Cardiovascular Drug Development

Protocol Design and Methodology

edited by
Jeffrey S. Borer
John C. Somberg

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MARCEL DEKKER, INC. NEW YORK · BASEL · HONG KONG

Cardiovascular Drug Development

ISBN: 0-8247-1927-1

This book is printed on acid-free paper.

Headquarters
Marcel Dekker, Inc.
270 Madison Avenue, New York, NY 10016
tel: 212-696-9000; fax: 212-685-4540

Eastern Hemisphere Distribution
Marcel Dekker AG
Hutgasse 4, Postfach 812, CH-4001 Basel, Switzerland
tel: 44-61-261-8482; fax: 44-61-261-8896

World Wide Web
http://www.dekker.com

The publisher offers discounts on this book when ordered in bulk quantities. For more information, write to Special Sales/Professional Marketing at the headquarters address above.

Current printing (last digit):
10 9 8 7 6 5 4 3 2 1

PRINTED IN THE UNITED STATES OF AMERICA

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who sheltered the weak, supported the struggling,
and embraced the vulnerable

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Introduction

As Editor-in-Chief of the ''Fundamental and Clinical Cardiology'' series, it is with tremendous pride and appreciation that I introduce this superb book by Drs. Jeffrey Borer and John Somberg. The new millennium is an especially exciting time to practice cardiology because of the exponential discoveries and implementation of cardiovascular drug development. Drs. Borer and Somberg have highlighted five critically important areas for general cardiovascular practitioners: congestive heart failure, hypertension, arrhythmia, hyperlipidemia, and coronary artery disease. Not only do they present didactic expositions but, importantly, they moderate controversial panel discussions. Having trained with John Somberg at the Peter Bent Brigham Hospital, I find it a personal pleasure to welcome the publication of *Cardiovascular Drug Development.*

Samuel Z. Goldhaber

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Preface

During the past 25 years, the progress of cardiovascular drug development has dwarfed all previous efforts in the area and has led to important benefits for public health. Nonetheless, cardiovascular drugs generally allow only a relatively small margin between useful efficacy and acceptable safety when used for treatment of the major cardiovascular diseases. As a result, development of therapeutic agents in this field presents unique challenges. These challenges have been complicated as the discovery of life-prolonging benefits of some regimens has mandated background therapy to which new drugs must be added. The attendant risk of deleterious drug interactions has importantly circumscribed the list of molecules that can be developed. Also, as therapeutic options have increased, standards of evidence for addition of new treatments have become increasingly rigorous, with concomitant and dramatic increases in development costs. The need for cost minimization and efficiency in drug development has generated multinational efforts to find appropriate study populations and other necessary resources. As a result, today molecular discovery, preclinical development, and pivotal clinical studies for drug approval routinely are performed on an international basis. These changes in the patterns of drug development reflect parallel changes in the previously insular pattern of biomedical research and, in turn, have led to considerable efforts to ''harmonize'' drug regulatory principles among the regulatory agencies of the United States, Europe, and Asia.

Eighteen years ago, John Somberg organized the first of what became an annual series of symposia entitled, ''Advances in Cardiovascular Pharmacology: Protocol Design and Methodology,'' held in

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Washington, D.C. The purpose of this effort was to bring together members of the regulatory, academic, and pharmaceutical development communities to discuss cardiovascular drug development. The annually recurring program consists of ''mini symposia'' on the development of antihypertensive agents, antiarrhythmic drugs, drugs for congestive heart failure, antianginal/anti-ischemic drugs, and antithrombotic, thrombolytic, and lipid-lowering as well as other antiatherosclerosis therapies. All these areas have undergone radical changes over the last two decades, in both molecular development and regulatory standards. However, application of the symposium format to review and consider this evolutionary process has proven enduring and useful.

Recognizing the international trends, Dr. Jeffrey Borer joined with Dr. Somberg in 1990 to extend the symposia beyond the United States to encompass the views and concerns of the international drug development communities. The result has been an annual companion series in which differences in approval standards and approaches to drug development among different nations are discussed. Three years later, portions of the United States and international symposia first were published. With the present publication, the long-planned goal of disseminating a volume of proceedings that touches upon all areas of cardiovascular drug development has finally been achieved.

This book includes material from both the spring (U.S.) and autumn (international) symposia of 1996 to 1997. The format of the symposia is composed of brief formal presentations followed by extended panel discussions. The publication presents the formal discussions, edited for clarity, followed by transcripts of the panel discussion, edited by Drs. Borer and Somberg. Each drug development area is introduced with a brief overview discussion of the state of the field, highlighting areas of controversy as well as accepted approaches to amassing the database necessary for drug approval by regulatory agencies, most particularly by the U.S. Food and Drug Administration. No effort has been made to be encyclopedic in discussing drug development trends in any single symposium, nor is this volume intended to provide such comprehensive coverage of the field. Expansion of this format is anticipated in future editions, which will result in such a comprehensive primer.

We hope that this volume will prove useful for those who have

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not been able to attend the symposia, as well as for those who wish to review and revisit materials covered in past meetings. Cardiovascular drug development is an important field because of the debilitating and potentially lethal nature of cardiovascular diseases and because of the high prevalence of these conditions in our society. The impact of medical therapeutics has been considerable and accounts for substantial reductions in cardiovascular morbidity and mortality. We hope the spring and autumn symposia, as well as this book, will contribute in some way to furthering development of these important therapies.

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Drug Discovery and Development

John C. Somberg

Change is part of the human condition that we often fail to notice. Over the last 100 years, the drug development process has undergone considerable, perhaps even revolutionary, change. But perhaps all that has passed will pale in comparison in the dramatic new information era, which will markedly alter the environment we work in and the drug development process.

Even the most powerful and financially stable companies engaged in drug discovery and development need to recognize the forces of change. The evolution of the computing age gave IBM the opportunity to expand and alter its business from analog systems and adding machines to punch cards and then to complex computer systems. As the computer age developed, IBM led the way with the innovative personal computer. The lead was then lost by IBM when ''software'' became the core of the information age, along with the chips that permit the exponential growth in machine computing performance. Thus, Microsoft, just a concept 20 years ago, is more dominant in today's information age than IBM. IBM remains a leader in technology advances, in new fundamental patents, and in strength of marketing and sales force. It kept up in technology, but its management failed to perceive the salient change in the information age from large computers to small, and then to the importance of the operation language that controls information processing, analysis, and communication.

Drug development is in an analogous situation. We have seen an

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evolution from the age of botanicals to the age of chemical synthetic discovery and now to the age of biotechnology and gene manipulation, which is dawning today. Each area can still grow, but the shift in direction is fundamental to scientific development. Taking these major changes into account, drug discovery and development will be fundamentally altered by the information age. The concept of the information age had been coined by Toffler and was correctly perceived to be revolutionary in its effects on society. The agricultural and the industrial revolutions brought about fundamental changes in society, as will the information age. In his book entitled *Future Shock* (1), Toffler describes an era when the pace of change in modern life is so great as to disenfranchise individuals from the process that society is undergoing. While this is a real problem for society and a problem with political dimensions, failure of our institutions and of our corporate structures to adjust will bring considerable societal and economic disruption. For these reasons, an understanding of the evolution of drug discovery and development and how this evolution will be affected by the information age is essential for those working in this area.

THE AGE OF BOTANICALS

Anthropologists tell us that even in the early times of hunters and gatherers, humans made use of herbals. Whether as foods, items of religious significance, or medication cannot be clearly discerned. As civilization progressed, remedies from plants further developed. Earliest folklore relates stories of plant medicinals. The bible contains passages eluding to medicinal herbs and plants. In fact, all the major religions discuss plant remedies as part of their sacred works. There are many stories in pharmacology relating to the use of medicinal plants and the work of herbalists in the early discovery of drugs. I recall the story of William Withering, the physician from Birmingham, England, who on his charity rounds in Shropshire saw that an herbal potion was used to treat a woman with dropsy (CHF) who then showed improvement. Withering's botanical training in Edinburgh permitted him to identify the probable active ingredient, the leaf of the foxglove plant. After 10 years of clinical experimentation, he developed a series of case studies ex-

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plaining the dose range from minimal effective dose to toxicity. He categorized the adverse side-effect profile of the digitalis leaf and its potentially life-threatening toxicities. He noted the adverse outcomes and carefully chronicled the conditions that the drug was most useful in treating. While he thought the agent increased urine volume and, thus, had diuretic properties, he commented in his thesis that the drug had a powerful action on the motion of the heart and, thus, recognized its cardiotonic action years before this was actually proven. Withering was a masterful botanist (he chronicled the plants of Great Britain later in his life). He was an exemplary clinical pharmacologist and demonstrated the best in botanical drug discovery and testing given the skills of his day. But Withering's observations may not be unique. The effect of the foxglove plant on disease was known to be part of European plant folklore. The use of these glycoside-yielding plants and the use of the skin of the toad for medicinal purposes goes back to ancient Egypt, and is also mentioned in Chinese herbal writings. Confucius talks of glycoside plants for edematous states and cardiac glycosides are a significant component of Chinese herbal medications. While Withering's observations were a defining moment for modern medicine, botanicals of similar action were used for over 2000 years. Clearly, botanicals have been an important component to therapeutic advances. Whether we are discussing digitalis or atropine or any number of other drugs, plants have contributed much to drug discovery. The use of quinidine in atrial fibrillation or quinine to treat malaria are other examples of the importance botanicals have played in therapeutics. In fact, in the 1700s and 1800s, botanicals were the only source of drugs for development. The anti-infective agents have depended on extracts from molds and fungus for a very long time. Recent therapies are derived from nature with some chemical modifications to improve activity. We often think of the age of botanicals as one that has gone by. Indeed, it was the first step in the field of drug discovery and development, but one that continues to this day to play a major role. While reserpine was used for a thousand years in India and parts of China, it was only in the 1950s that it was purified and used as an effective antihypertensive agent. The recent use of taxol in oncology is an example of a botanical that was in very short supply. Until a synthetic pathway for commercial production was developed, the bark of the hew

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tree became a very valuable commodity and caused the hew tree to be endangered. In fact, some companies like Schaman Pharmaceuticals have made it their corporate purpose to discover and develop pharmaceuticals from botanical sources. We read about Merck & Company and Pfizer, to name but a few of the corporate giants, who have formed special alliances with botanical gardens, countries in South America or Africa, or both, to find new drug products. Is this a denial of the evolution of drug discovery, a last chance for the botanical pioneers, or a shrewd business decision? I would venture to say a bit of each. The biodiversity of the planet, the potential to find new antibacterials and other potentially useful pharmaceuticals is great. However, the need to assay so many compounds for a host of disease states and the imperfect capacity of our assays makes the odds of success much less likely than one might first estimate. Another critical aspect to the drug development process from botanicals is the fallacy of uniqueness. By this I mean the assumption that nature will provide a unique agent that can be purified and have a salutary action on a disease state with little to no organ toxicity. These assumptions are naïve and may not be correct. However, the biodiversity may provide chemical structures that can be modified or redesigned, which can be useful starting points for the drug discovery process. However, we must be smart enough to use the information we collect. Techniques are going to be needed for the categorization and analysis of what the botanical explorers find.

Another aspect is that once we find a useful agent, can we utilize today's technology to amplify its utility and insure its availability in industrial quantities. These considerations are most important to industry. Supplies of plant pharmaceuticals can be very limited. We need to employ the technologies of recombinant DNA biotechnology to provide for commercially available quantities of many of these botanicals that may be discovered. It may be that the chemical synthetic process is cheaper and this also must be considered as an alternative supply route once the novelty of the compound and its utility at clinical practice has been established. There are indeed drugs that can potentially be obtained through botanical sources. However, a systematic program is going to be needed to develop possible leads, explore them, and then to provide for adequate quantities of the substance.

The evolutionary process has created a great biodiversity. This

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does offer great potential, but we must realize that there is a limited window of opportunity to make use of this opportunity. Humans have unfortunately negatively impacted on the environment and perhaps this adverse impact of the industrialization of the world is unavoidable. However, this diversity does offer tremendous possibilities for drug discovery, but as the diversity is impacted upon and diminished, the potential for discovery is also diminished. Utilizing this diversity is a challenge, one that has been assumed by a number of recently devised projects. To successfully deal with the challenge requires the application of the most modern techniques, the most important of which may well be those related to handling the vast amount of information that can be collected. Clearly, computer applications to the exploration of the plant world, its categorization, automated process for analysis, and chemical categorization with innovative storage, organization, and retrieval will be required to make the drug discovery process effective. The systematic computerization of knowledge in ethnobotany and pharmacognosy, with emphasis on plant categorization across primitive societies, will be helpful to sustain the discovery process. Using sophisticated computer techniques to look for similarities in medicinal plant use among primitive peoples to ascertain potentially useful observations can greatly aid the ethnobotanist. Hopefully, these computerized techniques will replace the hundreds, if not thousands, of years that are needed for serendipitous observations such as that made by William Withering 200 years ago, which led to the introduction of the digitalis glycosides in clinical medicine.

CHEMICAL SYNTHETIC DISCOVERY

Over the last 75 years, the majority of new molecules have come from synthetic chemistry. In cardiology, the beta blockers and calcium channel blockers have revolutionized cardiovascular therapeutics. Beta agonists in respiratory therapy and H_2 antagonists in gastrointestinal ulcer disease therapy are a few examples of the work of the synthetic chemist that has greatly changed our treatment of patients. These advances represent all that is created in synthetic chemistry, as well as the proven model of finding a useful transmitter in a physiological system, finding

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a receptor to which the transmitter acts, and then modifying the agonist structure to find a specific antagonist. This has worked well with major advances in a number of fields. As new receptors and new physiological systems are revealed, the synthetic chemist will surely be making considerable contributions to the field of drug discovery. This process is indeed ongoing. For instance, as the role of the endothelium becomes better understood, its impact on pharmaceutical research greatly expands. What was once called endothelial derived relaxing factory (EDRF) has been characterized as a locally released gas, nitric oxide. Studies on endothelium function have found endogenous substances involved in the modulation of vasodilation and vasoconstriction at the local endothelial level. There are endogenous substances opposing the vasodilating properties of nitric oxide. Endothelin is one of these transmitters and the development of specific endothelin antagonists is an exciting new field. Whether these endothelin antagonists will be effective therapies in angina, hypertension, or congestive heart failure remains to be determined, but the process shows that the synthetic discovery of drugs, combined with physiological transmitter research, is still spawning drugs of great potential. Even here, with well-established approaches, we see the influence of the information age. Employing computers to determine receptor structure and, thus, possible receptive blockers has become a useful tool in the drug discovery process. Computer-assisted drug synthesis has great potential. In fact, there is at least one company that has this technology central to its commercial activities. The revolution in this aspect of synthetic chemistry is analogous to the revolution where computers have very greatly changed the animation industry. Where once dozens of artists were necessary computers have now replaced them, creating ''lifelike'' animations that were not feasible previously. The same type of revolution will occur in the chemical synthetic industry. Besides design, there are the categorization and synthetic pathways that are so readily applied to computerization. I believe the application of computer sciences to chemistry will lead to considerable advances in this field. The application of computers to the steps beyond modeling systems, identifying chemical structures and automatically developing synthetic approaches, will be of considerable impact. Synthetic antagonists with optimum potency can be developed from a host of chemical possibilities. With a heightened

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receptor selectivity and potency, the increased yield of these procedures will be noticeable.

However, the information age applications to synthetic modeling will be inherently limited unless we can improve our screening techniques. For many years, I have given considerable thought to the link between drug synthesis, discovery, and development. Almost 15 years ago, I had the good fortune to visit Jansen Pharmaceuticals and discuss the drug discovery process with Paul Jansen, a genius in the field. I was most impressed with his grasp of chemistry, his diverse interests, and his unparalleled success in the discovery of novel entities. Jansen was a chemist looking for novel compounds that could then be assessed to find biological activity. A new promising compound would be processed through hundreds of models, looking for possible pharmacological activity. The question arose about the ability to screen for biological activity. This is a critical linkage point in the discovery and development process, one to which the great potential of the information age can be effectively applied.

The Jansen approach fascinated me, but to this day has created deep abiding concerns. Since I have been interested in the field of antiarrhythmic drug development for many years and have participated in all stages of drug development from chemical synthesis to the clinical arena of programmed electrical stimulation studies, I was particularly interested in Jansen's approach as applied to antiarrhythmic pharmacology. I had been working on Lorcainide, a drug Jansen developed at Bersa, and wondered how this compound came out of discovery and how it compared to other agents screened. Jansen employed a costly dog model of PVC suppression postcoronary artery ligation. Lorcainide, being a Ic Vaughan Williams agent, was a sodium channel blocker. With this profile, lorcainide was predicted to be effective in the PVC suppression model. But PVC suppression and the Ic agents have not shown prolongation of life in post-MI studies. The type III agents appear to be most effective clinically, although not shown to prolong life in randomized controlled (EMIAT and CAMIOT) trials. However, a meta-analysis of drugs of the type III variety and, specifically, amiodarone have suggested them to be far more effective with much less proarrhythmia than the sodium channel blockers. This leads one to consider what would be the effect of the clinically valuable agent

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amiodarone in the screening model that Jansen was using to pick out his antiarrhythmic to go into clinical development. In fact, the records at Bersa were so accurate that the scientists in that department could look up the results in a few minutes and describe the actions of other known antiarrhythmic agents in the drug model. The answer they gave was that amiodarone was much less effective and, in fact, hardly effective at all in the model in which Lorcainide was extremely effective. It is no wonder that the pharmaceutical industry in the 1980s found a host of Ic agents (flecainide, encainaide, lorcainide, propafenone, indecainide, ethmozine, etc.), since that is what their assays were best at picking up as active agents. Thus, the model is what is so very important in the drug discovery process and what will often determine development. We could synthesize thousands of compounds and select for development a few that may not be optimum for therapy. These agents though would fit the characteristics being sought by the model employed in the screening process. This is a major problem and one not given enough consideration. We can only think of the possibility that there may be hundreds, if not thousands, of compounds buried in analytical hoppers such as Jansen's Bersa research establishment that could have been extremely useful, but were discarded because they were not identified as biologically active in an inherently flawed screening model.

In addition to the models used in drug screening is the fundamental difference in discovery between mass screening and receptor-targeted research. The latter has proved more successful in the last decade, but some major advances have come out of pure chemistry and follow-up screening to determine biological activity. Can the revolution of the information age and computer sciences be applied to synthesis and screening? These are cogent questions that will challenge us in the coming years. I believe a revolution will occur in this area. Synthesis on a grand scale will be tied to automated focused biological activity screening that will permit the evaluation of tens of thousands of molecules on a daily basis. Clearly, how we screen will determine the validity of this approach.

While we are in transition from the age of synthetic chemistry to biotechnology and gene manipulation, synthetic discovery still will play a major role in advancing the therapeutic armamentarium.

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BIOTECHNOLOGY AND GENE MANIPULATION

The area of biotechnology and gene manipulation is in the early stages, but has already made considerable impact. The largest companies are busy positioning themselves by acquiring or ''joint venturing'' with the biotechnology companies, usually small startup enterprises. They are undertaking these acquisitions to be prepared to benefit from the coming revolution in biotechnology and gene manipulation, products, and procedures. Biotechnology has not advanced as rapidly as some have predicted. The science has made tremendous strides, but a number of factors have limited the advances and commercialization. The scale-up and commercialization of biotechnology processes is limited by expense and the difficulties that are technologically imposed. The first generation of compounds has been effective at times, as growth hormone and recombinant tissue plasminogen activator (rTPA) demonstrate. However, there have been major failures such as the antibodies to counteract the effects of septic shock. While science permits the creation of drugs to evaluate, the compounds themselves may not be effective. This dichotomy stems from our imperfect knowledge of the pathophysiology of disease states, such as is the case with gram-negative sepsis and shock. Another problem revolves around a constantly changing target, such as the AIDS virus. Genetech and Amgen have been successful in bringing drugs to the marketplace, but even these companies have struggled to remain viable and continue adequate cash flow to undertake the research and development for the next generation of products. The hundreds, if not thousands, of smaller companies may not fare as well, and it is safe to predict that only a small fraction will indeed find a successful product. Besides the discrepancy between the ability to make a compound and its clinical efficacy lies the problems of corporate capitalization and effective drug development. The mergers of biotech concerns and the established pharmaceutical industry will go beyond improved capitalization and will bring more expertise in drug development and the regulatory approval process to this fledgling industry. But there are further impediments to success. Many of the products of biotechnology synthesis are proteins that are not orally active. A major area of research is going to be to convert the

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intravenously active compounds to ones with a facilitated means of delivery. Novel drug delivery systems to overcome the problems of lack of oral activity will be crucial. Carrier molecules, topical transport enhancers, nasal absorption enhancers and methodologies are but a few of the possible solutions to the drug delivery problem that considerably hampers the biotechnology field. Another approach has been the development of chemical molecules that have similar key structural elements that may permit the chemical compound to act like the protein molecule. If this is possible, we may find ourselves using the tools of biotechnology to enhance the drug discovery process through chemical synthesis. Despite the problems and inherent limitations, the field of biotechnology will greatly increase the possible compounds available for drug development and, in fact, promote development in many novel areas that have been very much lacking effective therapies. The initial cost and the pressures for successful development are so great that the critical elements of the development process will need to be more effectively used if we are not to repeat the mistakes of yesterday. For example, demonstrating the blood clot lysing capabilities of rTPA and reversal of an acute MI in development was not enough for commercial viability of the product. Genetech persisted and undertook to perform a comparative study of rTPA with streptokinase demonstrating superiority of the rTPA product. The superiority of the rTPA combined with an aggressive marketing strategy permitted Genetech to dominate the thrombolytic market. In the development process of biotechnology products, their value and place in the therapeutic armamentarium may be as important as the demonstration of efficacy in a pivotal trial. When we talk so often of pharmacoeconomic impact of new therapies and take into consideration the very great expense of the biotechnology-derived drugs, the benefits of the drug, its place in therapy, and especially its cost-benefit ratio will become critical factors in the product's success.

GENE THERAPY

Gene manipulation strategies may lie at the core of disease treatment. It seems that not a day goes by without a new gene being ''discovered'' that is the cause of a well-known disease. That there would be a single

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gene responsible for a metabolic disease like gout or homocystinuria, for example, seems reasonable. That a single gene mutation could cause a condition like Eulers Danos syndrome also seems reasonable. But breast cancer, lupus erythematosus, or coronary artery disease caused by a single abnormal gene is surprising to say the least. A mounting body of evidence supports many of these claims. This is exciting and may represent a new age of possible effective therapies for some of the most important conditions affecting humans. But the identification of the gene itself, though an important first step, is only the initial part of a very long process to cure the disease. The techniques for gene modification are rudimentary and certainly need further study. An area of cardiology where gene therapy should be most promising is restenosis following acute angioplasty. Angioplasty entails placing the catheter in the coronary vessel, inflating a balloon at the tip of the catheter, pushing aside the atherosclerotic lesion. This is rather a successful technique; however, a major problem limiting the success of angioplasty is restenosis. At the time of the initial angioplasty, there are stimuli that initiate cell proliferation of the media leading to restenosis.

