循環器疾患等総合研究事業

糖尿病における血管合併症の発症予防と進展抑制に関する研究(JDCStudy)

(臨床研究実施チームの整備)

平成17年度　総括研究報告書

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平成18年3月

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厚生労働科学研究費補助金（循環器疾患等総合研究事業）

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研究要旨

日本人における糖尿病ならびにその合併症の有病率は上昇しており、国民の健康を著しく障害している。我々のグループは過去9年間にわたり、糖尿病とその血管合併症の発症・進展要因を解明し予防・抑制する目的で、「糖尿病における血管合併症の発症予防と進展抑制に関する研究（JDCS：Japan Diabetes Complication Study）」を実施してきた。これは、2型糖尿病患者のライフスタイル改善効果を大規模で検討した世界初の研究であり、同時に日本人2型糖尿病患者の代表的コホートでもある。全国 59 カ所の糖尿病専門施設外来に通院中の患者 2205 名が追跡調査されている。このコホートの解析により、欧米人と日本人との2型糖尿病の病態背景の相違や、日本人2型糖尿病患者における合併症の発症率や発症のリスクファクターに関するデータなど、日本人2型糖尿病患者に関する多くの有用な臨床エビデンスが生まれつつある。さらに近年の治療ガイドラインの強化に伴い、2型糖尿病患者の心血管リスクファクターに対して治療目標を厳格化した多因子介入治療に行うために、2型糖尿病患者の新たなコホートを設定し、臨床研究実施チームを組織した。近年、一般診療や保健施策は大規模臨床研究によるエビデンスに基づいて行われることが求められている。本研究によるエビデンスは、このような社会の流れに科学的裏付けを与えるものと考えられる。

A．採択された効果的医療技術の確立推進臨床研究事業での研究概要

日本の糖尿病有病率は、平成14年度糖尿病実態調査によると疑い例を含めて成人国民の6人に1人を占める。これに伴って糖尿病合併症も増加し、患者のQOLを著しく障害している。我々のグループは過去9年間にわたり、厚生労働科学研究として「糖尿病における血管合併症の発症

予防と進展抑制に関する研究（JDCS：Japan Diabetes Complication Study）」を実施運営してきた。その目的は、糖尿病とその血管合併症の発症・進展要因を解明し予防・抑制を目指すことである。本研究は、世界初の2型糖尿病患者のライフスタイル改善効果を大規模臨床研究で検討した研究であると共に、わが国の2型糖尿病患者の代表的コホートともなっている。

現在、全国59カ所の糖尿病専門施設に通院中の2205名が追跡調査されており、日本人2型糖尿病患者に関する多くの有用なエビデンスが生まれつつある。例えば、日本人2型糖尿病患者における細小血管症や動脈硬化性疾患の発症率や増悪因子に関する詳細なデータや、白人と日本人の2型糖尿病の病態背景の著しい相違などについてである。これらは国際誌に掲載され、わが国の糖尿病診療に役立つエビデンスになった。

近年、生活習慣改善の重要性も声高に叫ばれており、一般診療や保健施策は大規模臨床研究によるエビデンスに基づいて行われることが求められている。ライフスタイルを含めた治療介入については、わが国の専門施設の医療水準が元々高かったため、その差は比較的小さなものではあったが、ライフスタイル介入が長期血糖コントロール改善に有意な効果を持つことが証明された。

今回はこれまでの経験と結果をもとに、2型糖尿病患者に対して、さらに強力な生活習慣介入を含む多因子介入を実施するために、臨床研究実施チームを組織した。これにより心血管リスクファクターをどこまで改善させ得るかを検討し、生活習慣病のEBMの確立に貢献する。

本研究によるエビデンスは、このような社会の流れに科学的裏付けを与えるものと考えられる。すなわち現代人が，生活習慣病と対峙しながら「健康に」長寿を全うするために必要な基礎データとなるのみならず，長期的視野に基づく保健行政上においても，さらに限られた医療資源を有効に活用するためにも貢献しうる重要なデータとなるものと考えられる。

B．採択された効果的医療技術の確立推進臨床研究事業での研究方法

JDCSの事務局は、茨城県つくばの筑波大学大学院臨床医学系内分泌代謝糖尿病内科におかれ、さらに東京

お茶の水の糖尿病データセンターにおいても、データの収集・解析・事務などの作業が実施されている。登録症例のすべてのデータはこの糖尿病データセンターにおいて一元的に管理されている。

