Discussion

During late fetal development through shortly after birth, there is a vulnerable period when death occurs at a rate of 6 to 12 per 1000 live births per year,[20] and congenital arrhythmia susceptibility may be a significant contributor to this problem.[21,22] Life-threatening cardiac arrhythmias during infancy and the perinatal period may go unnoticed owing to the lack of routine use of electrocardiographic monitoring of the fetus and newborn. Studies of 2 large series of autopsied SIDS victims demonstrated that up to 10% of SIDS cases may represent genetic disorders of congenital arrhythmia susceptibility such as the LQTS,[3,23] short-QT syndrome,[24,25] and catecholaminergic polymorphic ventricular tachycardia.[26] Understanding the genetic risks for perinatal mortality should promote efforts to identify and treat at-risk newborns.

Malignant Perinatal Variant of LQTS

The profoundly dysfunctional *SCN5A* mutation, G1631D, produced a clinical entity distinct from typical LQTS (LQT3 subtype). Clinically, subjects with typical LQTS first develop symptoms (syncope, cardiac arrest, and sudden death) during late childhood, adolescence, or early adulthood.[9,27] Many mutation carriers may in fact be asymptomatic. The 2 probands we described seem to be affected by a very severe and life-threatening process.

At the molecular level, most *SCN5A* mutations associated with LQTS cause a subtle gain-of-function defect characterized by increased persistent current.[16,17] The markedly abnormal channel function we observed for G1631D including a 10-fold slowing of inactivation, substantial shifts in voltage dependence of activation and inactivation along with greatly impaired recovery from inactivation represent distinct molecular defects that distinguish this mutation from typical LQT3 alleles. Other *SCN5A* alleles may similarly predispose to early onset and severe perinatal arrhythmia syndromes,[4,5,28,29] but the functional aberrations associated with most of these reported alleles resemble mutations found in older individuals.

Negative Selection Against *SCN5A* Mutations

Mutations in *SCN5A* are represented disproportionately among SIDS victims who carry occult congenital arrhythmia susceptibility gene mutations when compared with older LQTS subjects. The lower proportion of *SCN5A* mutations among older children and young adults with LQTS when compared with the higher proportion in SIDS victims may be the result of negative selection against mutations in the sodium channel gene. Negative selection would cause an ascertainment bias for genotypes in living individuals in whom survival is favored when carrying mutations having less severe physiological consequences. In the case of SCN5A-G1631D, we assumed that without immediate treatment, this mutation would have been lethal. However, survival after successful treatment confounds the argument for negative selection.

Congenital arrhythmia susceptibility occurring in the perinatal and neonatal periods caused by *SCN5A* mutations appears biologically distinct from LQTS in older subjects. Carriers of certain *SCN5A* mutations may present with earlier onset and severe congenital arrhythmia syndromes. An illustration of this idea is recurrent third-trimester fetal loss attributable to inheritance of an *SCN5A* mutation (R1623Q) from a mother who was mosaic for this deleterious allele.[8] The R1623Q mutation, which affects a conserved residue in the D4/S4 segment nearby the location of G1631D, was originally identified in a Japanese child with a severe clinical presentation of LQTS,[30] and the molecular defect associated with this allele compromised inactivation to a greater extent than typical LQT3 mutations.[31] Our observations regarding the severity of biophysical defects associated with G1631D also support the idea that earlier onset cardiac symptoms may sometimes correlate with a severe molecular phenotype.

Genotype-Specific Pharmacological Treatment

The clinical consequences of G1631D were perinatal arrhythmias successfully managed in part by pharmacotherapy with the combination of mexiletine and propranolol. Mexiletine as well as other sodium channel blockers have been proposed as gene-specific therapeutic agents in LQT3.[32–34] In vitro studies have demonstrated the capability of these drugs to selectively suppress increased persistent current conducted by mutant channels[29,35] and to normalize ventricular repolarization in animal models.[36,37] One study suggested that certain biophysical properties of mutant $Na_V1.5$ channels may be predictive of mexiletine responsiveness. Specifically, Ruan et al[38] found that among 4 distinct *SCN5A* mutations, clinical benefit from mexiletine treatment was observed only in subjects carrying mutations that caused a hyperpolarizing shift in steady-state inactivation and this correlated with in vitro effects of the drug. However, this observation cannot be extrapolated to all *SCN5A* mutations as evidenced by the favorable response of G1631D to mexiletine both clinically and experimentally despite a depolarizing shift in steady-state inactivation (Figure 3). Similarly, another recently reported *SCN5A* mutation (F1473C) was also associated with a favorable clinical response to high-dose mexiletine despite having depolarized steady-state inactivation.[29] Additional factors besides those emphasized by Ruan et al[38] are likely to determine the clinical efficacy of mexiletine.