The medial cells that proliferate are very homogeneous and this process seems to occur quite rapidly in about 20 to 60% of individuals having a single-vessel angioplasty. But even this simple model for gene therapy has proven a difficult target. There has been some very interesting work done with antisense therapy with promise shown in the area of restenosis. Clinical trials are currently in progress using antisense material. However, so much of the methodology is new as to impede clinical development. The use of a viral vector to insert the material in the medial cells to turn off protein synthesis is a limitation due to the caution required in using a viral vector. Major questions arise. Can the virus replicate? Will the gene be correctly inserted or will additional genetic material of the virus be inserted? Thus, validation and safety aspects are formidable and can markedly slow the development process. As experience increases with product development, manufacturer as well as the skill in conducting clinical trials, the overall time for developing gene manipulation strategies will decrease. Recently, the report of the effectiveness of probucol in preventing restenosis is an example of the role serendipitous observations still play in the development of new therapeutic approaches. We are only at the initial frontiers

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of gene manipulation. The possibilities are phenomenal. Whether the promise be realized cannot be answered at this time, but the concept of preventing or even treating serious diseases like cancer in advanced stages or incurable conditions is so exciting as to make the concept scientifically irresistible.

THE DEVELOPERS

Along with the evolution in the process of discovery and the tremendous influence the revolution in information handling will have on drug development, changes in the participants in the development process will also have considerable impact. There is also an evolution occurring in the parties to the development process. Observing the trends makes one think of the theories of the origins of the universe with oscillations in mass accumulating, exploding, and reaccumulating, forming large aggregates and small breakoff components. Perhaps the process started with the entrepreneurs who led the field successfully and developed the large corporate giants of today. Merck and Hoffman-LaRoche are examples of a one-man entrepreneur expanding into a major companies. In fact, the major companies dominate the pharmaceutical industry to an unparalleled extent. Perhaps 10 to 20 companies represent over 90% of new drugs emanating from the corporate phalanx. In fact, over the last 20 years, mergers have continued and indeed the last few years have seen even further consolidation of the pharmaceutical industry. One analyst reported in the *Wall Street Journal* that for a company to survive it must be able to compete with the major players in the pharmaceutical field. This is just not because of funding requirements for drug development programs, but because of the development impediments established by these very large competitors. Impediments can be something simple like the number of patients exposed to a new entity or more complex such as a survival study or the use of experimental ancillary technologies that are prohibitively expensive and would not be automatically required for the development of a compound. These impediments can create an impression, both to the FDA and other companies, that they are requisite making development of a second or third agent in the field much more difficult, time consuming,

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and expensive. The time factor is especially important since the longer it takes to develop a compound, the more dominance in the market the first drug has gained. Time is the same as money and the loss of product lead can all but destroy the market potential for an agent.

SMALL DEVELOPMENT COMPANIES

Considering all these obstacles to development and the considerable regulatory maze, the trend to conglomeratization with bigger and bigger companies is not surprising. What is indeed surprising is the simultaneous opposing trend of the development of the very small niche startup companies proliferating along with the ever-increasing size of the major players in pharmaceutical development. In fact, it is not just how small these companies are, it is that they only encompass an aspect of the drug discovery and development process. Some companies are focusing on discovery, others specialize in clinical development. Some companies plan that once the NDA is granted, the company licenses the product to a larger firm for marketing. Then there are other companies that neither discover nor develop drugs but place their energy in the marketing of developed pharmaceuticals. One may argue that the niche enterprises are doomed to failure. But a number of factors combine to make this approach viable. The total overhead of the very large companies limits development to compounds expected to have sales of at least $100 million. At times, a drug will have a smaller market and a large company will develop the product for public relations because of interest in the field to bolster sales of existing products in their product line or out of sheer miscalculation of market potential. However, the small companies look to a potential market of $5 to $50 million a year as a bonanza. Their costs are far lower, permitting adequate profit margins to be recouped after development, marketing, and discovery costs are accounted for and expenses for sales covered. Small companies cannot carry out clinical trials at the same level expected of a Pfizer or a Merck. Thus, the studies are fewer, smaller, and aimed at proving the efficacy and safety as directly as possible. Clearly, though, the niche company will play a major role in drug development. They will service areas not considered appropriate in terms of market

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size by the larger companies. They will represent the dynamic growth of academic entrepreneurs who look to the commercialization of their ideas especially in biotechnology and gene manipulation.

ACADEMICIANS AND ENTREPRENEURS

Many of these companies are investor driven and, thus, have intense dedication to development and success. But can a company with one or two products compete? It appears it can. There are a number of such examples. For instance, Medco Research is one such example that developed a rather novel therapy for supraventricular tachycardia (SVT), adenosine, and has become quite a success for a very small pharmaceutical company. While Medco is involved in the traditional pharmaceutical development approach of synthetic chemistry, in fact they developed an existing product not unique to the Medco research. However, most small companies are in the biotechnology field. The biotechnology industry seems most appropriate for the small company approach. Whether companies besides Genetech and Amgen can climb out of the startup phase remains to be seen. Centicor, Genzine, and US Bioscience have all made attempts, some more successful than others, but it is difficult to develop a viable product and then to sustain research and development to continue to grow. But the trend is clearly established. Academicians with a novel idea no longer publish their results and go on to the next project. Rather, patents are obtained and a company is started. I marvel at the recent reports of a new technique in cardiothoracic surgery being performed using the laparoscopic approach. Instead of reading about the advances in JAMA, the discussion occurs in the *Wall Street Journal* and centers on the possible IPO that will be forthcoming. Entrepreneurs and academicians are forming alliances that may speed a procedure or chemical entity into a viable product for development. While the free exchange of ideas may be limited and scientific discourse suffers a bit, the possibility of widespread clinical use facilitated by commercial development is enhanced. The pros and cons of this approach are not for us to debate, but rather to accept as a trend that is ongoing and growing considerably. I do think that the fast-moving nimbleness of these small dynamic companies, coupled

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with their lower overhead cost, offers considerable benefit to pharmaceutical discovery and development. Drugs are being developed that the larger concerns would not have considered. The advancement in niche areas like orphan drugs are for the most part being pursued by smaller companies. I believe this is a healthy trend and one that will force all of the industry to streamline. Combined with the trend of small niche companies in drug development has come the parallel corporate trend of downsizing and the hesitancy to expand divisions to take on temporary projects. More and more of the large companies are contracting out for critical aspects of drug discovery and development. Compounds can be manufactured under contract. Consultants can put together manufacturing specifications and preclinical testing and stability work can be done under contract. Clinical studies are performed by clinical research organizations (CROs) with the data handled by contract statistical analysis. A consulting team can put together a NDA all under the supervision of a small core group at corporate headquarters. This can be done for the small company or the very largest of the pharmaceutical giants. Parts of a project can be subcontracted. Indeed it is not uncommon for intermediate to small projects at the largest companies to be entirely subcontracted. For these reasons, the CROs and other contract service companies (CSAs) have been most successful. A bonanza of new business has created exponential growth for these types of companies. The companies are competitive and the work is relentless, but results are what make the industry thrive, and drug development has been speeded up considerably in some instances using this ''piece work'' approach. To some extent, the ''virtual'' pharmaceutical company has materialized.

There are dangers with the fragmented approach. Outside companies can be less dependable, projects can fall apart when the capitalization of the company is inadequate and they go under, less than favorable schedules can sometimes develop since the project is not necessarily the highest priority of the contracting company. The fragmented approach can create situations where the contracting company may be less alert to important clinical findings that should alter the development program or to serious toxicities that need to be taken into account. If studies are performed outside the U.S., as they often are, the quality of the data and the important aspects of clinical study acumen by the

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site investigators is often lacking. Important information about the drug may not be passed along and this can seriously impede the development process. In addition, corporate rapport with the site investigators may be lost and the important ''seeding'' of the market with experienced investigators with a product may not occur when contract organizations are involved and non-U.S. data are employed. However, there may be significant cost savings and increased patient accession with the CRO and foreign study data approaches that may make their utilization advisable. Clearly, a balanced program giving careful considerations to the limitations of CROs running the studies, providing statistical analysis, and complete monitoring services as well as CROs coordinating non-U.S.-performed studies need to be carefully evaluated and balanced against the more traditional approaches to drug development.

THE GOVERNMENT AND DRUG DEVELOPMENT

The influences of the federal government are pervasive in our society, from our tax structure to the actions of regulatory agencies, all aspects of industry, and especially the pharmaceutical industry, are greatly influenced. Recently, some very manipulative politicians targeted the pharmaceutical industry in their rhetoric to pander to voters. But, for the most part, there is a finely balanced tension between the Democrats representing more government and the Republicans representing less government and deregulation. This is, of course, a simplification, but one with historic justification. Clearly, there is a trend against government as the provider of solutions. How the trend will develop in the short term is difficult to predict. Even with the progression away from government and regulation, the impact this trend may have on the pharmaceutical industry will remain substantial. The loosening of OSCHA regulations and environmental impact statements are more likely than changes at the FDA. This is despite a lot of discussions by the new Republican congressional leadership regarding FDA. However, the specter of an unprotected public is a difficult political cry to oppose and one I believe not readily taken except for the most ardent of Republican zealots. The industry itself, especially the larger pharmaceutical companies, appear to support FDA rather vigorously. They operate successfully within its framework and, in a way, the FDA has become part of

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the process to limit competition and diminish the effectiveness of the smaller companies not able to compete against the more formidable pharmaceutical giants. Additionally, FDA, especially at the scientific level, well serves industry, insuring efficacy and safety and instilling a very high degree of confidence on the part of the public in pharmaceutical products. Thus, significant change from the status quo is unlikely in the immediate future.

GOVERNMENT RESEARCH

The importance of the defense and space-related technology on drug development has been minimal and will probably continue to be most disappointing. A more effective utilization of research funding coming from space research and the military defense research consortium could be obtained by a granting system based along the NIH and NSF lines with more decentralization. While the NSF and NIH are most imperfect systems, they are far better at supporting the advancement of knowledge than the military or a space administration's approach. Whether the government turns in this direction is not to be predicted and, in fact, may be unlikely. However, the trend toward very big scientific projects has slowed and a more reasonable decentralized approach is taking shape under the new congressional leadership. This is especially encouraging since by supporting new programs, small programs, and diverse projects, we are more likely to see important advances as opposed to the results seen when only the established industrialized scientific complex and its bureaucracy are the recipients of support.

Still, there is a paucity of support for pharmaceutical-related research, clinical pharmacology research, and research related to drug development in terms of governmental support. This is truly unfortunate since there is tremendous public health benefit to be obtained in this area. This is not to suggest that government should compete with industry; but in areas where industry is not working or in more fundamental areas that lead to the discovery and development process or are ancillary to drug discovery and development, government could and should play an important role. However, a major component of the nation's public health remains solely funded by for-profit pharmaceuti-

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cal enterprises. The federal government's genome project appears much more promising for the biotechnology gene manipulation sector of drug discovery and development. This information is fundamental and will form the information base of so many discoveries in this area for the future. That the government would patent its findings and not facilitate the dissemination and utilization of this information in research and practical product development is counterproductive. That this approach has stopped and the government is once again returning to its role as a facilitator, not a competitor, and one not aimed at accumulating wealth, is very good indeed. That the direction of the genome project is recoiling from the concept of patenting in competition with the private sector is a sign that the federal bureaucracy can be modified and responsive to the needs of society.

THE FDA REGULATORS

The drug development process occurs within the structure defined by the FDA. From initial clinical testing in phase I to later phase II and III clinical trials, the FDA has considerable influence and control while at the same time exercising a minimal degree of interference that is often surprising. Unlike European agencies, for example, the scientific levels of the FDA are most accessible at all stages of development from pre-IND, pre-phase II, or pre-NDA meetings, the FDA can provide meaningful guidance in a drug development program. Yes, they will be the judges of the data presented and the ''keepers of the regulations,'' but their assistance comes more from experience in the drug development process. The scientific division chiefs and other senior individuals at FDA see a tremendous number of clinical trials, have often encountered clinical development problems, and can, without the disclosure of confidential information, provide considerable assistance to those involved in drug development. While an individual in a company may be involved in four or five compounds over a career in terms of major development programs, the FDA senior people may see that in a week and from many different perspectives. Clearly, the FDA is the nexus of pharmaceutical development information and training that unfortunately has not been tapped into as effectively as it should be.

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To be involved in drug development and consult FDA is a most advisable approach. The FDA and industry working together on a product will often bring about a development program that is more effective and more efficient in time and resources. Too many may take FDA's advice as dictum. There is what could be termed ''the shadow FDA.'' Those regulatory advisors in industry telling us what FDA requires and wants are all too often distortions and impediments to effective drug development. FDA should be looked upon as an important resource, with whom those pivotally involved in drug development in industry should communicate directly. Regulatory advisors, consultants, past regulators, facilitators, and legal advisors all have their place, but should not be interposed between those at the companies who are the critical links in drug development. No advice should be binding, everything needs to be discussed and reasonable approaches need to be taken. The individuals at FDA are not omniscient. A development plan may not work out and may need substantial modification. Failure to realize this and blindly going forth after an FDA conference can lead to failure. Coming back to FDA and saying, ''But this is what we were instructed to do,'' is foolish and in a sense undercuts the free and open exchange of ideas between the regulators and the developers. Advice is what is given and reproach later because of changing circumstances, developments in the field, or just lack of efficacy of a compound is counterproductive. In fact, it may deter the critical assistance from FDA that can be so very helpful to a drug development team.

These impressions, of course, need to be modified in the context of the divisions and the individuals involved. There are differences among and between divisions and individuals and those at FDA giving advice and this needs to be factored into the equation. But, clearly, the most successful in development have created a working relationship with the FDA and made use of the extensive scientific experience, these individuals have with drug development. Having been the organizer of a course on cardiovascular drug development, protocol design and methodology for 15 years, I can attest to the unselfish assistance of so many senior individuals at FDA. Their knowledge of the drug development field and their interest in successful drug development and in finding scientific truth is clear cut. While the course involves many leading academics and industry physicians who have considerable

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knowledge, each year the Symposium demonstrates that the FDA participants who are senior at the agency consistently demonstrate a broad knowledge of the field of drug development.

Clearly, FDA can facilitate drug development further in what is currently being done. There are times that the delays are needless, that the debate is not helpful, but the era of the ''drug lag'' behind Europe that so severely crippled therapeutics in the 50s, 60s, and the 70s no longer exists. However, excessive drug regulation is not the goal. Rather, more expeditious, less costly, development in the information age should be the goal of the FDA. A case-by-case review is no longer necessary. Each data point to be separately chronicled and meticulously reviewed for efficacy and toxicity by a junior reviewer is an immense waste of time. Having the primary reviewer recreate the NDA piece by piece and then producing their own summary is a laborious process that obviously can take a year or more. The NDA is put together by hundreds of individuals highly trained in the pharmaceutical industry and having one or two people go through this on a line-by-line basis and check every data point and reanalyze the presentations is going to be a most arduous and time-consuming process. Quality assurance techniques are in place to ensure accuracy and integrity of a NDA data base. The FDA could make use of these techniques and clearly it will need to strengthen procedures by the end of the century, applying sophisticated computer techniques to make analyses as expeditious as possible. To keep up with the information age, the FDA will be one of the links in the drug development process that is most stressed by forthcoming change. User fees and more FDA revenues are not the answer; placing the cost of submission beyond the capacity of small startup companies is ill advised. Using these funds for more and more reviewers, thus expanding the laborious approach to data review is fallacious. Many of these programs are not objected to by the giants of industry and in fact are encouraged, since once again it appeases those who want to speed up the process and, at the same time, places impediments on the more formative, dynamic small companies thus, forming anticompetitive practices in which that FDA is lured into being an unwitting ally.

The statement that the FDA needs to ''take its time'' to ''plow through each data point'' to protect the public is one that is heard often.

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By never approving a drug, FDA would be the most protective, since no adversity would ensue from approved drugs. However, the adverse effects of no therapeutic advances would be intolerable. Thus, a compromise in the tension between the regulators charged to protect the public and the public's need for new effective therapies needs to be struck. The use of the information revolution to facilitate drug development needs to be explored. We are at the beginning of this exciting period and the government will evolve more slowly perhaps than other centers in the development process, but it will indeed evolve.

A number of approaches are possible. The use of quality assurance techniques for partial to comprehensive data verification on a random basis certainly needs to be validated and then applied. Perhaps data analysis performed by certified groups that are paid for by the company, but at the same time are licensed by the FDA, would eliminate the need for data reentry and reapplication of analytical techniques. Focusing in on quick review techniques for the critical pivotal studies and ascertaining their veracity needs to be placed at the top of the review list. With the acceptance of efficacy, rapid computerized analysis of the product's toxicity and comparison of the results to those obtained with other agents could permit an estimation of the agent's potential benefits and toxicity. This could facilitate early presentation of the NDA material to an advisory committee that would be able to understand its place in the therapeutic armamentarium and decide whether a more prolonged and thorough evaluation is needed or an early release could be considered. Of course, an early release might be combined with a more prolonged preliminary period, where information is collected on adverse experiences and efficacy and these items are then used for continued drug evaluation.

The process of approving a drug, getting very little additional information after the approval, and allowing the drug to remain on the market forever is really as wrong as a very slow and time-consuming initial development process. In fact, the fact that it is so difficult to get a drug off the market and that we have so little postmarketing information reinforces the regulators' need to make the initial approval so stringent. It would be far better to look to a system such as that in Great Britain, where there may be a more provisional stage of approval, where there is a very detailed program of postmarketing surveillance that is quite

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simple for practitioners to participate in. We must understand that drugs can be marketed and then knowledge and information developed that changes our initial impression. A drug could be severely limited in its labeling, have warnings issued to physicians who will be using it, or possibly even taken off the market when our knowledge base on the product changes. A drug withdrawal should not be looked at as a criticism of the FDA, but a realization that our knowledge continues to grow. Unfortunately, transcripts exist of congressional committees led by inquisitors who severely criticize regulators when adversity is later discovered from an agent that was approved on quite a meritorious application. If we can get the ground rules straight and be able to understand that our knowledge base expands constantly and that we might have to take a different regulatory decision-making course as this knowledge advances, then we can accept the earlier approval without faulting our regulatory colleagues. This approach is necessary if we are to fundamentally change for the better the drug development process. This is a difficult change, since so much of the process is developed by lawyers who view it as litigation with guilt or innocence to be determined rather than a scientific pursuit, where knowledge is continuously growing as more information is collected.

ISSUES AND CONCEPTS IN DRUG DEVELOPMENT

The field of drug development is vast and often specific to a given compound and the indications sought for its use. No chapter can provide the ABC guide to development. What is often a surprise is that development is applied in a general manner without a clear understanding of the market needs or careful preclinical testing of the drug's effectiveness, especially as compared to other available agents. The remaining portions of this chapter are directed toward cardiovascular drug development; however, the discussion could be generalized to other areas of drug development as well. When one is considering developing an antiarrhythmic, there is a need to go beyond the antiarrhythmic label. Are we discussing a drug aimed at the treatment of supraventricular arrhythmias or are we discussing a drug that will be used for the treatment of ventricular arrhythmias? Are we talking about

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arrhythmia prevention, acute conversion, or a long-term prophylaxis? What is the drug's mechanism of action? What alternatives for therapy are available? A sodium channel blocker needs to have a specific attribute—perhaps less toxicity, perhaps less proarrhythmia. Have animal studies unambiguously shown the drug warranting the program to go forward. Some of these issues appear obvious, but some of the considerations are often not addressed in the preliminary stages of drug development. When the class I sodium channel blockers were made suspect after the CAST study, the rush was on to find and develop type III amiodaronelike agents. However, there was no evidence that a pure type III drug was superior to a mixed function agent like amiodarone that had beta blocking and some sodium channel blocking properties as well. Why industry went off on a quest for pure, specific potassium channel blockers is an interesting example of herd psychology. This is an area where animal models could have been developed to test the hypothesis of which drugs should be sought for development and which would be optimum for clinical testing. It seems that this was not done. This is not an indictment of the pharmaceutical industry, but of the entire academic community. The development of preclinical in vivo models is underemphasized. Could we not develop a CAST arrhythmia model in rats to look at post-MI mortality? Could not proarrhythmia be assessed in an atrial fibrillation animal model? It seems that counting bodies in rats, mice, or guinea pigs, for that matter, is far less expensive and far less disturbing than assessing the impact of these agents on mortality and clinical trials. Clearly, the model needs to be validated, but this is certainly possible when the clinical outcome has been assessed in at least one large-scale clinical study. ACE inhibitors in post-MI and CHF patients are another example. Indeed, some of pioneering work was done by investigators facile in the animal laboratory. A good post-MI animal model of ACE efficacy does exist. But when the A_2 receptor antagonists came to the fore for development, they were not evaluated in terms of mortality in the existing animal model. It would be useful to evaluate the ACE inhibitors in this model since there are differences between the ACE inhibitors and the A_2 antagonists. One difference is that ACE inhibitors increase bradykinin while the A_2 receptor blocker antagonizes the effects of angiotensin without changing the amounts of bradykinin in the system. This difference may be imma-

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terial, or bradykinin may even be deleterious and the A_2 antagonists could show greater beneficial effect. Testing in an animal model would go a long way in testing this hypothesis and helping us design optimum clinical studies to evaluate the A_2 effects. Undoubtedly, animal studies employing models need to be validated, but they also need to be employed frequently to aid in determining an optimum development strategy. In animal models, varying dose and combination of drugs is feasible. In a definitive clinical mortality trial, one or two doses of the therapy is probably all that is possible.

Another aspect where modeling could be so very useful is with surrogate endpoints. Whether it be blood pressure reduction, lipid lowering, VPC suppression, or thrombus dissolution, the endpoint often used and readily obtainable clinically is a surrogate endpoint. Surrogate endpoints are an important basis for drug development, but quite precarious. Targeting VPCs for developing an antiarrhythmic in the 90s post-CAST is of no value and, in fact, would be the subject of ridicule. All surrogates are suspect and need to be validated. The possibility of validation with animal studies even if only partial, is an area needing further evaluation.

