

Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION



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Circulation 2002;106;1015-1021

DOI: 10.1161/01.CIR.0000023260.78078.BB

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ISSN: 1524-4539

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Principles From Clinical Trials Relevant to Clinical Practice: Part I

Robert M. Califf, MD; David L. DeMets, PhD

The first 2 parts of this review discussed lessons learned from cardiovascular clinical trials about the design and interpretation of clinical trials. In the next 2 parts, we will attempt to apply these lessons to decision-making in clinical practice. We undertake this effort with trepidation, recognizing that translating research findings into the care of an individual patient is a frontier that has not been adequately explored. Yet the potential for an empirical-based medical practice that would improve on the intuitive-based practice of the past, when combined with traditional clinical skills and patient preferences, demands that we move forward to apply what we have learned in populations to the care of individual patients.

Principle 1: Treatment Effects Are Modest

The benefit of most cardiovascular therapies is much smaller than was anticipated before the first large-scale outcome trials. Relative risk reductions of 25% are rarely exceeded, as demonstrated in Figure 1, for post-myocardial infarction (MI) patients. This means that the patient's outcome is determined more by the natural history of the disease than by the treatments we deliver, and that multiple combined treatments will be needed in most cases to achieve the best possible outcome.

At the other extreme, from chronic therapies designed to prevent events, Guyatt and Sackett popularized the concept of the $n=1$ clinical trial, which is oriented toward symptomatic treatments.^{1,2} This approach engages the clinician and the patient in an experiment in which the treatment, or placebo, is randomly allocated and symptoms are measured until treatment efficacy or failure is proved. Although this approach may have merit in many clinical situations, it can be treacherous in chronic disease therapies in which the acute response does not predict the long-term outcome, or when the anticipated treatment effect is so small that a response to treatment is difficult to differentiate from random fluctuations in the measurement of unrelated changes in the natural history of the disease.

A practitioner's individual experience is simply not adequate to recognize treatment effects of the size usually seen in therapies to prevent future events in a chronic disease. In fact,

a practitioner's personal experience has a reasonable probability of misleading him or her about what to expect when the next patient is treated. Within any large clinical trial, multiple practitioners will experience outcomes that differ from the overall results of the trial. Although monitoring each individual patient closely for symptomatic and physiological improvement is critical in any clinical practice, it is not the best way to determine whether proposed treatments are effective (with the exception of suitable situations for the $n=1$ trial), especially when the treatment is primarily given to alter the long-term course of a chronic disease. Furthermore, the experience with the last patient says little about what to expect in the next patient; rather, to detect modest treatment effects, large randomized trials are needed.³

Another important implication of the modest treatment effect of most therapies is the need for the clinical community to give more thought to the degree of benefit it considers to be a "clinically meaningful difference." If the construct for developing new therapies is to demonstrate a clinically meaningful difference in a generalizable clinical trial, and if most such differences are small, then many marginally incremental therapies will need to be evaluated in trials and used in practice. In addition to the specifics of the disease in the individual patient, the overall magnitude of the disease as a societal issue must be considered; small effects in epidemic diseases deserve serious consideration because of the overall impact of the treatment. For example, in acute coronary syndromes, a relative reduction of 15% in recurrent clinical events has recently been considered clinically important; this level is far below the perceived threshold that drove the sample size calculations for clinical trials just a decade ago. As we develop more incrementally beneficial therapies for the epidemics of hypertension, heart failure, coronary artery disease, and sudden death, it is likely that the minimally important clinical difference will become even smaller.

Principle 2: Qualitative Interactions Are Uncommon, but Quantitative Interactions Are Usual

Clinical thinking has traditionally been oriented toward finding the exception rather than the rule. Yet the aggregate of

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This is Part III of a 4-part article. Parts I and II appeared in the August 6 and August 13, 2002, issues of the journal, respectively (*Circulation*. 2002;106:746–751; and *Circulation*. 2002;106:880–886), and Part IV will appear in the August 27, 2002, issue.

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(*Circulation*. 2002;106:1015-1021.)

