PURPOSE

The JCAD Study aims at offering fundamental data which can contribute to evidence-based medicine (EBM) for the treatment and management of patients with CAD by investigating sequentially how CAD patients are treated and how their risk factors are managed in Japan, and further, by gaining information on the incidence of major cerebrocardiovascular events.

STUDY DESIGN AND SUBJECTS

This study has two concurrently ongoing arms, one following the same subjects for three years with a follow-up examination every six months (Follow-up Study), the other enrolling new subjects every six months with a follow-up period of six months (Trend Study) (see Figure 1). For both the Follow-up and Trend Studies, at the time of performing cardiac catheterization during the enrollment period, patients having significant stenosis of at least 75% according to the AHA classification in one or more branches of a coronary artery and whose clinical information six months later is available to investigators were continuously enrolled until the target number of cases allocated to each institution was achieved. Subjects were enrolled regardless of age or sex. Subjects whose cerebrocardiovascular event, including death was confirmed within six months of enrollment were included in the study, even though their clinical information six months later was not available.

Follow-up Study (to follow the same subjects for three years. Simultaneously serves as the first enrollment of the Trend Study:

i) Age/sex: no preference.

ii) To enroll all the subjects who have received cardiac catheterization during a one-year period from April 2000 through March 2003 and who meet all of the following three conditions:

(1) Subjects who have significant stenosis of at least 75% according to the AHA classification in a coronary artery at the time of cardiac catheterization;

(2) Subjects who are retained as outpatients of the same institution six months after cardiac catheterization; and

(3) Subjects who are not retained as outpatients of the institution but whose cardiac event (including death) is confirmed within six months of cardiac catheterization.

Trend Study (to enroll subjects every six months who are not enrolled in the Follow-up Study to follow them for six months only.):

i) Age/sex: no preference.

ii) To enroll subjects who have undergone cardiac catheterization during the following period. Other criteria are the same as for the Follow-up Study.

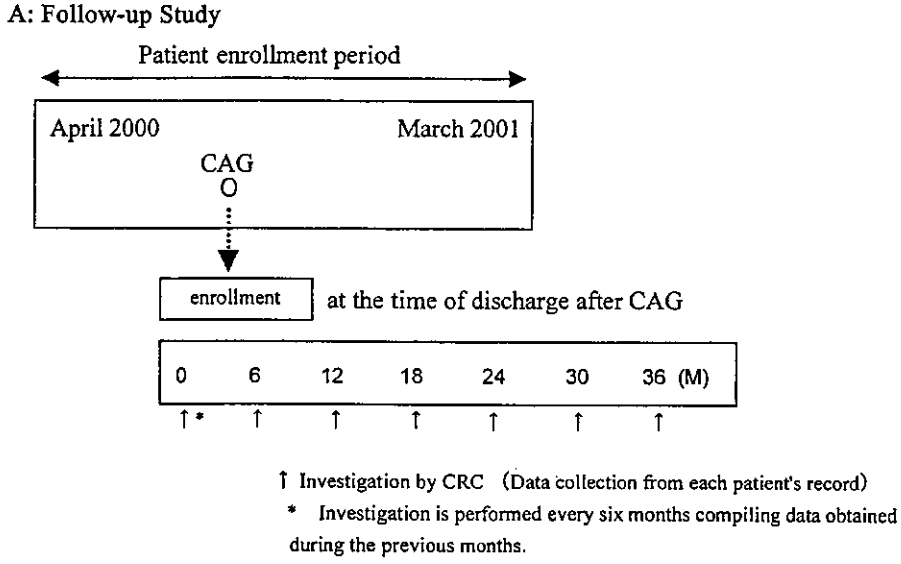

Figure 1. Schematic represetation of the Follow-up (A) and Trend (B) Studies.

