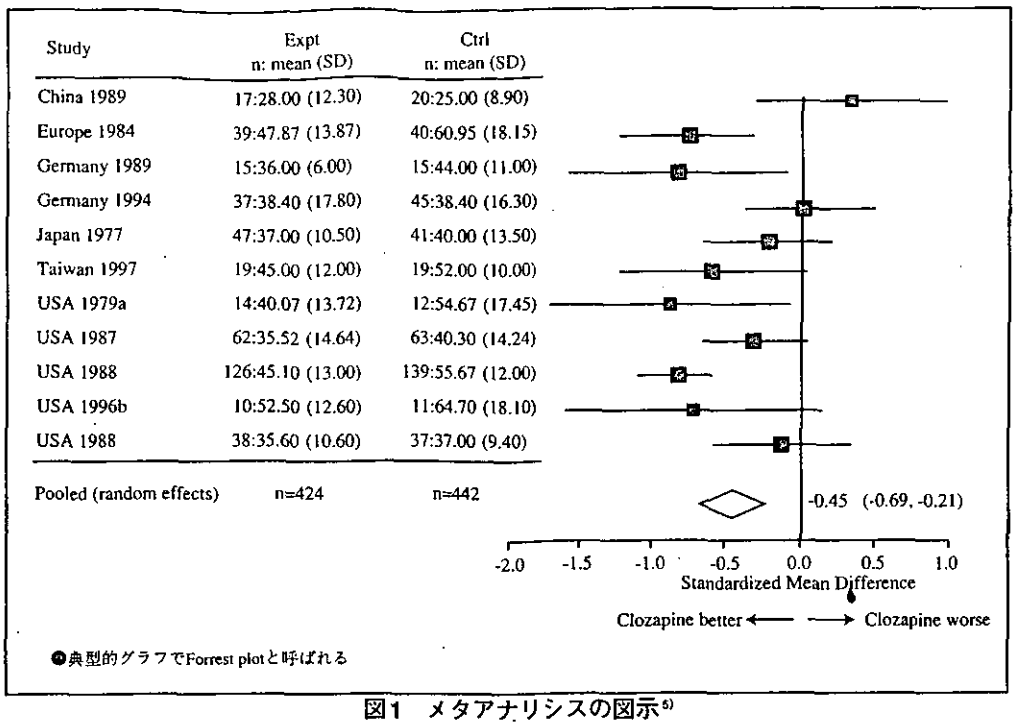


図1　メタアナリシスの図示[5]

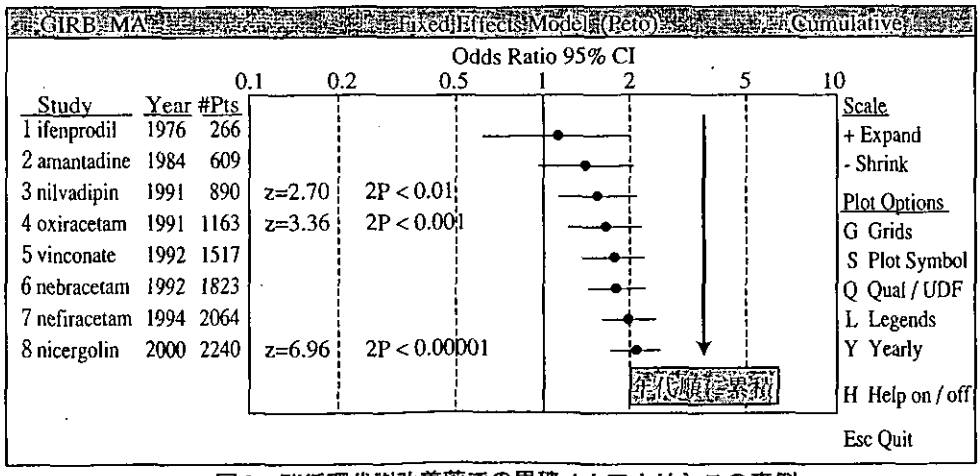


図2　脳循環代謝改善薬での累積メタアナリシスの事例

表2　2種類のメタアナリシス

- 文献情報データを併合する
  - Analysis according to summary data
- 個別データを併合して、併合解析する
  - Analysis according to individual data
  - 臨床研究者が共同することが必須
  - 各研究は1つの要因とみなす

表3　2つの解析方法

- 固定効果モデル (Fixed effects model)
  - 研究ごとの治療効果の違いは誤差とみなす
  - 真の治療効果は1つ(固定)と考える
  - Peto method, Mantel-Haenszel methodなど
- 変量効果モデル (Random effects model)
  - 研究ごとの治療効果の違いは存在すると仮定する
  - それらの違いはある分布に従っていると考える
  - DerSimonian-Laird methodなど
  - こちらのほうが併合信頼区間の幅は広くなる

メタアナリシスの最大の欠点は出版バイアスと言われている。出版された研究は肯定的な結果に偏りがちであり、そのためバイアスが生じるというものである。これを確認するための手法として漏斗プロット（Funnel plot）がある。図3に示したように逆にした漏斗のようになればよいが、そ

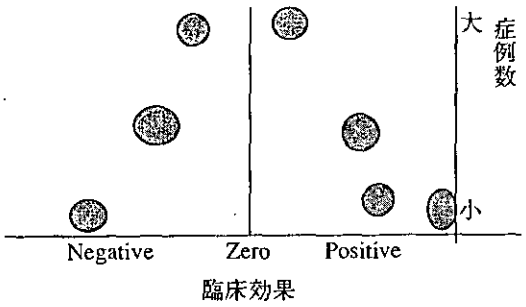
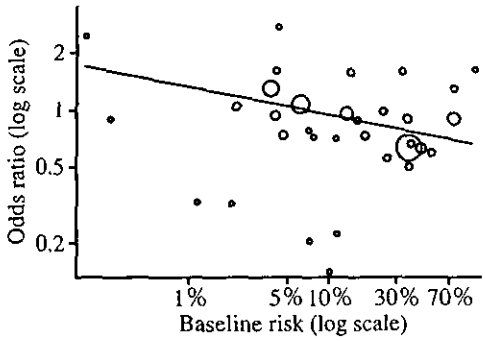


図3　漏斗プロット(Funnel plot)



● 結果の相違を予後因子で回帰させる解析法

図5　メタ回帰(Meta-regression)[5]

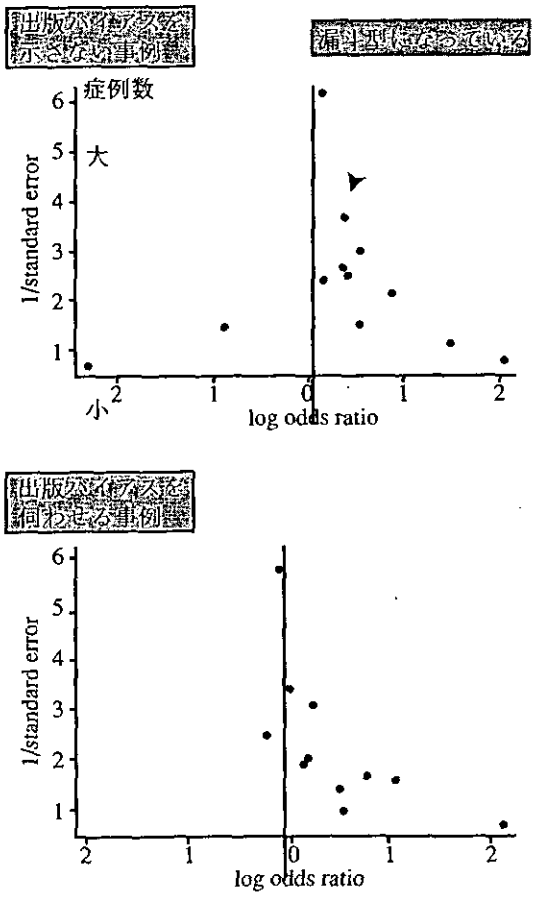


図4　出版バイアス点検のための漏斗プロット[5]

れからずれると出版バイアスが疑われる。図4の2例を見ると、左上のプロットは漏斗型になっているので問題ないが、右下のプロットでは出版バイアスが疑われる。

メタアナリシスはある治療法について複数の研究結果を併合することであるが、研究ごとに背景が異なるのはよくある。しかもその背景が結果に影響することもあろう。つまり予後因子や共変量を考慮したい場合である。それを可能にしたのがメタ回帰という手法である。これを実施するには、

表4　メタアナリシス研究の手順

- テーマを明確に決める
- 関連する文献を検索して収集する
- 各論文のチェックリストを作り要約する
- 必要となる結果データを抜き出してメモする
- 統計解析ソフトなどを用いて併合解析する
- 報告書を書く

各研究の結果に加えて共変量（例えば年齢がそうなら、各研究の平均年齢が必要）情報も必要になる。そこで図5のように、縦軸に治療効果、横軸に共変量の平均値をとり、各研究をプロットするのである。この図では、症例数の大きさに応じて各研究のプロットの大きさを変えているようである。

ここまでがメタアナリシスの基礎であるが、参考となるであろう図書を数冊[4)~6)]、総説を数編[7)~10)]挙げておく。いくつかの例はそれらから引用させていただいた。

Ⅱ　メタアナリシスの手順

表4に6つの手順をまとめた。手順1としてはテーマを明確に決めることである。患者層、介入内容、期待効果についてである。手順2は関連する文献（論文）を検索することである。用いたデータベース、検索式などを控えておく。手順3ではQUOROM声明[11)]も参考にして論文のチェックリストを作り、論文を読みながら点検する。この作業は2名で独立に行うと信頼性が上がる。手順4は、メタアナリシスに必要な結果データ部分を抜き出す作業である。表5のように、エンドポイントが連続か二値では少し異なる。手順5で抜き出したデータを用いて統計解析を実施し、手順6で報告書を書く。統計解析ソフトとして、例えばComprehensive Meta-Analysis®やRevMan®などが知られている。

表5　手順4について

● 必要となる結果データ部分を抜き出してメモする

・連続データの場合

	ARM 1			ARM 2		
試験	N	Mean	SD	N	Mean	SD
A	30	7.5	1.5	27	8.5	1.9
B						

・二値データの場合

	ARM 1	ARM 2
試験	#Events/Total	#Events/Total
A	3/111	11/142
B		

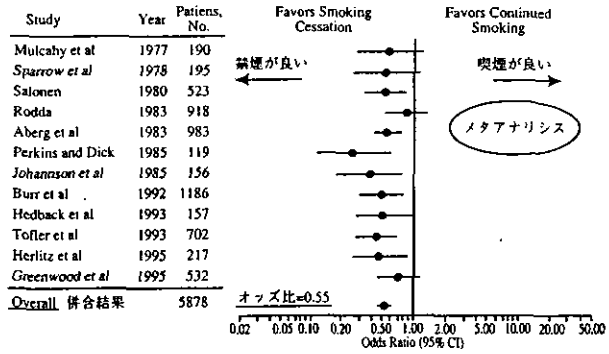


図6　禁煙メタアナリシス例での特徴的Forrest plot[12]

表6　禁煙メタアナリシス論文での質の評価事例[12]

