voglibose administration (Table 1).

Table 2
Multivariate regression analysis of risk factor for AveIMT

Risk factors	Univariate correlation coefficient	Partial regression coefficient	F-value	Significance
Treatment				
Insulin injection[a]		−0.022	3.932	0.0503
α-Glucosidase inhibitor[b]		−0.0689	54.46	<0.0001
Hypolipidemic drug[c]	−0.108			
Initial value				
Initial AveIMT (mm)	−0.126			
Mean value				
Hemoglobin A1c (%)	0.459	0.0137	13.52	0.0004
Total cholesterol (mM)	0.152			
Triglycerides (mM)	0.022			
HDL cholesterol (mM)	−0.075			
Systolic blood pressure (mmHg)	−0.029			
Diastolic blood pressure (mmHg)	−0.069			
Smoking[d]	0.080			

AveIMT: average intima plus media thickness.
[a] 1 as with insulin injection and 0 as without insulin injection.
[b] 1 as with voglibose and 0 as without voglibose.
[c] 1 as with hypolipidemic drugs and 0 as without drug.
[d] 1 as current smokers and 0 as never having smoked or former smokers.

Multivariate regression analysis was performed to evaluate the factors affecting the progression of AveIMT of diabetic subjects with and without voglibose administration. The administration of voglibose was a primary factor, which reduced the annual progression of AveIMT by −0.0689 mm/year independently of the decrease in mean hemoglobin A1c levels. The increase in the mean hemoglobin A1c levels was found to be a secondary factor, which increased the progression of AveIMT by 0.0137 mm/year per 1% increase in hemoglobin A1c. Insulin treatment was also a possible factor ($P = 0.050$), attenuating the progression of AveIMT by −0.022 mm/year (Table 2).

4. Discussion

In this study, treatment with an α-glucosidase inhibitor in addition to treatment with diet, SU, or insulin injections for 3 years significantly reduced the progression of AveIMT or MaxIMT of diabetic subjects. Some of them wanted to continue oral medication in spite of poor glycemic control. Without administration of the α-glucosidase inhibitor, the other regimens such as diet control, oral administration of SU, or insulin injections could not stop the progression of IMT of the carotid artery in subjects with diabetes, which progressed at a rate of 0.056 ± 0.046 mm/year for AveIMT and of 0.098 ± 0.122 mm/year for MaxIMT, as shown in several previous studies [11–13].

The annual change in AveIMT showed a significant linear relationship with mean hemoglobin A1c levels during the follow-up period in the diabetic subjects without voglibose administration. Addition of voglibose significantly reduced hemoglobin A1c levels by 0.6%. Multivariate regression analysis clearly showed that addition of voglibose significantly reduced the progression of AveIMT by as much as 0.0689 mm/year, independent of the change in hemoglobin A1c levels. In addition, hemoglobin A1c augmented the progression of AveIMT by 0.0137 mm/year per 1% increase in hemoglobin A1c levels. Therefore, the decrease in hemoglobin A1c by voglibose administration might account for the decrease in the annual change of AveIMT by 0.008 mm/year (0.0137 × 0.6%). In this study, however, adding administration of voglibose slowed progression of AveIMT by 0.08 mm/year on a group basis, which is about 10 times greater than estimated. Therefore, reduction of hemoglobin A1c levels by administration of voglibose can only partially explain the remarkable anti-atherogenicity of this drug. It was reported that voglibose attenuated the postprandial glycemic rise [18,19], which was not evaluated in this study. Also, voglibose improved insulin sensitivity in non-diabetic hyperinsulinemic subjects [20] as acarbose [21]. However, to explore these possibilities, the magnitude of the decrease in postprandial glycemia or improvement of insulin sensitivity by voglibose needs to be evaluated in subjects with type 2 diabetes mellitus.

We also found in this study that voglibose could significantly reduce plasma total cholesterol and triglyceride concentrations as well as cause a significant increase in plasma HDL cholesterol concentration. The improvement in the plasma lipid profile may at least partially contribute to the retardation of carotid atherosclerosis. Most recently, the STOP-NIDDM study showed the anti-atherogenic effect of acarbose, reducing the relative risk of developing atherosclerosis and cardiovascular disease by 49% in subjects with impaired glucose tolerance [17].

The findings of this study suggest that voglibose, an α-glucosidase inhibitor, may be a potent anti-atherogenic drug in Japanese subjects with type 2 diabetes. To ascertain the anti-atherogenicity of α-glucosidase inhibitors, a large-scale prospective study on subjects with type 2 diabetes must be conducted.

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Is the Diagnosis of Metabolic Syndrome Useful for Predicting Cardiovascular Disease in Asian Diabetic Patients?