PHARMACEUTICAL STRUCTURE

The structure of the group working on drug development is most important. Individuals with familiarity in their field are requisite. Pharmacologists, pharmacokineticists, those with expertise in trial design, and individuals with strong preclinical study knowledge all are necessary components. Occasionally, one or two individuals have the expertise, but often a team is needed to pursue the objective. At least an advisory group with broad expertise should be interposed in the development process to take a number of areas into consideration early in the planning stages. With an adequate structure, the resources must also be available. One cannot be ahead of the preclinical development program and make rational decisions. The appropriate technology is needed but so is a coordination of resources in manufacturing (including placebos and positive controls) with packaging and regulatory considerations. Marketing needs to be involved. Developing a drug for supraventricular

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arrhythmias when the treatment of all arrhythmias is the goal of the company can be a disaster. While for medical reasons, some groups will be excluded in SVT development, excluding groups with very severe left ventricular (LV) dysfunction and ventricular arrhythmias from a general antiarrhythmic development program would not be acceptable. The capabilities of the compound must be assessed by the development group and fitted in with the corporate goals for drug development of that compound. Then a rational drug development plan can be devised.

DOSE AND SERUM CONCENTRATION MEASUREMENTS

Perhaps the most fundamental issue in drug development is establishing the dose for a study. This is indeed a difficult area and one that is inadequately handled in many instances. It would be safe to say that perhaps three-quarters to 95% of all drugs are being employed at doses that are not optimum. Dose ranging is difficult, expensive, and time consuming, but so very important. Finding a minimally effective dose can help in reducing adverse side effects of agents and can be an important step in an effective drug development program. For years, the dose of the thiazide diuretics were perhaps 50 times the needed dose for antihypertensive therapy. This is both bad for drug development and bad for the patient taking the medication. We can do better than this and more and more studies, due to FDA insistence more often than not, are rather elegantly determining the effective dose range. It is also important to state that an effective dose for one individual may not be an effective dose for another individual. Thus, differences may not just vary on an individual basis, but may vary within special populations. In fact, it is rather important early on to try to look at a more homogeneous population and exclude the special populations to come up with a reasonable dose range. The other population can be studied at a later date. In fact, later studies to establish dose in special populations are very important. The FDA has mandated the inclusion of women in studies because they have been woefully underrepresented previously. A drug's effect in the African American or Asian population is also very important to discern and clearly there are racial differences in drug

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handling that can significantly affect the appropriate dose for a given population. As important is the consideration of the disease state in the different racial groups. While hypertension is very prevalent to the African American population, it is usually manifested by low renin hypertension and ACE inhibitors do not seem to be useful in treating this type of hypertension. This is not a major problem for the effective treatment of hypertension since alternative agents can be used. However, the problem is certainly an important consideration in terms of heart failure therapy. Heart failure is common among African Americans as an end result often of hypertensive cardiovascular disease. Whether ACE inhibitors have the same salutary effects in reducing mortality in this group as it does in the general heart failure group has still not been clearly determined. Establishing dose and also utility of an agent in special populations is a matter that needs more attention.

What we are usually faced with early on is the need for a dose to initiate clinical studies. Even the most rudimentary of phase I and II studies needs a starting dose. For first-time studies in humans, perhaps exploring the lower estimated dose range from preclinical studies is optimum. Further, dose escalation following a log arrhythmic approach may then be appropriate. All exposures in humans should be based on milligram, per kilogram, exposures in prior animal models with some previous experience in that model's correspondence to the human condition. Incremental dose escalation is helpful to give some guidance, but time/action relationships and accumulation of drug combine to limit this technique. Establishing a dose in fixed combination is especially important and the FDA does require a synergistic effect to be established for the combined compound A and B as contrasted to either A or B alone at the peak of their dose response curve.

Dose escalation studies to toxicity are to be avoided. Investigational review boards (IRBs) and clinical common sense are not going to tolerate dangerous dose escalations. Careful exploration, even to what appears to be astronomical doses, is appropriate in controlled situations when the lower doses have been explored. A log exploration is to be recommended as the most appropriate choice. When possible, exploration of 0.1, 1, and 10 is better than the more usual 1, 5, and 10 dose titration approach. If no toxicity or mild toxicity is observed in a subject and none is observed in animals at higher doses, the effects of higher doses should then be

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explored in humans. If 10 is tolerated, then perhaps 50 and 100 should be explored to further determine the concentration effect curve. As one creeps up to the higher doses, caution is certainly needed. I was involved in one study where doses of an oral nitrate preparation of 30, 60, 120, and then up to 240 mg were used. The 240-mg dose was looked upon with horror by most investigators and, if that was the starting dose, their reaction would have been correct. Giving 240 mg without previous titration would result in a lot of adverse side effects. However, the lower doses were explored first, and then a two- or three-step titration was used to get to that higher dose. This enhanced safety while still exploring the full dose response range of the agent.

Perhaps the most dependable approach is a parallel design, with escalating dose in each group. Group comparisons are best and a dose can be established without having carryover effect from the previous dose and missing the peak action of the previous dose in the patient. But these are just guidelines to the selection process and by the very nature are simplifications. Each situation presents unique problems to consider and there is no one dose-finding technique for all circumstances.

Let us consider two situations that indeed impact on drug development. If we are developing an antiarrhythmic agent, what endpoint do we use to establish dose? PVCs have been employed, although even for the class Ia or Ic, the dose of PVC suppression may not correlate with the dose for ventricular tachycardia (VT) suppression at programmed electrical stimulation (PES) and neither may correlate with a dose that reduces mortality over a 6-month to 1-year follow-up after electrophysiological (EP) testing. The type III agent is even more problematic, since a dose at EP testing and the results at EP testing for that matter may or may not correlate with outcome. VPC suppression with a type III agent would be even less likely to correlate with outcome. Using prolongation of the action potential duration (APD) employing a monophasic action potential catheter may be the most promising technique with the type III Vaughan Williams agents, since action potential prolongation is inherent in the pharmacodynamic action of the drug. Thus, dose should be tied to the critical marker of the electrophysiological mechanism of action of the drug, which in this case is action potential duration prolongation.

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Another approach that might improve results is obtaining serum concentrations and correlating this to drug action. Serum concentration varies less and this is a potential advantage (at least this is the claim of PK/PD proponents). However, the correlation of serum concentration to drug action is not well established in most areas in cardiovascular therapeutics and, in fact, one can generalize to most areas of therapeutics. In cardiology, PK/PD relationships are virtually nonexistent. Serum concentrations of beta blockers do not correlate with drug action. Levels of antiarrhythmic agents do not really correlate with outcome. Myerburg and associates once reported that if a minimal defined concentration with an antiarrhythmic agent (mostly type I) is obtained, patients had a better outcome than if a lower concentration was obtained (2). But clearly defined target levels do not exist and studies have not reported any difference in blood levels in patients who were ''protected'' by Holter analysis or at PES testing compared to those who were not protected. In the field of CHF, dose is also a difficult and vexing question. Digitalis is employed at the most minimum of doses to avoid toxicity; whether high doses would be more beneficial is currently unknown since the specter of toxicity is what we try to avoid clinically. The ACE inhibitors are a major contribution to the field and, clearly, in a number of studies, have shown that they reduce mortality in patients with severe and also moderate congestive heart failure. But what dose is the most effective? What should be the dose that is targeted clinically? These are unanswered questions despite the body of evidence attesting to the efficacy of ACE inhibitors in congestive heart failure. ACE inhibitors lower blood pressure and a dose of ACE that lowers blood pressure but does not cause prohibitive side effects is one that is often selected for testing in clinical trials. We must ask ourselves what is the correlation of the effect of the ACE inhibitor on blood pressure and the outcome in heart failure patients? The answer to this important question is clearly unknown. A substudy of the NIH program in heart failure (SOLVD) reported that patients with a greater inhibition of converting enzyme did better than those showing a lower inhibition (3). Perhaps dose should be established on the basis of ACE inhibition. Clearly, there is considerable confusion in the field and the confusion probably diminishes the use of ACE inhibitors because this degree of uncertainty to physicians decreases their likelihood of em-

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ploying the ACE and encourages them to use such low doses of ACE as to be homeopathic.

Lipid therapy is another area where correlation of the dose has not been established for clinical effect. The surrogate of reduction in cholesterol is the target we have chosen for clinical therapy. However, in clinical studies, a fixed dose was employed, cholesterol was reduced but was not necessarily pushed to a target cholesterol level. We see benefit in secondary prevention in some trials. This is very different than pushing to a target cholesterol and seeing what would happen in terms of outcome. However, the target cholesterol must be considered suspect since we really have no definitive evidence that it is the cholesterol lowering to a target level that is causing benefit. Do we know that the cholesterol target is optimum or should cholesterol be even further lowered? The Simvastatin trial showing a marked secondary prevention gain may not relate to cholesterol lowering per se, but to changes caused in the vascular biology altering plaque rupture proclivity and platelet aggregation (4). The gain in luminal diameter has only been modest as demonstrated by quantitative angiography studies and, thus, the small improvement documented in luminal diameter is unlikely to be the mechanism of the mortality benefit. Thus, what dose should be employed in future lipid trials is another conundrum in drug development. We have certain doses that work. We have certain targets for cholesterol and perhaps studies are needed to validate the concept that lowering blood cholesterol to a target concentration will offer us the most benefit as compared to a fixed dose of a lipid lowering agent.

METHODOLOGIES AND DRUG DEVELOPMENT

There is considerable importance to sequential drug development. The coordination of phase I studies, dose finding, key pivotal studies, and then drug interaction trials with follow-up of special populations and further patient exposures, is a basic tenet of drug development. Further dose evaluations and studies looking at combination with other known concomitant drugs that would be used are important to drug development. The advantage of parallel studies as opposed to crossover design trials can be argued. The use of placebo-controlled trials, as opposed

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to positive control studies, is an important aspect of the decision that needs to be made in the development program. Especially important is how drugs are to be assessed and what indices ought to be employed. This is in part a discussion of surrogate endpoints, partly a discussion of medical approaches to a problem, and partly a discussion of philosophy. Recently, discussions with the FDA centered on the development of an IV antiarrhythmic for the most life-threatening of ventricular arrhythmias, essentially patients undergoing a cardiac arrest who are unresponsive to electroshock therapy. The discussion of the relevant endpoint is most critical. Is the relevant endpoint arrhythmia termination, survival at 1 h, at 24 h, or survival at 3, 6, or 12 months? There are no answers to these questions, but there are intervening factors that affect our decision of endpoint selection in drug development. These patients are critically ill. If nothing can be done for them, they will die rapidly. If they live for a few more minutes with the arrhythmia terminated, there is maybe enough time to utilize an assist device. If they live longer and stabilize, some will do well but most will be scheduled for a diagnostic procedure such as a cardiac catheterization with probable angioplasty to follow if a culprit coronary lesion is identified that can be technically approached. With all of the intervening therapies, the endpoints further out become a result of the initial intervention and the result also of the additional medical therapies provided. Thus, it is essential to determine outcome related to the intervention. In this case, the administration of the study antiarrhythmic agent, not to a host of other procedures that will be performed, needs to be assessed. Looking at all endpoints might be most appropriate and useful, but the critical benefit that the antiarrhythmic can offer is termination of an arrhythmia that previously could not be terminated.

The determination of dose and endpoints is critical. The appropriate statistical powering of the number of patients to enter and the study are very important. The subtleties of the selection of endpoint and dose are critical to the design and possible successful outcome to the study. As the clinical community becomes more sophisticated and more agents appear, more definitive outcomes are required. Thus, in the field of cardiovascular drug development, mortality endpoints are often required to prove efficacy and safety. For an antiarrhythmic or a heart failure treatment agent, mortality has become critical. This is

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not at the exclusion of other concerns for mechanism and antiarrhythmic and anti-CHF effects, but still mortality is a powerful regulatory persuader. For an antiarrhythmic, the effect in the PES laboratory, the reduction in symptoms like syncope, and the reduction in mortality are hoped for and must correlate to deem the drug an antiarrhythmic. But still the effect on mortality outcome and especially the effect on sudden death is expected to be evaluated and to be associated with mortality reduction. When moving along into the field of atrial fibrillation (AF), the prevention of the arrhythmia is not felt to be sufficient, but rather remaining in sinus rhythm without adverse side effects such as embolization or stroke appears to be requisite. But are we testing an anticoagulant or an antiarrhythmic? Both could possibly prevent embolization and stroke, but by entirely different mechanisms. Thus, the antiarrhythmic effect must be demonstrated as well as a favorable outcome and each might require a different study to be demonstrated. The field of CHF drug development is a complex one. The ACE inhibitors demonstrate significant hemodynamic action, and this is expected to correlate with a favorable mortality effect. However, establishing a dose on the hemodynamic actions may not be appropriate. A common therapy with digitalis and diuretics may be beneficial or adverse. The beta blockers may have a significant role to play and maybe they have to be given concomitantly with the ACE inhibitor. Finally, when several studies have shown benefit, can approval for CHF therapy be based on hemodynamic surrogates and a class effect be granted in terms of mortality and ACE inhibition. Clearly, further ACE inhibition mortality studies are not possible and a positive control study would not prove comparability in terms of mortality since the number of patients to prove that would be prohibitive.

I believe that novel endpoints such as hemodynamic effects of a drug and the correlation with converting enzyme inhibition can and will be employed. Validated animal models that show correlative results with the pivotal mortality studies in humans with other agents of the class will lend credence to a class effect claim. If for ACE inhibitors, one had a hemodynamic effect, one showed short-term improvement in exercise capacity in heart failure patients, one had similar effects on converting enzyme inhibition, and one also provided data from an animal mortality study that showed benefit; all this would lead to

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the possibility of a mortality claim. However, potentially significant differences, and I emphasize the word potentially, may make one ACE inhibitor different enough from the others to question the class effect in terms of mortality. In this situation, animal models will be especially important in terms of mortality trials in humans with new agents similar to the ACE inhibitors, the A_2 antagonists.

INTEGRATING TECHNOLOGIES

Perhaps one of the most vexing questions in drug development relates to the often observed problem of finding a field in evolution where the endpoints, diagnostic techniques, and methodologies are changing rapidly, at times, making drug development part of the changing process. When I became interested in antiarrhythmic drug development, the technique of therapy selection employing programmed electrical stimulation was developing. The field was undergoing rapid change. Programmed electrical stimulation studies were not validated and, thus, using PES protection as an endpoint in drug development was a major leap of faith. Not to use the PES technique would have been remiss, but to utilize PES studies solely as an endpoint would likewise have been a mistake for the development program. At that time, the appropriate role of PES was not defined clearly and different responses among the classes of drugs were also not known. Problems like this often appear in the preliminary stages of drug development. They can even be more problematic. For antiarrhythmic drug development, PES studies still are utilized to demonstrate ''drug effect''; in fact, not exposing a new antiarrhythmic to testing in the PES laboratory will raise serious regulatory questions.

In the development of an antianginal agent, a similar evolution was occurring. Holter monitoring was used to identify ischemia without chest pain and the concept of silent ischemia was emerging. Validating studies employing techniques like the nuclear vest were underway, which show wall motion abnormalities during silent ischemia and confirmed that the EKG changes were not artifact or positional, but rather the ST depression without pain was true ischemia. In fact, subsequent studies have found that increased episodes of silent ischemia are corre-

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late with an adverse outcome to the patient and reduced episodes of silent ischemic correlate with an improved outcome. In fact, other studies have not always found a correlation between overt anginal pain, its frequency, and silent ischemia. This is especially true in the diabetic population. The validation of the importance of silent ischemia endpoint was, and is, pretty good, especially in comparison to other endpoints often employed in drug development. However, utilizing silent ischemia studies would not serve the drug development program well. The FDA does not recognize silent ischemia as an independent endpoint, and grants no indication for the treatment of silent ischemia and maintains the singular primacy of the exercise anginal study for antianginal drug development. Indeed, there is no anti-ischemic drug development despite the widespread acceptance by the community of clinical cardiovascular specialists of the importance of silent ischemia and the validity of the Holter methodology to assess it. In this field, a marked dichotomy has developed with trials designed to test a monotherapy in terms of exercise time to angina compared to a clinical cardiology approach of combined therapy with the assessment of reversible ischemia regardless of whether it is silent or overt anginal pain. In cardiology, the goal is to reduce the ischemic burden first procedurally, if possible, and then to provide medical therapy when ischemia is still present at rest or on exercise.

Knowledge of the nuances of the given field, the intricacies that the development drug process must abide by are so very crucial. After organizing a course on cardiovascular drug development for 15 years, I can appreciate the complexity of the process and the need for familiarity with the issues. Not to take part intimately in this evaluative process and to casually walk onto the scene, review other development plans, and discuss some issues with clinicians in the field dooms a plan to excessive expense and often whole aspects of it will be nonproductive or lead to outright failure. No wonder the costs of development are so high and the results so poor.

DECISIONS IN DEVELOPMENT

With the development program underway, a number of branch points often develop that require critical decisions. Establishing dose, blinding

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studies, organizing centers, and dealing with IRBs, are all part of development vagaries. Especially vexing is a need for studies clearly demonstrating effect and the IRB's pressures to optimize patient care and the administration of potentially beneficial established therapies. Tension develops between these cross purposes and the clinical demands are often pressing. Compromise is often needed, but the team guiding the development program needs to resist some of these substantial pressures. Compromises that limit knowledge about the drug are to be avoided. Developers must be encouraged to be relentless and not easily compromise study integrity. This is because all too often the perceived requirement for therapy is based on little evidence. I can remember a leader in the heart failure field blocking a comparative evaluation of an ACE inhibitor without digitalis even though so many doubt the effectiveness of the digitalis glycosides. Another situation was with a vociferous investigator pushing so very hard to prevent a study of digitalis acutely withdrawn in CHF patients receiving ACE inhibitors. It was ''unethical'' not to use digitalis. But this is despite the known incidence of up to 60% of patients with the diagnosis of CHF who are not being treated with ACE inhibitors. The question arises, is it unethical to withdraw digitalis and administer ACE inhibitors in patients? The study prevailed and to this day is one of the best demonstrations of the utility of digitalis in patients with signs of pulmonary congestion (5).

There are many critical times in drug development that require a strong will and clear purpose to stay the course. The drug development program may come upon adversity in terms of adverse toxicity or lack of efficacy that may severely question the continuation of the project. To fail to terminate a project appropriately may lead to needless expenditures and inappropriate liability. However, far too often, programs are jettisoned prematurely when indeed the project needs further study. Premature cancellation of a study by a data monitoring or safety board can be extremely adverse; loss of further data collection could show results quite different. If at all possible, a study should not be terminated based on a trend. The study should be pursued until statistical significance is found for the adverse endpoint. If additional precautions can be undertaken for patients' safety without study termination, this would be the recommended course to take.

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An example of a trying period in development was the increased toxicity reported with the calcium channel blocker, bepridil. Since the drug prolonged the QT interval, it seemed appropriate not to administer the agent to patients with an already prolonged QT interval and with the most severe LV function. However, this course would probably have limited prescribing the drugs, which might have led to the FDA placing a ''black box labeling'' with a statement that the drug might be unsafe for the population excluded or that it was possibly unsafe because the drug was not studied in this population. Because of these considerations, which were in opposition to the corporate plan for the drug, it was decided to expose the drug in the population that was previously excluded. With the change in the development strategy, the drug was exposed to patients with poor LV function and those with QT prolongation. With the randomization of the first patients, severe arrhythmias and death were experienced when previously the safety record was pristine when the conservative entrance criteria was employed. Clearly, the suspicions of possible proarrhythmia were well founded in these high-risk patients. While development was continued and some of the studies were redirected, the change in strategy could well have led to the termination of drug development.

A more limited indication can still lead to approval and appropriate drug availability while unselected drug exposure can lead to severe adversity and drug development termination. It is nice, in fact desirable, to develop a blockbuster product, but more often than not, reality needs to set in and an agent may continue in development for a more limited group and this may be appropriate given the pharmacodynamic and kinetic considerations for a given agent. A drug will eventually find its rightful place in the market in any event and, thus, initial self deception wins nothing in the long run for the company.

THE SCIENTIFIC ADVANCEMENT OF KNOWLEDGE

A major fault in the drug development process is that it is aimed solely at commercial success. Often this goal is compatible with scientific knowledge advancement. But this is not invariably the case. Forcing a development program to yield results can, and often does, backfire.

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A limited approval and a smaller initial market is better than a failed program. Appropriate studies helping physicians place the drug in the existing therapy context is requisite in many European countries, but, sadly, this is not the case in the U.S. A drug can often receive approval showing efficacy in a field such as antihypertensive therapy. What we do need are agents that work in people who do not respond to the first-line drugs, agents that work in people that do not respond even to second line agents. We need to know how the agent fits in these more difficult to treat populations. Unfortunately, we do not always know how the agents work in combination. Thus, the approval process often does not provide the information necessary for the clinician or for marketing strategies to further drug sales. These studies are often undertaken as part of a phase IV program since they are needed to assist marketing. The antihypertensive field is an example where a new agent needs to be positioned to make a significant impact. The A_2 antagonists are an example of an exciting new category of treatment. The pharmaceutical industry does not want the A_2 antagonists they are developing, that they are pouring funds into, to be limited to those patients who cannot tolerate the cough that occurs in between 8 and 15% of patients taking ACE inhibitors. The pharmaceutical industry would like a far larger market, but without further studies, beyond those necessary for gaining approval, physicians are not aided in placing these agents in antihypertensive therapy. In fact, the economic forces at work in medicine of the 90s and beyond further inhibit a new agent's use by blocking entry into formularies and prescription plans except for the most revolutionary of products.

The FDA has in fact brought up the subject of the importance of novelty of a drug in development and that the novel agents should be given expeditious consideration in development and regulatory review. We hear of the time wasted in the development of ''me too'' products. This pharmaceutical elitism fails to take into account the previous experience in pharmaceutical drug development. Often the first agent in a series is not the best and most prescribed drug. A drug developed later may have a kinetic advantage or a better side-effect profile. The second-generation H_2 blocker ranindine is favored over cimetidine by many because of fewer drug interactions or a more favorable side-effect profile. The first beta blocker, propranalol, has given way to the polar once-

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a-day beta blocker, atenelol, with what has been reported to be a lower CNS side-effect profile. The once-a-day ACE inhibitors appear to offer advantage over the shorter acting agent in terms of patient compliance and effective antihypertensive therapy. In fact, the once daily ACE inhibitors appear to be gaining in CHF therapy as well. Once again, the first agent of a class may not be the one of greatest advantage or most frequent clinical use. A development program thus needs to define an agent well enough that its attributes can be determined and used to gain approval and then permit the company to appropriately position the product to attract physician attention. Development plans need to go beyond the rudiments of the approval process.

