冠動脈疾患

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KEY WORDS
●心臓リハビリテーション

はじめに

わが国では，冠動脈疾患に対する心臓リハビリテーション(以下心リハ)はその重要性が認識されているにもかかわらず，急性期における病院内での心リハはもとより，回復期・維持期心疾患患者に積極的に実施している施設は少ない。Gotoらは，日本における急性心筋梗塞後患者の回復期心リハ参加率が，保険診療算定のための施設基準を満たしている病院では34.7%であるのに対し，満たしていない病院でのそれは8.0%と極端に少ない事実を報告している。そしてわが国における心筋梗塞後患者の回復期心リハ参加率は4.8～11.7%と算出している[1]。また，冠動脈バイパス術(CABG)後の患者に対する心リハにおいても実施施設は限られており，心臓外科医は心リハの重要性を認識しているにもかかわらず，心リハに関わる時間がなく，スタッフ不足や施設不備などで実施に踏み切れないとの報告がある[2]。

冠動脈疾患の心リハの目的は，体力回復もしくは向上，心疾患に起因する症状(たとえば呼吸困難，胸痛)の軽減，再発予防，クオリティーオブライフ(QOL)の向上ならびに生命予後の延長にある。より具体的に述べるなら，冠動脈疾患患者が与えられた疾患の範囲内で，できるだけ長期にわたり活動的ならびに生産的な生活を獲得するのを援助していくことが心リハの究極目標なのである。その内容として，①身体的，精神的，職業的そして余暇における状態の最適化，②疾患の根本にある動脈硬化の進展や悪化の阻止，③再梗塞や突然死のリスク予防と狭心痛の軽減など[3]があげられる。このように考えると心リハの実施内容は単に運動療法のみならず，食事療法，生活指導，禁煙指導，ストレスマネージメントを含めた包括的なリハを目指すべきであると考えられる。

Coronary artery disease.
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Ⅰ．心臓リハビリテーションの効果と機序(表1)

心リハの予後改善効果についてはすでにメタ分析などで実証されており，さらにそれ以外の多面的効果が認められている。近年では運動療法における分子生物学的機序についても徐々に明らかにされつつある。

1．予後改善

運動療法を主体とした包括的心リハの予後改善効果に関しては，1989年にO'Connorらが22のrandomized trialの結果を報告している[4]。4,554名の患者を平均3年間フォローアップした結果，総死亡のオッズ比は0.80，心血管系死亡は0.78，致死的な心筋梗塞は0.75であり有意な減少効果が導き出された。また梗塞後の突然死に関しては，1年後のオッズ比が0.63と有意であったが，2年後，3年後では減少は認められたものの有意ではなかった。また，非致死的な心筋梗塞に関しては有意差が出なかった。以上から，心リハによりおよそ20%のリスク軽減効果が期待できるとしている。

2．動脈硬化退縮

Ornishは，1990年のThe Life Style Heart Trialにおいて，48人の冠動脈疾患患者に対してコントロールをおいた前向きのランダム研究を1年間実施した[5]。その結果，包括的な生活改善を行った介入群では冠動脈の平均動脈狭窄が61.1%から55.8%に有意に退縮し，コントロール群は61.7%から64.4%に増悪した。全体としては介入群の患者の82%が退縮方向に改善したとしている。介入群の包括的生活改善の内容であるが，1年間の長期にわたる低脂肪の野菜中心の食事療法，禁煙，ストレスコントロールと中程度の運動療法である。このTrialをOrnishはさらに5年間継続した[6]。その結果，コントロール群では冠動脈の平均動脈狭窄が40.7%から51.9%に悪化したのに対し，介入群は40.7%から37.3%に改善し，どちらの群も1年後より5年後のほうが顕著な結果が出た(図1)。

表1．運動療法の身体効果

項目	内容	ランク
運動耐容能	最高酸素摂取量増加	A
	嫌気性代謝閾値増加	A
症状	心筋虚血閾値の上昇による狭心症発作の軽減	A
	同一労作時の心不全症状の軽減	A
呼吸	最大下同一負荷強度での換気量減少	A
心臓	最大下同一負荷強度での心拍数減少	A
	最大下同一負荷強度での心仕事量(心臓二重積)減少	A
	左室リモデリングの抑制	A
	左室収縮機能を増悪せず	A
	左室拡張機能改善	B
	心筋代謝改善	B
冠動脈	冠狭窄病変の進展抑制	A
	心筋灌流の改善	B
	冠動脈血管内皮依存性，非依存性拡張反応の改善	B
中心循環	最大動静脈酸素較差の増大	B
末梢循環	安静時，運動時の総末梢血管抵抗減少	B
	末梢動脈血管内皮機能の改善	B
炎症性指標	CRP，炎症性サイトカインの減少	B
骨格筋	ミトコンドリアの増加	B
	骨格筋酸化酵素活性の増大	B
	骨格筋毛細管密度の増加	B
	Ⅱ型からⅠ型への筋線維型の変換	B
冠危険因子	収縮期血圧の低下	A
	HDLコレステロール増加，中性脂肪減少	A
	喫煙率減少	A
自律神経	交感神経緊張の低下，副交感神経緊張亢進	A
	圧受容体反射感受性の改善	B
血液	血小板凝集能低下	B
	血液凝固能低下	B
予後	冠動脈性事故発生率の減少	A
	心不全増悪による入院の減少	A(CAD)
	生命予後の改善(全死亡，心臓死の減少)	A(CAD)

A：証拠が十分であるもの，B：報告の質は高いが報告数が十分でないもの
CAD：冠動脈疾患
心血管疾患におけるリハビリテーションに関するガイドライン(2007年改訂版)
循環器病の診断と治療に関するガイドライン(2006年度合同研究班報告)
日本循環器学会ホームページ：http://www.j-circ.or.jp/guidelinendex.htmより

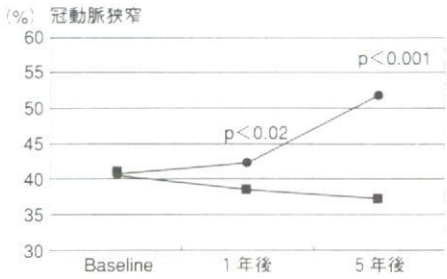

図1．心臓リハビリテーションの長期介入による冠動脈狭窄症に及ぼす効果[6]
●：コントロール群，■：介入群

3．血管内皮機能改善

SchulerやHambrechtらは，運動トレーニングにより冠動脈の動脈硬化が進行した症例においても心筋灌流の改善が認められることを報告し[7]，それを裏付ける根拠として運動が冠動脈における血管内皮機能に及ぼす影響を調べた[8]。アセチルコリン投与により冠攣縮を生じる内皮機能異常を示す19人の患者を，コントロール群と運動療法群に無作為に分けた。4週間の間隔をあけアセチルコリン冠動脈内注入による血管径変化と血流速度を計測した。コントロール群は通常の生活を継続した。その結果，開始前は両グループとも，同様なアセチルコリンに対する血管反応を示したが，4週間の運動トレーニング後はアセチルコリン7.2 μg/分投与に対する血管収縮反応は54％減少した。血管径の収縮はトレーニング前0.41±0.05mm(mean±SE)であったのに対しトレーニング後は0.19±0.07mmに改善した。これはコントロール群に比べ有意であった。

以上より，運動トレーニングは冠動脈における血管内皮依存性の拡張反応を改善させ，これは心外膜側血管のみならず抵抗血管においても認められたと結論している。

4．自律神経系改善

心筋梗塞後の運動療法における自律神経機能改善効果が注目されているが，Schwarzらのグループによるこの研究は，運動トレーニングが副交感神経活動を亢進させ不整脈による突然死を長期に予防することを報告している[9]。副交感神経機能を反映するbaroreflex sensitivity(BRS)をマーカーとして梗塞後の死亡率の減少をみたものである。95名の初回心筋梗塞男性連続症例を無作為に4週間の運動トレーニング群とコントロール群に振り分けた。その結果，4週間後，トレーニング群はBRSが26%改善したが，コントロール群に変化はなかった。さらにトレーニング群のなかでBRSが3 ms/mmHg以上変化したものをresponder，3ms/mmHg未満をnon-responderとして10年間の死亡率の差をみたところ，responderは16例中死亡0，コントロール群とnon-responderを加えたグループは79例中死亡18例(23％)と両者間に有意な差が認められた。したがって，運動トレーニングは副交感神経活動を亢進させ，自律神経のバランスを好ましい方向に変える結果，梗塞後患者の長期予後を改善させると結論している。

5．冠動脈インターベンション後の心臓リハビリ

Belardinelliらは PTCAまたはステント治療後の運動トレーニングが運動耐容能，QOLに与える影響をみるために，118名(平均年齢57±10歳，男性：女性99：19)の冠動脈インターベンションを実施した虚血性心疾患連続症例をコントロール群(59名)と運動療法群(59名)に無作為に振りわけた[10]。この研究は，期間中抗高脂血症薬の投与は行わず，インターベンション施行の25±7日後に運動負荷試験を行い観察期に入った。その結果，運動療法群はpeak VO2が26%，QOLスコアが26.8%有意に向上した。また冠危険因子については，運動療法群に関してのみ有意に減少した(表2)。冠動脈造影上再狭窄率についてはコントロール群33%，運動療法群29％と有意差は認められなかった。以上より，中程度の運動トレーニングは冠動脈インターベンションを実施した患者においても耐容能ならびにQOLを向上させ，再狭窄率には悪影響を及ぼさず，さらにイベント発生率ならびに再入院率を低下させたと結論づけている。

6．炎症反応ならびに酸化ストレス抑制

粥状動脈硬化病変の形成には，酸化LDLによる内皮細胞の障害と単球・マクロファージの内皮細胞への接着と侵入が発端となる。その際，接着因子やケモカイン(MCP-1，IL-8)の発現が亢進し，単球・マクロファージの病巣への遊走と内皮下への侵入が進行する。内皮下に侵入したマクロファージは酸化LDLを取り込み泡沫細胞化し，粥腫内で炎症性サイトカイン(IL-6，TNF-α，