Analysis from the Japan Diabetes Complications Study

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OBJECTIVE — The metabolic syndrome (MetS) is believed to be associated with an increased risk of cardiovascular disease (CVD). Although its prevalence is extremely high among diabetic patients, its prevalence in those with no history of CVD has not been determined. Moreover, prospective studies published on the association between MetS and cardiovascular events in diabetic populations have used only the World Health Organization (WHO) definition of MetS and included only white European subjects. The aim of this study was to determine the prevalence of MetS, as defined by both the WHO and the National Cholesterol Education Program (NCEP), and its predictive value for CVD in Asian diabetic patients in a long-term, prospective setting.

RESEARCH DESIGN AND METHODS — The baseline characteristics and incidence/hazard ratio of cardiovascular events (coronary heart disease and stroke) were determined in 1,424 Japanese type 2 diabetic patients with and without MetS, as defined by WHO (WHO-MetS) or the NCEP.

RESULTS — A high prevalence (38–53%, depending on sex and definition) of MetS was found among diabetic patients, even those with no history of CVD. During the 8-year study period, only WHO-MetS was a predictor for CVD in female patients. In male patients, although both definitions of MetS were significant predictors for CVD, individual components of MetS, such as hyperlipidemia or hypertension, were equivalent or better predictors.

CONCLUSIONS — We found that MetS is relatively common in diabetic patients with no history of CVD. We suggest that the commonly used definitions of MetS, at least in their present forms, have limited clinical usefulness for Asian diabetic patients and may need some ethnic group–specific modifications for global use.

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The metabolic syndrome (MetS) is an important cluster of metabolic abnormalities linked with insulin resistance and cardiovascular disease (CVD) (1). The diagnostic criteria of MetS proposed by the World Health Organization (WHO-MetS) (2) and the National Cholesterol Education Program (NCEP-MetS) (3) are currently the most widely used. Although the prevalence of MetS in the general population reportedly differs widely among ethnic groups (4–8) and according to the definition of MetS used (7,9–11), the prevalence among patients with known diabetes is consistently high (70–90%) regardless of ethnicity or definition (12–20). Considering the high prevalence of CVD in the diabetic population (21) and the fact that subjects with a history of CVD often have multiple cardiovascular risk factors, it has been speculated that the extremely high prevalence of MetS among diabetic patients (12–20) may be due to the large number of patients who already have a history of CVD. However, the prevalence of MetS in diabetic patients without CVD has not been widely investigated to date. It is rational to examine this because diabetic patients with MetS have a higher incidence of CVD than those without MetS (15,16) and MetS is a stronger risk factor for CVD in patients with type 2 diabetes than in nondiabetic subjects (12).

Most prospective studies have shown that subjects with MetS are at increased risk of incident CVD (22,23) and mortality due to CVD (9,24–27). However,

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Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; ECG, electrocardiogram; HOMA-IR, homeostasis model assessment of insulin resistance; JDCS, Japan Diabetes Complications Study; MetS, metabolic syndrome; NCEP, National Cholesterol Education Program; UKPDS, U.K. Prospective Diabetes Study; WHO, World Health Organization; WHR, waist-to-hip ratio.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

many of these studies excluded diabetic patients from their study populations (9,22–24). Diabetic patients are known to be at greater risk for CVD than nondiabetic subjects (21), and it has been suggested that MetS is responsible for the increased prevalence of coronary heart disease (CHD) seen in diabetic patients (20). Therefore, it is important to evaluate the predictive value of MetS on incident CVD in diabetic patients in long-term, prospective studies. To the best of our knowledge, there have been four cohort studies specifically targeting diabetic patients to determine the relative risk of MetS on the incidence of CVD (12,15,16) and mortality due to CVD (17). Although these studies involved only white European subjects and used only the WHO definition of MetS, most of them (12,15,16) demonstrated, as expected, that the presence of MetS is associated with at least a severalfold increase in the risk of CVD. The above findings notwithstanding, it remains unclear *1*) whether such predictive values of MetS are also applicable to diabetic patients of other ethnicities, 2) which features of MetS are the best predictors of CVD and should become the critical therapeutic targets for the optimal management of CVD risk in diabetic patients (28), and 3) whether the commonly used NCEP definition of MetS (3) possesses the same predictive value for CVD as the WHO definition in diabetic patients.

