Atherosclerosis Reviews

Volume 12

End Points for Cardiovascular Drug Studies

Editor

Ruth Johnsson Hegyeli, M.D.

Atherosclerosis Reviews

Volume 12

End Points for Cardiovascular Drug Studies

Editor

Ruth Johnsson Hegyeli, M.D.
Assistant Director for International Programs
Office of the Director
National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland

Raven Press ■ New York

Raven Press, 1140 Avenue of the Americas, New York, New York 10036

Library of Congress Cataloging in Publication Data
Main entry under title:

End points for cardiovascular drug studies.

(Atherosclerosis reviews; v. 12)
Includes bibliographical references and index.
1. Atherosclerosis—Congresses. 2. Atherosclerosis—Chemotherapy—Congresses. 3. Cardiovascular agents—Congresses. I. Hegyeli, Ruth Johnsson. II. Series.
[DNLM: 1. Cardiovascular Diseases—drug therapy—congresses. 2. Cardiovascular Agents—pharmacodynamics—congresses. 3. Cardiovascular Agents—therapeutic use—congresses. 4. Arteriosclerosis—diagnosis—congresses. 5. Ultrasonics—diagnostic use—congresses.
W1 AT385 v.12 / WG 166 E56 1983]
RC692.A729 vol. 12 616.1'36 s [616.1'061] 84-17898
ISBN 0-89004-955-6

ATHEROSCLEROSIS REVIEWS

Volume 12

Atherosclerosis Reviews

Preface

Modern drug therapy has made dramatic contributions to the prevention and treatment of cardiovascular diseases. Drugs are now available for a range of cardiovascular conditions, from hypertension to arrhythmias. This volume addresses one of the key problems in the further development of new and more effective drugs—the need to find reliable biological end points that will aid scientists and physicians in the early determination of the drug or combination of drugs and other therapy that may be most effective in the prevention and management of a particular condition or disease.

Current clinical research tends to rely on end points such as morbidity and mortality. These end points may take years to develop, necessitating costly clinical trials, which may require hundreds of millions of dollars, and involving thousands of participants over many years. The U. S. National Heart, Lung, and Blood Institute has funded a number of trials of this magnitude. In addition to the huge costs and delays in obtaining objective, reliable results from these trials, they are also difficult to manage from a logistic standpoint. There is a continuing problem of maintaining patient adherence and double-blind protocols for the experimental group receiving drug therapy and the control group receiving placebo.

This volume brings together specialists with a broad range of expertise in research dealing with the clinical entities, biological end points, means of intervention, and monitoring techniques pertinent to the topic of cardiovascular drug studies. These specialists discuss a number of drugs that have been shown to be of value in the prevention and treatment of atherosclerosis, thrombosis, coronary spasm, and arrhythmias. They consider new pharmaceutical agents currently under development that may offer advantages over traditional agents in terms of selectivity, specificity, side effects, interaction with other drugs and body functions, and clearance processes. These will need to be evaluated through basic and clinical research and compared with more traditional agents.

The end points for such drug studies need further development. While morbidity and mortality continue to be important indices for large-scale population studies, the noninvasive assessment of alterations in atherosclerotic lesions and arterial walls themselves and the effect of drugs in inhibiting or regressing these changes are extremely promising lines of inquiry for cardiovascular research.

In the case of atherosclerosis, certain drugs can affect the regression or progression of lesions. Combined therapies are evaluated as a means of lowering lipids, and a new drug that has only a moderate effect on cholesterol levels is reported to completely inhibit atherosclerotic lesions in rabbits. The role of coronary thrombosis in the etiology and pathogenesis of acute myocardial infarction is now known to be significant, and interest has been renewed in thrombolytic therapy using two

available agents, streptokinase and urokinase, for activating plasmin. Other newer drugs may also be of value. With better understanding of myocardial necrosis and more precise means for measuring infarct size, the authors propose that it may be timely to consider clinical studies to evaluate such agents.

