④降圧薬関連遺伝子多型を用いた降圧薬の選択などが検討されている．なかでも最も早期に実現が期待されるのは，遺伝子情報を用いて降圧薬の選択をおこなう高血圧テーラーメイド診療の確立である．われわれは，国立循環器病センターにおいておこなわれたMGPならびにその後のポストミレニアム研究において降圧薬のファーマコゲノミクスを重視して研究をおこなってきた．

本稿では，その成果も含めて高血圧のテーラーメイド診療の確立の可能性につき述べる．

1．高血圧素因の遺伝子診断

高血圧の遺伝子多型研究のはじまりは1992年のアンジオテンシノーゲン遺伝子多型（*AGN* M235T）と高血圧[3]，ならびにACE遺伝子（*ACE* I/D）と心筋梗塞の関連性[4]が報告されてからスタートした．*ACE* I/Dは日本人男性の高血圧に関連することが吹田研究大規模一般住民を対象にした研究で明らかとなり[5]，高血圧素因遺伝子としても注目されるようになった．これらのレニン・アンジオテンシン系関連遺伝子多型を用いた高血圧テーラーメイド診療が期待されてきた．現在，一部の検査メーカーや健診施設が消費者直結型（direct to consumer：DTC）の形で*ACE* I/Dなどのタイピングをしている場合があるが，うまく機能していないのが現状である．

その原因として，高血圧素因遺伝子多型を臨床検査として調べることの意義が確立していないことにある．これには以下のような種々の問題が関係する．①既報の高血圧素因遺伝子多型の高血圧発症への寄与率が小さい（オッズ比で1.2～1.4程度），②研究対象集団間での再現性が低い，③本来高血圧の素因の有無を検索すべき若年期での積極的遺伝子診断が倫理的には受け入れられていない，などの点があげられる．しかしながらGWASを含めて多くの高血圧素因遺伝子の同定を目指した研究が施行されており，今後より強力な関連性を有する遺伝子多型が明らかになって来る可能性はある．また腎血管性高血圧や原発性アルドステロン症などの頻度の多い二次性高血圧への遺伝素因の関与は明らかにされていないが，弧発例での遺伝子の関与は考えられるので，今後これらの病気の関連遺伝子多型，変異が明らかになれば，疾患の診断への応用が期待される．

2．高血圧合併症の遺伝子診断

同じ高血圧の重症度でも，患者個々で臓器障害や合併症の発症の程度には違いがある．これには個々の患者の遺伝素因が関係している可能性があるため，種々の高血圧臓器障害や合併症関連の遺伝子多型の研究が進んでいる．もし遺伝子診断で高血圧臓器障害の進行をある程度でも予測できれば，たとえガイドライン上のリスクが低リスク群と判断されても，中等あるいは高リスクに準じた高血圧治療，降圧目標の設定，降圧薬の選択をおこなうといった将来の臓器障害の発症を予防するテーラーメイド治療の実現が考えられる．さらには臓器障害関連遺伝子多型を複数有すると臓器障害や心血管合併症が発症しやすい可能性が考えられる．われわれは遺伝子解析をおこなった約950人の高血圧患者のなかで，高血圧性心肥大（*IGF1R* 2SNPs），動脈硬化（*MMP2* 1SNP），腎障害（*ACE* I/Dほか，4SNPsのうち一つ）のリスク多型を重ねて有する高血圧患者の心血管イベント発症を検討したところ，**表1**に示すように12人中8人がメジャーな心血管疾患を発症していることがわかった[6]．これはこれらの遺伝子多型を単独でもっている場合の心血管イベント発生率と比較して明らかに高率であり，リスク遺伝子多型の集積も今後のテーラーメイド高血圧診療においては考慮すべき点である．

3．生活習慣改善に対する反応性への関与

大阪大学のKatsuyaら[7]は日本人には食塩感受性を示す遺伝子多型を有する人が欧米人より多いことを自験のデータをもとに提唱している（**図1**）．つまり日本人は食塩摂取量が多いのみならず食塩感受性が強いために高血圧になる可能性が高い可能性がある．逆に食塩制限が高血圧の発症抑制や降圧治療として有効である可能性が高い．事実，Huntら[8]はTOHP（Trials of Hypertension Prevention）phase Ⅱにおいて高血圧のリスクアレルである*angiotensinogen* T235アレルを有する患者ではM235を有する患者よりも減塩が有効であったと報告し

表 1. 高血圧臓器障害関連遺伝子多型を複数有する患者と心血管合併症

症例	年齢	心肥大関連多型 IGF1R C-328T	心肥大関連多型 IGF1R A275124C	動脈硬化関連多型 MMP2 A26223C	腎障害関連多型	心血管イベント	
					ACE I/D	3/3	
1	56	CC	AA	CC	DD	Stroke	
2	67	CC	AA	CC	DD	AMI	
3	77	CC	AA	CC	DD	AMI	
					MLR C850G	1/2	
4	76	CC	AA	CC	CC	Stroke	
5	56	CC	AA	CC	CC	None	
					SOD3 C-1708T	1/2	
6	86	CC	AA	CC	CT	Effort AP	
7	58	CC	AA	CC	CT	None	
					ECE1 T65251C	2/2	
8	56	CC	AA	CC	GG	Stroke	
9	60	CC	AA	CC	GG	Stroke	
					NPR1 G2979C	1/3	
10	71	CC	AA	CC	GC	DAA	
11	69	CC	AA	CC	GC	None	
12	60	CC	AA	CC	GC	None	計 8/12

（神出計ほか，2005[5]より改変引用）

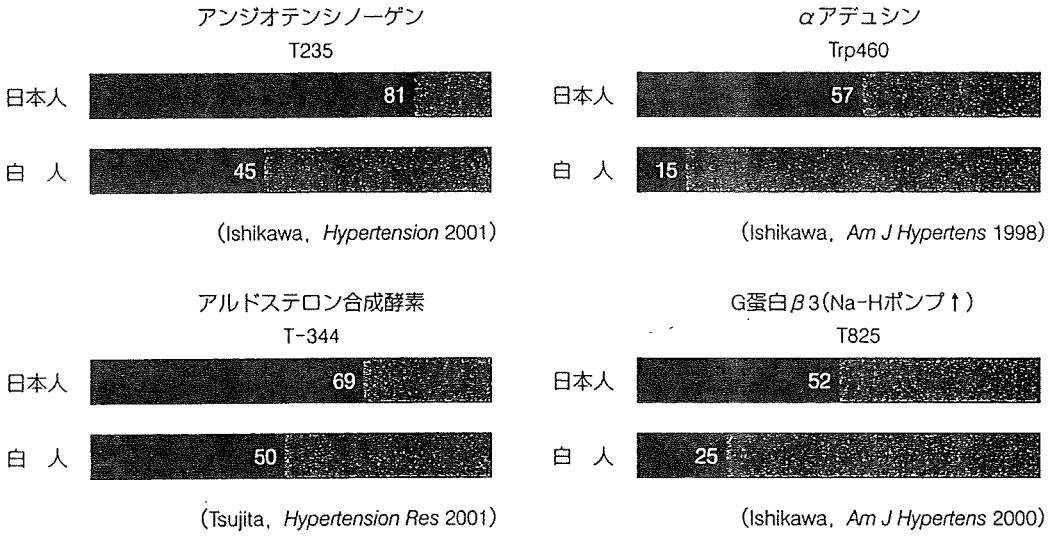

図 1. 食塩感受性関連の遺伝子多型-日本人と白人の比較
（Katsuya T *et al*, 2003[7]より改変引用）

ている．このように生活習慣改善療法にも，その人が有している遺伝子多型の違いにより反応性が違っており，遺伝情報をもとにしたテーラーメイド治療が期待される．大規模な前向き介入試験により，もっと確実な生活習慣改善の効果と遺伝子多型の関連性が明らかになることが望まれる．

4．降圧薬のファーマコゲノミクス

もっとも実現しやすく臨床的に有用性が高いと考えられるのは降圧薬関連遺伝子多型を用いて薬剤選択をおこなうテーラーメイド診療である．しかしながら肺癌治療薬のゲフィチニブの効果を上皮成長因子受容体（EGFR）の遺伝子変異で予測するといったテーラーメイド医療が癌治療の分野ではおこなわれるようになっているが，高血圧治療においてはこの方法はまだ確立していない．こ

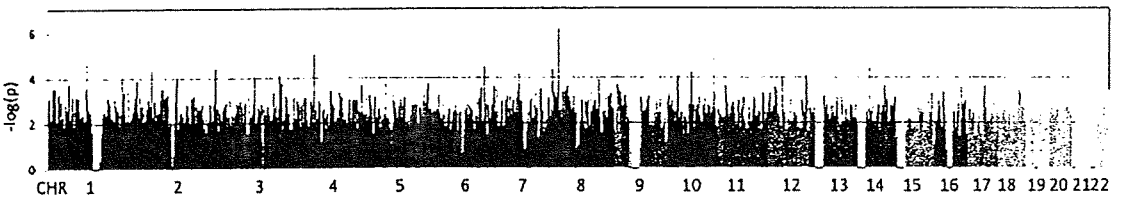

図 2. サイアザイド系利尿薬関連 SNP（GEANE より）
インダパミド投与後の血圧値を投薬前の血圧値で補正後，レスポンダー・ノンレスポンダーを判定し，GWAS をおこなった．染色体 7 番に $p<10^{-6}$ を超える最も強い関連 SNP を認めた．

