Illustrative cases

Case 1

A 46 year old right-handed female was admitted after sudden onset of severe headache accompanied by a loss of consciousness. On admission, she was drowsy without focal neurological deficits (Hunt and Kosnik grade III). Computerised tomography of the head demonstrated thick SAH in the left Sylvian and basal cisterns. Three-vessel angiography showed an aneurysm at left MCA bifurcation without evidence of vasospasm. She underwent emergency clipping of the aneurysm on day 1. She regained full consciousness and showed good postoperative course until day 13. On day 14, she gradually deteriorated to lethargy and developed right hemiparesis and nonfluent dysphasia. At the time, the mean flow velocity of the M_1 portion of the left MCA by TCD increased to 125 cm/s. Cerebral angiography confirmed the vasospasm at the proximal and distal branches of the left MCA (Fig. 1A). On day 15, papaverine hydrochloride was administrated using a microcatheter into the left MCA, resulting in a significant dilatation of the vessels (Fig. 1B). The hemiparesis and dysphasia temporarily improved over the next 20 h, but again deteriorated. On day 16, mild hypothermia was employed to protect the ischaemic brain. Follow-up angiogram performed on day 22 during hypothermia revealed a progression of the vasospasm of the left MCA, indicating that mild hypothermia itself could not prevent the progression of the cerebral vasospasm (Fig. 1C). After 8 days of hypothermia, the hemiparesis and dysphasia gradually improved and the patient was neurologically normal by day 40. Six months later, her GOS was evaluated as GR. The changes in the lowest value of rCBF of the left frontoparietal cortex, where were the territory of the spastic left MCA and responsible for neurological deficits were as follows: before onset of DINDs; 46.3, at onset; 27.8, during hypothermia; 19.5, rewarming phase; 30.2, and after treatment; 45.8 ml/100 g/min. Thus mild hypothermia was considered to exert brain protective effect against the critical cerebral ischaemia caused by severe vasospasm.

Case 7

A 47-year-old male had a severe headache without loss of consciousness 10 days prior to referal to our hospital. On admission, he complained of continuous occipital headache and left hemiparesis. Computerised tomographic scan of the head revealed an old haematoma in the right Sylvian cistern with perifocal oedema, and angiography demonstrated an aneurysm at the bifurcation of the right MCA with moderate vasospasm (Fig. 2). The lowest rCBF of the right frontal cortex was 34.1 ml/100 g/min. He underwent aneurysmal neck clipping under mild hypothermia on day 10, and hypothermia was continued until day 19. He received intraarterial administration of papaverine hydrochloride (180 mg) on day 13 and angioplasty on day 14. The lowest rCBF value of the frontal lobe during hypothermia was 25.7 ml/100 g/min, and the rCBF increased to 41.2 ml/100 g/min during the rewarming stage. After 10 days of mild hypothermia, he became alert and the hemiparesis improved gradually. He was neurologically intact at the time of discharge.

DISCUSSION

Rationale for mild hypothermia in cerebral vasospasm

In patients with intracranial aneurysm rupture, cerebral ischaemia as a result of vasospasm accounts for delayed ischaemic neurological deficits (DINDs). Although the mechanism of cerebral vasospasm following SAH remains not fully defined, it is commonly agreed that varying degrees of regional and/or global cerebral ischaemia over a period of several days or longer is the final

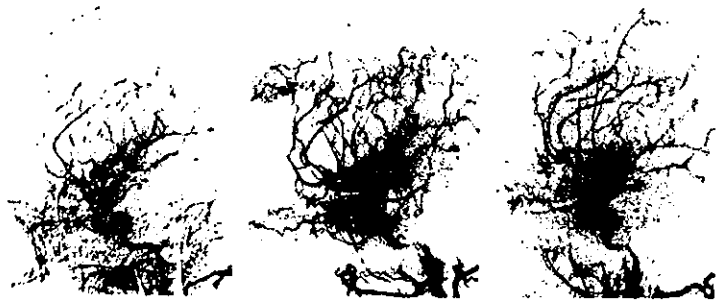

Fig. 1 Postoperative angiograms with lateral view before (Left) and after (Center) intraarterial administration of papaverine hydrochloride and during mild hypothermia (Right).

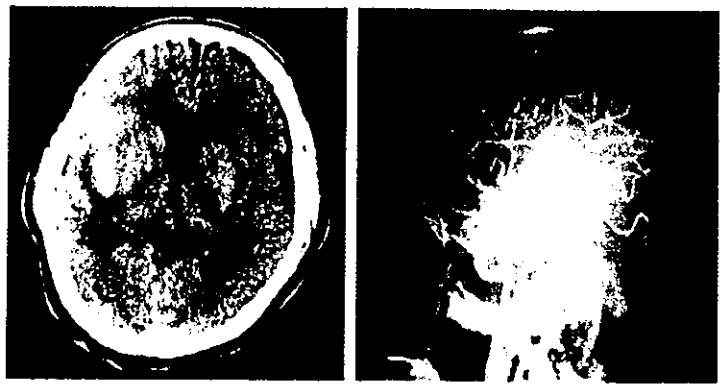

Fig. 2 Computerised tomography scan (Left) and angiogram (Right) with lateral view on admission. (⇒) indicates aneurysm.

common pathway.[15–19] In experimental studies of cerebral ischaemia in primate, brain electrical activity diminishes at CBF below approximately 20 ml/100 g/min, whereas membrane failure and cell death occurs in CBF below approximately 10 ml/100 g/min.[20–26]

Intravascular volume expansion with induced arterial hypertension has been employed to ameliorate cerebral ischaemia following vasospasm and has proven to be effective on reversing neurological deterioration over 75% of the patients.[1] Transluminal angioplasty with or without intraarterial administration of papaverine hydrochloride has been employed for cerebral vasospasm that was refractory to conventional medical treatments.[2–7] These results have shown a significant relief of vasospasm and subsequent clinical improvement. In another study, however, the use of intraarterial papaverine hydrochloride showed only transient effects and did not improve final clinical outcomes.[27] Furthermore, angioplasty has been shown to lead favorable outcomes in patients with proximal vasospasm (M_1), but to result in significant rates of morbidity and mortality in patients with distal or diffuse vasospasm.[5]

Recent experimental studies have shown that mild hypothermia (32–34 °C of brain temperature) has been beneficial on cerebral ischaemia. The main mechanism of hypothermic brain protection is the reduction of ischaemia-induced neurotoxic glutamate release and intracellular Ca^{2+} accumulation. Hypothermia has also been shown to prevent the depletion of high-energy phosphate compounds,[11] and reduce free radical production[14] and tissue acidosis[9] caused by ischaemic insults as well as to protect the blood–brain barrier from disruption, thereby preventing postischaemic cerebral oedema[10] and ameliorating postischaemic neuronal injury.[12]

In severe head injury, mild hypothermia has been used to reduce intracranial hypertension[28] and secondary brain injury[29] and improve mortality and morbidity rates. Brain hypothermia demonstrated favorable effects on ICP, outcome and acute derangements of cerebral physiology and metabolism.[28,29] Four patients with cerebral embolism were treated with mild hypothermia for 3–5 days, and the results were more favorable than expected due to suppression of brain oedema and haemorrhagic infarction.[30] Although the beneficial effects of mild hypothermia on long-lasting critical ischaemia due to cerebral vasospasm have not been definitely established, we have employed mild hypothermia in progressive ischaemia for neuronal protection. In the Group 1 patients, mild hypothermia was applied to ameliorate ischaemic neuronal damage by critical ischaemia following vasospasm that could not be controlled with conventional medical and intravascular treatments. In the Group 2 patients, hypothermic treatment was applied to reduce further ischaemic brain injury by preexisting symptomatic vasospasm.

Cerebral blood flow analysis

Because all patients were completely sedated and cooled under controlled ventilation, frequent measurements of CBF using ^{99m}Tc-ECD SPECT were technically difficult. We performed the CBF study in 7 of 8 patients. In patients who developed DINDs, the CBF values were 11–34 (mean 26.7) ml/100 g/min in the region of the affected hemisphere. This finding agrees with the results of Symon,[31] who reported that the CBF values in patients showed an altered level of consciousness and mild to moderate motor and/or sensory deficits were between 18 and 30 ml/100 g/min. Finnerty et al.[32] also demonstrated that the symptoms of global cerebral ischaemia appear when the CBF falls to approximately 30 ml/100 g/min. Mild hypothermia resulted in 6.4 ml/100 g/min decrease in rCBF in our study which was compatible with previous reports[28,29] and rCBF increased by a mean value of 10.8 ml/100 g/min by rewarming.