Additional clinical and therapeutic studies are also needed to evaluate pharmacological treatment of disturbances in blood flow leading to pathological conditions. Agents that improve red blood cell deformability may be advantageous. For the prevention of arterial thrombosis, drugs with primary effects on platelet function are also needed, since there are indications that the inhibition of platelet activation might delay the progression of atherosclerosis. The discrepancy in aspirin function in laboratory tests and clinical trials suggests that clinical investigation with low-dose aspirin may be of value. Study of its effects on other tissues and other agents is also warranted. A review of the mechanisms of action and effects of nitrates and calcium antagonists in the treatment of coronary artery spasm suggests that a combination of drugs is effective in reducing the end points associated with this disease problem. A more rational approach can also be taken today in the treatment and prevention of arrhythmias with clearer delineation of the pharmacokinetic parameters of new agents as well as traditional ones.

The biological end points for lipids include cholesterol and triglyceride levels. Synthetic peptides designed to bind and transport plasma lipids may be valuable in altering lipid metabolism and promoting the removal of cholesterol. Weight control and changes in diet also have resulted in favorable changes in plasma lipids.

Two major prevention programs are reported in this volume: the special intervention program of the Multiple Risk Factor Intervention Trial (MRFIT), and the Rome Project of Coronary Heart Disease Prevention (PPCC). The program goals and results of a 6-year follow-up are reported for both: The specific effects of treating hypertension with diuretics is related from the MRFIT, and the PPCC reports that the treated groups in that study showed a decrease in coronary risk of almost 40% and a decrease in mortality from coronary heart disease of more than 25%. This volume includes the first international publication of the follow-up results from the PPCC.

Three techniques important to early diagnosis of asymptomatic atherosclerosis are discussed in this volume; they are ultrasonic tissue characterization, ultrasound B-mode imaging of the arterial wall, and echo-Doppler examination. These techniques also have a role in monitoring the progression or regression of disease and the effects of drug therapy.

The direction of future research points toward earlier end point measures, more effective drugs, improved understanding of the atherosclerotic process, and earlier detection of cardiovascular disease. Clinical testing of new pharmacological agents will be important, as will the continued development of more precise noninvasive diagnostic techniques. This book will be of interest both to research scientists for its review of the state of the art in drug therapy and to practicing clinicians interested in the treatment of major cardiovascular disorders.

Claude Lenfant

Acknowledgments

The chapters in this volume of *Atherosclerosis Reviews* were developed following a joint United States–Italy Symposium on Endpoints for Cardiovascular Drug Studies. This fifth joint symposium was held June 20 to 22, 1983, in Rome, Italy, in accordance with the United States–Italy Agreement for Collaboration in the Field of Health and Medicine signed in November 1977 and renewed in 1980 and 1983 for additional 3-year terms.

This symposium follows in a series of symposia held between American and Italian scientists conducting research in the cardiovascular area. Other topics have been the measurement and control of cardiovascular risk factors, prostaglandins and cardiovascular disease, nutrition and cardiovascular disease, and methods of noninvasive diagnosis in atherosclerosis research. The proceedings of each of these meetings have been published for dissemination to the scientific community.

This latest symposium on end points for cardiovascular drug studies was co-chaired, on the U. S. side, by Dr. Claude Lenfant, Director, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland, and Professor Antonio M. Gotto. The cochairmen on the Italian side were Professor Rodolfo Paoletti, Director, Institute of Pharmacology and Pharmacognosy, University of Milan, and Professor Francesco Pocciari, Director, Istituto Superiore di Sanitá, Rome. Dr. Eugene Passamani, Associate Director for Cardiology, Division of Heart and Vascular Diseases, is the Institute liaison for United States–Italy Cooperation in the Cardiovascular Area.

Contributors

Ralph W. Barnes
Department of Neurology
Bowman Gray School of Medicine of Wake Forest University
Winston-Salem, North Carolina 27103

David H. Blankenhorn
School of Medicine
University of Southern California
2025 Zonal Avenue
Los Angeles, California 90033

M. Gene Bond
Department of Comparative Medicine
Bowman Gray School of Medicine of Wake Forest University
Winston-Salem, North Carolina 27103

Arlene W. Caggiula
Department of Epidemiology
Graduate School of Public Health
University of Pittsburgh
Pittsburgh, Pennsylvania 15261