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Circulation is available at <http://www.circulationaha.org>

DOI: 10.1161/01.CIR.0000023260.78078.BB

Therapy	Indication	# pts	Reduction in Deaths	
			Relative	Absolute
Aspirin	MI	18,773	23%	2.4%
Fibrinolytics	MI	58,000	18%	1.8%
Beta blocker	MI	28,970	13%	1.3%
ACE inhibitor	MI	101,000	6.5%	0.6%
Aspirin	2nd prev	54,360	15%	1.2%
Beta blocker	2nd prev	20,312	21%	2.1%
Statins	2nd prev	17,617	23%	2.7%
ACE inhibitor	2nd prev	9,297	17%	1.9%
ACE inhibitor	CHF	7,105	23%	6.1%
Beta blocker	CHF	12,385	26%	4.0%
Spironolactone	CHF	1,663	30%	11%

Figure 1. Overview of treatment effects in acute MI, secondary prevention, and heart failure. The major point of this figure is that the treatment effects are modest, with relative risk reductions (RRRs) of 10% to 25%. These small but important reductions require a quantitative, systematic approach to realize the potential for a substantial impact on the public health.

clinical trial results indicates that most therapies that are effective in a population with a given diagnosis are effective in most members of that population. One of the most striking findings of the Antiplatelet Trialists' Collaboration,⁴⁻⁶ the recent Angiotensin-Converting Enzyme (ACE) Inhibitor Collaboration,⁷⁻⁹ and the Fibrinolytic Therapy Trialists' Collaborative Group,¹⁰ is the consistency of treatment effects in subgroups (Figure 2). Across the spectrum of subgroups within a trial, reversal of a treatment effect is rare; a treatment that is beneficial for most patients with a diagnosis is rarely detrimental in a subgroup of patients with that diagnosis. Although notable exceptions exist, such as patients without ST-segment elevation MI who are given fibrinolytic therapy,⁸ this finding is remarkably common across systematic over-

views. A similar consistency is found across trials in heart failure that use β -blockers.¹¹⁻¹³

The clinical consequence of this finding is that when a therapy is shown to be beneficial for patients with a clinical condition, the therapy can be applied systematically to the population in clinical practice. The burden is on the clinician to justify failing to treat rather than having to justify treating each patient with the diagnosis. This approach allows practices and health systems to develop clinical practice standards and performance measures that can be introduced into hospitals and clinics to ensure reliable use of effective practices.

A quantitative interaction occurs when there is a significant difference in response to treatment in one group compared with another, but the direction of the treatment effect (benefit or harm) is the same in both groups. Quantitative interactions are common, and the sicker patients almost always have a greater benefit from treatment than do the less sick patients. This finding that sicker patients derive more benefit from treatment is at odds with what practitioners commonly observe in their own patients, which is that less sick patients have better outcomes with treatments. This intuitive lesson from "clinical experience" is incorrect, of course, because it cannot take into account the fact that less sick patients also do better without treatment.

This principle has important implications for treatment selection. Rather than selecting patients who have the best outcomes with a given therapy, the important construct is to select patients in whom the outcome with therapy is most favorable compared with what would have happened without the therapy. Multiple studies have shown that selection of patients for angiography¹⁴ and revascularization¹⁴⁻¹⁶ tends to err toward low-risk patients who get less benefit rather than high-risk patients who get the greatest benefit. Similarly, the elderly are less likely to be treated with secondary prevention therapies, despite consistent findings that show greater ben-

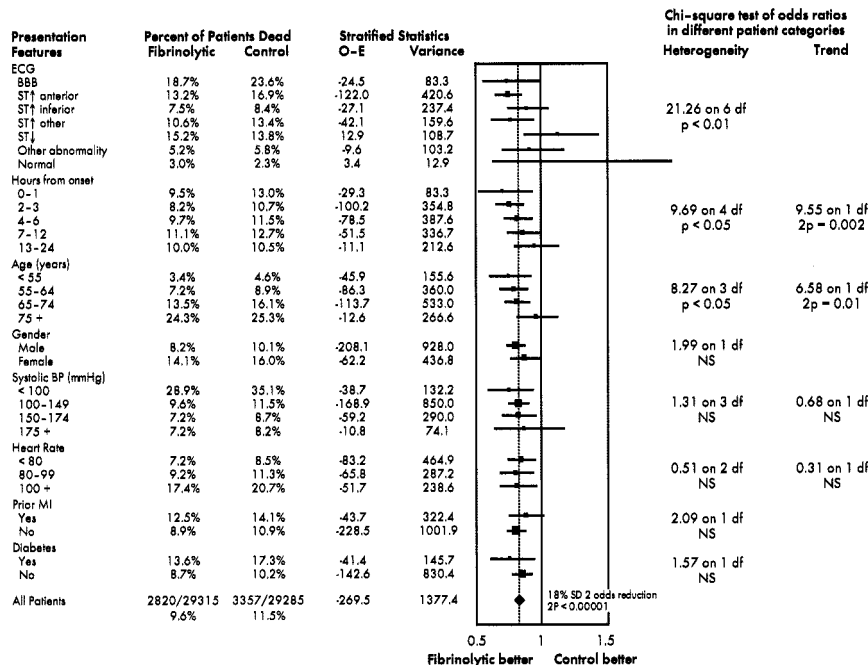


Figure 2. Overview of treatment effect of fibrinolytic therapy in myocardial infarction. This figure demonstrates several key points: the treatment effects are modest; the only qualitative interaction is a reversal of the treatment benefit seen in all other subgroups in patients with ST-segment depression; and there are many quantitative interactions, with the greatest absolute benefit seen in the highest-risk patients. Adapted with permission from Elsevier Science: the Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomized trials of more than 1000 patients. *Lancet*. 1994;343:311-322.¹⁰