対象者は、主治医が積極的に生活習慣改善を中心とした強化治療を行う「介入群」と、通常の外来診療を継続する「非介入群」に割り付けられており、両群間で、血糖コントロールや血管合併症などについて差があるかどうかを検討している。介入群の患者には、体重、血糖、血圧、血清脂質、飲酒・喫煙などについて「治療到達目標」が設定されており、主治医も患者もこれを到達するように努力することが求められている。

追跡年数の経過にともない、合併症の発症・進展を来した症例が増加してきており、今後は各合併症のリスクファクターの解析に重点的に取り組む必要がある。各合併症の診断基準は予めプロトコールで定められており、それぞれ専門家の判定委員により判定されている。各種データはコンピューターに入力し、統計専門家による解析や効果判定を実施している。

追加コホートは、対象は、診断後1年以上で血糖コントロールが安定（過去6ヶ月の平均 HbA_{1c}8％以下、変動±0.5％以下）している外来で経過観察中の2型糖尿病患者131人である。これらの患者より同意取得後、連続的に中央登録し、無作為に対照群と介入群に2群に割り付け、対照群については従来通りの外来治療を継続している。介入群については上記に加え、従来のＪＤＣＳより強力な強化治療を実施している。プロトコールは本文の最後にまとめて掲載している。

(倫理面への配慮)

従来の欧米の大規模臨床介入試験のように、非介入群をコントロール不良のまま放置することは倫理的配慮から避け、非介入群についても通常の外来管理を継続する。経過中、HbA1c2％を上回る増悪がみられた場合には、その時点をエンドポイントとして、介入期間終了を待たずに、薬物療法の導入または強化ができるようになっている。したがって研究遂行のために、患者をコントロール不良のまま据え置くことはなく、患者の不利益になることはない。また介入自体も、薬剤やインスリンによる介入と比較して安価で、低血糖などの副作用がないという点でも安全

性に優れている。なお本研究は、筑波大学「医の倫理」審査委員会において審査承認済みである。

C. 採択された効果的医療技術の確立推進臨床研究事業での研究結果

ＪＤＣＳは、平成８年４月１日より積極的に糖尿病治療の介入を行う群と通常治療群とに分けて開始され９年が経過した。本研究では、このほかにも欧米とは異なる日本人糖尿病患者の興味深い特徴が数多く捉えられた。たとえば肥満度や摂食量の違い、日本人糖尿病患者と欧米人糖尿病患者とのアルコール摂取の影響の違いなども明らかになっている。すなわち、最近の欧米人糖尿病患者を対象にした研究のメタアナリシスによると、適度（エタノール換算で一日 38ｇ以下）のアルコール摂取は、冠動脈疾患抑制効果を有することが示されている。しかし JDCS 登録患者ではそのような現象は認められなかった。したがって日本人２型糖尿病患者に対しては、たとえ適量だとしても、飲酒はあまり勧められないことになる。このような日本人糖尿病の特徴を抽出していくことは、その病態背景を理解し、日本人糖尿病患者に適した対策を考える上で重要であろう。

前向き研究によって得られた、日本人患者における細小血管合併症の発症率とリスクファクターのデータはこれまで多くなかった。各血管合併症のエンドポイントに達した症例の詳細な検討・解析により、わが国の 2 型糖尿病患者の各血管合併症の病態と危険因子が次第に明らかになりつつある。

細小血管合併症に関する解析結果としては、網膜症とメタボリック症候群との関連が示唆された。最近の欧米の研究では糖尿病神経障害と心血管リスクファクターとの関連が指摘されていることとあわせて考えると興味深い結果である。

腎症に関する解析結果では、収縮期血圧が 140 mmHg 以上の患者の腎症発症のリスクは、130 mmHg 未満の患者の 2.7 倍に上昇していた。また HbA_{1C} 9%以上以上の患者の腎症発症のリスクは、7%未満と比較して 3.3 倍であり、あらためて腎症における血圧と血糖の両方の管理の重要性が浮き彫りになった。