The patients who showed a good recovery or moderate disability had relatively high rCBF values which were 27 and 34 ml/100 g/min at the onset of DINDs and 19–28 ml/100 g/min during hypothermia. The rCBF values continued to increase by rewarming, and reached to the normal values after the hypothermic treatment. The patient with severe disability showed relatively low rCBF value (11 ml/100 g/min) at the onset of DINDs, and also during and after the hypothermic treatment. Powers et al.[33] reported that in patients with cerebral vasospasm, the hemiparesis eventually recovered when the rCBF values were greater than 15.0 and 16.2 ml/100 g/min and failed to recover when the rCBF values were 12.0 and 11.7 ml/100 g/min using positron emission tomography. In the study of Xenon-enhanced computerised tomography, CBF values fell below 15 ml/100 g/min resulted in an infarction on CT scan and CBF values greater than 18 ml/100 g/min caused neither significant complications nor neurological deterioration.[34] Other previous studies have shown a poor correlation between a focal decrease in CBF and the presence of neurological deficits.[35–38]

While the present findings indicate that measurements of CBF at the onset of DINDs, and during and after mild hypothermia may be useful in differentiating indication and prediction of outcome of hypothermic treatment, we could not draw any definite conclusions regarding this particular treatment in terms of severity, duration or extent of ischaemia, because the fact that cerebral vasospasm is not a static process and we evaluated this dynamic process with only a few measurements during the progress of vasospasm and hypothermic treatment.

Clinical significance of mild hypothermia in vasospasm

Among the 5 patients who proved refractory to medical and intravascular treatments for cerebral vasospasm (Group 1), 4 patients showed favorable outcomes (3 GR, 1 MD) following mild hypothermia. Because the underlying pathology of the cerebral vasospasm is a varying degree of critical ischaemia lasting for more than several days, long-term application of mild hypothermia is a reasonable strategy in reducing neuronal injury. In fact, without hypothermic treatment such patients might exhibit progressive deterioration and poor outcome. However, it must be noted that mild hypothermia does not abrogate or relieve the progression of cerebral vasospasm, as indicated in case 1. When the DINDs are evident in a patient with an untreated aneurysm, surgeons face a dilemma in deciding whether or not to operate; that is, manipulation of spastic arteries inevitably worsens the vasospasm, leading to clinical deterioration, and aggressive hyperdynamic therapy to overcome vasospasm cannot be started without obliterating the aneurysm. In the present study, we applied mild hypothermia to protect the critically ischaemic brain during and after the surgery. Transluminal angioplasty and intraarterial infusion of papaverine hydrochloride were performed postoperatively when angiography and CBF study indicated a progression of the vasospasm. Thus mild hypothermia exerted protective effects on critical ischaemia and provided a significant therapeutic time window to employ an interventional therapy. All 3 patients in Group 2 achieved favorable outcomes. Good outcomes in Groups 1 and 2 with mild hypothermia, indicates the therapeutic benefit of this treatment with respect to neurological improvement.

Complications of prolonged mild hypothermia

It is important to be aware of the harmful effects of mild hypothermia. During the hypothermia therapy, cardiopulmonary

suppression, serum electrolytes abnormalities, abnormal coagulopathy and multiple organ failure were occasionally encountered. Such complications were examined daily and treated according to the laboratory data and close physical monitoring.

Pneumonia was the most common and serious complication, which was treated with antibiotics, frequent intratracheal irrigation and suction and changes in body position. Multiple organ failures, including liver, heart and kidney, were also encountered and were treated with intensive medical care. Of the two fatalities encountered in this study, neither was attributed to any of the above complications.

CONCLUSION

Mild hypothermia led to a significant favorable outcome in patients with severe cerebral vasospasm that was refractory to medical and intravascular treatments. This therapy is recommended in patients with good preoperative neurological grade and in patients who receives a delayed aneurysmal clipping with DINDs due to vasospasm. Although the present cohort was relatively small, the promising results suggest that the application of this treatment is warranted in selective patients with uncontrollable severe cerebral vasospasm following SAH.

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特　集
循環器疾患における最近のメガトライアル

トピックス

わが国における医師主導による臨床試験の現状

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Current Investigator Initiated Clinical Trials in Japan

KEY WORDS
医師主導／Evidence-based Medicine／臨床試験

主な略語

EBM：
evidence-based medicine
(科学的根拠に基づく医療)

PROBE：
prospective randomized open blinded-endpoint
(前向き無作為オープン結果遮断)

SMO：
site management organization
(治験施設支援機関)

IRB：
institutional review board
(倫理審査委員会)

CARDIAC PRACTICE
VOL.15 NO.1

はじめに

日本人は欧米人と比較して，体格，生活習慣，使用薬剤の投与量，疾病構造が異なることから，人種間の薬物反応性，感受性の遺伝的差異を考えると，欧米における臨床試験の結果を直接わが国に当てはめることの妥当性が問題となる。このため，治療選択に関するわが国独自のエビデンスの確立が必要とされている。しかし，わが国独自のエビデンスが少ないことから，日常診療では欧米のエビデンスを参考にして治療を行っているのが現状である。また，近い将来に個人の遺伝的素因や生活習慣に基づいたテーラー・メイド医療が盛んになると考えられることから，「日本人のためのevidence-based medicine(EBM)構築」が急務とされている。

臨床試験における現状と問題点

「臨床試験(研究)」とは，人(患者)を対象にし，治療を兼ねた試験のことである[1]。わが国では，従来基礎研究が重視され，臨床試験に基づく患者のためのEBMが乏しく，欧米諸国からの臨床分野での論文に比べてエビデンスのレベルが低いため，国際誌に掲載された論文ではその引用件数が少ない[2]。大規模臨床試験を推進する場合のわが国における問題点として，①試験登録

特集■循環器疾患における最近のメガトライアル

■ わが国独自の「日本人のためのエビデンス」の確立が求められている。
■ 臨床研究(試験)に関する倫理指針が公表された。
■ 社会の理解と協力を得て，臨床試験の適正な推進を図り，社会に貢献することが求められている。

患者不足，②プロトコール違反，脱落症例が多い，③データ欠損が多い，④試験期間の長期化，などが指摘されている。その理由として，①わが国の国民皆保険制度により，患者への金銭的なメリットが少なく，試験参加への患者の同意が得られにくい，②臨床試験支援システム不備による個々の医師に対する過度の労力依存，③臨床試験の意義，重要性に対する個々の医師の認識不足，徒弟制度的経験と直感が優先される習慣，④医師個人へのインセンティブ，業績評価が低いことや試験計画書が実際の医療現場を反映していない，⑤試験実施施設の倫理審査委員会の不備などが問題として挙げられている[3]。

臨床研究に関する倫理指針

臨床において最善であると認められた予防方法，診断方法および治療方法であっても，科学技術の進展に伴い，その有効性，効率性，利便性および質に関する臨床研究(試験)を通じて，絶えず再検証されなければならない。また，臨床研究(試験)においては，被験者の福利に対する配慮が科学的および社会的利益よりも優先されなければならない。医学研究の推進を図る上で，臨床研究(試験)の重要性を踏まえつつ，世界医師会によるヘルシンキ宣言に示された倫理規範や個人情報保護を踏まえ，個人の尊厳，人権の尊重，その他の倫理的観点および科学的観点から，臨床研究(試験)に携わるすべての関係者が遵守すべき事項(臨床研究に関する倫理指針)が新たに公表された[1]。臨床研究(試験)の実施にあたっては，すべての臨床研究(試験)の関係者がこの指針に従い，社会の理解と協力を得て臨床研究(試験)の適正な推進を図ることで，社会に貢献することが求められている。

わが国の主な医師主導臨床試験

すでにわが国では，高脂血症に対してスタチンを用いたいくつかの大規模臨床試験が実施されている。約5万例を対象にしたJ-LIT(Japan Lipid Intervention Trial)，高齢者を対象にしたPATE (Pravastatin Anti-atherosclerosis Trial in the Elderly)，一次予防試験であるMEGA study，KLIS(Kyushu Lipid Intervention Study)，CLIP (Chiba Lipid Intervention Program)，スタチンを基礎薬としてエイコサペンタエン酸(EPA)の上乗せ効果をみるJELIS (Japan EPA Lipid Intervention Study)，スタチンによる冠動脈硬化進展抑制効果を検討するJUST (Japan Utilization of Simvastatin Therapy) study，ATHEROMA studyなどの介入試験が実施され，日本人における高脂血症と心血管疾患の発症・再発に関するエビデンスが集積されつつある[4)-10)]。高血圧症に対しては，ACE阻害薬またはカルシウム(Ca)拮抗薬を用いたGLANT (The Evaluation Group of Long-Term Antihypertensive Treatment) 研究とPATE (Practitioner's Trial on the Efficacy of Antihypertensive Treatment in the Elderly Hypertension)がある。現在，冠動脈疾患，心不全，不整脈などについても各学会を中心に，わが国独自のエビデンスの確立を目指して多くの臨床試験が開始されている。