efit in older versus younger patients.¹⁷ This pattern of treatment selection needs to change, and doing so will require that clinicians understand the paradox that patients who benefit the most from treatment are not necessarily those who tend to do best with therapy.

Multiple studies have also demonstrated that patients enrolled in clinical trials tend to be different from the general population of treated patients. Early studies of coronary bypass grafting enrolled only a small minority of eligible patients.¹⁸ Later studies documented a surfeit of women and older patients in trials evaluating acute MI.¹⁹ A recent evaluation of trials funded by the National Heart, Lung, and Blood Institute found little change in the underrepresentation of women in studies enrolling both sexes,²⁰ but single-sex studies focused on women have resulted in women accounting for 54% of the overall study population in NHLBI-funded studies. Lee and colleagues²¹ recently demonstrated that enrollment of the elderly and women in large acute coronary syndrome trials continues to lag behind observed community demographics, and other studies have demonstrated that excluded patients have a much higher mortality rate. Thus, despite the general principles of interactions, the quantification of these observations is often lacking in clinical trials because of lack of enrollment of relevant populations.

A popular notion is that postmarketing surveillance can make up for this deficiency in the ability to generalize. Indeed, observational postmarketing studies can provide support for broader use of therapies that have been proved effective,^{22,23} but these studies are plagued by uncertainty about confounding factors that cannot be excluded as a cause for observed differences in outcomes without randomization. There is little that a clinician can rationally do about this issue except to participate in clinical trials that enroll relevant populations.

Principle 3: Unintended Targets Are Common

Therapies are developed in the context of a construct of pathophysiology. A target for therapy is developed on the basis of an abnormality in a biological system; the therapy is typically aimed at blocking or augmenting some aspect of the biological pathway. All too often, the treatment affects an array of biological targets broader than the intended target. Sometimes, this unintended target results in a clinical benefit, as in the case of ACE inhibitors. Initially, the class was developed with the simple concept that lower blood pressure or systemic resistance would result in clinical benefit. With time, the concept of tissue remodeling has become integral to our still rudimentary understanding of why ACE inhibitors provide such benefit.²⁴ In the Antihypertensive and Lipid Lowering treatment to prevent Heart Attack Trial (ALLHAT), the dramatic difference in outcomes observed between diuretic and α -blockade raises doubts about blood-pressure lowering as a surrogate, because it apparently does not carry all of the effect on clinical outcome,²⁵ and the question of the degree to which the blood pressure alone is the critical issue in antihypertensive therapy remains under debate. These lessons should be sobering to the practicing clinician. At the time of the Cardiac Arrhythmia Suppression Trial (CAST) trial, as described in the first part of this series of articles,

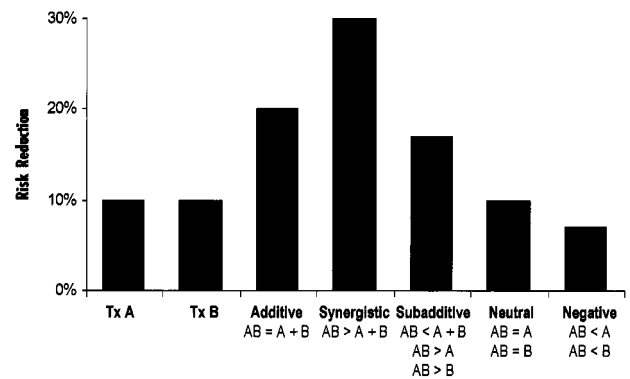


Figure 3. Possible outcomes when 2 individually beneficial therapies are given together. A synergistic effect occurs when the effect of giving both treatments exceeds the sum of the individual effects. An additive effect occurs when the effect is equal to the sum of the individual effects. A subadditive effect occurs when the effect is greater than the effect of each individual effect but less than completely additive. A neutral effect occurs when the combination is neither better nor worse than each individual agent. A deleterious effect occurs when the combination is worse than either treatment alone.

antiarrhythmic drugs were being used in hundreds of thousands of patients for asymptomatic ventricular arrhythmias.²⁶ The inability of practitioners to detect the excess risk of sudden death from their individual practices led to a large number of preventable deaths.