The incidence of CVD in Asian subjects is known to be much less than in white subjects in general (29) and in diabetic populations in particular (30). In addition, the degree of obesity is very different between white and Asian diabetic patients (31,32), and the impact of obesity on CHD risk is known to be entirely different between whites and Asians (33,34). These differences could affect the apparent clinical significance of MetS (35,36), so that it is questionable whether the overall concept of MetS itself and the diagnosis of MetS under the present definitions based on data from mostly European and American patients are applicable to the evaluation of CVD risk in Asian diabetic patients. Therefore, in this long-term, prospective study of Japanese diabetic patients with no history of CVD, we determined the prevalence of MetS and analyzed its individual features and predictive value for incident CVD using the two most widely used definitions of MetS (2,3). Such comparisons are helpful in possibly establishing a global definition of MetS (10,37) and are also warranted to determine if there is heterogeneity in the power of individual MetS components to predict CVD (28).

RESEARCH DESIGN AND METHODS— The Japan Diabetes Complications Study (JDCS) is a nationwide, multicenter, prospective study of type 2 diabetic patients (38). In 1996, 2,205 patients aged 40–70 years with previously diagnosed type 2 diabetes and HbA_{1c} levels >6.5% were recruited and registered. The eligibility criteria for participating patients has been previously described (38). The duration of the study was 8 years. Of the 2,205 patients, the present study focused on 1,424 patients (771 men and 653 women) who had a complete set of data, including those parameters necessary to satisfy the WHO (2) and NCEP (3) criteria for the definition of MetS at baseline. The JDCS protocol, which is in accordance with the Declaration of Helsinki, received ethical approval from the institutional review boards of all of the participating institutes and was undertaken in accordance with the Ethical Guidelines for Clinical Studies of the Japanese Ministry of Health, Labor, and Welfare. All of the study participants gave written informed consent.

Both the WHO (2) and the NCEP (3) definitions were used to diagnose MetS in this study. However, because the original cut-off for abdominal obesity in the NCEP definition (waist circumference ≥102 cm for men and ≥89 cm for women) has previously been shown to be inappropriate for Asian populations (35,37) and the number of subjects who met these criteria was extremely low, the cut-off limit was adjusted according to the criteria proposed by the Japan Society for the Study of Obesity (≥85 cm for men or ≥90 cm for women), which were based on the risk of obesity-related disorders in a Japanese population (39). The WHO criteria for obesity were adopted because the waist-to-hip ratio (WHR) was used rather than waist circumference. The criteria used for analysis in this study are shown in Table 3. Because all of the study subjects were diabetic, those who fulfilled two or more of criteria 1a, 2a, 5, or 6 were classified as having WHO-MetS and those who fulfilled two or more of criteria 1b, 2b, 3, or 4 were diagnosed as having NCEP-MetS, using a modified NCEP definition (Table 3). For comparisons with other traditional risk factors for CVD, we also evaluated high LDL cholesterol levels, cigarette smoking, and excessive alcohol intake (40). Medication use, including agents for hypertension and hyperlipidemia, were not considered when diagnosing MetS in this study.

Waist and hip circumferences were measured at the umbilicus and trochanter level, respectively. A baseline dietary survey, comprised of food records and a food frequency questionnaire that included alcohol consumption, was undertaken. Information regarding cigarette smoking was collected using a standardized questionnaire. All laboratory tests were undertaken using the standard methods of each of the participating institutes, apart from the HbA_{1c} assays, which used a common standard, with 5.8% as the upper normal limit. Plasma LDL cholesterol was calculated using Friedewald's equation, except for triglyceride levels >400 mg/dl, in which case the LDL cholesterol data were treated as "missing." To estimate insulin resistance, the homeostasis model assessment of insulin resistance (HOMA-IR) was used (41). Plasma insulin levels and the HOMA-IR were not evaluated in patients treated with insulin.

Patients were assessed for CHD and stroke at baseline and yearly thereafter. In all subjects, a 12-lead electrocardiogram (ECG) was recorded at each assessment. Fatal and nonfatal CHD and stroke events identified during follow-up were certified by at least two members of the experts' committee who were masked as to risk factor status and the other member's diagnosis. With regard to CHD, myocardial infarction was defined according to the WHO Monitoring of Trends and Determinants in Cardiovascular Disease criteria (42) and angina pectoris was defined as typical effort-dependent chest pain or oppression relieved at rest or by using nitroglycerine, as validated by exercise-positive ECG and/or angiography. Stroke events were defined as a constellation of focal or global neurological deficits of sudden or rapid onset and for which there was no apparent cause other than a vascular accident, as determined by a detailed history, a neurological examination, and ancillary diagnostic procedures such as computed tomography, magnetic resonance imaging, cerebral angiography, and lumbar puncture. Stroke events were

classified as cerebral infarction (including embolus), intracranial hemorrhage (including subarachnoid hemorrhage), transient ischemic attack, or stroke of undetermined type in accordance with WHO criteria (43). No cases of asymptomatic lesions detected by brain imaging (i.e., silent infarction) were included. Only "first-ever" CHD or stroke events during the study period were counted for the analysis; if a patient had both CHD and stroke events, each event was counted separately.