大血管合併症については、わが国では従来より冠動脈疾患より脳血管障害の頻度が多かったにも関わらず、

糖尿病患者では、冠動脈疾患の発症率が脳血管障害の発症率を上回っており、言わば欧米型の動脈硬化疾病構造に変化しつつあることが注目される。これらの大血管イベント発症患者を、それぞれエンドポイントに達しなかったものと比較すると、日本人2型糖尿病患者においても、大血管合併症予防には、血糖コントロールと共に脂質や血圧のコントロールも重要であることが判明した。

上記に加えて、本年度に新たに明らかになったこととしては、糖尿病網膜症の発症には、血糖コントロールとの関連に加え、血圧や尿中アルブミンとの関連が示唆され、網膜症の進展とメタボリックシンドロームとの関連が示唆された。また糖尿病腎症の正確な発症率が今回初めて明らかになり、血圧や血糖コントロールの程度、降圧剤の使用に応じた腎症発症リスクの程度が明らかになった。

さらに2型糖尿病患者にメタボリックシンドロームが合併した際の大血管合併症発症に及ぼす影響が明らかになり、従来のメタボリックシンドローム診断基準が、日本人2型糖尿病患者の大血管合併症予知に必ずしも鋭敏な指標でなかったことが判明した。このような日本人糖尿病の特徴を抽出していくことは、その病態背景を理解し、日本人糖尿病患者に適した対策を考える上で重要であろう。

なお JDCS のこれまでの中間成績は、後記のように多くの国際誌で出版されており、次第に国際的注目を集めるに至っている。今後もさらに多くの成果が発表される予定である。

D. 考察

本研究ように長期にわたる大規模介入試験では、主治医や患者の移動に伴う登録症例の脱落が起きやすいため、その点には特に留意しながら研究を進めている。また血糖コントロール、脂質代謝、体重調整、血圧管理などの不良な患者には特に指摘して、治療成果を上げるよう主治医に連絡した。このような研究の質を保つのに最も重要なポイントにおいて、臨床研究実施チームの活躍が奏功した。

本研究ではこれまで、欧米の教科書に記載された事実とは異なる、日本人の糖尿病の特徴が明らかにされてきた。たとえば、UKPDS の白人のデータと、JDCS のデータを比較してみると、両コホートの糖尿病罹患期

間、年齢、血糖コントロール状態、血清脂質などは、よく近似しているにも関わらず、肥満度に著明な差（JDCS の Body mass index (BMI)約 23 に対して、UKPDS では約 29）が見られた。また白人糖尿病患者は、一般人口(BMI 約 24)と比較してもかなり肥満しているのに対して、日本人糖尿病患者の BMI は、一般人口とあまり変わらないことも判明した。
日本人における糖尿病と肥満との特徴的な関係が、どのような遺伝・環境的背景に基づくのかはまだ明らかではないが、両者の関係が、欧米人と日本人ではこれほど異なるという事実は、日本人患者の診療には、欧米の研究結果でなく日本人の大規模臨床データに基づくエビデンスが必要なことを示唆する一例である。

糖尿病教育の介入効果については現時点ではまだ十分ではないが、今後、介入内容を強化したコホートの成績が待たれる。

E．健康危険情報

該当事例なし。

F.知的財産権の出願・登録状況

該当事例なし。

G．結論

臨床研究実施チームの活躍のもとに、わが国におけるこれまでの糖尿病に関する無作為割り付け前向き臨床試験の中では最も規模の大きい Japan Diabetes Complications Study (JDCS)を進行させている。追加コホートの成績も合わせて、将来の日本の糖尿病診療および保健施策に役立つエビデンスが続々と生み出されるものと期待される。

H．研究発表

F. 研究発表

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「2 型糖尿病を対象とした強化治療介入研究(新 JDCS)」