Before it was recognized that substantial toxicity was occurring with mibefradil, a novel calcium channel blocker, >400 000 patients had been treated.²⁷ The problems encountered included heart failure, heart block, and sudden death—hardly clinical events that are difficult to detect. These examples point out that relying on clinical experience to decide which therapies to use is not adequate. A similar experience has now occurred with cerivastatin,²⁸ and questions have been raised about cyclooxygenase-2 inhibitors.²⁹

The common occurrence of the unintended target has implications for the clinical dictum, “Do no harm.” Indeed, anyone who has sat on a Data Monitoring Committee for a large clinical trial is aware of the many unusual but real examples of unpredictable harm done to individuals by therapies that, on average, are significantly beneficial. Perhaps a better dictum would be: “Always attempt to do more good than harm with treatment selection.”

Principle 4: Interactions Are Unpredictable

Clinical trials tend to focus on the assessment of one treatment at a time. Yet most patients are treated with multiple therapies simultaneously. Unfortunately, the array of possible effects of combining 2 treatments, each of which is beneficial, is complex (Figure 3).

In the development of glycoprotein (GP) IIb/IIIa inhibitors, it was known that the interaction with thrombin inhibitors would be critical. Initial trials evaluated the use of abciximab as an adjunct to percutaneous coronary intervention (PCI), and full-dose heparin was used. The Evaluation of c7E3 for the Prevention of Ischemic Complications (EPIC) trial demonstrated a reduction in ischemic events but an increase in hemorrhage.³⁰ This combination of outcomes led to a request

by the Food and Drug Administration for additional trials to attempt to reduce the bleeding. In subsequent trials, the dose of heparin was reduced; not only was bleeding reduced, but in indirect comparisons the magnitude of the benefit of abciximab increased. The investigators had no conceptual basis for a better effect in preventing ischemic events by reducing the dose of thrombin inhibitor below levels shown to be effective in many previous studies of heparin in PCI. In retrospect, perhaps this situation resulted from prevention of bleeding with plaque hemorrhage and hypotension, both of which may precipitate new ischemic events.

The concomitant use of aspirin and ACE inhibitors provides another instructive example. Conceptual reasons can be garnered for an additive benefit of these two classes of drugs in the treatment of patients after MI. However, physiological experiments and observational studies provided ample reason to be concerned that aspirin would nullify the benefits of ACE inhibitors. A careful systematic overview in post-MI patients clarified the issue by demonstrating that ACE inhibitors were beneficial in patients treated with aspirin, although the magnitude of the benefit was less than in patients not treated with aspirin.⁹

The disastrous experience with mibefradil underscores how complex and difficult this issue can be. During its development, investigators noted the metabolism of mibefradil by cytochrome P-450 pathways and raised concern about pharmacokinetic interactions with other drugs metabolized by this pathway.³¹ Most experts and the manufacturer of the drug felt that these interactions would not cause major clinical difficulties. Unfortunately, a number of complications resulted, including deaths, before the drug was pulled from the market.

These examples point out that assumptions by clinicians about untested combinations of potent therapies may not only be incorrect, but they could also lead to widespread negative outcomes. Caution is needed to withstand the temptation to prescribe untested combinations. The imperative is growing to conduct more trials with the use of a factorial design so that such interactions can be sorted out.³² These examples also bring up the important issue of the interaction of the clinical community with regulatory agencies. Unless regulatory agencies require trials to include more representative patients and to evaluate therapies in the context of the complex clinical world of multiple interactions and comorbidities, it is unlikely that the medical products industry will be motivated to conduct such studies. However, even when everything possible is done before marketing, unforeseen effects of therapies will occur, and the clinical community needs to enhance its interaction with regulators to avoid missing important information from postmarketing surveillance.

Principle 5: Long-Term Effects Deserve Evaluation

Many therapies have different effects in the short term than in the long term. This phenomenon has been recognized for some time with regard to surgical procedures in which the patient accepts an early perioperative risk in return for long-term benefit. With coronary artery bypass grafting, the benefit of surgery does not exceed the early hazard until a

year after the average procedure.³³ Similarly, fibrinolytic therapy increases the risk of death in the first day and then reduces the risk of death after this period of early hazard.³⁴

A graphic example that has captured the attention of the national press is the diet combination phenfluramine dexpheneramine (fen phen).³⁵ In small clinical trials performed over short periods of time, the combination caused weight loss. Only longer-term clinical observations raised the issue of valvular insufficiency.³⁶ Yet, because longer-term randomized clinical trials were not done, the community is unclear about the extent to which the valvular lesions caused irreversible harm.