表2．冠動脈インターベンション後の心臓リハビリテーションの効果

	Exercise Group		Control Group		p
	Entry	6 Months	Entry	6 Months	
cardiopulmonary exercise test					
Peak VO2	18.6±4.6	23.7±7.9	20.5±4.4	19.4±4.2	<0.001
AT	10.3±4.2	13.1±4.5	10.8±3.8	9.9±4.4	<0.001
O2 pulse$_{75watts}$	8.7±3.2	10.4±2.8	7.9±3.5	7.4±3.7	<0.001
coronary risk factors					
Smoking(%)	40(68)	5(8.5)	37(62)	16(27)	0.005
T-Chol	235±33	212±31	225±41	255±45	<0.001
LDL	148±41	131±42	138±38	148±41	<0.001
HDL	34±19	39±16	36±25	32±28	0.02
TG	178±55	155±41	181±62	189±58	0.02

ETICA trial(Exercise Training Intervention after Coronary Angioplasty)より

IL-1β)やMMPsを産生し，プラークを脆弱化する。以上の動脈硬化の機序でわかるように，動脈硬化発生・進展には炎症に関わるさまざまな因子が関わっていることがわかる。一方，心リハにおいてCRP(C-reactive protein)が減少する事実も報告されるようになってきている[11]。

血管内皮機能障害には，酸化ストレスが密接に関わっている。すなわちeNOSの産生を酸化ストレス物質が抑え内皮機能を低下させることが知られている。Adamsらは冠動脈バイパス手術を行う冠動脈疾患患者の内胸動脈を用いて，運動トレーニングの抗酸化作用について無作為コントロール研究を行い[12]，運動トレーニング群のほうがコントロール群と比較してNADP(H)産生が有意に低下し，ROS(reactive oxygen species)産生も減少すること，そしてmRNAレベルでのAT_1-R(angiotensin Ⅱ type1 receptor)の発現が低下し，AT_2-R(angiotensin Ⅱ type2 receptor)の発現が増加することを報告した。これより，運動トレーニングがAngⅡによる血管収縮を改善させる分子生物学的機序として，トレーニングがNADP(H) oxidaseとAT_1-R発現を減少させ，その結果局所のROS産生を低下させることから，血管内皮機能が改善したと結論づけた。

Ⅱ．心臓リハビリテーションの運動療法

運動の種類は，有酸素運動が主体になる。強度のコントロールが容易であることから，回復期は歩行・速歩運動が中心となる。維持期では，スポーツ種目を取り入れるなどしてコンプライアンスの維持を図る。また，主運動の前後には，ストレッチングを含めた準備運動と整理運動を実施するようにしたい。

運動強度の設定が，安全確保のうえで最も重要である。強度は心拍数で指示するのが一般的であるため，患者には自己の脈の触診法について必ず指導しておく。運動強度設定は，運動負荷試験を行ってその結果をもとに処方する。処方心拍数の決定法にはいくつかあり，最近ではAT(anaerobic threshold：嫌気性代謝閾値)を利用した処方が循環器領域で行われている。最高酸素摂取量の40～60%，最高心拍数の50～70%あるいは心拍数予備能の40～60%とされている。簡便にはKarvonenの式を用いて，k値を0.4から0.6として求めた値を，トレーニング心拍数として指導する。またボルグ指数の12から14を用いるのも実際的である。運動負荷試験において，狭心痛やST低下が生じた場合は，その時点の心拍数を最高心拍数とする。

運動時間は，主運動としての有酸素運動を最低20分(20分から60分)行う。運動頻度は，最低週3回(週3回から5回)確保したい。また運動実施前には，運動指導者による実地指導を受けておくことが望まれる。回復期の1～2ヵ月は，運動耐容能の改善が最も顕著に現れるので，この時期に運動負荷試験を再度行い，社会復帰の判断と復帰後の運動指導の資料とする。維持期になり，状態が安定してくれば，運動負荷試験は6ヵ月ごととして処方変更を行っていく。当院ではスポーツ種目(太極拳，卓球や低強度エアロビクス)を用いた集団スポーツ運動療法を行っている[13](図2)。スポーツを用いた集団運動療法(集団スポーツ運動療法またはスポーツリハビリテーション)は，ドイツにその源流をみることができる。集団スポーツ運動療法は，回復期の虚血性心疾患患者が主な適応であるが，維持期の患者や冠危険因子保有患者などを含めてもよい。スポーツを用いるために運動自体に楽しみがありコンプライアンスもよく，長期間実践することにより効果が十分期待できる[14]。さらに野外特別プログラムとして，四季折々にあわせたハイキングなどを計画すると，患者のみならずスタッフの運動療法への取り組みが積極的になる。

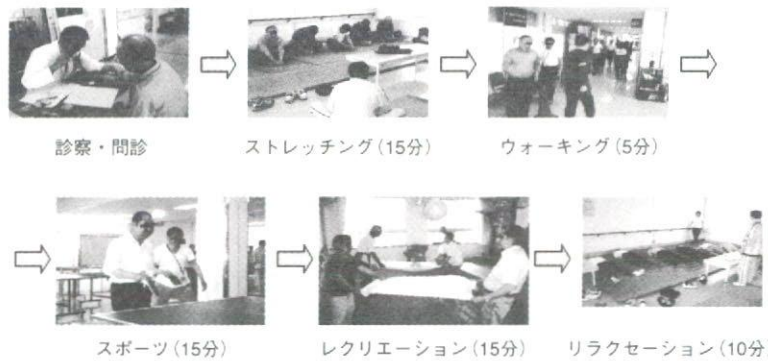

図2．埼玉医科大学病院における集団スポーツ運動療法

筆者のグループはこれまでに，慢性期の安定した虚血性心疾患患者を対象に富士登山や琵琶湖一周サイクリングなどを実践してきており，その安全性と効果を報告している[15][16]。

従来は禁忌とされていたレジスタンストレーニングであるが，心リハ領域におけるレジスタンストレーニングの意義は，特に運動能力の低い患者やデコンディショニングの影響の残る患者に対して作業能力を高めるとされている。また，その他の患者においては有酸素能力の増大には貢献しないものの，筋力がアップすることにより患者の社会復帰や日常活動性を高め，QOLを向上させる目的で実施されている[17]。

おわりに

現在のわが国の心リハの問題点は，心リハ実施施設が少ないことがあげられる[18]。その理由として，心リハシステムがまだ発展していないことのほかに，循環器医を中心とした医療者に循環器疾患予防としての心リハの意義がまだ十分理解されていないこと，そしてわが国独自の心リハのエビデンスがまだ十分でないことが考えられる。わが国の心リハの実態，効果と予後，費用効果分析，安全性や心リハ導入のための具体例や必要資源などの報告が待たれる。

文　献

1) Goto Y, Itoh H, Adachi H, et al：Use of exercise cardiac rehabilitation after acute myocardial infarction. Circ J 67：411－415, 2003
2) 小山照幸，山田純生，宮野佐年，他：心臓術後心臓リハビリテーションの現状と課題-外科医の立場から-．心臓リハビリテーション 6：91－93, 2001
3) Hamm LF, et al：Exercise training for the coronary patient. *in* Rehabilitation of the coronary patient, ed by Wenger NK, Hellerstein HK, New York. Churchill Livingstone, 367－402, 1992
4) O'Connor GT, Buring JE, Yusufs, et al：An overview of randomized trials of rehabilitation with exercise after myocardial infarction. Circulation 80：234－244, 1989
5) Ornish D, Brown SE, Scherwitz LW, et al：Can life style changes reverse coronary heart disease? Lancet 336：129－133, 1990
6) Ornish D, Scherwitz LW, Billings JH, et al：Intensive lifestyle changes for reversal of coronary heart disease. JAMA 280：2001－2007, 1998
7) Schuler G, Hambrecht R, Schlierf G, et al：Myocardial perfusion and regression of coronary artery disease in patients on a regimen of intensive physical exercise and low fat diet. JACC 19：34－42, 1992
8) Hambrecht R, Wolf A, Gielen S, et al：Effect of exercise on coronary endothelial function in patients with coronary artery disease. N Engl J Med 342：454－460, 2000
9) La Rovere MT, Bersano C, Gnemmi M, et al：Exercise-induced increase in baroreflex sensitivity predicts improved prognosis after myocardial infarction. Circulation 106：945－949, 2002
10) Belardinelli R, Paolini I, Cianci G, et al：Exercise training intervention after coronary angioplasty：The ETICA Trial. JACC 37：1891－1900, 2001
11) Caulin-Glaser T, Falko J, Hirdman L, et al：Cardiac rehabilitation is associated with an improvement in c-reactive protein levels in both men and women with cardiovascular disease. J Cardiopul Rehabil 25：332－336, 2005
12) Adams V, Linke A, Krankel N, et al：Impact of regular physical activity on the NADP(H) oxidase and angiotensin receptor system in patients with coronary artery disease. Circulation 111：555－562, 2005
13) Nohara R, Kambara H, Mohiuddin IH,

et al：Cardiac sports rehabilitation for patients with ischemic heart disease. Jpn Circ J 54：1443－1450，1990
14) 牧田　茂，森川修一，浜崎　博，他：8年間にわたる長期集団スポーツ運動療法の実績とその評価-運動施設のない一般病院の試み-．京都医学会雑誌 45：1－7，1998
15) 浜崎　博，他：心臓病運動療法における登山の試み．臨床スポーツ医学 10：1354－1358，1993
16) 今井　優，他：集団スポーツ心臓リハビリテーション-サイクリングを実践して-．日本病院会雑誌 41：549－554，1994
17) American College of Sports Medicine Position Stand：The recommended quantity and quality of exercise for developing and maintaining cardiorespiratory and muscular fitness，and flexibility in healthy adults. Med Sci Sports Exerc 30：975，1998
18) Goto Y，Saito M，Iwasaka T，et al：Poor implementation of cardiac rehabilitation despite broad dissemination of coronary interventions for acute myocardial infarction in Japan -a nationwide survey -. Circ J 71：173－179，2007

Original Article

The Optimal Target Blood Pressure for Antihypertensive Treatment in Japanese Elderly Patients with High-Risk Hypertension: A Subanalysis of the Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) Trial

