厚生労働科学研究費補助金(循環器疾患等生活習慣病対策総合研究事業)
分担研究報告書

都市部一般住民を対象とした糖尿病・メタボリックシンドロームの発症要因と脳卒中・心筋梗塞の発症に関する研究

分担研究者　小久保喜弘　国立循環器病センター　予防検診部医長

研究の要旨

都市部一般住民を対象とした吹田研究により、以下のことが分かった。メタボリックシンドロームの日本の診断基準では、循環器疾患発症の相対危険度が、働き盛りの男女(60歳未満)で関連が見られ、退職後(60歳以降)では関連性が弱いかまたは見られなかった。このことから、日本のメタボリックシンドロームの診断基準は、年齢依存性であり、吹田研究では60歳でその関連性が大きく変わることがわかった。

空腹時血糖は循環器疾患発症のリスクであり、正常型、境界型、糖尿病型と移行するにつれて、循環器疾患発症のリスクは、血圧のカテゴリーが、正常高値血圧、正常血圧、至適血圧と一つずつ血圧のカテゴリーが下がってくることがわかった。このことから、耐糖能異常者の血圧のコントロールおよび、生活習慣の改善が循環器疾患発症予防になることがわかった。

15年間の間に、糖尿病型に男性で7%、女性で4%移行することが分かり、糖尿病型でない者が、年間に男性で約0.5%、女性で0.3%糖尿病に罹病することがわかった。また、15年間の間に正常型の男性50%、女性35%が耐糖能異常に移行していたことがわかった。

A. 研究目的

我が国では特に男性を中心とした肥満者の増加により糖尿病とメタボリックシンドロームの増加が指摘されている。しかし、同一集団において糖尿病とメタボリックシンドロームの有病率を長期にわたって比較した研究はほとんどみられない。国立循環器病センター予防検診部では1990年より1995年度まで経口糖負荷試験を用いて住民を対象とした糖尿病の有病率調査を実施している。本研究は同一集団に対して、同様の調査を実施することで、①1990年代との有病率を比較して、糖尿病、耐糖能異常の推移を縦断的に把握する、②本データを用いて糖尿病および食後高血糖、メタボリックシンドロームの罹患要因を明らかにする、③経口糖負荷試験をベースラインに脳卒中、心筋梗塞の循環器疾患発症との関係を追跡研究することを目的とする。

B. 研究方法

(1)メタボリックシンドロームと循環器疾患との関係

平成元年に吹田市住民台帳から性年齢階層別に12,200名を、さらに平成8年に3,000名を無作為に抽出し、そのうち国立循環器病センターで基本健診を受診された者

を研究対象者とした。この研究対象者は、平成元年に抽出された健診受診者の1次コホート対象者(6,485人)、平成8年に抽出された健診受診者の2次コホート対象者(1,329人)、そしてボランティア集団(546人)からなる。現在はこのうち、1次コホート対象者で、平成元年～平成4年度の初診時健診で脳卒中、心筋梗塞の既往のない追跡可能の男性2,492名(平均年齢56.0歳)、女性2,840名(同54.6歳)を今回の解析対象とした。初診時健診後、2年毎の健診、毎年の問診、発症登録制度、病院カルテ調査により、2005年末まで新規脳卒中、心筋梗塞の発症を追跡した。糖尿病は空腹時血糖126mg/dl以上または随時血糖200mg/dl以上または糖尿病治療歴有と定義した。糖尿病と循環器疾患(脳卒中、心筋梗塞)との関係は、性年齢、さらに喫煙、飲酒、高血圧、高脂血症で調整したCox比例ハザードモデルを用いて解析した。

(2)空腹時血糖と脳卒中・心筋梗塞発症との追跡研究

平成元年に大阪府吹田市の住民台帳から性年齢別に無作為抽出され、平成元年～平成4年度の初診時健診で脳卒中、心筋梗塞の既往のない男性2,486名(平均年齢55.9歳)、女性2,835名(同54.1歳)を2005年末まで追跡し、新規脳卒中、心筋梗塞の発症を登録した。境界型は空腹時血糖100mg/dl以上126mg/dl未満、糖尿病型は空腹時血糖126mg/dl以上または糖尿病治療歴ありと定義した。血圧はESH-ESC 2007ガイドラインを用い、至適血圧、正常血圧、正常高値血圧、高血圧群に分け、高血圧治療は高血圧群に分類した。糖尿病と循環器疾患発症との関係は、性年齢調整のCox比例ハザードモデルを用いて解析した。さらに、血圧の糖尿病と循環器病との交互作用をCox比例ハザードモデルで解析した。

(3)糖負荷検査

予防検診部で健診を受診している吹田市住民(年齢40歳～79歳)で文書により調査に同意を得た対象について実施する。基本健診の採血時に空腹時血糖を測定し、75g糖質を服用してもらう。服用2時間後に血糖採血管(2ml)と血清採血管(2ml)を用いて採血し、血糖を測定する。

除外基準: 問診により今までに糖尿病治療のあるもの、前回の健康診断で明らかな糖尿病治療中の者は、経口糖負荷試験を実施しない。

なお、解析データは、糖負荷検査の結果に基本健診、生活習慣問診(喫煙、飲酒、運動習慣、食事(半定量食物摂取頻度調査)と合わせて解析を行う。糖尿病、食後高血糖と生活習慣との関係を解析して、生活習慣改善方法を見出す。

C. 研究結果

(1)メタボリックシンドロームと循環器疾患との関係

男性28,345人年、女性33,501人年の観察より(平均追跡期間12.5年間)、脳梗塞130人、脳出血31人、くも膜下出血22人、分類不能脳卒中17人、心筋梗塞117人(56人の可能性のある心筋梗塞・心原生突然死を含む)の発症が確認された。

図1は、日本の診断基準(A1)とNCEP-ATPIII(B1)の診断基準による性年代別のメタボリックシンドロームの頻度をしめしたものである。日本の診断基準は、NCEP-ATPIIIの診断基準と比べて、メタボリックシンドロームの頻度が低かった。特に女性の頻度は約半分ほどであった。男性のメタボリックシンドロームの頻度は、女性と比

べて頻度が低いが、NCEP-ATPIIIでは、60代から男性とほぼ同程度の頻度になった。図1－A2は、内臓肥満がなく、メタボリックシンドロームの構成因子がない群を基準にして、内臓肥満の有無別にメタボリックシンドロームの構成因子数別に循環器疾患の相対危険度を示したものである。同じ構成因子数内で、内臓肥満の有無別の循環器疾患の危険度はほぼ同程度であった。

一方、NCEP-ATPIIIによる診断基準(アジアの肥満基準を用いる)で、メタボリックシンドロームの構成因子数がない群を基準にすると、男性では構成因子数が3個以上、女性では構成因子数が1個以上で循環器病発症のリスクとして有意であった。

日本の診断基準によるメタボリックシンドロームでは、女性の循環器疾患発症の危険因子となっていた(多変量調整ハザード比＝2.20;95%信頼区間1.31-3.08)。一方、男性は、年齢全体では循環器疾患発症の危険因子とならなかった(多変量調整ハザード比＝1.34;95%信頼区間0.96-1.87)。しかし、60歳未満において、日本の診断基準によるメタボリックシンドロームが循環器疾患発症と関連が認められた(多変量調整ハザード比＝2.92;95%信頼区間1.54-5.55)。女性でも、年齢カテゴリーに分けて考えると、60歳未満の方が循環器疾患発症との関連がより強くみられた(60歳未満:多変量調整ハザード比＝6.25;95%信頼区間2.08-18.79、60歳以上:多変量調整ハザード比＝1.80;95%信頼区間1.01-3.20)。

一方、NCEP-ATPIIIの診断基準(腹囲はアジア基準)では、男女とも循環器疾患及びその病型いずれもメタボリックシンドロームと関連が見られた(男性:多変量調整ハザード比＝1.75;95%信頼区間1.27-2.41、女性;多変量調整ハザード比＝1.90;95%信頼区間1.31-2.77)。