METHOD, PROTECTION OF PRIVACY, AND ETHICS

An enrollment system was established within the University Hospital Medical Information Network (UMIN) and subjects were enrolled through the web by participating institutions located throughout Japan. For security purposes, an ID

and password used exclusively by a responsible investigator at each institution and a cryptocommunication system (SSL128bit) were employed. To protect subject privacy, only the system manager was allowed access to case card numbers and birth dates which identify the individual patients. Other participants, including the secretariat and administrators of the study, were denied access to such information. Access to individual patient data was givin only to the attending physician in charge of each patient. Further, in principle, case records were to be prepared by physicians themselves or by a Clinical Research Coordinator (CRC) being overseen by physicians. In addition, each physician was to confirm whether the data had been entered correctly.

Table I. JCAD Study Items to be Investigated (A: Follow-up Study, B: Trend Study)

A: Follow-up Study (Following-up each patient for 3 years)

	CAG*	6M	12M	18M	24M	30M	36M
Background	○						
CHD diagnosis	○						
Coronary imaging & treatment	○						
Patient's medical history	○						
CHD risk factors	○	○	○	○	○	○	○
Medication	○	○	○	○	○	○	○
Lifestyle improvement therapy Y/N	○	○	○	○	○	○	○
Event	○ (observation throughout the study period)						

The investigation items have to be determined on the date defined above or before/after one month from the date.

B: Trend Study (enrolling new patients every six months, following the patients only for six months thereafter)

	CAG*	6M
Background	○	
CHD diagnosis	○	
Coronary imaging & treatment	○	
Patient's medical history	○	
CHD risk factors	○	○
Medication	○	○
Lifestyle improvement therapy Y/N	○	○
Event	○	○

The investigation items have to be determined on the date defined above or before/after one month from the date.
* At the time of CAG: values obtained on the latest date before discharge (during hospitalization for check-up) have to be entered.

1) Clinical Research Review Board

In principle, the Clinical Research Review Board of each participating institution reviews and approves the study protocol and other documents, and evaluates the study on an ongoing basis.

2) Informed Consent

In principle, each attending physician explains the study to each candidate patient and obtains his or her voluntary written informed consent prior to enrollment.

3) Confidentiality of Data

In reporting the data collected, the physician, CRC, staff members of the Study Secretariat, and others use a case card number or subject number (designated by UMIN after enrollment).

PARAMETERS TO BE DETERMINED

For the subjects who were enrolled after cardiac catheterization, data on medications administered before cardiac catheterization, risk factors, and results of the catheterization procedure, diagnosis at the time of catheterization procedure, previous disease (treatment), if any, site of stenosis, extent of stenosis, treatment performed after catheterization procedure (percutaneous transluminal angioplasty, coronary artery bypass, etc.) were recorded. Further information regarding how coronary risk factors such as hyperlipidemia, impaired glucose tolerance, hypertension, smoking, and drinking are managed, as well as laboratory data obtained at that time regarding total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), low density lipoprotein cholesterol (LDL-C; Friedewald formula), fasting blood glucose (FBG), HbAlc, blood pressure, body mass index (BMI), uric acid (UA), lipoprotein small a (Lp (a)), C-reactive protein (CRP), and cardiac failure, if any, were collected at enrollment and every six months thereafter. In the case of acute disease such as myocardial infarction, hematological data obtained during a stable phase were recorded. These data were to be entered every six months (see Table I).

With the endpoint being all cerebrocardiovascular events, in case such an event should occur after enrollment, a description of the event, treatment, and outcome were recorded any time such an event occurred. "Event" is defined as the case where the subject develops a new cerebrocardiovascular disease or experiences a recurrence of such a disease after the cardiac catheterization procedure or treatment performed following such a procedure. If there are no symptoms of ischemia and restenosis is confirmed by regular cardiac catheterization, such a case is to be excluded from "event".