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For hypertensive patients, it has been recommended that antihypertensive treatment strategies be chosen on the basis of the patients' conditions and age. In this sub-analysis of the Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) trial, we aimed to compare the effects of candesartan and amlodipine on cardiovascular mortality and morbidity in Japanese elderly patients with high-risk hypertension and to determine their optimal target blood pressures (BPs). The effect of the two drugs on cardiovascular events was compared across different age subgroups (<65, 65–74, and 75–84 years) by use of Cox regression analysis. We also evaluated the associations between the achieved BP and the incidence of cardiovascular events, irrespective of the allocated drugs in multiple Cox regression analyses. The incidence of cardiovascular events was independent of the assigned treatment for each of the age subgroups. For systolic BP (SBP), cardiovascular risk increased steeply when control of SBP was inadequate (higher than 140 mmHg) for patients younger than 65 years old and those between 65 and 74 years old. Patients aged 75 to 84 years old showed a significantly increased risk when their SBP was ≥150 mmHg. For diastolic BP (DBP), the risk significantly increased for the subgroup aged 75 to 84 years when the DBP was ≥85 mmHg. The present results show that candesartan and amlodipine are equally effective in Japanese elderly patients with high-risk hypertension. Moreover, it is important to control BP levels to less than 150/85 mmHg for patients 75–84 years old. (*Hypertens Res* 2008; 31: 1595–1601)

Key Words: **hypertension, elderly, blood pressure, Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J)**

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The CASE-J trial was funded by EBM Research Center, Kyoto University of Graduate School of Medicine, with an unrestricted grant from Takeda Pharmaceutical Co. The Japanese Society of Hypertension supported the trial. T.O., K.N., K.U., K.S., H.M., and T.S. have received lecture fees from Takeda Pharmaceutical Co. and Pfizer Japan Inc.

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Received April 6, 2008; Accepted in revised form May 14, 2008.

Introduction

Diuretics and calcium channel blockers (CCBs) are generally recommended for the treatment of hypertension in elderly patients, and many reports have provided evidence of their efficacy (*1–4*). However, the SCOPE trial and a sub-analysis of the LIFE study demonstrated that angiotensin II receptor blockers (ARBs) have beneficial effects for hypertension in the elderly or in patients with isolated systolic hypertension (ISH), which often affects older people (*5, 6*). Therefore, it is important to compare the efficacy of ARBs and CCBs in senior patients.

The Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) trial demonstrated that ARB candesartan and CCB amlodipine equally suppressed total cardiovascular (CV) morbidity and mortality in high-risk Japanese hypertensive patients under strict blood pressure (BP) control (*7*). The ages of the subjects in the study varied widely, from 20 to 84 years of age, with an average age of 63.9±10.5 years.

The target BP for treatment of elderly patients with hypertension (*8*) is generally lower than 140/90 mmHg, although this target is not necessarily supported by direct evidence (*9*). Although lower target BPs are epidemiologically associated with better outcomes, one intervention trial indicated that a systolic BP (SBP) lower than 150 mmHg is optimal (*10*), whereas other results have suggested the existence of a J-shaped phenomenon (*11, 12*). Thus, a consensus regarding the optimal target BP for elderly hypertensive patients has not yet been determined. Furthermore, it has been reported that, for some senior age categories (>80 or 85 years old), patients with lower BPs have lower survival rates compared with patients with higher BPs (*13–15*).

The present sub-analysis of the CASE-J trial was conducted to compare the efficacies of ARB candesartan and CCB amlodipine in high-risk Japanese elderly hypertensive patients, particularly in those aged 75 years or older. Additionally, we sought to determine an adequate target BP for elderly patients by examining associations between the achieved BP and the incidence of CV events.

Methods

Trial Design

The CASE-J trial was a prospective, randomized, open-label study with a blinded endpoint assessment comparing the efficacy of candesartan with that of amlodipine in high-risk Japanese hypertensive patients. The Ethics Committee at the Kyoto University Graduate School of Medicine approved the CASE-J trial protocol according to the principles of the Helsinki Declaration. Details of the primary results from this study have been described elsewhere (*7*).

Briefly, the trial involved 4,728 high-risk hypertensive patients. High risk was defined as the presence of any one of the following factors: severe hypertension; type 2 diabetes; history of stroke or transient ischemic attack; history of myocardial infarction, angina pectoris, or left ventricular hypertrophy; renal dysfunction; or arteriosclerotic peripheral artery disease (*16*). The ages of the patients ranged from 20 to 84 years old. After randomization, 2,364 patients were assigned to the candesartan group, and 2,364 patients were assigned to the amlodipine group (the mean of 3.2 years follow-up). The primary endpoint of the CASE-J trial was CV mortality and morbidity, which was a composite of sudden death; cerebrovascular events, including stroke or transient ischemic attack; cardiac events, including heart failure, angina pectoris, or acute myocardial infarction; renal events, including a serum creatinine concentration ≥4.0 mg/dL or a doubling of the serum creatinine concentration; and vascular events, including dissecting aortic aneurysm or arteriosclerotic occlusion of a peripheral artery (*7, 16*). The CASE-J trial followed the CV events repeatedly until a patient died, and a 97.1% follow-up rate was achieved. BP was measured every 6 months after registration. According to the guideline proposed by the Japanese Society of Hypertension, two consecutive BP measurements were taken from each patient in a sitting position at a clinic (*17*).

Patients were categorized by age into three subgroups (<65, 65–74, and 75–84 years old) in the sub-analysis. Outcome measures were the same as for the CASE-J trial, which was a composite of CV mortality and morbidity. Additionally, each endpoint, which is sudden death, cerebrovascular events, cardiac events, and renal events, was independently assessed.

Statistical Methods

Patient characteristics were reported as mean±SD or percentage for each of three age subgroups. A Cox proportional hazard model stratified by diabetic status at baseline (a stratified factor for the allocation in the CASE-J trial) was used to assess differences between the candesartan and amlodipine groups in the time to a CV event for each age subgroup. The treatment effect of candesartan compared with that of amlodipine was measured using the hazard ratio (HR) and a 95% confidence interval (CI). Only the time to the first CV event was considered for the composite primary endpoint. Similarly, only the first event in each category was counted for each endpoint (sudden death, cerebrovascular events, cardiac events, or renal events).

To determine the optimal target BP levels for each of the three age groups, we targeted patients who had at least one follow-up visit without a CV event. We defined the achieved BP as the BP measured during the most recent visit before the occurrence of a CV event or as the BP obtained at the end of the follow-up. The achieved SBPs and DBPs were classified into five categories (for SBP, <130 mmHg, 130–139 mmHg, 140–149 mmHg, 150–159 mmHg, and ≥160 mmHg; for DBP, <75 mmHg, 75–79 mmHg, 80–84 mmHg, 85–89

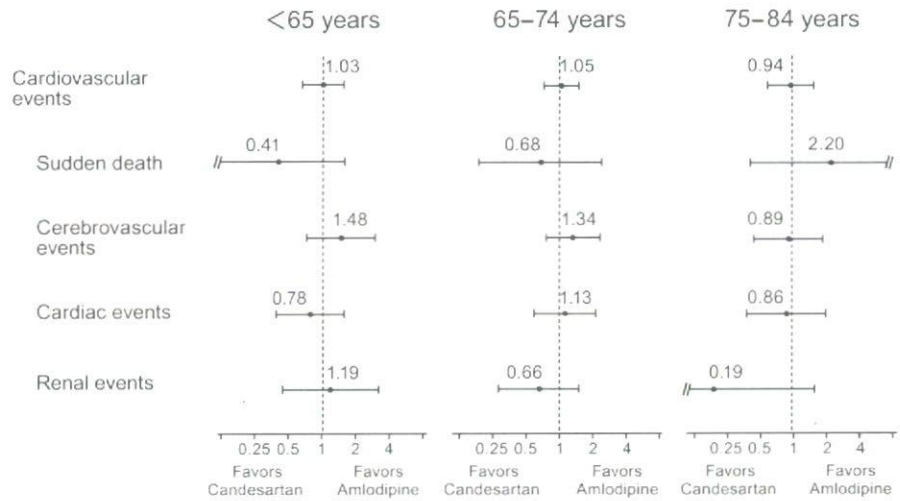

Fig. 1. *Comparison of cardiovascular mortality and morbidity by age between the two treatment-based regimens. The numbers above the circles indicate the HRs. The bars indicate the 95% confidence intervals.*

mmHg, and ≥90 mmHg). The HR for the CV event was estimated by comparing the results with those from a reference group, which included patients with a SBP level <130 mmHg and a DBP level of 75–79 mmHg. Differences in baseline characteristics, such as sex, body mass index, treatment group, antihypertensive drug use before starting the CASE-J trial, smoking, drinking, type 2 diabetes, hyperlipidemia, severe hypertension, history of cerebrovascular events, history of cardiac events, renal dysfunction, and the other achieved BP (*e.g.*, the achieved DBP in the analysis of the optimal SBP), were adjusted using multiple Cox regression analysis.

The statistical tests were two-sided, and the significance level was set at 5%. All statistical analyses were performed using SAS version 9.1 (SAS Institute, Cary, USA).

Results

Efficacies of Candesartan and Amlodipine for the Three Age Subgroups

There were 2,247 patients (1,132 patients in the candesartan group and 1,115 patients in the amlodipine group) in the <65-year-old subgroup, 1,705 patients (862 patients and 843 patients, respectively) in the 65–74-year-old subgroup, and 751 patients (360 patients and 391 patients, respectively) in the 75–84-year-old subgroup. Both treatments controlled BP well during the follow-up (for ages 75–84 years old, SBP/DBP at 3 years after enrollment was 137.6/74.7 mmHg in the candesartan group and 136.5/73.3 mmHg in the amlodipine group; for ages 65–74 years old, 136.1/75.5 mmHg and 135.2/75.4 mmHg; and for ages <65 years old, 135.6/79.4 mmHg and 133.0/78.7 mmHg, respectively).