(2)空腹時血糖と脳卒中・心筋梗塞発症との追跡研究

境界型は男性で35.2%、女性で21.6%、糖尿病型は6.2%、3.5%であった。正常群を基準にすると、循環器病の年齢調整ハザード比は、男性の糖尿病型で1.7 (95%信頼区間:1.1-2.8)、女性の境界型で1.6 (1.1-2.3)、糖尿病型で3.3 (1.8-6.0)であった。心筋梗塞の年齢調整ハザード比は、女性の糖尿病型で4.1 (1.5-10.9)であった。脳卒中、脳梗塞のハザード比は、循環器病とほぼ同じ結果であった。血圧カテゴリー順に循環器病と糖尿病との関係では、血糖正常かつ至適血圧群を基準に性年齢調整ハザード比が、血糖正常群で1.6、2.3*、2.5*、境界群で1.5、1.9*、2.2*、3.1*、糖尿病群で3.7*、5.5*、5.1*、3.8*であった(*:P＜0.05)。

(3)糖負荷検査

平成2年から7年にかけて、糖負荷検査を受けた30-59歳の男女のうち、今年度健診を受けられた方を対象に、説明と同意を取得し、809名(男性272名、女性437名)が糖負荷検査を実施した。糖負荷検査を実施したもののうち、70歳未満の者に対して、半定量食物摂取頻度調査を実施した。次年度も糖負荷検査を継続する。

15年前と今回(平成19-20年度)の両方に糖負荷検査を実施した、809名を対象に、糖尿病の病態の推移をみた。15年前の糖尿病の病型は、男性で正常型60%、IFG27%、IGT13%、女性で正常型81%、IFG 10%、IGT 9%であった。この同一対象者の15年後の病型別の割合は、男性で、正常型29%、IFG 35%、IGT 29%、DM型7%、女性で、正常

型 53%、IFG 24%、IGT 19%、糖尿病型4%であった。

D. 考察

内臓肥満の有無別に分けて、NCEP-ARP Ⅲの診断基準(腹囲はアジア基準)の構成因子の数別に検討すると構成因子数が増えると循環器疾患のリスクが上昇するが、内臓肥満別有無別ではその危険度は変わらないことがわかった。これらのことから、ウェスト周囲径は独立した危険因子とは言い難いことがわかった。

日本の診断基準では、メタボリックシンドロームの循環器疾患に対する相対危険度は、働き盛りの男女で循環器疾患発症と関連が見られ、退職後(60歳以降)では関連性が弱いかまたは見られなかった。このことから、日本のメタボリックシンドロームの診断基準は、年齢依存性であり、吹田研究では60歳でその関連性が大きく変わることがわかった。

女性の境界型、糖尿病型で、心血管病との関連が見られ、男性よりも関連性がよりはっきりと見られた。これは、日本の他のコホート研究でも同様の傾向が見られ、日本人においては、女性の方で糖尿病が循環器病に感受性が高い可能性があると思われる。

さらに、正常型、境界型、糖尿病型別に、血圧のカテゴリー別に、循環器疾患の発症のリスクをみた。血糖が正常型で、血圧が至適血圧である群を基準とした場合、空腹時血糖が正常群では、正常高値血圧から循環器疾患発症のリスクが有意に高くなり、空腹時血糖が境界型の場合、正常血圧から、循環器疾患のリスクが高くなり、糖尿病型では、至適血圧から循環器疾患発症のリスクが高くなった。このことから、血糖の状態が、正常型、境界型、糖尿病型と移行するにつれて、血圧のカテゴリーは、正常高値血圧、正常血圧、至適血圧と一つずつ血圧のカテゴリーが下がってくることがわかった。都市部一般住民を対象に、血糖と血圧との関連性について初めて示すことができた。

15年間の間に、糖尿病型に男性で7%、女性で4%移行することが分かり、糖尿病型でない者が、年間に男性で約0.5%、女性で0.3%糖尿病に罹病することがわかった。また、15年間の間に正常型の男性50%、女性35%が耐糖能異常に移行したことになる。

E. 結論

日本のメタボリックシンドロームの診断基準で、働き盛りの男女とも循環器疾患発症との関連性がみられ、同じ危険因子の数の中で、内臓肥満有無別で、循環器疾患発症のリスクに差がないことがわかった。糖尿病は循環器疾患のリスクであることが分かり、血糖が境界型、糖尿病型へとカテゴリーが上がるにつれて、血圧のカテゴリーが正常高値血圧、正常血圧、至適血圧へとカテゴリーがひとつずつ下がることも明らかになった。都市部一般住民を対象とする集団において、糖尿病への移行率も男性で0.5%、女性で0.3%であった。

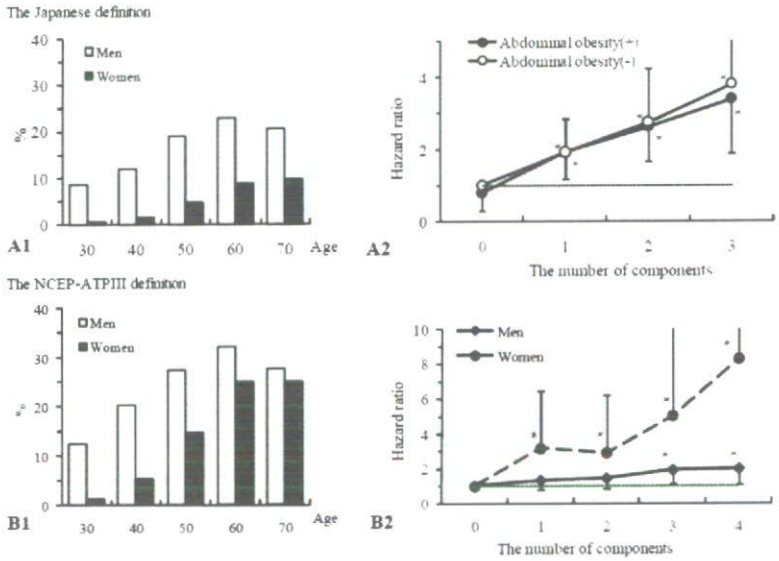
最終年度は、糖負荷検査による糖尿病、境界型の循環器疾患の危険度を生活習慣を考慮に入れて、どのような生活習慣が発症予防に繋がるかをアプローチする。また、耐糖能異常に移行する群(増悪群)と移行しない群(改善群)との間でどのような生活習慣の違いがあるのかを解析して、生活習慣の改善指導の資料を作成する。

F. 健康危険情報

特になし

研究協力者:岡村智教、渡邊至、東山綾、小野優（国立循環器病センター予防検診部）、古川曜子（奈良女子大人間文化学科公衆栄養学）

図1．メタボリックシンドロームの頻度および構成因子数別循環器疾患相対危険度



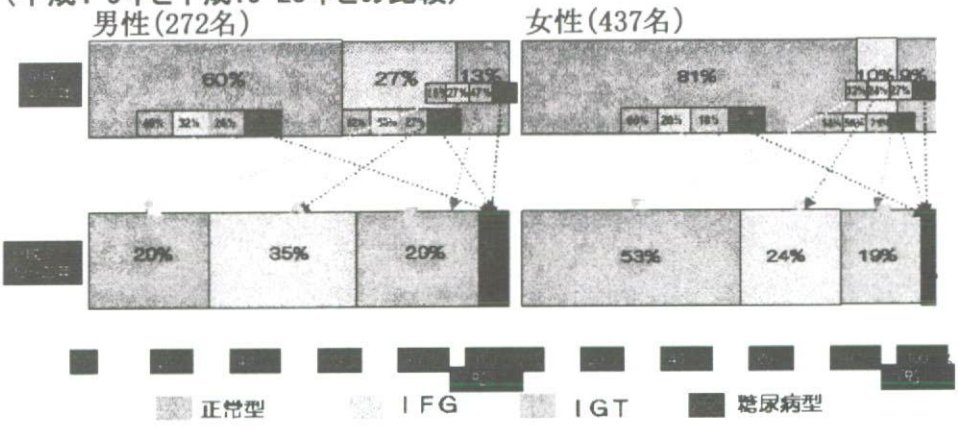
日本の診断基準(A1)、NCEP-ATPIIIの診断基準(B1)による性年代別メタボリックシンドロームの頻度、□は男性、■は女性を示す。日本の診断基準によるメタボリックシンドロームの構成因子数別の腹部肥満有無別の相対危険度(A2)。*:腹部肥満(－)構成因子数＝0を基準としてP<0.05。NCEP-ATPIIIの診断基準によるメタボリックシンドロームの構成因子数別の男女別による相対危険度。*:構成因子＝0を基準としてP<0.05。