C. Richard Conti
Department of Cardiology
University of Florida
Box J-277
Gainesville Florida 32610

Cesare Dal Palú
1st Medical Clinic
University of Padua
Via Giustiniani, 2
35100 Padua, Italy

Biagio De Simone
Institute of Internal Medicine and Metabolic Diseases
2nd Medical School
University of Naples
Via S. Pansini, 5
80131 Naples, Italy

Tullio Di Perri
Institute of Special Medical Pathology
University of Siena
Istituti Clinici
Viale Bracci
53100 Siena, Italy

Piera Fabbrini
Center of Research on Atherosclerosis
Institute of Pathologic Anatomy
University of Siena
Via della Scotte
53100 Siena, Italy

Fulvio Faccenda
Institute of Internal Medicine and Metabolic Diseases
2nd Medical School
University of Naples
Via S. Pansini, 5
80131 Naples, Italy

Sandro Forconi
Institute of Special Medical Pathology
University of Siena
Istituti Clinici
Viale Bracci
53100 Siena, Italy

Claudio Galli
Institute of Pharmacology and Pharmacognosy
University of Milan
Via Andrea del Sarto, 21
20129 Milan, Italy

Jean F. Gardin
Department of Comparative Medicine
Bowman Gray School of Medicine of Wake Forest University
Winston-Salem, North Carolina 27103

Antonio M. Gotto, Jr.
Department of Medicine
Baylor College of Medicine, and The Methodist Hospital
Methodist Mail Station A-601
6535 Fannin
Houston, Texas 77030

Richard H. Grimm, Jr.
Laboratory of Physiological Hygiene
School of Public Health
University of Minnesota
Stadium Gate 27
Minneapolis, Minnesota 55414

Maurizio Guerrini
Institute of Special Medical Pathology
University of Siena
Istituti Clinici
Viale Bracci
53100 Siena, Italy

Luigi Landini
Faculty of Engineering
C.N.R. Institute of Clinical Physiology
University of Pisa
Via P. Savi, 8
56100 Pisa, Italy

Mario Mancini
Institute of Internal Medicine and Metabolic Diseases
2nd Medical School
University of Naples
Via S. Pansini, 5
80131 Naples, Italy

Alessandro Menotti
Laboratory of Epidemiology and Biostatistics
Istituto Superiore di Sanità
Viale Regina Elena, 299
00161 Rome, Italy

John A. Oates
Departments of Medicine and Pharmacology
Vanderbilt University School of Medicine
Nashville, Tennessee 37232

Rodolfo Paoletti
Institute of Pharmacology and Pharmacognosy
University of Milan
Via Andrea del Sarto, 21
20129 Milan, Italy

Eugene R. Passamani
National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland 20205

Paola Patrignani
Centro di Studio per la Fisiopatologia dello Shock del C.N.R.
Catholic University School of Medicine
Via Pineta Sacchetti, 644
00168 Rome, Italy

Carlo Patrono
Department of Pharmacology
Catholic University School of Medicine
Via Pineta Sacchetti, 644
00168 Rome, Italy

Eugenio Picano
C.N.R. Institute of Clinical Physiology
University of Pisa
Via P. Savi, 8
56100 Pisa, Italy

Paolo Pignoli
Department of Surgery, and Institute of Pharmacology and Pharmacognosy
University of Milan
Via Andrea del Sarto, 21
20129 Milan, Italy

Loretta Resi
Center of Research on Atherosclerosis
Institute of Pathologic Anatomy
University of Siena
Via della Scotte
53100 Siena, Italy

Gabriele Riccardi
Institute of Internal Medicine and Metabolic Diseases
2nd Medical School
University of Naples
Via S. Pansini, 5
80131 Naples, Italy

Dan M. Roden
Departments of Medicine and Pharmacology
Vanderbilt University School of Medicine
Nashville, Tennessee 37232

Paolo Rubba
Institute of Internal Medicine and Metabolic Diseases
2nd Medical School
University of Naples
Via S. Pansini, 5
80131 Naples, Italy

Roberta Sarnelli
Pathological Anatomy Institute
University of Pisa
Via P. Savi, 8
56100 Pisa, Italy

Janet K. Sawyer
Department of Comparative Medicine
Bowman Gray School of Medicine of Wake Forest University
Winston-Salem, North Carolina 27103