Figure 1 shows the effects of the two treatment–based regimens on CV events and each endpoints. The HR for CV events for ages 75–84 years was 0.94 (95% CI=0.58–1.53; p=0.808), for ages 65–74, it was 1.05 (95% CI=0.73–1.51; p=0.787), and, for those <65, it was 1.03 (95% CI=0.67–1.56; p=0.904). Similarly, there were no significant differences between candesartan and amlodipine on each endpoint among the three age subgroups. Thus, the patients in each age subgroup were considered to form an observational cohort of high-risk hypertensive patients who had received antihypertensive therapy. In this context, in the following section we examine the relationship of the achieved BP levels and the CV events rate for each of the age subgroups irrespective of the allocated drug.

Associations between the Achieved BP and CV Events Rate for the Three Age Subgroups

Table 1 shows the baseline characteristics of patients with at least one follow-up visit without a CV event, and the mean BP during the follow-up. At baseline, older patients had a higher mean SBP, whereas the mean DBP was lower in older patients. There were fewer men in the subgroup for 75–84-year-olds than in the other subgroups. Table 2 shows the crude CV events rates for each BP category in each of the age subgroups, and Fig. 2 shows the corresponding adjusted HR. For patients younger than 65 years old and those 65–74, CV risk increased steeply when control of the SBP was inadequate (SBP≥140 mmHg); in particular, the HRs for SBPs≥160 mmHg were 9.30 (95% CI=4.13–20.95; p<0.001) for the patients aged <65 years old and 8.45 (95% CI=4.04–17.66; p<0.001) for those aged 65–74 years old. Meanwhile, CV risk in the subgroup of 74–85-year-olds sig-

Table 1. Baseline Characteristics and Mean Blood Pressures during Follow-Up*

	<65 years	65–74 years	75–84 years
n	2,176	1,658	719
Age (years old)	55.0±7.1	69.3±2.8	78.3±2.7
Candesartan	1,097 (50.4)	835 (50.4)	346 (48.1)
Male	1,373 (63.1)	872 (52.6)	272 (37.8)
Body mass index (kg/m^2)	25.1±3.7	24.2±3.4	23.6±3.6
Severe hypertension†	488 (22.4)	267 (16.1)	144 (20.0)
Type2 diabetes mellitus	927 (42.6)	781 (47.1)	250 (34.8)
Cerebrovascular history†	137 (6.3)	218 (13.2)	109 (15.2)
Cardiac history†	922 (42.4)	728 (43.9)	321 (44.7)
Renal dysfunction†	488 (22.4)	402 (24.3)	200 (27.8)
Hyperlipidemia	982 (45.1)	745 (44.9)	301 (41.9)
Antihypertensive drugs before starting the CASE-J trial	1,306 (60.0)	1,245 (75.1)	549 (76.4)
Current smoking	850 (39.3)	465 (28.1)	128 (17.8)
Current alcohol	1,281 (58.9)	677 (40.8)	204 (28.4)
SBP (mmHg)			
Baseline	160.7±14.8	163.2±13.5	167.6±12.2
During follow-up‡	137.6±13.5	138.6±13.7	140.0±13.5
DBP (mmHg)			
Baseline	94.3±10.9	89.3±10.7	88.9±11.4
During follow-up‡	81.2±9.4	77.4±9.1	76.2±9.1

*Data are shown as mean±SD or *n* (%) in each category. †Severe hypertension: blood pressure ≥180 and/or ≥110 mmHg; cerebrovascular history: history of stroke or transient ischemic attack; cardiac history: left ventricular hypertrophy, angina pectoris, or history of myocardial infarction; renal dysfunction: proteinuria or serum creatinine concentration ≥1.3 mg/dL. ‡Mean blood pressures during follow-up; the occurrence of a CV event (excluding baseline). CASE-J, Candesartan Antihypertensive Survival Evaluation in Japan; SBP, systolic blood pressure; DBP, diastolic blood pressure; CV, cardiovascular.

Table 2. Cardiovascular Events and Achieved Blood Pressure*

	<65 years		65–74 years		75–84 years	
	Events (*n*)	Rates† (95% CI)	Events (*n*)	Rates† (95% CI)	Events (*n*)	Rates† (95% CI)
SBP (mmHg)						
<130	15 (667)	6.6 (3.7–10.9)	18 (438)	12.0 (7.1–19.0)	8 (161)	15.3 (6.6–30.1)
130–139	21 (780)	7.9 (4.9–12.0)	28 (587)	14.0 (9.3–20.2)	18 (243)	23.0 (13.6–36.3)
140–149	17 (468)	10.8 (6.3–17.3)	28 (419)	20.4 (13.6–29.5)	12 (199)	18.5 (9.6–32.4)
150–159	15 (150)	34.8 (19.5–57.4)	18 (114)	52.2 (30.9–82.5)	9 (50)	58.9 (27.0–111.9)
≥160	18 (111)	58.8 (34.8–92.9)	20 (100)	88.6 (54.1–136.8)	13 (66)	80.1 (42.6–136.9)
DBP (mmHg)						
<75	28 (607)	13.6 (9.1–19.7)	43 (722)	17.8 (12.9–23.9)	21 (339)	19.3 (11.9–29.5)
75–79	6 (341)	5.1 (1.9–11.1)	13 (248)	15.6 (8.3–26.6)	7 (113)	19.5 (7.8–40.1)
80–84	19 (665)	8.4 (5.1–13.2)	22 (438)	14.9 (9.4–22.6)	18 (189)	29.7 (17.6–47.0)
85–89	12 (260)	14.0 (7.3–24.5)	15 (136)	35.5 (19.8–58.5)	8 (46)	57.1 (24.6–112.5)
≥90	21 (303)	22.7 (14.1–34.8)	19 (114)	66.3 (39.9–103.5)	6 (32)	81.1 (29.8–176.5)

*The achieved BP was defined as the BP measured during the most recent visit before the occurrence of a CV event, or as the BP obtained at the end of follow-up. †Rates are given per 1,000 person-years. SBP, systolic blood pressure; DBP, diastolic blood pressure; CI, confidence interval; BP, blood pressure; CV, cardiovascular.

nificantly increased at SBP levels ≥150 mmHg, although the increase was milder than for the other subgroups; the HR for SBPs≥160 mmHg was 3.90 (95% CI=1.44–10.54; $p=0.007$), and for SBPs 150–159 mmHg it was 2.91 (95% CI=1.01–8.39; $p=0.048$). Regarding the DBP, a J-shaped phenomenon was observed in patients <65 years (HR for

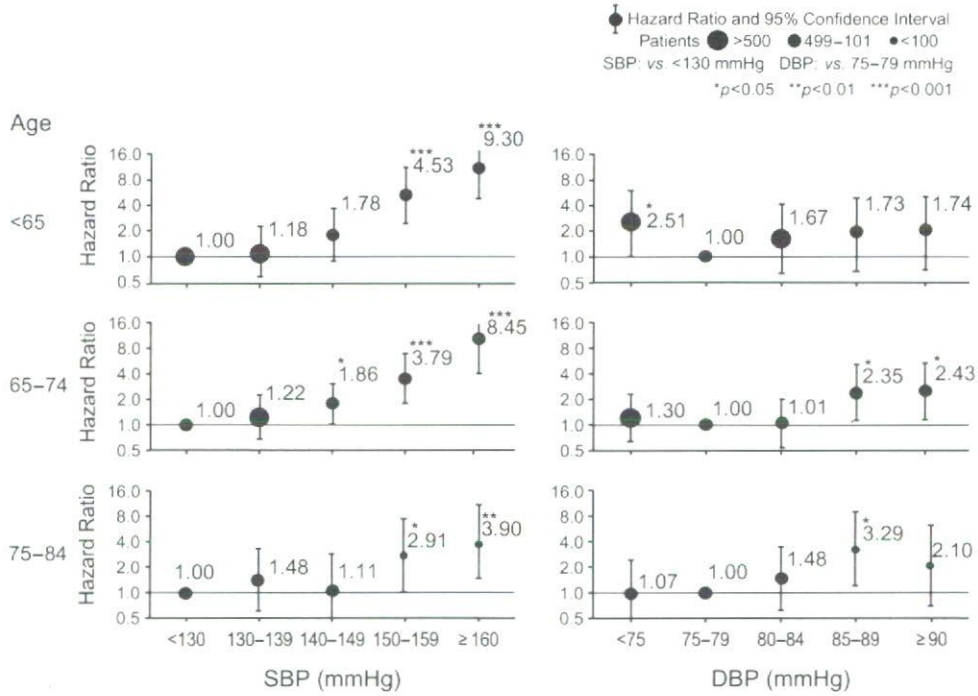

Fig. 2. *Adjusted hazard ratio of cardiovascular mortality and morbidity by age and the achieved blood pressure level. Sex, body mass index, treatment group, antihypertensive drug use before starting the CASE-J trial, smoking, drinking, type 2 diabetes, hyperlipidemia, severe hypertension, history of cerebrovascular events, history of cardiac events, renal dysfunction, and the other achieved BP (e.g., the achieved DBP in case the analysis of the optimal SBP) were adjusted using multiple Cox regression analysis. *$p<0.05$, **$p<0.01$, ***$p<0.001$.*

DBP<75 mmHg =2.51; 95% CI=1.03–6.10; $p=0.042$), but not in patients aged 75–84 years.

Discussion

CCBs are commonly used for the treatment of elderly hypertensive patients (*1–4*). Recently, ARBs have also been used for elderly patients or patients with ISH (*5, 6*). Hardly any reported studies, however, have directly compared the effects of CCBs and ARBs in Asian elderly patients (*18*). In the present subanalysis, the effects of lowering BP were comparable in the two treatment groups. When patients were divided into three age subgroups (younger than 65, 65 to 74, and 75 to 84 years old), both treatments exhibited significant antihypertensive effects in each of the subgroups, indicating that the ARB-based and CCB-based regimens are equally beneficial in terms of their hypotensive efficacy as well as in reducing the risk of CV events. Therefore, these data indicate that, similar to CCBs, ARBs are beneficial as first-line agents for elderly patients, because of their wide range of indications in hypertensive patients with co-morbidities, the lack of unfavorable effects on metabolism, and their antidiabetic properties (*19*).