By contrast, use of β-blockers in the setting of *SCN5A* mutations has less certain benefits. Three studies have reported that β-blockers are generally less efficacious in LQT3 subjects, but the specific drug used varies considerably.[9,39,40] For example, in the report by Priori et al[40] the specific β-blocker was known in 69% of cases, and this was either propranolol or nadolol. As we have demonstrated in this study, propranolol may offer specific advantages in treating certain *SCN5A* mutations because of apparent local anesthetic-like properties of the drug.[18,19] By contrast, we recently determined that nadolol has no activity against sodium channels (Wang DW, unpublished observations, 2007). The role of propranolol in treating individuals with *SCN5A* mutations warrants further study.

Combination pharmacotherapy in the 2 probands with G1631D may have uniquely contributed to their survival. In the Japanese newborn, mexiletine alone was not adequate to control ventricular arrhythmia despite shortening of the QT interval. The addition of propranolol to the treatment regimen conferred better arrhythmia control and survival. In the Italian

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proband, the coadministration of mexiletine with propranolol was efficacious, but this subject was also treated with ventricular pacing. Our study demonstrated additive effects of the 2 drugs at a pulsing frequency of 2 Hz (Figure 8). This observation suggested that a combination of mexiletine with propranolol in the setting of modest tachycardia were protective of ventricular arrhythmia caused by G1631D. We explain this effect by a combination of the intrinsic activity-dependent loss of channel availability observed for G1631D (Figure 4B) with the use-dependent drug effects.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Mutations in *SCN5A* encoding the cardiac voltage-gated sodium channel have been associated with a spectrum of increased sudden death risk extending from fetal life to adulthood. We studied the functional and pharmacological properties of a novel de novo *SCN5A* mutation associated with an extremely severe perinatal presentation of congenital long-QT syndrome, characterized by late third trimester intrauterine fetal heart rhythm disturbances and life-threatening ventricular arrhythmia occurring within hours of emergency cesarean birth. The same mutation (G1631D), which was discovered in two subjects of different ethnic backgrounds with the same clinical presentation, caused a profound degree of sodium channel dysfunction that was more severe than that observed for any previous *SCN5A* variant. Despite the extreme nature of the mutation and the associated dire clinical scenario, the subjects survived owing to prompt therapeutic interventions, including treatment with the combination of mexiletine and propranolol, two drugs that exhibited enhanced and additive activity against the mutant allele. These observations illustrate the role of severe sodium channel mutations in a malignant perinatal variant of long-QT syndrome and successful use of combination pharmacotherapy to prevent perinatal mortality in this setting. Our data also illustrate the potential therapeutic benefits of a propranolol block of mutant sodium channels.

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Editorial Comment

The Relationship between White Blood Cell Count and Risk of Hypertension in Populations with High Prevalence of Smoking

Tomonori OKAMURA[1] and Makoto WATANABE[1]

(*Hypertens Res* 2008; 31: 1279–1281)

Key Words: white blood cell, inflammation, smoking, cohort studies, neutrophils

Recently, markers of chronic inflammation have been recognized as risk factors of cardiovascular disease. Although various inflammatory factors, such as C-reactive protein (CRP), albumin, and fibrinogen, have been examined in many epidemiologic studies, WBC count is a widely used examination to detect inflammation in a routine blood test. Previous population-based cohort studies indicated that WBC count was associated with the risk of coronary heart disease (*1–3*) and stroke (*2–4*). Furthermore, several studies have also demonstrated a positive relationship between WBC count and hypertension (*5–7*). For example, in a 10-year NHANES I epidemiologic follow-up study, Gillum *et al.* showed a statistically significant 50% increase in risk of hypertension in white men aged 25–74 years with WBC count >8,600 compared to men with WBC count <6,200 cells/mm^3 (*6*).