ANALYSES

In the Follow-up and Trend Studies, enrolled cases will be analyzed by the "intention-to-treat" method. The following analyses are planned for each of the studies:

Follow-up study: How the risk factors each CAD patient with stenosis of 75% according to the AHA classification has are managed during the three-year period and how such management influences the endpoint are to be analyzed. The chi-square test is used for qualitative data, while the *t*-test is used for quantitative data in the case of a comparison between two groups. In the case of comparison among three or more groups such data are subjected to variance analysis, and if there is any significant difference, Scheffe's post hoc analysis is also to be performed. The χ^2 test is used for any change in risk factors, while changes in parameters are to be evaluated by variance analysis and then subjected to Scheffe's multiple comparison. Relation between the endpoint and the presence (or absence) of any risk factors, such as treatment after cardiac catheterization procedure, medication administered, risk factor parameter, and expenses incurred (in treatment, drugs, etc.) are to be analyzed by multivariate studies based on Cox's proportional hazard model. Further, multiple regression analysis based on these factors is to be performed in an attempt to construct a linear model to forecast the occurrence of cardiovascular events.

Trend study: The trend in the selection of treatment for CAD patients in Japan for each six-month period is to be investigated and how the difference in the selection of treatment correlates with the endpoint is to be studied. The risk factors for each subject and the changes in parameters are to be studied using the same analytical methods as in the Follow-up Study. Analysis of events is to be performed in the same manner as in the Follow-up Study. In addition, relative risk is to be calculated for every six-month period, and how the occurrence of cardiovascular events is influenced by the presence (or absence) of any of the risk factors, medication administered, and changes in risk factor parameters is to be studied.

FUTURE SCHEDULE

Enrollment began in April 2000 and the initial enrollment of 15,506 cases for the Follow-up Study ended on September 30, 2003. In the Follow-up Study, the patient enrollment procedure was completed by the end of March, 2004 and the data entry period will expire as of the end of September 2004. In April 2005, how risk factors and treatment given to each patient correlate with the recurrence

rate of CAD will be reported based on the Follow-up Study and background factors of Japanese CAD patients, while how they are treated and the change in the recurrence rate of short-term cerebrocardiovascular events will be reported based on the Trend Study.

Subsequently, various subanalyses, including analysis by sex, existence of concomitant coronary risk factors, treatment following the cardiac catheterization procedure, and a cost versus benefit study will be performed and the results will be reported at a later date.

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研究報告

evidence scoreによるEBMの実践
―ARBの大規模臨床介入試験を用いて―

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緒　言

Evidence-based medicine (EBM)の概念が日本でも浸透し、大規模臨床介入試験の結果がわれわれの日常臨床に及ぼす影響は増えつつある。米国健康政策研究局によれば「randomized controlled trial (RCT)のメタアナリシスから得られた根拠」がevidence levelの最高位にあたり、「少なくとも一つのRCTから得られた根拠」は次点になる[1]。このRCTもプロトコール作成から結果までに多大な時間と費用を要する上、その後のメタアナリシスとなれば、さらに大きなものとなる。

われわれ臨床医がEBMを実践するにあたり、その根拠(evidence)を自ら検証することが重要であるが、実際には日常臨床に追われるあまり、製薬会社のもたらす情報やシンポジウム等にその多くを依存し、鵜呑みにしていることは否めない。

近年、数多く発表されている大規模臨床介入試験等においても、その試験の結果に都合のよい解釈がもたらされているケースが多々あり、かなりのバイアスが予想される。また、自身で一つ一つの試験論文を熟読し、要点を把握したとしても、「脳血管疾患予防に最も優れるevidenceを持つ薬剤選択」など、各々の試験の比較検討は容易ではない。

したがって、EBMをより実用化するためには、客観的な視点でevidenceを評価する方法が必要と考えられる。

そこで、筆者は難解な統計学的手法を用いず、平易に大規模臨床介入試験の比較検討が可能なevidence score(以下ES)を考案した。今回は、近年、本邦においても汎用著しい降圧薬であるアンジオテンシン受容体拮抗薬(angiotensin receptor blocker；ARB)の試験を用いて、以下解説・報告する。