A lower target BP is not necessarily beneficial in senior patients, as was described in the review by August (*9*). Little clear evidence has been reported regarding target BPs for senior patients receiving antihypertensive treatment. Epidemiologically, it is well known that the risks for BP and CV are linearly related and that elderly people with lower BPs are at less risk for CV events (*20*). A sub-analysis of the SHEP study, however, showed that the incidence of stroke was less frequent in patients with SBP levels lower than 150 mmHg compared with those with SBP levels lower than 140 mmHg (*10*) and that the risk of stroke increased in patients with DBP levels lower than 55 mmHg (*21*). Additionally, sub-analysis of the HOT study, which examined patients aged 65 years or older, did not identify any significant differences in the CV risk of groups with different BPs obtained in response to antihypertensive treatment with felodipine (*22*).

The Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients (JATOS) was recently conducted to compare the 2-year effect of a strict treatment to maintain SBP below 140 mmHg (group A) with that of a mild treatment to maintain SBP between 140 and 160 mmHg (group B) in Japanese hypertensive patients. Among patients aged 65 years or older, no significant difference was observed

in the incidence of CV events between group A (a mean SBP of 135.9 mmHg after 2 years) and group B (a mean SBP of 145.6 mmHg after 2 years). However, among patients aged 75 years or older, group B had a lower incidence of CV events compared with group A, although the difference was not significant (*23*, *24*). These results suggest that the target SBP should be lower than 150 mmHg, particularly in patients aged 75–84 years old. The Japanese treatment guidelines for hypertension recommend both using an intermediate target BP of 150/90 mmHg for elderly patients over 75 years old and attempting to lower the patient's BP to 140/90 mmHg after reaching this intermediate target, if possible, while closely observing the condition of the patient (*25*).

In the present subanalysis of the CASE-J trial, it is thought that "the lower, the better" applies to the achieved SBP, particularly in younger, Japanese, high-risk hypertensive patients. But, in those aged 75 years or older, the CV risk for an SBP of 140–149 mmHg did not change compared with that for SBPs lower than 130 mmHg. This result is consistent with a rightward shift of risk threshold for SBP with age, which was observed with horizontal spline regression analysis of the data from the Framingham study by Port *et al.* (*26*). Thus, the results of the present sub-analysis support the idea of using SBP targets lower than 150 mmHg for hypertensive patients older than 75 years. In addition, the results of the study for the Hypertension in the Very Elderly Trial (HYVET) were reported recently (*27*). In HYVET, 3,845 patients who were 80 years of age or older and had a sustained SBP of 160 mmHg or more were randomly assigned to either an active treatment group (given indapamide with or without perindopril) or a placebo group. HYVET provided evidence that active treatment in the very elderly, aimed at achieving a target BP of 150/80 mmHg, is beneficial and is associated with reduced risks of heart failure, death from stroke, and death from any cause. This result is compatible with our results. However, since nearly 50% of such patients reached the target BP in HYVET, it is not yet clear whether further reduction is beneficial. A J-shaped phenomenon was observed in patients aged <65, whereas DBPs of 75–79 mmHg yielded the lowest CV risk in the oldest age subgroup. This may indicate that the patients whose DBPs were much lower than expected had advanced arteriosclerosis. However, we think that this remains a matter of future discussion. Oates and his coworkers have previously noted that special attention should be paid to patients aged 80 years or older (*13*) because the prognosis for these patients with lower BPs is poorer than that for patients with higher BPs (*28*).

We must mention some limitations of the present study. First, examination of the optimal target BP for hypertensive patients was post hoc. The CASE-J trial was not designed to determine optimal target BPs. Second, because of the smaller number of CV events in CASE-J trial compared with other trials conducted in Western countries, the statistical power may be limited. Finally, the present study examined the association between the optimal target BP and the rate of CV events in the specific setting of high-risk Japanese hypertensive patients.

Currently, the Valsartan in Elderly Isolated Systolic Hypertension (VALISH) study, which compares patients with SBPs lower than 140 mmHg with those with SBPs lower than 150 mmHg, is underway in Japan (*29*). The results of this study may further clarify the appropriate target BPs for elderly patients being treated for hypertension.

In conclusion, the ARB candesartan and the CCB amlodipine are equally effective in Japanese elderly patients with high-risk hypertension. Moreover, it is important to control BP levels to less than 150/85 mmHg for patients 75–84 years old.

Acknowledgements

We thank the investigators and members of the CASE-J trial group. We also thank Professor Tosiya Sato for useful statistical comments on this manuscript. The CASE-J trial was registered at www.ClinicalTrials.gov (number NCT00125463).

References

1. SHEP Cooperative Research Group: Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final Results of the Systolic Hypertension in the Elderly Program (SHEP). *JAMA* 1991; **265**: 3255–3264.
2. Staessen JA, Fagard R, Thijs L, *et al*, Systolic Hypertension in Europe (Syst-Eur) Trial Investigators: Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. *Lancet* 1997; **35**: 757–764.
3. Liu L, Wang JG, Lui G, Staessen JA: Comparison of active treatment and placebo in older Chinese patients with isolated systolic hypertension. Systolic Hypertension in China (Syst-China) Collaborative Group. *J Hypertens* 1998; **16**: 1823–1829.
4. Gong L, Zhang W, Zhu Y, *et al*: Shanghai trial of nifedipine in the elderly (STONE). *J Hypertens* 1996; **14**: 1237–1245.
5. Lithell H, Hansson L, Skoog I, *et al*, SCOPE Study Group: The study on cognition and prognosis in the elderly (SCOPE) principal results of a randomized double-blind intervention trial. *J Hypertens* 2003; **21**: 875–886.
6. Kjeldsen SE, Dahlöf B, Devereux RB, *et al*, LIFE (Losartan Intervention for Endpoint Reduction) Study Group: Effects of losartan on cardiovascular morbidity and mortality in patients with isolated systolic hypertension and left ventricular hypertrophy: a Losartan Intervention for Endpoint Reduction (LIFE) substudy. *JAMA* 2002; **288**: 1491–1498.
7. Ogihara T, Nakao K, Fukui T, *et al*, CASE-J Trial Group: Effects of candesartan compared with amlodipine in hypertensive patients with high cardiovascular risks: candesartan antihypertensive survival evaluation in Japan trial. *Hypertension* 2008; **51**: 393–398.
8. Mancia G, De Backer G, Dominiczak A, *et al*: 2007 ESH-ESC Practice Guidelines for the Management of Arterial Hypertension: ESH-ESC Task Force on the Management of

Arterial Hypertension. *J Hypertens* 2007; **25**: 1751–1762.
9. August P: Initial treatment of hypertension. *N Engl J Med* 2003; **348**: 610–616.
10. Perry HM Jr, Davis BR, Price TR, *et al*: Effect of treating isolated systolic hypertension on the risk of developing various types and subtypes of stroke: the Systolic Hypertension in the Elderly Program (SHEP). *JAMA* 2000; **284**: 465–471.
11. Staessen J, Bulpitt C, Clement D, *et al*: Relation between mortality and treated blood pressure in elderly patients with hypertension: report of the European Working Party on High Blood Pressure in the Elderly. *BMJ* 1989; **298**: 1552–1556.
12. Ogihara T, PATE-Hypertension Study Group in Japan: A Practitioner's Trial on the Efficacy of Antihypertensive Treatment in the Elderly Hypertension (The PATE-Hypertension Study) in Japan. *Am J Hypertens* 2000; **13**: 461–467.
13. Oates DJ, Berlowitz DR, Glickman ME, Silliman RA, Borzecki AM: Blood pressure and survival in the oldest old. *J Am Geriatr Soc* 2007; **55**: 383–388.
14. Rastas S, Pirttilä T, Viramo P, *et al*: Association between blood pressure and survival over 9 years in a general population aged 85 and older. *J Am Geriatr Soc* 2006; **54**: 912–918.
15. van Bemmel T, Gussekloo J, Westendorp RG, Blauw GJ: In a population-based prospective study, no association between high blood pressure and mortality after age 85 years. *J Hypertens* 2006; **24**: 287–292.
16. Fukui T, Rahman M, Hayashi K, *et al*, CASE-J Study Group: Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) trial of cardiovascular events in high-risk hypertensive patients: rationale, design, and methods. *Hypertens Res* 2003; **26**: 979–990.
17. Japanese Society of Hypertension Guidelines Subcommittee for the Management of Hypertension: Guidelines for the management of hypertension for general practitioners. *Hypertens Res* 2001; **24**: 613–634.
18. Zanchetti A, Julius S, Kjeldsen S, *et al*: Outcomes in subgroups of hypertensive patients treated with regimens based on valsartan and amlodipine: an analysis of findings from VALUE trial. *J Hypertens* 2006; **24**: 2163–2168.
19. Elliott WJ, Meyer PM: Incidence diabetes in clinical trials of antihypertensive drugs: a network meta-analysis. *Lancet* 2007; **369**: 201–207.
20. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R, Prospective Studies Collaboration: Age-specific relevance of usual blood pressure to vascular mortality, a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002; **360**: 1903–1913.
21. Somes GW, Pahor M, Shorr RI, Cushman WC, Applegate WB: The role of diastolic blood pressure when treating isolated systolic hypertension. *Arch Intern Med* 1999; **159**: 2004–2009.
22. Kjeldsen SE, Kolloch RE, Leonetti G, *et al*: Influence of gender and age on preventing cardiovascular disease by antihypertensive treatment and acetylsalicylic acid. The HOT study. *J Hypertens* 2000; **18**: 629–642.
23. JATOS Study Group: The Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients (JATOS): protocol, patient characteristics, and blood pressure during the first 12 months. *Hypertens Res* 2005; **28**: 513–520.
24. Ishii M, Goto Y, the JATOS Study Group: Principal results of the Japanese trial to assess optimal systolic blood pressure in elderly hypertensive patients. *J Hypetens* 2006; **24** (Suppl 6): S30.
25. Japanese Society of Hypertension: Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2004). *Hypertens Res* 2006; **29**: S1–S105.
26. Port S, Demer L, Jennrich R, Walter D, Garfinkel A: Systolic blood pressure and mortality. *Lancet* 2000; **355**: 175–180.
27. Beckett NS, Peters R, Fletcher AE, *et al*, HYVET Study Group: Treatment of hypertension in patients 80 years of age or older. *N Engl J Med* 2008; **358**: 1958–1960.
28. Gueyffier F, Bulpitt C, Boissel JP, *et al*: Antihypertensive drugs in very old people: a subgroup meta-analysis of randomised controlled trilas. *Lancet* 1999; **353**: 793–796.
29. Ogihara T, Saruta T, Matsuoka H, *et al*, VALISH Study Group: Valsartan in Elderly Isolated Systolic Hypertension (VALISH) study: rationale and design. *Hypertens Res* 2004; **27**: 657–661.