A lack of information from the drug development process is a considerable liability. The selective publication of drug development information makes our knowledge very imperfect. The development program of a drug can be stopped because of negative material from a single abstract. Recently, the development program of d-sotalol was stopped prematurely with the report of an adverse profile in the SWORD study. This has considerable impact in the antiarrhythmic drug development world suggesting that pure type III agents may not be nearly as safe as the mixed function drugs such as sotalol that has both type III activity and beta blocking activity. However, with so little information on this subject for over a year, the true ramifications of the SWORD results cannot be discerned. The lack of early reporting limits the dissemination of information. So much information is lost due to the bias of both investigators and editors of journals against publishing negative or incomplete studies. However, without availability of this information, physicians may repeat the mistakes in development or other developers may retrace these same nonproductive paths. For this reason, the concept of a repository of information on negative or adverse study outcomes that would provide sources for those interested in drug development to learn of past mistakes and past failed ideas has been set forth. Perhaps an online journal of clinical trials would be well suited for this type of publication and would certainly enhance the rapidity of the information's availability. This information, I believe, would prove very valuable to those involved in drug development, those involved in designing clinical trials, and those involved in evaluating the efficacy in drugs in clinical testing. However, it is uncer-

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tain that we will ever be able to make use of the vast body of information that the pharmaceutical industry has accrued, which will never see the light of day for publication. This sets back the field of clinical drug development and it sets back our understanding of pharmaceuticals. The process of publication, the disclosure of this information, would bring the drug development process and its literature closer to science than commercialism. This is a goal worth pursuing.

FROM TRIAL RESULTS TO APPROVAL

The development process is unending and needs to be attended to throughout its course. Once the critical pivotal studies are ongoing, the next step needs to be planned. Adequate patient exposure needs to be insured. Many of the patients need not be exposed to controlled randomized trials, but could be exposed through treatment studies or prolonged chronic exposure. However, failure to maintain contemporaneous control groups can be quite devastating to a program. If liver enzyme elevations are noted just in a few patients, a program could be placed in severe jeopardy. However, if it is clear that both in the control group and in patients receiving the drug under development there is an elevation in liver enzymes, then the drug would appear exonerated and the development program would proceed unhindered. Controls are critical for the evaluation of adverse side effects as well as for the evaluation of drug efficacy.

Beside establishing safety through patient exposure, adequate drug interaction studies are needed. In cardiology, several drug interaction studies are standard, such as evaluating a possible interaction with digoxin. Others can be predicted by knowing the route of elimination of the new agent and if, for instance, the liver is involved, there is likely a need to study interactions with drugs that induce liver enzymes. If a drug is significantly protein bound, then agents that may displace it from its protein binding need to be evaluated. From the known pharmacodynamic and kinetic properties of the drug, potential interactions can be determined. Another aspect of the drug interaction evaluation comes from the pharmacodynamic properties of a drug. For instance, if a drug is going to be used as an antianginal, it may be used in combi-

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nation with a calcium channel blocker or beta blocker. Clearly, concomitant studies with the use of these combined agents is indicated to see if there is a dynamic interaction. These studies go a long way in placing the drug in the proper context, aiding the physician in its use, and reassuring them in terms of safety.

Another critical aspect at this time is the exposure of special populations. Women need to be included in the drug development process at all stages, but especially in terms of drug efficacy and safety. While most antianginal, antihypertensive, and heart failure studies are performed in men, it turns out that as many, if not more, women are being treated with these medical therapies. It is appropriate to suspect that the pharmacodynamic response, as well as the kinetic handling of the drugs, may be different between genders and thus adequate exposure and careful comparison of the female group to the male group needs to be undertaken. The effect of drugs in other special populations such as Asians and African Americans in terms of kinetics is most important. There is a well known belief that the Asian population handles drugs in terms of elimination much more poorly and therefore much smaller doses are needed for effect and also to essentially have the same degree of clearance from the body. While this is a general rule of thumb, it is something worth being looked at in the special population studies. There is also the aspect of pharmacodynamic action and this is so very important in the African American population where some of the pathophysiology such as in hypertension may differ. For this reason, it seems appropriate to study ACE inhibitors, A_2 blockers, and beta blockers in this as well as the Caucasian population. Often the exposure is there, but subset analysis has not been performed. This is very important and it is especially incumbent upon the pharmaceutical industry to go back, to review their data pool, and to see if the information that was so effective in the drug approval process can also aid physicians in knowing the utility of an agent in the subpopulations who might receive it. I think this is a responsibility of the pharmaceutical industry and one that should be vigorously pursued.

A drug development program must not be complacent while the NDA is being prepared and then reviewed. In some instances, where a mortality study may be indicated, such as in heart failure, hemodynamic and exercise data may form the basis of the submission with the

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mortality study pending as the initial review process goes forward. As the study is completed, this type of information can be added to the NDA review or even after provisional drug approval is received. The concept of receiving approval of a drug pending the completion of a critical mortality trial has precedence in the field of heart failure and also lipid lowering agents. Also, the planned postmarketing studies do not have to wait for approval, but can be initiated during the NDA preparation and review process.

The NDA preparation can be a target for streamlining and improvement. Clearly, the NDA needs to be structured in advance, the computer formats established, and as the data come in they need to be evaluated, refined, and then analyzed. The templates of summaries should already be in place, data fitted in, and obviously the information that is new and novel could be viewed and added to the data summaries. The NDA cannot be written over months after the data are collected, but needs to be put together in a short period of time to optimize the information-gathering techniques to shorten the submission process.

The FDA can go a long way in facilitating of the review process. By utilizing disks provided by industry and by having compatible systems, the FDA reviewer can interact with the data and the company for a given section of the NDA. Queries can be immediately answered and facilitate the NDA application review. Clearly, as computer techniques become more sophisticated, we will be able to make use of the information age advances by employing our computer systems to handle the vast data overload that is typical of an NDA application. It is also important that, after the NDA is complete, most of its data are incorporated in papers that are rapidly put together. All too often industry waits for an investigator to come forward who may publish a small excerpt of the data base in which he or she was involved. This can give rise to a misleading impression of the data or the publication of data that does not have the power to stand statistical scrutiny. The FDA has stated that the published data are unimportant and have no relation to the NDA they have just reviewed and, in fact, the published data are of little use. This is unacceptable. The published data should be consonant with that in the NDA; the FDA, as physicians who are going to use the drug, should look at information in the public sector, evaluate it, and make a judgment. The scientific data in the public domain should

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be complete, accurate, and informative. That is not to say that the NDA should be far more complex and thorough than a publication, but that the information is misleading or vastly incomplete is a considerable disservice to the scientific community and to the physicians who will use the drug clinically. This is especially important in terms of secondary claims or ''off label'' uses of a new drug that often will never undergo adequate study. Indeed, if the medical literature was more complete, the FDA could more readily rely on this information and permit its dissemination to physicians with the understanding that the information is not definitive and not the subject of FDA critical review.

While there have been a number of attempts to fully automate the NDA process with electronic data entry and electronic NDA submission, there have been limitations on most systems that have been undertaken. However, this has only been tested for a short period of time and for sure, over the next few years, electronic data entry, special data handling techniques, quality assurance, and NDA automated submissions will be the rule, not the exception.

The FDA reviewers will require considerable computer assistance. They will be able to rapidly cross-check the data bases to ensure data integrity, completeness, as well as establish a system that will permit checking parts of the data analysis and summaries for validity without going through a line-by-line analysis. Once this is done, the work of the FDA reviewer will be vastly simplified, and the capacity work with superiors on-line through e-mail systems and automated data review algorithms will permit a timely and much more thorough and complete evaluation of the database. Having reviewers recreate the NDA piece by piece, making their own reviews and analyses, and having the NDA broken up and reviewed individually at different sections of FDA is a very laborious, time-consuming process that is at the heart of the slow-moving NDA review process. This could be expedited in the information age and this will be a great contribution to speeding up the process as well as ensuring the validity of the review.

At the completion of the submission of the NDA, a number of aspects of drug development must continue. There will be ongoing studies, some spawned by the questions that have arisen during the development program in the NDA analysis. Phase IV studies will be underway and should be planned. Many companies will embark upon

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seeding programs to enhance the experience of critical prescribers in the field with the product in question. Clearly, these studies must be well controlled and well designed. They should also be monitored and contrived in such a way as to produce useful exposure data. This both protects the drug, diminishing the chance for adversity during a critical period of regulatory review, as well as making the expenditure of time and effort worthwhile by increasing patient exposure. When this is done in a controlled fashion, even a more serious blip on the curve will usually be ironed out with this being seen in a concomitantly treated population on a control or standard therapy. Uncontrolled exposure really places the drug in considerable jeopardy and every report that builds up on the reviewer's desk is another question. The question, was there a trend that has so far not been revealed, will only slow the drug's evolution.

Another area that needs to have attention paid is the development of the product insert. Clearly, the entire development program has been aimed at determining the indications, the pharmacokinetics, the preclinical pharmacology, the adverse profile, and the appropriate doses. From the very beginning, the product insert has been sketched out, but as the process has progressed, more information has been obtained and this should be a working document that has already been drafted and now is in final stages. Also, during this period, it is time to review the data base and see if clues are given to other potential uses of the drug that could then be explored. If an antiarrhythmic agent is being developed, and considerable benefit has been seen in the field of ventricular arrhythmias, this may be the time to start developing a program around a supraventricular arrhythmia indication. A drug that reduces sudden death mortality in the heart failure population, such as has been reported with vesnarinone, which has type III antiarrhythmic properties, may need to be evaluated at this stage as an antiarrhythmic agent in other populations (6). Perhaps there are niches that the drug could be fit into and explored. To many, this is something that the clinicians do, that is not worth the time and effort of industry. This is a very misguided approach. The benefits gained, the additional information that can be disseminated and aid in prescribing guidelines can be helpful to all. If the drug turns out to be adverse in some situations, we then have guidelines and parameters of when not to use the drug. If it turns

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out that the drug is beneficial, that is even more reason for its use. There is a certain regulatory rapport that can be developed and confidence that can be built by exploring the scientific aspects of the drug that will help guide the medical community. These are very important considerations and ones that are often overlooked. In the field of antihypertensive therapy, a program that has defined hemodynamic action may naturally lead into the field of congestive heart failure. In the field of lipid lowering therapy, one may have an agent that modulates vascular biology, that reduces second myocardial infarctions, and that might have a role in the prevention of death in ischemic heart disease. I think after the NDA filing would be the time in the development process to plan out these further developmental strategies that could lead to a far greater expansion of the market.

It is probably not a good idea to look for the holy grail of approval and then consider that everything else will fall into place after that, or that additional claims and indications are of dubious benefit. Experience has demonstrated that additional information in the medical literature leads to further indications for a drug. Having additional use of the drug may lead to further development; additional claims in the product insert may contribute to physicians more readily using the product for the initial indication and for the other indications. In terms of costs, this is a far more economical means of promotion and a far more rational one. Depending upon ''off-label'' use and then proceeding with additional studies is wrong, especially in our current regulatory framework that limits ''off-label'' promotion. Sure, these types of studies are expensive, but industry has not pursued a more collaborative approach with academia and government agencies. The need to monitor these studies as one would for a pivotal trial and for the same stipends to the investigators is just not required. Still, the information may prove to be very useful and for collateral claims the FDA may depend more and more on published materials as long as they accurately contain the information necessary for review.

CONCLUSION

Drug development and discovery is a most exciting field. It is creative, intellectually taxing, and organizationally demanding. Those involved

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are to be congratulated for undertaking efforts that are usually anonymous, but that impact on clinical therapeutics to a considerable degree. The drug discovery process has gone through the botanical phase, the synthetic chemistry phase, and is now into a most exciting era of biotechnology and gene manipulation. There is an awful lot of hoopla in this arena, but we must remember, it is just one of the rings of a three-ring circus. There is a tremendous evolution in our understanding of medicine, disease processes, and statistical evaluation of clinical trials. These are ongoing arenas that are important and dynamically interact with the drug discovery process. A third arena, the drug development program itself, is being markedly affected by the third wave, the information age. We can only think back to when a chapter like this would be handwritten, typed on a typewriter with carbon paper, corrections made and then a copy sent off to the publisher. Word processing has revolutionized this approach and will continue to revolutionize it in the next couple of years. This is the same revolution that totally changes the drug development process, facilitates it, and further facilitates the review of the data base presented. All phases will undergo radical change and we will be better for it. This is a most exciting era and one that will be both fun and worthwhile in which to participate.

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I

DEVELOPMENT OF CONGESTIVE HEART FAILURE THERAPY

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2

Background Therapy in Congestive Heart Failure Studies

Jeffrey S. Borer

During the last 10 years, treatment for symptom relief and hemodynamic improvement in congestive heart failure increasingly has been evaluated long-term not only for safety, but also for efficacy in reducing mortality rate and associated hospitalization rate (''major morbidity''). Some treatments have shown sufficient effectiveness in improving natural history in congestive heart failure populations that they have been given regulatory approval for prophylaxis as well as for therapeutic use. These agents are labeled for prophylaxis and it is possible to advertise them for this purpose. The effect of these approvals has been salutary in providing guidance, particularly for prescribers who have not had the opportunity to assess the voluminous relevant data in order to draw firm conclusions about appropriate therapy. But, to an increasing extent, such approval has been interpreted as part of a mandate for the routine prophylactic use of these drugs. In addition, at a time when managed care increasingly is becoming a factor in management decisions, patterns of treatment increasingly are being codified, with legal and economic implications for doctors who do not abide by practices defined by third parties. The FDA did not cause this situation, but it has to deal with the results. Together with sponsors, regulators must attempt to resolve a problem that has resulted unintentionally from approval of drugs that beneficially alter natural history of CHF: preventing development of other, potentially better agents, which manifest

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potentially deleterious interactions with approved drugs. This is a problem of considerable magnitude. For example, drugs that have been approved for prophylactic use to reduce the rate of development of natural history of endpoints include several angiotensin converting enzyme inhibitors and the alpha- and beta-blocker carvedilol. In addition, though not yet approved by the FDA, drugs reported to improve natural history include vasodilators that are non-ACE inhibitors, some beta-blockers, and some positive inotropic agents or agents of unknown mechanism. Included in this last category is vesnarinone, even though its range of efficacy is unclear. In addition, of course, digitalis and diuretics are approved for symptom relief and can be additive in their effects with other agents for this purpose.

To develop a new agent for use in congestive heart failure, a sponsor now must discover either a new molecule that is effective despite the use of ''standard therapy'' with representatives of the above list, or a new and previously untested patient subset with congestive heart failure or a disease known reliably to cause CHF, but for which ''standard therapy'' is not yet mandated by current consensus. It can be very difficult to find such patients or subsets for study. For example, it is very difficult to develop a new ACE inhibitor for congestive heart failure. Class approval for ACE inhibitors has not been granted for congestive heart failure symptom relief, for prophylaxis of major events in patients with CHF, nor even for hypertension, the first indication for the use of these drugs. Class approval has been withheld because it is believed that individual ACE inhibitors differ in ways that may importantly affect therapeutic efficacy. The drugs act directly on the myocardium and on vessel components in addition to modulating levels of circulating hormones that originate outside the heart and vessels. It is not possible to argue effectively that class labeling for ACE inhibitors should be allowed because the mechanism by which ACE inhibitors exert benefit in congestive heart failure is not very well understood. To some extent, of course, it seems to be related to ACE inhibition, but there are many effects in patients with congestive heart failure, and the relation between systemic ACE inhibitors, local ACE inhibitors, any other cellular effects, and pharmacological findings is poorly understood. For prophylactic use, the situation is really cloudy: not only are the mechanisms of action unclear, but the dose-response relations

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for survival are virtually unknown. The differences among ACE inhibitors that already are known include lipophilicity and tissue penetration. These probably are very important characteristics in determining capacity to prevent, for example, pathological fibrosis and other myocardial effects that are thought to be caused by autocrine and paracrine release of angiotensin. Another difference among ACE inhibitors is in the time-action relations, which may define the adequacy of delivery to the unknown primary sites of action for the beneficial effects. Third, there are variable antioxident properties among ACE inhibitors. There seems to be a variation among ACE inhibitors regarding effects on nitroglycerin tolerance, potentially important in patients with congestive heart failure and coronary disease. For example, captopril seems to enhance nitrate tolerance, while nonsulfhydril-containing ACE inhibitors do not. This may account in part for the apparent anti-ischemic effect of captopril. There are different effects of various ACE inhibitors on sympthathetic tone and tissue catecholamine levels. For example, when they are titrated to similar blood pressure effects, lisinopril results in lower blood catecholamine levels than captopril. Finally, the fifth important difference is the extent of partial dissociation of the ACE inhibition effect from the blood pressure effect. That is very important because it suggests variation in the underlying mechanism of action of these drugs. It is partially ACE inhibition, but there also seems to be some other important mechanism at work.

The established method for studying new drugs in areas where older drugs are already approved for routine use and/or are mandated for use by current consensus is to use the established drug as background therapy and to randomize the new drug and placebo on the background. This would be difficult with a new ACE inhibitor for heart failure: hypotension is a frequent side-effect of even relatively low doses of established ACE inhibitors in heart failure so that use of a new ACE inhibitor in addition to an approved one would be precluded or its dose range might be so severely limited by the background therapy that it would be difficult to determine any additive effect. It follows, for example, that the current approval of enalapril and captopril for natural history benefit may inappropriately preclude the study of newer and possibly better agents. Equally important, availability of ACE inhibitors approved for prophylaxis makes it very difficult to study new

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groups of drugs with vasodilating effects, like the angiotensin-2 (A_2) receptor blockers, in heart failure. This may be true even when one is studying the agent for symptom relief. The A_2 blockers differ from ACE inhibitors in at least one potentially important general pharmacological effect: they do not block bradykinin metabolism and therefore do not directly alter any beneficial or detrimental effects of the kinins in congestive heart failure. The potential for hypotension may limit the capacity of sponsors to develop A_2 blockers in CHF. This is a major problem.

What about beta-blockers? The FDA recently approved carvedilol for treatment in heart failure. The studies presented to the FDA strongly suggested reduction in mortality plus major morbidity (hospitilizations for worsening heart failure) associated with the use of the drug (vs. placebo) in patients on all the currently accepted background treatments. Sufficient data exist to reasonably hypothesize that carvedilol improves survival in a definable subset of CHF patients. However, its mechanism of action is not known. This drug blocks beta and alpha receptors, has antioxidant properties, may be a direct vasodilator, and may have other important properties that have not yet been described. In the evaluation process, how does one deal with the background of vasodilating drugs and beta-blockers? Data suggest that short-acting metoprolol also reduces mortality in CHF. These data may not be as compelling as for carvedilol, but the use of metoprolol, propranolol, timolol, and other beta-blockers is accepted in undifferentiated post-MI populations. Though overt congestive heart failure patients generally were excluded from the primary studies employed for approval of these agents, nonetheless, clinical practice has extended their application even to patients with some evidence of CHF immediately post-MI. Two-thirds of the heart failure population has coronary artery disease, and therefore has prior MI as the basis for heart failure. How does one recruit a population for study of a new beta-blocker? Should the drug be studied only in non-CAD patients and labeled that way? What about the problem of dose? I mentioned the obvious potential restriction of dose range of a new ACE inhibitor or A_2 blocker if ACE inhibitor background must be employed. To some extent this is true of beta-blockers, too, when an ACE inhibitor is employed because the loss of reflex responses to positional changes in blood pressure can

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cause important homeostatic problems for patients who are on ACE inhibitors, particularly if they have heart failure or are otherwise sensitive to these changes.

Of course, alternatively the dose problem serendipitously may potentiate discovery of drug effects because potential benefits may be found at doses far below those used clinically during IND studies. For example, vesnarinone was developed in Japan for mitigation of heart failure symptoms. It appeared to reduce mortality rate in certain patient subsets during U.S. development and the Japanese data were consistent with this finding. More recent studies have brought this conclusion into question. However, in my own laboratory, we recently showed that, at approximately one-tenth the dose recommended clinically, cardiac fibroblast survival is suppressed in experimental animals, both when the animals are normal and, even more importantly and more markedly, in the setting of chronic aortic regurgitation from which congestive heart failure predictably results, in part due to pathological fibrosis. Therefore, dose reduction in clinical studies might provide important benefits and enhanced therapeutic-to-toxic ratio.

Given these problems, what are the potential solutions? As a corollary, must the regulatory agencies seek to develop solutions? To answer the latter question first, it must be understood that regulators, by definition, are reactors, not actors, in drug development. They do not discover molecules, they do not define development goals. Discovery is carried out by the pharmaceutical industry and development goals are the response of the industry to the perceived needs of the user community or, more correctly, to the user community's perception of needs. Strictly speaking, the regulators determine only whether data developing from drug studies support a sponsor's claim (whatever that claim may be), whether the claim can be considered a therapeutic benefit rather than a pharmacological effect, and, finally, whether the data support the proposed formulation and dosage range. Nonetheless, I suggest that regulatory agencies have the capacity to play an important creative role in defining strategies for development of novel therapies and that they should do this. I do not know which will be the best or most acceptable strategies, but I would suggest the following new approaches.

First, it might be possible to select populations in which develop-

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ment of congestive heart failure and death is predictable, but CHF is not yet overt: for example, patients with decreased left ventricular ejection fraction from any cause, but without overt congestive heart failure; patients with certain forms of valvular disease without congestive failure; or patients with metabolic diseases like diabetes, amyloid, or even iron storage diseases, which inexorably progress and ultimately cause CHF regardless of currently available specific therapy for the underlying cause. If this strategy is followed, in addition to approval for the primary indication of preventing the development of CHF, the prevention of CHF in patients imminently likely to develop this syndrome might be used as a surrogate for prevention of major sequelae (hospitalization and death) in patients with overt CHF (if the data were sufficiently consistent with this conclusion) or even as a surrogate for the capacity to treat for symptom relief in CHF. The latter, of course, is a much bigger jump, which might be made easier by observational studies or by short-term randomized withdrawals after long-term therapy. How far is it reasonable to extrapolate the results of these kinds of studies? Since current approval principles do not mandate independent verification of CHF treatment efficacy as a function of etiology, it might be reasonable to extrapolate widely in populations such as the ones suggested. What about extrapolation from prophylaxis in patients without the CHF syndrome to patients with the syndrome, or, even further, from phophylaxis to treatment? These are difficult problems.

Another strategy might be to define a statistically acceptable basis for an equivalency claim for drugs tested not against placebo, but against active control, based on point estimates of acceptable variations from differences previously defined between the active control and placebo. This approach has been accepted for thrombolytics in the U.S.

Finally, we might define acceptable physiological surrogates. This is a very difficult and questionable practice. However, ejection fraction maintenance as a surrogate for reduction in tissue loss has been accepted as a goal for thrombolytic therapy for approval, as it was when tPA was approved. Any other therapy for acute MI might be judged similarly. Would reduction in LV function be a reasonable surrogate for prophylaxis for clinical events in CHF?

None of these strategies is immune from criticism. None of them is as compelling as a randomized, prospective, placebo-controlled trial.