れは降圧薬の効果や副作用を確実に予測できる遺伝子多型がわかっていないことが原因である．われわれは MGP 施行当時より降圧薬関連遺伝子多型を明らかにするために降圧薬のファーマコゲノミクス研究をおこなってきた．その一環でおこなわれた降圧薬感受性遺伝子多型同定のための多施設共同研究 GEANE（Gene Evaluation for ANtihypertensive drug Effect）は国立循環器病センターが中心となり全国の大学・医療センター計 24 施設とともにおこなった研究である．GEANE では同一患者にサイアザイド系利尿薬（TD）インダパミド，ジヒドロピリジン系 Ca 拮抗薬アムロジピン，ARB バルサルタンをクロスオーバー法で服用させて降圧効果を調べ，遺伝子多型はゲノム網羅的に 50 万 SNPs を検討している．最終的に 154 例の症例登録があり，最近解析結果が発表された．GEANE ではこれら 3 剤の降圧効果関連 SNP のみならず，TD 系利尿薬投与後の尿酸上昇やカリウム低下に関わる SNP も検討している．その結果の一部を**図 2** に示す．TD の効果関連で最も強い関連性を示す SNP は，染色体 7 番にあり，その他，Ca 拮抗薬，ARB 関連 SNP，さらには TD 後の尿酸上昇やカリウム低下に関連する SNP も多数明らかになった．GEANE で得られた膨大な基礎情報から，降圧薬を選択する方法を現在われわれは模索している．現在，SNP から降圧薬を選択する方法の有用性を前向きに検討する GEANE2 も準備段階であり，遺伝子情報を用いた降圧薬選択法を用いた高血圧テーラーメイド診療の実現も近いと考えている．

おわりに

テーラーメイド医療の実現に向けて

高血圧のテーラーメイド医療実現には適確な研究成果の集積と出てきた遺伝子多型を用いた迅速遺伝子診断システムの開発，このような遺伝子診断システムを導入した場合の有用性を確かめる前向き試験による遺伝子を考慮することの有用性の証明が必要と考えられる．今後は遺伝子多型診断を考慮した新しい高血圧治療ガイドラインの制定なども必要になる可能性がある．無駄が少なく，より安全で，合併症を減少させることができるような高血圧診療を患者に提供することを最終目標に研究を進めることが重要である．

謝辞

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各種降圧薬の中心動脈圧の低下効果

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降圧薬は上腕血圧とともに中心動脈圧（中心血圧）を低下させるが，両者への効果は必ずしも同様ではない．Ca 拮抗薬，RA 系抑制薬といった血管拡張性の降圧薬は，β遮断薬や利尿薬に比較して中心血圧の降圧効果が大きいことが認められている．大規模臨床試験の成績とあわせると，中心血圧をよく下げる薬剤は心血管予後の改善効果が大きいことが示唆される．しかし，硝酸薬や直接の血管拡張薬は中心血圧への効果は大きいが，臓器保護や心血管予後への効果は明らかではない．したがって，降圧薬による心血管保護には中心血圧の低下が関連するであろうが，これのみで決定されるわけではないと考えられる．

はじめに

中心動脈圧あるいは中心血圧は，心臓に近い部位への圧負荷を反映することから，上腕血圧より高血圧性臓器障害に強く関係し，降圧治療における測定意義が提唱されている[1)~3)]．降圧薬は上腕血圧とともに中心血圧を低下させるが，両者への効果は必ずしも同様ではない．薬剤の中心血圧への影響については，以前より小規模な基礎的および臨床的研究はなされてきたが，Ca 拮抗薬とβ遮断薬を一次薬として治療効果を比較検討した大規模臨床試験 ASCOT（Anglo-Scandinavian Cardiac Outcomes Trial）のサブスタディである CAFE（Conduit Artery Function Evaluation）研究によって脚光を浴びることになった[4)]．

KEY WORDS
中心血圧，高血圧，降圧薬

本稿では，各種降圧薬の中心血圧への効果について，上腕血圧との差や薬剤間の違いを含めて概説する．

1．Ca 拮抗薬

Ca 拮抗薬は中心血圧を比較的大きく低下させることが，いくつかの臨床研究において示されている．Morgan ら[5)]は，少数例ではあるが，高齢の高血圧患者における Ca 拮抗薬，利尿薬，ACE 阻害薬，β遮断薬の効果を，プラセボ対照無作為交叉法により検討している．中心血圧は，シグモコア®を用いて測定された．Ca 拮抗薬は上腕血圧も大きく下降させたが，中心血圧の降圧も最も大きく，また上腕血圧より中心血圧への効果がやや大であった（**図 1**）．

CAFE 研究は，ASCOT 試験のサブスタディであるが，2,199 名の高血圧患者について，Ca 拮抗薬アムロジピンあるいはβ遮断薬アテノロールを中心とする治療法の中心血圧への効果を調べている[4)]．上腕血圧の降圧効果には両群間に差を認めなかったが，Ca 拮抗薬中心の治

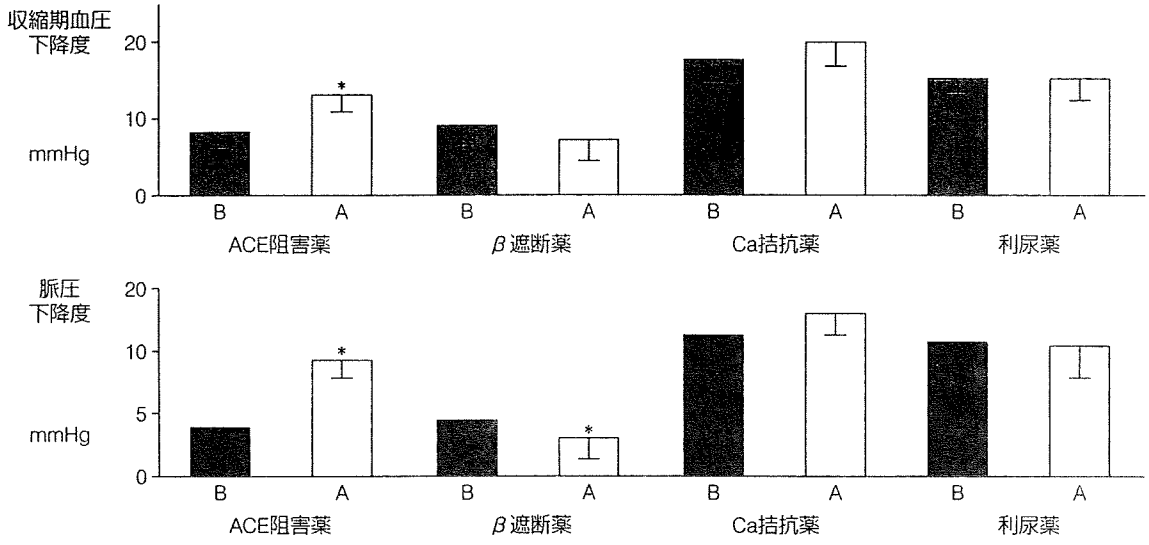

図 1. 4種の降圧薬の上腕動脈および大動脈の収縮期血圧および脈圧への効果
B：上腕動脈，A：大動脈，*両血管における効果に有意差あり．
(Morgan T *et al*, 2004[5]より引用)

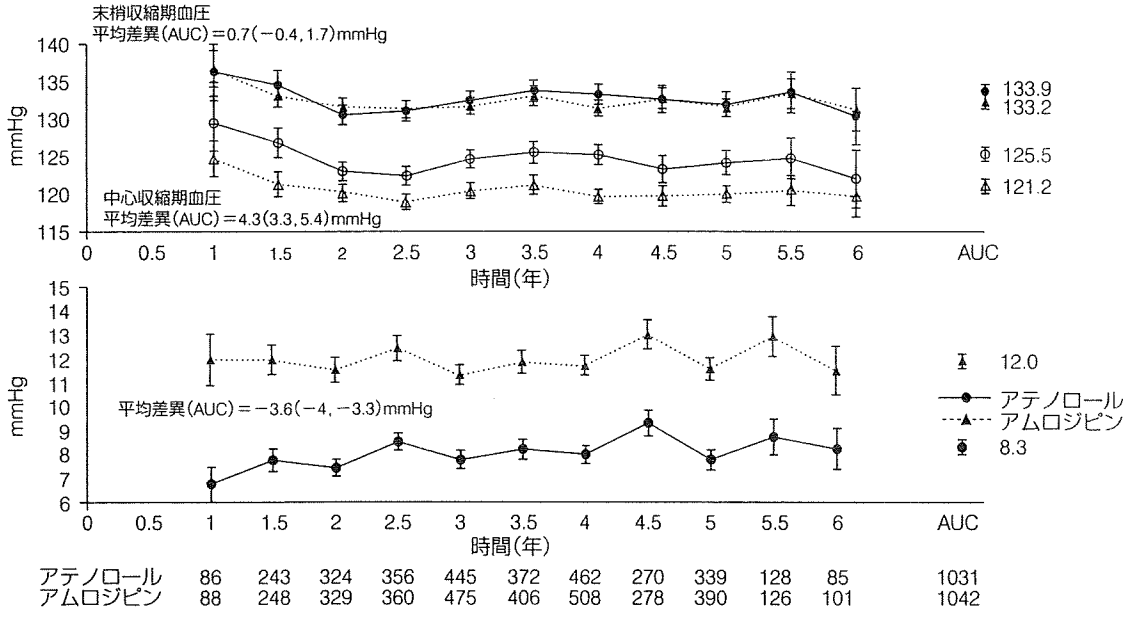

図 2. ASCOT-CAFE 研究におけるアムロジピン群とアテノロール群の上腕および中心血圧（上）およびその差（下）の推移
(Williams B *et al*, 2006[4]より引用)

療のほうが中心血圧はより低下していた（**図 2**）[4]．ASCOT の主試験においては，前者が後者より心血管合併症の発生が少なかったとの結果が得られており，両群における中心血圧の差が心血管予後に関係したことが示唆される．

わが国でも，自治医科大学や筆者らの施設を含む共同研究の ABC-J 研究（Antihypertensives and Blood pressure of Central artery study in Japan）において，各種の降圧薬の中心血圧への効果が検討されている[6]．これは観察的研究であるが，1,712 名の治療中の高血圧患者および未治療の 1,049 名について，血圧脈波検査装置（HEM-9000AI®）を用いて中心血圧を推計したものであ