対象と方法

解析対象は、本邦においてすでに臨床応用されているARB五剤(ロサルタン、カンデサルタン、バルサルタン、テルミサルタン、オルメサルタン)を用いたdesign paper[2)~10)]がすでに掲載されている一〇〇〇例以上の大規模臨床介入試験のoriginal paper[11)~21)]のみとした(表1a)。

一〇〇〇例以上と限定した理由は、すべてのRCTとした場合、論文検索、収集およびscoreの計算に多大な労力を要し、ESの趣旨である「簡易」であることに反するためである。この時点で、テルミサルタン、オルメサルタンには該当する試験がなく、対象からは除外された。

また、design paperのあるoriginal paperと限定し、層別解析結果を除外したのは、集積したデータから何か有意差が得られたものを発表するというような後付け解析結果の疑いを排除するためであり、ESに採用したendpointも事前に論文に明記されたもののみ(安全性・忍容性に関するものは含まない)とした。

ESのスコアを規定するにあたり、参考となる類似したスコアを検索したが、該当するものが見当たらなかった。したがって、本scoreは筆者が生物統計学に準じ独自に規定した。primary endpointとsecondary endpoint以降のものとはその試験における結果の重要度に差があると判断して[22)]、スコアに二倍の差をつけた。また対照がplaceboか実薬かによっても、その試験結果の持つ臨床的意味は異なると考えられ、この差も二倍とし、最終的には四

段階にスコア化した(表1b)。

ESの結果は、合計点(total)と論文に明記されたendpointの数で除した平均点(mean)にて示し、evidenceの量と質を表す指標とした。また、各ARBを用いた試験について総合、対象疾患別および臓器別にESを算出し検討した。

表1　evidence score対象と基準

a. 対　象

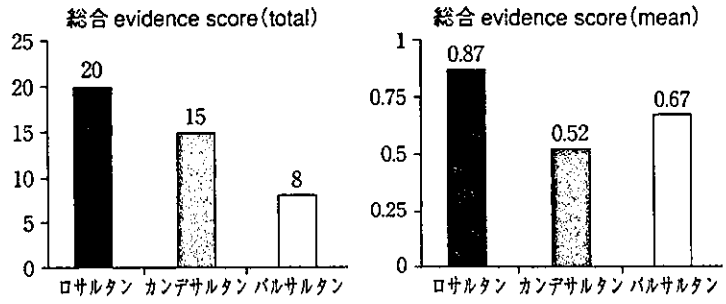
薬　剤	ロサルタン	カンデサルタン	バルサルタン
対象試験	LIFE[2] OPTIMAAL[3] RENAAL[4] ELITE II[5]	CHARM-Alternative[6] CHARM-Added[7] CHARM-Preserved[8] SCOPE[9]	VALUE[10] VALIANT[11] Val-HeFT[12]

b. 基　準

	対　照	スコア
primary endpointに有意差あり	薬　剤	8
	プラセボ	4
他のendpointに有意差あり	薬　剤	2
	プラセボ	1

上記以外はスコアは0

図1　薬剤別evidence score



結　果

ARBにて検証した結果を図1に示す。total, meanともにロサルタンが他より高いスコアを示した。

対象疾患別ES(表2a)では、高血圧患者を対象とした場合、ロサルタンのみがpositive scoreを有し、カンデサルタン、バルサルタンは対象試験を有するものの、ESは0となった。一方、心不全患者の場合、ロサルタンは0で、カンデサルタン、バルサルタンがpositive scoreを示した。糖尿病および腎症患者に関するES対象試験はロサルタンのRENAALのみであり、また、心筋梗塞においては、ロサルタン、バルサルタンが対象試験を有したが、スコアは0であり、カンデサルタンを用いた試験はなかった。