図2．血圧カテゴリー・糖尿病型別にみた循環器病発症の相対危険度：吹田研究

	血圧カテゴリー			
	至適	正常	正常高値	高血圧
正常型	1(基準)	1.6	2.3	2.5
境界型	1.5	1.9	2.2	3.1
糖尿病型	3.7	5.5	5.1	3.8

灰色に示したものは、基準と比較して、循環器疾患発症が有意に高いことを示している。

図3．同一対象者における耐糖能異常の15年間推移:吹田研究
(平成4-5年と平成19-20年との比較)



※平成4-5年の結果が、正常型・境界型のみの対象者を15年間経過観察した

Ⅲ. 研究成果の刊行に関する一覧表

別紙４

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
清原　裕	メタボリックシンドロームの疫学	日本糖尿病学会	糖尿病学の進歩	診断と治療社	東京	2008	238-243
清原　裕	わが国の心血管疾患とそのリスク因子の変遷と現状を識る	狩尾七臣 島田和幸 吉川純一 笠貫　宏 土師一夫 別府慎太郎 松崎益徳	新・心臓病診療プラクティス 高血圧を識る・個別診療に活かす	文光堂	東京	2008	50-54
清原　裕	わが国の脳卒中の病型変化	柳澤信夫 篠原幸人 岩田 誠 清水輝夫 寺本 明	Annual Review 神経 2008	中外医学社	東京	2008	362-369
清原　裕	老年医学的観点の久山町研究,	日本老年医学会雑誌編集委員会	老年医学 update 2008-09	メジカルビュー社	東京	2008	132-142

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	出版年	ページ
Kokubo Y, Kamide K, Okamura T, Watanabe M, Higashiyama A, Kawanishi K, Okayama A, Kawano Y.	Impact of high-normal blood pressure on the risk of cardiovascular disease in a Japanese urban cohort: the Suita study.	Hypertension.	52(4)	652-659	2008 Oct
Okada S, Makino H, Nagumo A, Sugisawa T, Fujimoto M, Kishimoto I, Miyamoto Y, Kikuchi-Taura Akie, Soma T, Taguchi A, Yoshimasa Y.	Circulating CD34-Positive Cell Number Is Associated With Brain Natriuretic Peptide levrl in Type 2 Diabetic Patients.	Diabetetes Care	31(1)	157-158	2008

Okamura T, Kokubo Y, Watanabe M, Higashiyama A, Miyamoto Y, Yoshimasa Y, Okayama A.	Low-density lipoprotein cholesterol and non-high-density lipoprotein cholesterol and the incidence of cardiovascular disease in an urban Japanese cohort study: The Suita study.	Atherosclerosis.			2008
Kawano Y, Horio T, Matayoshi T, Kamide K.	Masked hypertension: subtypes and target organ damage.	Clin Exp Hypertens.	30(3)	289-296	2008
Nishida H, Horio T, Suzuki Y, Iwashima Y, Kamide K, Kangawa K, Kawano Y.	Plasma adrenomedullin as an independent predictor of future cardiovascular events in high-risk patients: comparison with C-reactive protein and adiponectin.	Peptides.	29(4)	599-605	2008
DOi Y, Kubo M, Yonemoto K, Ninomiya T, Iwase M, Arima H, Hata J, Tanizaki Y, Iida M, Kiyohara Y.	Fasting plasma glucose cutoff for diagnosis of diabetes in a Japanese population.	J Clin Endocrinol Metab	93	3425-3429	2008
Arima H, Kubo M, Yonemoto K, Doi Y.	High-sensitivity C-reactive protein and coronary heart disease in a general population of Japanese: the Hisayama Study.	Arterioscler Thromb Vasc Biol	28	1385-1391	2008

Maebuchi D, Arima H, Ninomiya T, Yonemoto K, Kubo M, Doi Y, Tanizki Y, Matsumura K, Iida M, Kiyohara Y.	Arterial stiffness and QT interval prolongation in a general population: the Hisayama Study.	Hypertens Res	31	1339-1345	2008
Kubo M, Hata J, Doi Y, Tanizaki Y, Iida M, Kiyohara Y.	Secular trends in the incidence and risk factors of ischemic stroke and its subtypes in the Japanese population.	Circulation	118	2672-2678	2008
Ninomiya Y , Kiyohara Y, Tokuda Y, Doi Y, Arima H, Harada A, Ohashi Y, Ueshima and for the Japan Arteriosclerosis Longitudinal Study Group	Impact of kidney disease and blood pressure on the development of cardiovascular disease: an overview from the Japan Arteriosclerosis Longitudinal Study.	Circulation	118	2694-2701	2008
Ohnishi H, Saitoh S, Akasaka H, Mitsumata K, Chiba M, Furugen M, Furukawa T, Mori M, Shimamoto K.	Incidence of Hypertension in Individuals with Abdominal Obesity in a Rural Japanese Population: The Tanno and Sobetsu Study.	Hypertension Research	31	1385-1390	2008
大西浩文、斎藤重幸、赤坂　憲、三俣兼人、千葉瑞恵、古堅　真、古川哲章、森　満、島本和明.	メタボリックシンドローム、危険因子集積と尿中微量アルブミンとの関連-端野・壮瞥町研究-.	日本循環器病予防学会誌	43	132-138	2008

Mizuta E, Kokubo Y, Yamanaka I, Miyamoto Y, Okayama A, Yoshimasa Y, Tomoike H, Morisaki H, Morisaki T.	Leptin gene and leptin receptor gene polymorphisms are associated with sweet preference and obesity.	Hypertens Res.	31(6)	1069-1077	2008
Makino H, Okada S, Nagumo A, Sugisawa T, Miyamoto Y, Kishimoto I, Akie TK, Soma T, Taguchi A, Yoshimasa Y.	Pioglitazone treatment stimulates circulating CD34-positive cells in type 2 diabetes patients.	Diabetes Res Clin Pract.	81(3)	327-330	2008
Nagaoka I, Shimizu W, Itoh H, Yamamoto S, Sakaguchi T, Oka Y, Tsuji K, Ashihara T, Ito M, Yoshida H, Ohno S, Makiyama T, Miyamoto Y, Noda T, Kamakura S, Akao M, Horie M.	Mutation site dependent variability of cardiac events in Japanese LQT2 form of congenital long-QT syndrome.	Circ J.	72(5)	694-699	2008
Sakaguchi T, Shimizu W, Itoh H, Noda T, Miyamoto Y, Nagaoka I, Oka Y, Ashihara T, Ito M, Tsuji K, Ohno S, Makiyama T, Kamakura S, Horie M.	Age- and genotype-specific triggers for life-threatening arrhythmia in the genotyped long QT syndrome.	Cardiovasc Electrophysiol.	19(8)	797-799	2008

Nakayama M, Kudoh T, Kaikita K, Yoshimura M, Oshima S, Miyamoto Y, Takeya M, Ogawa H.	Class A macrophage scavenger receptor gene expression levels in peripheral blood mononuclear cells specifically increase in patients with acute coronary syndrome.	Atherosclerosis.	198(2)	426-433	2008
Makino H, Doi K, Hiuge A, Nagumo A, Okada S, Miyamoto Y, Suzuki M, Yoshimasa Y.	Impaired flow-mediated vasodilatation and insulin resistance in type 2 diabetic patients with albuminuria.	Diabetes Res Clin Pract.	79(1)	177-82	2008
Kokubo Y, Okamura T, Yoshimasa Y, Miyamoto Y, Kawanishi K, Kotani Y, Okayama A, Tomoike H.	Impact of metabolic syndrome components on the incidence of cardiovascular disease in a general urban Japanese population: The Suita Study.	Hypertens Res.	31	2041-2049	2008