喫煙程度の評価
追跡率
心筋梗塞の定義

Study	Well-Defined Sample (2)	Consecutive Entries of Patients (2)	Smoking Status Clearly Defined (1)	MI Clearly Defined (1)	Follow-up, % (2)	Objective Assessment of Smoking Status (2)	Difference in Baseline Factors Accounted for (2)	Total Score (10)
Mulcahy et al, 1977	Yes	Yes	Yes	Yes	100	No	No	7
Sparrow et al, 1978	Yes	Yes	Yes	Yes	97	No	No	7
Salonen, 1980	Yes	Yes	Yes	Yes	99	No	Yes	8
Rodda, 1983	Yes	Yes	Yes	Yes	100	No	No	7
Aberg et al, 1983	Yes	Partial (1)	Yes	Yes	100	Partial (1)	Yes	8
Perkins and Dick, 1985	Yes	Yes	Yes	Yes	97	No	Yes	8
Johansson et al, 1985	Yes	Partial (1)	Yes	Yes	100	No	Yes	7
Burr et al, 1992	Yes	Yes	Yes	Yes	100	No	Yes	8
Hedback et al, 1993	Yes	Partial (1)	Partial (0.5)	Yes	100	No	Yes	6.5
Tofler et al, 1993	Yes	Yes	Yes	Yes	100	No	No	8
Herlitz et al, 1995	Yes	Yes	Yes	Yes	100	No	Yes	8
Greenwood et al, 1995	Yes	Yes	Yes	Yes	100	No	Yes	7

Ⅲ　メタアナリシスの実例

実例として3つ挙げる。第一は、心筋梗塞を起こした中年男性に対して、禁煙させることで長生きできるかというテーマである[12]。まず表6のように含めた研究の質評価、あるいはデザイン要約のリストが見られる。この例では心筋梗塞の定義、追跡率、喫煙の評価などが含まれている。また、このテーマからして含まれた研究はすべて観察研究である。禁煙についてのRCTは難しい。なぜなら半分の対象には喫煙させることになるからである。さらに、図6のようなForrest plotが通常示される。この場合、併合結果としてオッズ比が0.55と分かる。つまり禁煙により、死亡リスクを相対的に45%減少させるという総合評価になる。

次はアスピリンによる一次予防の例である。最近3つの論文[13]~[15]が続けて出て、アスピリンによる血管系イベントの一次予防ガイドラインが示された。ガイドラインの根拠データとしてメタアナリシスが使われていた。基礎となるデータは5つのランダム化比較試験（RCT）であり、表7に示すように対象数は全部で5万例を超えている。また、心臓死、脳卒中、総死亡という3つのエンドポイントに関する結果が図7に示されている。これらのデータからアスピリンの便益を要約すると、アスピリンには出血という副作用もあるが、心血管への便益もありそうだということになる。表8に示されているMIに関する結果を見ると、オッズ比の95%信頼区間は0.60～0.87である。仮に心筋梗塞の5年リスクが1%（100人に1人の割合）だとすると、40%Reduction（オッズ比=0.6だから）なので、100人に0.4人減少（つまり1000人当たり4人減少）になる。上限の0.87のほうから13%Reductionなので、100人に0.13人減少（つまり1000人当たり1人；本当は1.3人だが端数を取って）減少となる。このような計算から、結局のところ1000人当たり1～4人心筋梗塞を減らすことになる。ベースラインリスクが5倍のハイリスク集団に適用すると、アスピリンの予防効果はもっと高くなり、1000人当たり6～20人予防

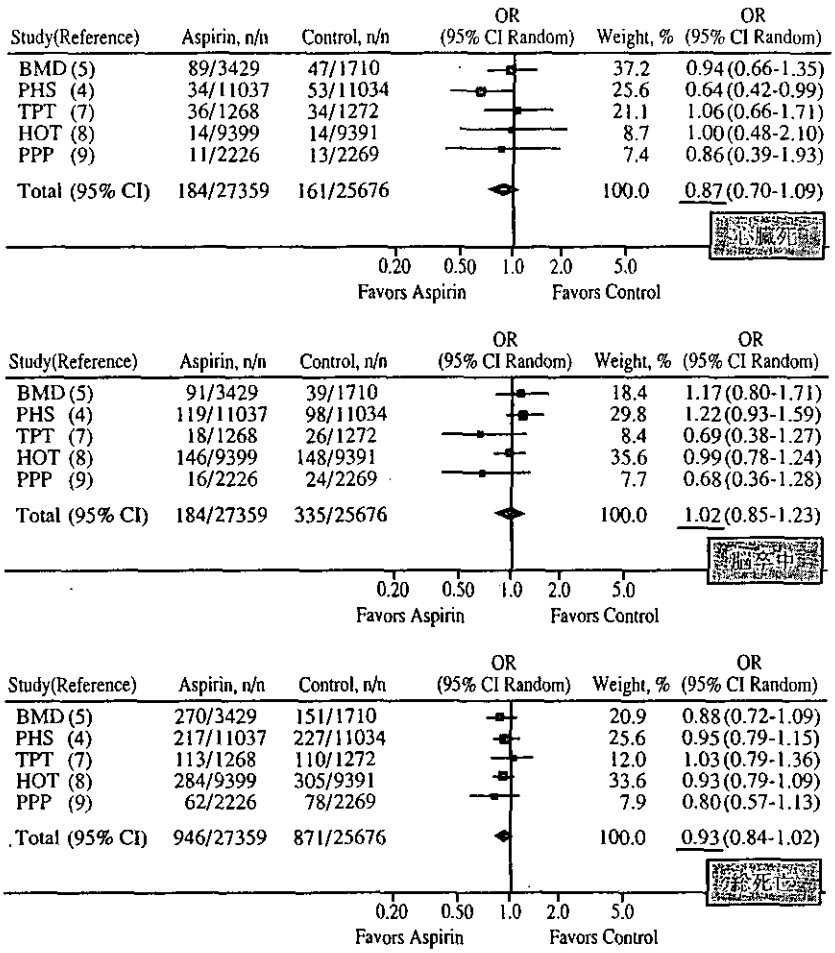


図7　3つのエンドポイントに関するアスピリン・メタアナリシス[13]

表7　アスピリンによる心血管イベントの一次予防メタアナリシス[13]

- Five selected RCTs
  - British Male Doctors' Trial (N=5,139)
  - *Physicians' Health Study (N=22,071)*
  - Thrombosis Prevention Trial (N=2,540)
  - Hypertension Optimal Treatment Trial (N=18,790)
  - *Primary Prevention Project (N=4,495)*
- A total of more than 50,000 patients

表8　アスピリン効果の要約推定値[13]

Outcome	Odds Ratio (95% CI)
Benefits	
MI	0.72 (0.60-0.87)
CHD death	0.87 (0.70-1.09)
Total stroke	1.02 (0.85-1.23)
All-cause mortality	0.93 (0.84-1.02)
Harms	
Hemorrhage stroke	1.4 (0.9-2.0)
Major gastrointestinal Bleeding events	1.7 (1.4-2.1)

できる結果になる。

次の事例は高血圧治療のメタアナリシスである。2000年のLancet誌に2つのメタアナリシスが公表された[16)~17)]。1つはWHO/ISH共同研究、もう1つはPahor-Furbergの研究であった。前者ではACE阻害薬とカルシウム拮抗薬は良好だが、疾患群によって効果に違いが見られた、という結論であった。後者では、カルシウム拮抗薬は第一選択薬として相応しくないという結論であった。Pahor-Furbergの結果を図8に示した。確かに心筋梗塞と心不全はカルシウム拮抗薬でリスク大であった。一方、WHO/ISHでは図9～10に示したように、ACE阻害薬に比べると心筋梗塞・心不全へは結果が悪いが、β遮断薬・利尿薬に比べると同等であり、脳卒中には逆に優れるという結果であった。これについては過去から論争が耐えなかったが、今回もいろいろとあった[18)~20)]。まず、含めた試験に違いが見られた。Pahor-Furbergのほうが多かったので良いと思いがちであるが、その中にはABCD試験[21)]のような途中中止例が含まれていた。しかも、それがカルシウム拮抗薬に不利な結果に大きくシフトしていたのである。こうし

た途中中止の試験が含まれているときにはバイアスが入りがちなので[22]、解釈に当たって少し注意が必要である。また、比較法が異なっていた。

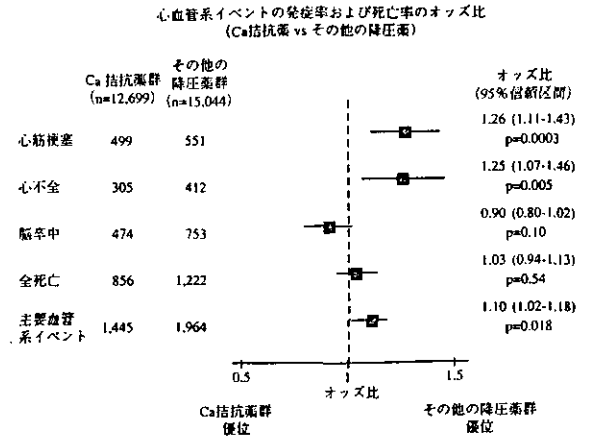


図8　Pahor-Furbergらによるメタアナリシス結果[17]

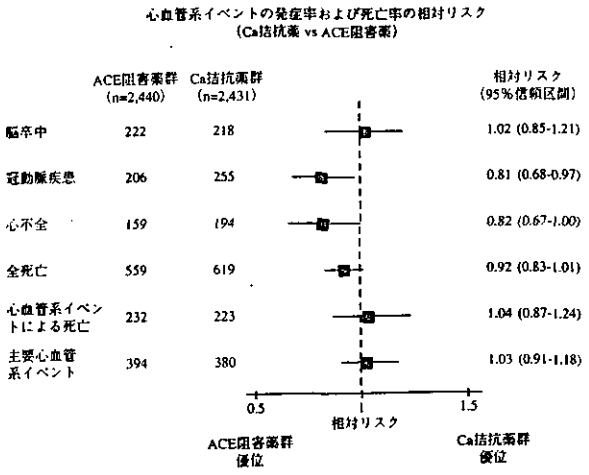


図9　WHO/ISHによるACE阻害薬との比較メタアナリシス[16]

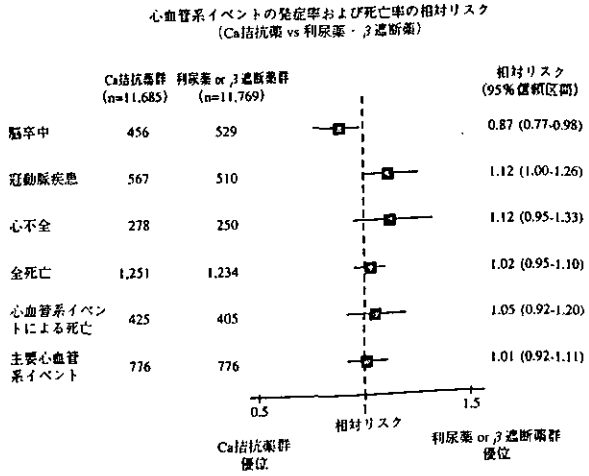


図10　WHO/ISHによる利尿薬・β遮断薬との比較メタアナリシス[16]

Pahor-Furbergではカルシウム拮抗薬に焦点を当てており、WHO/ISHでは様々の比較を行っていた。総じて見れば、結果は同様のように思われる。ACE阻害薬は心筋梗塞・心不全に優れているが、カルシウム拮抗薬は脳卒中に優れていた。カルシウム拮抗薬では血管を拡張させ血圧をより下げるが、ACE阻害薬のほうは臓器保護作用がより強いのかもしれない。また、疾病構造が異なると薬剤選択にも影響する可能性がある。日本では脳卒中のほうが重要なので、それを減らすカルシウム拮抗薬は重要だという判断もできる。

Ⅳ　メタアナリシスの影響力

メタアナリシスというのは、EBMでいうEvidence水準はトップクラスにあるため（表9）、その結果は相当医療現場で強い影響を及ぼすことがある。その第一の例がアスピリンの効能追加での事例である。アスピリンは消炎鎮痛剤であるが、心筋梗塞・脳梗塞などの血管性疾患の予防にも効果のあることが知られていた。メタアナリシスが時々刻々更新され、3つ出版されてきた[23)~25)]。2000年にはついに、厚生労働省が血栓・塞栓形成の予防薬としてアスピリンを認可した。最近のメタアナリシスであるATTによると、心筋梗塞の既往がある集団では血管系イベント抑制が25％減少、脳卒中の集団では22％減少、他のハイリスク集団で26％減少したという結果であった（表10）。