臓器別ES(表2b)においては、ロサルタンは脳・心・腎関連endpoint, 糖尿病新規発症および複合endpointすべてがpositive scoreを示したが、カンデサルタンは心関連のみ、バルサルタンは心関連と複合endpointのみであった。

各試験別のESを図2に示す。positive scoreを示したのは、ロサルタンを用いた試験ではLIFE, RENAAL, カンデサルタンではCHARM-Alternative, CHARM-Added, バルサルタンではVal-HeFTのみであった。meanにて高い順に列記すると、LIFE, RENAAL, Val-HeFT, CHARM-Added, CHARM-Alternativeとなった。

考　察

一九九二年に提唱されたEBM[23]は「信頼できる外部根拠に基づいて医療上の判断を遂行するプロセス」と定義されるが、本邦では独自の「信頼できる外部根拠」がきわめて少なく、以前より問題視されている[24]。脳卒中と虚血性心疾患の発症割合が欧米諸国と著しく異なるという疾病構造[24]からも、海外の大規模臨床介入試験結果をそのまま本邦に当てはめることは疑問ではあるが、独自のevidenceがない現状では海外のevidenceに依存せざるをえないこと

も事実である[24]。

今回、筆者はより臨床に役立つ簡易な外部根拠の提示と整理を目的として、大規模臨床介入試験のESを考案し、ARBを用いた海外の大規模臨床介入試験を対象に適用し報告した。

その結果、臓器保護のevidenceを最も多く持つARBはロサルタンとなった。早期に臨床応用されたため、evidenceを多く持つのは当然ともいえるが、論文に明記されたendpointの数にて除したmeanでも、ロサルタンは突出した値を示した。この結果は、ロサルタンの持つevidenceが他の二つの薬剤に比し、数だけではなく質的にも優れたものであることを示唆している。

またendpoint対象臓器別の保護効果は、ESにおいてカンデサルタン、バルサルタンは心保護作用のみしかevidenceを所持しなかったが、ロサルタンは脳・心・腎および糖尿病新規発症抑制と多岐にわたり有していた。各々のRCTを一読しただけでは、理解し難いことも、ESにより明確に整理され、示すことが可能となった。

次に各試験のESに関してであるが、その結果が製薬会社のもたらす情報により構築されたイメージと乖離しているものがあったことは興味深い。本報告にて対象となった一一試験のうち、primary endpointで有意な効果を示さなかった六試験はすべて0となった。

筆者が独自に提唱したESの計算方法は前述したように、生物統計学に準じている。臨床試験は検証したい「仮説」を立てて実施すべきであり、その仮説は通常一つで、それがprimary endpointとして示される。しかしながら、臨床試験を実施する場合、多大な労力と莫大な費用を要するため、研究者は一つの試験に対し、多くの仮説(endpoint)を立て、同時に検定することが多い。多数のend-