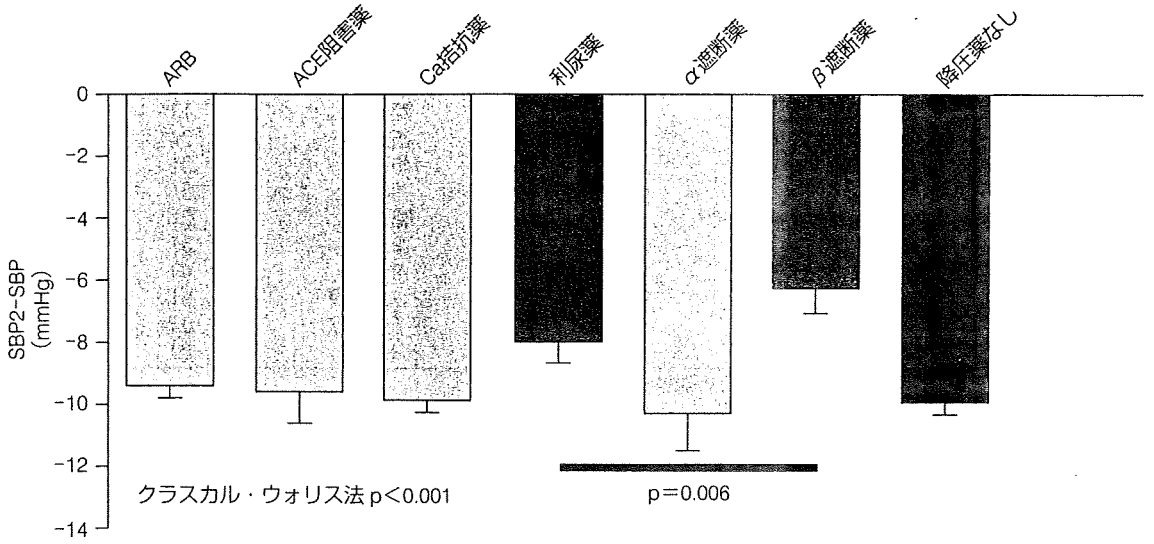

図 3. ABC-J 研究における各種降圧薬により治療中の高血圧患者および未治療者における推定中心血圧（SBP2）と上腕血圧（SBP）の差
（河野雄平ほか，2008[6]発表データ）

る．Ca 拮抗薬，RA 系抑制薬，α遮断薬といった血管拡張性の降圧薬は，β遮断薬や利尿薬に比較して，中心血圧の降圧効果が大きいことが認められた（**図 3**）．

Ca 拮抗薬の中心血圧への効果が大きい理由としては，末梢血管（小動脈）を拡張させることにより脈波の反射波が減弱し，augmentation index（AI）や augmentation pressure が小さくなることが，おもな機序であろうと考えられる．

2．レニン・アンジオテンシン（RA）系抑制薬

ACE 阻害薬や ARB といった RA 系の抑制薬も血管拡張作用が比較的強く，中心血圧を効果的に低下させることが認められている．

1）ACE 阻害薬

Morgan らの比較研究では，ACE 阻害薬は上腕血圧への効果は小さいが，中心血圧への効果は比較的大きいことが示されている（**図 1**）[5]．両血管における降圧効果の差は有意であった．ABC-J 研究においても，ACE 阻害薬はβ遮断薬や利尿薬に比較して，中心血圧への効果が大きかった（**図 3**）[6]．

REASON 研究（Preterax in Regression of Arterial Stiffness in a Controlled double-blind study）のサブスタディにおいては，ACE 阻害薬ペリンドプリルと利尿薬インダパミドの併用が，β遮断薬アテノロールにくらべ，上腕血圧への効果も大きかったが，中心血圧の収縮期血圧と脈圧をよく低下させている[7]．また，前者が後者よりも左室肥大軽減をもたらし，心筋重量の変化は上腕血圧より中心血圧の変化とより関連していることが認められている．

Hirata ら[8]は，ラミプリルとアテノロールの急性効果を検討し，上腕血圧に対する中心血圧の下降度は前者が後者より大きいことを観察している．しかし，この研究では上腕血圧への効果もラミプリルがアテノロールより大であった．また，大動脈の脈波速度は同程度に低下したが，上下肢の脈波速度への効果は前者が後者より大であった．

利尿薬と比較した場合の ACE 阻害薬の中心血圧への効果については，成績が一致していないが，ACE 阻害薬がややすぐれているようである．Morgan らの研究や ABC-J 研究では，ACE 阻害薬が利尿薬より，上腕血圧と比較しての中心血圧への効果はいくらか大きかった[5][6]．一方，ACE 阻害薬と利尿薬を基礎薬とする大規模臨床試験である ANBP 試験（Australian National Blood Pressure Trial）のサブスタディでは，中心血圧お

表 1. β遮断薬服用中および非服用中の患者における血行動態指標

血行動態指標	β遮断薬なし	β遮断薬あり	p値
上腕収縮期圧（mmHg）	144±22	146±25	.64
上腕拡張期圧（mmHg）	77±15	72±15	.13
上腕脈圧（mmHg）	66±23	75±20	.07
大動脈収縮期圧（mmHg）	125±21	140±21	.01
大動脈拡張期圧（mmHg）	77±16	78±12	.81
大動脈脈圧（mmHg）	47±19	62±20	.01
心拍数（beats/min）	71±15	73±13	.57
脈波速度（m/s）	8.5±2.6	8.9±2.0	.46
AI（%）	22.3±14	28.7±11.9	.04
AI 75（%）	20.1±11	27.7±10.7	.005
大動脈内中膜最大厚（mm）	2.4±1.2	2.8±1.6	.20

AI：augmentation index，AI 75：心拍数補正 AI
（Olafiranye O *et al*, 2008[12]より引用）

よび上腕血圧の下降度は，両群ほぼ同等であった[9]．しかし，Jiang らのラミプリルとインダパミドを比較した無作為研究においては，前者が後者より中心血圧および AI への効果が大きいことが示されている[10]．

2）ARB

ARB の中心血圧への効果を調べた研究は少ないが，ACE 阻害薬と同様に比較的大きいと考えられる．ABC-J 研究における中心血圧と上腕血圧の差は，ARB 群は ACE 阻害薬群と同等で，β遮断薬や利尿薬より中心血圧への効果が大きかった（**図 3**）[6]．

Dhakam ら[11]は，少数例の高血圧患者を対象に，ARB エプロサルタンとβ遮断薬アテノロールの効果を無作為交叉法により検討した．この研究では，上腕血圧への効果は同等であったが，中心血圧の低下度は前者が後者より大であった．一方，大動脈脈波速度の低下度は後者が前者より大きく，AI は前者で減少，後者で増加した．したがって，ARB による中心血圧低下には大血管のスティフネスの変化は寄与せず，小血管の拡張による AI 減少の関与が大きいと考えられる．

3．利尿薬

利尿薬の中心血圧への効果は，あまり大きくはない．Morgan らの研究や ABC-J 研究においては，上腕血圧との比較では，利尿薬による中心血圧の低下度は Ca 拮抗薬や RA 系抑制薬よりいくらか小さく，β遮断薬よりやや大きい（**図 1，3**）[5][6]．ACE 阻害薬との比較でも，利尿薬の効果は同等か弱いことが示されている[9][10]．

しかし，高齢高血圧患者を対象とした Morgan らの研究では，利尿薬による中心血圧の低下度自体は上腕血圧と同等であり，また ACE 阻害薬に勝るとも劣らず，β遮断薬より大きい（**図 1**）[5]．利尿薬は長期的には末梢血管抵抗を減少させることから，中心血圧に対してもかなりの効果が期待できると考えられる．

4．β遮断薬とα遮断薬

β遮断薬の中心血圧への効果は，前述したようにほかの降圧薬，とくに血管拡張性の薬剤にくらべると小さい（**図 1，3**）．β遮断薬を服用している患者と服用していない患者について検討した Olafiranye らの研究においても，β遮断薬服用者は上腕血圧は同等でも中心血圧や AI は高値であった（**表 1**）[12]．中心血圧への効果が比較的弱いことが，アテノロールを主薬とする治療を Ca 拮抗薬と比較した ASCOT や，ARB ロサルタンと比較した LIFE 試験（Losartan Intervention For Endpoint reduction in hypertension）といった大規模臨床試験において，β遮断薬が劣った理由の 1 つではないかと考えられている．

β遮断薬の中心血圧への効果が小さい理由としては，中心血圧には AI が強く関係しており，心拍数は AI の規定因子（負の）であることから[13]，心拍数減少が AI および中心血圧を比較的高くなるように働くことが推定される．実際，ABC-J 研究におけるβ遮断薬と他薬との差は，心拍数補正により減弱した[6]．しかし，Olafiranye らの研究ではβ遮断薬服用者と非服用者とのあいだに

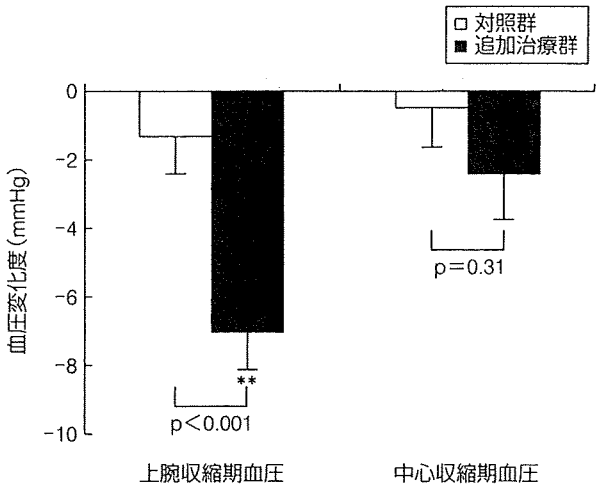

図 4. Japan Morning Surge 1 研究における α 遮断薬（および β 遮断薬）による治療強化群および対照群の上腕および中心血圧の変化
（Matsui Y *et al*, 2008[14] より引用）