However, these findings could not be globally generalized since most of previous studies were reported from Western populations. Smoking is a major risk factor for cardiovascular disease and also raises WBC count (*8*). Accordingly, the relationship between WBC count and cardiovascular disease or hypertension should be examined in Asian populations, where male smoking prevalence is much higher than Westerner males. To our knowledge, three cohort studies in Japanese general populations reported the relationship between WBC count and cardiovascular disease or hypertension. Imano *et al.* showed that increased WBC count was associated with incidence of myocardial infarction in middle-aged Japanese workers, both in smokers and non-smokers (*9*). In NIPPON DATA90 (the National Integrated Project for Prospective Observation of Non-communicable Disease And its Trends in the Aged, 1990), Tamakoshi *et al.* also demonstrated that subjects who never smoked with WBC counts of 9,000–10,000 had a 3.2-fold risk for cardiovascular mortality compared with those having WBC counts of 4,000–4,900 (*10*). Furthermore, Nakanishi *et al.* reported that WBC count was a risk factor for hypertension, and the increased risk for hypertension associated with WBC count was more pronounced in non-smokers (*11*). In a study of Koreans whose smoking status is similar to that of the Japanese, the association of increased WBC count with cardiovascular mortality was more evident among those who never smoked compared to smokers (*12*). These results suggest that the elevated WBC count is a risk factor for cardiovascular disease or hypertension independent of smoking even in East Asian populations.

Tatsukawa *et al.* have now added further evidence concerning the relationship between WBC count and hypertension incidence from a 40-year cohort of 9,383 Japanese men and women published in this issue of *Hypertension Research* (*13*). They showed that elevated WBC count predicted an increased incidence of hypertension in both men and women after adjusting for smoking status, although WBC count for men was a significant risk for hypertension only in the time-varying model. In many cohort studies, a single medical examination and questionnaire was performed as a baseline survey. However, because biological data and lifestyle status of the participants have changed during the follow-up periods, the predictive power of data from a single baseline survey was attenuated, especially with a long-term follow-up

From the [1]Department of Preventive Cardiology, National Cardiovascular Center, Suita, Japan.

Address for Reprints: Tomonori Okamura, M.D., Department of Preventive Cardiology, National Cardiovascular Center, 5–7–1 Fujishirodai, Suita 565–8565, Japan. E-mail: okamurat@hsp.ncvc.go.jp

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period. Furthermore, all data include random errors, which are also evident when data are based on a single measurement. Thus, the above-mentioned study design produces "a kind of misclassification," which underestimates the relationship between candidate risk factors and outcomes. Usually, underestimation is not a problem because overestimation should be avoided in scientific research. There are some methods to remove these "misclassifications." Adjustment for regression dilution bias is used for decreasing random errors (*14*). However, time-varying Cox regression or pooled logistic regression (*15*) is used for accounting for the long-term change of risk factors. The relationship between WBC count and hypertension for men was only detected by a time-varying Cox model in this study. A single measurement of WBC count for men may not reflect lifetime WBC count due to dramatic changes in the prevalence of smoking over 40 years. We should pay attention to this underestimate when dealing with a long-term cohort study with a single baseline survey.

Tatsukawa *et al.* also suggested that the neutrophils for women were contributing to the increased risk of hypertension in differential WBC counts (*13*). Although there are pathological findings that monocytes, the precursor of macrophages, are present during the progression of atherosclerosis, neutrophils may be a marker of systemic inflammation and a risk factor for cardiovascular disease and hypertension among those who had advanced atherosclerosis. Horne *et al.* showed that the neutrophil count was more strongly associated with the risk for myocardial infarction compared with monocyte count among patients undergoing coronary angiography (*16*). Activated neutrophils tend to adhere on vascular endothelium, which are increasing vascular resistance (*17*). Furthermore, neutrophils release reactive oxygen species, which may impair endothelium-dependent vasorelaxation (*18*).

What are the underlying mechanisms for an association between WBC count and cardiovascular disease? First, as already discussed, WBC count is a marker for inflammation in the process of atherosclerosis. Second, WBCs may stimulate platelets and promote thrombosis (*19*). Finally, WBCs migrate into the vessel wall and cause the release of chemical products from proliferating endothelial cells and from WBCs, such as neutrophils, which may cause hypertension. However, to clarify the effect of *in vivo* inflammatory status on hypertension and cardiovascular disease, further cohort studies are warranted in large populations using measurements of other inflammatory markers, such as CRP, albumin (*20*) and pro-inflammatory cytokines.