表2　対象疾患別および臓器別evidence score

a. 対象疾患別

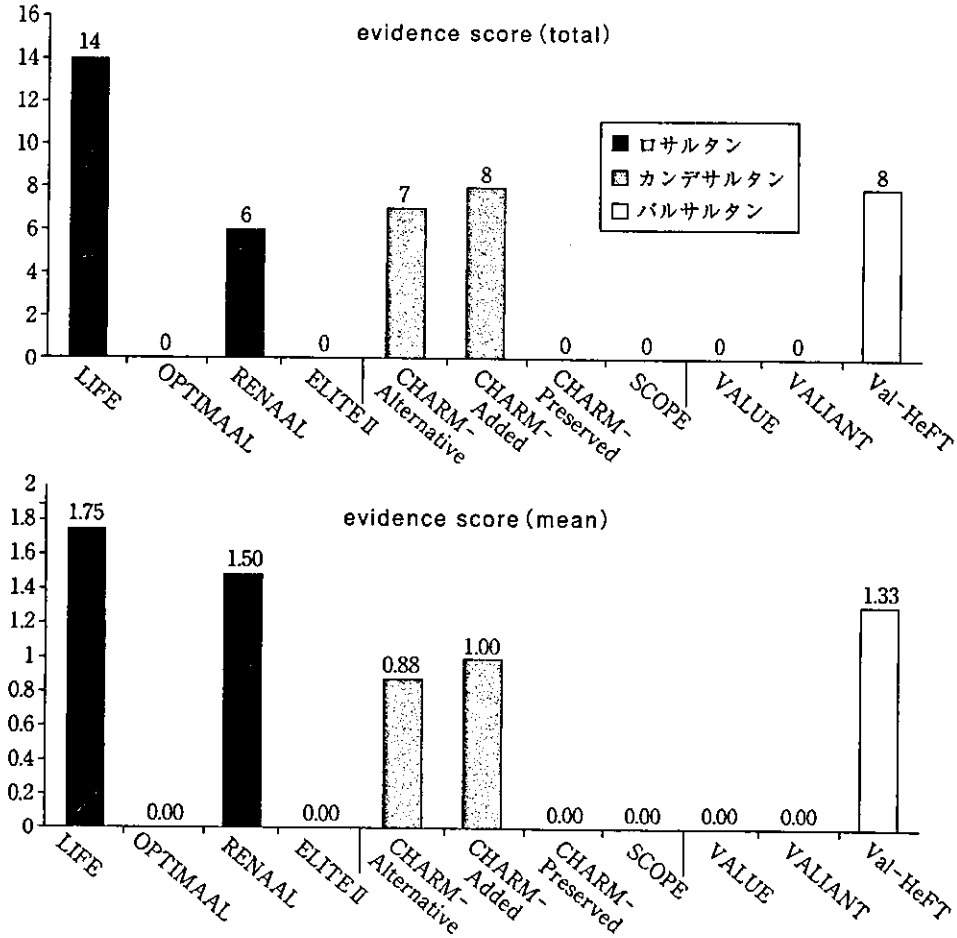
対象疾患	カテゴリー	ロサルタン	n	カンデサルタン	n	バルサルタン	n
高血圧	total	14	8	0	6	0	4
	mean	1.75		0		0	
心不全	total	0	5	15	23	8	6
	mean	0		0.65		1.33	
心筋梗塞	total	0	6	−	−	0	2
	mean	0		−		0	
糖尿病／腎症	total	6	4	−	−	−	−
	mean	1.50		−		−	

b. 臓器別

臓　器	カテゴリー	ロサルタン	n	カンデサルタン	n	バルサルタン	n
脳	total	2	2	0	2	−	−
	mean	1.00		0		−	
心	total	2	11	15	20	3	7
	mean	0.18		0.75		0.43	
腎	total	2	2	−	−	−	−
	mean	1.00		−		−	
糖尿病新規発症	total	2	1	−	−	−	−
	mean	2.00		−		−	
複合endpoint*	total	12	2	0	1	4	1
	mean	6.00		0.00		4.00	

*：複数臓器または総死亡を含む複合endpoint
−：該当データなし

図2　各試験別のevidence score



pointは偶然による有意差を得る危険性を増加させることになるが、研究の効率を高めるというメリットもある。

したがって、最良の方法は、事前にいくつかの仮説を立てた上で特に重視する仮説であるものをprimary endpointとすることと考えられる[22]。これらを踏まえたESの点数を規定したが、妥当かどうかは今後の検討課題である。しかし、primary endpointがnegativeな場合、その試験が評価されないという結果から概ね的確なものであったと考えている。