1．HOMED-BP研究

HOMED-BP研究(Hypertension Objective treatment based on Measurement by Electrical Devices of Blood Pressure Study；電子血圧計を用いた客観的な高血圧治療に関する多施設前向き無作為オープン研究)は，家庭血圧を指標として軽中等症高血圧患者9,000例を7年間追跡し，ACE阻害薬，Ca拮抗薬およびアンジオテンシンII受容体拮抗薬による降圧効果，予後，臓器障害進展の差を検討すると同時に，降圧目標レベルの差による予後，臓器障害進展の差を検討することを目的としたPROBE(前向き無作為オープン結果遮断)試験である。試験の進行は，ICメモリー内蔵家庭血圧計からオンラインで転送される家庭血圧情報とホストコンピューターのアルゴリズムにより制御される点が特徴である。

■ 最善と認められる診断・治療法でも臨床試験を通じて絶えず再検証する必要がある。

■ わが国独自のエビデンスの確立を目指してそれぞれ特徴のある多くの臨床試験が実施されている。

2．JATOS

JATOS (Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients；高齢者高血圧の治療効果に関する研究)は，日本高血圧学会と日本臨床内科医会が共同で，年代別に定められた日本高血圧学会「高血圧治療ガイドライン2000年版」(JSH-2000)における高齢者高血圧の至適降圧目標値の妥当性を検証するため，収縮期血圧が160mmHg以上の65～85歳の本態性高血圧症外来患者4,508例を対象にした試験である。塩酸エホニジピンを基礎薬とし，収縮期血圧を140mmHg未満に下げる群と，140～160mmHg未満の間に維持する群の2群に無作為に割り付け，2年間にわたり両群間の治療効果を比較する。一次エンドポイントは，脳心血管疾患の発症率およびそれらの疾患による死亡率である。

3．CASE-J

CASE-J (Candesartan Antihypertensive Survival Evaluation in Japan)は，日本高血圧学会後援のもと京都大学EBM共同研究センターが中心となって，JSH-2000で定義されている高リスク本態性高血圧患者4,728例を対象として，心血管系イベントの発症を指標に，アンジオテンシンⅡ受容体拮抗薬であるカンデサルタンとCa拮抗薬であるアムロジピンの有効性を3年間以上追跡して心血管系イベント発症率を比較検証する無作為介入試験である。

4．COPE Trial

COPE Trial (Combination Therapy of Hypertension to Prevent Cardiovascular Events Trial)は，日本高血圧学会後援のもと山口大学と民間との共同試験として，中等症以上の高血圧症患者を対象に，目標降圧値への達成度と脳心血管疾患の発症予防効果について，Ca拮抗薬であるベニジピンを基礎薬とし，アンジオテンシンⅡ受容体拮抗薬，β遮断薬あるいはサイアザイド系利尿薬のいずれの組み合せが優れているかを検討するため，各地域の循環器専門医で構成される試験参加医師ネットワークと共同研究依頼者による市販後臨床試験として，多施設共同中央登録方式のPROBE法で実施されている試験である。本試験では，SMO (site management organization；治験施設支援機関)が臨床試験にかかわる医師を支援することで，医師の負担を軽減し，各地域ネットワークを同一のプラットフォームとして，臨床試験の品質確保とスピード向上を目指している(図)。

5．J-CHF

J-CHF (Assessment of Beta-Blocker Treatment in Japanese Patients with Chronic Heart Failure；慢性心不全におけるβ遮断薬による治療法確立のための大規模臨床試験)は，日本循環器学会後援のもと北海道大学のJ-CHF事務局を中心として，症状の安定した軽症～中等症慢性心不全患者(NYHA Ⅱ～Ⅲ，左室駆出率40%以下)を対象に，β遮断薬であるカルベジロール3用量群(2.5mg/日，5mg/日，20mg/日)の有効性，安全性の比較により至適用量を知り，レスポンダー，ノンレスポンダー患者の背景探索を行い，本治療法におけるテーラー・メイド医療を確立するための多施設共同オープン・ラベル無作為化群間並行比較試験である。本試験では，β遮断薬の遺伝的素因に基づく薬物動態的あるいは薬力学的な個体差の関与を検討するため，βアドレナリン受容体遺伝子多型の解析も行われる。

6．J-CAD Study

J-CAD Study (Japanese Coronary Artery Disease Study)は，東京大学を中心とし，日本循環器学会後援のもとわが国における冠動脈疾患患者の危険因子管理状況・治療法を経時的に調査し，その予後と危険因子を把握するとともに，今後の治療方針の検討を行う目的で，冠動脈造影で確定した心筋梗塞あるいは狭心症例を対象に，3年間トレンド調査を行うコホート研究である。J-CADは，すでに発表されたJ-LIT二次予防例より糖尿病，高血圧の合併例が多く，ハイリスク症例を対象とした研究であり，イベント発症は

■ 学会を中心に医師主導臨床試験が実施されている。
■ 被験者数の確保，質，スピードの向上を目的に地域ネットワークを用いた臨床試験の効率化が試みられている。

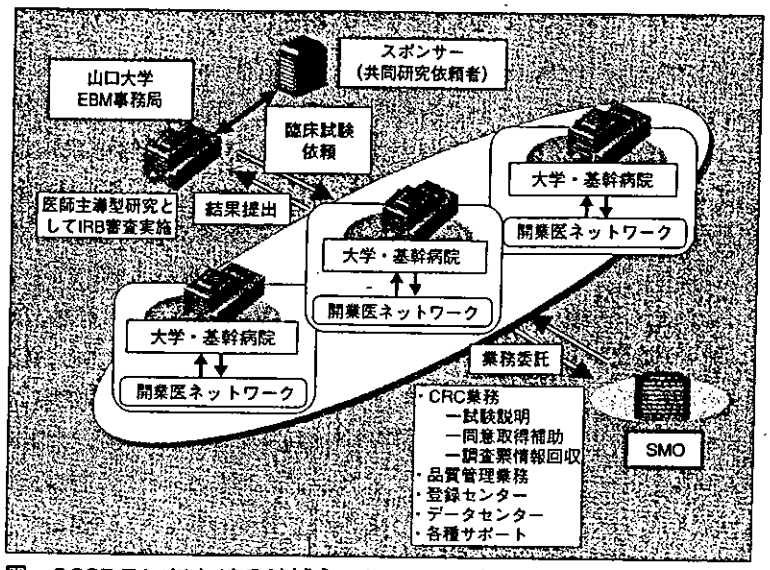

図 COPE Trialにおける地域ネットワークのネットワーク化システムの模式図

COPE Trialでは，各地域ネットワークの基幹病院を，IRBをもつ緊急時の対応病院として機能させるとともに，SMOを導入することで試験実施医師の負担を軽減し，それぞれの地域ネットワークをさらにネットワーク化する「ネットワークのネットワーク化システム」を構築して，臨床研究の質の確保と研究の効率化を推進している。
IRB：institutional review board(倫理審査委員会)，
CRC：clinical research coordinator(治験コーディネーター)，
SMO：site management organization(治験施設支援機関)

J-LITの5～10倍と報告されている。

7．J-SAP Study

わが国では，インターベンションを第一選択とする施設が多いこと，冠動脈硬化症の程度も欧米と比較して軽度でスパスムが多く，さらにわが国には薬物療法とインターベンションとの信頼できる無作為比較試験が全くないため，どちらが患者にとって有利か，また，医療コストについても不明である。そこで，岐阜大学のJ-SAP事務局を中心に，日本循環器学会を含む7学会などの後援で実施するJ-SAP Study (Japanese Stable Angina Pectoris Study；低リスク安定労作性狭心症に対する薬物療法とインターベンション療法の“短期予後とコスト”および“短期予後”に関する無作為介入試験)では，わが国における冠動脈疾患治療の現状を明らかにし，実状に即した治療ガイドラインを策定するため，低リスク安定労作性狭心症例のみを対象とし，初期治療を薬物治療群とインターベンション群に無作為に割り付け，1～3年間の予後と1年後のコストを比較検討する。

8．J-RHYTHM

J-RHYTHM (Japanese Rhythm Management Trial for Atrial Fibrillation；心房細動の薬物療法に関する多施設共同無作為化比較試験)は日本心電学会が主催し，日本循環器学会，JALT (Japanese Antiarrhythmics Long-Term Study)の協賛で実施される洞調律維持治療群および心拍数調節治療群の有用性を検証する無作為化多施設共同群間比較試験である。本試験は，発作性心

■ 研究支援体制など臨床試験に関わる多くの解決すべき問題点がある。
■ わが国にはEBMを作る作業である臨床試験における国際的貢献が求められている。

房細動と持続性心房細動2,600例を対象に，複合エンドポイント〔総死亡，有症候性脳梗塞，全身性塞栓症，入院・輸血を必要とする大出血(脳出血を含む)，静注用利尿薬を必要とする心不全による入院，被験者の基本的治療法に対する認容性〕を一次エンドポイントとし，あわせて，各種抗不整脈薬による心房細動に対する有効性と安全性を検証する。