心拍数の差はなく（**表 1**）[12]，他の要因も関与すると考えられる．また，β 遮断薬には多くの種類があり，心拍数への影響が小さいものや，血管拡張に働くものもある．これらの β 遮断薬は中心血圧にも異なった効果を示すと考えられる．

α 遮断薬の中心血圧への効果を調べた研究は少ないが，ABC-J 研究においては，α 遮断薬は Ca 拮抗薬，RA 系抑制薬と同様に，比較的大きい効果が認められた（**図 3**）[6]．しかし，降圧治療中で早朝高血圧を呈する患者に α 遮断薬ドキサゾシンを投与した（不十分な場合にはアテノロールを追加）Japan Morning Surge 1 研究では，上腕血圧はよく下がったのに対し，中心血圧への効果は小さいことが示されている（**図 4**）[14]．これらの差の理由は明らかではないが，β 遮断薬の併用のみではなさそうであり，さらに検討を要すると考えられる．

5．その他の血管拡張薬

硝酸薬は降圧薬としてはあまり用いられないが，強力な血管拡張作用を有しており，ニトログリセリンは上腕動脈圧より中心動脈圧を大きく低下させることが示されている[15]．ヒドララジンなどの血管拡張薬にも，同様の効果が得られるであろう．

しかし，これらの血管拡張薬は反射性の交感神経系や RA 系の活性化をもたらし，中心血圧の低下がそのまま心血管保護になるかどうかは疑わしい．硝酸薬の長期の心血管保護効果は，臨床的には明らかでない．ヒドララジンは主要降圧薬としては用いられず，実験的には，血圧を下げるが臓器保護効果に乏しい薬として他薬の対照に用いられている．

おわりに

各種の降圧薬の中心血圧への効果について述べた．Ca 拮抗薬，RA 系抑制薬といった血管拡張性の降圧薬は，β 遮断薬や利尿薬に比較して中心血圧の降圧効果が大きいことが認められており，α 遮断薬については結果が一致していない．最近の大規模臨床試験の成績と合わせて，中心血圧をよく下げる薬剤は心血管予後の改善効果が大きいことが示唆されている．しかし，降圧薬の心血管保護効果は中心血圧の低下だけで決まるものではないであろう．この領域におけるさらなる研究の進展と知見の集積が期待される．

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Comparison between carotid-femoral and brachial-ankle pulse wave velocity as measures of arterial stiffness

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Background **Arterial stiffness is an important risk factor for cardiovascular disease. Carotid-femoral pulse wave velocity (cfPWV) is the most recognized and established index of arterial stiffness. An emerging automatic measure of PWV primarily used in the Asian countries is brachial-ankle PWV (baPWV).**

Method **To systematically compare these two methodologies, we conducted a multicenter study involving a total of 2287 patients.**

Results **There was a significant positive relation between baPWV and cfPWV ($r = 0.73$). Average baPWV was approximately 20% higher than cfPWV. Both cfPWV and baPWV were significantly and positively associated with age ($r = 0.56$ and 0.64), systolic blood pressure ($r = 0.49$ and 0.61), and the Framingham risk score ($r = 0.48$ and 0.63). The areas under the receiver operating curves (ROCs) of PWV to predict the presence of both stroke and coronary artery disease were comparable between cfPWV and baPWV.**

Conclusion **Collectively, these results indicate that cfPWV and baPWV are indices of arterial stiffness that exhibit similar extent of associations with cardiovascular disease risk factors and clinical events.** *J Hypertens* **27:2022–2027 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Keywords: arterial distensibility, arterial elasticity, vascular assessment

Abbreviations: AUC, area under the curve; baPWV, brachial-ankle pulse wave velocity; CAD, coronary artery disease; cfPWV, carotid-femoral pulse wave velocity; CHD, coronary heart disease; eGFR, estimated glomerular filtration rate; PWV, pulse wave velocity; ROC, receiver operating characteristics

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See editorial commentary on page 1960

Introduction

Arterial stiffness is associated with a number of deleterious cardiovascular conditions [1–3] and has been identified as an independent risk factor for cardiovascular disease [4]. Because of its clinical importance, a number of indices have been developed and introduced to characterize arterial stiffness [5–8]. However, clinicians and researchers still report great difficulties in selecting the most appropriate methodology for their specific use [7]. Parenthetically, a measure of arterial stiffness has not been fully incorporated in routine clinical practice. Although no one methodology has been proved superior, pulse wave velocity (PWV) is the most recognized and established index of arterial stiffness [7]. The most frequently studied index to date among a variety of PWV measures is carotid-femoral PWV (cfPWV). cfPWV has been used in landmark studies of arterial stiffness conducted in Europe [2,9] and Australia [10] as well as in the Framingham Heart Study in the USA [11]. Despite the accumulating clinical evidence, this measure of PWV has not been fully included in routine clinical settings. An emerging measure of PWV that has been widely used in Japan and other east-Asian countries in the past 10 years is brachial-ankle PWV (baPWV) [8,12–15] (or some have referred to as brachial-ankle PWV index [14]). This automated measure of PWV is very unique in that it has been widely used in routine clinical settings, at least in Japan, with impressive number of machines (~10 000) already been incorporated in various clinics and hospitals.

Although these two PWV measures are widely used in the Western and Eastern societies, respectively, associations between the two are not clear. A few studies that have attempted to address this issue are small scale in nature [8,13]. Additionally, it is not known how each of the arterial stiffness measures are associated with coronary heart disease (CHD) risk factors. Moreover, how both techniques are comparatively related to clinical events is not currently known. In an attempt to systematically address these issues, we conducted a multicenter study to determine associations between cfPWV and baPWV.

Methods

Patients

Patients were participants in the community-based research studies from six different institutions in Japan and one in the USA. A total of 2287 adults (1265 men and 1022 women) were studied. All procedures were reviewed and approved by the local Human Research

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Committees. Each patient provided written consent to participate in the study.

Before the experiments, patients abstained from alcohol and caffeine and fasted for at least 3 h. Patients were studied under supine resting conditions in a quiet, temperature-controlled room.

Pulse wave velocity measurements

Electrocardiogram, bilateral brachial and ankle blood pressures, and carotid and femoral arterial pulse waves were simultaneously measured with a vascular testing device (VP-2000; Omron Healthcare) [12]. This machine was originally developed as a screening device for hypertension (via blood pressure), peripheral artery disease (via ankle brachial index), and arterial stiffness (via PWV), and this necessitated the use of four blood pressure cuffs on each limb. Carotid and femoral arterial pressure waveforms were stored for 30 s by applanation tonometry sensors attached to the left common carotid artery (via a neck collar) and left common femoral artery (via elastic tape around the waist). Bilateral brachial and post-tibial arterial pressure waveforms were stored for 10 s by extremities cuffs, connected to a plethysmographic sensor and an oscillometric pressure sensor, wrapped around both arms and ankles.

Pulse wave velocity was calculated from the distance between two arterial recording sites divided by transit time. Transit time was determined from the time delay between the proximal and distal 'foot' waveforms. The foot of the wave was identified as the commencement of the sharp systolic upstroke, which was automatically detected by a band-pass filter (5–30 Hz). Time delay between right brachial and tibial arteries (Tba), between carotid and femoral arteries (Tcf), and between femoral and tibial arteries (Tfa) were obtained. The path length from the carotid to the femoral artery (Dcf) was directly assessed in duplicate with a random zero length measurement over the surface of the body with a nonelastic tape measure [16]. For patients whose distance between the carotid and femoral artery was not available, Dcf was estimated using the equation [0.318 × height (cm) + 10.56] [17]. Agreement between cfPWV obtained using the estimated Dcf and directly measured Dcf was excellent ($r = 0.99$). The path lengths from the suprasternal notch to brachial artery (Dhb), from suprasternal notch to femur (Dhf), and from femur and ankle (Dfa) were calculated automatically by the machine using the following equations [13]:

$$\text{Dhb} = (0.220 \times \text{height}\{\text{cm}\} - 2.07)$$

$$\text{Dhf} = (0.564 \times \text{height}\{\text{cm}\} - 18.4)$$

$$\text{Dfa} = (0.249 \times \text{height}\{\text{cm}\} + 30.7)$$

Pulse wave velocity was calculated by the following equations:

$$\text{Carotid–femoral PWV} = \frac{\text{Dcf}}{\text{Tcf}}$$

$$\text{Brachial–ankle PWV} = \frac{\text{Dhf} + \text{Dfa} - \text{Dhb}}{\text{Tba}}$$

The results obtained with right side and left side baPWV were identical ($r = 0.97$). As such, right baPWV is reported in the present study. The validity and reliability of the automatic device for measuring PWV have been established previously [12].

Blood samples

A blood sample was collected from the antecubital vein using venipuncture after an overnight fast. Plasma concentrations of glucose, lipids, and lipoproteins were determined by use of a standard enzymatic technique as previously described [16]. Glomerular filtration rate (eGFR) was calculated using the following equation introduced by the Japanese Society of Nephrology [18].

$$\text{Men}: \ \text{eGFR}\,(\text{ml/min per } 1.73\,\text{m}^2) = 194 \times \text{Cr}^{-1.094} \times \text{age}^{-0.287}$$

$$\text{Women}: \ \text{eGFR}\,(\text{ml/min per } 1.73\,\text{m}^2) = 194 \times \text{Cr}^{-1.094} \times \text{age}^{-0.287} \times 0.739$$

Statistical analyses

Univariate regression and correlation analyses were used to analyze the relations between variables of interest. Forward stepwise multiple-regression analyses were used to determine the influence of central and peripheral arterial stiffness on baPWV. To do so, only variables that had significant univariate correlations with cfPWV and/or baPWV were included in the model. Receiver operating characteristic (ROC) curves for both cfPWV and baPWV were constructed, and area under the curves (AUC) was calculated. This analysis was performed in a cohort of 814 patients [36 strokes and 40 coronary artery disease (CAD)] collected in three different institutions. Statistical significance was set *apriori* at $P < 0.05$. Data are expressed as means ± SEM.