Richard B. Shekelle
School of Public Health
University of Texas Health Science Center at Houston
P.O. Box 20186
Houston, Texas 77225

Piero Tanganelli
Center of Research on Atherosclerosis
Institute of Pathologic Anatomy
University of Siena
Via della Scotte
53100 Siena, Italy

Elena Tremoli
Institute of Pharmacology and Pharmacognosy
University of Milan
Via Andrea del Sarto, 21
20129 Milan, Italy

Peter N. Walsh
Room 320, Jones Hall
Thrombosis Research Center
Department of Medicine
Temple University School of Medicine
3400 North Broad Street
Philadelphia, Pennsylvania 19140

Giorgio Weber
Center of Research on Atherosclerosis
Institute of Pathologic Anatomy
University of Siena
Via della Scotte
53100 Siena, Italy

Babette B. Weksler
Division of Hematology–Oncology
Department of Medicine
Cornell University Medical College
1300 York Avenue
New York, New York 10021

Sharon K. Wilmoth
Department of Comparative Medicine
Bowman Gray School of Medicine of Wake Forest University
Winston-Salem, North Carolina 27103

Raymond L. Woosley
Departments of Medicine and Pharmacology
Vanderbilt University School of Medicine
Nashville, Tennessee 37232

Contents

Clinical Entities

Biological End Points and Means of Intervention

Monitoring Techniques

Atherosclerosis Reviews, Vol. 12, edited by
R. J. Hegyeli. Raven Press, New York 1984.

Drugs to Produce Atherosclerosis Regression

David H. Blankenhorn

School of Medicine, University of Southern California, Los Angeles, California 90033

There are two general strategies to test the efficacy of drugs that may cause atherosclerosis regression in humans. The first is to study drug effects on morbidity or mortality of atherosclerosis, a strategy that has been accepted for many years and was used in the Coronary Drug Project (1), the Multiple Risk Factor Intervention Trial (MRFIT) (2), and the World Health Organization trial of clofibrate (3). It is assumed that drug effects will be powerful enough to emerge despite the presence of advanced complicated lesions, because these are largely responsible for morbidity and mortality due to atherosclerosis.

The second strategy to test the efficacy of drugs that may cause atherosclerosis regression employs auxometry, measurement of the rate of atherosclerotic lesion change in test and control groups. It is assumed that drug effects will be more pronounced on early-stage lesions, but that long-range benefit will accrue if growth of these can be reversed or retarded. Selective arterial angiography is now used to measure lesions, and although there is good reason to believe that angiography will be augmented by less invasive, more flexible procedures, the nature of angiography largely determines the charcteristics of current studies. Selective angiography involves significant cost, plus some discomfort and risk to patients. This tends to restrict the number of measurements that can be made per subject and the number of subjects included in a trial. As a consequence, the drugs selected in current trials have generally been chosen with the expectation that they will produce a major alteration in atherosclerotic risk factors in hopes that large changes in atherosclerosis growth rates will result.

Eight auxometric trials in progress were described at a symposium sponsored by the National Heart, Lung, and Blood Institute and the American Heart Association in February, 1982 (4), and, since that time, two new trials have entered a start-up phase (B. G. Brown, *personal communication*, 1983; E. L. Alderman, *personal communication*, 1983). Lipid-lowering drugs are being tested in 7 of the 10 trials. The two drugs most frequently tested are colestipol and niacin, which are administered together in 5 of the 10 trials. Since this drug combination is a first choice of a majority of investigators who hope to produce relatively large effects on atherosclerosis, the characteristics of the combination are worth considering in detail. This chapter describes drug effects observed to date with combined

TABLE 1. *Characteristics at entry*

Characteristic	Mean	SD	Range
Age	52	4.8	42–59
Systolic BP (mm Hg)	123	15	97–161
Diastolic BP (mm Hg)	80	10	50–104
FBS (mg/dl)	92	13	70–136
Weight (lb)	182	25	135–243
Relative weight	1.2	0.14	0.9–1.6

BP, blood pressure; FBS, fasting blood sugar.

use of colestipol and niacin in an angiographic auxometric trial of atherosclerosis treatment.