次の事例は、乳がんでのTamoxifen投与による癌死減少への影響である。これも2つほどメタアナリシス論文がある[26),27)]。第一のメタアナリシスが公表されたのが1988年のことであった。図11はイギリスで実施されたアウトカム研究[28)]であるが、メタアナリシスの結果が出た1988年を境にして、乳がん死亡率が激減していることがわかるだろう。

表9　Evidence水準

- RCTによるメタアナリシス
- RCT
- Cohort研究
- Case-control研究、前後比較研究
- Cross-sectional研究、Case series

高い ↓ 低い

表10　ATTメタアナリシスの結果

Disease category	RR	#Avoided
OMI	0.75	80
Stroke / TIA	0.78	75
Other high risk	0.74	60

over 5 years per 1000 pts

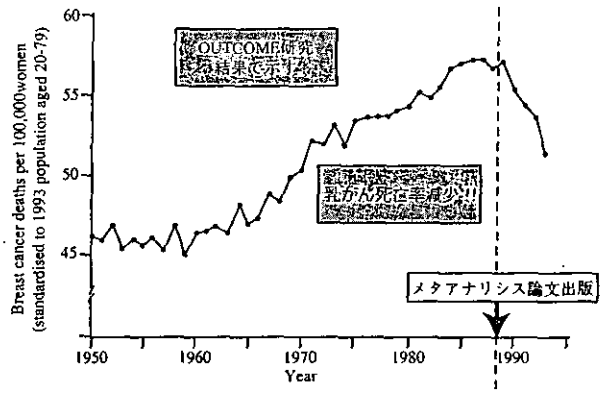


図11　メタアナリシス論文出版後乳がん死亡率激減を示した研究[28]

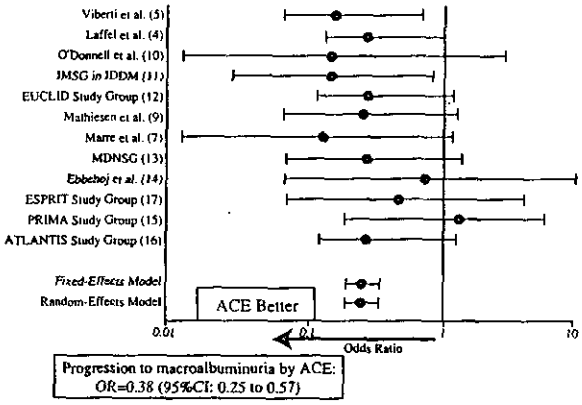


図12　微量アルブミン尿を示す1型糖尿病患者に対するACE阻害薬の有効性[29]

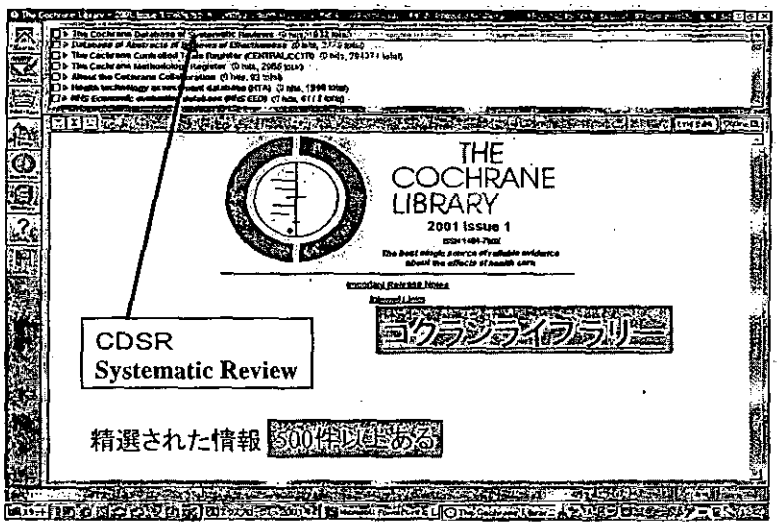


図13　コクランライブラリーにおける系統的レビュー集積

因果ははっきりしていないが、メタアナリシスの結果によりTamoxifenという薬剤の使用度が増し、最終的に乳がん死亡率まで下げたと想像される。

最後の事例は、微量アルブミン尿を示す1型糖尿病に対するACE阻害薬の効果を示したものである[29]。図12からオッズ比が0.38なので、顕性腎症への進展を62%も抑制するという結果であった。これを受けて、本邦では塩酸イミダプリル（タナトリル®）というACE阻害薬が1型糖尿病腎症で適応追加を取れたことはご存知のとおりである。また、米国糖尿病学会（ADA）の2002年診療ガイドラインにも[30]、1型糖尿病腎症への第1選択薬としてACE阻害薬が挙がった。

V　ま　と　め

メタアナリシスとは、近年発展してきた医療技術評価の一手法である。根拠水準が高いので影響力も大きい。但し、これには功罪がある。功としては、データに基づく客観的評価、中立的な総合評価が得られる、そして精度の高い推定が得られるなどが挙げられる。罪としては、レベルが高いとされるので誤解を招きやすい、こうした研究には様々のバイアスが混入しやすいことが挙げられる。メタアナリシスのポイントをまとめると、1）テーマの明確性（特に比較アーム）、2）併合する研究の網羅性（但し質の低い研究、結果評価が疑わしいものは除くこと）、3）含めた研究の要約をすること、4）適切な統計手法で併合すること（特に異質性評価を忘れずに）、最後に5）メタアナリシスは作業量がとても多いのでチームワークで行うことが肝要であろう。このような系統的レビューを世界的レベルからチームで行っているのに、コクラン共同計画が知られている。図13に示したように、CDSRという精選された系統的レビューが500件以上集積されている。計画中のものまで含めると1,200件以上のテーマが挙がっている

が、日本からの提案を強く望む次第である。最後に、系統的レビューあるいはメタアナリシスを行うことで、診療ガイドラインに反映させたり、薬剤の適応追加につなげていくことを期待する。

（本論文の要旨は、第37回日本循環器管理研究協議会総会・日本循環器病予防学会：教育講演Ⅰにおいて発表された）

文　献

1) 折笠秀樹．臨床研究デザイン．東京：真興交易医書出版部, 1995.
2) 折笠秀樹．メタアナリシスとコンバインドアナリシスとは？　臨床医, 2001; 27(5): 725-726.
3) Yusuf S, Peto R, Lewis J, et al. Beta blockade during and after myocardial infarction: an overview of the randomized trials. Prog Cardiovas Dis 1985; 27: 335-371.
4) Petitti DB. Meta-analysis, decision analysis, and cost-effectiveness analysis. Oxford University Press 1994.（福井次矢・青木則明監訳. EBMのためのデータ統合型研究．東京：メディカル・サイエンス・インターナショナル, 1999）.
5) Sutton AJ, Abrams KR, Jones DR, et al. Methods for meta-analysis in medical research. New York: John Wiley 2000.
6) Stangle DK, Berry DA(ed). Meta-analysis in medicine and health policy. New York: Marcel Dekker 2000.
7) 折笠秀樹．癌化学療法のメタアナリシス．癌と化学療法, 1998; 25: 1641-1649.
8) 折笠秀樹．メタアナリシス研究の結果の読み方．「脳卒中学」（山口武典ら，編集），東京：医学書院, 1998; 298-303.
9) 折笠秀樹．システマティックレビュー　JOHNS, 2001; 17(7): 11-16.
10) 折笠秀樹．EBM実践にさいして必要な統計学―ランダム化比較試験とメタアナリシス論文の読み方を中心に．「EBM循環器疾患の治療」（三田村秀雄・山科章・川名正敏・桑島巌編集）．東京：中外医学社, 2001: 1-20.
11) Moher D, Cook DJ, Eastwood S, et al. Improving the quality of reports of meta-analyses of randomized controlled trials: the QUOROM statement. Lancet 1999; 354: 1896-1900.
12) Wilson K, Gibson N, Willan A, et al. Effect of smoking cessation on mortality after myocardial infarction. Arch Intern Med 2000; 160: 939-944.
13) Hayden M, Pignone M, Phillips C, et al. Aspirin for the primary prevention of cardiovascular events: a summary of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med 2002; 136: 161-172.
14) U.S. Preventive Services Task Force. Aspirin for the primary prevention of cardiovascular events: recommendation and rationale. Ann Intern Med 2002; 136: 157-160.
15) Sox HC. Disease prevention guidelines from the U.S. Preventive Services Task Force. Ann Intern Med 2002; 136: 155-156.
16) Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of ACE inhibitors,calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomized trials. Lancet 2000; 356: 1955-1964.
17) Pahor M, Psaty BM, Alderman MH, et al. Health outcomes associated with calcium antagonists compared with other first-line antihypertensive therapies: a meta-analysis of randomized controlled trials. Lancet 2000; 356: 1949-1954.
18) 桑島巌，折笠秀樹．大規模臨床試験にみる真のエビデンスとは－高血圧治療の大規模臨床試験とメタアナリシスの読み方．臨床と薬物治療, 2002; 21: 588-596.
19) 桑島巌，Staessen JA，折笠秀樹，他．メタアナリシスが示す収縮期血圧の重要性．日経メディカル, 2002; 6月号：54-59.
20) 折笠秀樹．高血圧治療のメタ解析を検証する－3．メタ解析の手法と意義．Mebio, 2001; 18(6): 140-143.
21) Estacio RO, Jeffers BW, Hiatt WR, et al. The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin-dependent diabetes and hypertension. N Engl J Med 1998; 338: 645-652.
22) 折笠秀樹．メタアナリシスとその危険性．日本病院薬剤師会雑誌, 2000; 36(2): 191-192.
23) Antiplatelet Trialists' Collaboration. Secondary prevention of vascular disease by prolonged antiplatelet treatment. Br Med J 1988; 296: 320-331.
24) Antiplatelet Trialists' Collaboration. Collaborative overview of randomized trials of antiplatelet therapy - I, II, III. Br Med J 1994; 308: 81-106, 159-168, 235-246.
25) Antithrombotic Trialists' (ATT) Collaboration. Prevention of death, myocardial infarction and stroke by antiplatelet therapy: collaborative meta-analysis of 266 trials involving 200,000 patients at high risk of occlusive vascular events. Br Med J 2002; 324: 71-86.
26) Early Breast Cancer Trialists' Collaborative Group. Effects of adjuvant tamoxifen and cytotoxic

therapy on mortality in early breast cancer-an overview of 61 randomized trials among 28996 women. N Engl J Med 1988; 319: 1681-1692.
27) Early Breast Cancer Trialists' Collaborative Group. Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy-133 randomised trials involving 31000 recurrences and 24000 deaths among 75000 women. Lancet 1992; 339: 71-85.
28) Beral V, Hermon C, Reeves G, et al. Sudden fall in breast cancer death rates in England and Wales. Lancet 1995; 345: 1642-1643.
29) The ACE Inhibitors in Diabetic Nephropathy Trialist Group. Should all patients with type 1 diabetes mellitus and microalbuminuria receive angiotensin-converting enzyme inhibitors? A meta-analysis of individual patient data. Ann Intern Med 2001; 134: 70-79.
30) The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. American Diabetes Association: clinical practice recommendations 2002. Diabetes Care 25(Suppl.1): S1-S147.