Results

Table 1 shows the clinical and biochemical characteristics as well as PWV for the patients. On average, baPWV was approximately 20% higher than cfPWV.

As demonstrated in Fig. 1, there was a significant positive relation between baPWV and cfPWV ($r = 0.73$). Subgroup analyses revealed no systematic differences between men and women or between Japanese and

Table 1 Patient characteristics

Variable	Mean ± SD
n	2287
Age (years)	56 ± 16
Sex (%male)	56
CVD (%)	4.8
Height (cm)	162 ± 9
Body weight (kg)	61 ± 12
Systolic BP (mmHg)	128 ± 19
Diastolic BP (mmHg)	81 ± 13
Total cholesterol (mg/dl)	209 ± 36
LDL-cholesterol (mg/dl)	124 ± 33
HDL-cholesterol (mg/dl)	59 ± 16
Triglyceride (mg/dl)	127 ± 93
Plasma glucose (mg/dl)	103 ± 25
cfPWV (cm/s)	1256 ± 388
baPWV (cm/s)	1484 ± 342
eGFR (ml/min per 1.73 m^2)	79 ± 20

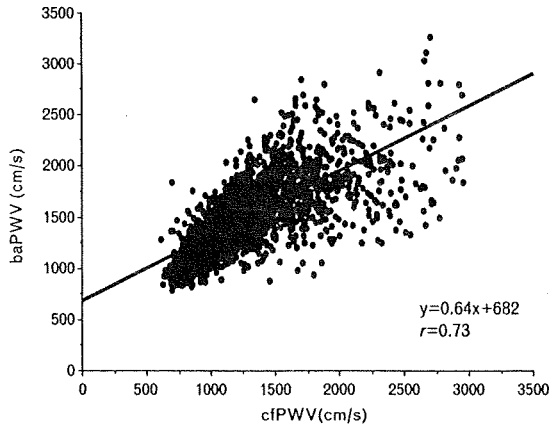
BP, blood pressure; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; PWV, pulse wave velocity.

American populations. Both cfPWV and baPWV were significantly and positively associated with age ($r = 0.56$ and 0.64; Fig. 2 and Table 2), systolic blood pressure (SBP) ($r = 0.49$ and 0.61), and the Framingham risk score ($r = 0.48$ and 0.63; Fig. 3). Stepwise multiple regression analyses indicated that the two primary determinants of both cfPWV and baPWV were age and SBP, explaining 43 and 60% of variances associated with cfPWV and baPWV, respectively. Figure 4 shows the results of the cross-sectional analyses involving the ROC of PWV to predict the presence of both stroke and CAD in a cohort of 814 patients (36 strokes and 40 CAD). The areas under the ROC curve for cfPWV and baPWV were comparable in stroke (0.62 and 0.63) and CAD (0.60 and 0.60).

Discussion

Pulse wave velocity is an established index of arterial stiffness and its first clinical use can be traced to Bramwell and the Nobel laureate, A.V. Hill [5]. In the present study, we performed comparative analyses of cfPWV and baPWV in a large number of patients who participated in the multicenter study. First, we demonstrated that baPWV was significantly and positively associated with cfPWV in the pooled population. Second, both PWV measures exhibit similar associations with various risk factors for CAD. Third, the areas under the ROC curve to predict the presence of CAD and stroke were comparable for cfPWV and baPWV. Collectively, these results indicate that cfPWV and baPWV are indices of arterial stiffness that are similarly related to CHD risk factors and predict clinical events to similar extents.

Fig. 1



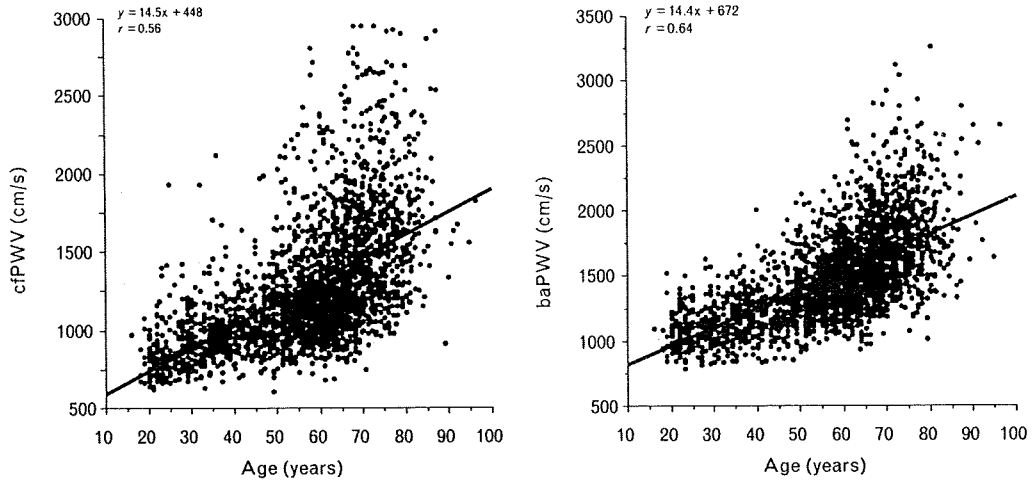
Association between carotid-femoral pulse wave velocity (cfPWV) and brachial-ankle pulse wave velocity (baPWV).

There was a strong positive association between cfPWV and baPWV, suggesting that both measures of PWV are indices of 'central' (or cardiothoracic) artery stiffness. These results are consistent with previous small-scale studies showing that baPWV is more closely associated with the index of central artery stiffness [8,13,19]. We have also previously reported that changes in central artery stiffness induced by a lifestyle modification are closely associated with the corresponding changes in baPWV [8]. Thus, in contrast to the prevailing notion, baPWV appears to reflect central arterial stiffness rather than peripheral artery stiffness. However, the regression line between cfPWV and baPWV deviated from the line of identity. On average, baPWV was approximately 20% higher than cfPWV. This finding indicates that some (albeit small) portions of baPWV may be determined by 'peripheral' (or muscular) arterial stiffness as suggested by a previous study [8].

The comparative assessment and analyses of different indices of arterial stiffness, particularly the comparisons with cfPWV, are becoming increasingly important given the recent European guidelines for the management of arterial hypertension proposing that a cfPWV value of more than 1200 cm/s be used as an index of subclinical organ damage [9]. The regression line obtained in the present study reveals that a baPWV value of 1450 cm/s is equivalent to the threshold value of 1200 cm/s proposed by the European Society of Hypertension and the European Society of Cardiology [9]. Such setting of a threshold PWV value may become a necessity if arterial stiffness measures were to be fully integrated into routine clinical settings.

Carotid-femoral pulse wave velocity has been shown to be accurate, reliable, and relatively simple to use and has been strongly linked with cardiovascular disease [1,2,14]. However, this methodology has not been widely incorporated in the routine clinical settings. The use of pressure transducers or Doppler probes on target arteries may be perceived as somewhat difficult to clinical staff. Additionally, some patients may feel uncomfortable exposing the inguinal area during the acquisition of

Fig. 2



Relation between age and pulse wave velocity (PWV) measures.

femoral pressure waveforms. These trends were particularly evident in generally demure Japanese population and required a development of a novel arterial stiffness index. baPWV has a procedural advantage of being very simple to use, only requiring the wrapping of blood pressure cuffs on four extremities. As a result, it has become a very popular modality to assess arterial stiffness in Japan [13], and it has been incorporated in thousands of local (i.e. nonresearch-oriented) clinics and hospitals.

Brachial-ankle pulse wave velocity has been criticized that the pulse wave does not travel directly from the brachial arteries to the post-tibial arteries in the same arterial tree and that the nomenclature of PWV is inappropriate. However, the same argument can be made for the well established cfPWV. cfPWV measures the velocity of pulse wave from carotid to femoral arteries, and these two arteries are not connected directly in the same arterial tree. Another issue pertaining to cfPWV is that there has been no consensus in terms of how the arterial path length should be measured. In large epidemiological studies from France that yielded the most clinically significant findings on cfPWV [1,20,21], the straight distance between the carotid and femoral arteries was applied. On the contrary, different investigations, including the Framingham Heart Study, employed the subtraction of the carotid artery length from the carotid to femoral straight distance in order to account for the pulse traveling in the opposite direction [22]. Rajzer *et al.* [23] recently compared the values of aortic PWV obtained with different arterial path length measurement: the carotid to femoral straight distance vs. the subtraction of the carotid artery length from the suprasternal notch to femoral straight distance. They reported that PWV measured with the former method was 25% higher compared with that using the latter method. We recently measured the aortic path lengths directly by the three-dimensional transverse magnetic resonance image arterial tracing in 256 apparently healthy adults and found that PWV calculated with the straight distance between carotid and femoral sites 26% overestimated the actual arterial path length [24]. Thus, it should be acknowledged that both cfPWV and baPWV have inherent problems with regard to the measurement of arterial path length.