More recent examples include the Heart and Estrogen/progestin Replacement Study (HERS) and Prospective Randomized Flosequin Longevity Evaluation (PROFILE) trials. In HERS, the administration of hormone replacement therapy to postmenopausal women with an intact uterus and with documented coronary heart disease led to excess thrombotic events in the first year and fewer thrombotic events between the first and fourth years of follow-up.³⁷ In PROFILE, flosequin was shown to improve quality of life in the first several months of treatment, but over subsequent follow-up, both quality of life and survival were adversely affected.³⁸ This same pattern emerged in the evaluation of vesnarinone.³⁹ The recent example of the Long-term Intervention with Pravastatin in Ischemic Disease (LIPIDS) study demonstrates the benefit of monitoring patients even when the randomized portion of the trial is stopped early for benefit. In this case, the event-rate curves have continued to diverge, enabling the investigators to have more power to look at key subgroups and ancillary questions and to add important extra data to support the benefits of pravastatin therapy.⁴⁰

The increasing number of implantable devices in cardiovascular medicine raises similar issues. No one would advocate withholding access to new cardiac valves until after a decade of follow-up, yet we know differences among valves that could be highly significant will not emerge until long-term follow-up. Recently, a clinical trial of a new valve aimed at reducing thrombotic events unfortunately demonstrated an excess rate of perivalvular leak compared with a standard valve⁴¹; it is unlikely that this difference could have been detected without a randomized trial. Similar issues will exist for newer biological approaches to dealing with restenosis, such as radiation or chemotherapy.

These findings should motivate clinicians to help develop more long-term evidence about the effects of chronically administered therapies. Multiple therapies have been recalled recently through postmarketing surveillance,⁴² but the fact that postmarketing surveillance is sometimes effective should not obscure the obvious problems with nonrandomized postmarketing observation. The absence of a control group or a true denominator often makes it difficult or impossible to know whether observed findings are because of random variation or whether the observed rate of events is even above the expected rate for the population. Unfortunately, too little research support is oriented towards understanding how to conduct long-term studies in a rapidly changing medical care environment.

Principle 6: Class Effects Can Be Uncertain

Once a biological target is identified, multiple approaches to modifying that target can be devised. These approaches will have the target in common but may have different mechanisms of action, ancillary effects, or toxicities. The term *class effect* has been used to describe the effect of drugs with the same biological target. Yet, basic pharmacology points to the likelihood that these drugs will have some qualities in common and will differ with regard to others.

The Antiplatelet Trialists' Collaboration made the point that antiplatelet drugs generally reduce ischemic events.⁴⁻⁶ However, the effort tended to lump all such agents together. When the trials with aspirin alone were evaluated, little effect could be discerned in patients with peripheral arterial disease. Whether this represents an agent-specific lack of effect continues to be debated, and the Food and Drug Administration labeling for aspirin did not include an indication for patients with peripheral arterial disease. The Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial then demonstrated a small but significant benefit of clopidogrel over aspirin,⁴³ and interestingly, the largest benefit of clopidogrel was in patients with peripheral arterial disease. Most recently, despite the profound effects of orally administered GP IIb/IIIa inhibitors on platelet aggregation, it has been found that not only do they not reduce ischemic events, their administration actually increases ischemic events.⁴⁴

In the arena of intravenous GP IIb/IIIa inhibitors, tremendous debates have occurred about "class effects." Recently, a direct comparison pitted tirofiban against abciximab in the setting of PCI.⁴⁵ Not only did tirofiban fail as a noninferior therapy compared with abciximab, but it turned out to be significantly inferior for the primary end point of 30-day major cardiac events. However, with longer-term follow-up,⁴⁶ the significant benefit of abciximab was no longer present, raising a justifiable debate about the appropriate duration of follow-up to demonstrate therapeutic superiority or equivalence. Just before this direct comparison as an adjunct to PCI, abciximab was found to be ineffective in medical stabilization of acute coronary syndromes,⁴⁷ whereas both tirofiban and eptifibatid had been shown to be effective for acute coronary syndromes.^{48,49} More recent pharmacokinetic data⁵⁰ demonstrated that the dose of abciximab may have variable inhibition of platelet aggregation, raising the issue of whether different doses in the same "class" act differently. Thus, this class of drugs is distinguished by different molecules with proven effectiveness in different clinical situations, and multiple clinical studies have been incapable of predicting these findings on the basis of biological data. Assuming a homogeneous class effect would have been a major error.