おわりに

わが国における臨床試験の現状は，欧米と比較するとスタートしたばかりである。研究支援体制，研究参加医師や患者へのインセンティブ，医師や支援スタッフへの疫学・統計学の教育，データの管理・セキュリティ，研究参加施設の研究体制と質，臨床試験の必要性に関する一般国民へのキャンペーン，臨床試験のスポンサーである製薬会社との研究費・使用薬剤の問題など，臨床試験をより活性化させ，EBMを普及させるために改善すべき点が多い。EBMを作る作業である臨床試験における国際的な貢献も，今後より一層求められると思われる。

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慢性心不全に対するアンジオテンシンII受容体拮抗薬の評価(CHARM:カンデサルタン)

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Benefits of candesartan in the treatment of symptomatic heart failure —CHARM Programme—

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Abstract

The CHARM programe, which recruited 7,601 patients, compared the angiotensin-receptor blocker, candesartan, with a placebo in three different populations with class II-VI heart failure. Candesartan reduced cardiovascular mortality and/or hospitalization for heart failure in patients with heart failure and ejection fractions of greater than 40% or less, and total mortality was reduced in these patients as well. Similar benefits were seen whether or not background therapy with ACE inhibitors, β blockers, or spironolactone was used. Pooled analysis of the three studies showed that candesartan provided a significant reduction in cardiovascular death and also demonstrated a positive trend in the overall reduction in all cause mortality. The major adverse effects were hyperkalemia, increase in creatinine concentration and hypotension.

Key words: Heart failure, Angiotensin II, Receptor, Clinical trial

はじめに

β遮断薬およびACE阻害薬を中心とする薬物療法は，臨床試験から得られた豊富なエビデンスによりその有効性が確認され，慢性心不全(CHF)に対する標準治療となっている．しかし，これらの薬剤を投与しても，いまだ十分なCHF患者の予後改善は達成されておらず，また，ACE阻害薬に忍容性のない患者も少なからず存在する．新たに発表された大規模臨床試験Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity(CHARM)プログラムでは，ACE阻害薬に対する忍容性，薬剤併用，左室機能などの点で様々な臨床像を示すCHF患者におけるアンジオテンシンII受容体拮抗薬(ARB)カンデサルタンの有用性を検討することを目的に実施された．

I. CHARMプログラムの概要

欧州・米国をはじめとする26カ国(総患者数7,601例)において実施されたCHARMプログラムは，ACE阻害薬に対する忍容性のないCHF

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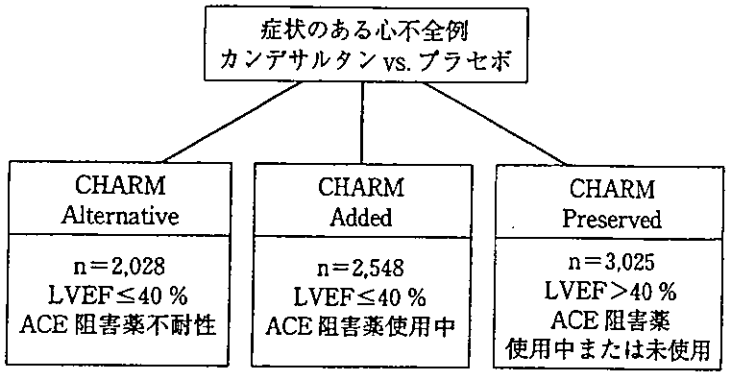

図1 CHARMの試験デザイン

CHARM試験は，カンデサルタンとプラセボを比較する3つのランダム化比較試験であり，対象基準，カンデサルタン投与プロトコル，試験評価項目などに共通の規定が使用され，3試験のデータを統合したOverall解析が可能となっている．3つの試験の1次エンドポイントは，心血管死または心不全による入院であり，CHARM-Overall試験の1次エンドポイントは総死亡である．

患者[左室駆出率(LVEF)≤40%]を対象としたCHARM-Alternative試験，ACE阻害薬に対する上乗せ効果(同≤40%)を検討したCHARM-Added試験，また，大規模臨床試験としては初めて，左室機能が保持されているCHF患者(LVEF>40%)を対象としたCHARM-Preserved試験の3つの独立した試験から成る(図1)[1,2]．いずれもプラセボ群を対象としたランダム化比較試験であり，3試験のデータを統合したOverall解析も可能となるように対象基準(18歳以上，NYHAクラスII-IV)，カンデサルタン投与プロトコル(8-22mg/日を漸増投与)，試験評価項目(1次エンドポイント：心血管疾患死または心不全(HF)による入院)などに共通の規定が使用された．

II. CHARM-Alternative試験

ACE阻害薬に対する忍容性のない左室機能低下患者においてカンデサルタンの有用性を検討したCHARM-Alternative試験では，全2,028例がカンデサルタン群(1,013例)またはプラセボ群(1,015例)に無作為割付けされた[3]．患者背景では，平均年齢67歳，女性32%，平均LVEF 30%であり，既往歴は心筋梗塞が61%，糖尿病27%，高血圧50%，心房細動25%であった．ベースライン時には55%がβ遮断薬を，24%がスピロノラクトンを併用していた．ACE阻害薬不忍容の主な原因は，咳72%，低血圧13%，腎機能障害12%であった．

中央値34カ月間の追跡の結果，カンデサルタン群はプラセボ群に比べて，1次エンドポイントの発生率が23%有意に低下した(図2)．また，2次エンドポイントである心血管疾患死(15%低下)，HFによる入院(32%低下，p<0.0001)，主な心血管イベント(心血管疾患死，HFによる入院，心筋梗塞，脳卒中，冠血行再建術)(19%低下)などの発生率も，カンデサルタン群において低下傾向ないし有意な低下が認められた．一方，副作用や試験中止率には両群間で有意差はなかった(p=0.23)．また，同試験の対象患者において，ACE阻害薬で問題となった咳などの副作用は非常に低率であり，カンデサルタンの良好な忍容性が確認された．

III. CHARM-Added試験

ACE阻害薬が既に投与されているLVEF40%以下を示す左室機能低下CHF患者を対象に実施したCHARM-Added試験は，従来のCHF治療薬に対するARBの上乗せ効果を検討することが目的であり，ACE阻害薬(投与率100%)のほか，β遮断薬などが投与されているCHF患者2,548例を対象とした[4]．

患者の背景因子は，平均年齢64歳，女性21%，平均LVEF 28%であり，CHARM-Added

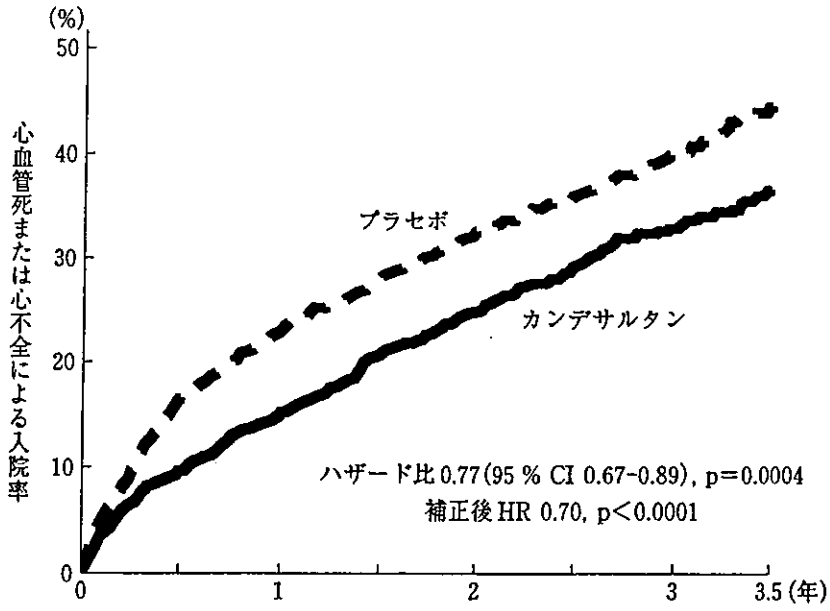

図2　CHARM－Alternative 試験における1次エンドポイント(心血管死または心不全による入院)のカプラン－マイヤー累積イベント曲線[3)改変]

試験は，CHARMプログラムの他の2試験に比べ比較的NYHAクラスの高い重症患者が多く，NYHAクラスIII度が73％を占めていた(CHARMプログラム全体群のNYHAクラス：II度45％，III度52％，IV度3％)．併用薬として，ACE阻害薬が全患者(100％)に投与されていたほか，β遮断薬(56％)，スピロノラクトン(17％)などが投与されていた．