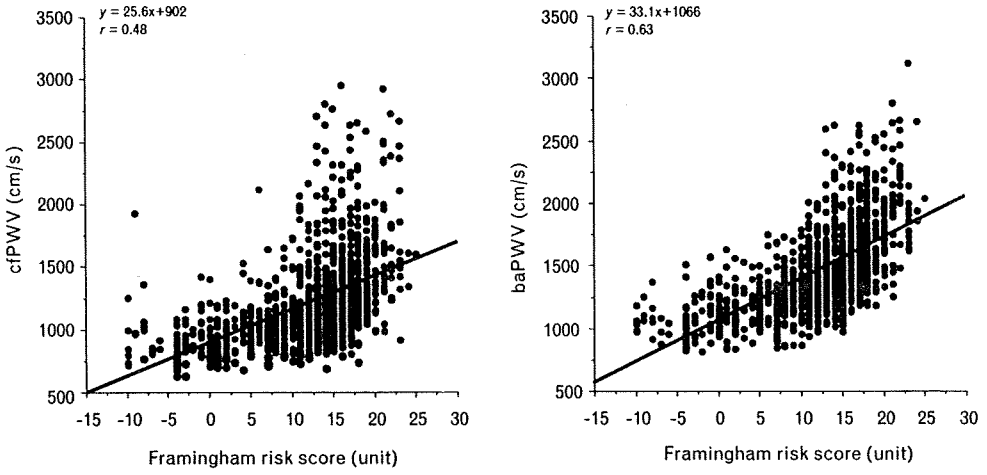
Table 2 Associations between pulse wave velocity (PWV) and risk factors for coronary heart disease

Variable	cfPWV	baPWV
Age	0.56	0.64
Systolic BP	0.49	0.61
Diastolic BP	0.13	0.23
Mean BP	0.48	0.58
Pulse pressure	0.50	0.56
FRS	0.48	0.63
eGFR	−0.32	−0.25

BP, blood pressure; eGFR, estimated glomerular filtration rate; FRS, Framingham risk score; PWV, pulse wave velocity. Values are Pearson correlation coefficients. All are significant at $P < 0.001$.

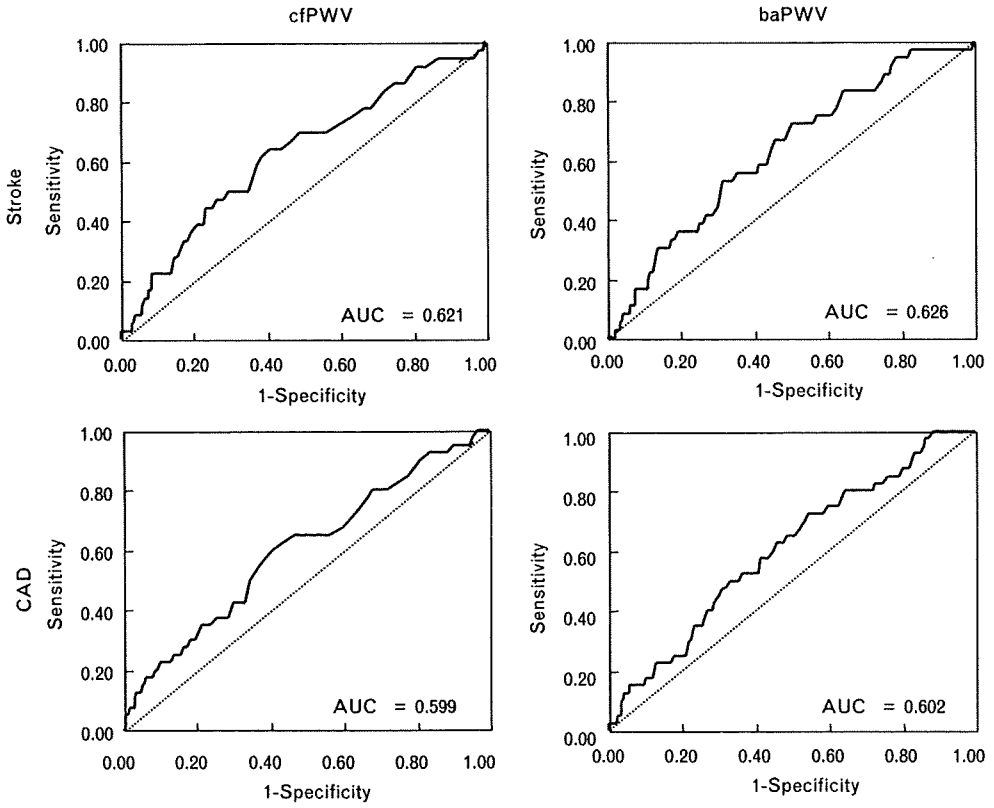
Both cfPWV and baPWV were significantly and similarly associated with various risk factors for CAD in the present study. Multiple regression analyses revealed that the two primary determinants of cfPWV and baPWV were the same (age and SBP). Interestingly, the strength of associations was somewhat greater for baPWV. These results are consistent with a recent epidemiological study [14] showing that both cfPWV and baPWV were significantly associated with the presence and severity of coronary calcification among overweight postmenopausal women. Interestingly, baPWV displayed stronger associations with the presence of coronary calcium than cfPWV

Fig. 3



Relation between the Framingham risk scores and pulse wave velocity (PWV) measures.

Fig. 4



Receiver operating characteristic (ROC) curves for incidences of stroke and coronary artery disease (CAD). AUC, area under the curve.

[14]. A similar finding that baPWV is more strongly related to left ventricular mass than cfPWV has also been reported [15]. Although baPWV is predominantly a measure of central artery stiffness [8], it also displays a modest correlation with peripheral artery stiffness (e.g. leg PWV) [8]. Thus, baPWV may be affected by more peripheral or systemic disease processes.

The areas under the ROC curve were also similar for baPWV and cfPWV. The results from this cross-sectional analysis indicate that both cfPWV and baPWV have similar abilities to associate with the presence of CAD and stroke. However, the values depicting the areas under the ROC curve were somewhat lower than what have been reported in the literature. This may be related to a lower cardiovascular risk in the Japanese population. Future prospective longitudinal studies are warranted to properly address this issue.

Carotid-femoral pulse wave velocity values reported in the present study appear high compared with some of the previously published studies [3,11] but are consistent with other studies [1,25]. The divergent cfPWV values are attributed to a different method used to measure the arterial path length (20% differences in mean values). In the latter studies, the arterial path length is the distance between the carotid and femoral recording sites, whereas the distance between carotid and femoral recording sites minus the distance from the carotid location to the supersternal notch is used in the former studies. Although this choice of methodology would produce approximately 20% differences in cfPWV values [24], it is still a matter of debate which arterial path length should be measured for the calculation of cfPWV. However, Sugawara *et al.* [24] have recently demonstrated that subtraction of the distance from the carotid location to the supersternal notch is the closest to the actual aortic length directly measured by the three-dimensional MRI. In baPWV, arterial path length is automatically estimated from one's height.

In summary, the newer automated measure of PWV (baPWV) was strongly associated with the gold standard measure of PWV (cfPWV). Additionally, both cfPWV and baPWV exhibit similar association with established risk factors for CAD and provide similar areas under the ROC curve for both stroke and CAD. Given the simplicity of the technique, baPWV is a promising new technique that is ideal for large-scale population studies and for incorporation into routine clinical settings. However, a more thorough analysis against a conventional technique is desirable.

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Relationship Between Blood Pressure Category and Incidence of Stroke and Myocardial Infarction in an Urban Japanese Population With and Without Chronic Kidney Disease

The Suita Study

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Background and Purpose—Chronic kidney disease (CKD) is increasingly recognized as an independent risk factor for stroke and myocardial infarction (MI). Few studies, however, have examined the relationship between blood pressure (BP) category and these diseases in subjects with and without CKD.

Methods—We studied 5494 Japanese individuals (ages 30 to 79, without stroke or MI at baseline) who completed a baseline survey and received follow-up through December 2005. The glomerular filtration rate (GFR) was estimated using the Modification of Diet in Renal Disease study equation modified by the Japanese coefficient. CKD was defined as an estimated GFR <60 mL/min/1.73m^2. BP categories were defined by the European Society of Hypertension and European Society of Cardiology 2007 criteria.

Results—In 64 395 person-years of follow-up, we documented 346 incidences of cardiovascular diseases (CVD; 213 strokes and 133 MI events). Compared with the GFR (≥90 mL/min/1.73m^2) group, the hazard ratios (95% confidential intervals) for stroke were 1.9 (1.3 to 3.0) in the GFR 50 to 59 mL/min/1.73m^2 group and 2.2 (1.2 to 4.1) in the GFR <50 mL/min/1.73m^2 group. Results for cerebral infarction were similar. Compared with the optimal BP subjects without CKD, the normal BP, high-normal BP, and hypertensive subjects without CKD showed increased risks of CVD and stroke; however the impact of each BP category on CVD (*P* for interaction: 0.04 in men, 0.49 in women) and stroke (0.03 in men, 0.90 in women) was more evident in men with CKD.

Conclusions—CKD may increase the association of BP and CVD in a Japanese urban population. (***Stroke.* 2009;40:2674-2679.**)

Key Words: chronic kidney disease ■ blood pressure category ■ stroke ■ myocardial infarction ■ epidemiology ■ prospective studies ■ general population

Recently, chronic kidney disease (CKD) has become a major public health problem and a risk factor for all-causes mortality, stroke, and myocardial infarction (MI).[1] In end-stage renal disease, the cardiovascular disease (CVD) mortality rate is more than 10 times as high as that in the general population.[2] In asymptomatic general populations or outpatients, a severely or moderately decreased glomerular filtration rate (GFR) has been shown by most but not all studies to be an independent risk factor for stroke and MI.[1] However, in low-risk or general populations, the relationship between levels of kidney function and clinical outcomes has not been as clear. Some studies have demonstrated no association between CKD and CVD,[3,4] whereas others have shown CKD as an independent risk factor for CVD.[5–8] These inconsistencies may be attributable to differences between the selected study populations as well as the severity of the CKD.

The frequency of hypertension is relatively higher in Japanese than in Western countries.[9] Hypertension is one of the major risk factors for both CVD and CKD. Recently, a larger prospective study has indicated that CKD increased the association between blood pressure (BP) categories and CVD, although the relevant data were gathered from 10 rural areas with different methods

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for the measurement of creatinine.[10] A few studies in general population have demonstrated a stronger association between BP and CVD in subjects with CKD.[5,10] We examined the association between BP category and incidence of stroke and MI subjects with and without CKD in a Japanese urban population.

Methods

Study Subjects

Suita city is located adjacent to Osaka city, which is the second largest metropolitan area in Japan. The Suita Study,[11–13] an epidemiological study of cerebrovascular and cardiovascular diseases, was based on a random sampling of 12 200 Japanese urban residents. As a baseline, participants (aged 30 to 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 people underwent regular health checkups between September 1989 and March 1994.