The Cholesterol Lowering Atherosclerosis Study–I (CLAS-I Study) is now in progress at the University of Southern California (USC). The primary end point measure is atherosclerosis change rate as determined from selective femoral angiograms. The sample size, 80 in a drug treatment group and 80 in a placebo group, is planned to provide a test with a type I error of 0.05 and a type II error of 0.15, assuming a 2% per year difference between the drug and placebo groups. Secondary end point measures are provided by selective coronary angiograms, an aortic arch injection angiogram, and 9-MHz ultrasound imaging of the right common carotid artery. The interval between angiograms is 2 years. A total of 180 men will be randomized to adjust for dropouts so that 80 men per group will complete a second angiogram. To date, 137 men have been randomized, 71 to drug therapy and 66 to placebo. An additional 2-year period of observation followed by a third angiogram is planned (CLAS-II).

Major selection criteria are male sex, nonsmoking status, and ages 40 to 59 years on entry. Additional criteria require coronary bypass surgery 6 months to 5 years before entry and exclude those with total plasma cholesterol greater than 350 mg/dl or less than 185 mg/dl. The first 100 men who have been randomized had characteristics at entry shown in Table 1.

Randomized men have all passed a 6-week pretrial of drug therapy during which colestipol, 30 g/day, and niacin, 3 g/day, are given. Niacin is started at a dose of 100 mg three times a day and increased to reach 1,000 mg three times a day within 2 weeks. After the full niacin dose is reached, the total plasma cholesterol level must have been reduced 15% compared to baseline levels to be accepted for randomization. Angiography is performed immediately after the pretrial in those who pass. Following angiography, patients are randomly assigned to drug or placebo treatment for 2 years. Patients randomized to placebo have colestipol and niacin stopped immediately after angiography. Patients randomized to colestipol plus niacin continue on 30 g colestipol, but have the niacin dose adjusted according to plasma lipid response. Dosage of niacin averages 6.3 g/day (3–12 g range). A diet prescription for the drug group provides 23% of calories from fat (5% saturated

TABLE 2. *Plasma lipids in drug and placebo groups, all subjects*

Lipid (mg/dl)	Group	Baseline	Current	Percent change	Difference
Chol	Drug	249	185	−25[a]	22
	Placebo	242	234	−3	
Trig	Drug	142	111	−15[a]	16
	Placebo	153	144	1	
HDL-chol	Drug	45	61	37[a]	34
	Placebo	45	46	3	
LDL-chol	Drug	176	102	−41[a]	37
	Placebo	167	159	−4	

[a]Percent change is different from 0 when tested at the 0.01 level.
Chol, cholesterol; Trig, triglycerides; HDL-chol, high-density lipoprotein cholesterol; LDL-chol, low-density lipoprotein cholesterol.

fat) and less than 125 mg cholesterol/day. Diet in the placebo group provides 27% of calories from fat (5% saturated fat) and less than 250 mg cholesterol/day.

Table 2 presents the status of plasma lipid levels at the end of April, 1983. The data are for 62 men in the drug group and 61 in the placebo group and are averages obtained using the lipid levels at the last clinic visit for each patient. Some patients in Table 2 have been in their assigned group almost 2 years, and others have been in their assigned group only a short period. Plasma lipid determinations presented in Tables 1 and 2 were performed in the USC Lipid Research Laboratory, which is standardized by the Center for Communicable Diseases in Atlanta, Georgia.

Changes during the first year of therapy, where six plasma lipid level determinations contribute to the average value for each patient, are shown in Table 3. These data are based on the first 29 patients to complete 1 year of treatment.

TABLE 3. *Plasma lipids in drug and placebo groups at 1 year*

Lipids (mg/dl, mean ± SEM)	Group	Baseline	1 Year	Change[a]	Percent change
Total cholesterol	Drug	245 ± 8	172 ± 7	−73 ± 11[b]	−29
	Placebo	247 ± 10	248 ± 12	1 ± 10	0
Triglycerides	Drug	189 ± 22	106 ± 11	−83 ± 19[b]	−41
	Placebo	193 ± 32	168 ± 31	−25 ± 13	−12
LDL cholesterol	Drug	164 ± 7	95 ± 6	−69 ± 9[b]	−40
	Placebo	168 ± 10	173 ± 9	5 ± 9	3
HDL cholesterol	Drug	44 ± 3	57 ± 4	13 ± 3[b]	33
	Placebo	40 ± 2	42 ± 2	2 ± 2	8
LDL/HDL ratio	Drug	3.9 ± 0.3	1.7 ± 0.2	−2.2 ± 0.3	−54
	Placebo	4.4 ± 0.4	4.3 ± 0.3	−0.1 ± 0.3	−3

[a]In each treatment group, change is analyzed using a two-sided *t*-test of Ho: expected change is zero.
[b]Significant at the 0.01 level.