中央値41カ月間の追跡の結果，カンデサルタン群はプラセボ群に比べて，1次エンドポイントの発生率が有意に15％低下した(**図3**)．また，2次エンドポイントである心血管疾患死(16％低下)，HFによる入院(17％低下)などの発生率も，カンデサルタン群においてそれぞれ有意に低下したが，特に再入院の抑制効果が明らかであった．これらの結果から，カンデサルタンはACE阻害薬をはじめとする従来のHF治療薬に対して，代替薬以上の有効性をもつことが示唆された．

また，サブグループ解析した結果では，β遮断剤の上乗せ効果による1次エンドポイントの有意な低減効果が認められ，ACE阻害薬推奨用量使用群でのみカンデサルタンの有効性が得られていた(**図4**)．なお，副作用発現率はプラセボ群が18.3％に対し，カンデサルタン群24.2％と有意に高く(p=0.0003)，クレアチニン値上昇(同4.1％，7.8％，p=0.0001)，カリウム値上昇(同0.7％，3.4％，p<0.0001)が主な副作用であった．

IV. CHARM－Preserved 試験

CHFの発症機序は，収縮不全と拡張不全に分類される．実際の臨床現場では収縮能が維持され，むしろ拡張能低下が主体のCHF患者も約50％存在するが，これらの患者の治療についてはこれまでほとんど評価されていなかった．CHARM－Preserved試験は，左室収縮機能を保持したCHF患者に対するARBの効果を検討した初めての大規模介入試験である[5]．

CHARM－Preserved試験の対象は，NYHA II－IVの症状を有するCHF患者で，LVEF>40％(全体の平均LVEFは54％)を保持する3,025例．平均年齢67歳で，女性が4割と，他の2つの試験より女性の比率が高かった．中央値で37カ月間追跡し，中途脱落はわずか3例だった．CHARM－Preserved試験の1次エンドポイントである'心血管死またはHFによる入院'は，カンデサルタン群が22.0％，プラセボ群が24.3％と，カンデサルタン群において減少傾向が認められた(ハザード比0.89; p=0.118)．主要背

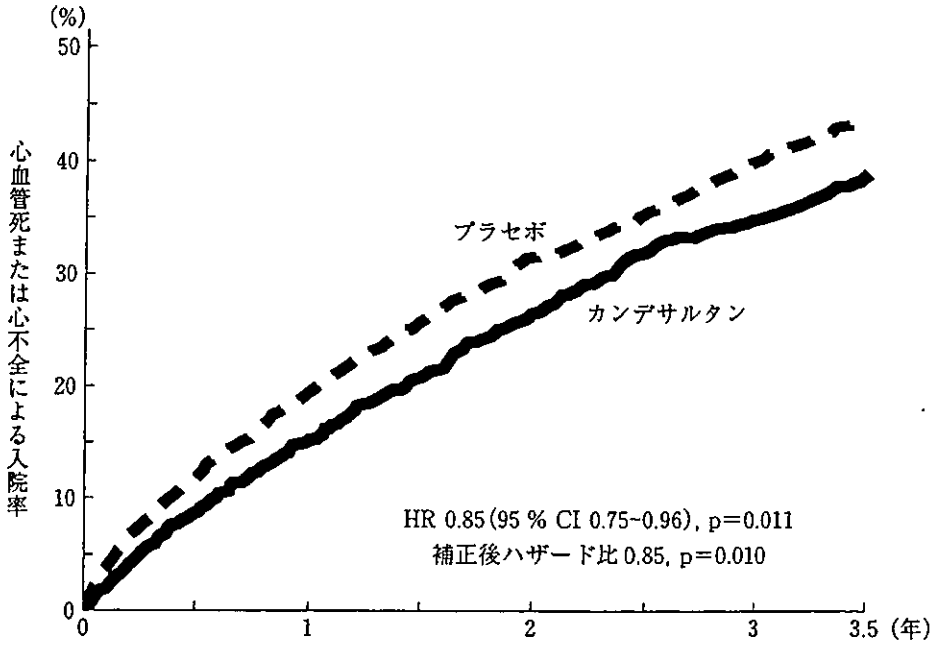

図 3 CHARM-Added 試験における 1 次エンドポイント(心血管死または心不全による入院)のカプラン-マイヤー累積イベント曲線[4改変]

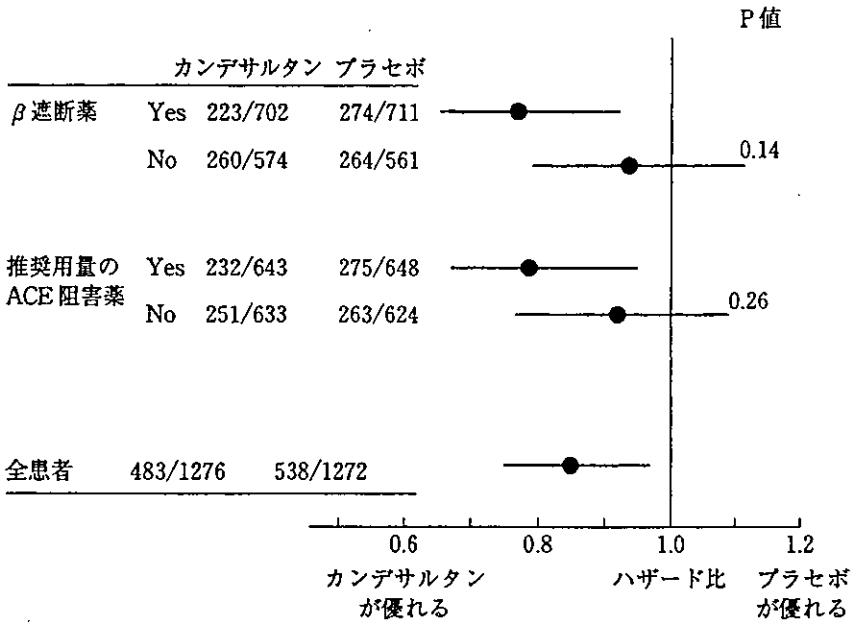

図 4 CHARM-Added 試験における全患者における 1 次エンドポイント(心血管死または心不全による入院)に対するカンデサルタンの効果と試験開始時の β 遮断薬および推奨用量の ACE 阻害薬投与の有無による 1 次エンドポイントに対する効果[4改変]

景因子補正後のハザード比は 0.86(p=0.051)で，統計学的有意差はなかったが，カンデサルタン群で 14％リスクが低下した．

HF による入院に関しては，入院した患者の割合，全体の入院総数のいずれにおいても，カンデサルタン群に有意な減少が認められた(図 5)．しかし，カンデサルタン群では低血圧，クレアチニン上昇，カリウム上昇などの副作用による服用中止が 17.8％と，プラセボ群の 13.5％よりも有意に高かったことから(p=0.001)，