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 the baseline examination (n=534). After applying these exclusions, a total of 5494 participants aged 30 to 79 years old were selected. Informed consent was obtained from all participants. This study was approved by the Institutional Review Board of the National Cardiovascular Center.

Measurement of Blood Pressure and Covariates

Well-trained physicians measured BP 3 times using a mercury column sphygmomanometer, an appropriate-size cuff, and a standard protocol. Before the initial BP reading was obtained, participants were seated at rest for at least 5 minutes. First, systolic blood pressure (SBP) was measured for the purpose of obtaining approximate SBP levels. SBP and diastolic blood pressures (DBP) were taken as the average of the second and third measurements, which were recorded more than 1 minute apart.

At the time of the baseline examination, subjects were classified into 1 of the 5 BP categories based on the European Society of Hypertension and European Society of Cardiology (ESH-ESC) 2007 criteria[14]: 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 BP (SBP 130 to 139 mm Hg or DBP 85 to 89 mm Hg), and hypertensive (SBP ≥140 mm Hg or DBP ≥90 mm Hg). Antihypertensive drug users were classified according to their BP levels at the baseline survey. If the SBP and DBP readings for a subject were in different categories, the subjects were categorized into the higher of the two BP categories.

At the baseline examination, we performed routine blood tests that included serum total cholesterol, HDL cholesterol, and glucose levels. Physicians or nurses administered questionnaires covering personal habits and present illness. Body mass index (BMI) was calculated as weight (kilograms) divided by height (meters) squared. Hypercholesterolemia was defined as total cholesterol levels ≥5.7 mmol/L or current use of antihyperlipidemic medications. Diabetes was defined as a fasting plasma glucose level ≥7.0 mmol/L, a nonfasting plasma glucose level ≥11.0 mmol/L, or current use of antidiabetic medications.

Definition of CKD

Serum creatinine (Cre) was measured by noncompensated kinetic Jaffé methods. The glomerular filtration rate (GFR) of each participant was calculated from the Cre value and the age, using the MDRD equation modified by the Japanese coefficient (0.881), as follows[15]:

$$\text{GFR (ml/min/1.73 m}^2\text{)} = 0.881 \times 186 \times \text{age}^{-0.203} \times \text{Cre}^{-1.154} \text{ (for men)}$$

$$\text{and GFR (ml/min/1.73 m}^2\text{)} = 0.881 \times 186 \times \text{age}^{-0.203} \times \text{Cre}^{-1.154} \times 0.742 \text{ (for women).}$$

CKD was defined as an estimated GFR <60 mL/min/1.73m^2.

Confirmation of Stroke and MI and End Point Determination

The confirmation of stroke and MI in the Suita Study has been described elsewhere.[11–13] In brief, the 5 hospitals in this area, where acute stroke and MI patients were admitted, were all capable of performing computed tomographic scans or MRI. Medical records were reviewed by registered hospital physicians or research physicians who were blinded to the baseline data. Strokes were defined according to the U.S. National Survey of Stroke criteria.[16] For each stroke subtype (ie, cerebral infarction [thrombotic or embolic infarction], intracerebral hemorrhage, and subarachnoid hemorrhage), a definite diagnosis was established based on examination of computed tomographic scans, magnetic resonance images, or autopsies. Definite and probable MIs were defined according to the criteria set out by the MONICA project.[17] Sudden deaths of unknown origin were deaths that occurred within 24 hours from the onset of symptoms, and were also classified as MI. In this study CVD was defined as stroke or MI.

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. In addition, to complete our surveillance for fatal strokes and MIs, we conducted a systematic search for death certificates. All the data (health check-ups, questionnaires, and death certificates) were checked against medical records to confirm the incidence of CVD. 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 bearing a diagnosis of probable stroke or MI without registration of CVD incidence.

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).

Statistical Analysis

Analyses of variances and χ^2 tests were used to compare mean values and frequencies. The Cox proportional-hazard ratios (HRs) were fitted to the GFR categories and CKD after adjusting for sex and age in 5-year increments as stratified variables and other potential confounding factors at the baseline survey: namely, present illness of hypertension, hypercholesterolemia and diabetes, smoking status (never, quit, and current smoker), and drinking status (never, quit, and current drinker). The Cox proportional HRs were fitted to the combination of the BP categories and CKD (positive or negative) after adjusting for sex and age in 5-year increments as stratified variables and other potential confounding factors including an interactive term for CKD and BP categories. The fit of the proportional hazards model was evaluated by examining discrete regression models and by permitting the proportionality assumption to vary with time, and assessments of nonlinearity involving associations with blood pressure and GFR categories were made. The probability values for the model of interaction between CVD incidence and log (person year) were 0.38 in men and 0.81 in women. Proportionality was also checked by log-log survival plot.

To express the impact of CKD on CVD occurrence in the participants, we estimated the population attributable fraction (PAF, %). PAF was estimated as follows:

$$Pe \times (HR-1)/HR,$$

in which Pe is the proportion of incident cases in CKD, and HR is the multiple-adjusted hazard ratio.[18] All statistical analyses were conducted using the SAS statistical package software (release version 8.2, SAS Institute Inc).

Results

Figure 1 shows that the frequency of CKD increases with age in both men and women. At the baseline survey, both men and women with CKD (8.9% for men and 11.3% for women)

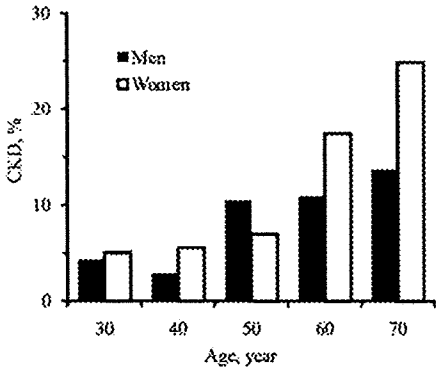

Figure 1. Frequencies of CKD according to sex and age.

were older, had higher prevalence of hypertension and hypercholesterolemia, and had a lower frequency of current drinking than those without CKD (Table 1).

During an average 11.7-year follow-up period, we documented 213 strokes and 133 MIs. In men and women combined, compared with subjects for GFR ≥90 mL/min/1.73m^2 the multivariable HRs (95% confidence intervals; CIs) for CVD incidence were 1.75 (1.22 to 2.50) in GFR=50 to 59 mL/min/1.73m^2 and 2.48 (1.56 to 3.94) in <50 mL/min/1.73m^2 (Table 2). In addition, the risks of CVD for each GFR category in men and women separately were similar to the risks for all participants. The multivariable HR (95% CIs) of CVD incidence for CKD was 1.70 (1.30 to 2.23) in all subjects (data not shown).

In Table 3, the multivariable HRs (95% CIs) for strokes were 1.94 (1.26 to 2.98) in the GFR=50 to 59 mL/min/1.73m^2 and 2.19 (1.18 to 4.06) in the GFR <50 mL/min/1.73m^2 compared with subjects for GFR ≥90 mL/min/1.73m^2 Results for cerebral infarction were similar to strokes. Age-adjusted HRs (95% CIs) for intracerebral hemorrhage were 1.93 (0.77 to 4.85) in the GFR=50 to 59 mL/min/1.73m^2 and 2.52 (0.72 to 8.80) in the GFR <50 mL/min/1.73m^2 (supplemental Table I, available online at http://stroke.ahajournals.org).

In Figure 2, compared with the optimal BP subjects without CKD, the normal BP, high-normal BP, and hypertensive subjects without CKD showed increased risks of CVD, whereas the impact of each BP category on CVD was more evident in subjects with CKD (probability values for interaction between CKD and BP category were 0.04 in men, 0.49 in women, and 0.06 in all subjects). Results of stroke were similar (probability values for the interaction were 0.03 in men and 0.90 in women, data not shown). Supplemental Table II shows the hazard ratios for the association between 10 mm Hg of SBP and the risk of CVD in subjects with or without CKD.

Using the HRs, we estimated the population attributable fraction of CVD to exposure for CKD at baseline by sex. We found that 8.3% in men and 17.6% in men with CVD incidences could be described as excessive incidence attributable to CKD.

Discussion

In this cohort study of a general urban Japanese population, CKD was a risk factor for CVD and its subtypes. A stronger association between BP and the incidence of CVD was

Table 1. Baseline Characteristics of Study Subjects According to Chronic Kidney Disease

	Men			Women		
Variables	CKD (−)	CKD (+)	*P* Value	CKD (−)	CKD (+)	*P* Value
No. of subjects	2341	229		2593	331	
Age at baseline, y	55±13	61±12	<0.001	53±13	62±12	<0.001
Body mass index, kg/m^2	22±3	23±3	<0.001	22±3	22±3	0.332
Blood pressure category, %			0.005			<0.001
Optimal	31.7	24.0		43.9	27.2	
Normal	19.2	14.4		16.6	15.4	
High-normal blood pressure	16.2	20.5		14.0	14.8	
Hypertension	32.9	41.1		25.5	42.6	
Present illness, %*						
Hypercholesterolemia	28.1	35.8	0.014	40.7	54.7	<0.001
Diabetes	6.1	6.6	0.791	3.2	5.4	0.036
Smoking status, %			0.007			0.713
Current	51	42		12	12	
Quit	30	40		4	4	
Never	19	18		84	83	
Drinking status, %			0.024			0.017
Current	76	68		34	26	
Quit	3	6		2	3	
Never	21	26		65	71	

*Hypercholesterolemia; antilipidemic drug use or total cholesterol ≥5.7 mmol/L (220 mg/dl), diabetes; antihyperglycemic drug use or fasting blood sugar ≥7.0 mmol/L (126 mg/dl).

Plus–minus values are means±SD.