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Table 1 Strategies to Enable Development of New CHF Drugs

1. Select populations in which development of CHF, and death, is predictable but not yet overt. a. low LVEF without CHF b. valvular diseases of various types c. metabolic abnormalities predictably predisposing to CHF 2. Extrapolate from these results to the treatment of patients for relief of CHF symptoms (e.g., with short-term randomized withdrawals).
1. Define a statistically acceptable basis for an equivalency claim for drugs tested not against placebo but against active control, based on point estimates of acceptable differences between new drug and active control. 2. Employ the putative placebo difference from active control, defined from the many prior CHF trials and natural history studies, to develop a virtual comparator.
1. Define acceptable physiological ''surrogates.'' For example, reduction in LV dilatation or reduction in rate of EF deterioration as a surrogate for improvement in natural history. 2. Define a standard based on historical or contemporaneous active controls to determine that mortality is not increased while the surrogate is improved.

However, if we do not develop some strategies that enable new drug development accounting for the increasing number of ''mandatory'' backgrounds, we may stultify drug development at a time when we are very far from optimal therapeutic efficacy (Table 1).

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3
Congestive Heart Failure Trial Design

Raymond John Lipicky

The following comments should be taken neither as formal Agency policy nor as guidance. They are offered here only for the purpose of eliciting questions during the following discussion period, since assertions are incompletely developed and problems related to drug development programs are only partially identified.

Developing therapies in congestive heart failure represents a challenge for exactly the reasons noted in Chapter 2, all present problems when outlining a development plan. As in the area of antianginal drug therapy, it could be possible to consider the treatment of heart failure as providing symptomatic benefit without major attention being paid to morbidity or mortality. At one time in the recent past, this was, in fact, the major developmental program aim and a basis of approval. Only a point estimate for effects on survival (and the confidence interval could be large) was needed, provided there was a definitive effect on symptoms.

Approval of the new therapy is highly likely if there is a symptom benefit as well as a mortality benefit. If both symptoms and mortality worsen, then disapproval is obvious. The approval/nonapproval decision is ambiguous in the case where symptoms get better but mortality gets worse, or conversely where mortality gets better and symptoms get worse. The problem is that several of these ambiguous outcomes have been documented. That is, in trials of several months duration, symptoms have been shown to be improved, but mortality has been

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clearly shown to be adversely affected and, in a longer term, so have symptoms. Additionally, it has also been shown that there are therapies that produce symptomatic benefit as well as a mortality benefit. Moreover, no surrogates have been identified that can be measured in place of symptoms, morbidity, and/or mortality. Throughout this last decade of development, placebo has also been shown to be an indispensable tool for identifying drug effect. Consequently, it is no longer possible to consider a development program that would document only symptomatic benefit for the treatment of chronic heart failure.

The problem of what to measure continues without clear solution. Certainly, symptoms by historical description or an interrogation instrument are valuable, as is exercise tolerance evaluation (whether it be maximal exercise tolerance or VO_2, 6-min walks, etc). It seems inconceivable that one would entertain studying a treatment of congestive heart failure, where the principal complaint is, ''I get short of breath when I exercise,'' without evaluating the effects of treatment on that symptom. However, if a new therapy is shown to improve exercise time, we cannot necessarily infer that it is ''safe and effective'' and therefore approvable. Furthermore, even therapies that are definitely determined to be ''safe and effective'' do not reliably increase exercise tolerance time. One can measure effects on New York Heart Association Functional Class, do visual analog scales, set up questionnaires, or devise novel devices to allow an evaluation of symptoms. Formal questionnaires such as The Minnesota Living With Heart Failure Scale, measuring ''quality of life,'' actually do evaluate symptoms and are useful. The problem is that measures of this sort do not all change appropriately, or in a statistically significant manner even when therapy is generally judged to be useful by consensus. Nonetheless, such measurements should be part of every development program. Certainly, one ought to look at heart size and pulmonary congestion in CHF trials. It is difficult to believe that people would feel better and live longer (even if data showed statistically significant benefit in such indices) when increases in heart size and/or pulmonary congestion are also documented. The situation is even worse if these measurements were not made at all.

Hospitalizations for (1) congestive heart failure, (2) cardiovascular problems, or (3) all causes, have been endpoints of studies in recent

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congestive heart failure drug development programs and were important to approval. It is not entirely clear how these measures should be interpreted (e.g., are they symptom evaluations or something else). The clearest endpoint of the three is to evaluate all causes of hospitalizations because there is no ambiguity in the measure: patients are either hospitalized or not. Hospitalizations for congestive heart failure are the most difficult to evaluate, since the principal reason for hospitalization may have been to get a dose or two of diuretics under close observation, and that is not the same state as when the need for hospitalization was acute decompensation that required intravenous inotropic therapy.

The problems alluded to in Chapter 2 are very real. For example, a new angiotensin converting enzyme (ACE) inhibitor is very difficult to study in a patient population that is already receiving ACE inhibitors. It is not possible to think of the situation where one could exclude ACE inhibitors from a study population. Finding individuals who are not receiving ACE inhibitors because they are intolerant for one reason or another is hard, but not impossible. Thus, placebo-controlled trials must be conducted on top of background therapy (this includes diuretics, digitalis, ACE inhibitors, and carvedilol). Clearly, this may preclude finding a new entity that will not work in the absence of these agents. It may also preclude finding a new entity that would, if used alone, work better than these agents combined. Design problems are indeed challenging.

It might be possible to define the action of a new drug alone (absent background therapy) in steps. For example, it is now reasonable to conclude that digitalis does not improve survival. So, a new drug could be studied in a population that does not have digitalis as background therapy, using the argument that symptoms can be controlled with diuretics, ACE inhibitors, and carvedilol, so no person is being denied appropriate therapy while participating in the study. If survival were neutral, or better yet favored (numerically, not necessarily statistically) in a trial with a new drug versus placebo (in a digitalis-free background therapy setting), then the next item of background therapy could be addressed, and so on, using each successive trial to build on the previous trial; this procedure is long, complicated, and of unclear outcome, but probably is achievable.

There is no insightful approach that has a proven track record. Many things should be measured, the changes that are observed should

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all make sense in some framework of reference. As said above, it is hard to argue that a statistically significant beneficial effect on hospitalizations for heart failure combined with decreased mortality should be believed if filling pressures rose, the heart size got bigger, and patients became cyanotic. Such ''nonclinically relevant''measurements must be made.

It is not clear that the concept of positive control trials is applicable in the field of congestive heart failure, although no person has yet done the requisite ''homework.'' Positive controlled trials rely on a well-documented historical treatment effect. For the most part, such documentation for morbid/mortal effects depends exclusively upon a single trial, and the results of a single trial usually do not adequately document the size of a historical treatment effect. As stated above, symptom relief cannot be relied upon as always being better than placebo. Thus, there is almost no hope that a historical treatment effect can serve as the basis for a positive controlled trial in congestive heart failure.

If one embarks upon a congestive heart failure development program, it does seem clear that placebo-controlled trials are almost certainly needed and that the trials must be large. It is also clear that attention needs to be paid to prospective and detailed definition of (a) the endpoints that are to count (the principal hypotheses); (b) the statistical tests to be used for principal evaluation; and (c) the alpha spending on each of the principal hypotheses tested, including those of planned interim analyses. No p values need be calculated for any of the other variables measured (i.e., simple descriptive statistics are all that are needed). In this type of trial, some centers could evaluate symptom-limited exercise, other centers could evaluate symptoms, other centers could implement The Minnesota Living With Heart Failure Scale, etc. The entire trial would be a ''simple,'' morbid/mortal trial, yet would allow other needed evaluations to be reasonably studied concurrently in the same population.

It could be that before doing the one large trial as described above, that a number of smaller trials (where endpoints are not so carefully defined, but where sample sizes would be in the hundreds) could be conducted and those variables found to be most uniformly affected could then form the basis of a large trial's hypothesis or hypotheses.

Last are considerations related to the development of intravenous

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therapies for the treatment of congestive heart failure. Although many scenarios are possible for purposes of discussion, consider that there are only two broad development concepts that could surround drug development in this area

1. Both an intravenous and oral formulation are to be developed. The principal documentation of safety and efficacy of the chemical entity will be derived from studies of the oral formulation through trials of 3 to 6 months or longer, enrolling patients with chronic heart failure.
2. Only an intravenous formulation is to be developed (e.g., dobutamine, nitroprusside, nitroglycerine). All data pertinent to safety and efficacy will be derived from studies of the intravenous formulation.

Within either of these two broad contexts, at least four purposes could exist:

1. An intravenous formulation may be developed simply to make continued therapy possible when a patient cannot take oral medications; the intended use is occasional and intended to replace between one to a few doses of oral medication.
2. An intravenous formulation may be developed, which in addition to fulfilling the purpose of number 1 is intended to treat patients with acute decompensation of chronic heart failure; the intended use is ''short term'' (less than 48 h) to treat acute decompensation in an ''intensive care setting.''
3. An intravenous formulation may be developed which, in addition to fulfilling the purposes of numbers 1 and 2, is intended to treat patients intermittently as outpatients, even if the decompensation is mild (i.e., in a prophylactic sense).
4. An intravenous formulation may be developed which, in addition to fulfilling the purposes of numbers 1–3, is intended to treat patients who have ''temporary'' myocardial dysfunction as occurs when there is difficulty coming off cardiopulmonary bypass.

Of course, the development of the oral and intravenous formulations may be concomitant. If so, one development program could finish be-

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fore the other; usually the intravenous development (e.g., milrinone, amrinone) is completed first.

For an intravenous therapy being developed alone, one could measure appropriate hemodynamics, but it would be difficult to know whether or not those hemodynamics had some beneficial clinical correlate. Consider, for example, number 4 above, an intravenous therapy developed for use in patients who have difficulty ''coming off the pump'' after cardiopulmonary bypass. An endpoint could be time-to-come-off-pump, and the study would be considered complete as soon as the patient left the operating room. A ''positive'' result would have no clear clinical interpretation. For example, if all patients who come off the pump quickly died in the recovery room, since recovery room events were not measured, one would not know that coming off the pump quickly was deleterious. In other words, short-term evaluation is not good enough. It may be reasonable to conclude that it would be necessary to document some form of symptom, morbidity, or mortality benefit in order to gain approval of an intravenous agent in the absence of long-term oral data.

In the context of an oral, chronic dosing regimen that has been shown to benefit both symptoms and morbidity/mortality and where the associated hemodynamic changes are well described, then defining the dose-related hemodynamic effects of the intravenous formulation of the same drug would seem to be sufficient for approval. For the ''in-between'' cases, various requirements would need to be decided, case by case.

This area is one of rapid change, both conceptually and with regard to considerations related to development programs. In the last decade, therapies have been found that both make patients feel better (improve symptoms), allow patients to live longer, and to live longer without requiring hospitalization. Approval, however, is still predicated on differentiating drug from placebo in terms of clinical benefit, and it appears that the concept of positive controlled trials in this area is not a promising avenue of pursuit.

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4

Angiotensin Converting Enzyme Inhibitors for Mortality Reduction in Congestive Heart Failure: Should Approval Be Granted for a Class Effect?

Jeffrey S. Borer and John C. Somberg

One consistent finding in heart failure therapy for the last decade has been the singular utility of the angiotensin converting enzyme (ACE) inhibitors. At least six of these agents currently are approved for use in the U.S., and more than a dozen are in some stage of development. However, despite their well-demonstrated utility in symptom attenuation and, in some studies, mortality reduction, how these drugs achieve their clinical effects still needs to be elucidated. At the biochemical level, they inhibit the action of angiotensin converting enzyme in mediating the conversion of angiotensin I to angiotensin II as well as interfering with the degradation of bradykinin. However, the role of these pharmacological effects in mediating clinical efficacy and toxicity is not clear.

A considerable literature has developed during the last decade documenting various actions of these drugs and, in particular, on the impact of ACE inhibitor therapy on survival in CHF. The CONSENSUS study was published in the *New England Journal of Medicine* in 1987 (1) and was the first trial to demonstrate mortality reduction from

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ACE inhibitor therapy. Only 127 patients with New York Heart Association class 3 or 4 heart failure received enalapril and 126 received placebo. Thus, the study was relatively small, but the results were statistically and clinically significant in demonstrating the life-prolonging effects of enalapril. Treatment-related reductions were found in total and cardiovascular deaths.

In 1992, the SOLVD study, sponsored by the National Institutes of Health, demonstrated similar, if less marked, benefits among patients with clinically milder, class 2 and 3, heart failure (2). However, though the study population was considerably larger in the more recent study, enalapril-mediated benefit was statistically significant only when several endpoints, including mortality and heart failure exacerbation, were combined. Mortality alone was not significantly reduced, though a trend was evident.

The V-HEFT II study (3) also demonstrated the capacity for reduced mortality with ACE inhibitors, although the magnitude of the difference between enalapril and ISDN-hydralazine is small. In summary, the V-HEFT II study demonstrated that enalapril is superior to the combination of isosorbide dinitrate and hydralazine in its effects on survival in patients with clinically severe CHF. This study is important because the combination therapy, shown to be more effective than placebo in V-HEFT I (4), included potent preload reducers which, hemodynamically, can be assumed to have been equivalent or superior to enalapril. Thus, these results suggest that enalapril may act at least in part by mechanisms other than its hemodynamic effects alone.

An earlier supportive study by Pfeiffer and Braunwald (5) demonstrated that in patients recovering from myocardial infarction, treatment with captopril during the year after infarction resulted in a smaller increment in heart size than that seen with placebo. Similarly, pulmonary pressures progressively fell in the group that received captopril, but rose among the placebo controls.

In an extension of this trial, published in 1992 (6), captopril diminished both cardiac morbidity plus total mortality, compared with placebo. This was not a pure post-MI study since patients may have had heart failure and cardiac enlargement. Survival curves were parallel for the first year. Subsequently, they diverged to clearly favor captopril therapy, with a relative risk reduction of approximately 20%. Similar results

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have been reported with the ACE inhibitor ramipril in the European study reported in the Lancet (7). These studies favor the class effect approach. They also support the observation that ACE inhibitors post-MI are effective in preventing CHF development, possibly by reducing infarct expansion and cardiac enlargement progressing to overt heart failure.

Finally, in the SOLVD substudy, Dr. Konstam and colleagues assessed enalapril and placebo in patients with heart failure (8). During a year of observation, left ventricular end diastolic pressure and heart size both were found to diminish and ejection fraction was found to increase in the enalapril-treated patients, but not in the placebo group. Therefore, this study, too, suggested lack of progression to cardiac dysfunction, and that the reduction in heart size is associated with mortality reduction. Additionally, the AIRE study employing ramapril has shown a decrease in mortality in a post-MI population.

Based on these studies, three converting enzyme inhibitors can be expected to reduce mortality in CHF. These agents differ in several characteristics: one has an intermediate half-life, one has a short half-life (captopril) and carries a sulfhydryl group (enalapril); enalapril is a prodrug, the active form of which is devoid of the sulfhydryl group, yet in different populations both reduce the incidence of heart failure and death due to heart failure. In addition, one drug is lipophilic (ramapril) and may also act at the local level; this action is called ''tissue ACE'' effect. Given these results, both clinicians and regulatory agencies must ask whether all ACE inhibitors, as a ''class,'' should be recognized as effective both for minimizing the symptoms of heart failure and for prolonging life in patients with this syndrome. If the decision is negative, it must be recognized that further development in this area will be difficult because ethical concerns associated with withholding approved drugs of this class for patients with CHF will minimize opportunity for placebo-controlled trials. Nonetheless, before extrapolating results with enalapril, captopril, and ramipril to other drugs, a number of questions must be asked: (1) Are the hemodynamic effects of these drugs similar? (2) What is the role of tissue angiotensin in the genesis of CHF and are there differences among these agents in tissue-level effects? (3) What is the role of bradykinin in the protective action of ACE inhibitors and are the A-II receptor blockers flawed because they do not increase bradykinin levels.

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When results of published studies are reviewed, definitive answers to these questions are not readily found, though some insights are available. Regarding hemodynamics, it is reasonable to infer that the agents have similar effects: all reduce systemic vascular resistance and capillary wedge pressure, and increase cardiac output with very little change in heart rate. While it is possible that dose-response curves may differ for different hemodynamic effects, this seems unlikely; qualitatively, there seems to be little difference among the hemodynamic effects of different ACE inhibitors.

Less is known regarding possible variations in presumed tissue angiotensin-inhibiting effects as well as in effects on circulating converting enzymes. Moreover, the hypothesized differential clinical effects of such variations are poorly documented. The local effects of angiotensin as a cell growth promoter, as a vasoconstrictor of arteries, and as a promoter of myocardial hypertrophy are beyond dispute from experimental studies. The clinical correlates of these findings have not been clearly demonstrated. Zau has reviewed the pathophysiology of heart failure and has constructed a theoretical scheme suggesting that, early in the course of disease, circulating angiotensin predominates in the genesis of CHF; subsequently, compensation for these effects occur, but tissue angiotensin remains active, as demonstrated by in vivo measurements (9). However, the importance, role, and correlation with therapeutic action of inhibiting tissue ACE remains obscure, needing further study. Enalapril and captopril are weak in their action on tissue ACE. Ramipril has much greater potency in this regard, but no increased effect on mortality post-MI was seen with ramipril.

Though few data exist, theoretical considerations suggest that structural characteristics of ACE inhibitors may well produce variable therapeutic effects. Thus, the agents with relatively high lipophilicity manifest higher tissue levels than those which do not: quinipril and ramipril, which are relatively lipophilic, are more readily apparent in tissues than comparable doses of enalapril or lisinopril, which are more polar and therefore less lipid-soluble. This finding could have clinical importance. In one experimental study, ramipril was administered to animals made hypertensive by aortic banding (10). With doses of ramipril that did not affect blood pressure, LV hypertrophy was reversed to the same extent as with doses that did reduce blood pressure. These

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data have been interpreted to support the concept that tissue ACE rather than afterload, per se, is directly responsible for ventricular hypertrophy and remodeling. Similar results were obtained among animals that had myocardial infarction in which hemodynamically insignificant doses of ramipril were sufficient to inhibit remodeling. While these results are intriguing, no parallel data exist in humans.

Nonetheless, there is evidence of some clinically relevant differences among ACE inhibitors. Differences in half life and differences related to the presence of the sulfhydryl group and the antioxidant properties of these molecules have been noted, although the relation to therapeutic outcomes remains speculative. Are some of these differences relevant to the possible existence of a ''class effect?'' One interesting observation that suggests such relevance is that captopril, which contains the sulfhydryl group, may be useful in modifying development of nitroglycerin tolerance (11), while nonsulfhydryl ACE inhibitors like enalapril or lisinopril do not evidence this effect. After myocardial infarction, many patients receive chronic nitrate therapy and some manifest recurring or ongoing ischemia. Thus, it is conceivable that some of the reported ''anti-ischemic'' effects of captopril might be mediated via nitrate tolerance prevention. In fact, experimental evidence supports this possibility. Nitrate-induced increase in coronary blood flow during 24-h infusion is greater when given with captopril than without. Concomitantly, it was shown that 24 h of nitroglycerin infusion in the absence of captopril is associated with a progressively diminishing response, suggestive of tolerance, while this pattern was precluded by simultaneous administration of captopril.

Another potentially important difference among ACE inhibitors is their variable effects on sympathetic tone. Many studies have demonstrated that tissue catecholamine levels and circulating catecholamine levels vary directly with the clinical severity of CHF. While the relation of catecholamine levels to pathophysiology of CHF is unclear, accumulating evidence suggests that certain ACE inhibitors are effective in reducing these levels, and that this effect may be at least in part dissociated from hemodynamic effects. In one study, in which two ACE inhibitors, captopril and lisinopril, were compared, lisinopril caused a significantly greater reduction in catecholamines than did captopril when both drugs were titrated to similar effects on blood pressure (12). The

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mechanism responsible for this difference is unclear, but the observation, per se, raises important questions about inferring ''class effects'' on clinical outcome merely because different drugs all affect circulating angiotensin-II levels similarly.

Additionally, studies have shown that even 24-h blood pressure response can differ importantly with different ACE inhibitors (13). Consistent with this observation, the relation of plasma ACE response to blood pressure response also has been shown to vary among different ACE inhibitors. Thus, for example, in one study, lisinopril significantly reduced mean arterial pressure compared with placebo or perindopril while the fall with enalapril was significantly later and greater than after captopril or perindopril. Nonetheless, despite its less impressive effect on blood pressure, perindopril caused a greater inhibition of tissue ACE than did the other agents tested.

Since we are not sure exactly how the mortality benefit of ACE inhibition occurs in CHF, it is difficult to infer a ''class''-mediated benefit in the face of the obvious variation among agents in achieving certain of the other documented drug actions. Since ethical considerations may limit placebo-controlled mortality trials in humans, and since active agent-controlled studies may require unachievable study sizes for adequate power to demonstrate efficacy of new agents, an animal ''surrogate'' theoretically could be quite useful. Neglecting for the moment the theoretical objections to extrapolating directly from animal data to humans for regulatory approval purposes, the potential use of animals in this way has been nicely demonstrated in a study employing perindopril (14,15). In this study, perindopril therapy was associated with enhanced survival compared to placebo. The inferences possible from this study might be greater if other ACE inhibitors, with some different characteristics than those of perindopril, could achieve similar mortality effects in an experimental model. Unfortunately, this interesting study is missing several critical design features: treatment was not randomized, and there was neither placebo control nor comparison to an agent known to be effective in mortality reduction in humans (enalapril, ramipril, or captopril). If these latter agents were not effective in this model, then the ability to extrapolate from the model must be questioned.

In summary, the concept that mortality reduction in CHF is a

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''class'' effect associated with ACE inhibition is attractive. This is especially so since the possibility of undertaking randomized mortality trials with an ACE inhibitor versus placebo must be considered unethical at this time. However, the variability of pharmacological effects of different ACE inhibitors, as well as differences in some of their clinical effects, precludes generalizing the mortality-reducing effect among ACE inhibitors. Nonetheless, if the hemodynamic effects of a new ACE inhibitor were demonstrated to be similar to approved ACE inhibitors and animal studies in a validated model reduced mortality, then the possibility of a class-effect-based approval would be far more promising. Clearly, the developers of a new ACE inhibitor must aggressively develop a viable animal model, validate the model with currently approved ACE inhibitors, and then characterize the new ACE inhibitor (in humans) in terms of its hemodynamics, kinetics, and tissue effects. Additional information regarding hypertrophy regression and lack of post-MI ventricular dilatation would further help in the agent's characterization. There is no certain path for this type of approval for a mortality indication, but this would seem the only ethical path available for an ACE inhibitor not currently approved.