Ⅳ. 研究成果の刊行物・別刷

Impact of High-Normal Blood Pressure on the Risk of Cardiovascular Disease in a Japanese Urban Cohort

The Suita Study

Yoshihiro Kokubo, Kei Kamide, Tomonori Okamura, Makoto Watanabe, Aya Higashiyama, Katsuyuki Kawanishi, Akira Okayama, Yuhei Kawano

Abstract—Few prospective studies have examined the association between high-normal blood pressure and cardiovascular disease (CVD) in Asia. We examined the impact of high-normal blood pressure on the incidence of CVD in a general urban population cohort in Japan. We studied 5494 Japanese individuals (ages 30 to 79 years without CVD at baseline) after completing a baseline survey who received follow-up through December 2005. Blood pressure categories were defined on the basis of the ESH-ESC 2007 criteria. In 64 391 person-years of follow-up, we documented the incidence of 346 CVD events. The frequencies of high-normal blood pressure and hypertension Stage 1 and Stage ≥2 were 18.0%, 20.1%, and 10.1% for men and 15.9%, 15.6%, and 8.8% for women, respectively. Antihypertensive drug users were also classified into the baseline blood pressure categories. Compared with the optimal blood pressure group, the multivariable hazard ratios (95% confidence intervals) of CVD for normal and high-normal blood pressure and hypertension Stage 1 and Stage ≥2 were 2.04 (1.19 to 3.48), 2.46 (1.46 to 4.14), 2.62 (1.59 to 4.32), and 3.95 (2.37 to 6.58) in men and 1.12 (0.59 to 2.13), 1.54 (0.85 to 2.78), 1.35 (0.75 to 2.43), and 2.86 (1.60 to 5.12) in women, respectively. The risks of myocardial infarction and stroke for each blood pressure category were similar to those of CVD. Population-attributable fractions of high-normal blood pressure and hypertension for CVD were 12.2% and 35.3% in men and 7.1% and 23.4% in women, respectively. In conclusion, high-normal blood pressure is a risk factor for the incidence of stroke and myocardial infarction in a general urban population of Japanese men. (***Hypertension*. 2008; 52:652-659.**)

Key Words: cardiovascular diseases ■ epidemiology ■ general population ■ high-normal blood pressure ■ myocardial infarction ■ prospective studies ■ stroke

Many cohort studies have demonstrated that hypertension is a strong risk factor for total mortality and cardiovascular disease (CVD)[1–5] in both developing and developed countries.[2,6,7] The guidelines of the Joint National Committee 7 from the United States has recently introduced a category, designated "prehypertension," for people with blood pressures ranging from 120 to 139 mm Hg for systolic pressure or 80 to 89 mm Hg for diastolic pressure.[8] The European Guidelines[9] and Japanese Society of Hypertension Guidelines,[10] however, divide this population into 2 groups: those with systolic blood pressures between 120 and 129 mm Hg or diastolic blood pressures between 80 and 84 mm Hg are classified as normal, whereas those with systolic blood pressures between 130 and 139 mm Hg or diastolic blood pressures between 85 and 89 mm Hg are classified as high-normal. Although the association of cardiovascular risk with elevated blood pressure is well accepted,[1–4,6] only a few studies have addressed the absolute and relative risks of CVD for the population with blood pressure values in the high-normal range. The Framingham Heart Study revealed an association of high-normal blood pressure with increased risk of CVD.[11] The Framingham coronary heart disease prediction functions perform well for whites and blacks in different settings; these findings can be applied to other ethnic groups, like in the ARIC study, after recalibration for differing prevalence of risk factors for coronary heart disease events.[12] Few studies have investigated the association between blood pressure category and the incidence of CVD in Japan,[5,13] where there is a higher incidence of stroke and lower incidence of myocardial infarction (MI) than those in Western countries.[7] We performed a prospective examination of the risk of stroke and MI in men and women according to blood pressure category comparing normal and high-normal blood pressures in a general urban Japanese population.

Received June 17, 2008; first decision July 7, 2008; revision accepted July 25, 2008.

From the Department of Preventive Cardiology (Y. Kokubo, T.O., M.W., A.H., A.O.) and the Division of Hypertension and Nephrology (K. Kamide, Y. Kawano), National Cardiovascular Center, Osaka, Japan; The Suita Medical Association (K. Kawanishi), Osaka, Japan; and the Japan Anti-Tuberculosis Association (A.O.), Tokyo, Japan.

Correspondence to Yoshihiro Kokubo, MD, PhD, Department of Preventive Cardiology, National Cardiovascular Center, 5-7-1, Fujishiro-dai, Suita, Osaka, 565-8565 Japan. E-mail ykokubo@hsp.ncvc.go.jp

Hypertension **is available at http://hypertension.ahajournals.org** **DOI: 10.1161/HYPERTENSIONAHA.108.118273**

Methods

Study Subjects

The Suita Study,[5,14,15] an epidemiological study of cerebrovascular and cardiovascular disease, was based on a random sampling of 12 200 Japanese residents of Suita. As a baseline, participants between the ages of 30 and 79 years were randomly selected from the municipality population registry and stratified into groups by sex and age in 10-year increments in 1989. Of these, 6485 men and women underwent regular health checkups between September 1989 and March 1994. Subjects have continued to visit the National Cardiovascular Center every 2 years since that time for regular health checkups.

Cohort members in the study population were excluded from these analyses if they had a past or present history of CVD at baseline (n=208), were missing data (n=170), attended health checkups after April 1994 (n=79), or failed to complete the follow-up health surveys or questionnaires after baseline examination (n=534). After applying these exclusions, 5494 individuals were included in the analysis.

Measurement of Blood Pressure and Covariates

Well-trained physicians measured blood pressure 3 times in a seated position with a mercury column sphygmomanometer and an appropriately sized cuff according to standard protocol after at least 5 minutes of rest before the initial blood pressure reading was obtained. Systolic blood pressure was measured first to obtain approximate systolic blood pressure levels. Systolic (SBP) and diastolic (DBP) blood pressures were the average of the second and third measurements recorded more than 1 minute apart.

At baseline examination, subjects were classified into one of the 5 blood pressure categories based on the criteria of ESH-ESC 2007: optimal (SBP <120 mm Hg and DBP <80 mm Hg), normal (SBP 120 to 129 mm Hg or DBP 80 to 84 mm Hg), high-normal blood pressure (SBP 130 to 139 mm Hg or DBP 85 to 89 mm Hg), hypertension Stage 1 (SBP 140 to 159 mm Hg or DBP 90 to 99 mm Hg), or hypertension Stage ≥2 (SBP ≥160 mm Hg or DBP ≥100 mm Hg).[9,10] Antihypertensive drug users were classified according to their blood pressure levels at baseline survey. Due to the small sample size for Grade 3 hypertension, both Grades 2 and 3 were combined. Therefore, we compared optimal blood pressure with Grade 1 and Grades 2 plus 3 hypertension in this study. In addition, after antihypertensive drug users were classified into the hypertension Stage ≥1 group, subjects were classified into one of the 4 blood pressure categories: optimal, normal, and high-normal blood pressure and hypertension Stage ≥1 group. If the SBP and DBP readings for a subject were in different categories, the subjects were categorized into the higher of the 2 blood pressure categories.