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心血管イベントにおける危険因子とは？ —NIPPON DATA80 より—

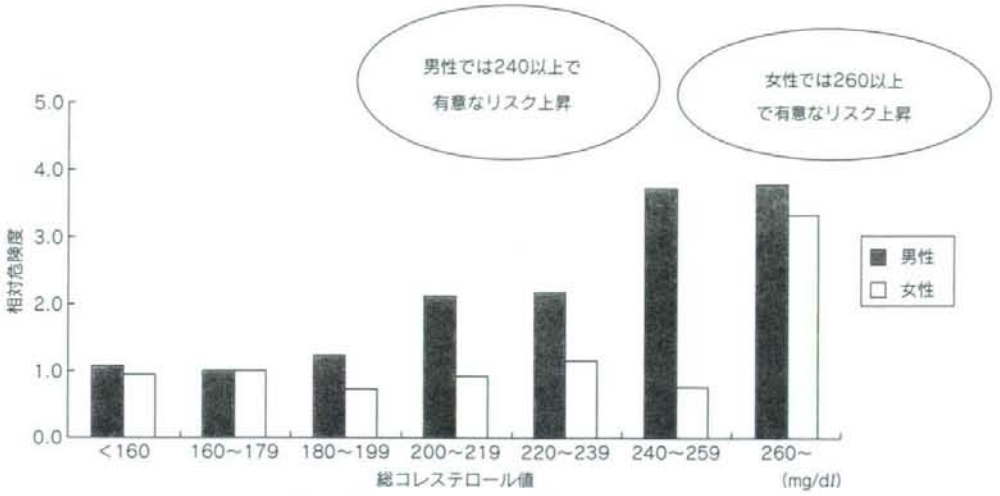
岡村 智教[*1]　東山　綾[*2]
Okamura Tomonori, Higashiyama Aya
[*1]国立循環器病センター予防検診部
[*2]滋賀医科大学社会医学講座福祉保健医学

NIPPON DATA80 は厚生省循環器疾患基礎調査の追跡研究である．対象者は 1980 年に無作為に抽出された全国 300 地区の住民 10,567 名である．本研究は報告書が公表された当時から「健康日本 21」の基礎資料として活用されるなど社会的に大きな役割を果たしており，近年ほぼ月に 1 本のペースで論文公表されつつある．最新の研究成果として①総コレステロールと総死亡，②血清アルブミンと要介護状態，③年代別の高血圧と循環器疾患，④高血圧既往歴と循環器疾患，⑤随時血糖測定の意義，⑥喫煙と総コレステロールの循環器疾患死亡に対する交互作用，などの関連が示されている．NIPPON DATA80 は①地域的な偏りがなく，②総人口ベースでの高い参加率（77%）と 19 年間の追跡で 90%以上の追跡率を有し，③すべての対象者が血圧やコレステロールなどの検査所見を実測値でもっているという点に特徴がある．

KEY WORDS
循環器疾患基礎調査　コホート研究　総コレステロール　アルブミン　血圧　高血圧既往歴　随時血糖　喫煙　保健所

はじめに

NIPPON DATA80（National Integrated Project for Prospective Observation of Non-communicable Diseases and Its Trends in the Aged, 1980）は 1980 年に実施された第 3 次循環器疾患基礎調査の追跡研究であり，1994 年に厚生省（当時）の補助を受けて日本循環器管理研究協議会の「国民の代表集団による高齢者の日常生活動作（Activities of Daily Living：ADL），生活の質低下の予防に関するコホート研究」として開始された．循環器疾患基礎調査は 10 年ごとに厚生労働省が全国の保健所を通じて実施している．この調査の目的は循環器疾患の実態を把握し，その予防と治療に役立てる基礎資料をつくることにあり，わが国における循環器疾患危険因子の有病率を示す代表的な調査である．対象者は全国から無作為に抽出されており，特定の地域に偏らない国民の代表集団と考えられる．当初，1980 年から 1994 年までの 14 年間の追跡調査が実施され（平成 6 年度老人保健事業推進費等