Table 2. Age and Multivariable Adjusted Hazard Ratios (95% CIs) for Incidence of Cardiovascular Disease† According to Category of Glomerular Filtration Rate by Sex

	Glomerular Filtration Rate, ml/min/1.73m^2				
Variables	≥90	60 to 89	50 to 59	<50	*P* for Trend
Men and Women					
Cases, n	94	176	51	25	
Person-years	28 736	29 336	4764	1558	
Age-adjusted	1	1.22 (0.94–1.58)	1.71 (1.20–2.42)	2.49 (1.59–3.90)	<0.001
Multivariable adjusted*	1	1.21 (0.93–1.58)	1.75 (1.22–2.50)	2.48 (1.56–3.94)	<0.001
Men					
Cases, n	50	124	24	11	
Person-years	12 092	14 835	1928	522	
Age-adjusted	1	1.20 (0.85–1.70)	1.63 (1.00–2.68)	2.17 (1.11–4.23)	0.008
Multivariable adjusted*	1	1.21 (0.85–1.70)	1.78 (1.08–2.94)	2.38 (1.21–4.68)	0.004
Women					
Cases, n	44	52	27	14	
Person-years	16 644	14 502	2836	1036	
Age-adjusted	1	1.22 (0.81–1.83)	1.79 (1.09–2.92)	2.81 (1.53–5.18)	<0.001
Multivariable adjusted*	1	1.21 (0.80–1.84)	1.76 (1.05–2.93)	2.31 (1.20–4.43)	0.002

*Multivariable adjusted for age, BMI, smoking, drinking, and present illness (hypertension, diabetes, and hypercholesterolemia).
†Cardiovascular disease includes both stroke and MI.

observed in the presence of CKD. Furthermore, we found that 8% in men and 18% in women of CVD incidence may be derived from CKD cases.

Go et al reported that both severe and moderate renal diseases were risk factors for CVD incidence.[6] A pooled analysis of community-based studies demonstrated that CKD is an independent risk factor for the composite of all-cause mortality in blacks and whites and CVD incidence in blacks.[5] In contrast, NHANES I did not provide relationships between mortality and moderately higher serum creatinine levels.[4] The Framingham Heart Study and Offspring cohorts have shown no significant association between the presence of kidney disease and CVD incidence.[3]

The results of our study are essentially compatible with previous cohort studies in Japan. The Hisayama study demonstrated that CKD was a risk factor for incidence of coronary heart disease in men and ischemic stroke in women.[8] The Ohasama study indicated that decreased kidney function increased the risk of first symptomatic stroke events.[19] This study used creatinine clearance rather than estimated GFR. Irie et al showed that subjects with GFR <60 had a higher risk of CVD mortality[7] but did not examine the risk of GFR 50 to 59 mL/min/1.73m^2 The NIPPON DATA 90 indicated that CKD was an independent risk factor for cardiovascular death in a community-dwelling Japanese population.[20] The end point of these studies was also mortality. Ninomiya et al

Table 3. Age-Sex and Multivariable Adjusted Hazard Ratios (95% CIs) for Incidence of All Strokes, Cerebral Infarction, and Myocardial infarction According to Category of Glomerular Filtration Rate

	Glomerular Filtration Rate, ml/min/1.73m^2				
Variables	≥90	60 to 89	50 to 59	<50	*P* for Trend
Person-years	28 258	28 690	4528	1446	
All strokes					
Cases, n	65	99	36	13	
Age and sex adjusted	1	1.02 (0.73–1.41)	1.78 (1.17–2.70)	1.93 (1.05–3.54)	0.004
Multivariable adjusted*	1	1.04 (0.74–1.45)	1.94 (1.26–2.98)	2.19 (1.18–4.06)	<0.001
Cerebral infarction					
Cases, n	42	66	24	9	
Age and sex adjusted	1	0.99 (0.66–1.49)	1.72 (1.03–4.19)	2.01 (0.97–4.19)	0.020
Multivariable adjusted*	1	0.98 (0.65–1.49)	1.81 (1.07–3.07)	2.26 (1.07–4.78)	0.008
Myocardial infarction					
Cases, n	29	77	15	12	
Age and sex adjusted	1	1.68 (1.08–2.61)	1.64 (0.87–3.09)	4.26 (2.14–8.45)	<0.001
Multivariable adjusted*	1	1.60 (1.03–2.49)	1.51 (0.80–2.88)	3.56 (1.73–7.30)	0.002

*Multivariable adjusted for age, sex, BMI, smoking, drinking, and present illness (hypertension, diabetes, and hypercholesterolemia).

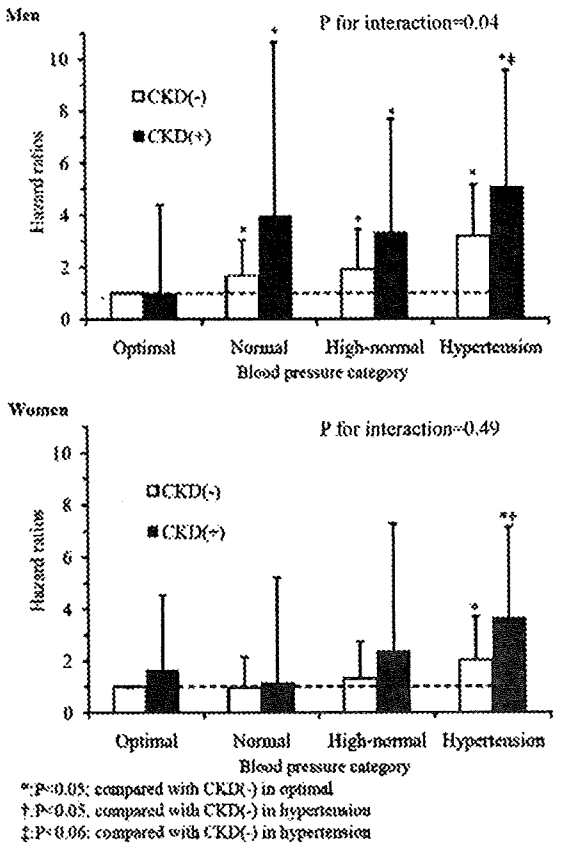

Figure 2. The combination of CKD and BP categories on multivariable hazard ratios for CVD. Data for men and women are presented separately. Multivariable analyses are adjusted age in 5-year increments as stratified variables and other potential confounding factors of hypercholesterolemia, diabetes, and smoking and drinking status.

has recently reported that CKD was risk factors for CVD and stroke in women and that CKD increased the association between BP category and CVD in all subjects from 10 combined different cohort studies using different methods of creatinine measurement.[10] All of our samples were measured using the same analyzer at one laboratory.

Compared with the previous studies, our study has several methodological strengths. First, we could perform subanalysis by age and CVD subtype, because we evaluated a large cohort of participants. Second, each participant's health status was checked during a clinical visit at the National Cardiovascular Center every 2 years. In addition, each year, a health questionnaire was given to each participant via mail or telephone. We could evaluate the registry of CVD incidence with the data obtained from clinical visits, annual questionnaires, or death certificates. Finally, our cohort population was selected at random from an urban population, in contrast to most other cohort studies in Japan, which have relied on rural populations.[7,8,19]

There may be some reasons why CKD is more positively associated with CVD in blacks or Japanese than in whites. Blacks and Japanese are more likely to have hypertension at an earlier age.[9,21] Therefore, the period of hypertension exposure tends to be longer in blacks and Japanese than in whites. The GFR estimation has been adjusted by a factor suitable for Japanese populations.[15]

Reduced kidney function is associated with increased levels of inflammatory factors,[22,23] abnormal apolipoprotein levels,[22] elevated plasma homocysteine,[22] enhanced coagulability,[23] anemia, left ventricular hypertrophy, increased arterial calcification, endothelial dysfunction, and arterial stiffness.[2,24] How these and other factors interact to increase the risk of adverse outcomes remains unclear but is the focus of ongoing investigations.[24]

Subjects with GFR levels of 50 to 59 mL/min/1.73m^2 were observed to be at risk for stroke. It is desirable to prevent CVD in subjects with both high-risk (<50 mL/min/1.73m^2) and less severe kidney disease (50 to 59 mL/min/1.73m^2), although an accelerated decline in GFR occurred for the subjects whose initial GFR <50 mL/min/1.73m^2.[25]

Hypertension is a strong risk factor for early decline in kidney function; hypertensive patients (BP ≥160/95 mm Hg) have a 5-fold greater decline in GFR (2.7 mL/min/1.73m^2/yr) compared with patients with BP <140/90 mm Hg.[26] Furthermore, in this study, the association between BP and the incidence of CVD were evident by CKD. The risk of CVD was higher in CKD subjects with normal and high-normal BP than in non-CKD subjects in the same BP categories. Using the combination of BP and CKD, it could be possible to screen more efficiently for higher risk of stroke and MI. This is compatible with the CKD clinical guidelines, which state that the preferable BP for subjects with CKD is 130/80 mm Hg.[27] For the prevention of CVD incidence for all hypertensive subjects in health check-ups, it might be desirable to measure serum creatinine levels and to intervene in lifestyle modification such as reducing salt intake, more frequent exercise, or quit smoking.

Our study has several limitations. The primary limitation is dilution bias,[28] in that the current study was based on single-day measurement of creatinine levels. The creatinine levels might have been misclassified, despite the fact that measurements of creatinine levels on a single day have been found to be accurate in other epidemiological studies. Second, we did not perform a creatinine clearance test or 2 measurements of serum creatinine at least 3 months apart. Although our definition of CKD is based on a single assessment of serum creatinine, the equation provides an accurate estimated GFR value.[15] Third, even with the moderate sample size (n=5494) and 12-year duration, the numbers of end points were limited, especially when the data were stratified by 2 variables, such as sex and glomerular filtration rates. A study with more participants with the same protocol is required to validate to the association between BP category and CVD by CKD.

In conclusion, CKD was associated with an increased risk for stroke and MI in a general urban Japanese population. Furthermore, the association between BP and CVD may be evident by CKD. To prevent the incidence of stroke and MI, it is necessary for subjects with CKD to control their BP by lifestyle modification and proper clinical treatment.

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Disclosures

None.

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