Although differences among the β -blockers have been recognized for some time, they have usually been lumped into the same class. In the treatment of heart failure, 3 β -blockers have been shown to reduce mortality, whereas a fourth failed in a major trial.^{11,12,51} Furthermore, indirect comparisons have claimed that carvedilol has a superior effect on left ventricular (LV) function than metoprolol, stimulating a direct comparative trial.⁵²

A variety of statins have been developed with the goal of preventing atherosclerotic events by lowering low-density lipoprotein (LDL) cholesterol. Several of the statins have been evaluated in definitive trials and have demonstrated profound effects on clinical events. Others have been shown to produce greater lowering of LDL cholesterol but in the absence of definitive mortality trials. The clinical community must decide whether to believe the class effect and use the drugs interchangeably on the basis of the surrogate of LDL-lowering, or on the basis of whether there is enough distrust of the class effect to lead them to preferentially use the statins that have been shown to reduce mortality. Some experts have voiced concern that the different molecular structures may lead to different clinical effects,⁵³ whereas others have focused on the mounting evidence that the effect of statins on clinical events may be because of multiple effects beyond LDL-cholesterol lowering.⁵⁴

The ACE inhibitors have produced a dramatic effect on mortality and morbidity in patients with heart failure, and multiple ACE inhibitors have been shown to be effective in mortality trials. However, only one ACE inhibitor, ramipril, has been shown to have a definitive major influence on cardiac events in patients with preserved LV function.⁵⁵ This ACE inhibitor, like several others, has been shown to have a high level of tissue penetration. Again, the clinical community is left in the quandary of whether to embrace the class effect or to preferentially use the particular ACE inhibitor that has been shown to benefit patients with preserved LV function.

The area of thrombin inhibition has also created a major controversy. Unfractionated heparin became standard therapy in acute coronary syndromes without definitive trials by current standards. Subsequently, multiple trials have been completed with several different low-molecular-weight heparins. When all of the low-molecular-weight heparin trials are combined, the evidence for superiority over unfractionated heparin is not definitive.⁵⁶ However, a particular low-molecular-weight heparin, enoxaparin, has been found to be superior to unfractionated heparin on its own in 2 separate trials. Because each of the low-molecular-weight heparin preparations has different pharmacological properties, many have made the argument that the different trials of low-molecular-weight heparin should not be combined.⁵⁷

This issue of class effect raises major questions for both doctor-patient interactions and health system decisions. When a particular drug or device has been shown to have a specific benefit, would it be appropriate to substitute a less-expensive agent from the same class? Given the uncertainties reviewed above, clinicians should carefully evaluate such situations to ensure that there is not a substantial question about the class effect in that case. If such a question arises, the clinician must perform the difficult task of weighing that uncertainty against the likelihood of compliance with more affordable medicine for the patient or the financial benefit to the health system. In any case, the examples reviewed above make a strong case against therapeutic substitutions' being administrative decisions, and for clinicians' having a primary role when therapeutic substitution is considered.

In the final installment of this four-part series, we will present the last 5 of the 11 principles we have gleaned from the past 15 years of clinical research in cardiovascular medicine. Together, these principles should help the practicing clinician understand the statistical issues that surround clinical trials and appropriately apply the lessons of those trials in their daily care of patients with heart diseases.

Acknowledgments

This project was supported in part by an Agency for Healthcare Research and Quality (AHRQ) Centers for Education and Research on Therapeutics (CERTs) cooperative agreement, grant No. U18HS10548. The authors thank Penny Hodgson and Karen Staman for their help with the multiple revisions of these manuscripts. They would also like to express their appreciation to the thousands of collaborators who have made these observations possible by participating in the clinical trials effort.