図❶ 総コレステロール値と冠動脈性心疾患死亡
(Okamura T *et al*, 2007[1]より引用)

補助金：主任研究者；滋賀医科大学福祉保健医学 上島弘嗣教授)，5年後の1999年には19年目の調査が，2004年には24年目の調査が同じ主任研究者のもとでおこなわれた．現在論文公表されているのは14年または19年の追跡調査結果である．

NIPPON DATA80とは？

第3次循環器疾患基礎調査（1980年）は全国から無作為抽出された300地区の満30歳以上の全住民13,771名を対象としており，10,567名が調査を受診した(response rateは77%)．追跡調査は基礎調査の実施を担当した各地区の保健所の協力を得ておこなわれている．また在籍状況については住民基本台帳法にもとづいて，対象者の居住市町村に住民票の請求をおこない確認している．死亡例は除票から死亡年月日と死亡地を同定し，これらをキーコードとして総務庁（当時）の許可を得て人口動態テープと照合して国際疾病分類（ICD）にもとづいた死因を入手している．生死に関する追跡率は90%を超えている．

本研究は厚生科学研究の報告書として公表された時点から，厚生労働省の「健康日本21」の基礎資料として活用されるなど社会的に大きな役割を果たしてきたが，ここ数年でpeer-review journalへの論文公表が活発におこなわれ，純粋な疫学研究としての意義も高い．本稿では最新の研究成果から心血管イベントの危険因子について概説する．

最新の研究成果から

1）日本人で総コレステロールは総死亡と関連するか？[1]

欧米の研究では総コレステロールが高いほうが総死亡率は高いが，日本人集団で総コレステロールと総死亡の関連を検討した報告は少ない．NIPPON DATA80の19年追跡において総コレステロールと総死亡の関連を検討した．比例ハザードモデルでほかの循環器疾患の危険因子を調整すると男性では総コレステロール240 mg/dl以上，女性では260 mg/dl以上で虚血性心疾患死亡率の上昇を認めた（**図❶**）．逆に160 mg/dl未満の集団では男女とも肝臓疾患（肝炎，肝硬変，肝臓がん）死亡率の上昇を認めた．総コレステロールと総死亡の関連は160 mg/

dl 未満と 260 mg/dl 以上の両端で有意に高い U 字型の関連を示した．しかしながら肝臓疾患と 5 年以内の早期死亡者を除外すると，160 mg/dl 未満のリスク上昇は消失した．C 型肝炎ウイルスキャリアからの発がん率を観察した既存の研究などから考察すると，低総コレステロール血症は総コレステロールを測定した時点の肝臓疾患の重症度を反映しており，低総コレステロールが肝臓疾患を引き起こしたわけではないと考えられた．結論として，わが国でも欧米同様に「高コレステロール血症」が集団全体の健康リスクである．この論文の総コレステロールと虚血性心疾患の関連は日本動脈硬化学会の「動脈硬化性疾患予防ガイドライン 2007 年版」の主要な根拠論文として引用されている．

2）血清アルブミンの低値は要介護状態と関連する[2]

わが国で血清アルブミンと ADL の関連を長期的に検討したコホート研究はほとんどない．また総コレステロールはアルブミンとともに栄養状態の指標であるが，両者の交互作用を含めて高齢者の ADL との関連を検討した報告はない．NIPPON DATA80 において，1980 年に 60～74 歳だった 1,844 名を追跡して 12 年後の ADL との関連をみた．男女とも血清アルブミンが低くなるほど死亡＋ADL 低下のオッズ比が高くなる傾向を示し，4.5 g/dl 以上を基準とした場合，女性の 4.0 g/dl 以下のオッズ比は 3.06（95%信頼区間：1.89～4.95）であった．総コレステロールが中央値未満では，女性の 4.0 g/dl 群の死亡＋ADL 低下のオッズ比は 4.50(：2.25～9.02) に上昇した．総コレステロールが中央値以上の群ではこのような関連を認めなかった．この傾向は男性でも同様であった．総コレステロールが低めの群における血清アルブミンの低値は，日本人高齢者の健康寿命短縮の危険因子である．この結果は低アルブミンかつ高コレステロールで死亡率が高いという 60 歳未満の死亡に関する報告[3]とは逆であり，アルブミンとコレステロールの交互作用が年齢層によって異なることも示唆している．