1. Randomized clinical trials. The prospective randomized clinical trial is the consummate clinical experiment designed to minimize ambiguity in the interpretation of study results by striving for equality between comparison groups at the time of their assembly. It is widely regarded as the most powerful and sensitive tool for comparing therapeutic interventions (85). As discussed above, this experience has derived largely from trials of drugs for mild-to-moderate HF. Despite the theoretical strengths of the method, and its pivotal importance in trials of pharmaceutical agents in HF, there are daunting challenges in applying randomized clinical trials to the evaluation of potentially life-saving devices for end-stage heart failure. Many of these challenges arise from the differences between drugs and devices as detailed above, particularly with regard to the ethical issues arising from the inability to blind the patient or physician to the treatment arm. The unique nature of these challenges was discussed in detail in the preceding section. It should be emphasized, however, that knowledge of the treatment assignment has immediate practical implications also because the patient's preferences for a device or for no device may compromise both enrollment in, and adherence to, the treatment assignment. In one of the original trials of therapy for AIDS, blood tests were positive for the investigational therapy in 9% of the patients in the placebo arm, indicating off-protocol drug acquisition (92).

Interpretation of outcomes is also influenced by knowledge of the treatment arm. Sham operations are very controversial (91,92) and would not be compatible with the palpable and audible function of current mechanical devices. Expectations by patients and physicians may influence the recognition of complications, the intensity of other therapies and perhaps even survival. Important study end points also include the subjective assessment of symptoms and quality of life. Even exercise performance, ostensibly more objective, is influenced by the expectations of patients and physicians.

Measuring survival in trials that compare devices to medical therapies presents methodological concerns different from those presented when comparing similar therapies. When device therapy involves a high up-front operative risk, with a subsequently reduced mortality compared with controls, the survival curves are likely to cross. Analyzing the differences between such curves depends on the analytical method chosen and the time frame of the analysis. Most analyses such as the log-rank and Wilcoxon methods average risk over the follow-up period. Extending or reducing the follow-up time then has the potential to reverse the order of relative efficacy, because more or less weight will be given to the respective mortality in the perioperative period. Moreover, crossing survival curves imply lack of a consistent proportional relationship in the relative mortality of the two treatments. This violates the basic assumption in using proportional hazard methods, which have been the standard for survival analysis procedures.

Special needs in cancer and AIDS research have affected a number of advances in clinical trial methodology by employing statistical methods that permit not only more rapid and sensitive evaluation of toxicity but also adjustments in design based on the interim outcome experience within a trial (81). Further successful community-based strategies, particularly in the testing of anti-AIDS interventions, have overcome problems with patient recruitment, treatment and development of appropriate informed consent. Understanding of the special challenges involved in evaluating mechanical support will be necessary in the development of novel trial designs that lower obstacles while preserving the advantages offered by the randomized clinical trial.

Financial impediments have affected the conduct of VAD clinical trials profoundly. The issue of funding is central because device companies are often innovative organizations with limited cash reserves and few sources of income. Shrinking budgets for academic centers limit their resources in the face of the increased time required to prepare documents for institutional review boards, screen patients and provide detailed data for studies with limited enrollment. Moreover, the unreimbursed costs of the surgical procedure and recovery are substantial. Cutbacks in health care reimbursement prevent hospitals from continuing to support such visible programs internally as "loss leaders." These disincentives to patient enrollment ultimately increase the overall duration and cost of the study.

The decision by the executive branch of the federal government to begin reimbursing the routine treatment costs of Medicare patients enrolled in clinical trials is an important step in the right direction. Beyond payment for routine costs, the concept of conditional coverage is increasingly advocated, in which insurers (such as Health Care Financing Administration [HCFA]) support the costs of patient treatment associated with both arms of a well-designed clinical trial, while the sponsors (e.g., National Institutes of Health or Industry) cover the costs of conducting the research. There is strong support from this conference for such conditional coverage.

2. The REMATCH trial. Despite the above limitations, an RCT to determine the impact of a mechanical circulatory support device on outcomes with end-stage heart failure is nearing completion. The ongoing REMATCH trial compares the ThermoCardio System implantable LVAD as "destination therapy" with optimal medical therapy in patients who are not candidates for transplantation (13), using the criteria defined above. Initiation and enrollment into this study have been delayed for both centers and patients by many of the issues described. Sufficient patients have been randomized, however, to reach meaningful conclusions. If a survival benefit is proven for this device in this population, future control groups for destination therapy may be receiving this device or receiving continued medical therapy if they have established contraindications to its placement. Even if no statistically significant benefit is demonstrated in the mechanical device-supported patients, the information

JACC Vol. 37, No. 1, 2001
January 2001:340–70

obtained from both standard therapy and the assist device arms will influence device testing and population selection for future clinical device trials.

3. Modifications of the randomized controlled trial for mechanical circulatory support devices

a. OPTION OF LATER "COMPASSIONATE" USE OF DEVICE. It should be re-emphasized that the gold standard methodology for deriving firm information regarding the impact of the treatment on outcomes remains the randomized, double-blinded, placebo-controlled trial, with hard, well-defined primary end points of major clinical importance (23). It should also be recognized, however, that surgical interventions in patients with advanced illness may not appropriately lend themselves to all aspects of this methodologic gold standard, such as blinding to treatment. In designing trials for such interventions, one should begin by seeking to implement the ideal design and to deviate from the ideal only as is practically necessary. It is essential to take into account the impact of trial design modifications on the resulting data before drawing conclusions regarding the treatment effect.

Future design of a trial in which a circulatory device is compared with medical therapy might include a later offer of "compassionate cross-over" for interested patients. This would technically not be a "cross-over" trial because patients with HF would not routinely have the option to cross back from device to medical therapy and the patients receiving a device after randomization to the control arm would not be analyzed with the original device cohort. Provision of the device could be offered after a predetermined time period during which early survival and intermediate-term functional data would be obtained. Alternatively or additionally, the demonstration of certain pre-established criteria of disease progression could be considered as a surrogate end point, after which the device would be offered compassionately, recognizing that the operative risk might be higher at this time than at the time of randomization. The option of receiving a device in the future would offer hope to patients disappointed by initial assignment to no device. In addition to reducing some of the ethical concerns, this provision might actually render a more valid comparison of the two arms, by realigning the incentives for both physicians and patients to persevere through the control period without the device. It would hopefully decrease the risk of losing patients to follow-up as they seek this therapy in a less supervised setting elsewhere. For many of the reasons discussed above, these increased options would be expected to enhance enrollment and adherence to follow-up. This potential increase in enrollment needs to be balanced with the increase in sample size required to determine clinically significant differences.

b. POTENTIAL INFLUENCE OF INITIAL PATIENT PREFERENCE. The ability of a patient to select a particular modality of therapy in a clinical trial may not only significantly enhance enrollment but also potentially influence the outcomes after treatment (88–90). This argues for examining the preferences of patients as a factor that might influence the end point of the trial. One way of accomplishing this is to measure patient preferences for treatment assignment immediately before randomization and, if they are related to the primary end point, to use the results to adjust the primary comparison. A partially randomized design would give patients the option to either become part of a traditional randomized trial or take the therapy of their choosing. In a trial of two interventions, this results in four arms. The comparison of the two randomized arms offers the information of a standard RCT. Absolute confirmation regarding device outcome and complications is available for the patients choosing the device therapy, although there is no parallel control group. Comparisons between the randomized and nonrandomized arms, which must be treated as observational study, would give some indication of the effect of patient preferences on outcome.

4. Comparison of non-randomized cohorts. Alternative designs may be considered when the RCT is not considered appropriate, such as for established devices that incorporate limited improvements. It is also conceivable that cohort studies may be found acceptable when initial evidence of efficacy has persuaded the clinical community away from equipoise but has not yet led to formal device approval (Fig. 1). Cohort studies have employed both historical and prospective controls. With RCTs at the top of the hierarchy of research design, there are various levels of descending rigor for observational reports, all of which are susceptible to considerable bias. Controlling for selection bias can be improved by: 1) restriction of inclusion criteria to define relatively homogeneous cohorts with some loss of generalizability; 2) matching, such that each patient in one cohort is paired with one or more patients with a similar baseline profile for a limited number of key prognostic factors, which need to be better defined for advanced HF; 3) stratifying—comparing rates within subgroups with clinical characteristics that put them at the same risk of the outcome event, which can be done only for a few characteristics before statistical power is lost; and/or 4) adjusting for difference in clinical characteristics between the cohorts, using regression techniques. Unfortunately, none of these can control completely for the factors that led to the provision of a therapy to one patient and not to another, if the therapy was potentially available for both. An interesting example is the comparison of patients who received implantable LVADs as bridges to cardiac transplantation and those in the same centers who did not, for reasons attributed to device availability. This indicated a major benefit from devices used as bridges to transplantation, for which they were subsequently approved. However, generalization of the results to non-transplant candidates predicted a substantial benefit that was not borne out in the randomized pilot trial (52). Meta-analyses of observational trials have in some cases predicted the results of well-designed randomized trials (93,94) but in other cases have been contradicted and

supplanted by such trials (95). It has been suggested that "when recruitment of patients for an RCT is exceptionally difficult, threatening to make the sample of patients unrepresentative, neither reliance on RCTs nor reliance on observational studies is wholly satisfactory" (95,96).

a. HISTORICAL CONTROLS. There is a paucity of large "clinically rich" datasets in patients with class III and class IV heart failure. There is also little data on the components of medical therapy for truly class IV CHF patients. The Flolan International Randomized Survival Trial (FIRST) (97), examining the use of the vasodilator epoprostenol, and the recent Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME CHF) trial (98), examining the use of milrinone during HF hospitalization, demonstrated high mortality regardless of medical treatment. The Pre-Transplant Research Database (51) demonstrated high mortality in patients hospitalized or on intravenous inotropic agents, with mortality of only 13% for other patients awaiting transplantation (a younger population with fewer co-morbidities than patients currently considered for implantable devices). When concluded, the REMATCH trial will provide unique information on approximately 70 such patients receiving optimal medical therapy, and for a brief period, it will represent the most current data available. Historical controls provide useful information that requires interpretation in the context of the original reasons for data collection. Medical therapy is in a dynamic state, so reference to databases previously obtained may provide general guidance but is unlikely to sufficiently validate a new therapy unless it is in the breakthrough realm.

b. PROSPECTIVE CONTROLS. Some of the problems of historical controls can be addressed by assembling the control cohort prospectively, along with the "experimental" cohort group. Once patients have qualified for participation in the study, their assignment to a particular cohort will depend on the goals of the study. Patient assignment, however, must be made in light of the need to establish cohorts that are equally constituted with respect to the risk for the primary measure of outcome. Despite the use of restriction, matching and stratification, cohorts are rarely evenly matched, and comparisons between the cohorts require analytical adjustment to account for differences in baseline patient characteristics.

i. Timed graduation from control cohort to active therapy. One approach is to enroll patients formally for a fixed time period before the device is implanted. This provides a brief period during which early mortality for the population can be determined. There is reason to suspect, however, that the patients dying during this interval were at initially higher risk than those surviving the observation interval preceding implantation. Alternatively, the period of delay may lead to clinical deterioration that increases the operative risk to a higher level than it was at the time of enrollment. Several factors thus render the initial cohort different from the group later undergoing device implantation.

ii. Patient preference cohort studies. A patient preference study (a prospective cohort study allowing patients to choose which therapy they want) may be of considerable appeal to patients (see preceding text). Those patients selecting their preferred treatment rather than randomization would constitute the preference cohorts. Depending on the planned comparisons, patients might also be given the option to cross over to the newer therapy after specific early end points if their opinions change and the change is technically feasible. This type of trial might greatly enhance recruitment because eligible patients with end-stage HF who fear a device may be more willing to allow themselves to be followed in the medical treatment arm. Such patients are currently not likely to be enrolled in any device trials. Similarly, many patients who would be reluctant to enroll in a trial because they might have only a 50% chance of being assigned to a device would now enroll. The fundamental drawback to this design is the possibility that self-selection of a particular therapy is, in some way, associated with the primary measure of outcome, making the groups unequal at baseline. This has not been determined.

iii. Risk-based allocation cohort studies. One approach that is being investigated for breast cancer therapy is to allocate therapy in clinical trials based on risk assessment, such that those patients deemed at greater risk of dying from the underlying disease would receive the experimental therapy and those at less risk would receive standard therapy (99). The treatment effect is measured by comparing the observed results of the experimental group with a projection of the effect of standard treatment on the experimental group, based on a mathematical model. The model would be derived from observations made on the control group. Although this type of trial design is only now being examined, it may provide a novel method for studying the use of VADs in patients with complex heart failure. For investigating therapies of advanced HF, this trial design would be hindered by the limitations of our ability to identify risk profiles and predict outcomes in advanced HF.