研究目的：2 型糖尿病患者に対して血清脂質および血圧などの強化治療を行い、血管合併症の代替エンドポイントに対する有効性ならびに治療目標達成率を検討する。

研究方法：多施設共同前向き介入試験（通常治療群 vs 強化治療群の群間比較）

1）症例選択基準：

年齢 45-69 歳、HbA_{1C}6.5％以上の男女 2 型糖尿病患者で以下をすべて満たす者。

［細小血管合併症］

糖尿病性網膜症がないか、あっても単純性網膜症までの者（=軽症～中等症非増殖糖尿病網膜症までの者）

随時尿中アルブミン 150mg/gCRE 以下の者（血清 CRE1.3mg/dl 以上の者を除く）

［大血管合併症］

心疾患・脳血管疾患・閉塞性動脈硬化症の既往がない者

閉塞性動脈硬化症、明らかな家族性高コレステロール血症、Ⅲ型高脂血がない者

2）対象者の同意：各対象者に研究内容に関する文書を渡し、説明に基づく文書による同意を得る。

3）対象者の割付：対象者を、年齢、性別、HbA_{1C}、総コレステロールの 4 因子についてマッチさせて 2 群に割りつける。

4）介入内容

(A)通常治療群

各主治医のそれまでの方針で治療を継続し、治療目標値はとくに定めない。なおコレステロール降下療法にあたっては、できるかぎりスーパースタチン（アトロバスタチン（リピトール™）、ピタバスタチン（リバロ™））は用いずに、可能な限りプラバスタチン（メバロチン™）を用いる。

(B) 強化治療群

下記治療目標のすべてを達成するように、主治医による強化治療を実施する。

強化治療群の治療目標

①	HbA_{1C}： 6.5％未満
②	BMI： 22 kg/m^2 未満
③	血圧： 130 mmHg 未満／80 mmHg 未満［目標値に達しない場合は、ARB または ACE-I を用いる］
④	血清脂質：LDL コレステロール＜100 mg/dl（血清総コレステロール＜180 mg/dl）［目標値に達

しない場合は、スーパースタチンの中でもできるかぎりピタバスタチン（リバロ™）を用いる］

6）研究期間

平成17年9月1日より平成20年8月末（結果により延長または短縮される場合がある）

5）追跡観察項目

治療目標の達成　上記治療目標の項目別ならびに全体の達成

以下は補足的事項

（2）その他の観察項目

(a)糖尿病関連死

虚血性心疾患死（心筋梗塞、虚血による心不全死）

脳血管障害死

発症後3ケ月以内の死亡は最終死因が例えば肺炎でも血管障害死とする（臨床経過の報告をもとにイベント判定委員会で統一的に検討する）

腎不全死

高／低血糖死

突然死

(b)重大疾患（ただし、発生後も追跡は継続する）

・心筋梗塞・狭心症

・脳血管障害

24時間以上局所神経症状が継続し、CT、MRIまたは剖検にて診断が確定できたもの

・閉塞性動脈硬化症／糖尿病性壊疽

下肢・足趾切断、潰瘍、壊疽、間欠性跛行の新規発症、バイパス術施行

・糖尿病性網膜症による片眼／両眼の失明

3ヶ月以上継続する矯正視力0.1以下の状態

7）研究の中止基準

糖尿病関連死あるいは糖尿病に関連した重大疾患の発症率の群間の差異が明白になった場合　（log-rank testで3S.D.：P＜0.001）

別紙４

研究成果の刊行に関する一覧表レイアウト

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Hirohito Sone,Sachiko Mizuno,Hitomi Fujii,Yukio Yoshimura,Yoshimitu Yamasaki,Shun Ishibashi,Shigehiro Katayama,Ysushi Saito,Hideki Ito,Yasuo Ohashi,Yasuo Akanuma,Nobuhiro Yamada, J DC Study Group	Is the Diagnosis of Metaboric Syndrome Useful for Predicting Cardiovascular Disease in Asian Diabetic Patients?	Diadetes Care	28,6	1463-71	2005
Hirohito Sone,Sachiko Tanaka,Shun Ishibashi,Yoshimitu Yamasaki,Shinichi Oikawa,Hideki Ito,Yasushi Saito,Yasuo Ohashi,Yasuo Akanuma,Nobuhiro Yamada,JDCStudy Group	The New Worldwide Defintion of Metabolic Syndrome is Not a Better Diagnostic Predictor of Cardiovascular Disease in Japanese Diabetic Patients Than the Existing Definitions	Diadetes Care	29,1	145-147	2006

The New Worldwide Definition of Metabolic Syndrome Is Not a Better Diagnostic Predictor of Cardiovascular Disease in Japanese Diabetic Patients Than the Existing Definitions

Additional analysis from the Japan Diabetes Complications Study

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We previously reported (1) the limited clinical significance for Japanese diabetic patients of the widely used World Health Organization (WHO) (2) and National Cholesterol Education Program (NCEP) (3) definitions of metabolic syndrome and suggested that an international definition of metabolic syndrome that was applicable regardless of ethnicity was necessary (1).