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5
Sudden Death in Congestive Heart Failure Trials

John C. Somberg

When dealing with heart failure we think about shortness of breath, we think about decreased exercise capacity, and we think about survival. CHF usually is considered pathophysiologically as a continuum: your lungs get clear, your heart gets small, you live longer, or conversely, your lungs fill with fluid, your heart gets larger, and you die. I believe the issue is much more complex. I can foresee a situation in which the heart actually gets larger, but the patient is on amiodarone to cover electrical instability and the patient survives while the heart gets progressively larger. In addition, the periphery may be relatively more efficient in extracting O_2 in some patients who, if electrically stabilized, might be the few with severe CHF who survive. I do not believe most patients with CHF fit this profile, but a number of patients do. Why they behave like this, and what we can do to treat the majority of patients to make them behave like this, is a reasonable goal of research.

From this it follows that, along with the heart failure, the progressive increase in heart size, the lungs filling up with fluid, and the deterioration of exercise performance, one needs to deal with the problem of electrical instability, which leads to sudden death (SD) in anywhere from 30 to 48% of patients with congestive heart failure.

The most readily available sudden death databases are very difficult to interrogate because they are often based on the World Health

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Organization definition of sudden death (i.e., death within 24 h of an event). Many different causes of death can be manifest in 24 h. Sudden death can also apply to someone standing on a street corner and being hit by a taxi cab. How would that be classified in the WHO data base? That depends on the thoroughness of the data reporting and recording. Thus, the problem of defining sudden death is very difficult.

I have looked at a number of the heart failure trials to extract the sudden deaths or rapid deaths that were attributed to arrhythmia, or deaths that were unexpected because deterioration of symptoms was absent. Unfortunately, different trials dealt differently with these types of data. Possibly the best was the VHEFT study, in which just one person determined whether there was sudden death or not, at least providing consistency. Whether consistency equals accuracy is hard to say.

The incidence of SD in CHF and the proportion of total deaths that are sudden varies among studies and among populations. A population with severe heart failure and cardiac enlargement was employed in both Veteran's Administration (VHEFT) I and II studies. The second of these studies (VHEFT II) showed a high incidence of sudden death, but less when enalapril was given then when isordil plus hydralazine was given. This significant difference was unexpected. Patients who have milder heart failure, as in the SOLVD treatment and prevention studies (which involved patients with functional class I, II heart failure) show a lower sudden death incidence of approximately 5%. CONSENSUS I involved a population with very severe, class IV CHF, and a very strict definition of SD, but reported less SD then in VHEFT study. Then there is CONSENSUS II, which is really a post-MI population, and we have a much lower incidence of heart failure or sudden death in a population that has heart failure right after a myocardial infarction. The SAVE study population also was post-MI, with some patients having mild CHF and approximately one-third of patients with some form of CHF. In this study, about one-third of the deaths were sudden. In the vesnarinone study published in the *New England Journal of Medicine*, again, more than one-third of the population died suddenly. Visaranone also is a type III antiarrhythmic agent, perhaps explaining the reduction in death in the first study. Maybe the mortality problem at the higher (120 mg) dose was due to proarrhythmia with vesnarinone. Thus, a review of CHF mortality indicates that, as heart failure in-

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creases in severity, mortality increases, and a large proportion of the deaths are sudden.

The Dig Trial, which recently has been reported and published, evaluated digitalis versus placebo. Total mortality was not appreciably affected by digoxin. The total number of hospitalizations was small, and digoxin appeared to offer a modest reduction in hospitalization. The impact of digoxin on symptoms was rather modest. Moreover, sudden deaths appear to have been more frequent in the digitalis-treated group, while digitalis may have decreased mortality resulting from heart failure alone. Thus, digoxin may have a mild proarrhythmic effect in addition to a beneficial positive inotropic effect, and these two effects might balance so that total mortality is not different than seen with placebo. These data suggest that a therapy might improve heart failure symptoms and worsen electrical stability, and be neutral with regard to mortality effect.

Carvedilol, a beta-blocker with vasodilating (alpha-adrenergic blocking) properties, appears to have an impact on sudden death as well as CHF death. Dr. Bristow has pointed out that metoprolol and carvedilol reduce arrhythmias in CHF, which is not surprising since beta-blockers are well known to reduce arrhythmias and sudden death in the post-MI, low-ejection fraction (EF) population.

Amiodarone is an antiarrhythmic drug that has now been tested in the heart failure population. Steven Singh and the group from the Washington VA in the CHF-STAT study evaluated amiodarone in a CHF population. Left ventricular (LV) ejection fraction increased in the amiodarone-treated group, albeit a small amount. This increase is consistent through the study. However, there is no overall difference in survival in the population on amiodarone therapy versus the control population, though when you look at subgroups, there was a very marked difference in the group that has the dilated myopathy compared to the group with ischemic etiology at CHF. Dilated myopathy underlies CHF in a minority of patients in the U.S., comprising 33 to 40% of the heart failure population. Nonetheless, this is a sizable minority and may be a group that can be targeted for therapy with amiodarone. The result with amiodarone is similar to the result seen with the calcium channel blocker, amlodipine, although perhaps for different reasons.

Vesnarinone is another very interesting compound. It is in part a

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phosphodiesterace inhibitor and also an IK_r, blocker, making it a very potent type III, amiodarone-like antiarrhythmic agent. It also has some very interesting properties in preventing fibrosis that Dr. Jeffrey Borer has been the first to describe. This latter effect occurs at a relatively low dose. The mechanism by which vesnarinone produces benefit is not known; for the purpose of discussion, I will propose that it is a vasodilator, phosphodiesterase inhibitor and an antiarrhythmic agent. It seemed very promising, causing CHF symptom reduction and arrhythmia reduction, but in the recent VEST trial, vesnarinone had an adverse effect on mortality. The possible differential effect in the ischemic versus the congestive dilated myopathy groups has not yet been published.

One group from which interesting data have become available comprises those waiting for heart transplants. In the U.S., 75 to 80% of the people on transplant lists die before a transplant is available. In fact, some groups suggested that those who survive do not need a transplant (i.e., that they will survive as long without a transplant as if they receive one). Dr. Stevenson, at Brigham and Women's Hospital, has reported some promising preliminary results in this group when treatment with very large doses of ACE inhibitors is undertaken. I think the important aspect for drug development is the creative use of the transplant population for study. This population has a very high mortality as a result of progressive CHF with little therapeutic alternative. There is also a high incidence of sudden death in this population. Thus, the group awaiting transplant may be a good group to target for future drug studies.

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6
Panel Discussion

Dr. Borer (*Moderator*): Dr. Lipicky, in discussing the approval of an intravenous drug for use in heart failure you said that if the drug is being developed only as an intravenous preparation, you need to show mortality and/or morbidity benefit for approval. I'd like to ask you to discuss this a bit because it seems to me that the benefit you really need to show is that you can get to the next step of the management plan, that is, the patient can survive long enough to have a transplant or long enough to have another surgical procedure or long enough to take another drug. What kind of mortality or morbidity benefit were you specifically thinking of?

Dr. Lipicky: Those things that you said. If one could demonstrate that the intravenous drug served as an effective bridge to the next stage in management, this would clearly be a morbidity or mortality benefit. I'd be satisfied with even less than that. For example, consider the circumstance of open heart surgery and coming off the pump. Just coming off the pump isn't enough, but something significant happening during the in-hospital stay would be enough, for example, surviving to be intubated or to be off intravenous balloon counterpulsation. We have contemplated and, I believe, agreed with one sponsor, that a shorter time in the post-op ICU might be regarded as a clinical benefit, provided that the patient left the hospital. These type of endpoints are viable.

Dr. Borer: Dr. Singh, how would you deal with the issue of approval of I.V. drugs?

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Dr. Singh: I think we distinguish if it is purely an intravenous preparation. We are talking of the treatment of acute heart failure rather than unstable angina. (The endpoints for these would be different.) If we are talking about the development of intravenous, as well as oral preparations, then, according to European guidelines, the intravenous preparation and its effect either on hemodynamic measurements or on time in the ICU could be taken as encouragement to go onto phase III trials. But that alone would not allow for the license to be granted, since oral studies would need to show additional benefits.

Dr. Borer: John, I want to ask you a question with regard to sudden death versus congestive death. It seems reasonable to attempt to deal with different mechanisms of death with different types of agents. However, since all these drugs have potentially important toxicities, I wonder whether it would be useful to have some predictor of benefit, in other words, some descriminator of the underlying pathophysiology, to guide selection of therapy. If so, how would you do that? Would a catheterization be necessary? If a sponsor had to develop a drug for reducing one type of death versus the other, and had to add demonstration of pathophysiology in the cost of patient management to apply the drug, would that be acceptable to a sponsor?

Dr. Somberg: You are trying to get at, for instance, what came out of the amiodarone CHF studies where the patients with congestive myopathy responded and those with ischemic myopathy didn't. In other words, you might want to break up the groups in terms of etiology, atherosclerotic versus congestive. This is difficult. Someone might have had a silent MI, had an EKG 5 years ago that was abnormal but, nonetheless, now he has a congestive myopathy. Despite such classification problems, I think for too long we have looked at heart failure as a monolithic entity, just lumping patients together. They don't all have the neurohumoral storm. Some people react with hypersympathetic tone and others have much reduced sympathetic activity. I think it is useful to try to subdivide rather than to lump, since lumping leads to the need to follow Dr. Lipicky's recommendation to do large studies to mea-

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sure ''everything'' and then come up with a hypothesis to test. That's fine, but is terribly expensive, and it's very hard to get clinicians and academicians to agree to that because they will have their own thesis of what heart failure is and how to treat it and they like to lecture as opposed to doing your study. I think it is probably better to look at specific populations. Outside of congestive myopathy versus ischemic, which are obvious subgroups, additional subgrouping is very hard to determine. I talked of sudden death, but sudden death is different in people who have myopathic disease versus atherosclerotic disease, with patchy ischemic areas causing a reentrant arrhythmia and death. These latter patients may have calcium overload and they have EADs or DADs and triggered atomanticity, and different drugs will affect these things differently. Until you have some data to warrant your looking at target population or subpopulation, how to stratify is problematic. There are many possibilities. I might suggest that in addition to ischemic versus nonischemic populations, there are some patients who are relatively well adjusted to their very low ejection fraction; they are a totally different population than people who are markedly symptomatic with minimally elevated filling pressures. These, in turn, from a very different population from patients post-MI who have rales and who have arrhythmias and have another ischemic event triggering worse heart failure. A lot of patients may have ischemic events triggering heart failure. Patients with QT dispersion may be a group to separate out as well as those with heightened autonomic activity despite ACE inhibition therapy. The latter group may benefit especially from beta-blockers.

Dr. Lipicky: The intent of your question, Dr. Borer, as I understood it was that the trick is to have something that is easily identifiable, that has predictive value, that is measurable, and that clinicians can do whenever they want to. On that basis, if one identifies a subgroup that one thinks responds differently, and randomizes that subgroup for clinical trials, indeed, that would be a reasonable approach because all morbidity/mortality trials should be analyzed by intent to treat. If one takes all comers into the trial, and

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prespecifies subgroups that will respond differently, randomizes on this basis, and proves the hypothesis, something very useful has been achieved. However, the discriminator must be something that a physician can readily measure or identify.

Dr. Borer: John, what about the amiodarone trials in post-myocardial infarction patients? Do they impact on your belief that you can identify subsets (e.g., heart failure) that really ought to respond to amiodarone? Those trials were not overwhelmingly impressive in their results. How would you extrapolate from those results to the use of type III antiarrhythmics in patients with heart failure?

Dr. Somberg: The studies support the concept that arrhythmia suppression *does* reduce sudden death when using a type III agent. This is the opposite of what CAST showed. However, total mortality was not affected, possibly because of the agent chosen. The benefits of the agent were small and the toxicity was considerable, and there lies the problem. We know that toxicity is a long-term problem with amiodarone. We have also learned that amiodarone is not proarrhythmic in a wide variety of patient populations, including a CHF population. Therefore, there is hope that a nonproarrhythmic agent with a low incidence of serious side effects might reduce mortality and be well tolerated.

Dr. Borer: Dr. Shah, what do you think about that?

Dr. Shah: Last year the CPMP guidelines for cardiac failure were issued. In those guidelines and its predecessors we talked about acute and chronic heart failure. Since the data on milrinone and enoximone became available following the intravenous use and oral use, we have failed to be impressed. The data from the acute intravenous formulations and the oral formulations were disappointing. The new guideline now distinguishes clearly between the acute and chronic cardiac failure investigations. For practical purposes, the two development programs are different. Regarding the criteria that we accept for efficacy for acute heart failures, we have said symptomatic improvement, which is what you want immediately. Then there are hemodynamic improvements, as cor-

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roborated by increased perfusion in a number of tissues, such as brain and kidneys. Also, we look at the period of hospitalization and are interested in in-hospital mortality. For us, that would constitute reasonable evidence of efficacy for acute cardiac failure for an intravenous formulation. If you want to look for chronic heart failure, it is a different matter altogether.

Dr. Borer: Do you have to see benefit in all three areas before the intravenous preparation is approvable?

Dr. Singh: We look at the whole picture in a composite way. We have not rated any particular index as being more important than the other. Certainly if you were to press me on this point I would have to say that the most important thing would be perfusion and in-hospital mortality. Now, coming to chronic heart failure, we see congestive heart failure as being a complex of a number of different etiologies. Instead of just considering etiology as ischemic or nonischemic, one might stratify patients according to biochemical inclusion criteria, sympathetic storm, other measurable characteristics. If you want a homogeneous population in a particular study, then you should select by biochemical responses rather than just by ischemic or nonischemic characteristics.

Dr. Borer: Ray, how would you deal with the suggestion that a biochemical or pathophysiological stratification should be employed? I assume it's acceptable to do it, but would you *mandate* that sponsors do it or suggest that they do this stratification?

Dr. Lipicky: No. The selection of study patients comes down to whether one thinks the action of the drug is indeed the rate-limiting step in that patient's disease process. Let me just expand on that. Patients with acute myocardial infarction who have VPCs at the time of discharge have a poorer prognosis long-term than patients who have survived a myocardial infarction and don't have VPCs at discharge. We have learned that patients selected by that criterion do not have an arrhythmia as the rate-limiting step in their lifetime. Something else hurts them. So one can prevent all arrhythmias and never affect mortality, because that was the wrong way to select patients. It may not be that the drug

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doesn't work. It is an alternative way of looking at the same things that I've been talking about and, indeed, amiodarone does alter things in the sense that a number of trials have shown that the patient population's characteristics are what make arrhythmic deaths important to survival. If one can prevent arrhythmias from occurring in an appropriately selected population, one might affect their survival. It isn't that the efficacy of the drug is different, it is what's going on in the disease process. These considerations are also pertinent in the heart failure arena, especially in acute heart failure. It seems rather difficult in people with acute pulmonary edema to document that they feel better. So if one wants to document that they feel better it's probably not going to be a successful approach. One can consider an arena where people are coming off bypass surgery, post-op and similar situations where inotropes are used a lot. The approach would be that you select a patient population where you think an inotropic effect is going to have some clinical meaning, as in affecting ICU stay. One can then reasonably expect that the endpoint of the trial, if the drug in fact works, will be affected. If one chooses acute pulmonary edema as the defining characteristic of the patient population (of all comers) and attempts to document clinical benefit, it may not be possible to do so even if the drug works. How you identify the population is a very difficult problem, but when you believe you've identified a descriptor of the disease that importantly affects outcome, and perhaps from a preliminary study, can be affected by a drug, then you randomize this population in a new study.

Dr. Borer: Dr. Hoppe, how would you approach this issue of studying patients when sudden death versus congestive heart failure death is the issue? How would you advise sponsors to select the study populations?

Dr. Hoppe: Personally, I would try to distinguish first between diastolic and systolic dysfunction. I think the studies like Praise I suggest that prognosis, or maybe interaction between disease and drug, may be different based on these characteristics. These hypothesis are now explored in Praise II and CEBUS II. I would

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suggest to make a differentiation between ischemic and nonischemic heart disease and between the presence or absence of serious life-threatening arrhythmias. I consider in-hospital or, at least, in ICU mortality to be a very important endpoint. I consider that a drug that shows beneficial effects on acute hemodynamics that these effects should translate into reduced mortality.

Dr. Borer: Dr. Singh, do you have any additional thoughts about the stratification issue?

Dr. Singh: I support what Ursula Hoppe has said. Stratification based on neuroendocrine history is not necessary. If somebody has provided data because it was collected that is a different matter. For recruitment of patients at the beginning of a trial, it is not mandatory. If I was conducting a trial for chronic heart failure, I would like to do three things. (For acute I agree with Dr. Hoppe's view.) For chronic CHF, I would certainly like to differentiate between ischemic and nonischemic. The second thing is to have as large a number of patients as possible. Certainly I would provide some clinical endpoint along with the morbidity data in because that is what matters. Fifty percent of class IV ambulatory patients die within a year. That's a pretty definite endpoint—either you are dead or you are not. If you can demonstrate that 1-year mortality comes down significantly with treatment, that would be very important information for registration.

Dr. Shah: In the last 8 years we have lost no less than seven drugs. This list includes enoximone, milrinone, xemotorol, amrinone, flosequinan, neobentin, and vesnarinone. We don't seem to be getting very far with this cardiac failure business. We have been discussing this for a long time. The CONSENSUS study with enalapril in 1987 is about 10 years old now and I don't think we have gotten very much further since then. Now let's look at one of the problems. The seven drugs that I mentioned belong to at least four different chemical classes. Xemotorol is a beta-blocker, amrinone is a benzofuran, vesnarinone is a quinolone, flosequinan is a quinolone, and milrinone and enoximone are benzofuran compounds. What are the pharmacological effects of the drugs? You

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asked us earlier about amiodarone, whether the beneficial effect could be linked to its class III activity. I don't know, because vesnarinone has been shown to have fairly important class III activity, but the VEST TRIAL results suggest absence of benefit with this type of drug. Does it lie with class IV effect? We saw some good data recently with amlodipine, and vesnarinone has the opposite effect, increasing calcium conductance instead of decreasing it. Does it lie with class I effect? Amiodarone also has some class I effect and class II effect. Well, the action of amiodarone and vesnarinone are opposite in terms of class I activity (i.e., sodium conductance). Does it then lie with beta-blocking action? The data are conflicting here. Amiodarone has beta-blocking activity, but the others don't. So maybe we are looking for some other action, alpha receptor or inositol phosphokinase activity or phosphodiesterase inhibitors. We run into problems looking for novel actions. You've got to stratify patients somehow and this is why I offered as a new proposal for investigation, that you stratify patients by their responses to specific drugs. So far, we have no information about such stratification and maybe this kind of information is to be generated.

Dr. Fenichel: I don't know what strata to use. I think the ischemic versus nonischemic distinction is very tantalizing in part because of what we saw in the PRAISE study and in some of the data that John Somberg referred to. But, there may be many other strata (different kinds of endocrine phenomena, diastolic vs. systolic dysfunction, and so on), as Ursula referred to. I think that it may be that we are not thinking in terms of stratification because of the splendid success of the ACE inhibitors. The consequence is that, even if it is true that ACE inhibitors only work in some subset of the great number of congestive failure patients, the efficacy is most impressive. Furthermore, the ACE inhibitors are pretty harmless in the rest of the population, and so we see an effect in using them very broadly. If it were true that ACE inhibitors had a significant downside, the beneficial effect overall in CHF patients would be attenuated. But then, one could ''tease out'' data as did the PRAISE study and define specific subpopulations that might

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benefit from drugs, people who are benefiting while everyone else is being dragged down in having this hypothetical ill effect of the drug. That would have sent us stratifying years ago. That didn't happen and it's very nice when something comes along that is harmless in the people it doesn't benefit and beneficial to the people it does benefit. That will probably not be the rule. I'm sure stratification is going to be the name of ''the game.''

Dr. Lipicky: One would stratify presumably for the purpose of making sure that randomization is complete, but, still do an intent-to-treat analysis. So the only thing stratification does is to insure that somehow things are not unbalanced. If you have powered the study for total mortality and you don't find it and then you look to subgroups you still have a negative result. You can't draw any more definitive conclusion having stratified than if you didn't stratify, unless you power the study independently for each stratum and pay the statistical penalty for testing two hypotheses in the same study.

Dr. Fenichel: I think we have collectively misspoken using the word, ''stratify,'' when I think we all had meant simply that one will probably adopt more restrictive entry criteria, that one will not be developing drugs for congestive failure as a monolithic entity, but rather that, one will be developing drugs for nonischemic congestive failure or drugs for congestive failure in people who used to be hypertensive. I think something useful has been brought out by misuse of the term ''stratification,'' and that is that there is some benefit to stratification as correctly understood, as follows. Suppose, for example, that this drug will be effective in congestive failure, but it will only be effective in patients with relatively low ejection fraction and suppose you don't really know what that means. You don't know if that means EF $< 20\%$, $< 25\%$, $< 15\%$, etc. Still, that is your model. If you go into the trial with that model and you say all right, it is a wash overall, we took all comers and there was no overall benefit but, any way we slice it the worse the ejection fraction, with net benefit apparent at 23%, for example. Well, that would depend on exactly how the stratification hypothesis had been phrased at the beginning of the trial

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and might constitute pretty convincing evidence that you had something that worked you just didn't know exactly the nature of the benefit when you started, but now you do. I don't necessarily think that, as a single trial, such data would suffice for approval, and there is a lot more to be said about that particular topic, but the idea of identifying a priori the plausible subgroups is a very important one. Certainly, if you listen to people describing the PRAISE trial, the pivotal issue is how much was the issue of ischemic versus nonischemic cardiomyopathy a prespecified endpoint and how did it sort out. To what extent is this simply picking or to what extent is it a genuine finding that was in some sense prehypothesized and thus now a valid endpoint.

Dr. Lipicky: So, in fact, we have all been saying the same thing: it is critically important to select patients that fit the hypothesis being tested.

Dr. Somberg: I don't agree that we were all in agreement. Different things were being said. Dr. Lipicky suggested stratifying to make sure there was appropriate randomization of important subgroups, and then to do a study in all heart failure patients I think others of us were saying that a body of evidence suggests that a drug may behave differently in special, well-defined populations, and outcome should be assessed in these subpopulations.

Dr. Lipicky: There was a semantic problem and I didn't recognize that.

Dr. Somberg: So what we are doing is we're going ahead and now truly balancing the study, but also having, a priori, defined subgroups within which to evaluate outcome and to ensure balance among the subgroups.

Dr. Lipicky: You are entering people who you think the drug may help. You are not evaluating all-comers.

Dr. Somberg: You could do an all-comer evaluation as well as subgroup analyses. Take people who have ischemic myopathy vs. congestive myopathy: you could prospectively give them the therapy, and might generate results suggesting that one group would

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do better than the other on drug, but you would still follow both groups because that would further support your hypothesis.