F. The Vital Importance of Registries

1. Outcomes database for advanced heart failure. The growing national burden of advanced heart failure argues for the establishment of an ongoing registry at a number of institutions that would include information regarding therapies and outcomes. The large heart failure databases that have generated new mechanistic hypotheses have been of mild-to-moderate heart failure rather than the more severe heart failure responsible for most of the morbidity and mortality associated with this diagnosis. The complexity of this condition, with multiple etiologies, co-morbidities, therapies and modes of death, poses greater challenges to risk profiling and modelling than those encountered with specific cancers or AIDS. Despite the prevalence of advanced HF, however, there have been no national resources devoted to collaborative efforts to assemble such data.

JACC Vol. 37, No. 1, 2001
January 2001:340–70

There are several scientific and societal reasons for a greater commitment to this population. A registry of advanced heart failure would accelerate progress in developing mechanical circulatory support and other new therapies. Greater confidence in our ability to identify high-risk populations would accelerate the recognition of devices in the breakthrough realm. Indications for specific populations could be more readily defined. By virtue of its larger size, a registry offers a better opportunity for matching characteristics of an experimental group with a cohort of controls selected from the dataset. Moreover, a registry would support the development of a regression model that can be used to adjust for differences in assembled cohorts, multivariate regression modeling being the major technique employed for diminishing bias in cohort comparisons. The design of RCTs would be streamlined by better selection of target populations and prediction of event rates.

2. Registries for implantable devices. There is now broad consensus that there should be a mandatory registry for all implantable mechanical circulatory support devices. The impact and implications of device approval and acceptance are much greater than for those of any pharmacologic component of the medical regimen. The number of devices and patients that form the basis of approval is of necessity relatively small, and extensive further experience is required to optimize the clinical utility of new devices. The current consensus is that further development of implanted circulatory devices without plans for such a registry is unethical.

The same factors of technical complexity—cost outlays for the device and consoles, requirements for site expertise and the transparent impact of devices—that hinder large randomized trials prior to device approval may in fact facilitate ongoing surveillance after device release. In recent years, there has been increased attention to the potential of post-marketing studies to accelerate the process of approval. By contrast with pharmaceutical therapies, which are easier to study before approval and harder to supervise afterward, mechanical circulatory support devices may be supported by a weight of evidence distributed differently between pre- and post-approval experiences.

Past experience with all manufacturers has, however, demonstrated the numerous limitations of a voluntary registry, including a lack of uniform criteria for device insertion, variable surgical experience, incomplete data submission at all time points, cost issues and proprietary/marketing issues. There is nonetheless strong precedence for maintaining registries for implanted valves and pacing devices. Device manufacturers as well as health care providers must report information indicating that a device may have caused or contributed to a death or serious injury. In the case of high-risk devices, companies must keep records of patients with implanted devices. It should be possible to require specific baseline data collection on patients with mechanical assist devices after device approval if that stipulation is formally linked to the initial approval of the device.

In addition to patient survival data, regulatory agencies are likely to require post-approval clinical studies to expand on specific components of the safety profile for devices, such as infections or thromboembolic events and documented device failures and replacement. It is not known to what extent a mandatory registry can require specific detailed data, but a registry would provide a useful common denominator as a template. While post-marketing studies have generally used observational methods, the concomitant development of improved registries both for devices and advanced HF should allow more sophisticated modeling to determine relative outcomes of devices versus medical strategies. If there are numerous post-marketing studies that address the same issue, meta-analyses can be used to statistically combine the results of these individual studies to a degree justified by the similarity of devices. This form of analysis can help to resolve uncertainty when studies disagree as well as to answer questions that were not posed at the start of the individual studies. Moreover, it can improve estimates of the magnitude of therapeutic benefits and risks. Compared with trials of drugs and drug classes, meta-analysis has perhaps been underutilized for the analysis of the effects of mechanical assist devices.

It is unclear how the responsibility of supporting such registries should be allocated between industry and governmental agencies. The greater challenge is presented by the larger and more diffuse population with advanced HF, for whom there is no industry incentive to support systematic recording of outcomes. There are currently a number of proposals in the process of submission to direct and maintain a registry of implantable devices.

V. FUTURE DEVICES ENTERING CLINICAL DEVELOPMENT

A. Existing Minimum Standards for Pre-Clinical Device Evaluation

There is presently no standard for the pre-clinical evaluation of devices used in mechanical circulatory support systems. The FDA Office of Device Evaluation still provides useful information and interaction for blood pump developers, but officially, there is no existing standard for the pre-clinical evaluation of these devices. Consequently, it is recommended that circulatory support system developers schedule a pre-investigational device exemption (IDE) submission meeting with the FDA to educate the reviewers in advance on the specifics of their system and to receive feedback from the FDA on the appropriate criteria for the review of their system. Two guidelines for pre-clinical device evaluation do exist. First, the Preliminary Draft Guidance for Ventricular Assist Devices and Total Artificial Hearts issued by the FDA in December 1987 is the original document. Although it is useful in presenting criteria for device evaluation, it is considered obsolete. It also needs to be recognized that the document was issued early in the clinical experience of using VADs and total artificial hearts for bridging to transplan-

tation. The full extent of the circumstances in which these devices would be used (i.e., in and out of the hospital and for durations of months to over a year) could not be fully anticipated by that document. Hence, the periodic revision of the criteria for evaluation became both necessary and appropriate for the evaluation process and a source of frustration for device developers and investigators.

The second guideline comes from a joint paper developed by an ASAIO and the STS interdisciplinary working group (including participants from academia, industry, the NIH and the FDA). This working group jointly published a reliability recommendation for long-term blood pump systems in 1998 (100). This recommendation has been used to guide the reliability evaluations for blood pump systems that are currently under development or that have recently entered clinical trials. It needs to be emphasized, however, that this recommendation is limited to reliability concerns for long-term devices, so there is still a need for a more comprehensive standard with specific criteria for pre-clinical in vitro and in vivo testing and evaluation of devices.

As long-term clinical experience has been gained with circulatory support systems in bridge-to-transplant, bridge-to-recovery and alternative-to-transplant settings, it has become clear that the performance goals for these systems needs to be revised from values stated in or related to the FDA Preliminary Draft Guidance. Controversy has existed over the required duration of pre-clinical animal implantation tests and reliability mission life duration. Concern has been expressed over the recommended duration of pre-clinical reliability mission life duration (some consider the recommended minimum of one year to be too short for a long-term system) and the duration of the animal implantation trials (some consider the recommended 90 days to be too long), but there is insufficient evidence to address these concerns at this time. It also needs to be recognized that although the longer use of these circulatory support systems is the primary motivation for updating minimum criteria for pre-clinical device evaluation, the pre-clinical criteria for devices intended for short-term use (i.e., post-cardiotomy CS and transient right heart failure after LV assist implantation) and bridge-to-recovery also need to be examined and accommodated in a new standard. The revision of these guidelines becomes even more crucial as the definitions for short- and long-term devices become less clear based on clinical applicability. Previously, patients undergoing post-cardiotomy support were felt to require periods of support not extending beyond 10 days to 2 weeks. There are now anecdotal reports showing that recovery has, in fact, been seen with periods of support extending several weeks to several months. In addition, there is the distinct possibility that the patient may become device-dependent, changing what was originally anticipated to be a short-term support period to an extended period as either destination therapy or a bridge to cardiac transplantation. Another perspective to consider is that devices need to be specifically designed to meet the needs of the identified patient population.

The FDA Preliminary Draft Guidance Document and the ASAIO/STS Reliability Recommendation are still considered to be useful documents by several blood pump development groups. However, the need for a current and comprehensive standard for pre-clinical evaluation of devices remains. To begin to address this need, the Association for the Advancement of Medical Instrumentation (AAMI)[1] is presently leading the interdisciplinary development (including participation by the FDA[2] of a Technical Information Report (TIR). The AAMI TIR is in the final development stages. It is expected to be available from the AAMI by the end of the summer of 2000. It must be recognized that due to the uniqueness of each blood pump system, this document provides a comprehensive review of blood pump system issues to be evaluated and considered for inclusion in a FDA IDE submission, but it does not provide a checklist of specific performance requirements. However, the AAMI document does provide several references to guidelines and standards on specific topics related to blood pump systems. Ultimately, the comprehensive design, implementation and documentation of a blood pump system development program with validated in vitro and in vivo testing using sound scientific protocols for data collection and analysis will lead to a successful FDA device review.

Finally, some criteria need to be developed to clearly identify system standards for devices that can be used in different situations for variable clinical indications as the definitions of bridge-to-transplantation, bridge-to-recovery and destination therapy become less distinct. It is not uncommon for example, for a device to be implanted for a post-cardiotomy indication, and then removed much later (three to six months) than intended, because the recovery process may be longer than anticipated. In addition, at some point if the patient cannot be weaned, he or she can be converted to a transplant candidate. On the other hand, if adverse events occur that preclude transplantation, the device may have to perform in the mode of destination therapy. Thus, reliability requirements, which may have been sufficient for post-cardiotomy use, are now ill-defined for permanent use.

The development of a comprehensive standard for the pre-clinical evaluation of blood pump systems, though needed, is not presently being planned. The effort to create such a standard would require a rigorous interdisciplinary effort over a period of three to five years. Until such a standard is developed, it is incumbent upon the members of the blood pump development community and the FDA Device Evaluation staff to share the lessons they have learned to advance the understanding of the pre-clinical blood pump evaluation process. It is also incumbent upon the FDA Device Evaluation staff to continue their difficult

[1] AAMI, 3330 Washington Boulevard, Suite 400, Arlington, VA 22201-4598, Tel: (703) 525-4890.

[2] U.S. FDA, Center for Devices and Radiological Health, Office of Device Evaluation, Division of Cardiovascular and Respiratory Devices, 9200 Corporate Boulevard, Rockville, MD 20878, Tel: (301) 443-8262.

JACC Vol. 37, No. 1, 2001
January 2001:340–70

job of fairly and expeditiously submitting reviews, while being cognizant of the need to revise their criteria as the clinical experience with circulatory support systems grows. Because of the uniqueness of each blood pump system and its intended use, the development of a fixed true standard may be an unachievable goal. A more farsighted approach may be a continuing, interdisciplinary revision of a guidance document for blood pumping systems.

B. Devices Currently in Clinical Development

The first section of this conference document reviewed the devices currently available in the U.S. for intermediate or long-term support. This section reviews the mechanical circulatory support systems that are likely to enter clinical trials as chronic support devices in the U.S. within the next five years. Such devices fall into four major categories: 1) continuous flow LVADs (including axial flow and centrifugal flow pumps), 2) pulsatile LVADs, 3) the total artificial heart and 4) devices without blood contact.

In general, these new devices first undergo extensive ex-vivo reliability testing followed by chronic animal implantations. The third phase is human trials, which generally begin with a single site and then expand to five to twenty centers, testing the device initially as either a bridge to transplantation or as a chronic implant. Clinical trials are then performed to obtain PMA.