Contemporary Clinical Trials 30 (2009) 97–101

Contents lists available at ScienceDirect

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial

Long-term effects of candesartan and amlodipine on cardiovascular mortality and morbidity in Japanese high-risk hypertensive patients: Rationale, design, and characteristics of candesartan antihypertensive survival evaluation in Japan extension (CASE-J Ex)☆

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ARTICLE INFO

Article history:
Received 26 May 2008
Accepted 10 September 2008

Keywords:
CASE-J
Candesartan
Amlodipine
Cardiovascular events
Diabetes mellitus

ABSTRACT

Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) trial was conducted to compare the effects of the angiotensin II receptor blocker (ARB) candesartan and the calcium channel blocker (CCB) amlodipine on the incidence of cardiovascular (CV) events in Japanese high-risk hypertensive patients. After 3.2years follow-up, CV events rate was 17.6–17.7 per 1000 person-years in each group, which was much lower than we expected. Since it has not been known whether the same efficacy of two drugs is sustained beyond the current trial, a longer follow-up period will be needed. The Steering Committee of CASE-J trial decided to extend the trial for 3years as an observational study (CASE-J Ex). In CASE-J Ex, the primary end point is a composite of CV events and the secondary endpoints are all-cause death and new-onset diabetes. After Committee's decision, 245 doctors agreed to participate in CASE-J Ex and 2236 patients (1141 with candesartan-based regimens and 1095 with amlodipine-based regimens) were re-enrolled. The baseline characteristics of CASE-J Ex participants were similar to CASE-J participants and still balanced well between candesartan and amlodipine. Recently, the interest of antihypertensive treatment has focused to differentiation of the effects of antihypertensive agents on the incidence of CV events as well as blood pressure lowering effect. CASE-J Ex will clarify the long-term effects of ARB and CCB on CV mortality and morbidity. Additionally, because the number of diabetic patients is increased, the evidences from CASE-J Ex will be valuable.

1. Introduction

In recent decades, antihypertensive medical therapy has been shown to reduce cardiovascular (CV) events in a wide range of patients [1–6]. Recently, the focus has shifted to clarification and differentiation of the effects of antihypertensive agents on the incidence of not only CV events but also the associated disease in addition to blood pressure lowering

☆ Names of grants: The CASE-J Ex was funded by EBM Research Center, Kyoto University of Graduate School of Medicine with unrestricted grant from Takeda Pharmaceutical Co. Drs. K Ueshima, K Fukiyama, J Azuma, T Ogihara, T Saruta, K Nakao have received lecture fees from Takeda Pharmaceutical Co. and Pfizer Japan Inc. The other authors declare that they have no conflicts of interest.

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doi:10.1016/j.cct.2008.09.006

effect [7–9]. Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) trial was conducted to compare the effects of the angiotensin II receptor blocker (ARB) candesartan and the calcium channel blocker (CCB) amlodipine on the incidence of CV events, represented as a composite of sudden death, cerebrovascular, cardiac, renal, and vascular events in Japanese high-risk hypertensive patients. The design and outcomes of CASE-J trial have been published previously [10,11]. CASE-J trial disclosed that candesartan and amlodipine equally suppressed total CV mortality and morbidity in high-risk hypertensive patients under strict blood pressure control during the average of 3.2years follow-up. However, CV events rate was 17.6–17.7 per 1000 person-years in CASE-J trial and it was much lower than we expected. It has not been known whether the same efficacy of two drugs is sustained beyond the current trial, and whether the benefits are observed in subgroups of patients at varying risk. A longer follow-up period will be needed to clarify the beneficial effects of two drugs on CV events.

Furthermore, a recent network meta-analysis showed that both angiotensin-converting enzyme inhibitors (ACEI) and ARBs, which block renin–angiotensin system, have a favorable effect on the incidence of new-onset diabetes [12]. Interestingly, ARB candesartan significantly reduced the incidence of new-onset diabetes compared to CCB amlodipine for a 36% of relative risk reduction in CASE-J trial as well as in other clinical trials [11,13]. Although the prognostic significance of new-onset diabetes has been debated, several studies showed an adverse effect of new-onset diabetes on the incidence of CV events in hypertensive patients [14,15].

In this context, as a continuation of CASE-J trial, CASE-J Extension (CASE-J Ex) was designed to evaluate long-term or any lag effects of ARB candesartan compared with CCB amlodipine in relation to CV mortality and morbidity or new-onset diabetes. We present the rationale, design, methods, and the patients' characteristics of CASE-J Ex.

2. Study design

2.1. Outline of CASE-J Ex

The main CASE-J trial was a prospective, multicenter, randomized, open-label, active-controlled, 2-arm parallel-group comparison study in Japanese high-risk hypertensive patients [10]. Eligible patients were enrolled from September 2001 until December 2002. Follow-up was continued until December 2005. The Steering Committee of CASE-J trial decided to extend the trial for 3years (from 2006 to 2008) as an observational study to examine whether the prolonged treatment with candesartan or amlodipine reduce the inci-

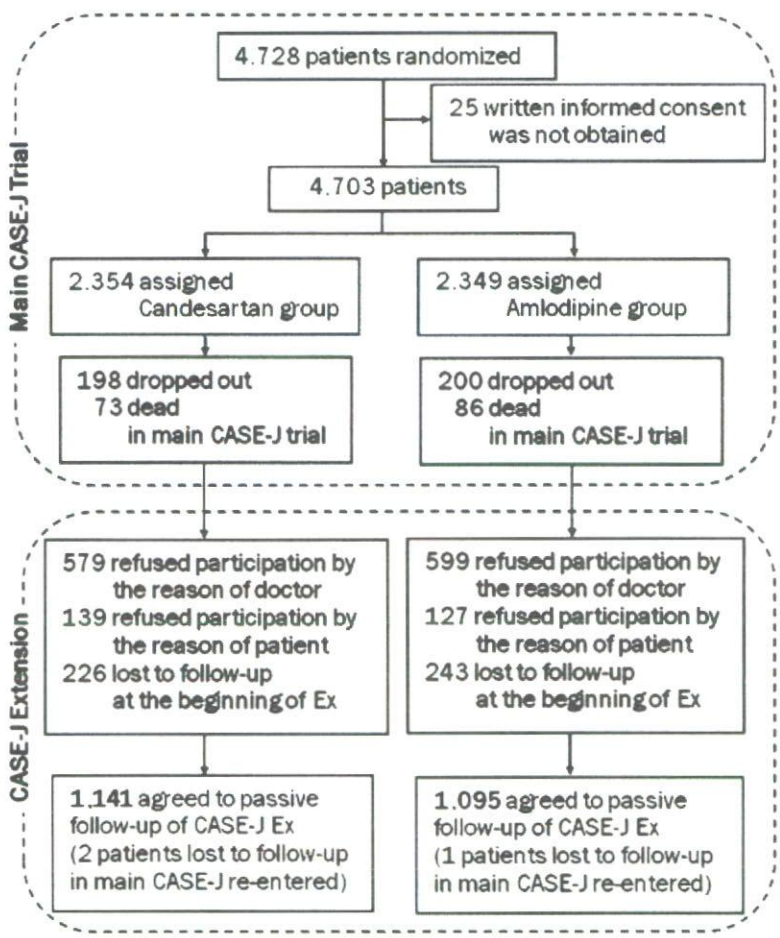

Fig. 1. Study profile of CASE-J Ex.

Table 1
Schedule for data collection

The data of each year to be collected annually
Information on medication at the last visit of each year
1) Allocated drugs: continuation or discontinuation; daily dosage;
2) Other antihypertensive drugs: existence or nonexistence; class of antihypertensive drug
3) Start of treatment with anti-diabetic drug: yes or no; drug name; initiation date
Information on cardiovascular events
1) Existence or nonexistence; date; outcome
2) Details of event
Information on adverse events
1) Existence or nonexistence; date; outcome
2) Causal relationship to medication
3) Degree of severity
Information on physical examination
1) Blood pressure and pulse rate at the sitting position
2) Body weight
3) Waist circumference*
Information on laboratory test
1) General laboratory test
2) HbA1c**
3) Brain natriuretic peptide**
4) Cystatin C**

*Newly additional data to be reported.
**Newly additional data to be performed when feasible.

dence of CV events or new-onset diabetes on December 2006.

After this decision and the approval of CASE-J Ex protocol from the Ethics Committee at the Kyoto University Graduate School of Medicine, all collaborating doctors were invited to participate in the extension trial. Two hundred and forty-five of 526 doctors agreed to participate CASE-J Ex. All patients who were alive at the end of CASE-J trial at each of the collaborating doctors were invited to participate in the extension trial. If patient died between January and December 2006, we attempt to collect the information from the collaborating doctor. Written informed consent was obtained before the patient was re-enrolled, after explaining the objectives of the study, the voluntary nature of participation, the freedom to withdraw from the study at anytime, and the protective measures of privacy. There were a total of 2236 patients (1141 with candesartan-based regimens and 1095 with amlodipine-based regimens) originally randomized in CASE-J trial (Fig. 1). Three out of 2236 patients were lost to follow-up in the main CASE-J trial, but they were included in the CASE-J Ex follow-up population because they revisited the clinics.

2.2. Organization

The organizational structure of the CASE-J Ex is principally similar as the main CASE-J trial. The Steering Committee is responsible for the scientific conduct and publication of the study in addition to finalizing the protocol, case report form, and informed consent form. The Event Evaluation Committee, independent and masked to the assignment of treatment arms, is responsible for evaluating CV events. The EBM Research Center at the Kyoto University Graduate School of Medicine is working as a data management center along with receiving, cleaning, and conducting statistical analysis of all patients' data. The Data and Safety Monitoring Board is responsible for evaluating possible adverse events.