Data are presented as means ± SD or as a proportion, unless otherwise specified. To compare the distributions of baseline characteristics between groups, Wilcoxon's rank-sum test or Fisher's exact test was used. Incidence rates in the two groups were assessed by a score test under the Poisson assumption. Cox regression analysis was used to calculate the adjusted hazard ratio (HR) and 95% confidence interval (CI) of MetS risk factors with CHD, stroke, or both. Statistical analyses were performed separately by sex. The SAS software package (Version 8.0, Cary, NC) was used for all analyses. $P < 0.05$ was considered to be significant.

RESULTS

Baseline characteristics and prevalence of the metabolic syndrome

The baseline characteristics of the study subjects are shown in Table 1. In all, 51% of male and 53% of female subjects met WHO criteria for MetS, whereas 45% of male and 38% of female subjects met NCEP criteria for MetS. Plasma insulin levels and HOMA-IR were significantly higher in patients with MetS (both definitions) than in those without MetS; however, there were no significant differences in HbA_{1c} or the frequency of oral hypoglycemic agent use. Insulin usage was significantly lower in women with MetS by either definition and in men with NCEP-MetS. Blood pressure and serum triglycerides were significantly higher and HDL cholesterol was significantly lower in MetS patients, despite the fact that the use of medications for both hypertension and hyperlipidemia was much more common than in patients without MetS. Daily energy intake did not differ between patients with and without MetS (data not shown).

Incidence of cardiovascular disease during follow-up

During the 8-year study period, the total number of CVD events was 117, comprised of 62 CHD and 59 stroke events. The combined incidence (per 1,000 patient-years) of CHD and/or stroke was significantly greater in patients with MetS (except in female patients with NCEP-MetS) than in those without MetS (Table 2).

Hazard ratios of the metabolic syndrome and its individual components for coronary heart disease and stroke

HRs were calculated to determine which definition of MetS was the better predictor of CVD and which of the individual MetS components (or other classic risk factors) could most efficiently predict CVD events in our subjects (Table 3). In male patients, WHO-MetS was not significantly associated with an increased risk for either CHD or stroke separately, but was associated with the combination of both (HR = 1.6). Triglyceride, LDL cholesterol (both for CHD), and blood pressure (≥140/90 mmHg) levels (for stroke) showed higher HRs. NCEP-MetS was a significant predictor of CHD in male patients, although its HR (1.9) was lower than that for triglycerides (2.9) or LDL cholesterol (2.1). Thus, neither definition of MetS was a substantially better predictor of CVD than the component parts in male patients. In contrast, in the female patients, WHO-MetS was a significant and strong predictor of CHD (HR = 2.8), stroke (HR = 3.7), and both CHD and stroke (HR = 3.2). In female patients, none of the individual elements nor the other classic risk factors showed significant increases in HRs, with the exception of hypertension (≥140/90 mmHg) for stroke, although its HR (2.4) was still lower than that for WHO-MetS. NCEP-MetS was not a significant risk factor for CHD or stroke in female patients (Table 3).

To examine the clustering effects of the individual components of MetS, the association between CVD risk and the number of MetS components fulfilled (other than diabetes) was analyzed (Table 3). Increasing the cut-off component number for the diagnosis of NCEP-MetS from ≥2 to ≥3 in male subjects did not dramatically improve the HR but did greatly reduce the number of patients diagnosed as having MetS, from 45 to 14.5% (Table 3). In female patients, changing the diagnostic cut-off component numbers was not particularly beneficial in improving the prognostic value of WHO-MetS (Table 3).

CONCLUSIONS — The prevalence of MetS in our diabetic patients who were free from CVD was not as high as that reported in previous studies that included patients with previous CVD (12–20) but was nevertheless relatively high (38–53%). Although we did not have age-matched nondiabetic control subjects, the prevalence of MetS was much higher than that reported in Japanese general population workers, namely 19.5% in men and 7.9% in women (33). Hypertension and dyslipidemia are much more common in diabetic patients than in nondiabetic subjects (21), and it has been speculated that the features of MetS more easily aggregate, even in the absence of current or previous CVD, leading to the observed increase in the prevalence of MetS. On the other hand, the prevalence of NCEP-MetS in the U.S. general population age 50 years and older is 44% (20), which is relatively close to that in our Japanese diabetic patients. However, even in the U.S. (excluding Asian Americans), the prevalence of MetS in those who have a BMI range equivalent to that of Japanese subjects is not >10% (44). This implies that in the U.S., obesity has a potent impact on the prevalence of MetS, as has also been shown in a recent study (45). This is in contrast to findings in Japan, where diabetes rather than obesity may have the greater influence on the prevalence of MetS, as Japanese diabetic patients are not obese by comparison with white diabetic patients or nondiabetic Japanese subjects (31,32).