1. Continuous flow left ventricular assist devices. Continuous flow, or rotary devices, are currently of two basic types: axial flow pumps and centrifugal flow pumps. They have several potential advantages over current pulsatile pumps: 1) they are smaller devices and therefore can be used in smaller patients (less than the 1.5 m^2 body surface area (BSA) required for most pulsatile devices); 2) they are relatively simple, have fewer moving parts than pulsatile pumps and thus may be less prone to mechanical failures, although this is unproven; 3) because of the continuous flow characteristics, they do not require a compliance chamber in the system; 4) they have lower energy requirements; and 5) the small size of the device and the pocket may decrease the risk of infection, although this is also unproven. These devices also have potential disadvantages that remain to be quantified: 1) current axial flow pumps use bearings lubricated by blood, and this area of relative stasis is a potential source of in-situ thrombus or thromboemboli; 2) chronic anti-coagulation is necessary; 3) some degree of hemolysis is common, the long-term effects of which are unknown; 4) the long-term effects of non-pulsatile (or essentially non-pulsatile) flow are unknown; and 5) feedback control mechanisms for pump speed are complex and unproven.

a. AXIAL FLOW PUMPS. Three axial flow pumps are likely to undergo "first generation" chronic device trials in the U.S., with several trials underway in Europe. They include the Nimbus/TCI IVAS, the Jarvik 2000 IVAS and the DeBakey/MicroMed IVAS. The axial flow motor is small and contains rotary blades that spin at 10,000 to 20,000 rpm and can pump approximately five to six l/min. Because of the continuous flow properties of the axial flow pumps, there are no valves in the system.

The Nimbus IVAS (HeartMate II) is a small (7 cm length) axial flow pump that connects to the LV apex for inflow and the ascending aorta for outflow (101). Under normal operation, the inlet pressure to the axial flow pump will be cyclical, varying with the systolic-diastolic phases of the LV, creating some degree of pulsatility. An electromagnetic motor (pump rotor) turns the turbine. A low-pulse mode produced by variable motor speed will also be available. Two cup-socket ruby bearings support the pump rotor. The outer boundary of the bearing's adjacent static and moving surfaces is washed directly by blood flow. The pump's speed can be controlled manually and by a proposed auto-mode that relies on an algorithm based on pump speed, inherent native cardiac pulsatility and current. A first version of this device is powered through a percutaneous small-diameter electrical cable connected to the system's external electrical controller. A fully implantable system is under development.

The Jarvik 2000 Heart is a similar, compact (5.5 cm length, 85 gm weight) axial flow pump that receives inflow from the LV apex and outflow through a Dacron graft anastomosed to the descending thoracic aorta (102). The rotor constitutes the only moving part of the device and is supported at each end by tiny blood-immersed ceramic bearings (103). The currently existing device is tethered to an external electrical power source through a percutaneous wire, but a subsequent totally implantable version will contain a microprocessor-based controller that can sense and change pump speed according to different phases of the cardiac cycle and receive power via a transcutaneous energy transfer system coil.

The MicroMed DeBakey Axial Flow Pump is an electromagnetically actuated, implantable titanium axial flow pump that connects to the LV apex and ascending aorta. The pump is designed to produce flows of 5 l/min against 100 mm Hg pressure with a rotor speed of 10,000 rpm (104). The currently existing design of this pump includes a fixed rpm rate that can be adjusted through an external device. During periods of patient mobilizations, power can be supplied by two 12-volt DC batteries for several hours.

b. CENTRIFUGAL FLOW PUMPS. Centrifugal flow devices are somewhat larger than axial flow pumps and provide non-pulsatile flow, but the rotational speeds are much slower (about 2,000–4,000 vs. 10,000–20,000 rpm). The same general advantages and disadvantages apply to centrifugal flow pumps as to axial flow pumps.

The AB-180 Circulatory Support System is a small, durable implantable centrifugal pump that receives inflow from the left atrium and empties into the ascending aorta (105,106). The rotor is powered by electromagnetic coupling. A solution of distilled water and heparin provides a high local concentration of anticoagulant within the pump.

An occluder device prevents retrograde flow from the aorta to the left atrium in the event of pump failure. Although it is potentially useful for long-term support, the AB-180 CSS will first be tested as a support device for post-cardiotomy shock.

The HeartMate III LVAD is a centrifugal pump powered by magnetic levitation, a process that combines the functions of levitation and rotation in a single magnetic structure. The small pump rotor does not contain bearings and is completely encased in titanium.

The CorAide® centrifugal blood pump is an implantable *LVAD with a suspended rotor that is noncontacting.* The pump produces 8 liters/min flow at 6.5 W.

2. Pulsatile flow devices. Excluding the Novocor and TCI HeartMate (discussed under "Current State of Devices"), pulsatile LVADs likely to enter long-term clinical trials within the next five years are the Thoratec Intracorporeal Ventricular Assist Device (IVAD), the Novacor II, the Worldheart HeartSaver VAD and the Arrow Lionheart VAD. Each of these chronic LVADs requires chronic anti-coagulation with coumadin.

The Thoratec IVAD is designed as a small lightweight device for left or biventricular support (107,108). This IVAD maintains the same blood flow path, valves and polyurethane blood pump sac as the paracorporeal Thoratec device. The major advantage of this IVAD is its relatively small size (339 gm) and simplicity in a pulsatile system that can be implanted in patients ranging in weight from 40 to ≥100 kg. Only the small blood pump is implanted in a pre-peritoneal position with a small (9 mm) percutaneous *pneumatic drive line for each VAD connected to a more* complex control unit externally, where it can be serviced and replaced. The pump is controlled with a small briefcase-sized, battery powered pneumatic control unit.

The Novacor II miniaturized pulsatile pump is an extension of the current Novacor technology that substantially reduces pump size. The single pump is replaced by two small sac-type pumps, each driven by a central pusher plate mechanism, supporting the LV output through multiple pump cycles. The pusher plate is driven by direct electromagnetic actuation, resulting in a simple bearingless system.

The Worldheart HeartSaver VAD was designed as a totally implantable chronic VAD and has several major attributes: 1) the device is totally implantable and requires no percutaneous connections; 2) it is designed for implantation in the left hemothorax adjacent to the natural heart and can be anchored to the rib cage; 3) the device is remotely monitored and controlled; 4) an internally implanted and rechargeable battery allows the patient to *partake in a variety of activities, unencumbered by any* external components; and 5) the device can be implanted without cardiopulmonary bypass. The blood contact surface of the sac is fabricated from polyurethane and the valves are porcine tissue valves. An electromagnetic coupling device transfers power across the intact skin and tissue. Wireless monitoring and control of the device is provided by a transcutaneous infrared biotelemetry system.

The Arrow LionHeart VAD is another totally implantable LVAD system with tilting disc valves in which transcutaneous energy is transferred to implanted batteries (109). The energy converter is based on a roller screw mechanism, which in turn causes linear motion at a circular pusher plate that compresses the polyurethane blood sac during systole. In diastole the motor reverses to withdraw the pusher plate. An intrathoracic compliance chamber maintains near-thoracic pressures in the energy converter airspace. External electronics consist of the energy transmission source, a power pack, a battery charger and portable power supplies.

3. Total artificial hearts. Two total artificial heart systems are expected to enter clinical trials in the U.S. within the next five years. They include the Abiomed Total Artificial Heart and the Penn State Total Artificial Heart. Both pumps require chronic anticoagulation with warfarin ± anti-platelet agents.

The Abiomed Total Artificial Heart (AbioCor) is a completely implantable system that can generate cardiac output in excess of 10 liters/m. Powered by transcutaneous energy via coils, an internal battery is included for 20 to 40 min of tether-free time. All blood-contacting surfaces, including the two blood pumps and four tri-leaflet valves, are fabricated from seamless polyurethane (angioflex). Blood flow is maintained by a high-efficiency miniature centrifugal pump, which operates unidirectionally, while a cylindrical rotary valve alternates the direction of the hydraulic fluid flow between the left and right pumping chambers. Left/right balance is achieved by adjusting the right prosthetic ventricle stroke volume via a hydraulic shunt mechanism that incorporates a balancing chamber attached to the left prosthetic ventricle inflow port (110).

The Penn State/3M Total Artificial Heart is a totally implantable device based on a rotor screw mechanism that produces 8 liters/min with a stroke of 64 ml (111). Circular pusher plates are attached to the two ends of the rotor screw shaft, and a brushless DC electric motor rotates the screw 6.3 revolutions to provide a full pusher plate stroke with 1.9 cm linear motion. One pump empties while the other fills, and the motor then reverses to eject the opposite pump. A seamless polyurethane blood sac fits within each titanium pump case, and Bjork-Shiley convexo-concave or Delrin monostrut valves (2.5 mm inlet, 27 outlet) provide unidirectional flow. Left/right balance is achieved by the use of estimated end-diastolic volume from motor speed and voltage. A compliance chamber is coupled to the housing to accommodate volume changes caused by gas diffusion from the blood and changes in atmospheric pressure. Energy is *passed through a transcutaneous system to an implanted* controller box and Nilco rechargeable battery (45 min tether-free). There is a subcutaneous port for access to the compliance chamber.

4. Devices without blood contact. Currently existing devices without blood contact are designed for short-term

support. However, the development of similar devices for chronic therapy appears likely. The Abiomed Heart Booster combines an LV volume constraining device with a contractile component. Control of LV dilatation is effected by a conical "jacket" that fits over the apex of the heart. The contractile component is based on a change in the shape of multiple thin-walled tubes from a circular cross-section to a highly elliptical or flat cross-section, and vice versa. Rapid hydraulic inflation of the tubes (toward a circular shape) results in a smaller enclosed volume, and rapid deflation of the tubes (toward highly elliptical shape) results in a larger enclosed volume. When negative pressure is applied to the tubes during diastole, the tubes collapse completely in such a way that the pericardial wrap becomes a thin structure that is relatively pliable and does not impede diastolic filling. The device wraps around the apex of the heart and, like other volume constraining devices, does not require cardiopulmonary bypass for implantation. A smooth outer surface is used to prevent tissue ingrowth around the outer surfaces of the device and reduce diastolic dysfunction.

C. Conclusions

Results and lessons learned from trials such as the REMATCH trial will inevitably influence future trial design in the field of mechanical circulatory support. As the field moves ahead, it has become clear that no one trial design will be ideal or appropriate for all devices, populations and stages of development. A variety of research designs will be necessary. Creation of a national outcomes database for advanced HF will facilitate effective trial design and identify populations that may potentially benefit.

Responsible progress in this field requires the establishment and maintenance of a mandatory registry that includes all implantable devices, both before and after approval. The combined effort of the various stakeholders is required to address issues of funding, data format and management, compliance and access, while balancing proprietary concerns. A major achievement of this conference is the recognition that the field will advance further and more rapidly if the various groups involved in developing and testing new devices can collaborate effectively in the future.

STAFF

The conference was conducted with assistance from the Staff of the American College of Cardiology. Special thanks to Carolyn Carney Lanham, Grace Ronan, Jayne Jordan, Sabriya Wyatt, Betty Holloway, Angela Mensah, Paula Thompson and Vidya Gopal.