Recently, the International Diabetes Federation published a long-awaited new worldwide definition of metabolic syndrome (4) that is intended to be applicable to various ethnic groups. The new definition is similar to the NCEP definition (3) but has several important differences. Notably, most components of the new definition now include subjects who are receiving specific treatments for the abnormalities that comprise metabolic syndrome. Also, central obesity (defined by waist circumference with ethnic modification in its thresholds) has become a mandatory component in the new definition. In this report, we evaluated the predictive power of the new international definition for cardiovascular disease (CVD), as compared with that of previous definitions, in Japanese diabetic patients.

RESEARCH DESIGN AND METHODS— The Japan Diabetes Complications Study (JDCS) has been described in detail elsewhere (1,5). The same dataset was used for evaluation so that the new definition of metabolic syndrome could be directly compared with the WHO and NCEP definitions (1–4). A total of 1,424 Japanese patients (771 men and 653 women, age 58.4 ± 7.4 years [means ± SD]) with previously diagnosed type 2 diabetes but without known CVD were followed for 8 years for coronary heart disease (CHD) and stroke events. Fatal and nonfatal CHD and stroke were defined as previously reported (1). The new International Diabetes Federation definition (4) was used with a recommended ethnic modification for Japanese subjects in relation to waist circumference (men ≥85 cm, women ≥90 cm). Since all of the subjects had diabetes, metabolic syndrome diagnosis was made in patients who met criteria for central obesity plus one or more of the following: increased triglycerides, increased blood pressure, or reduced HDL cholesterol (see Table 1 for detailed thresholds). Incidence rates in the two groups (with and without metabolic syndrome) were estimated under the Poisson assumption using person-year methods. Cox regression analysis was used to calculate the age-adjusted hazard ratio (HR) and 95% CI of metabolic syndrome risk factors with CHD, stroke, or both. The SAS software package (version 8.0; SAS Institute, Cary, NC) was used for all analyses. $P < 0.05$ was considered statistically significant.

RESULTS— At baseline, the prevalence of metabolic syndrome, using the new definition (Table 1), was notably lower, especially in female patients, than the prevalence under the WHO (2) and NCEP (3) definitions, which was ~50% on average (1). Diabetes duration in patients with (9.9 ± 6.9 years) or without (10.7 ± 7.3 years) metabolic syndrome did not differ significantly ($P = 0.07$). The proportion of patients that met the central obesity criterion (an essential component of the new definition) was 36.7% for men and 9.7% for women, such that 87% of men and 95% of women with central obesity had metabolic syndrome.

The incidence (per 1,000 patient-years) of CHD (13.5 [with metabolic syn-

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Received for publication 20 July 2005 and accepted in revised form 24 September 2005.

*Members of the JDCS Study Group have been listed previously (1).

Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; JDCS, Japan Diabetes Complications Study; NCEP, National Cholesterol Education Program; WHO, World Health Organization.

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

Table 1—*Patient prevalence at baseline, age-adjusted HRs with 95% CIs, and incidence of CHD, stroke, or both in 1,424 Japanese patients with type 2 diabetes (771 men and 653 women) according to individual cardiovascular risk factors comprising the metabolic syndrome as defined by the International Diabetes Federation (b, c, and d include specific treatment for each abnormality)*

	Prevalence at baseline (%)		HR for CHD		HR for stroke		HR for CHD and/or stroke	
	Men	Women	Men	Women	Men	Women	Men	Women
a) Waist circumference ≥85 cm (men), ≥90 cm (women)	36.7	9.7	1.68 (0.92–3.08)	1.13 (0.26–4.86)	0.91 (0.44–1.86)	1.11 (0.31–4.05)	1.32 (0.83–2.10)	1.13 (0.43–2.97)
b) Triglycerides ≥150 mg/dl	26.5	23.4	2.93 (1.55–5.53)	2.03 (0.81–5.04)	1.10 (0.51–2.36)	0.59 (0.20–1.78)	1.96 (1.21–3.19)	1.13 (0.56–2.26)
c) HDL cholesterol <40 mg/dl (men), <50 mg/dl (women)	19.3	36.3	1.82 (0.94–3.54)	1.48 (0.63–3.49)	0.99 (0.41–2.40)	1.34 (0.61–2.94)	1.53 (0.90–2.61)	1.34 (0.74–2.40)
d) SBP ≥130 mmHg or DBP ≥85 mmHg	64.1	68.8	1.04 (0.53–2.01)	1.05 (0.39–2.84)	2.08 (0.90–4.82)	1.63 (0.60–4.37)	1.29 (0.77–2.17)	1.29 (0.64–2.59)
a plus one or more of *b*, *c*, or *d*	32.0	9.2	1.72 (0.94–3.15)	1.15 (0.27–4.90)	1.14 (0.56–2.34)	1.13 (0.31–4.11)	1.47 (0.91–2.35)	1.14 (0.44–3.01)