The clinical importance of MetS is related to its putative impact on CVD morbidity and mortality. Among Italian patients with type 2 diabetes, the risk for CVD was 4.9 (CI 1.2–20.7) times higher in patients with WHO-MetS than in those without it (16), which was a higher rate than that seen in our male (1.6 [CI 1.0–2.6] times) and female (3.2 [CI 1.6–6.5] times) patients. These results suggest that the clinical impact of MetS on diabetic patients varies by ethnic group. Comparing cardiovascular risk factors in our Japanese patients to those in patients in the U.K. Prospective Diabetes Study (UKPDS) (46,47), hypertension is a common

Table 1—*Baseline characteristics of study subjects, grouped by metabolic syndrome status*

		WHO-defined metabolic syndrome			NCEP-defined metabolic syndrome		
	Total	Without	With	*P*	Without	With	*P*
n							
Men	771	376 (48.8)	395 (51.2)	—	424 (55.0)	347 (45.0)	—
Women	653	310 (47.4)	343 (52.6)	—	405 (62.0)	248 (38.0)	—
Age (years)							
Men	58.2 ± 7.4	57.4 ± 7.6	58.9 ± 7.2	0.01	58.0 ± 7.6	58.4 ± 7.2	0.50
Women	58.7 ± 7.4	57.9 ± 7.7	59.5 ± 7.0	0.01	58.4 ± 7.4	59.4 ± 7.2	0.11
Diabetes duration (years)							
Men	10.9 ± 7.6	11.0 ± 7.6	10.9 ± 7.6	0.66	11.5 ± 7.8	10.2 ± 7.4	0.01
Women	10.1 ± 6.7	10.7 ± 7.3	9.5 ± 6.0	0.10	10.6 ± 7.0	9.4 ± 6.0	0.07
BMI (kg/m^2)							
Men	22.9 ± 2.6	22.0 ± 2.4	23.7 ± 2.6	<0.01	21.8 ± 2.3	24.2 ± 2.4	<0.01
Women	23.4 ± 3.3	22.3 ± 3.0	24.3 ± 3.3	<0.01	22.6 ± 3.1	24.6 ± 3.3	<0.01
Waist circumference (cm)							
Men	82.3 ± 7.7	79.0 ± 7.1	85.3 ± 7.0	<0.01	78.4 ± 6.4	87.0 ± 6.5	<0.01
Women	76.5 ± 9.8	72.4 ± 8.3	80.1 ± 9.7	<0.01	74.1 ± 8.6	80.4 ± 10.4	<0.01
Waist-to-hip ratio							
Men	0.89 ± 0.07	0.86 ± 0.05	0.92 ± 0.06	<0.01	0.87 ± 0.06	0.92 ± 0.06	<0.01
Women	0.83 ± 0.08	0.80 ± 0.06	0.86 ± 0.07	<0.01	0.82 ± 0.07	0.86 ± 0.08	<0.01
Blood pressure (mmHg)							
Men	132 ± 16/78 ± 10	124 ± 13/74 ± 9	139 ± 15/81 ± 10	<0.01	127 ± 16/75 ± 9	137 ± 15/81 ± 9	<0.01
Women	132 ± 17/76 ± 10	124 ± 13/73 ± 9	139 ± 16/79 ± 11	<0.01	128 ± 17/74 ± 10	138 ± 14/80 ± 10	<0.01
HbA_{1c} (%)							
Men	7.61 ± 1.36	7.53 ± 1.42	7.67 ± 1.30	0.05	7.54 ± 1.36	7.68 ± 1.36	0.18
Women	8.05 ± 1.45	8.07 ± 1.51	8.04 ± 1.40	0.79	8.09 ± 1.47	7.99 ± 1.42	0.41
Fasting plasma glucose (mmol/l)*							
Men	8.3 (7.2–10.0)	8.2 (7.0–9.7)	8.6 (7.4–10.4)	<0.01	8.2 (7.1–9.8)	8.6 (7.4–10.3)	0.02
Women	8.6 (7.3–10.2)	8.6 (7.2–10.2)	8.6 (7.3–10.2)	0.74	8.6 (7.2–10.3)	8.5 (7.4–9.9)	0.77
Fasting plasma insulin (pmol/l)†‡							
Men	6.2 (0.5–1.9)	5.4 (0.5–1.9)	7.2 (0.5–1.9)	<0.01	5.2 (0.5–1.9)	7.7 (0.5–1.9)	<0.01
Women	7.1 (0.5–1.9)	5.9 (0.5–1.9)	8.3 (0.6–1.8)	<0.01	6.2 (0.5–1.9)	8.7 (0.5–1.9)	<0.01
HOMA-IR‡							
Men	3.1 ± 3.1	2.6 ± 2.6	3.6 ± 3.4	<0.01	2.4 ± 2.1	3.9 ± 3.8	<0.01
Women	3.3 ± 2.6	2.8 ± 2.2	3.8 ± 2.8	<0.01	2.9 ± 2.1	4.1 ± 3.1	<0.01
Serum total cholesterol (mmol/l)							
Men	5.01 ± 0.90	4.93 ± 0.84	5.09 ± 0.94	0.01	4.97 ± 0.82	5.07 ± 0.98	0.16
Women	5.44 ± 0.85	5.38 ± 0.84	5.50 ± 0.86	0.05	5.41 ± 0.83	5.50 ± 0.89	0.28
Serum HDL cholesterol (mmol/l)							
Men	1.34 ± 0.39	1.42 ± 0.39	1.27 ± 0.38	<0.01	1.48 ± 0.38	1.18 ± 0.34	<0.01
Women	1.47 ± 0.44	1.57 ± 0.45	1.37 ± 0.41	<0.01	1.65 ± 0.43	1.17 ± 0.26	<0.01
Serum triglycerides (mmol/l)†							
Men	1.2 (0.6–1.6)	1.0 (0.7–1.5)	1.5 (0.6–1.6)	<0.01	1.0 (0.7–1.5)	1.6 (0.6–1.6)	<0.01
Women	1.1 (0.6–1.7)	0.9 (0.6–1.6)	1.4 (0.6–1.6)	<0.01	9 (0.7–1.5)	1.6 (0.6–1.6)	<0.01