References

- Guyatt G, Sackett D, Adachi J, et al. A clinician's guide for conducting randomized trials in individual patients. *CMAJ*. 1988;139:497-503.
- Guyatt G, Sackett D, Taylor DW, et al. Determining optimal therapy—randomized trials in individual patients. *N Engl J Med*. 1986;314:889-892.
- Collins R, Keech A, Peto R, et al. Cholesterol and total mortality: need for larger trials. *BMJ*. 1992;304:1689.
- Collaborative overview of randomised trials of antiplatelet therapy—I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. Antiplatelet Trialists' Collaboration. *BMJ*. 1994;308:81-106.
- Collaborative overview of randomised trials of antiplatelet therapy—II: maintenance of vascular graft or arterial patency by antiplatelet therapy. Antiplatelet Trialists' Collaboration. *BMJ*. 1994;308:159-168.
- Collaborative overview of randomised trials of antiplatelet therapy—III: reduction in venous thrombosis and pulmonary embolism by antiplatelet prophylaxis among surgical and medical patients. Antiplatelet Trialists' Collaboration. *BMJ*. 1994;308:235-246.
- ACE Inhibitor Myocardial Infarction Collaborative Group. Indications for ACE inhibitors in the early treatment of acute myocardial infarction: systematic overview of individual data from 100 000 patients in randomized trials. *Circulation*. 1998;97:2202-2212.
- Flather MD, Yusuf S, Kober L, et al. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. *Lancet*. 2000;355:1575-1581.
- Latini R, Tognoni G, Maggioni AP, et al. Clinical effects of early angiotensin-converting enzyme inhibitor treatment for acute myocardial infarction are similar in the presence and absence of aspirin: systematic overview of individual data from 96 712 randomized patients. *J Am Coll Cardiol*. 2000;35:1801-1807.
- Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. *Lancet*. 1994;343:311-322.
- The MERIT-HF Investigators. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet*. 1999;353:2001-2007.
- The CIBIS II Investigators. The cardiac insufficiency bisoprolol study II (CIBIS II): a randomised trial. *Lancet*. 1999;353:9-13.
- Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med*. 2001;344:1651-1658.
- Pilote L, Miller DP, Califf RM, et al. Determinants of the use of coronary angiography and revascularization after thrombolysis for acute myocardial infarction. *N Engl J Med*. 1996;335:1198-1205.
- Batchelor WB, Peterson ED, Mark DB, et al. A comparison of US and Canadian cardiac catheterization practices in detecting severe coronary artery disease after myocardial infarction: efficiency, yield and long-term implications. *J Am Coll Cardiol*. 1999;34:12-19.
- Llavadot J, Giugliano RP, Antman EM, et al. Availability of on-site catheterization and clinical outcomes in patients receiving fibrinolysis for ST-elevation myocardial infarction. *Eur Heart J*. 2001;22:2104-2115.
- Califf RM, DeLong ER, Ostbye T, et al. Underuse of aspirin in a referral population with documented coronary artery disease. *Am J Cardiol*. 2002;89:653-661.
- Califf RM, Hlatky MA, Mark DB, et al. Randomized trials of coronary artery bypass surgery: impact on clinical practice at Duke University Medical Center. *Circulation*. 1985;72:V136-V144.
- Gurwitz JH, Col NF, Avorn J. The exclusion of the elderly and women from clinical trials in acute myocardial infarction. *JAMA*. 1992;268:1417-1422.
- Harris DJ, Douglas PS. Enrollment of women in cardiovascular clinical trials funded by the National Heart, Lung, and Blood Institute. *N Engl J Med*. 2000;343:475-480.
- Lee PY, Alexander KP, Hammill BG, et al. Representation of elderly persons and women in published randomized trials of acute coronary syndromes. *JAMA*. 2001;286:708-713.
- Chen J, Radford MJ, Wang Y, et al. Effectiveness of β -blocker therapy after acute myocardial infarction in elderly patients with chronic obstructive pulmonary disease or asthma. *J Am Coll Cardiol*. 2001;37:1950-1956.
- Radford MJ, Foody JM. How do observational studies expand the evidence base for therapy? *JAMA*. 2001;286:1228-1230.
- Pfeffer MA. Left ventricular remodeling after acute myocardial infarction. *Ann Rev Med*. 1995;46:455-466.
- ALLHAT Collaborative Research Group. Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). *JAMA*. 2000;283:1967-1975.
- The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Preliminary report: effect of encainide or flecainide on mortality in a randomized trial of arrhythmic suppression after myocardial infarction. *N Engl J Med*. 1989;321:406-412.
- Reimer KA, Califf RM. Good news for experimental concept but bad news for clinically effective therapy. *Circulation*. 1999;99:198-200.
- SoRelle R. Baycol withdrawn from market. *Circulation*. 2001;104:e9015-e9016.
- Mukherjee D, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. *JAMA*. 2001;286:954-959.
- The EPIC Investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. *N Engl J Med*. 1994;330:956-961.
- Krayenbuhl JC, Vozeh S, Kondo-Oestreicher M, et al. Drug-drug interactions of new active substances: mibefradil example. *Eur J Clin Pharmacol*. 1999;55:559-565.
- Simon R, Freedman LS. Bayesian design and analysis of two x two factorial clinical trials. *Biometrics*. 1997;53:456-464.
- Yusuf S, Zucker D, Peduzzi P, et al. Effect of coronary artery bypass graft surgery on survival: overview of 10-year results from randomised trials by the Coronary Artery Bypass Graft Surgery Trialists. *Lancet*. 1994;344:563-570.
- Kleiman NS, White HD, Ohman EM, et al. Mortality within 24 hours of thrombolysis for myocardial infarction. The importance of early reperfusion. *Circulation*. 1994;90:2658-2665.
- Connolly HM, Crary JL, McGoon MD, et al. Valvular heart disease associated with fenfluramine-phentermine. *N Engl J Med*. 1997;337:581-588.
- Jollis JG, Landolfo CK, Kisslo J, et al. Fenfluramine and phentermine and cardiovascular findings: effect of treatment duration on prevalence of valve abnormalities. *Circulation*. 2000;101:2071-2077.
- Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA*. 1998;280:605-613.
- Moe GW, Rouleau JL, Charbonneau L, et al. Neurohormonal activation in severe heart failure: relations to patient death and the effect of treatment with flosequinan. *Am Heart J*. 2000;139:587-595.
- Cohn JN, Goldstein SO, Greenberg BH, et al. A dose-dependent increase in mortality with vesnarinone among patients with severe heart failure. Vesnarinone Trial Investigators. *N Engl J Med*. 1998;339:1810-1816.
- Marschner IC, Colquhoun D, Simes RJ, et al. Long-term risk stratification for survivors of acute coronary syndromes. Results from the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) Study. *J Am Coll Cardiol*. 2001;38:56-63.
- St Jude Medical, Inc. St Jude Medical recalling heart valve products with silzone coating. St Jude Medical News Room/Press Releases [web site]. January 24, 2000. Press release available at: <http://www.corporate-ir.net/>