At the baseline examination, we performed routine blood tests, including serum total cholesterol, high-density lipoprotein cholesterol, triglycerides, and glucose levels. Physicians or nurses administered questionnaires regarding individual personal habits and present illnesses. Subjects were classified as current smokers, nonsmokers, and past smokers. We also measured height and body weight in a fasting state. Body mass index was calculated as weight (kg) divided by the square of the height (m^2). Hyperlipidemia was defined as total serum cholesterol levels ≥5.7 mmol/L (220 mg/dL) and/or current use of antihyperlipidemic medications. Diabetes was defined as fasting plasma glucose levels ≥7.0 mmol/L (126 mg/dL) and/or current use of antidiabetic medications. We obtained informed consent from all participants. This study was approved by the Institutional Review Board of the National Cardiovascular Center.

Confirmation of Strokes and Myocardial Infarctions

Five hospitals in the Suita area were capable of performing CT scans and/or MRI, all of which were the major hospitals to which patients with acute stroke and those with MI were admitted. Medical records were reviewed by registered hospital or research physicians who were blinded to the baseline data. Stroke and MI events were registered if they occurred between the date on which the baseline health examination was performed and December 31, 2005. Strokes were defined according to the US National Survey of Stroke criteria,[16] which require rapid onset neurological deficits lasting at least 24 hours or until death. For each stroke subtype (cerebral infarction [thrombotic or embolic infarction], intracerebral hemorrhage, and subarachnoid hemorrhage), a definitive diagnosis was established based on CT, MRI or autopsy. Definitive and probable MIs were defined according to the criteria set by the MONICA project,[17] which requires electrocardiographic evidence, cardiac enzyme elevations, and/or autopsy. Sudden death was defined as death of unknown origin occurred within 24 hours from onset.

To complete our surveillance for fatal strokes and MIs, we conducted a systematic search for death certificates. We identified possible strokes or MIs using data from (1) the health examination and questionnaires from the stroke and MI registries without informed consent for medical records survey; and (2) death certificates without registration of CVD incidence, which were defined as probable stroke or MI. CVD was defined as stroke and MI in this study.

End Point Determination

The end points of the current follow-up study were (1) date of the first MI or stroke event; (2) date of death; (3) date of leaving Suita; and (4) December 31, 2005 (censored). To detect MI and stroke occurrences, each participant's health status was checked at clinical visits to the National Cardiovascular Center every 2 years. Yearly questionnaires by mail or telephone were also completed for all participants. We also obtained informed consent to review in-hospital medical records for 86.2% participants who were suspected to have signs or symptoms related to stroke or MI events.

Statistical Analysis

Analysis of variance and χ^2 tests were used to compare the mean values and frequencies by sex according to blood pressure category. For each subject, person-years of follow-up were calculated from the date of baseline survey, to the first end point, CVD event, death, emigration, or December 31, 2005. The Cox proportional hazard ratios (HRs) were fit for each blood pressure category after adjusting for age and other potential confounding factors, including age, present illness of hypercholesterolemia or diabetes, smoking status (nonsmoker, past smoker, and current smoker), and drinking status (nondrinker, past drinker, and current drinker) at baseline survey.

To express the impact of blood pressure categories on CVD occurrence in the participants, we estimated the population-attributable fraction (%). Population-attributable fraction was estimated as $Pe \times (HR-1)/HR$, in which Pe is the proportion of incident cases in the blood pressure category and HR is the multiple-adjusted hazard ratio.[18] All statistical analyses were conducted using SAS statistical package software (release version 8.2; SAS Institute Inc, Cary, NC).

Results

At baseline, we observed several differences in the distribution of CVD risk factors according to blood pressure categories (Table 1). The percentages of subjects with optimal, normal, and high-normal blood pressure and hypertension Stage 1 and Stage ≥2 were 31%, 20%, 18%, 20%, and 11% for men and 42%, 17%, 16%, 16%, and 9% for women, respectively. On average, both men and women with higher blood pressure were older and had higher serum total cholesterol levels, higher body mass index, and higher incidences of hyperlipidemia and diabetes than those with optimal blood pressure. The percentages of antihypertensive drug users classified as having hypertension Stages 1 and ≥2 at baseline were 21.3% and 37.7% for men and 24.2% and 40.6% for women, respectively.

Table 1. Baseline Characteristics of Study Subjects According to Blood Pressure Category

Groups and Variables	Blood Pressure Category*					*P* Values
	Optimal	Normal	High-Normal	Stage 1	Stage ≥2	
Men						
No. of subjects	803	502	463	516	286	
Age, years	50.8±13.2	54.0±12.9	57.5±12.2	60.1±11.7	62.0±11.1	<0.001
SBP, mm Hg	107.8±7.5	121.7±5.4	131.4±5.8	143.9±8.5	167.0±17.4	<0.001
DBP, mm Hg	68.2±6.7	76.6±6.3	81.2±6.9	87.5±8.2	97.0±11.7	<0.001
Total cholesterol, mmol/L†	5.1±0.8	5.2±0.9	5.3±0.9	5.3±0.9	5.3±0.9	<0.001
High-density lipoprotein cholesterol, mmol/L†	1.3±0.3	1.3±0.4	1.3±0.3	1.3±0.3	1.3±0.3	0.332
Body mass index, kg/m^2	22.0±2.7	22.7±2.6	23.2±2.7	23.3±3.0	23.6±3.2	<0.001
Antihypertensive medication, %	0.6	3.9	7.7	21.3	37.7	<0.001
Hyperlipidemia, %	23.7	27.4	30.6	34.4	31.4	<0.001
Diabetes, %	3.8	5.3	5.6	8.9	9.7	<0.001
Current smokers, %	59.7	49.6	46.3	44.3	40.9	<0.001
Current drinkers, %	71.7	77.0	75.0	76.8	79.6	0.045
Women						
No. of subjects	1240	504	465	457	258	
Age, years	47.8±11.9	54.0±11.5	58.9±11.5	61.6±9.4	62.9±9.6	<0.001
SBP, mm Hg	105.5±7.9	122.4±4.8	132.4±4.9	145.7±7.8	169.9±14.0	<0.001
DBP, mm Hg	66.4±6.6	75.5±7.1	79.7±6.9	85.0±9.0	92.3±13.9	<0.001
Total cholesterol, mmol/L†	5.2±0.9	5.6±1.0	5.7±0.9	5.9±0.9	5.8±1.0	<0.001
High-density lipoprotein cholesterol, mmol/L†	1.5±0.3	1.4±0.3	1.4±0.3	1.4±0.3	1.4±0.3	<0.001
Body mass index, kg/m^2	21.1±2.7	22.5±3.0	22.8±3.2	23.2±3.3	23.7±3.7	<0.001
Antihypertensive medication, %	0.9	4.3	11.3	24.2	40.6	<0.001
Hyperlipidemia, %	28.8	44.2	50.9	58.6	58.1	<0.001
Diabetes, %	1.5	3.3	4.0	6.7	5.8	<0.001
Current smokers, %	15.6	11.7	9.2	6.9	8.9	<0.001
Current drinkers, %	37.0	32.5	27.9	29.8	25.4	<0.001

*Optimal blood pressure was defined as systolic pressure <120 mm Hg and diastolic pressure <80 mm Hg. Normal blood pressure was defined as systolic pressure 120 to 129 mm Hg or diastolic pressure 80 to 84 mm Hg. High-normal blood pressure was defined as systolic pressure of 130 to 139 mm Hg or a diastolic pressure of 85 to 89 mm Hg. Stage 1 hypertension is a systolic pressure 140 to 159 mm Hg or a diastolic pressure 90 to 99 mm Hg. Stage 2 and 3 hypertension is a systolic pressure ≥160 mm Hg or a diastolic pressure ≥100 mm Hg. If the systolic and diastolic pressure readings for a subject were in different categories, the higher of the 2 categories was used. Plus–minus values are means±SD.

†To convert cholesterol values to mg/dL, multiply ×38.67.

During an average 11.7-year follow-up period, we documented 213 strokes (155 definitive strokes and 58 probable strokes) consisting of 141 cerebral infarctions, 32 intracerebral hemorrhages, 22 subarachnoid hemorrhages, and 18 unclassified strokes. We also documented 133 MIs (64 definitive MIs and 69 probable MIs or sudden cardiac deaths). Subjects who moved from Suita (16.8% of the total participants) were censored at that time.