Current smoker (%; men/women)	43.9/8.7	46.6/8.1	41.3/9.2	0.08/0.38	44.7/7.1	42.9/11.3	0.33/0.049
Excessive alcohol intake (%; men/women)§	12.4/0.2	8.2/0.0	16.4/0.3	<0.01/0.51	7.7/0.3	18.4/0.0	<0.01/0.62
OHA use (without insulin) (%; men/women)	72/77	72/76	73/78	0.38/0.33	72/75	72/79	0.50/0.20
Insulin use (with or without OHA) (%; men/women)	16/20	18/24	15/16	0.16/0.01	20/22	11/15	<0.01/0.02
Medication for hypertension (%; men/women)	22/29	12/17	32/40	<0.01/<0.01	16/23	30/40	<0.01/<0.01
Medication for hyperlipidemia (%; men/women)	15/35	11/30	19/39	<0.01/<0.01	10/32	21/40	<0.01/0.02

Data are *n* (%), means ± SD, *median (interquartile range), or †geometric means (1 SD). ‡Patients with insulin therapy were excluded. §Excessive alcohol intake was defined as more than three drinks (38 g ethanol) per day. OHA, oral hypoglycemic agent.

and potent risk factor for stroke (Table 3) (46). By contrast, HDL cholesterol levels, hypertension, and smoking, all of which were identified as significant risk factors for CHD in UKPDS patients (47), were not associated with a significant elevation of HRs in our Japanese patients (Table 3). Instead, triglyceride levels, which were not significant in UKPDS patients (47), were a strong predictor for CHD in male Japanese patients. These findings imply that the critical therapeutic targets among the components of MetS for preventing cardiovascular complications (28) may need to be modified according to a patient's ethnic group.

Most of the previous studies evaluating the predictive power of MetS for CVD calculated the HRs by including sex as one of the independent variables for statistical adjustment, and very few studies have analyzed CVD risk separately by sex (24). Sex is reportedly an independent predictor for CVD, with an odds ratio of 2.6, which is larger than that of age, HbA_{1c}, and even of MetS itself in type 2 diabetic patients (16). Our results revealed drastic differences in the HRs between sexes. In our female patients, WHO-MetS presented an increased risk for CVD events to a greater degree than could be predicted by the sum of the individual components (Table 3), whereas, in contrast, in our male patients, WHO-MetS was not even a significant risk factor for CVD. At baseline, obvious sex differences were observable in the proportion of subjects who smoked or consumed excessive alcohol, both of which were much higher in male patients. Of particular interest, the proportion of male subjects with excessive alcohol intake was at least twice as high in male patients with MetS than in those without MetS, whereas the proportion of current smokers did not differ in patients with and without MetS (Table 1). It can be speculated that excessive alcohol intake could be closely associated with MetS in male Japanese diabetic patients. Moreover, moderate alcohol intake, which has been shown to be beneficial for preventing CHD in U.S. and European diabetic patients, is not beneficial for Japanese patients (40).