TABLE 4. *Plasma apolipoproteins in drug and placebo groups at 1 year*

Apolipoproteins (mg/dl, mean ± SEM)	Group	Baseline	1 Year	Change[a]	Percent change
AI	Drug	129 ± 5	138 ± 7	9 ± 5	8
	Placebo	115 ± 5	122 ± 5	7 ± 4	8
B	Drug	124 ± 8	84 ± 11	−40 ± 13[b]	−31
	Placebo	111 ± 6	129 ± 10	18 ± 6[c]	12
CIII ratio	Drug	1.2 ± 0.1	2.5 ± 0.3	1.3 ± 0.2[b]	136
	Placebo	1.1 ± 0.1	1.1 ± 0.2	0.0 ± 0.1	−3
CIII total serum	Drug	11.5 ± 0.7	10.8 ± 0.9	−0.7 ± 1.1	−2
	Placebo	12.7 ± 1.3	12.9 ± 1.9	0.2 ± 1.0	4
CIII heparin supernate	Drug	5.9 ± 0.5	7.0 ± 0.6	1.1 ± 0.7	26
	Placebo	6.1 ± 0.8	5.7 ± 0.6	−0.4 ± 0.5	4
CIII heparin precipitate	Drug	5.6 ± 0.4	3.2 ± 0.4	−2.4 ± 0.5[b]	−41
	Placebo	6.1 ± 0.6	6.5 ± 0.9	0.4 ± 0.6	14

[a]In each treatment group, change is analyzed using a two-sided *t*-test of Ho: expected change is zero.
[b]Significant at the 0.01 level.
[c]Significant at the 0.05 level.
Courtesy of Dr. Petar Alaupovic, Oklahoma Medical Research Foundation.

TABLE 5. *Blood chemistry values at baseline and 1 year (mean ± SE)*

Determination and laboratory normal	Group	*N*	Baseline	1 Year	*p* Value[a]
Glucose	Drug	35	94 ± 2	94 ± 3	
(62–110 mg/dl)	Placebo	36	91 ± 2	87 ± 2	
Total bilirubin	Drug	35	0.8 ± 0.1	0.8 ± 0.1	
(0.2–1.5 mg/dl)	Placebo	36	0.7 ± 0.3	0.8 ± 0.1	0.04
Uric acid	Drug	35	6.0 ± 0.2	7.7 ± 0.3	0.0001
(3.0–7.5 mg/dl)	Placebo	36	6.1 ± 0.2	6.4 ± 0.2	0.03
Alkaline phosphatase	Drug	11	2.0 ± 0.1	2.7 ± 0.2	0.003
(1.0–3.0 U/liter)	Placebo	10	1.8 ± 0.1	1.8 ± 0.1	
Creatine phosphokinase[b]	Drug	34	194 ± 23	192 ± 43	
(25–200 IU/liter)	Placebo	36	153 ± 17	109 ± 12	0.0004
LDH	Drug	11	424 ± 23	562 ± 17	0.001
(200–500 henry)	Placebo	10	394 ± 24	420 ± 19	
SGPT	Drug	11	35 ± 12	32 ± 3	
(5–40 karmen)	Placebo	10	35 ± 10	25 ± 2	
SGOT	Drug	11	37 ± 8	42 ± 7	
(5–40 karmen)	Placebo	10	31 ± 2	28 ± 2	

[a]In each treatment group, change is analyzed using a two-sided *t*-test of Ho: expected change is zero.
[b]Extreme case with entry value of 2750 IU/liter identified as an outlier and not included in means for drug group at baseline or 1 year.