We determined the age- and multivariable-adjusted hazard ratios for CVD, MI, and stroke according to blood pressure categories in the presence or absence of antihypertensive medication (Table 2). In men, the multivariable HRs (95% CIs) of CVD incidence were 2.04 (1.19 to 3.48), 2.46 (1.46 to 4.14), 2.62 (1.59 to 4.32), and 3.95 (2.37 to 6.58) for men and 1.12 (0.59 to 2.13), 1.54 (0.85 to 2.78), 1.35 (0.75 to 2.43), and 2.86 (1.60 to 5.12) for women with the normal and high-normal blood pressure and hypertension Stage 1 and Stage ≥2 groups, respectively. The risks of MI and stroke for each blood pressure category were similar to the risk of CVD. In a combined analysis of men and women, the multivariable HR of CVD incidence were 1.62 (1.08 to 2.43), 2.08 (1.42 to 3.05), 2.06 (1.42 to 2.98), and 3.53 (2.43 to 5.13) for the normal and high-normal blood pressure and hypertension Stages 1 and ≥2 groups, respectively (data not shown). In addition, the multivariable HR of CVD incidence in men and women younger than 60 years old were similar to those seen in men and women older than 60 years of age (data not shown).

In a second analysis in which all antihypertensive drug users were categorized to the Stage ≥1 group, we determined the age- and multivariable-adjusted HRs for CVD, MI, and stroke according to blood pressure category (Table 3). In men, the multivariable HRs (95% CIs) of CVD incidence were 1.83 (1.05 to 3.20), 2.11 (1.22 to 3.64), and 3.20 (2.01

Table 2. Age- and Multivariable-Adjusted HRs for CVD According to Blood Pressure Category With and Without Antihypertensive Medications

	Blood Pressure Category*				
Groups and Variables	Optimal	Normal	High-Normal	Stage 1	Stage ≥2
Men					
Person-years	9724	5889	5127	5611	3025
Cardiovascular disease					
Case	23	34	43	57	52
Age-adjusted	1	2.03 (1.19–3.46)	2.42 (1.45–4.03)	2.44 (1.49–3.99)	3.71 (2.25–6.16)
Multivariable-adjusted	1	2.04 (1.19–3.48)	2.46 (1.46–4.14)	2.62 (1.59–4.32)	3.95 (2.37–6.58)
MI					
Case	10	14	19	25	20
Age-adjusted	1	2.07 (0.92–4.68)	2.56 (1.18–5.53)	2.45 (1.16–5.17)	3.47 (1.60–7.51)
Multivariable-adjusted	1	2.14 (0.94–4.86)	2.65 (1.20–5.85)	2.72 (1.26–5.84)	3.89 (1.76–8.56)
Stroke					
Case	13	20	24	32	32
Age-adjusted	1	2.13 (1.06–4.30)	2.39 (1.21–4.71)	2.49 (1.30–4.78)	4.17 (2.17–8.01)
Multivariable-adjusted	1	2.12 (1.04–4.30)	2.43 (1.21–4.86)	2.62 (1.35–5.09)	4.38 (2.24–8.56)
Women					
Person-years	15 438	6100	5391	5272	2812
Cardiovascular disease					
Case	25	17	28	29	38
Age-adjusted	1	1.05 (0.56–1.95)	1.48 (0.85–2.59)	1.32 (0.75–2.30)	3.00 (1.77–5.09)
Multivariable-adjusted	1	1.12 (0.59–2.13)	1.54 (0.85–2.78)	1.35 (0.75–2.43)	2.86 (1.60–5.12)
MI					
Case	7	5	10	9	14
Age-adjusted	1	1.09 (0.34–3.48)	1.71 (0.63–4.59)	1.38 (0.50–3.80)	3.56 (1.39–9.08)
Multivariable-adjusted	1	1.44 (0.42–4.90)	2.27 (0.78–6.57)	1.69 (0.56–5.10)	5.24 (1.85–14.85)
Stroke					
Case	18	12	18	20	24
Age-adjusted	1	1.05 (0.50–2.19)	1.39 (0.71–2.75)	1.29 (0.66–2.52)	2.83 (1.49–5.39)
Multivariable-adjusted	1	1.05 (0.49–2.24)	1.29 (0.63–2.67)	1.21 (0.61–2.45)	2.20 (1.07–4.50)

*Optimal blood pressure was defined as systolic pressure <120 mm Hg and diastolic pressure <80 mm Hg. Normal blood pressure was defined as systolic pressure 120 to 129 mm Hg or diastolic pressure 80 to 84 mm Hg. High-normal blood pressure was defined as systolic pressure of 130 to 139 mm Hg or a diastolic pressure of 85 to 89 mm Hg. Stage 1 hypertension is a systolic pressure 140 to 159 mm Hg or a diastolic pressure 90 to 99 mm Hg. Stage 2 and 3 hypertension is a systolic pressure ≥160 mm Hg or a diastolic pressure ≥100 mm Hg. If the systolic and diastolic pressure readings for a subject were in different categories, the higher of the 2 categories was used. Multivariate analyses were adjusted for age, body mass index, hyperlipidemia, diabetes, and smoking and drinking status. Antihypertensive drug users were classified according to their blood pressure levels at baseline survey.

to 5.09) for normal and high-normal blood pressure subjects without antihypertensive medication and subjects with hypertension Stage ≥1 with or without antihypertensive medication, respectively. In women, the multivariable HR of CVD incidence was 2.13 (1.25 to 3.62) for the hypertension Stage ≥1 group with or without antihypertensive medications. The risks of MI and stroke for high-normal blood pressure and hypertension Stage ≥1 group were observed in men (HR=2.32, 95% CI: 1.02 to 5.27 and HR=3.35, 95% CI: 1.64 to 6.80 for MI; HR=2.04, 95% CI: 1.00 to 4.22 and HR=3.33, 95% CI: 1.80 to 6.15 for stroke, respectively). HRs for CVD according to prehypertensive category excluding subjects taking antihypertensive drugs (Table 3) were similar but slightly lower than that category including subjects taking antihypertensive drugs (Table 2).

Using the HRs, we estimated the positive fraction of CVD attributable to exposure for each blood pressure category at baseline by sex (Figure). For men, 8.3%, 12.2%, 16.8%, and 18.5% of CVD incidence were excessive incidence due to normal and high-normal blood pressures and hypertension Stages 1 and ≥2 with values of 1.3%, 7.1%, 5.4%, and 18.0%.

Discussion

In this cohort study of a general Japanese urban population, we determined that high-normal blood pressure was a risk factor for the incidence of stroke and MI in men in comparison to subjects with optimal blood pressure. In this study, 20.5% and 8.4% of CVD incidence may derive from prehypertension cases in men and women, respectively. This is the

Table 3. Age- and Multivariable-Adjusted HRs for CVD According to Blood Pressure Category

	Blood Pressure Category*			
Groups and Variables	Optimal	Normal	High-Normal	Stage ≥1
Men				
Person-years	9670	5662	4805	9243
Cardiovascular disease				
Case	23	28	35	123
Age-adjusted	1	1.80 (1.03–3.13)	2.09 (1.23–3.55)	3.00 (1.91–4.72)
Multivariable-adjusted	1	1.83 (1.05–3.20)	2.11 (1.22–3.64)	3.20 (2.01–5.09)
MI				
Case	10	11	16	51
Age-adjusted	1	1.71 (0.72–4.03)	2.27 (1.02–5.03)	2.98 (1.49–5.93)
Multivariable-adjusted	1	1.78 (0.75–4.22)	2.32 (1.02–5.27)	3.35 (1.64–6.80)
Stroke				
Case	13	17	19	72
Age-adjusted	1	1.93 (0.93–3.98)	2.01 (1.00–4.08)	3.18 (1.75–5.79)
Multivariable-adjusted	1	1.92 (0.92–3.97)	2.04 (1.00–4.22)	3.33 (1.80–6.15)
Women				
Person-years	15 293	5890	4834	9002
Cardiovascular disease				
Case	24	12	20	81
Age-adjusted	1	0.80 (0.39–1.61)	1.28 (0.69–2.36)	2.12 (1.30–3.44)
Multivariable-adjusted	1	0.86 (0.42–1.72)	1.32 (0.69–2.53)	2.13 (1.25–3.62)
MI				
Case	7	4	7	27
Age-adjusted	1	0.91 (0.26–3.14)	1.38 (0.47–4.01)	2.23 (0.94–5.28)
Multivariable-adjusted	1	1.17 (0.31–4.34)	1.83 (0.58–5.75)	2.97 (1.11–7.91)
Stroke				
Case	17	8	13	54
Age-adjusted	1	0.76 (0.32–1.79)	1.22 (0.58–2.58)	2.12 (1.17–3.83)
Multivariable-adjusted	1	0.77 (0.32–1.83)	1.11 (0.50–2.49)	1.89 (1.00–3.58)