3）高齢者でも収縮期血圧の高値は循環器疾患の危険因子である[4]

高齢者の高血圧は動脈硬化により収縮期血圧とともに拡張期血圧も上昇することが特徴であり，収縮期・拡張期血圧の循環器疾患死亡に対する影響がほかの年代とは異なる可能性がある．NIPPON DATA80 の降圧薬を服用していない男性を収縮期・拡張期血圧値でそれぞれ 5 群に分け，循環器疾患死亡に対するハザード比（年齢調整あり）を 3 つの年代別（30～64 歳，65～74 歳，75 歳以上）に求めた．30～64 歳，65～74 歳では収縮期・拡張期血圧がともに，高くなるほど循環器疾患死亡のハザード比が上昇した．75 歳以上では収縮期血圧のみ循環器疾患死亡と有意な関連がみられ，拡張期血圧とは関連を認めなかった（**表❶**）．

4）自己申告の高血圧既往歴は循環器疾患死亡を予測する[5]

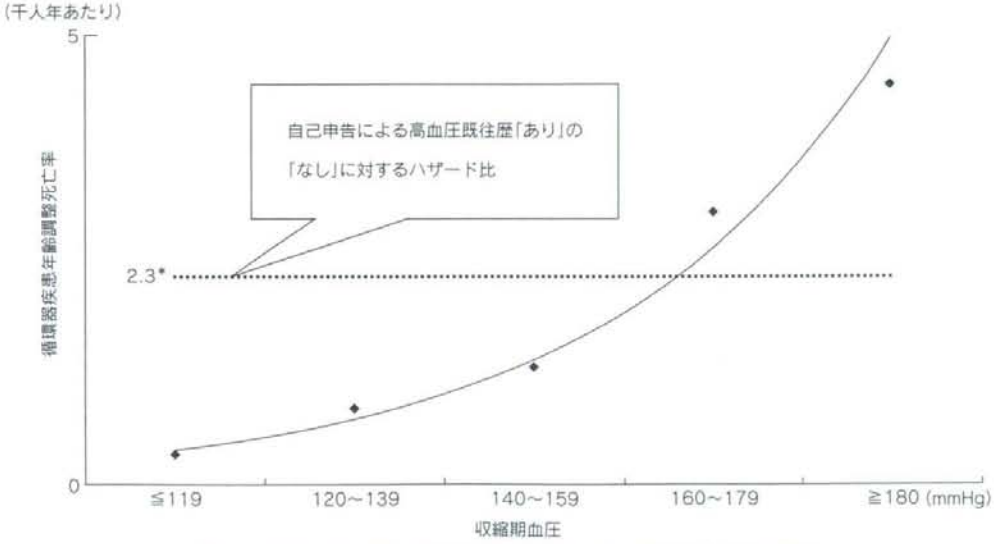
栄養疫学研究では自己申告にもとづく高血圧既往歴を危険因子や調整因子として用いている場合がよくある．そこで NIPPON DATA80 の 30～59 歳の男女 6,427 名を対象として，実測された高血圧に対する高血圧既往歴の感度と特異度，その循環器疾患死亡との関連を検討した．実測にもとづく高血圧（1980 年当時の診断基準；収縮期血圧160 mmHg以上かつ/もしくは拡張期血圧 95 mmHg 以上）に対する高血圧既往歴の感度は 52～65%，特異度は 95%であり，高血圧既往歴は実測高血圧の約半数を拾いあげることができた．高血圧既往歴の循環器疾患死亡に対するハザード比は有意に高かった（**図❷**）．対象者を既往歴と実測値の組み合わせで 4 群に分け，既往なしかつ実測値正常群を対照群とすると，他の 3 群の循環器疾患死亡のハザード比は 2～3 とそれぞれ有意に高かった．既往歴の有無によらず実測で高血圧と判定された人は循環器疾患死亡の危険性が高く，また 1 回の実測値が正常でも既往歴を有する場合は循環器疾患死亡の危険が高いことが示された．