DBP, diastolic blood pressure; SBP, systolic blood pressure.

drome] vs. 8.1 [without metabolic syndrome] in men; 5.8 vs. 5.5 in women) or stroke (8.1 vs. 7.5 in men; 8.8 vs. 7.0 in women) did not differ significantly between subjects with or without metabolic syndrome. Age-adjusted HRs were calculated to determine whether the new metabolic syndrome definition or its components could predict cardiovascular events (Table 1). Patients diagnosed as having metabolic syndrome, even when subgrouped by therapeutic contents (oral hypoglycemic agents or insulin use), did not show significantly raised HRs for CHD, stroke, or both compared with subjects without metabolic syndrome. However, male patients with raised triglyceride levels and/or having specific treatment for this condition had a significantly increased risk of CHD (HR 2.93, $P < 0.001$) and combined CHD and stroke (1.96, $P = 0.006$), regardless of whether they had metabolic syndrome (Table 1).

CONCLUSIONS — Our previous analysis (1) showed that HRs for CVD in patients with WHO-defined metabolic syndrome were significantly elevated compared with HRs in subjects without metabolic syndrome (although the HR for CHD in male patients was not elevated). Diagnosis of metabolic syndrome by the NCEP definition was less predictive but still associated with a significantly elevated HR for CHD in male patients. However, metabolic syndrome diagnosis by the new definition was not predictive for CVD in either male or female patients in the same prospective setting. Therefore, the new definition did not improve the prediction of adverse cardiovascular events, and its clinical usefulness in Japanese diabetic patients is rather less than that of the existing definitions or of hypertriglyceridemia alone in male patients.

The indispensability of central obesity to the new definition was a major cause of the decrease in the prevalence of metabolic syndrome observed using the new definition. The fact that most patients with central obesity were classified as having metabolic syndrome revealed that metabolic syndrome diagnosis by the new definition was highly dependent on waist circumference when applied to Japanese diabetic subjects. It also denoted that most patients with central obesity had at least one other cardiovascular risk factor, suggesting a close relationship between central obesity and other cardiovascular risk factors. However, this combination was not necessarily associated with an increased risk of CVD in our patients. This latter observation led us to further evaluate the significance of waist circumference in our patients by modifying the threshold within the 65- and 105-cm range and recalculating the HRs. Interestingly, we could not find any thresholds associated with significantly elevated HRs for cardiovascular events in either male or female subjects (data not shown). Therefore, the new definition's lower prediction power for CVD seemed to be derived from the indispensability of the waist circumference component.

To date, prospective trials examining the significance of metabolic syndrome as a predictor of CVD in diabetic patients (1,6–9) have been inadequate (10,11). Many important issues remain to be resolved. *1*) Is the new definition of metabolic syndrome a good predictor of CVD in diabetic patients of differing ethnicities (12)? 2) Are there any other combinations of components (or different thresholds) that are better predictors of CVD in Asian diabetic patients (13–15)? 3) Is the concept of metabolic syndrome truly applicable or relevant to diabetic patients in general? Investigations of these issues would aid the screening of diabetic patients at especially high risk of CVD, as well as inform and direct ethnic group–specific management of diabetes (16–19).

Acknowledgments— The JDCS was financially supported by the Ministry of Health, Labor, and Welfare of Japan.

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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.

Diabetes Care 28:1463–1471, 2005

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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Received for publication 3 December 2004 and accepted in revised form 17 February 2005.

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*A complete list of members of the Japan Diabetes Complications Study Group can be found in the APPENDIX.

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*

	Total	WHO-defined metabolic syndrome			NCEP-defined metabolic syndrome		
		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