REFERENCES

1. Sun BC. Device Selection. In: Goldstein DJ, Oz MC, editors. Cardiac Assist Devices. Armonk, NY: Futura, 2000:27–36.
2. Pennington DG, Swartz MT, Lohmann DP, McBride LR. Cardiac assist devices. Surg Clin North Am 1998;78:691–704, vii.
3. Curtis JJ. Extracorporeal support: centrifugal pumps. In: Goldstein DJ, Oz MC, editors. Cardiac Assist Devices. Armonk, NY: Futura, 2000:215–50.
4. Jeff GK. Extracorporeal support: the ABIOMED BVS 5000. In: Goldstein DJ, Oz MC, editors. Cardiac Assist Devices. Armonk, NY: Futura, 2000:235–50.
5. McBride LR, Naunheim KS, Fiore AC, Moroney DA, Swartz MT. Clinical experience with 111 thoratec ventricular assist devices. Ann Thorac Surg 1999;67:1233–8.
6. Chen JM, DeRose JJ, Slater JP, et al. Improved survival rates support left ventricular assist device implantation early after myocardial infarction. J Am Coll Cardiol 1999;33:1903–8.
7. Chen JM, Spanier TB, Gonzalez JJ, et al. Improved survival in patients with acute myocarditis using external pulsatile mechanical ventricular assistance. J Heart Lung Transplant 1999;18:351–7.
8. Hetzer R, Muller J, Weng Y, Wallukat G, Spiegelsberger S, Loebe M. Cardiac recovery in dilated cardiomyopathy by unloading with a left ventricular assist device. Ann Thorac Surg 1999;68:742–9.
9. Poirier VL. Worldwide experience with the TCI HeartMate system: issues and future perspective. Thorac Cardiovasc Surg 1999;47 Suppl 2:316–20.
10. El Banayosy A, Deng M, Loisance DY, et al. The European experience of Novacor left ventricular assist (LVAS) therapy as a bridge to transplant: a retrospective multi-centre study. Eur J Cardiothorac Surg 1999;15:835–41.
11. Farrar DJ, Hill JD, Pennington DG, et al. Preoperative and postoperative comparison of patients with univentricular and biventricular support with the thoratec ventricular assist device as a bridge to cardiac transplantation. J Thorac Cardiovasc Surg 1997;113:202–9.
12. Massad MG, Cook DJ, Schmitt SK, et al. Factors influencing HLA sensitization in implantable LVAD recipients. Ann Thorac Surg 1997;64:1120–5.
13. Rose EA, Moskowitz AJ, Packer M, et al. The REMATCH trial: rationale, design, and end points. Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure. Ann Thorac Surg 1999;67:723–30.
14. *Torrance GW. Measurement of health state utilities for economic* appraisal. J Health Econ 1986;5:1–30.
15. Katz AM. Evolving concepts of heart failure: cooling furnace, malfunctioning pump, enlarging muscle—Part I. J Card Fail 1997; 3:319–34.
16. Katz AM. Evolving concepts of heart failure: cooling furnace, malfunctioning pump, enlarging muscle. Part II: Hypertrophy and dilatation of the failing heart. J Card Fail 1998;4:67–81.
17. Young JB. Chronic heart failure management. In: Topol EJ, editor. Textbook of Cardiovascular Medicine. Philadelphia, PA: Lippincott-Raven, 1998.
18. Uretsky BF, Young JB, Shahidi FE, Yellen LG, Harrison MC, Jolly MK. Randomized study assessing the effect of digoxin withdrawal in patients with mild to moderate chronic congestive heart failure: results of the PROVED trial. PROVED Investigative Group. J Am Coll Cardiol 1993;22:955–62.
19. Packer M, Gheorghiade M, Young JB, et al. Withdrawal of digoxin from patients with chronic heart failure treated with angiotensin-converting-enzyme inhibitors. RADIANCE Study. N Engl J Med 1993;329:1–7.
20. The Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. N Engl J Med 1997; 336:525–33.
21. *Richardson A, Bayliss J, Scriven AJ, Parameshwar J, Poole-Wilson* PA, Sutton GC. Double-blind comparison of captopril alone against frusemide plus amiloride in mild heart failure. Lancet 1987;2:709–11.
22. Parker JD, Parker AB, Farrell B, Parker JO. Effects of diuretic therapy on the development of tolerance to nitroglycerin and exercise capacity in patients with chronic stable angina. Circulation 1996;93: 691–6.
23. Silverman WA. Human Experimentation: A Guided Step into the Unknown. Oxford: Oxford University Press, 1985.
24. Cohn JN, Archibald DG, Ziesche S, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans' Administration Cooperative Study. N Engl J Med 1986; 314:1547–52.
25. Cohn JN, Johnson G, Ziesche S, et al. A comparison of enalapril

with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. N Engl J Med 1991;325:303–10.
26. The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. N Engl J Med 1992;327:685–91.
27. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med 1987;316:1429–35.
28. Pfeffer MA, Braunwald E, Moye LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the Survival And Ventricular Enlargement trial. The SAVE Investigators. N Engl J Med 1992; 327:669–77.
29. Packer M, Carver JR, Rodeheffer RJ, et al. Effect of oral milrinone on mortality in severe chronic heart failure. The PROMISE Study Research Group. N Engl J Med 1991;325:1468–75.
30. Moulopoulos LA, Topaz SR, Kolff WJ. Extracorporeal assistance to the circulation and intraaortic balloon pumping. Transactions Am Soc Artif Internal Organs 1962;8:86.
31. Masters RG. Surgical options for the treatment of heart failure. Boston, MA: Clure Academic Publishers, 1999.
32. Alderman EL, Fisher LD, Litwin P, et al. Results of coronary artery surgery in patients with poor left ventricular function (CASS). Circulation 1983;68:785–95.
33. Murphy ML, Hultgren HN, Detre K, Thomsen J, Takaro T. Treatment of chronic stable angina. A preliminary report of survival data of the randomized Veterans Administration cooperative study. N Engl J Med 1977;297:621–7.
34. Varnauskas E. Twelve-year follow-up of survival in the randomized European Coronary Surgery Study. N Engl J Med 1988;319:332–7.
35. Young JB, Kirklin JK. Cardiomyoplasty-Skeletal Muscle Assist Randomized Trial (C-SMART): six month results. Circulation 1999;100:I–514.
36. Hochman JS, Sleeper LA, Webb JG, et al. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK Investigators. Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock. N Engl J Med 1999;341: 625–34.
37. Urban P, Stauffer JC, Bleed D, et al. A randomized evaluation of early revascularization to treat shock complicating acute myocardial infarction. The (Swiss) Multicenter Trial of Angioplasty for Shock-(S)MASH. Eur Heart J 1999;20:1030–8.
38. Stevenson LW. When is heart failure a surgical disease? In: Rose EA, Stevenson LW, editors. Management of End Stage Heart Failure. Philadelphia, PA: Lippincott-Raven, 1998.
39. Hosenpud JD, Bennett LE, Keck BM, Fiol B, Boucek MM, Novick RJ. The Registry of the International Society for Heart and Lung Transplantation: sixteenth official report—1999. J Heart Lung Transplant 1999;18:611–26.
40. United Network of Organ Sharing. 1999 Annual Report of the United States Scientific Registry of Transplant Recipients and Organ Procurement and Transplantation Network. Transplant Data 1989–1998. Washington D.C., Department of Health and Human Services. Health Resources and Services Administration, 1999.
41. United Network of Organ Sharing. 1997 Report OPTN: Waiting List Activity and Donor Procurement. Rockville, MD, UNOS, Richmond, VA, and the Division of Transplantation, Office of Special Programs, Health Resources and Services Administration, United States Department of Health and Human Services, 1997.
42. Willman VL. Expert panel review of the NHLBI Total Artificial Heart Program; http://www.nhlbi.nih.gov/resources/docs/tah-rpt.htm. 1999.
43. Gracin N, Johnson MR, Spokas D, et al. The use of APACHE II scores to select candidates for left ventricular assist device placement. Acute Physiology and Chronic Health Evaluation. J Heart Lung Transplant 1998;17:1017–23.
44. Fedullo AJ, Swinburne AJ, Wahl GW, Bixby KR. APACHE II score and mortality in respiratory failure due to cardiogenic pulmonary edema. Crit Care Med 1988;16:1218–21.
45. Goldhill DR, Sumner A. APACHE II, data accuracy and outcome prediction. Anaesthesia 1998;53:937–43.
46. American Heart Association. 1999 Heart and Stroke Statistical Update. 1999.
47. Holmes DR, Jr., Bates ER, Kleiman NS, et al. Contemporary reperfusion therapy for cardiogenic shock: the GUSTO-I trial experience. The GUSTO-I Investigators. Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries. J Am Coll Cardiol 1995;26:668–74.
48. Hochman JS, Boland J, Sleeper LA, et al. Current spectrum of cardiogenic shock and effect of early revascularization on mortality. Results of an International Registry. SHOCK Registry Investigators. Circulation 1995;91:873–81.
49. Hasdai D, Holmes DR, Jr., Califf RM, et al. Cardiogenic shock complicating acute myocardial infarction: predictors of death. GUSTO Investigators. Global Utilization of Streptokinase and Tissue-Plasminogen Activator for Occluded Coronary Arteries. Am Heart J 1999;138:21–31.
50. Lewis EF, Johnson PA, Johnson W, et al. Heart failure patients express strong polarity of preference for either quality of life or survival. Circulation 1998;98:I–86.
51. Kubo SH, Stevenson LW, Miller LW, et al. Outcomes in non-urgent patients awaiting transplantation. J Heart Lung Transplant 2001. In Press.
52. Moskowitz AJ, Shapiro PA, Sollano JA, et al. Left ventricular assist devices as long-term therapy for severe heart failure. Pilot study results demonstrate feasibility of randomized trial. Circulation 1999; 100 Suppl 1:I–514.
53. Aaronson KD, Schwartz JS, Chen TM, Wong KL, Goin JE, Mancini DM. Development and prospective validation of a clinical index to predict survival in ambulatory patients referred for cardiac transplant evaluation. Circulation 1997;95:2660–7.
54. Lucas C, Johnson W, Hamilton MA, et al. Freedom from congestion predicts good survival despite previous class IV symptoms of heart failure. Am Heart J 2001. In Press.
55. Black N, Brazier J, Fitzpatrick R, Reeves B. Health Services Research Methods: A Guide to Better Practice. London: BMJ Books, 1998.
56. Bourge RC, Naftel DC, Costanzo-Nordin MR, et al. Pretransplantation risk factors for death after heart transplantation: a multiinstitutional study. The Transplant Cardiologists Research Database Group. J Heart Lung Transplant 1993;12:549–62.
57. Naccarelli GV, Wolbrette DL, Dell'Orfano JT, Patel HM, Luck JC. A decade of clinical trial developments in postmyocardial infarction, congestive heart failure, and sustained ventricular tachyarrhythmia patients: from CAST to AVID and beyond. Cardiac Arrhythmic Suppression Trial. Antiarrhythmic Versus Implantable Defibrillators. J Cardiovasc Electrophysiol 1998;9:864–91.
58. Pennington DG, Reedy JE, Swartz MT, et al. Univentricular versus biventricular assist device support. J Heart Lung Transplant 1991;10: 258–63.
59. Farrar DJ, Hill JD, Gray LA, Jr., Galbraith TA, Chow E, Hershon JJ. Successful biventricular circulatory support as a bridge to cardiac transplantation during prolonged ventricular fibrillation and asystole. Circulation 1989;80:III147–III151.
60. Holman WL, Roye GD, Bourge RC, McGiffin DC, Iyer SS, Kirklin JK. Circulatory support for myocardial infarction with ventricular arrhythmias. Ann Thorac Surg 1995;59:1230–1.
61. Geannopoulos CJ, Wilber DJ, Olshansky B. Control of refractory ventricular tachycardia with biventricular assist devices. Pacing Clin Electrophysiol 1991;14:1432–4.
62. Kulick DM, Bolman RM, III, Salerno CT, Bank AJ, Park SJ. Management of recurrent ventricular tachycardia with ventricular assist device placement. Ann Thorac Surg 1998;66:571–3.
63. Keogh AM, Valantine HA, Hunt SA, et al. Impact of proximal or midvessel discrete coronary artery stenoses on survival after heart transplantation. J Heart Lung Transplant 1992;11:892–901.
64. Costanzo MR, Naftel DC, Pritzker MR, et al. Heart transplant coronary artery disease detected by coronary angiography: a multiinstitutional study of preoperative donor and recipient risk factors. Cardiac Transplant Research Database. J Heart Lung Transplant 1998;17:744–53.
65. Wong PM, Piamsomboon C, Mathur A, et al. Efficacy of coronary stenting in the management of cardiac allograft vasculopathy. Am J Cardiol 1998;82:239–41.
66. McGiffin DC, Savunen T, Kirklin JK, et al. Cardiac transplant coronary artery disease. A multivariable analysis of pretransplantation risk factors for disease development and morbid events. J Thorac Cardiovasc Surg 1995;109:1081–8.