2.3. Patient follow-up and endpoint assessment

Re-enrollment was started in January 2007 and follow-up period will be continued until December 2008. During CASE-J Ex, all clinical data as described in Table 1 are collected annually. The surveillance will be performed annually and the closest data at the end of each year were transmitted by collaborating doctors to EBM Research Center. The information on CV events, adverse events, and survey of discontinuation, if any, will be also reported to EBM Research Center at the same period. In other words, clinical data and the event informations which occurred during 2006, 2007, and 2008 were retrospectively surveyed in the beginning of 2007, 2008, and 2009 respectively.

Primary and secondary endpoints are summarized in Table 2. Although new-onset diabetes was a prespecified endpoint in the main CASE-J trial, this is placed as one of the secondary endpoints in CASE-J Ex. In patients without type 2 diabetes mellitus at baseline, individual case report forms and adverse-event databases are monitored for any information that the patients begin to use anti-diabetic drugs and/or for newly apparent cases of type 2 diabetes. During the extension, these data described above transmitted from collaborating doctors by facsimile will be checked by the staff members of the EBM Research Center. Data on the patients with possible CV events will be sent to the Event Evaluation Committee for evaluation and verification of CV events using the Virtual Event Evaluation Committee [10].

2.4. CASE-J Ex population

The number of enrolled patients who have still continued the assigned drug at entry for CASE-J Ex was 1076 patients (94.3%) in candesartan group and 1045 (95.4%) in amlodipine group at the end of CASE-J trial. The baseline characteristics at enrollment of CASE-J trial and BP measured at the last follow-up of CASE-J trial of all patients in main CASE-J trial, the remaining patients at the end of CASE-J trial, and all patients in CASE-J Ex were shown in Table 3. The baseline characteristics of the 2236 patients who agreed to participate in CASE-J Ex were almost similar to those of the remaining 4146 patients at the end of CASE-J trial. Meanwhile, the baseline characteristics of all patients in CASE-J Ex were well balanced between candesartan-based regimens and amlodipine-based regimens except for sex which was imbalanced in the main CASE-J trial.

Table 2
Outcome measures

Primary endpoint (composite of the following events)
Sudden death: unexpected death that happened within 24 h without external causes
Cerebrovascular events: stroke or transient ischemic attack
Cardiac events: heart failure, angina pectoris, or acute myocardial infarction
Renal events: serum creatinine concentration ≥4.0 mg/dL, doubling of the serum creatinine concentration (however, creatinine ≤2.0 mg/dl is not regarded as an event), or end-stage renal disease
Vascular events: dissecting aortic aneurysm or arteriosclerotic occlusion of a peripheral artery
Secondary endpoints
All-cause death, cardiovascular death
New-onset diabetes

Table 3
Baseline characteristics: all patients in the main CASE-J trial, remaining patients at the end of CASE-J trial, and all patients in CASE-J Extension

Characteristics	All patients in main CASE-J		Remaining patients at the end of main CASE-J		All patients in CASE-J Ex	
	Candesartan (n=2354)	Amlodipine (n=2349)	Candesartan (n=2083)	Amlodipine (n=2063)	Candesartan (n=1141)	Amlodipine (n=1095)
Women	1092 (46.4%)	1014 (43.2%)	975 (46.8%)	894 (43.4%)	561 (49.2%)	484 (44.2%)
Age	63.8±10.5	63.9±10.6	63.5±10.5	63.8±10.4	63.7±10.3	64.1±10.1
BMI [kg/m^2]	24.6±3.7	24.5±3.6	24.7±3.7	24.5±3.6	24.6±3.8	24.4±3.5
SBP [mm Hg] at enrollment	162.5±14.2	163.2±14.2	162.3±14.2	162.9±14.3	162.6±14.1	163.4±13.9
SBP [mm Hg] at the last follow-up of CASE-J	–	–	136.2±13.1	134.8±12.8	135.2±11.8	133.2±10.9
DBP [mm Hg] at enrollment	91.6±11.0	91.8±11.4	91.7±11.0	91.9±11.3	91.8±10.6	91.8±11.3
DBP [mm Hg] at the last follow-up of CASE-J	–	–	77.5±9.8	76.9±9.4	76.8±9.5	76.1±8.7
Current smokers	489 (20.8%)	536 (22.8%)	424 (20.4%)	477 (23.1%)	233 (20.4%)	236 (21.6%)
Severe hypertension	454 (19.3%)	493 (21.0%)	405 (19.4%)	425 (20.6%)	226 (19.8%)	237 (21.6%)
Type 2 diabetes mellitus	1011 (42.9%)	1007 (42.9%)	891 (42.8%)	873 (42.3%)	504 (44.2%)	472 (43.1%)
History of cerebrovascular events	248 (10.5%)	225 (9.6%)	212 (10.2%)	189 (9.2%)	128 (11.2%)	93 (8.5%)
History of cardiac events	1007 (42.8%)	1023 (43.6%)	879 (42.2%)	904 (43.8%)	413 (36.2%)	419 (38.3%)
History of renal events	572 (24.3%)	543 (23.1%)	513 (24.6%)	465 (22.5%)	254 (22.3%)	245 (22.4%)
Arteriosclerotic peripheralarterial obstruction	29 (1.2%)	24 (1.0%)	24 (1.2%)	22 (1.1%)	14 (1.2%)	13 (1.2%)

2.5. Planned statistical analysis

The aim of the primary analysis is to compare the incidence of CV events between the candesartan-based regimens and amlodipine-based regimens. The pre-defined primary data analysis will be based on the intention-to-treat principle according to the randomization in the main CASE-J trial [11]. For the primary analysis, we will include all available data on all 4703 CASE-J trial participants. The incidence proportions will be calculated using the Kaplan–Meier method and be compared with a log-rank test stratified by diabetic status at the randomization. The hazard ratios and 95% confidence intervals will be also estimated using the Cox regression analysis. Additionally, a sensitivity analysis will be conducted considering only patients who agreed to participate in CASE-J Ex. All statistical tests will be two-sided with an alpha level of 0.05.

3. Discussion

In clinical trials for hypertensive patients, the Heart Outcomes Prevention Evaluation (HOPE) study investigators extended the study to assess the long-term effects of ramipril compared to placebo on CV events and on diabetes as HOPE-The Ongoing Outcomes (HOPE TOO) trial [16,17]. Actually, HOPE TOO, of which additional follow-up period was 2.6 years, disclosed two new and major findings. First, the benefits observed during the HOPE trial were sustained during passive follow-up. Moreover, there were incremental benefits primarily in reducing the incidence of myocardial infarction as well as new-onset diabetes, despite similar ACEI use and blood pressure levels between the two study groups during the extension period. In the recent stream, the interest has been focused on the comparison between the different antihypertensive agents on the incidence of CV events and diabetes. It is important to clarify the long-term effects of ARB candesartan and CCB amlodipine on CV mortality and morbidity in CASE-J Ex.

Diabetes may develop in non-diabetic hypertensive patients during treatment, but the long-term CV implications of the new-onset diabetes during antihypertensive treatment have not been clear. Recently, the Progetto Ipertensione Umbria Monitoraggio Ambulatoriale (PIUMA) trial was conducted to determine the prognostic value of new-onset diabetes in hypertensive patients [14]. This trial demonstrated that new-onset diabetes has an increased risk for CV events and its adverse prognostic impact is not dissimilar from that of previously known diabetes. In addition, a subanalysis of VALUE trial showed that the patients with new-onset diabetes had significantly higher CV morbidity than those without diabetes [15]. These findings suggest that we should take care of the patients who develop diabetes during the antihypertensive treatments. In the CASE-J trial, 1343 patients in candesartan-based regimen and 1342 patients in amlodipine-based regimens did not have diabetes at baseline. As a result, a 36% relative risk reduction was observed in the incidence of new-onset diabetes with candesartan-based regimens. But, there was no significant difference in CV morbidity or mortality between two treatment-based regimens. The extension of the follow-up period in the CASE-J Ex may resolve this clinical discrepancy.

The previous studies such as the HOPE TOO trial and the PIUMA study were performed in the Western countries. Moreover, only 2.9% of the participants were from Asian countries even in the VALUE trial conducted as multinational study [18]. Since the CV events rate in Japan differs from those in Europe and USA [19], the outcome of CASE-J Ex trial will provide useful information for Asian people that share similar genetic predispositions and lifestyles to Japanese ones. Additionally, because the number of patients with diabetes and metabolic syndrome is increasing in Eastern countries as well as in Western countries, the evidences from a large-scale clinical trial such as CASE-J or CASE-J Ex in Eastern countries are needed.

References

[1] Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of ACE inhibitors, calcium-antagonists and other blood pressure lowering drugs: results of prospectively designed overviews of randomised trials. Lancet 2000;355:1955–64.
[2] Gueffiyer F, Boutitie F, Boissel JP, et al. Effect of antihypertensive drug treatment on cardiovascular outcomes in women and men: a meta-analysis of individual patient data from randomised controlled trials. Ann Intern Med 1997;126:761–7.
[3] Psaty B, Smith N, Siscovick D, et al. Health outcomes associated with antihypertensive therapies used as first-line agents: a systematic review and meta-analysis. JAMA 1997;277:739–45.
[4] Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta-blockade during and after myocardial infarction: an overview of the randomized trials. Prog Cardiovasc Dis 1985;27:335–71.