I also believe it is very important to analyze by intent to treat. But, at the same time, it is very intellectually unsatisfying when we see, for instance, in the amiodarone study I mentioned, that because of toxicity, up to 40% of patients randomized to the drug were not on amiodarone therapy by the end of the treatment period. Can we say in that study that amiodarone didn't work, when 40% or more of the patients were not being treated as intended, while patients on placebo may be on other potent therapies. That doesn't make any sense to me. I must say I find the intention-to-treat analysis very hard to understand and apply without wondering if we are missing some important medical findings. Probably an interaction to treat and on-therapy analysis are both needed.

Dr. Lipicky: This is another semantic argument. It is intellectually O.K. It is emotionally nonsense.

Dr. Somberg: I like to be emotionally and intellectually satisfied, Ray. I'm saying it is not intellectually O.K. How can you rely on the amiodarone study results when in one study, 35%, and in another study, 40% of the patients in the amiodarone-treated groups at the end of a year's therapy are not on amiodarone. Only approximately half of the people are getting the drug although you are attributing the benefit or the lack of benefit to 100% of the cohort. That doesn't make any sense. I mean why don't we all stop prescribing all medicines and just attribute what happens in the future to what we were on previously (intention to treat). If we are evaluating the endpoint and compliance, intention to treat is the correct analysis. In the case of amiodarone, the conclusion is that a very large group can't comply with therapy over a year. What we don't know is that if compliance was in the 95–100% range what would the result be on therapy. Clearly, an on-treatment analysis is essential.

Dr. Singh: If I was looking for patients with congestive cardiomyopathy and wanted to treat them for heart failure, and I wanted to

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know whether they would do better on amiodarone or on ACE inhibitors, I would select my population by defining the criteria for congestive cardiomyopathy in advance. There is no problem with that because that has to be a clear definition: I want to recruit this group of patients and once I have recruited them I'll randomize them to either amiodarone or ACE inhibitor. Here I have to side with Dr. Somberg. Tradition will not allow me to look at anything but intention-to-treat analysis, but I do not see any problem with *also* looking at outcome on therapy.

Dr. Borer: I'd like to ask Dr. Shah about the way you would characterize the patients in order to determine which subgroups might benefit from one therapy or another. You mention in your discussion of drug actions predominantly membrane phenomena and one intracellular function. These putative mechanisms are based on what's known about the pharmacology of the seven drugs that were promising and haven't seemed to work out so well yet. However, it is conceivable that many pharmacological effects of existing drugs have not yet been defined; some of these might be beneficial, and might have dose-response curves different from those of the effects we know. With vesnarinone, for example, activity on fibroblasts has been demonstrated in several systems. One could theorize that this pharmacological effect may be beneficial. Therefore, one might want to know what the fibrosis production profile of a given patient with heart failure might be. I mentioned the studies that we did with fibroblast survival which suggest another pharmacological effect that no one could evaluate if only currently clinically applied drug doses were employed. The point here is that, as we delve more deeply into the cell biology and molecular biology of different pathophysiological forms of heart failure, we find more and more potential disorders and more and more loci at which drugs can work. Once you look at the drugs more and more carefully, you find that some of them work in ways we didn't previously appreciate, and that many of the drugs we now use (and some of the drugs that are now in development) probably have many dose-response curves for many different responses. What we really need to know is where

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those curves cross. That is not to disagree with your proposition, but rather to suggest that if we are going to follow your proposal we probably shouldn't just base the characterization on those areas that we believe are important now. Perhaps we need to look far more intensely at the cell biology and must begin to characterize people according to a variety of characteristics that we think may be involved with the pathophysiology of heart failure, the importance of which we don't know. This is the process by which we can hope to develop the target for specific agents in the future.

Dr. Singh: This is precisely what I was suggesting, Mr. Chairman, that we need to define the pharmacological activities of drugs more carefully (i.e., with regard to some of these newer developments that you stated). In parallel, when you are recruiting patients into your studies, they should be selected according to their demonstration of a particular finding, which suggests they will respond best to the pharmacological agent that affects that parameter.

Dr. Lipicky: It's unusual for someone other than us to raise the issue of dose, but clearly there is a problem. The available data suggest that, with vesnarinone, the less you are on, the better and there might be some dose of vesnarinone that produces a net benefit. There may be many drugs studied that have been ruled out as being useful either because they were studied incorrectly or patients were selected incorrectly or because the right dose was not studied. It could be that at some other dose these drugs would not only make people feel better, but live longer. Wide dose ranges, at least four logarithmically changing factors of two, belong in all trials. They belong in morbidity and mortality trials. There ought to be significantly smaller doses than one thinks would work and significantly higher doses than what one thinks would work.

Dr. Borer: To illustrate the potential importance of what you are saying I will present briefly again some of the work that I mentioned on cardiac fibroblast survival with vesnarinone. The dose that maximally suppressed fibroblast growth was an order of magnitude lower than the dose which is commonly used clinically and

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when the dose was increased to the dose that is commonly used clinically the effect was lost in normal cells, though it was moderately retained in fibroblasts from volume-loaded hearts. By extrapolation, it is conceivable that what we think of as a very beneficial effect of suppression of pathological fibrosis is not seen at the dose that was used clinically. It is possible that, had one gone to a lower dose than the doses used clinically, one might have seen benefit without the toxic membrane effects.

Dr. Somberg: I can't resist but to play devil's advocate for a minute here. While I agree with you, Ray, and I am a strong supporter of your emphasis on dose finding and looking at a wide dose range. I also have to say that I do not know of a case of an inotropic agent or an ACE inhibitor where we know the correct dose to this day. Dose hasn't been worked out well, despite claims of a flat dose response curve for the ACE.

In fact, in studies with one failed compound, exploring a lower dose was not helpful. Dose ranging is a very good concept, but do you have proof that looking at dose range in a heart failure population actually would have distinguished an effective dose from the other doses that are toxic?

Dr. Lipicky: Absolutely none, nor do you that selecting patients properly would be useful.

Dr. Somberg: Yes, that is certainly true.

Dr. Lipicky: I have no evidence at all. We have been relatively unsuccessful in convincing anybody to study more than one dose. Still, even from a financial perspective, there is benefit in studying multiple doses since only one dose is such a great gamble.

Dr. Somberg: But even when the one dose failed with vesnarinone and a lower dose was looked, or with milrinone at a lower dose, no therapeutic benefit could be found. Unfortunately, for some classes of drug it has been unrewarding to explore the dose response. It has not been productive, while not exploring the dose response with ACE inhibitors and beta-blockers has yielded acceptable results.

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Dr. Lipicky: That is a yes and no statement. The ACE inhibitors have explored a maximally tolerated dose in all of their trials, so that, in fact, dose was evaluated, but it was the maximally tolerated dose and it turns out that for ACE inhibitors, that seems to be a good deal.

Dr. Somberg: I don't necessarily agree with you in that. In the SAVE study of enalapril there is a target dose. Some people reach the target, others don't.

Dr. Lipicky: That was the biggest dose you could legally prescribe.

Dr. Somberg: Legally is the operational word here: 20 mg of enalapril may not be optimum.

Dr. Lipicky: It was the biggest dose that was in the approved usage.

Dr. Somberg: Yes, but that's not the maximum tolerated dose clinically.

Dr. Lipicky: All people could not reach it. So in essence that study was the maximally tolerated dose for the group because everyone didn't get to the biggest dose, but they got to the biggest dose they could tolerate. That is true for all the ACE inhibitors. It turns out that beta-blockers are very much the same, and for one reason or another their maximally tolerated doses seem not to be unreasonable because, in fact, you can't get into too much trouble with an ACE inhibitor and can evaluate tolerance very well and the same thing is true with the beta-blocker. But with an antiarrhythmic or a class III or vesnarinone, it could be that people will tolerate high doses and you will not detect the fact that the dose is too high to optimize benefit.

Dr. Fenichel: I have two comments on that. First, there was an analysis at the AHA meetings earlier this fall in which someone evaluated enalapril doses in congestive heart failure and did essentially an E-Max model looking at the effect on mortality with dose, the effect increased progressively, with dose. The dose at which 90% of maximum effect was achieved was something like 100 mg of enalapril, which, of course, greatly exceeds the approved doses.

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The second thing is that certainly there are examples in this area of medicine, although perhaps not in congestive heart failure, of tolerated doses turning out to be bad. The best example is the thiazide diuretics. The wrong, excessively high, doses were used for a very long time, probably costing lives because of extremely high dose.

Dr. Borer: A sponsor raised concerns regarding the problems involved in doing a large trial with many of the new agents for patients with heart failure. The possibility of deleterious interactions with background therapy is, of course, one major potential problem. What is the way out? Let me propose again what I suggested earlier in a slightly different form. First, in a manner analogous to what was discussed this morning for thrombolytic agents, how about defining a statistically acceptable basis for an equivalency claim or employing a putative placebo value defined from prior CHF trials? Have the FDA or the European Regulatory Agencies considered the use of those kinds of analyses for approval of new drugs for heart failure?

Dr. Lipicky: I am glad you raised that problem. We had a little discussion at lunch about positive controlled trials. In our discussion, those involved in regulatory positions think of a positive controlled trial as valuable only if it can enable evaluation of the question as to whether, if placebo had been present, would placebo have been beaten? If that is the value of a positive controlled trial, one would pick the positive control agent on the basis of the availability of studies that show that for the endpoint to be measured, the control agent beats placebo. Since such studies would have been performed years ago, there may not be studies in more than one patient population for that same variable. If you listened to Dr. Fenichel's description of thrombolytic agents, the overall mortality rate from MI in the studies that were done varied a lot. For most agents, you have a single trial post-MI, and a single trial for preventing hospitalizations, each of those trials being reasonably convincing for that endpoint and that patient population but not overwhelmingly convincing. That is, in almost each of

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those circumstances, there was considerable controversy about whether those trials were convincing enough to support approval. Now, you are in the area of CHF and want to do a positive controlled trial, in essence, an equivalence trial. There isn't a positive control to pick from for which there are sufficient data to define a putative effect vs. placebo. So, on that basis, it would not be a good idea. One could always beat the positive control and gain approval. That's perfectly O.K. because anyone would be willing to accept that the positive control is not worse than placebo. Just because one couldn't beat placebo reproducibly (with positive control) does not mean that the positive control is *worse* than placebo. Therefore, one could do a positive, controlled trial for approval for CHF if one thinks that one has identified a drug that has a unique mechanism of action, or a unique population to study, such that the new drug would be superior to the positive control. But, the expectation would not be equivalence. The expectation would be to beat the positive control significantly.

Dr. Borer: I infer from what you said that there is no statistically acceptable basis for equivalency claims yet.

Dr. Lipicky: There is no scientific basis for it.

Dr. Borer: That is a unanimous opinion of all the regulators at the table because you all had lunch together. Is that correct? That it is not possible to achieve approval for another ACE inhibitor for congestive failure on the grounds of some kind of equivalence trial. There is also a consensus that this is a very unfortunate state of affairs. It is certainly possible that some new ACE inhibitor either will provide a medical advantage in some way, although certainly none of the others has distinguished itself for CHF thus far, or some new ACE inhibitor could be very much less costly, which would have immense public health importance. Our only path for approval would require a definitive trial which may no longer be possible.

Dr. Lipicky: When thrombolytics came along, in spite of the evidence that quickly developed, the European Community thought

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it was perfectly O.K. to keep doing placebo control trials. That's the source of the data base that provides a good opportunity to develop new thrombolytic agents. You did it last time, why can't you do it this time with thrombolytics, why can't you do it this time with ACE, for instance.

Dr. Singh: When you are studying the first drug for an indication where there is no existing treatment, it is easier to get through the review committee for a placebo-controlled study. Once you have established treatment for one or two or three ACE inhibitors, for the fourth one, to take it to the ethical committee and say that you want to conduct a placebo-controlled trial would be very difficult. I am certainly speaking for the United Kingdom, I don't know what the state of affairs is in other places, but in the U.K. a comparative controlled trial is acceptable.

Dr. Somberg: In developing an agent for the CHF indications one must progress stepwise to have a rational development program. One first has to establish the hemodynamic action of the agent. Then one selects a dose. In the case of ACE inhibitors, on the CONSENSUS I trial and the SOLVD studies are available and influence medical practices profoundly. To develop additional agents, the basis must be equivalency. We are fortunate to have trials confirming SOLVD. Still, I don't think placebo is possible. Wouldn't it be appropriate to establish that an ACE inhibitor provides quantitative responses within some predefined range of values and that it behaves according to expectations and is equivalent to other ACE inhibitors and thus should be approved on the basis of class effect?

Dr. Fenichel: There's no doubt in our minds that it was correct to approve enalapril for the treatment of congestive heart failure. There is also no doubt in our minds that it was a correct decision to approve disipramine for use in depression. Nevertheless, what we know of the tricyclic antidepressants is that they don't consistently beat placebo. They beat placebo enough to convince us that they work. They don't beat placebo in every trial. Consequently, a putative placebo-type trial for a new tricylic antidepressant or

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new antidepressant of some other kind, even using one of the tricyclics as the active control, is not feasible because we don't know where the placebo would fall. It is that sense in which we have said that the evidence for any particular ACE inhibitor in congestive failure is inadequate. It's not that it is inadequate to approve it, but inadequate to say in a confident way where placebo would fall if that ACE inhibitor were used in another trial with or without placebo in congestive heart failure. For that reason, the putative placebo construction is not something we can do for this group of drugs for CHF. It strikes us as socially unfortunate, but not intellectually unfortunate to say, on the one hand, that there is no way of ethically doing a trial that would meet regulatory standards. At the same time, it is not possible on the basis of what we know without such a trial to approve something. There are plenty of things in medicine that one might like to know and yet one must resign oneself to saying I will never know this. I will never know what the lifelong effect is of eating occasional asparagus. Maybe it decreases mortality by 5%? We will never know that. There are plenty of things that we don't know how to determine. It may very well be that there isn't any way of doing a trial to show that some new ACE inhibitor is more effective than placebo in the treatment of congestive heart failure, that it is not ethically possible to do any convincing trial. That is a little like saying it may be very difficult or perhaps impossible to do an antibiotic trial to show that some new antibiotic is better than chloramphenicol for H-flu meningitis. Maybe that's true. You can say that this problem is easy to solve, because you can approach the problem with in vitro studies and need not deal with an effect on people because, really, you are dealing with the effect on the bacilli. Even so, when you get right down to it, you must do a human trial and maybe that's just too bold. Maybe people are not going to volunteer. Some people might say chloramphenicol is good enough for me and I don't want to be possibly randomized to this other therapy. That doesn't strike us as being an intellectually difficult situation. That's just too bad. If the new agent comes along you may not be able to show that it is of value.

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Dr. Hoppe: I have a question for Ray. Did I understand you correctly to say that, in heart failure, no drug consistently beat placebo with regard to maximal exercise time?

Dr. Lipicky: Yes.

Dr. Hoppe: So why do you ask for it?

Dr. Lipicky: For the same reasons that one asks for information regarding drug effects on symptoms. No drug has reproducibly beat anything for symptom relief. For the same reason that one asks for measurements of ejection fraction: some drugs increase ejection fraction and some drugs don't change it. Whether they increase it or don't change it makes no difference to the regulatory decision. But one asks for it.

Dr. Hoppe: Several companies want to know what the drug may do.

Dr. Borer: Isn't it fair to say, though, Ray, that, in fact, by asking for all these characteristics to be defined you are expecting that several of them or most of them will at least move consistently in a beneficial direction if the drug actually works, even if they don't reproducibly reach statistically significant result. If you find one or two that are statistically significant for one drug and everything else sort of goes the same way, that provides a package suggesting drug-induced benefit.

Dr. Lipicky: Right, but it is indeed a nontrival question in the sense that usually it is recommended that sponsors should measure all these things, but a problem for statistical analysis of clinical trials is that one needs to have prospectively defined the principal endpoint. If one accepts this principle, then one has a major problem if one has picked the wrong thing: then, as the saying goes, ''You've spent all your alpha if you don't win,'' and then you can't even talk about the degree to which you have affected the other parameters because all of your precision is gone. It is a legitimate question that raises the problem of what a development program is going to look like. If you measure a large number of parameters and take the position that this was done to demonstrate the consistency of results, use that argument to convince people

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that the drug works, the conclusion may be disallowed by the statistical argument. I think the right thing to do is a few trials where you don't have a primary hypothesis at all, in which you just measure all the possible parameters. Based on those measurements, you can determine drug action.

Dr. Hoppe: This question is related to my concern with maximal exercise capacity because I have difficulty in believing that this endpoint is of value, that a patient with heart failure really needs improvement in maximal exercise capacity, and that it will be important or meaningful in the patient's life. Additionally, the correlation with maximal exercise is poor, for example, with quality-of-life measures. Additionally, morbidity endpoints or mortality are not very well associated with maximal exercise performance.

Dr. Lipicky: You're right. There isn't any question about that. So you would omit measuring exercise entirely?

Dr. Hoppe: Actually, it is a personal view and it can be questioned because there are not much data, but I think submaximal exercise may be much better associated with daily life of the patient. I think we should find out which test can best discriminate the different stages of severity of heart failure, a 9-minute or 12-minute test, and so on, and if it is practical to utilize to evaluate drug therapy. I think a submaximal exercise should be more clinically meaningful than maximal exercise performance.

Dr. Lipicky: That's fine. We don't tell people they have to measure maximal exercise they choose it. We accept any measure of exercise; a 6-minute walk is O.K. None of them turns out to be reproducible.

Dr. Somberg: For much of what we talk about, the science is not up to the needs for drug development. It is nice when you are going to put together a kit for your child and have all the tools present. When we are trying to develop a drug, we don't have all the tools. I believed that submaximal exercise is better, but there is a lot of question in the heart failure literature regarding the

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submaximal exercise test as an inadequate measure. Same patients can't perform the test—no endurance. For other people it is easier, and that may be an indicator that the test is of variable utility. I think one of the problems is we just don't know what to measure. Therefore, you could take Dr. Lipicky's suggestion and look at many parameters and tests. Another approach is to take a ''Peto-like'' approach where you just give a pill daily and then send a postcard back a year later, alive or not.

Dr. Borer: Let me suggest another way out of this dilemma. How about selecting populations in which the development of CHF and/or death is predictable and studying the drug for heart failure prevention in that population. What you are then going to request from a regulatory body is a new claim, that is, that the agent prevented something from happening in this population. Presumably, there is no treatment for the as yet nonexistent disease in this population. Therefore, I can study my new drug against placebo. What I prevented was congestive heart failure. Would it then be reasonable for me to infer that the drug is likely to be effective in treating for the manifestations of congestive heart failure so that I could give it to a population with known congestive heart failure for a few months and do short-term randomized withdrawal to placebo, thereby not exposing patients to drug for a long time, but perhaps demonstrating efficacy.

Dr. Lipicky: This is in a patient population that is new and that isn't known to have benefit. This is a way of getting around the background therapies.

Dr. Borer: The initial study would be in a population that is new. That is right.

Dr. Lipicky: That is perfectly reasonable, with one additional caveat. You'd want more than you say you want out of the study. There ought to be another treatment arm, in which ''you don't get the drug until you develop congestive heart failure, because you are doing two things at the same time. This is a perfectly reasonable way of finding that a drug was useful, and so placebo could be employed. But then you would want an indication for preventing

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heart failure. When should you start therapy? Age 6 months, 10 years, 35 years, etc. These considerations must be defined.

Dr. Borer: I would argue that when you start depends on the pathophysiology and natural history of the disease as it is currently understood.

Dr. Lipicky: That's O.K. You could suggest that you start it based on the same way you found the patients had the disease, for example, if they had mitral valve disease, but that is not the relevant issue. The important consideration is that you must have some way of describing the patients for whom a problem needs to be prevented. Right? That you should indeed prevent as opposed to wait for the first sign and then treat it. It could be that you are just as well off waiting until some sign or symptom of heart failure occurs and then treating with the drug as opposed to having a year or two, or however long it would be, on preventive therapy. That distinction has to be made in the trial. But that is a perfectly good way of trying to get to use placebo in order to make the difference from placebo.

Dr. Borer: If you took a population without heart failure (neglect for a moment the additional arm you suggested) and you showed that your agent could significantly retard the development of heart failure compared with the placebo, might it then be reasonable to take a population with heart failure and give the new drug, instead of some standard therapy or in addition to some, but not all, standard therapies, for a short enough period so that it would be acceptable to an IRB, even as short as 2 weeks, and then withdraw the drug randomly to placebo? You could measure anything you want to measure, exercise tolerance, symptom status, all the things we were talking about, and show that, in the short term, the drug is effective treatment for heart failure after you have shown long term that it prevents development of heart failure.

Dr. Lipicky: Could be. You wouldn't rule that out. If one looks at prior experience in CHF, the probability of detecting a drug effect in the short term is not very high. Most agents that have been shown to work take months to differentiate themselves from pla-

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cebo. The most convincing evidence that exists is based on hospitalizations. There you are talking about years of study, so if you could develop evidence that it was effective with any of the conventional measures that would be pretty interesting. I wouldn't think it likely that with just short-term exposure, one could reach a meaningful conclusion, let alone a positive one.

Dr. Borer: What about the final proposal, to define physiological surrogates? You noted heart size as one of the measures of antifailure efficacy, as opposed to reduction in mortality. What if you employed a composite endpoint, one which, for example, included mortality, hospitalizations, and reduction in heart size and you were able to show a significant reduction in heart size and an overall significant reduction in the endpoints you put together, but the mortality and morbidity alone weren't significantly reduced. How would you judge such a trial?

Dr. Lipicky: With great difficulty.

Dr. Borer: Yes. Is there any situation in which you could foresee employing one of the physiological measures we now use, like heart size, as a surrogate for a clinically important endpoint?

Dr. Lipicky: No.

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II

DEVELOPMENT OF ANTIHYPERTENSIVE THERAPY

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Antihypertensive Clinical Trials

Raymond John Lipicky

The following comments should be taken neither as formal Agency policy nor as guidance. They are offered here only for the purpose of eliciting questions during the following discussion period, since assertions are incompletely developed and problems related to drug development programs are only partially identified.

The basis for approval of antihypertensive drugs is lowering blood pressure (i.e., approval is based simply on the pharmacodynamic effect of the drug, taken as a surrogate of clinical efficacy). The results of many placebo-controlled clinical trials that measured morbidity and mortality and involved many different specific drugs, dosing regimens, and combination therapies over many pharmacological classes give a basis for this surrogate. Each study documented decreased morbidity and/or mortality associated with reduction of blood pressure, compared to placebo. When the results of these studies are combined with epidemiological evidence, blood pressure reduction is a very reasonable surrogate for clinical efficacy.