*Optimal blood pressure was defined as systolic pressure <120 mm Hg and diastolic pressure <80 mm Hg. Normal blood pressure was defined as systolic pressure 120 to 129 mm Hg or diastolic pressure 80 to 84 mm Hg. High-normal blood pressure was defined as systolic pressure of 130 to 139 mm Hg or a diastolic pressure of 85 to 89 mm Hg. Stage 1 hypertension is a systolic pressure 140 to 159 mm Hg or a diastolic pressure 90 to 99 mm Hg. Stage 2 and 3 hypertension is a systolic pressure ≥160 mm Hg or a diastolic pressure ≥100 mm Hg. If the systolic and diastolic pressure readings for a subject were in different categories, the higher of the 2 categories was used. Multivariate analyses were adjusted for age, body mass index, hyperlipidemia, diabetes, and smoking and drinking status. Antihypertensive drug users were classified into the hypertension Stage ≥1 group.

first cohort study to examine the impact of high-normal blood pressure on the risks of stroke and MI incidence in a general Japanese urban population, who have a relatively higher incidence of stroke and lower incidence of MI than those seen in Western countries.[7]

Compared with the previous studies, this study has several methodological strengths. First, we evaluated a large prospective cohort of people selected randomly from a general population in Japan, which allowed us to perform subanalyses by age and CVD subtype. Second, our cohort population was selected from an urban population in contrast to the majority of other cohorts in Japan, which have been selected from rural populations. Because approximately 66% of the Japanese population lives in urban areas, this is an important strength of our analysis. The health status of each participant was examined every 2 years during a clinical visit at the National Cardiovascular Center. In addition, a health questionnaire was administered to each participant yearly by mail or telephone. In combination with frequent evaluation of the CVD registry, we could effectively examine the incidence of CVD events in this population. Finally, we examined the risk of CVD incidence, which is a more direct measure of CVD risk than risk of CVD mortality, because mortality from CVD is significantly influenced by treatment.

This study revealed that normal and high-normal blood pressures were risk factors for CVD in Japanese urban men. The results of a multiple ethnic groups investigation has demonstrated that high-normal blood pressure is a risk factor for incidence of coronary heart disease in both men and women.[11] Compared with optimal blood pressure, the relative risk of CVD was 2.33 (1.85 to 2.92) for high-normal blood pressure and was 1.81 (1.47 to 2.22) for normal blood pressure among blacks.[19] An inverse association of optimal blood pressure and a positive association of Stage 1 hyper-

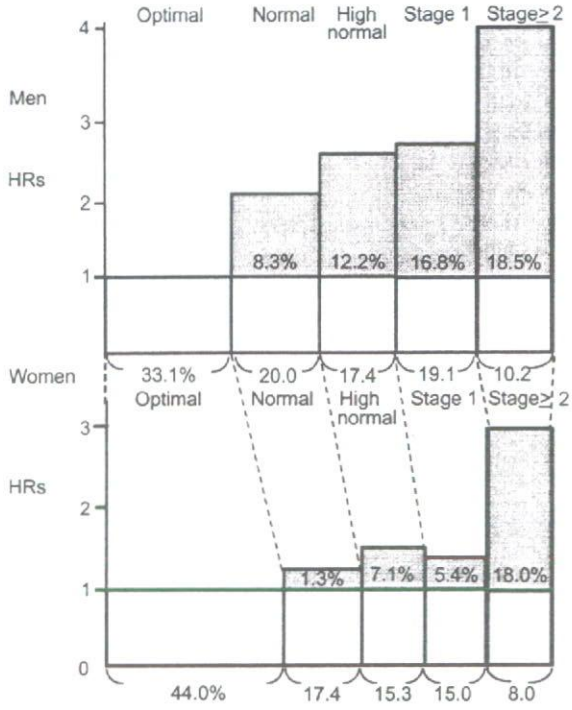


Figure. The HRs and positive fraction attributable to exposure to each blood pressure category (optimal, normal, and high-normal blood pressures and hypertension Stages 1 and ≥2) at baseline for CVD were estimated by sex. The gray area displays excessive incidence of CVD due to normal and high-normal blood pressures and hypertension Stages 1 and ≥2.

tension with coronary heart disease were observed in men compared with normal blood pressure.[12] The Framingham Heart Study revealed that 17.6% and 37.3% of subjects with baseline normal and high-normal blood pressure, respectively, were diagnosed with hypertension within 4 years. High-normal blood pressure has also been associated with increased risk of carotid atherosclerosis,[20] altered cardiac morphological features,[21] and diastolic ventricular dysfunction,[22] all of which may be precursors of incidence of CVD.

Some prospective studies have looked at mortality from CVD in Japanese populations. Murakami et al demonstrated a relationship between prehypertension and overall mortality by performing a meta-analysis of data from 13 population-based cohort studies conducted in Japan.[5] Sairenchi et al revealed that high-normal blood pressure was associated with an increased risk of CVD mortality in Japanese men.[23] The NIPPON DATA 80 also indicated that high blood pressure was a risk factor for mortality from all causes as well as death from CVD among Japanese.[24] All of these studies used end points of mortality. The risk of CVD incidence, like used in this study, is a more direct measure of CVD risk than is the risk of CVD mortality, which is heavily influenced by treatment.

In prospective studies examining the incidence of CVD in Japanese populations, the Ohasama study demonstrated that high-normal blood pressure was a risk factor for stroke by using homed blood pressure, but not by using causal blood pressure.[13] The Hisayama study, which observed the natural course of untreated hypertension in a general Japanese elderly population over a 32-year period, indicated that high-normal blood pressure was not a risk factor for cerebral infarction.[4] This cohort was approximately half the size of our cohort, and the subjects were older and observed for longer periods of time. Hypertensive risk for CVD decreased with advancing age.[25] Over very long periods, confounding factors, including advancing aging, menopause, lifestyle modifications, and medication, will affect blood pressure classification. The Tanno-Sobetu study determined that high-normal blood pressure, determined according to the 1999 World Health Organization/International Society of Hypertension criteria, was not a risk factor for CVD in comparison to optimal and normal blood pressures.[26]

In this study, we did not find an association between high-normal blood pressure and CVD incidence in women. The association between blood pressure category and coronary heart disease is well documented to be weaker in women than in men.[12] For each racial/ethnic group, the mean SBP and DBP values in men were 6 to 7 and 3 to 5 mm Hg higher, respectively, than the values in women.[27] Postmenopausal effects have been associated with elevated blood pressure.[28] Therefore, the period of hypertension exposure tends to be shorter in women than in men. The incidence of CVD was lower in women (3.9 per 1000 person-year) than in men (7.1 per 1000 person-years) in this study. The percentages of those with hypertension who were aware, treated, and controlled were higher for women than men.[27]Because the frequency of white coat hypertension is higher in women than in men,[29,30] blood pressure at baseline examination may be overestimated in women, which may result in the absence of an association between high-normal blood pressure and CVD incidence in women.