[5] Garg R, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. JAMA 1995;273:1450–6.
[6] Flather M, Yusuf S, Kober L, et al. Long-term ACE inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. Lancet 2000;355:1575–81.
[7] The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic. The Antihypertensive and Lipid Lowering treatment to prevent Heart Attack Trial (ALLHAT). JAMA 2002;288:2981–97.
[8] Lindholm LH, Ibsen H, Dahlöf B, et al. LIFE Study Group. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet 2002;359:995–1003.
[9] Julius S, Kjeldsen SE, Weber M, et al. VALUE trial group. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. Lancet 2004;363:2022–31.
[10] Fukui T, Rahman M, Hayashi K, et al. CASE-J Study Group. Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) trial of cardiovascular events in high-risk hypertensive patients: rationale, design, and methods. Hypertens Res 2003;26:979–90.
[11] Ogihara T, Nakao K, Fukui T, et al. For the Candesartan Antihypertensive Survival Evaluation in Japan Trial Group. Effects of candesartan compared with amlodipine in hypertensive patients with high cardiovascular risks: Candesartan Antihypertensive Survival Evaluation in Japan Trial. Hypertension 2008;51:393–8.
[12] Elliott WJ, Meyer PM. Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis. Lancet 2007;369:201–7.
[13] Kjeldsena SE, Julius S, Manciac G, et al. Effects of valsartan compared to amlodipine on preventing type 2 diabetes in high-risk hypertensive patients: the VALUE trial. J Hypertens 2006;24:1405–12.
[14] Verdecchia P, Reboldi G, Angeli F, et al. Adverse prognostic significance of new diabetes in treated hypertensive subjects. Hypertension 2004;43:963–9.
[15] Aksnes TA, Kjeldsen SE, Rostrup M, Omvik P, Hua TA, Julius S. Impact of new-onset diabetes mellitus on cardiac outcomes in the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial population. Hypertension 2007;50:467–73.
[16] The Heart Outcome Prevention Evaluation Study Investigators. Effect of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. N Engl J Med 2000;342:145–53.
[17] HOPE/HOPE-TOO Study Investigators. Long-term effects of ramipril on cardiovascular events and on diabetes. Results of the HOPE Study Extension. Circulation 2005;112:1339–46.
[18] Zanchetti A, Julius S, Kjeldsen S, et al. Outcomes in subgroups of hypertensive patients treated with regimens based on valsartan and amlodipine: an analysis of findings from the VALUE trial. J Hypertens 2006;24:2163–8.
[19] Death and DALY estimates for 2002 by cause for WHO Member States: Burden of Disease statistics. World Health Organization. (Accessed February 27, 2007, at http://www.who.int/entity/healthinfo/statistics/bodgbddeathdalyestimates.xls).

原　著

心臓リハビリテーション実施施設のインターネット上にみられる心臓リハビリテーションに関する情報量の検討

Disclosure of Information on the Internet about Cardiac Rehabilitation in Insurance-Approved Institutes in Japan

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抄　録

【目　的】心臓リハビリテーション（以下，心リハ）の普及を促進させる要因の一つとして，社会的認知の向上が挙げられる．また，インターネット（以下，IN）を用いることにより，誰もが様々な情報を容易に入手可能となった．今回，心リハに関する情報公開が IN 上で十分になされているか否かを検討する．

【対象と方法】日本心臓リハビリテーション学会ホームページに掲載されている心リハ認定施設143施設を対象に，それら施設の公式ホームページ（以下，HP）上より病床数，循環器医数，心臓血管外科医数，年間の経皮的冠動脈形成術（以下，PCI）症例数，年間の心臓手術症例数，心リハ内容の紹介記述，年間の心リハ症例数，心リハ指導士数を検索し，その記載率を求めた．また，医師数と心リハ指導士数との記載率の，年間の PCI 症例数，心臓手術症例数と心リハ症例数との記載率をそれぞれ比較検討した．

【結　果】病床数の記載率は100％であった．循環器医数と心臓血管外科医数の記載率は79.0％，67.1％であったのに対し，心リハ指導士数の記載率は10.5％であった（p<0.0001）．PCI 症例数と心臓手術症例数の記載率は62.9％，51.7％であったのに対し，心リハ症例数の記載率は13.3％であった（p<0.0001）．心リハ内容の紹介記述の記載率は45.5％であった．

【考察と総括】日本心臓リハビリテーション学会に登録された施設の HP でさえ，IN 上の心リハに関する情報の記述は不十分であった．心リハの普及のためには，HP 上での情報公開の充実が求められる．

〔心臓リハビリテーション（JJCR）14（1）：217-219，2009〕

Key words：インターネット，記載率，心大血管リハビリテーション，社会的認知，情報公開

目　的

心臓リハビリテーション（以下，心リハ）の効果は，運動耐容能の向上[1,2]の他にも，生存率の改善[1,3,4]，QOL の向上[1,5,6]など多岐にわたる．しかし，後藤らが[7]実施した全国的な実態調査では，日本循環器学会認定循環器専門医研修施設（以下，研修施設）の94％以上が冠動脈造影，経皮的冠動脈形成術（以下，PCI）を実施していたにも関わらず，退院後の外来通院型心リハを実施している施設は９％にすぎず，心リハ普及の促進が期待される．

心リハ普及を促進させる要因の一つとして，社会的認知の向上が挙げられる．

総務省の通信利用動向調査によると，2007年のインターネット（以下，IN）利用者は，8,811万人，人口に対する普及率は69％であり，年々増加傾向にある[8]．この結果は，IN を用いることで誰もが様々な情報を容易に入手でき，心疾患の情報や治療法の情報も容易に入手し得ることが示唆される．したがって，IN 上での心リハに関する情報公開の充実が心リハ普及の促進につながると考え，心リハに関する情報公開が IN 上で十分になされているか否かを検討した．

対象および方法

対象は，2008年６月１日時点で，日本心臓リハビリテーション学会（以下，心リハ学会）ホームページ（以

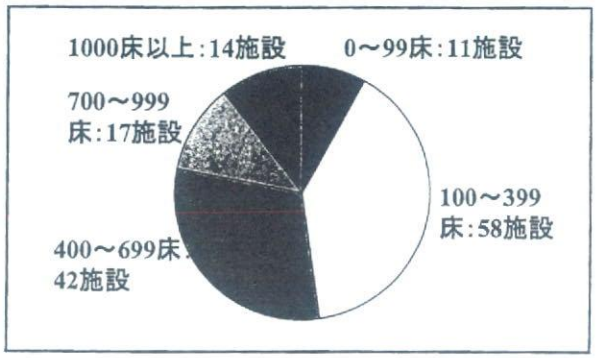

図１　病床数の割合

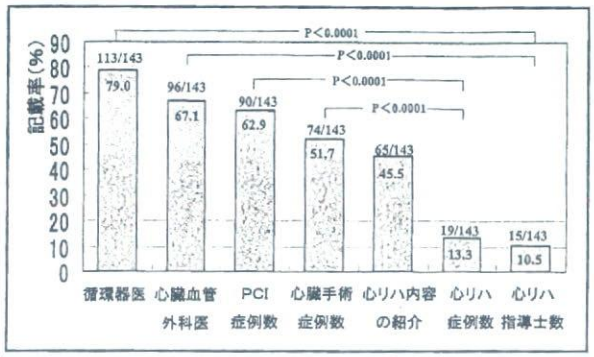

図２　各項目の記載率

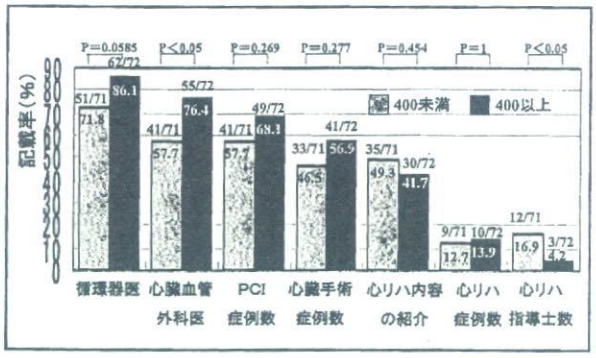

図３　病床数400未満／以上での検討

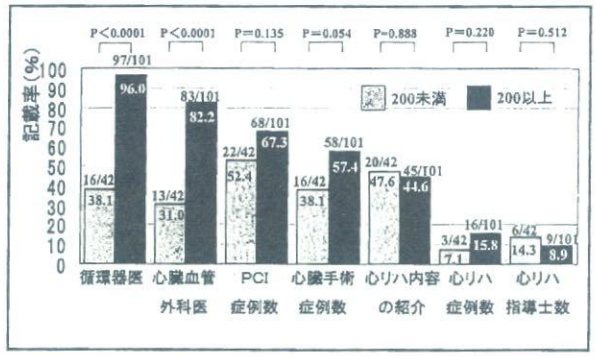

図４　病床数200未満／以上での検討

下，HP）に掲載されている，心リハ認定施設143施設である．

方法は，心リハ認定施設143施設の施設公式HPより，病床数，循環器医数，心臓血管外科医数，PCI症例数，心臓手術症例数，心リハ内容の紹介記述，心リハ症例数，心リハ指導士数の項目を検索し，記載のある施設数÷全体の施設数×100を記載率として求めた．病床数は，平均と割合を求めた．また，循環器医師数，心臓血管外科医数の記載率と，心リハ指導士数の記載率との比較を，PCI症例数，心臓手術症例数の記載率と，心リハ症例数の記載率とを比較検討した．そして，病床数400未満／以上の２群に分け，各項目に対して比較検討した．同様に，病床数200未満／以上についても検討した．なお，統計学的検定にはχ^2検定を用い，有意水準は５％とした．

結　果

１．病床数の記載率と割合

病床数の記載率は，クリニック２施設を除くと100％であった．平均病床数は470.7床であり，病床数の割合は図１に示す．また，86.7％（124/143）が，研修施設もしくは日本循環器学会認定循環器専門医研修関連施設（以下，関連施設）であった．

２．各項目の記載率および比較検討

各項目の記載率は図２に示す．循環器医数，心臓血管外科医数の記載率と心リハ指導士数の記載率を比較したところ，有意に心リハ指導士数の記載率が低かった（循環器医数79.0％，心臓血管外科医数67.1％ vs 心リハ指導士数10.5％；$p<0.0001$）．同様にPCI症例数，心臓手術症例数の記載率と心リハ症例数の記載率を比較したところ，有意に心リハ症例数の記載率が低かった（PCI症例数62.9％，心臓手術症例数51.7％ vs 心リハ症例数13.3％；$p<0.0001$）（図２）．心リハ学会に掲載されている施設HPでさえ，急性期治療や侵襲的治療に関する記載率に比べて，心リハの実績や従事者に関する記載は十分ではなかった．

３．400床未満／以上での比較検討

400床未満群，以上群の各項目の記載率を図３に示す．400床未満群の心臓血管外科医数の記載率は400床以上群に比べて有意に低く，心リハ指導士数の記載率は有意に高かった．有意差はなかったが，病床数の大きな施設において，急性期治療や侵襲的治療に比べて，心リ