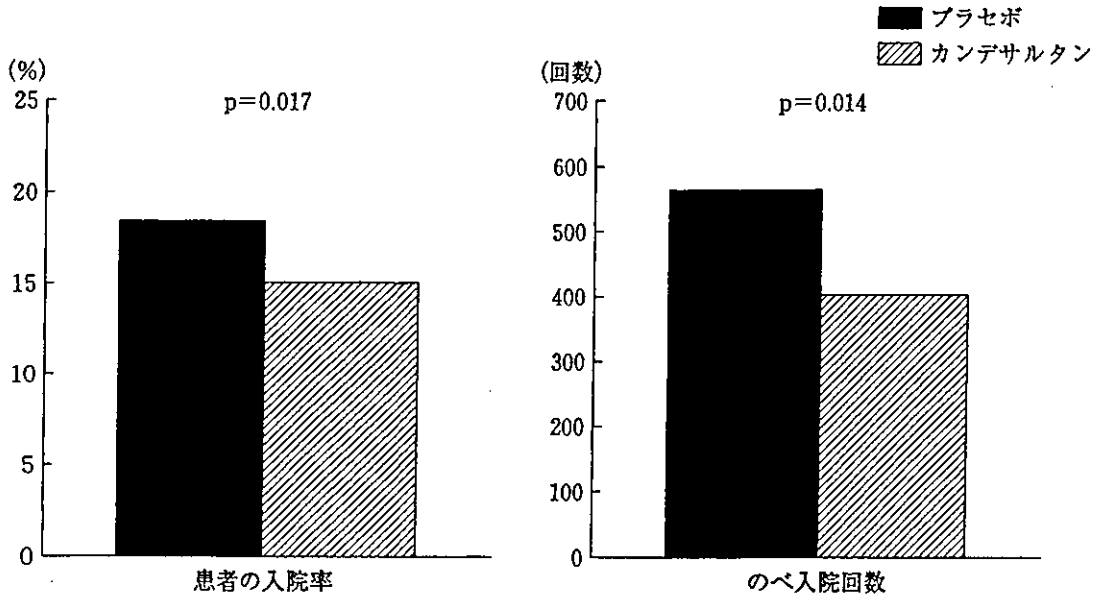

図5　CHARM－Preserved試験における試験実施医師の報告に基づく心不全増悪により入院した患者率と入院回数[5]改変

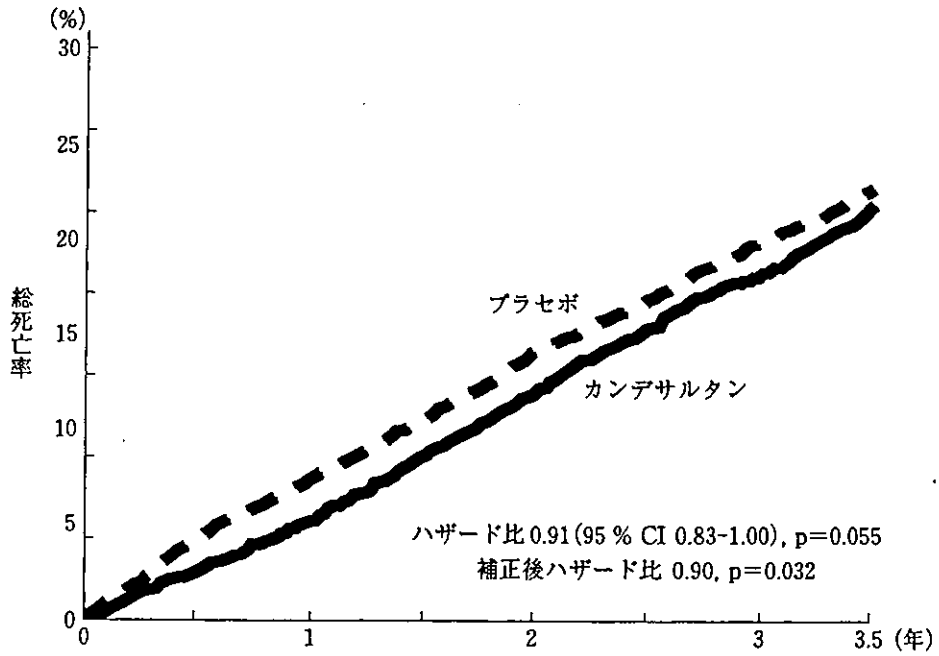

図6　CHARM－Overall試験における総死亡のカプラン－マイヤー曲線[6]改変

レニン・アンジオテンシン系抑制薬の多剤併用の際には，慎重な患者モニタリングが重要であることが示された．

V. CHARM－Overall試験

CHARM－Alternative試験，CHARM－Added試験，CHARM－Preserved試験の3試験の統合解析，CHARM－Overall試験では，CHARMプログラムに参加したNYHAクラスII－IVのCHF患者7,601例のうち，無作為化の時点で脱落した2例と，追跡期間中に脱落した10例を除く7,589例(カンデサルタン群3,796例，プラセボ群3,793例)が解析対象となった．プログラム全体の平均追跡期間は38カ月だった．心血管死

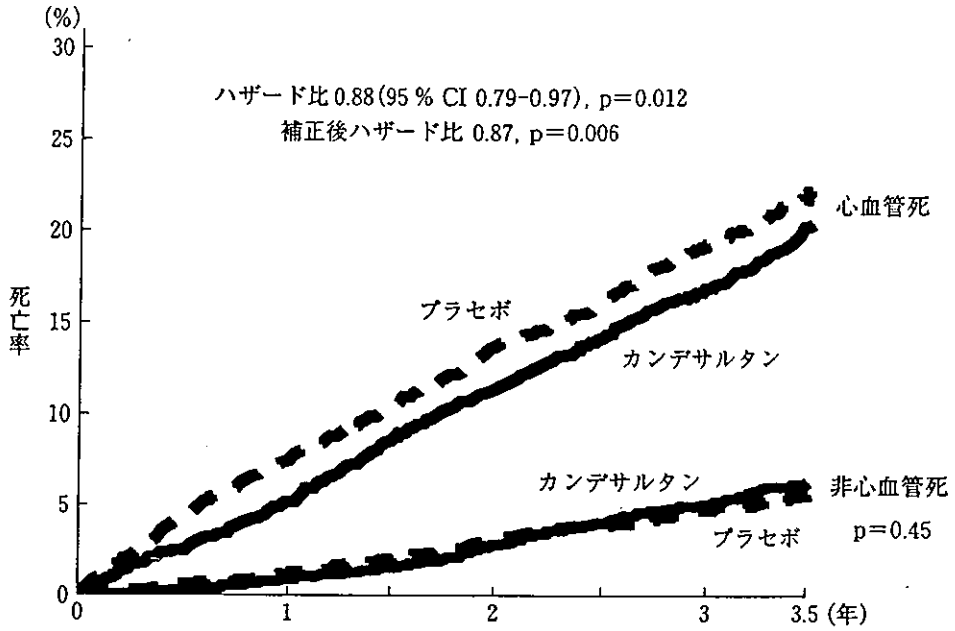

図 7 CHARM-Overall 試験における心血管死または非心血管死のカプラン-マイヤー曲線[6]改変

とHFによる入院を1次エンドポイントとしたCHARM-Alternative試験，CHARM-Added試験，CHARM-Preserved試験の3試験とは1次エンドポイントの定義が異なりCHARM-Overallの1次エンドポイントは，総死亡である[6]．

解析の結果，統計学的にはわずかに有意差を認めるには至らなかったが，総死亡率はカンデサルタン群が23％，プラセボ群が25％で，カンデサルタン群において9％のリスク低減が示された(図6)．背景因子で補正後のリスク低減率は10％(p=0.032)であった．特に，LVEF≦40％を対象としたCHARM-Alternative試験とCHARM-Added試験の2つの試験では有意な総死亡の抑制効果を認めた．

一方，カンデサルタン群の心血管死率は，プラセボ群より12％の有意な減少を示したが(図7)，非心血管死率は，両群間で差を認めなかった．致死的発癌率は，わずかながら有意にカンデサルタン群で高かった(p=0.038)が，非致死的発癌率に有意差はなかった．

各試験における1次エンドポイントである心血管死およびHFによる入院'の全体解析では，カンデサルタン群において4.3％の絶対リスク低下，および16％の有意な相対リスク低下が示された(図8)．HFによる入院は，カンデサルタン群で21％低下していた(p<0.0001)．カンデサルタン群において，心筋梗塞，脳卒中，血行再建術の施行に対するリスク軽減効果はみられなかったが，心血管死とHFによる入院に対する大きなリスク低減により，全体としてカンデサルタン群に優位な結果が得られた．

また，糖尿病の新規発症率は，カンデサルタン群で22％のリスク低減(p=0.020)が確認された．低血圧，クレアチニン上昇，カリウム上昇など，レニン・アンジオテンシン系の抑制に伴う副作用が原因の服薬中止は，全体解析においても，カンデサルタン群で多かった．

LVEFの低下した患者を対象としたCHARM-Alternative試験とCHARM-Added試験のみの総合解析では，総死亡，心血管死およびHFによる入院のみだけでなく，すべての理由による入院を加えても，カンデサルタン群で有意なリスク低減が認められた．最近のCHFに対する大規模薬剤介入試験では，既にβ遮断薬やACE阻害薬が高率で併用されていることから，総死亡でこれらの抑制効果を見出した意義は大きいと考えられる．