The multivariable HR of CVD incidence for normal blood pressure was 2-fold higher than that for optimal blood pressure. In the Honolulu heart program and the Puerto Rico heart health program, the multivariable HRs of CVD incidence for normal blood pressure were approximately 2-fold higher than those for optimal blood pressure.[12] Thus, lower blood pressure appears to prevent the incidence of CVD.

The crude 10-year cumulative incidences of CVD in this subjects who had optimal, normal, and high-normal blood pressure were approximately 2%, 6%, and 8% for men and 2%, 3%, and 5% for women, respectively (data not shown). In the Framingham Heart Study, those were 5%, 8%, and 10% for men and 1%, 3%, and 6% for women, respectively.[12] Compared with the Framingham Heart Study, the incidences of CVD for optimal blood pressure in the Suita study tend to be lower in men and similar in women.

Our study has several limitations. The primary limitation is a dilution bias[31]; this study was based on a single-day measurement of blood pressure, which may lead to a misclassification of blood pressure levels. Previous epidemiological evidence has suggested, however, that blood pressure measurements taken on a single day are accurate.[32] Second, approximately 10% of subjects who underwent baseline survey did not respond to our questionnaires thereafter. However, we found no clinical background difference be-

tween participants and nonparticipants, because the main denial reason for participation in this study was not a health problem. Age- and sex-adjusted systolic blood pressures were 127 mm Hg for participants and 128 mm Hg for nonparticipants ($P=0.08$). To achieve a minimum of failure study subjects, we performed close follow-up with health questionnaires annually and health checkups every 2 years.

In conclusion, high-normal blood pressure is a risk factor for MI and stroke in general Japanese urban men. Approximately 20% and 8% of CVD incidences can be attributed to normal and high-normal blood pressure in both men and women, respectively. To prevent the incidence of CVD, it is necessary for subjects with high-normal blood pressure to attempt to control these values through lifestyle modifications.

Perspectives

Although it is well accepted that hypertension is a strong risk factor for total mortality and CVD all over the world, only a few studies have addressed the absolute and relative risks of CVD for the population with blood pressure values in the high-normal range. In this study, the impact of high-normal blood pressure on the incidence of CVD was examined in a general urban population cohort in Japan. Blood pressure categories were defined on the basis of the ESH-ESC 2007 criteria. In 64 391 person-years of follow-up, 346 CVD events were identified. Compared with the optimal blood pressure group, the multivariable HR of CVD for high-normal blood pressure was 2.5 times in men but was not statistically significant in women. This might be due to a postmenopausal effect, higher frequency of controlled or medication for hypertension, and white coat hypertension in women compared with those in men, but it should be researched further whether these reasons can be applied in women. The risks of MI and stroke for each blood pressure category were similar to those of CVD. Approximately 20% and 8% of CVD incidences can be attributed to prehypertension in men and women, respectively. It is a remarkable finding that one fifth of CVD incidence is derived from prehypertension in men. Our results suggest that it is necessary for subjects with high-normal blood pressure to attempt to control blood pressure through lifestyle modifications to prevent the incidence of CVD.

Acknowledgments

We thank Dr Yasushi Kotani, the president of the Suita Medical Association, and Dr Hitonobu Tomoike, the director of the General of the Hospital, National Cardiovascular Center, for their support of the Suita study. We also thank the members of Suita City Health Center and the Suita Medical Association. We thank all of the researchers and staff of the Department of Preventive Cardiology for performing medical examinations and follow-up. We also thank Satsuki-Junyukai, the volunteers involved in the administration of the Suita Study.

Sources of Funding

This study was supported by grants-in-aid from the Ministry of Health, Labor, and Welfare of Japan (H20-SeiShu-013 and H19-SeiShu-017) and by a Research Grant for Cardiovascular Disease from the Ministry of Health, Labor, and Welfare (19K-8 and 18S-2).

Disclosures

None.

References

1. Kannel WB. Blood pressure as a cardiovascular risk factor: prevention and treatment. *JAMA*. 1996;275:1571–1576.
2. Blood pressure, cholesterol, and stroke in eastern Asia. Eastern Stroke and Coronary Heart Disease Collaborative Research Group. *Lancet*. 1998;352:1801–1807.
3. Stamler J, Stamler R, Neaton JD. Blood pressure, systolic and diastolic, and cardiovascular risks. US population data. *Arch Intern Med*. 1993; 153:598–615.
4. Arima H, Tanizaki Y, Kiyohara Y, Tsuchihashi T, Kato I, Kubo M, Tanaka K, Ohkubo K, Nakamura H, Abe I, Fujishima M, Iida M. Validity of the JNC VI recommendations for the management of hypertension in a general population of Japanese elderly: the Hisayama study. *Arch Intern Med*. 2003;163:361–366.
5. Murakami Y, Hozawa A, Okamura T, Ueshima H. Relation of blood pressure and all-cause mortality in 180,000 Japanese participants: pooled analysis of 13 cohort studies. *Hypertension*. 2008;51:1483–1491.
6. van den Hoogen PC, Feskens EJ, Nagelkerke NJ, Menotti A, Nissinen A, Kromhout D. The relation between blood pressure and mortality due to coronary heart disease among men in different parts of the world. Seven Countries Study Research Group. *N Engl J Med*. 2000;342:1–8.
7. Tanaka H, Yokoyama T, Yoshiike N, Kokubo Y. Cerevrovascular disease. In: Detels R, McEwen J, Beaglehole R, Tanaka H, eds. *Oxford Textbook of Public Health: The Scope of Public Health*, IV ed. Oxford: Oxford University Press; 2002:1193–1254.
8. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension*. 2003;42: 1206–1252.
9. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, Grassi G, Heagerty AM, Kjeldsen SE, Laurent S, Narkiewicz K, Ruilope L, Rynkiewicz A, Schmieder RE, Boudier HA, Zanchetti A, Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL, Erdine S, Kiowski W, Agabiti-Rosei E, Ambrosioni E, Lindholm LH, Viigimaa M, Adamopoulos S, Bertomeu V, Clement D, Farsang C, Gaita D, Lip G, Mallion JM, Manolis AJ, Nilsson PM, O'Brien E, Ponikowski P, Redon J, Ruschitzka F, Tamargo J, van Zwieten P, Waeber B, Williams B. 2007 Guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens*. 2007;25:1105–1187.
10. Japanese Society of Hypertension guidelines for the management of hypertension (JSH 2004). *Hypertens Res*. 2006;29(suppl):S1–S105.
11. Vasan RS, Larson MG, Leip EP, Evans JC, O'Donnell CJ, Kannel WB, Levy D. Impact of high-normal blood pressure on the risk of cardiovascular disease. *N Engl J Med*. 2001;345:1291–1297.
12. D'Agostino RB Sr, Grundy S, Sullivan LM, Wilson P. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. *JAMA*. 2001;286:180–187.
13. Asayama K, Ohkubo T, Kikuya M, Metoki H, Hoshi H, Hashimoto J, Totsune K, Satoh H, Imai Y. Prediction of stroke by self-measurement of blood pressure at home versus casual screening blood pressure measurement in relation to the Joint National Committee 7 classification: the Ohasama study. *Stroke*. 2004;35:2356–2361.
14. Inamoto N, Katsuya T, Kokubo Y, Mannami T, Asai T, Baba S, Ogata J, Tomoike H, Ogihara T. Association of methylenetetrahydrofolate reductase gene polymorphism with carotid atherosclerosis depending on smoking status in a Japanese general population. *Stroke*. 2003;34: 1628–1633.
15. Iwai N, Kajimoto K, Kokubo Y, Tomoike H. Extensive genetic analysis of 10 candidate genes for hypertension in Japanese. *Hypertension*. 2006; 48:901–907.
16. Walker AE, Robins M, Weinfeld FD. The National Survey of Stroke. Clinical findings. *Stroke*. 1981;12(suppl 1):I13–I44.
17. Tunstall-Pedoe H, Kuulasmaa K, Amouyel P, Arveiler D, Rajakangas AM, Pajak A. Myocardial infarction and coronary deaths in the World Health Organization MONICA Project. Registration procedures, event