67. Oz MC, Goldstein DJ, Pepino P, et al. Screening scale predicts patients successfully receiving long-term implantable left ventricular assist devices. Circulation 1995;92:II169–II173.
68. Thoratec VAD Voluntary Registry. Pleasanton, CA, Thoratec Laboratories Corporation, 2000.
69. Thermocardiosystem HeartMate Registry. Wooster, MA, Thermocardiosystems, 2000.
70. Sun BC, Catanese KA, Spanier TB, et al. 100 long-term implantable left ventricular assist devices: the Columbia Presbyterian interim experience. Ann Thorac Surg 1999;68:688–94.
71. Bourge RC, Kirklin JK, Naftel DC, White C, Mason DA, Epstein AE. Analysis and predictors of pulmonary vascular resistance after cardiac transplantation. J Thorac Cardiovasc Surg 1991;101:432–44.
72. Fukamachi K, McCarthy PM, Smedira NG, Vargo RL, Starling RC, Young JB. Preoperative risk factors for right ventricular failure after implantable left ventricular assist device insertion. Ann Thorac Surg 1999;68:2181–4.
73. Kormos RL, Gasior TA, Kawai A, et al. Transplant candidate's clinical status rather than right ventricular function defines need for univentricular versus biventricular support. J Thorac Cardiovasc Surg 1996;111:773–82.
74. Oz MC, Rose EA, Levin HR. Selection criteria for placement of left ventricular assist devices. Am Heart J 1995;129:173–7.
75. Bethesda Conference: conference for the design of clinical trials to study circulatory support devices for chronic heart failure. Ann Thorac Surg 1998;66:1452–65.
76. Moskowitz AJ, Weinberg AD, Oz MC, Williams DL. Quality of life with an implanted left ventricular assist device. Ann Thorac Surg 1997;64:1764–9.
77. Stevenson LW, Couper G, Natterson B, et al. Target heart failure populations for newer therapies. Circulation 1995;92:II174–II181.
78. Byock IR, Merriman MP. Measuring quality of life for patients with terminal illness: the Missoula-VITAS quality of life index. Palliat Med 1998;12:231–44.
79. Levenson JW, McCarthy EP, Lynn J, Davis RB, Phillips RS. The last six months of life for patients with congestive heart failure. J Am Geriatr Soc 2000;48:S101–9.
80. Food, Drug, and Cosmetic Act. 501–21. 2000.
81. Grage TJ, Zelen M. The controlled randomized clinical trial in the evaluation of cancer treatment—the dilemma and alternative trial design. UICC Tech Rep Ser 1982;70:20–46.
82. Freedman B. Equipoise and the ethics of clinical research. N Engl J Med 1987;317:141–5.
83. Hellman S, Hellman DS. Of mice but not men. Problems of the randomized clinical trial. N Engl J Med 1991;324:1585–9.
84. Passamani E. Clinical trials—are they ethical? N Engl J Med 1991;324:1589–92.
85. Marquis D. How to resolve an ethical dilemma concerning randomized clinical trials. N Engl J Med 1999;341:691–3.
86. Crispell K, Nauman D, Walker T, et al. Outpatient continuous inotropic therapy with end stage heart failure: palliative or life-prolonging? J Card Fail 1998;4:39.
87. Parker LS, Arnold RM, Meisel A, Siminoff LA, Roth LH. Ethical factors in the allocation of experimental medical therapies: the chronic left ventricular assist system. Clin Res 1990;38:537–44.
88. Torgerson DJ, Sibbald B. Understanding controlled trials. What is a patient preference trial? BMJ 1998;316:360.
89. Lambert MF, Wood J. Incorporating patient preferences into randomized trials. J Clin Epidemiol 2000;53:163–6.
90. Brewin CR, Bradley C. Patient preferences and randomised clinical trials. BMJ 1989;299:313–5.
91. McPherson K, Britton AR, Wennberg JE. Are randomized controlled trials controlled? Patient preferences and unblind trials. J R Soc Med 1997;90:652–6.
92. Volberding PA, Lagakos SW, Koch MA, et al. Zidovudine in asymptomatic human immunodeficiency virus infection. A controlled trial in persons with fewer than 500 CD4-positive cells per cubic millimeter. The AIDS Clinical Trials Group of the National Institute of Allergy and Infectious Diseases. N Engl J Med 1990;322:941–9.
93. Kern MJ, Cohen M, Talley JD, et al. Early ambulation after 5 French diagnostic cardiac catheterization: results of a multicenter trial. J Am Coll Cardiol 1990;15:1475–83.
94. Benson K, Hartz AJ. A comparison of observational studies and randomized, controlled trials. N Engl J Med 2000;342:1878–86.
95. Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. N Engl J Med 2000;342:1887–92.
96. Pocock SJ, Elbourne DR. Randomized trials or observational tribulations? [editorial comment]. N Engl J Med 2000;342:1907–9.
97. Califf RM, Adams KF, McKenna WJ, et al. A randomized controlled trial of epoprostenol therapy for severe congestive heart failure: the Flolan International Randomized Survival Trial (FIRST). Am Heart J 1997;134:44–54.
98. Cuffe MS, Califf RM, Adams KF, et al. Rationale and design of the OPTIME CHF trial: outcomes of a prospective trial of intravenous milrinone for exacerbations of chronic heart failure. Am Heart J 2000;139:15–22.
99. Finkelstein MO, Levin B, Robbins H. Clinical and prophylactic trials with assured new treatment for those at greater risk: I. A design proposal. Am J Public Health 1996;86:691–5.
100. Pantalos GM, Altieri F, Berson A, et al. Long-term mechanical circulatory support system reliability recommendation: American Society for Artificial Internal Organs and The Society of Thoracic Surgeons: long-term mechanical circulatory support system reliability recommendation. Ann Thorac Surg 1998;66:1852–9.
101. Butler K, Thomas D, Antaki J, et al. Development of the Nimbus/Pittsburgh axial flow left ventricular assist system. Artif Organs 1997;21:602–10.
102. Marlinski E, Jacobs G, Deirmengian C, Jarvik R. Durability testing of components for the Jarvik 2000 completely implantable axial flow left ventricular assist device. ASAIO J 1998;44:M741–4.
103. Kaplon RJ, Oz MC, Kwiatkowski PA, et al. Miniature axial flow pump for ventricular assistance in children and small adults. J Thorac Cardiovasc Surg 1996;111:13–8.
104. Wieselthaler GM, Schima H, Hiesmayr M, et al. First clinical experience with the DeBakey VAD continuous-axial-flow pump for bridge to transplantation. Circulation 2000;101:356–9.
105. Clark RE, Walters RA, Hughson S, Davis SA, Sr., Magovern GJ. Left ventricular support with the implantable AB-180 centrifugal pump in sheep with acute myocardial infarction. ASAIO J 1998;44:804–11.
106. Griffin WP, Savage EB, Clark RE, et al. AB-180 circulatory support system: summary of development and phase I clinical trial. ASAIO J 1998;44:M719–24.
107. Farrar DJ, Buck KE, Coulter JH, Kupa EJ. Portable pneumatic biventricular driver for the Thoratec ventricular assist device. ASAIO J 1997;43:M631–4.
108. Farrar DJ, K-rfer R, El Banayosy A, Posival H, Loisance DY, Tixier D. First clinical use of the Thoratec TLC-II portable VAD driver in ambulatory and patient discharge settings. ASAIO J 1998;44:35A.
109. Weiss WJ, Rosenberg G, Snyder AJ, et al. A completely implanted left ventricular assist device. Chronic in vivo testing. ASAIO J 1993;39:M427–32.
110. Kung RT, Yu LS, Ochs B, Parnis S, Frazier OH. An atrial hydraulic shunt in a total artificial heart. A balance mechanism for the bronchial shunt. ASAIO J 1993;39:M213–7.
111. Weiss WJ, Rosenberg G, Snyder AJ, et al. Steady state hemodynamic and energetic characterization of the Penn State/3M Health Care Total Artificial Heart. ASAIO J 1999;45:189–93.

医療用具の臨床試験の公正かつ効率的な実施のための科学的方法に関する研究

医薬品と比較した医療機器の特殊性

- 医療機器の持つ効果や作用機序の多様性
- 構成要素や構造の複雑性
- 新規な先進的技術の導入による未知の効果や評価が必要な事項の出現

問題点

医療機器の特殊性に起因して、国内外で、医療機器の臨床試験の本来の目的である有効性と安全性の評価に多大な労力と時間を費やする場合がみられている。

研究方法

- 多方面にわたる専門家の参画
- 国内、国外の臨床試験の問題点の抽出、解析
- ISO14155-2 などに基づいたガイドラインの作成

研究によるアウトプット

- 人工心臓、両心ペーシング、整形外科用デバイスなどのモデルプロトコール
- 重症末期心不全に対する治療機器の臨床試験ガイドライン
- 骨・軟骨欠損に対する再生治療の臨床試験ガイドライン
- 医療機器全般にわたるガイドライン

研究成果

- 臨床試験の準備段階から審査終了に至るまでの全過程に関しての論理的遂行
- 実施者、臨床評価者および機関、審査部門などの公正かつ効率的な参加
- 科学的臨床試験全体の体系の構築

介入試験の原則

富山医科薬科大学臨床疫学教授
折笠 秀樹

[Summary]
臨床研究の研究デザインは大きく分けて四つあるが，その中でも介入試験というのは最も厳密かつ困難な研究法である．しかし，新しい治療法の確立には欠かせない研究であることも事実である．ここでは介入試験の種類として，症例集積法，個人内比較法，個人間比較法について，その特徴について解説する．介入試験で最上位に位置付けられるものが，個人間比較の中のランダム化比較試験（RCT）というものである．このランダム化比較試験（RCT）に関して，試験を実施する際の組織作りの大切さについても述べる．最後に，このようなRCT研究論文の読み方と探し方について簡単に紹介する．

Key Words：
臨床試験／統計学／研究デザイン／疫学／メタアナリシス

介入試験とは

臨床研究というのは，患者あるいは住民を対象とした研究をいう．その計画法には4種類あるといわれている（表❶）．観察研究はあるがままを観察するもので，アンケートなどを用いる調査がそうである．医療では疫学研究と呼ばれることもある．介入研究とは日常診療と異なる新たなことを行う研究である．これはいわば臨床実験なので実行は難しいが，その結果の価値は高いとされる．介入研究を実施する際には，施設審査委員会（IRB）と文書同意（IC）が不可欠である．介入を伴う実験なので介入試験とも呼ぶことがある．本稿では同一語として用いている．同じようにして，臨床試験ということもある．観察研究と介入研究が臨床研究の代表であるが，特に看護研究などでは質的研究が実施されることもある．エイズの患者数名にインタビューして，いろいろ困っていることや悩みを話してもらう．そのテープを聞きなおして，問題点を構造的に整理する研究法である．最後の統合研究は別名メタアナリシス，あるいは系統的レビューと呼ばれているものである．近年，EBMとともに最高位に位置づけられるようになり，一躍注目を集めるようになった研究法である．それは，過去の同様の研究成績を統計学的手法で併合するものである．