VI. Val-HeFTとの相違点

CHARMプログラムで示された主な副作用の

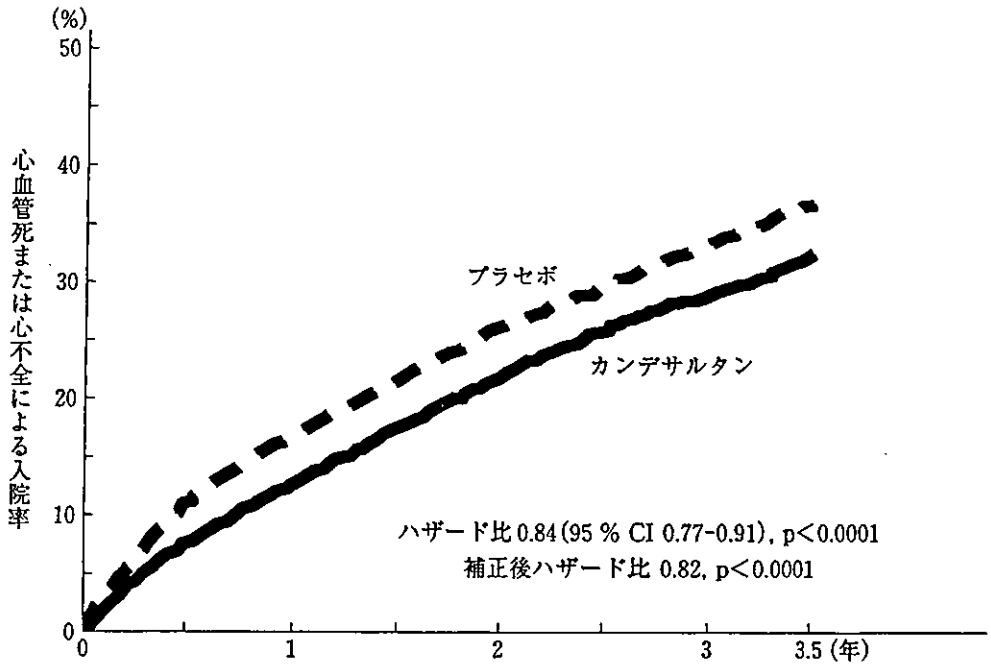

図8 CHARM-Overall試験におけるカンデサルタンの心血管死または心不全による入院に対する効果[6]改変

発現率はVal-HeFTよりも比較的低かった．また，Val-HeFTに比しCHARM-Added試験では，NYHA class III度の症例が多いこと(CHARM-Added試験：73%，Val-HeFT: 36%)，β遮断薬の併用率が高いこと(CHARM-Added試験：55%，Val-HeFT: 35%)など，より重症例を対象にした点がこのような結果になった可能性がある．また，Val-HeFTではACE阻害薬，β遮断薬，ARBの3剤併用は心血管イベントの発症を増加させる可能性を示唆したが，CHARM-Added試験では，むしろ予後の改善効果を示した(図4)．対象症例の臨床背景や，ACE阻害薬，β遮断薬，ARBの投与量など，今後詳細に検討する必要があると思われる．

おわりに

CHARM試験の成績は，カンデサルタンがLVEF，年齢，性別を問わず，すべてのCHF患者に対する治療薬であることを示唆しており，その有効性はACE阻害薬やβ遮断薬などとの併用によっても確認された．一方，CHARMプログラムで認められた結果がARBすべてに当てはまるクラス効果なのか，我が国で使用される投与量よりも高用量で臨床試験が実施されていること，今回の検討で致死性発癌率がカンデサルタン群で有意に高率であったことやVal-HeFTにおける3剤併用の結果との相違が果たしてchance findingなのか，また，CHARM-Preserved試験では，19%の症例でACE阻害薬が既に投与されていることから，ACE阻害薬投与の有無による更なる介入試験の必要性など，ARBがまだ歴史の浅い薬剤であることから，今後の更なる検証が必要であろう．

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Original Article

The Combination Therapy of Hypertension to Prevent Cardiovascular Events (COPE) Trial: Rationale and Design

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A number of major clinical trials have demonstrated the clinical benefits of lowering blood pressure and have indicated that a majority of patients with hypertension will require more than one drug to achieve optimal blood pressure control. However, there is little data showing which antihypertensive combination best protects patients from cardiovascular events and which best achieves the target blood pressure with the fewest adverse events. The Combination Therapy of Hypertension to Prevent Cardiovascular Events (COPE) trial is the first large-scale investigator-initiated multicenter study with a prospective, randomized, open, blinded endpoint evaluation (PROBE) design to directly compare cardiovascular mortality and morbidity, incidence of adverse drug reaction, and degree of blood pressure reduction in Japanese hypertensive patients for a combination of angiotensin receptor blockers, β-blockers or thiazide diuretics in addition to a calcium antagonist, benidipine hydrochloride, with a response-dependent dose titration scheme. The COPE trial is being conducted with the cooperation of more than 100 centers and clinics in Japan and involves 3,000 patients, who will be followed for 3 years. Eligible patients are being enrolled from May 2003 until May 2006. Results from the COPE trial should provide new evidence for selecting optimal combination therapies for hypertensive patients. (*Hypertens Res* 2005; 28: 331–338)

***Key Words*: hypertension, multicenter clinical trial, PROBE (prospective, randomized, open, blinded endpoint evaluation), combination therapy, benidipine**

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The trial was funded by an unrestricted grant from Kyowa Hakko Kogyo Co., Ltd. The trial is conducted as a collaborative research project between Yamaguchi University and Kyowa Hakko Kogyo Co., Ltd.

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Received January 24, 2005; Accepted in revised form February 8, 2005.

Introduction

Hypertension is an important risk factor for cardiovascular diseases (*1*, *2*). The treatment goal for hypertension is decreasing morbidity and mortality by reducing organ damage and preventing cardiovascular complications. Large-scale clinical trials comparing various antihypertensives have been conducted to investigate their benefits in preventing cardiovascular events due to hypertension. They have shown that treatment with any commonly used regimen reduces the risk of major cardiovascular events and that increased reductions in blood pressure produce a better outcome in decreasing cardiovascular events and mortality (*3–5*). It remains uncertain whether the results obtained in Western countries can be directly applied to the Japanese population because of the differences in intrinsic/extrinsic racial factors between Western countries and Japan, such as the dosage of the drugs, the dietary habits, including higher salt intake (*6*), and the cardiovascular event rates (*7*, *8*). In addition, various combinations of antihypertensive agents are often required to achieve optimal blood pressure control (*9*). Recent clinical guidelines for the treatment of hypertension recommend the combination therapy to achieve optimal blood pressure control (*3*, *10–12*). However, the effects of the combination of antihypertensive drugs have not been well investigated in regard to morbidity and mortality in patients with hypertension. Therefore, it is important to determine which combinations will achieve an optimal outcome with the fewest side effects.

Rationale

It has been reported that all antihypertensive drugs have similar long-term efficacy and safety for the prevention of cardiovascular events in patients with hypertension (*4*), with calcium antagonists being especially effective in stroke prevention (*4*, *13–15*). The Japanese Society of Hypertension Guidelines for Management of Hypertension in 2000 (JSH 2000) recommends calcium antagonists as a first-line drug for the treatment of hypertension (*12*). Prescription rates of the antihypertensive drugs in Japan are reported as follows: calcium antagonists, 73.0%; angiotensin-converting enzyme (ACE) inhibitors, 31.3%; angiotensin receptor blockers, 18.9%; β-blockers, 16.2%; and diuretics, 10.1% (*16*). Recent surveys in Japan revealed that only 50% of the subjects under antihypertensive treatment achieved the targeted blood pressure levels (*17*, *18*). Although selection of some antihypertensive drugs was based on evidence from previous trials on hypertensive patients with diabetes mellitus, chronic heart failure, and renal insufficiency, calcium antagonists were selected for most age groups and in most patients with various complications associated with hypertension. Japanese doctors do not appear to consider age or complications when choosing antihypertensive regimens (*16*). Meta-analysis of 354 randomized double-blind placebo-controlled trials (*19*) demonstrated that the blood pressure reduction effects of different categories of drugs were additive, and symptoms attributable to thiazides, β-blockers, and calcium antagonists were strongly dose-related, whereas angiotensin receptor blockers caused no increase in symptoms. Furthermore, the prevalence of symptoms with two drugs in combination was less than additive, and adverse metabolic effects (such as changes in cholesterol or potassium) were negligible at a half-standard dose, indicating that low-dose combination treatment increases efficacy and reduces adverse drug reactions (*19*). In Japan, Saito *et al.* reported that the most common first-choice drugs by hypertension specialists were a calcium antagonist (69%) or an ACE inhibitor (22%). They further described that 72% selected a calcium antagonist and an ACE inhibitor as a combination therapy, and 17% selected a calcium antagonist and angiotensin receptor blocker as their first-choice drug combination (*20*). Since calcium antagonists are widely and successfully used for the treatment of hypertension in Japan (*21*), it is most likely that combination therapy with a calcium antagonist and some other antihypertensive drug will be chosen as the first-choice combination therapy for the treatment of hypertension. In addition, in Japan, as opposed to Western countries, cerebrovascular events, which are significantly positively related to hypertension, are more frequent than cardiovascular events (*7*). According to the current status of hypertension treatment in Japan, as stated above, the Combination Therapy of Hypertension to Prevent Cardiovascular Events (COPE) trial was designed to investigate, in patients with hypertension, which combination of antihypertensive drugs—angiotensin receptor blockers, β-blockers, or thiazide diuretics in addition to a long-acting calcium antagonist, benidipine hydrochloride—is superior for achieving the targeted blood pressure and preventing cardiovascular events with the fewest adverse drug effects. The COPE trial is conducted as a collaborative research project between Yamaguchi University and Kyowa Hakko Kogyo Co., Ltd. (Tokyo, Japan).

Table 1. Inclusion Criteria for the COPE Trial

1. Outpatients who are required a combination therapy with sitting systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg
2. Outpatients aged over 40 years and less than 85 years (inclusive), regardless of sex
3. Previously untreated patients or patients who are on other therapy, which can be converted to 4 mg of benidipine
4. Patients who can be treated with benidipine, angiotensin receptor blockers, β-blockers, and thiazide diuretics

COPE, Combination Therapy of Hypertension to Prevent Cardiovascular Events.