表❶ 年齢別の収縮期血圧・拡張期血圧と循環器疾患死亡の関連

	血圧カテゴリー									
	I		II		III		IV		V	p 値
		HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI	
収縮期血圧										
30～64 歳	1.00	2.91	(0.71～11.92)	3.89	(0.92～16.51)	10.30	(2.78～38.11)	18.18	(4.22～78.29)	<0.001
65～74 歳	1.00	4.17	(0.65～26.70)	7.62	(1.43～40.52)	4.10	(0.60～27.84)	14.77	(3.30～66.12)	<0.001
75～歳	1.00	1.83	(0.74～4.54)	1.92	(0.78～4.71)	2.46	(1.01～6.04)	2.89	(1.12～7.45)	0.038
全年代	1.00	2.36	(1.17～4.77)	3.00	(1.51～5.94)	3.46	(1.75～6.84)	5.13	(2.59～10.16)	<0.001
拡張期血圧										
30～64 歳	1.00	1.06	(0.39～2.87)	1.75	(0.60～5.11)	1.67	(0.69～4.07)	3.34	(1.49～7.47)	0.01
65～74 歳	1.00	1.70	(0.67～4.27)	2.74	(1.07～7.01)	2.61	(1.16～5.87)	3.62	(1.53～8.57)	0.003
75～歳	1.00	0.85	(0.55～1.33)	1.26	(0.77～2.05)	1.16	(0.76～1.77)	1.37	(0.77～1.16)	0.156
全年代	1.00	0.98	(0.68～1.42)	1.50	(1.00～2.23)	1.42	(1.01～2.01)	2.05	(1.37～3.08)	0.001

収縮期血圧：I＜120 mmHg；II 120～139 mmHg；III 140～159 mmHg；IV 160～179 mmHg；V 180 mmHg 以上
拡張期血圧：I＜80 mmHg；II 80～84 mmHg；III 85～89 mmHg；IV 90～99 mmHg；V 100 mmHg 以上
p 値：Cox の比例ハザードモデルを使用し線形性について検定
HR はハザード比．血圧が I 群のグループの死亡率を 1.00 としている．CI：confidence interval（信頼区間）

（Okayama A *et al*, 2006[4] より引用）



図❷ 自己申告による高血圧既往歴，収縮期血圧値と循環器疾患死亡の関連

（Higashiyama A *et al*, 2007[5] より引用）

5）随時血糖値の上昇は循環器疾患および虚血性心疾患のリスクである[6]

地域での健康診査では受診率に影響するため空腹での採血を必須としていない場合も多い．しかし随時血糖が循環器疾患死亡に対する予測能を有するかどうかあまり検討されていない．そこで NIPPON DATA80 の男女 9,444 人を，随時血糖値（casual blood glucose：CBG）200 mg/dl，140≦CBG＜200 mg/dl，94≦CBG＜140 mg/dl，CBG＜94 mg/dl の 4 群に分け，19 年間追跡した．CBG＜94 mg/dl 群を対照として各群の虚血性心疾患死亡の多変量調整ハザード比を求めた．CBG140 mg/dl 以上の群ではハザード比は約 2.5 と有意な上昇を認め，CBG が高くなるほどハザード比も上昇した．循環器疾患死亡・総死亡においても同様の傾向であり，随時血糖値でも循環器疾患死亡に対する強い予測能を有することが示された．

表❷ 総コレステロール値で層別化した喫煙と循環器疾患死亡の関連

総コレステロール値区分	非喫煙者	男性				女性			
		禁煙者		現在喫煙者		禁煙者		現在喫煙者	
		HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI
Q1（<165 mg/dl）	1.00	0.64	(0.31~1.34)	0.85	(0.49~1.49)	1.42	(0.33~6.02)	3.11	(1.37~7.04)
Q2（165~185 mg/dl）	1.00	1.32	(0.56~3.11)	1.72	(0.88~3.37)	0.44	(0.06~3.47)	0.52	(0.17~1.60)
Q3（186~208 mg/dl）	1.00	1.53	(0.72~3.23)	1.81	(0.98~3.33)	1.52	(0.51~4.56)	1.03	(0.48~2.22)
Q4（≥209 mg/dl）	1.00	1.52	(0.69~3,35)	2.36	(1.14~4.87)	1.16	(0.38~3.50)	2.67	(1.55~4.58)

HR：ハザード比，CI：confidence interval（信頼区間）

（Hozawa A *et al*, 2007[7]より引用）

6）総コレステロールレベルで喫煙と循環器疾患の関連は異なる[7]