Few studies have applied both the WHO and NCEP definitions of MetS to the same subjects to compare the prevalence of MetS or its predictive value for CVD. It has been reported that the prevalence of WHO-MetS is generally higher than that of NCEP-MetS in both sexes (7,12). This was confirmed in our Japanese diabetic subjects, although the difference in prevalence was not great. Regarding the predictive value of MetS, in subjects without diabetes or other cardiovascular risks, Hunt et al. (27) reported that the NCEP-MetS tended to be more predictive for cardiovascular mortality than the WHO-MetS, whereas Lakka et al. (9) reported a contrary result. In our diabetic patients, the NCEP guidelines, even modified for optimal use by Japanese subjects, were not more predictive than the WHO guidelines in female patients nor did they show excellent clinical usefulness in male patients. One possible explanation for this difference in our patients could be the hypertension cut-off used, with 140/90 mmHg in the WHO defini-

Table 2—*Incidence of coronary heart disease and/or stroke (per 1,000 patient-years) among study subjects grouped by metabolic syndrome status*

		WHO-defined metabolic syndrome			NCEP-defined metabolic syndrome		
	Total (%)	Without (%)	With (%)	*P*	Without (%)	With (%)	*P*
Incidence among Men							
CHD	9.8	8.4	11.3	0.34	7.0	13.5	0.04
Stroke	7.7	5.1	10.3	0.05	6.6	9.1	0.35
CHD and/or stroke	17.1	12.7	21.6	0.03	13.0	22.6	0.02
Incidence among Women							
CHD	5.5	2.9	8.0	0.04	4.4	7.3	0.27
Stroke	7.2	2.8	11.2	<0.01	6.2	8.8	0.38
CHD and/or stroke	12.6	5.7	19.0	<0.01	10.7	15.6	0.22

Table 3—*Patient prevalence at baseline and hazard ratios for coronary heart disease, stroke, or both in Japanese study subjects grouped by metabolic syndrome status*

	Prevalence at baseline		Hazard ratios for CHD		Hazard ratios for stroke		Hazard ratios for CHD and/or stroke	
	Men	Women	Men	Women	Men	Women	Men	Women
Criteria of individual components								
1a. BMI >30 or WHR >0.90 (men) or >0.85 (women)	39.4	37.5	1.3 (0.7–2.5)	1.2 (0.5–3.0)	1.3 (0.7–2.6)	1.1 (0.5–2.3)	1.4 (0.8–2.2)	1.2 (0.6–2.1)
1b. Waist circumference ≥85cm (men) or ≥90 cm (women)	36.7	9.6	1.7 (0.9–3.0)	1.0 (0.2–4.4)	0.90 (0.4–1.9)	1.1 (0.3–3.7)	1.3 (0.8–2.1)	1.1 (0.4–2.8)
2a. SBP ≥140 or DBP ≥90 mmHg	38.9	38.9	0.8 (0.4–1.6)	1.0 (0.4–2.6)	2.1 (1.1–4.3)	2.4 (1.1–5.5)	1.3 (0.8–2.1)	1.8 (1.0–3.2)
2b. SBP ≥130 or DBP ≥85 mmHg	60.7	62.2	0.9 (0.5–1.6)	0.9 (0.4–2.2)	1.4 (0.7–2.9)	1.8 (0.7–4.5)	1.1 (0.6–1.7)	1.2 (0.7–2.4)
3. Triglycerides ≥150 mg/dl	24.8	21.0	2.9 (1.6–5.3)	1.7 (0.6–4.4)	1.1 (0.5–2.4)	0.7 (0.2–1.9)	2.0 (1.2–3.2)	1.1 (0.5–2.2)
4. HDL cholesterol ≤40 mg/dl	19.3	36.3	1.8 (0.9–3.5)	1.5 (0.6–3.6)	1.0 (0.4–2.5)	1.3 (0.6–2.9)	1.6 (0.9–2.6)	1.3 (0.7–2.4)
5. Triglycerides ≥150 mg/dl or HDL cholesterol <35 mg/dl	28.5	27.0	2.8 (1.6–5.2)	1.8 (0.7–4.5)	0.9 (0.4–1.9)	1.6 (0.7–3.5)	1.8 (1.1–2.9)	1.6 (0.9–2.9)
6. Urinary albumin excretion >30 μg/g creatinine	51.2	57.7	1.2 (0.6–2.3)	2.9 (0.9–8.7)	1.8 (0.9–3.8)	1.1 (0.5–2.4)	1.4 (0.9–2.3)	1.6 (0.8–3.0)
7. LDL cholesterol ≥120 mg/dl	45.1	65.2	2.1 (1.1–3.9)	1.2 (0.5–3.2)	0.9 (0.5–1.8)	0.6 (0.3–1.3)	1.4 (0.9–2.3)	0.8 (0.4–1.4)
8. Current smoker	43.9	8.7	1.4 (0.7–2.5)	0.6 (0.1–4.3)	0.9 (0.4–1.8)	2.5 (0.8–7.3)	1.2 (0.7–1.9)	1.6 (0.6–4.1)
9. Alcohol intake >3 drinks/day*	12.4	0.2	0.7 (0.3–2.1)	0.0 (0.0–0.0)	1.0 (0.4–2.8)	0.0 (0.0–0.0)	0.9 (0.4–1.8)	0.0 (0.0–0.0)
Number of components comprising WHO-MetS other than diabetes (i.e., among 1a, 2a, 5, and 6)								
0	18.6	16.4	1.00	1.00	1.00	1.00	1.00	1.00
≥1 (vs. <1)	81.5	83.6	1.7 (0.7–4.5)	3.9 (0.5–28.4)	1.0 (0.4–2.5)	2.3 (0.5–9.7)	1.2 (0.7–2.4)	2.8 (0.9–9.0)
≥2 (vs. <2; i.e., WHO-MetS)	51.2	52.5	1.3 (0.7–2.4)	2.8 (1.0–7.9)	2.0 (0.9–4.1)	3.7 (1.4–9.9)	1.6 (1.0–2.6)	3.2 (1.6–6.5)
≥3 (vs. <3)	21.8	20.7	1.8 (0.9–3.5)	1.3 (0.5–3.7)	2.1 (1.0–4.4)	1.1 (0.4–2.7)	1.9 (1.2–3.2)	1.2 (0.6–2.4)
Number of components comprising NCEP-MetS other than diabetes (i.e. among 1b, 2b, 3, and 4)								
0	20.1	21.6	1.00	1.00	1.00	1.00	1.00	1.00
≥1 (vs. <1)	79.9	78.4	1.9 (0.7–4.9)	1.6 (0.4–5.6)	1.0 (0.4–2.2)	6.4 (0.9–46.7)	1.3 (0.7–2.4)	2.7 (0.9–7.7)
≥2 (vs. <2; i.e., NCEP-MetS)	45.0	38.0	1.9 (1.0–3.6)	1.7 (0.7–4.0)	1.4 (0.7–2.8)	1.3 (0.6–2.8)	1.8 (1.1–2.8)	1.4 (0.8–2.5)
≥3 (vs. <3)	14.5	11.5	2.5 (1.3–4.9)	0.9 (0.2–3.7)	0.9 (0.3–2.4)	0.3 (0.0–2.2)	1.8 (1.0–3.2)	0.5 (0.2–1.7)