- ireye/ir_site.zhtml?ticker=STJ&script=460&layout=-6&item_id=228634&sstring=silzone. Accessed July 16, 2002.
42. Friedman MA, Woodcock J, Lumpkin MM, et al. The safety of newly approved medicines: do recent market removals mean there is a problem? *JAMA*. 1999;281:1728–1734.
 43. CAPRIE steering committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet*. 1996;348:1329–1339.
 44. The SYMPHONY Investigators. Comparison of sibrifiban with aspirin for prevention of cardiovascular events after acute coronary syndromes: a randomised trial. Sibrifiban versus Aspirin to Yield Maximum Protection from Ischemic Heart Events Post-acute Coronary Syndromes. *Lancet*. 2000;355:337–345.
 45. Topol EJ, Moliterno DJ, Herrmann HC, et al. Comparison of two platelet glycoprotein IIb/IIIa inhibitors, tirofiban and abciximab, for the prevention of ischemic events with percutaneous coronary revascularization. *N Engl J Med*. 2001;344:1888–1894.
 46. TARGET: one-year results show no difference in mortality between abciximab and tirofiban. Heartwire [web site]. November 7, 2001. Available at: <http://www.theheart.org>. Accessed July 24, 2002.
 47. The GUSTO IV-ACS Investigators. Effect of glycoprotein IIb/IIIa receptor blocker abciximab on outcome in patients with acute coronary syndromes without early coronary revascularisation: the GUSTO IV-ACS randomised trial. *Lancet*. 2001;357:1915–1924.
 48. The PRISM Investigators. A comparison of aspirin plus tirofiban with aspirin plus heparin for unstable angina. Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) Study Investigators. *N Engl J Med*. 1998;338:1498–1505.
 49. The PURSUIT Trial Investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatid in patients with acute coronary syndromes. *N Engl J Med*. 1998;339:436–443.
 50. Batchelor WB, Tolleson TR, Larson R, et al. Randomized COMparison of the early and late Platelet inhibition with Abciximab, tiRofiban and Eptifibatid during percutaneous coronary intervention: the COMPARE study. *Circulation*. In press.
 51. Krum H, Sackner-Bernstein JD, Goldsmith RL, et al. Double-blind, placebo-controlled study of the long-term efficacy of carvedilol in patients with severe heart failure. *Circulation*. 1995;92:1499–1506.
 52. Metra M, Giubbini R, Nodari S, et al. Differential effects of beta-blockers in patients with heart failure: a prospective, randomized, double-blind comparison of the long-term effects of metoprolol versus carvedilol. *Circulation*. 2000;102:546–551.
 53. Furberg CD. Natural statins and stroke risk. *Circulation*. 1999;99:185–188.
 54. Ridker PM, Rifai N, Pfeffer MA, et al. Inflammation, pravastatin, and the risk of coronary events after myocardial infarction in patients with average cholesterol levels. *Circulation*. 1998;98:839–844.
 55. Yusuf S, Phil D, Sleight P, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med*. 2000;342:145–153.
 56. Eikelboom JW, Anand SS, Malmberg K, et al. Unfractionated heparin and low-molecular-weight heparin in acute coronary syndrome without ST elevation: a meta-analysis. *Lancet*. 2000;355:1936–1942.
 57. Antman EM. The search for replacements for unfractionated heparin. *Circulation*. 2001;103:2310–2314.

KEY WORDS: trials ■ cardiovascular diseases ■ therapy ■ outcome assessment ■ statistics