日本人男性の喫煙率は非常に高いにもかかわらず，従来の疫学研究では喫煙と循環器疾患の関連はあまり強くなかった．日本人の血清コレステロールの平均値は欧米にくらべて低かったため，何らかの交互作用が喫煙とコレステロールのあいだに存在する可能性がある．そこで血清総コレステロールのレベルにより，喫煙と循環器死亡の関連に違いがあるかどうかを検討した．NIPPON DATA80で欠損値などのない男女8,912人を19年追跡した．総コレステロール値の4分位（Q1；165 mg/dl未満，Q2；165～185 mg/dl，Q3；186～208 mg/dl，Q4；209 mg/dl以上）ごとに，非喫煙者を対照として喫煙の循環器疾患死亡に対する多変量調整ハザード比を求めた．男性ではコレステロール値が高いほどハザード比が上昇する傾向がみられ，Q4のハザード比は2.36と有意に上昇していた（表❷）．虚血性心疾患死亡では男性のみで同様の結果が得られた．総コレステロール値の高い人では禁煙対策をとくに重点的におこなう必要性が示唆された．

おわりに

NIPPON DATAの問題点として，①エンドポイントが死亡であるため死亡率の高い疾患ほど有意差が出やすく，かつ死因に誤分類が含まれる可能性があること，②危険因子の把握がベースラインの1回のみであるため，分析結果に回帰性希釈バイアスを含むことがあげられる．しかしながら①地域的な偏りがなく，②総人口ベースで75%以上の高い参加率と90%以上の追跡率を有し，③すべての対象者が血圧やコレステロールなどの検査所見を実測値でもっているという点で貴重なコホート研究である．今後，追跡期間の延長などを通じてわが国のエビデンス構築のためにさらに有益な情報を提供しうるものと期待されている．

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岡村 智教（おかむら・とものり）

国立循環器病センター予防検診部 部長

1964年山口県萩市生まれ．88年筑波大学医学専門学群卒業後，厚生省健康政策局計画課を経て，高知県土佐山田保健所で勤務．93年大阪府立成人病センター集団検診第1部，96年同診療主任．2000年滋賀医科大学福祉保健医学講座助教授，02～03年 Department of Epidemiology and Public Health, Imperial Collage, London（英国）へ留学．07年滋賀医科大学社会医学講座准教授（職名変更），07年8月国立循環器病センター病院予防検診部長（現職）．医学博士．滋賀医科大学客員教授．専門は公衆衛生学と疫学（とくに循環器疾患および脂質異常症の疫学）．日本疫学会・日本動脈硬化学会評議員・編集委員．趣味は史跡探索とドライブ．

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.

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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

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Methods

Study Subjects

The Suita Study,[2,14,15] 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/m²	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/m²	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-

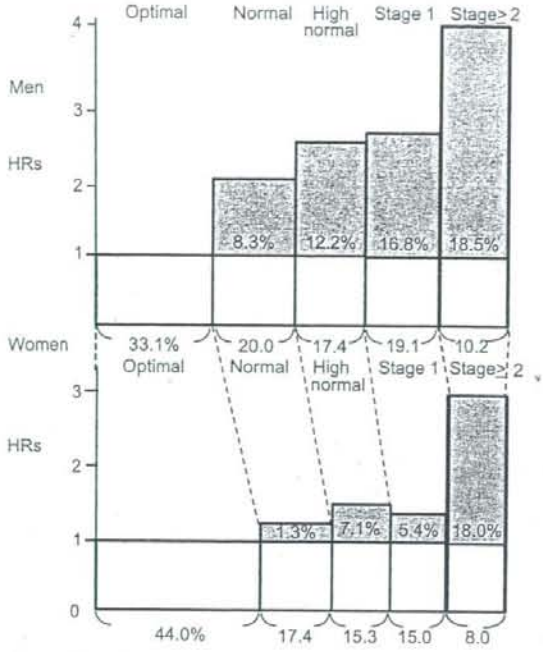

Figure. The HRs and positive fraction attributable to exposure to each blood pressure category (optimal, normal, and high-normal blood pressures and hypertension Stages 1 and ≥2) at baseline for CVD were estimated by sex. The gray area displays excessive incidence of CVD due to normal and high-normal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

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Disclosures

None.

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