Ethics Committee Procedure and Consent

The study protocol was approved by the ethics committees of

Table 2. Exclusion Criteria for the COPE Trial

1. Seated systolic blood pressure ≥200 mmHg or seated diastolic blood pressure ≥120 mmHg
2. Secondary hypertension
3. Type 1 diabetes mellitus or type 2 diabetes on insulin treatment
4. History of cerebrovascular disorder, myocardial infarction, angina pectoris, coronary angioplasty or coronary artery bypass graft surgery within 6 months prior to enrolment in the study
5. Heart failure (NYHA functional classification II, III or IV)
6. Chronic atrial fibrillation or atrial flutter
7. Congenital heart disease or a history of rheumatic heart disease
8. Severe peripheral arterial disease (Fontaine Class II, III or IV)
9. Serious liver dysfunction (AST or ALT ≥100 IU/l)
10. Serious renal dysfunction (serum creatinine ≥2 mg/dl)
11. History of malignancy 5 years prior to study entry
12. Pregnancy
13. Compliance rate <70% assessed by a patient interview
14. Known hypersensitivity or contraindication to benidipine, angiotensin receptor blockers, β-blockers, and thiazide diuretics
15. Other serious illness or significant abnormalities that the investigator judges inappropriate for the study

COPE, Combination Therapy of Hypertension to Prevent Cardiovascular Events; NYHA, New York Heart Association; AST, alanin aminotransferase; ALT, aspartate aminotransferase.

all institutions involved, and the trial was undertaken in accordance with the Declaration of Helsinki and the Ethical Guidelines for Clinical Studies in Japan (2003, Ministry of Health Labour Welfare of Japan: http://www.imcj.go.jp/rinri/index.html). All patients gave fully informed written consent.

Study Design

The COPE trial is an investigator-initiated, multi-center study with a prospective, randomized, open, blinded endpoint evaluation (PROBE) design (22) with a response-dependent dose titration scheme in Japanese hypertensive patients, who are prescribed a long-acting dihydropyridine calcium antagonist, benidipine, as an initial drug, and then assigned to receive either an angiotensin receptor blocker, β-blocker, or thiazide diuretic as a combination therapy. Benidipine has been widely used and proved beneficial for the treatment of hypertension (*23–25*). The target blood pressure of the COPE trial is less than 140/90 mmHg.

Patient Recruitment

Enrollment of eligible patients began in May 2003 and will continue through May 2006, and follow-up will be continued until May 2009. Inclusion and exclusion criteria are shown in Tables 1 and 2. The design outline of the COPE trial is shown in Fig. 1. Patients already receiving antihypertensive treatment are directly enrolled in the run-in phase of the COPE trial, discontinuing previous drugs and starting at an initial dosage of 4 mg of benidipine (step 0). All patients are required to be treated with benidipine for at least 4 consecutive weeks during the screening and run-in phases. During the run-in phase, blood pressure levels and compliance with benidipine are monitored. If the average blood pressure level at the last baseline visit is equal to or more than 140/90 mmHg and compliance is 70% or more, patients will be randomly assigned to receive an angiotensin receptor blocker, β-blocker, or thiazide diuretic and the initial dosage of benidipine as in step 1. Eligible patients are randomly assigned to one of the three study arms. The randomization is conducted at the COPE Trial Data Center by the dynamic allocation method (the modified minimization method) after stratification by regional block, health center, gender, age, systolic blood pressure (SBP), presence/absence of diabetes, and previous vascular events as adjusting factors in the minimization calculation.

Patient Follow-Up

Following randomization, patients receive follow-up visits over the remaining study period, during which safety parameters are checked annually, any adverse events are noted, and any interim endpoints are recorded. If a blood pressure target of <140/90 mmHg is not obtained, dose-titration is encouraged as shown in Fig. 1. A resting ECG is recorded and carotid bruit is examined at study entry and annually thereafter. During the course of the trial, if for any reason the investigator considers it advisable, the study drug can be withdrawn, but all such patients remain in the study and continue to receive full annual examinations and 6-month interim follow-up visits until the end of the study period. All the information obtained at every 6-month follow-up visit along with the information on cardiovascular events, adverse events, and investigations into discontinuation, if any, will be transmitted to the COPE Trial Data Center. Since patient withdrawal decreases the study's statistical power to detect

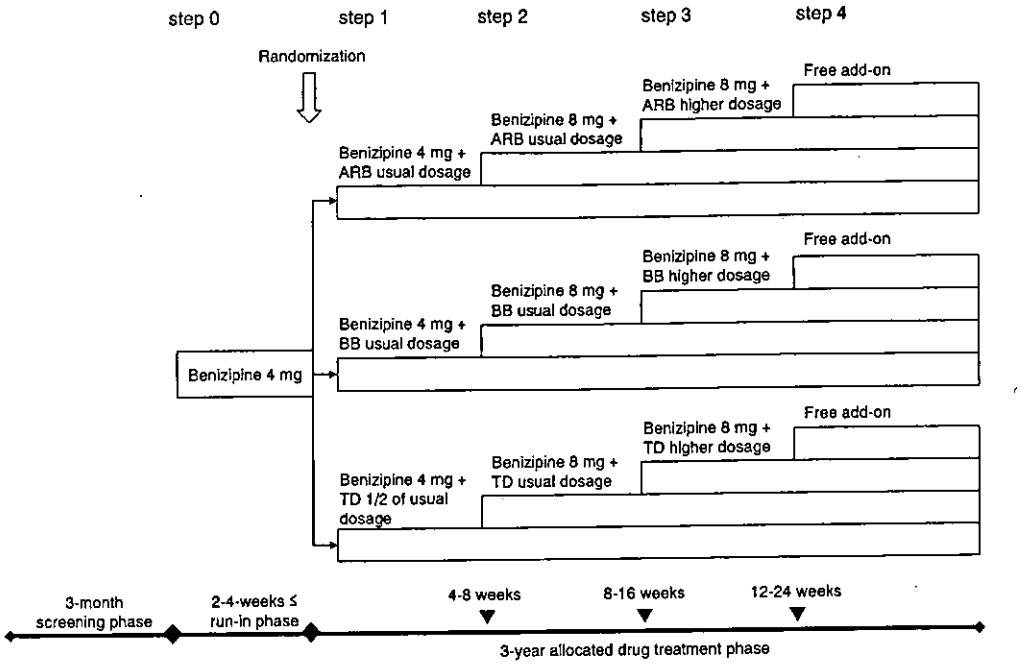

Fig. 1. *Outline of the design of the COPE trial. ARB, angiotensin receptor blockers; BB, β-blockers; TD, thiazide diuretics. "Free add-on" indicates that antihypertensive drugs other than those used for allocation—*i.e., *antihypertensive drugs other than calcium antagonists, angiotensin receptor blockers, β-blockers, or thiazide diuretics—can be added onto the drugs at step 4.*

the true effect of any intervention, all the collaborating investigators counsel their patients regarding the importance of the patients' adherence to the trial. In this way adverse event and clinical endpoint data continue to be collected on all patients. Patients withdrawn from the study drug during the treatment period may be switched to the other drugs or re-prescribed, if possible, at the investigator's discretion. If there is a need to start any therapy for any clinical indication during the study period, the investigator may prescribe additional therapy on top of the study drug. Drugs and dosages can be added at the investigator's discretion.

Endpoint Assessment

An Independent Endpoint Classification Committee will review and adjudicate cardiovascular events and all deaths and classify all potential cases without knowledge of assigned drugs according to criteria specified in the endpoint protocol. The classification of primary and secondary endpoints is shown in Table 3. For the review of the trial, the endpoint reports of the Endpoint Classification Committee will be sent to the Independent Data Monitoring Committee at 6-month intervals.

Adverse Events

All patients are questioned about adverse events at each follow-up visit. If a serious adverse event occurs, the investigators, at their discretion, may interrupt or discontinue the study drug. Both serious and non-serious adverse events are recorded, and the Safety Committee will review the data. The reports of the Safety Committee will be sent for review to the Independent Data Monitoring Committee at 6-month intervals.

Safety Considerations

The Independent Data Monitoring Committee, not involved in the administration of the trial, monitors all endpoints and medically serious and non-serious adverse events, and will perform interim analyses on the primary efficacy parameters at intervals throughout the study. The Independent Data Monitoring Committee receives safety reports from the Safety Committee and endpoint reports from the Endpoint Classification Committee at 6-month intervals, and will convene to review the trial. This Committee will have sole access to unblinded data and will inform the Steering Committee if there is a recommendation to discontinue the trial.

Statistical Considerations

Sample-Size Determination

The planned sample size (total 3,000, each arm 1,000) was determined mainly by considerations of feasibility. Regarding the proportion of patients attaining the target blood pressure levels, which is one of the primary endpoints, the