Data are percent or hazard ratios (95% CIs) and are grouped according to individual and combined cardiovascular risk factors mostly comprising the metabolic syndrome as defined by the World Health Organization or the National Cholesterol Education Program. *Equivalent to 38 g ethanol/day. DBP, diastolic blood pressure; SBP, systolic blood pressure; WHR, waist-to-hip ratio.

tion being a significant predictor for stroke, whereas 130/85 mmHg in the NCEP definition is not.

The strengths of our study were that *1*) it is the first prospective study to determine the predictive value of MetS on CVD in Asian subjects, 2) the two most widely used definitions of MetS were applied to the same cohort for the evaluation of their clinical usefulness, and 3) the follow-up was mainly carried out in university or large general hospitals, which facilitated the reliable assessment of follow-up data and event diagnosis/records. Nevertheless, we acknowledge that the study had certain limitations: *1*) Our study subjects were hospital-based patients with diabetes of a relatively long duration; therefore, we cannot make inferences beyond a similar group. 2) We analyzed both intervention (lifestyle modification through diabetes self-management care) and control (continuance of conventional care) groups of the JDCS together, although mild intervention produced only limited differences in glycemic control (0.1–0.2% in HbA_{1c}) as well as a lack of significant differences in known classical cardiovascular risk factors, as previously reported (38). 3) We did not consider medication use in the diagnosis of MetS in this study. 4) Mortality was not analyzed because we did not have sufficient occurrences at this stage of the study.

In conclusion, we found a high prevalence of MetS among diabetic patients with no history of CVD. For Japanese female patients with type 2 diabetes, WHO-MetS but not NCEP-MetS was predictive for CVD. In male patients, although both WHO-MetS and NCEP-MetS were somewhat predictive for CVD, hyperlipidemia or hypertension had equivalent or higher HRs for CVD and seemed to be sufficient for the prediction of CVD. We suggest that the commonly used definitions of MetS, at least in their present forms, have limited clinical usefulness for Asian diabetic patients and may need some ethnic group–specific modifications for global use.

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APPENDIX

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