また、今回の検討の中で、大規模臨床介入試験に関する疑問点とそれを踏まえたESの問題点が抽出されたので、以下に述べる。

対象とするend-pointを「design paperにて明記したもの」と定めたが、折しも本論文執筆直後、International Committee of Medical Journal Editors (ICMJE)より、二〇〇五年七月一日以降開始される臨床試験に関し、その事前登録をすることがICMJEに加わる主要医学雑誌の掲載条件とすることが発表された。おそらく、「positive dataばかりでnegative dataが掲載されない」「後付け解析結果が示される」など、臨床試験結果に対する懸念を払拭し、透明性を保持するための策と考えられる。

筆者も同様に考え、design paperでの明記という形でバイアスを削除しようと論文を検証したところ、本条件に該当しないend-point結果が半数以上original paperに記載されていた。primary endpointがこのケースに当たるものはなかったが、secondary endpoint以降では、design paperにて個々の独立したend-pointと記載されていたにもかかわらず、結果論文では複合して報告しているケース、design paperにまったく掲げていないendpointを結果に出す等が散見された。糖

尿病新規発症抑制などはまさにその後者にあたり、positiveな結果を出したLIFE, CHARM-Preserved, VALUEのうち、予めdesign paperに明記していたのはLIFEのみであった。このことから、集積したデータから何か有意差が得られたものを発表するというような後付け解析が実施されている疑いを持たざるをえなかった。

前述のごとく臨床試験は「仮説」を検証することを目的として行われるべきであるが、今回対象となった優れたevidenceとわれわれ臨床医が認識しているものでさえ、ESという観点から検証してみると、疑問を抱く部分が多々あったことは興味深い。

ESがprimary endpointを重視した点数とした理由はすでに述べたが、それ自身が同じ対象疾患の試験で異なって設定されていることに疑問を感じた。心不全の予後を検討した試験を例にとれば、primary endpointにELITE IIは「総死亡」、CHARMは「心血管系死亡または心不全による入院」、Val-HeFTは「総死亡」「総死亡を含む心血管系イベント」と二つ設定していた。当然、総死亡は心血管系イベントや心不全による入院などに比し、発生数が少なく有意差は得にくい。

また、今回の対象二一試験の中では唯一Val-HeFTのみが、primary endpointを二つ設定しており、この場合、当然有利な結果を得る可能性は高くなる。高血圧や高脂血症などの生活習慣病と違い、心不全のような予後不良な疾患を対象とした試験は、primary endpointを統一すべきであり、今後、これらの試験計画に関するガイドラインの構築の必要性を感じた。

また、今回示したESの問題点として、placebo対照の試験が有利となることが挙げられる。なるべく公平を期すようendpointに有意な結果を得ても点数は実薬対照に比し半分としたが、placebo対象のほうが当然多くの有意差が検出されやすいため、合計するとESが高い結果となる。加えて、多くのendpointをdesign時に設定していれば、有利となるのはいうまでもない。

また、「有意差なし」という結果を対照が「実薬」「placebo」の区別なくESを0と評価していること、対照に対し「劣性すなわち負の有意差を検出」したものも「有意差なし」と同等にESを0としていること等、さらにいくつかの問題点を内包している。

以上、大規模臨床介入試験の簡易な比較検討を可能とし、EBM実践への一助となるべくESを発案し報告した。前述の問題点も含め、筆者はさらにさまざまな角度から検証を重ね、本案をより完成度の高いESとすることを今後の課題と考えている。

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治　験

一般目標：医薬品開発において治験がどのように行われるかを理解するために，治験に関する基本的知識とそれを実施するうえで求められる適切な態度を修得する．

この第Ⅳ部では，医薬品開発における治験の重要性を学ぶ．

ここでは第Ⅰ相，第Ⅱ相，第Ⅲ相などの治験の内容，治験業務での薬剤師の役割，公平な治験を行うための制度，治験に際しての被験者への説明事項などを修得する．治験における被験者の人権の保護，安全性の確保などについて討議することになる．

特にインフォームドコンセントと治験情報に関する守秘義務については重要であり，ヘルシンキ宣言についてはその意図するところを理解することが求められる．