The development program which we usually find reasonable consists of randomized, placebo-controlled, parallel dose ranging trials that measure only blood pressure as the primary endpoint. We strongly recommend a factorial trial when both the new drug as well as an approved drug are each studied and their effects are evaluated as a function of the dose of each. The dose range we recommended (not always followed) for such studies is a range of about one-hundredfold from the

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lowest dose. Accumulated data show that the largest dose studied (of each agent alone or the largest dose of each together) has a larger effect than the next lowest dose and that there frequently are no dose-limiting side effects even with the hundredfold range. Therefore, for most (but not all) of the new antihypertensives, the upper limit on dose becomes simply the largest quantity of drug that can be put into a convenient tablet or capsule and actually has nothing to do with the pharmacodynamics of the drug or its effects on the body.

Our suggestion is that the duration of such trials be about 2 months, but this is totally arbitrary; 1 month or 3 months would also suffice. Ordinarily, by 1 month patients are pretty well at (or beyond) steady state with respect to their blood pressure response to drug or placebo, as best as we can tell without formal analysis. We continue to recommend 2 months or longer because other drug effects on blood pressure sometimes become apparent (e.g., hepatotoxicity), as time of exposure to drug becomes longer.

A program that includes both (1) one randomized, placebo-controlled, dose-ranging, parallel group design, trial involving only the new drug and (2) one randomized, placebo-controlled, factorial trial involving the new drug and an approved product, can gain two approvals (i.e., approval of the new chemical entity drug product and approval of a fixed-dose, combination product). It is important to recognize that antihypertensives are used in combination and to recognize that the smallest unit dose of the new chemical entity to be marketed ought to take into account the dose response when it is used in combination with something else. The information that comes from a properly designed factorial trial can provide a rational basis for deciding upon the smallest unit dose of the new chemical entity that would be marketed, even in the absence of a desire to develop a fixed-dose combination product.

When considering the smallest unit dose to be marketed, it seems appropriate to recognize that there can be unusual sensitivity in some populations which requires starting therapy at a lower than ''usual'' dose in that population (e.g., agents that affect the renin angiotensin system in patients with unilateral renal artery stenosis). It seems apparent that the decision of what doses to market requires well-defined dose-response information in a few populations, both when the drug is used alone and in combination with other antihypertensives.

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The reason that the design of trials in different phases will not be discussed (phase I, phase II, phase III) is that this construct generally has become inapplicable, especially in hypertension. There should be a very special reason to justify studies of antihypertensive drugs (and of almost any other drug) in normal volunteers. Ordinary and nonpurposeful use of normal volunteers appears to be senseless. For antihypertensive drugs, the trials that form the basis for approval are dose-ranging trials. Ordinarily such trials are considered ''phase II.'' When one has already determined that a drug has dose-related antihypertensive effects, and that the effect is maintained over a reasonable period, it is not necessary to redundantly confirm the same thing in some additional ''efficacy trial.''

Simply from a ''safety'' point of view, in the neighborhood of 2000 patients must be studied in randomized, controlled trials in order to identify adverse reactions that occur with a frequency of about 1 to 2 per 500 patients exposed. It is difficult to see the wisdom in approving a new chemical entity when many fewer than 2000 patients are exposed for a reasonable period of time *if* the new chemical entity is intended to be used over a lifetime by millions of essentially healthy individuals.

The important question is **not** ''is the drug an antihypertensive in humans'' (i.e., does it beat placebo)? After the drug has been identified as an antihypertensive in animals, one should be able to answer the question ''is it antihypertensive in humans'' in as few as two or three patients. The issue that needs to be considered is how to apportion the 2000 patients to randomized, controlled trials that will adequately define the following parameters: (1) dose response; (2) how dose response might be effected by other medication, age, sex, race; (3) time-action relationships; (4) pharmacodynamics; (5) pharmacokinetics; and/or (6) the relationship of the severity of hypertension to the response to the drug. In my mind, these seem to be the important questions to address.

The goals of an antihypertensive drug development program need to be rethought. The trial design and allocation of patients should be oriented toward answering the six questions outlined in the above paragraph, or others that I have not mentioned above. The goal of a development program no longer should be, ''can the new chemical entity beat

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placebo'' nor should trial design be based upon the notions connoted by phase I, phase II, or phase III terminology.

Professional societies that make recommendations regarding treatment regimens generally advocate that drugs and/or treatment regimens used to treat hypertension should be guided principally from the results of randomized, placebo-controlled trials that have demonstrated morbidity/mortality benefits. It seems reasonably clear that in studies as currently done, there is no chance of learning anything about effects on morbidity or mortality. For amplification of this point, in an ongoing division retrospective analysis of antihypertensive clinical trials, out of 31,885 randomized patients there were a total of 22 deaths, 29 myocardial infarctions, 20 episodes of congestive heart failure, 21 strokes, and 51 arrhythmias (for a total of 143 events, a total incidence of about 0.45%). Yet, most recent and current development programs for antihypertensives involve only 1000 to 3000 patients and the complaint is that this is too large a ''burden.'' As a consequence, there is increasing concern over the fact that a surrogate is relied on for approval.

Finally, we (as a divsion) are actively developing new data that may address two additional issues. First, regardless of the relative importance one might give to placebo in new antihypertensive drug trial design, it is not clear to us why there is objection to the use of placebo in short-term antihypertensive trials. We have spent about 12 person/months in a review of the literature and have found no clear evidence that short-term elevations in blood pressure are associated with measurable and documented untoward events. There are anecdotes of harm, but nothing well documented and no controlled trials aimed at answering that question. Although there is no question that chronic elevations of blood pressure are not a good thing, results of randomized controlled trials demonstrate this finding and form the basis of our acceptance of lowering blood pressure as a surrogate for clinical benefit. To further evaluate the consequences of short-term blood pressure control, we are in the process of reviewing all deaths and dropouts in all antihypertensive, placebo-controlled trials that have come to us through NDAs and NDA supplements. Data as abstracted from original case report forms are being double-entered into a data base, and any data entry differences are resolved by committee. The above cited 0.45% incidence of

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serious adverse effects came from a preliminary look at total events from this data base.

The second comment is related to methods of estimating drug effect if eliminating placebo in antihypertensive drug development trials should become necessary. One consequence of eliminating placebo would be that the magnitude of drug effect would not be determinable, since it is already well documented that office cuff blood pressure is decreased (sometimes as much as 8 mm Hg) by placebo during the course of a trial. The ambulatory blood pressure monitoring (ABPM) literature claims that ABPM data do not exhibit placebo effects. Should this be true when the ''universe'' is analyzed, one could still preserve measurement of the magnitude of drug effect, even in the absence of a parallel placebo arm. To evaluate this claim, we have collected all the ambulatory blood pressure monitoring data from all placebo-controlled trials submitted to the division through 1994. The data have come from the pharmaceutical industry. We are in the process of attempting to decide, among other things, whether one can detect a placebo effect in ABPM data. This effort is being undertaken under a Cooperative Research and Development Agreement (CRADA) with Medifacts, Ltd., and has established a cooperative undertaking between industry, a nonpharmaceutical private corporation, and the government. We expect to provide some preliminary analyses by mid-1998.

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Calcium Channel Blockers: Safety Issues

Jeffrey S. Borer

The safety of calcium channel blockers has become a prominent concern in cardiovascular therapeutics during the past 2 years. This group of relatively disparate drugs has been subjected to considerable scientific and public debate. The character of this debate can be instructive regarding the basis of defining safety from data available during and after drug development. Exploration of that issue must begin with consideration of the type of evidence needed to support one or another claim about drug action. In addition, one salutary result of the public debate about the calcium channel blocking drugs is that several large data bases have been reviewed and new knowledge has been created. This needs to be evaluated in drawing conclusions about the appropriateness of treatment with calcium channel blockers. The following discussion aims to clarify the bases of decision making and to evaluate the information available to support conclusions.

To achieve these aims, the presentation will focus primarily on three questions: first, is there a problem relating to calcium channel blocking drugs? If so, what is it? Second, what is the magnitude of this problem, if it exists? Finally, can we identify and evaluate any confounding influences? To answer these questions, reference will be made to the same studies I reviewed as a Consultant to the FDA Cardio-Renal Advisory Committee for the Committee Meeting on the appro-

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priateness of relabeling calcium channel blockers. These data came almost exclusively from randomized clinical trials. I will generally ignore the results of observational studies and meta-analyses, although I will review some newer data, as well, where they can be instructive, even if not from formal trials.

Different types of studies can be valuable in drug development and in the debate about safety. The types of studies that caused the debate about calcium channel blockers largely were not randomized clinical trials, but rather primarily were observational studies. Observational studies can be designed in two forms. They can be cohort studies, which, in turn, can be prospective or retrospective. They can be case-controlled studies, which by definition must be retrospective. The great value of observational studies is that they can highlight potential therapeutic effects or potential safety problems. In fact, that is why they are performed. It is likely that most observational studies are not likely published unless they highlight a good effect or a bad effect. Likelihood of publication may be directly related to the magnitude of the effect observed. This is a manifestation of what is called ''publication bias,'' and is one of the reasons why observational studies really can't serve as the only basis for drawing conclusions about drug actions. Observational studies may detect and amplify unexpected but real effects. However, several potential confounding biases are inherent in observational studies. Moreover, because of these biases and because of the unexpected nature of some of the results, observational studies are considered really convincing only if the observed effect is fairly striking. This is another reason why observational studies may not be published: nobody believes them unless the effect is striking, and this is a bias, as well. In fact, statisticians and epidemiologists have suggested that, to be convincing, an observational study should show a relative effect (drug vs. its comparator) of $>2:1$; 1.5–2:1 may be a gray zone. In addition, the putative effect should be statistically significant at the .05 level or better by a two-tailed test. The study that triggered the most recent debate about calcium channel blockers was from the Puget Sound Health Group near Seattle, Washington. That retrospective observational study highlighted a relative adverse effect of 1.32:1, not 1.5:1 or 2:1. Nonetheless, observational studies, even if less than compelling, can generate reasonable hypotheses.

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Clinical trials are the result of prespecified hypotheses, often developed from the outcome of observational studies. By definition, clinical trials are prospective, controlled either with placebo or active agent; they can be randomized and/or blinded. For statistically acceptable hypothesis testing, analysis of the data should be prespecified, though post hoc (i.e., retrospective) analysis of the prospectively collected data can generate additional hypotheses and may be sufficiently convincing to influence clinical practice. (This form of analysis seldom is acceptable as a basis for drug approval.)

The clinical trial can test hypotheses generated by observational studies; an additional advantage of the clinical trial over the observational study is that it can precisely define the magnitude of a drug effect. The larger the trial, the more precise the definition will be. (This really can't be done with an observational study.) The clinical trial is convincing if it is statistically significant. For purposes of drug approval, it must also be replicable; in other words, at least two such trials generally are needed to support drug approval. For approvability, the drug needs to evidence an effect, of any magnitude, that is not due to chance alone, as demonstrated by the statistically significant clinical trial result. The clinical trial can suggest, but cannot detect, unexpected effects because, by definition, a clinical trial cannot be performed without a prespecified hypothesis. If an effect was not expected, there would not be a hypothesis that it would occur and the trial would not be designed to measure it. If something unexpected is detected, another trial must be performed to ascertain that the outcome is real.

Another type of analysis that can be useful in evaluating a drug is the so-called meta-analysis, which is a summation of similarly controlled clinical trials. This type of study also can test hypotheses generated by observational studies, but there are some important limitations. Meta-analyses generally are considered to be convincing if they are highly statistically significant (i.e., if the p value is <0.01, or better, not $p < 0.05$). What are the limitations? The most obvious of course, is that no two clinical trials are exactly alike in patient selection, study duration, and various ancillary characteristics. If they are not really identical, it is not truly possible to combine them convincingly. In addition, if you sum all published controlled clinical trials in any area, it is obvious that the result will be most affected by the largest trial. If

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one study involves 5000 patients and five involve 20 patients each, the 5000-patient study will impact on the meta-analysis overwhelmingly, while the other trials will have considerably less impact and, because of their relative statistical instability, they may actually obscure rather than clarify the primary conclusion of the analysis. The addition of similarly controlled clinical trials presupposes that the characteristics of the trials are well understood, and that all relevant published trials are included in the analysis. That means you must have looked at them. This is a daunting task. The abstracting agencies do not necessarily include all of them. There is also the problem of finding articles published in different or even obscure languages. When the FDA reviewed calcium channel blockers, a meta-analysis of calcium channel blocker data was presented which included data available in five languages. I do not know if the authors managed to unearth all studies available in those languages, and five may not have covered the field. Therefore, it is possible that the calcium channel blocker meta-analysis may have missed some trials. However, if all trials are not included, then the meta-analysis can be biased. In addition, since positive findings are more likely to be published than negative findings, another potential bias must be considered.

These, then, are the three types of trials. Information can be obtained from all of them, though the information is of different kinds. All are important in drug development and evaluation, but their differences dictate that the conclusions drawn from them are different.

Calcium channel blockers are not a class but, rather, several groups of molecules that have at least one common feature (i.e., they affect the activity of calcium channels in physiological membranes). Other important characteristics often differ among calcium channel blockers, which precludes considering them as a class, according to the usual definition. Therefore, in reviewing the clinical trials data, three prototypes will be considered separately: (1) nifedipine and other dihydropyridines; (2) verapamil; and (3) diltiazem. The data within each group will be categorized according to specific diseases.

The dihydropyridines have been studied in clinical trials in patients with unstable angina and acute myocardial infarction. As we review the data, the most important observation may not relate to the available results, but rather to the paucity of data in most areas of inter-

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est. Most of the questions to which we seek answers never have been studied; some, if studied, were not published; and some, if published, did not make it into the review, which was not done in five languages. The largest of the dihydropyridine studies in patients with unstable angina or myocardial infarction was the so-called TRENT Study from England. Short-acting nifedipine was employed in this trial, which involved almost 4500 patients; there was a 28-day follow-up on therapy. Therapy was begun within 24 h of the onset of the event. The TRENT Study reveals a tendency toward a small mortality excess associated with short-acting nifedipine when drug is given within 24 h of the event. However, in magnitude, mortality rate was 6% greater on nifedipine compared with placebo. The difference did not reach statistical significance (i.e., it cannot be inferred confidently that the result was a consequence of any factor other than chance); moreover, the magnitude of the difference is not nearly comparable to that suggested by the Psaty study from Puget Sound, though the latter was performed in a different population for a different indication (hypertension, for which, of course, the drug never has been approved in the U.S.). Moreover, because of trials like TRENT, short-acting nifedipine never was approved for unstable angina or acute MI in the U.S.

The TRENT study is the largest in this disease area and the result is likely to be more stable statistically than that of some of the smaller studies. Nonetheless, qualitatively, the TRENT study is very similar to all other studies available in this area. Two studies (SPRINT I and II) were done in Israel. The first suggested a small mortality excess when nifedipine was used, but that excess seemed to be in patients who were given the drug early after infarction. Therefore, in a second study, the drug was not administered until at least a week after myocardial infarction, and the results were modestly different. A variety of statistical adjustments were undertaken in the two studies. However, regardless of adjustments, it is clear that short-acting nifedipine conferred no benefit on patients with acute MI or unstable angina in these studies. The other randomized trials provided results consistent with those of the TRENT and SPRINT. Nonetheless, some intriguing findings resulted from specific analyses. For example, in the Dutch HINT study, patients who received a beta-blocker, in this case, metoprolol, did better than on placebo. If nifedipine was added to the beta-blocker, the results tended

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to improve, though the difference hardly was significant. The clear and obvious conclusion from all these trials is that when short-acting nifedipine is administered to patients with acute myocardial infarction or unstable coronary syndromes, no benefit can be expected, and harm may result. However, the latter inference is not supported by any statistically significant findings in the largest trial, in any of the other, smaller studies, or when these trials are considered as a group. Once again, of course, the drug never was approved in the U.S. for this indication.

In contrast, short-acting nifedipine is approved in the U.S. for prevention of chronic, stable angina pectoris. To put this in context, it is important to remember that, in 1982, when the drug was approved in the U.S. it was considered a ''breakthrough'' drug for treatment of patients with vasospastic angina. In the same NDA in which the vasospastic angina data were presented, approximately 60 patients with chronic stable effort angina were studied in short-term trials that demonstrated significant drug-induced improvement in exercise tolerance. Thus, the drug also was approved for chronic stable angina, although the NDA submission contained very few data by current standards. Similar studies since then add little relevant data. The largest body of information about the long-term effects of short-acting nifedipine in patients with chronic stable angina have resulted from trials measuring atherosclerosis progression, specifically, the INTACT study, in Germany, and a somewhat larger study done in Canada, not with nifedipine with nicardipine. Neither of those studies was designed to assess natural history endpoints. Neither was designed to look at angina. They were designed to assess atherosclerosis progression. They were clinical trials. If a clinical trial is designed to assess atherosclerosis progression and something unexpected, like higher mortality, is found in people on drug than on placebo, it is necessary to study the findings that were unexpected in a clinical trial in order to draw a firm conclusion about cause and effect. This statistical nuance notwithstanding, both of these trials suggested that more events occurred in people on the dihydropyridine, whether short-acting nifedipine or short-acting nicardipine, than on placebo. Two other small clinical trials of the dihydropyridines, nicardipine and nisoldipine, employed crossover designs to evaluate antianginal efficacy and reported clustering of events while the patients were on active drug as compared with placebo. It is very difficult to

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evaluate these observations because of the possibility of carryover effects due to the crossover design. However, when all these results are taken together, they suggest that, among patients with chronic stable ischemic heart disease, short-acting nifedipines generally are antianginal, but may cause a problem. It may cause some people to have angina and it may even cause some to have acute events. Firm conclusions cannot be drawn, though, because study designs were inadequate to support rigorous judgments, numbers of patients studied were small, different drugs were employed, etc. Moreover, none of the available data are sufficient to permit evaluation of the magnitude of the problem, if indeed a problem exists.

Next, we will consider hypertension, perhaps not totally appropriately since the drug never was approved for the treatment of either chronic hypertension, hypertensive emergencies, or so-called (but never rigorously defined) ''hypertensive urgencies.'' However, one randomized clinical trial of a dihydropyridine is available; this assessed the effects of isradipine in hypertensive patients. However, isradipine was not compared with a placebo, but with a diuretic, and the prespecified primary dependent variable was not blood pressure or clinical events, but rather carotid atherosclerosis progression. This study showed a decided excess of cardiovascular events in the people on isradipine as compared with people on thiazide diuretic. However, what were these events? Two deaths occurred in one group and two in the other group. The myocardial infarctions also were virtually equal. Cardiovascular deaths were few and equal. The difference was in new angina. More people on isradipine had new angina than did people on thiazide diuretic. This may or may not constitute a reason to avoid use of a short-acting dihydropyridines, but these are the data. This study, the MIDAS trial, has received considerable attention but really did not show an excess of deaths or myocardial infarctions in either group.

One other study in hypertensive patients requires consideration. It has several potential design flaws, but is quite large and may be instructive. Certainly, at the very least, it is hypothesis-generating. The study in question is the STONIE Heart trial, performed in Shanghai, which recently was published in the *Journal of Hypertension,* although it was performed several years ago. The study involved more than 1600 elderly Chinese hypertensive patients. The trial was not randomized;

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assignment of therapy was alternated, providing potential for bias in selection of patients who are given active therapy or no therapy. In addition, if the calcium channel blocking drug under study did not reduce blood pressure to the target, other drugs could be added. Finally, if hypertension was severe (>115 mm Hg diastolic), patients were neither alternated nor randomized, but were mandated to active therapy because of ethical concerns. Thus, study design flaws limit confidence in conclusions drawn from this trial. However, the placebo group and the therapy group were very well matched for baseline characteristics when these were analyzed. Moreover, the results of this study were extraordinarily striking: cardiovascular event rate was far lower in the treated patients than among those receiving placebo, with a p value <0.0001 for most events. What was the calcium channel blocker? It was long-acting nifedipine, not short-acting nifedipine. The relative segregation of events was approximately 2.5 to 1 greater in the placebo than in the treated group. Therefore, even if considered an observational study, the STONE Heart trial would be relatively compelling as a basis for hypothesizing that the long-acting nifedipine is useful in preventing events in hypertensive patients.

The findings with verapamil differ from those with the short-acting dihydropyridines, but there are far fewer data to review. The findings with verapamil generally suggest event-reducing benefit. In patients with acute coronary syndromes, the results are strikingly different from those reported for nifedipine. Two large studies provide the bulk of the data. Both are from Denmark (DAVIT I and DAVIT II). In DAVIT I, more than 1400 patients were studied. In DAVIT II, even more were evaluated. The studies differed in the time at which therapy was given after acute infarction because DAVIT I suggested problems with early administration, but not problems with late administration. DAVIT II was designed to administer drug 7 to 14 days after infarction, rather than within the first week. Overall, DAVIT I suggested that verapamil might provide benefit. DAVIT II revealed a statistically significant reduction in cardiovascular events (death and reinfarction) when the drug was given at least a week after infarction. The magnitude of the verapamil-induced reduction was 20% when compared with placebo. There were several post hoc subanalyses. Since they were not prespecified, the firmness of conclusions is not as great

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as for the primary conclusion, and would have no regulatory standing. Nonetheless, the data suggested minimally greater risk when drug was given to people who developed heart failure during their acute myocardial infarction. This result was not statistically significant. There was a much stronger suggestion of benefit from the drug when it was given to people who were hypertensive at the time of their infarction. People with hypertension and infarction did particularly well when drug was given. No analysis was performed to define relative outcome in patients who were not hypertensive.

Very few data are available about the effect of verapamil in chronic stable angina. There are no primary prevention studies. One randomized trial is available in patients who underwent coronary angioplasty and were studied to assess drug effect or restenosis rate. This was a placebo-controlled, randomized trial and it showed a drug-related benefit. A breakdown of specific event rates was not reported, so it is not possible to isolate cardiovascular events. However, restenosis occurred significantly less frequently in patients with unstable angina who were given verapamil than in people with unstable angina who were given placebo prior to angioplasty. While this apparent benefit may be important clinically, it does not permit firm conclusions about the safety of verapamil in patients with chronic stable angina, or any other cardiovascular disease, for which rigorous evaluation has not been undertaken.

From this review, it should be apparent how few data are available to guide conclusions regarding the safety of verapamil. No data are available regarding patients with chronic stable angina. Debate has been triggered by observational studies that are largely unsupported by clinical trials. Diltiazem is the third prototype calcium channel blocker. It is very popular for use in patients with unstable angina and acute myocardial infarction. In one recent study published in *Lancet*, 129 patients received i.v. diltiazem as soon as possible after hospitalization for unstable angina. During a 48-h follow-up, the combination of recurrent unstable angina or myocardial infarction was significantly lower on diltiazem than on placebo. This supports the concept that intravenous diltiazem is useful in the setting of unstable angina. Two large clinical trials of oral diltiazem have involved patients with acute coronary syndromes. The first, smaller study was performed in patients with non-

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Q-wave myocardial infarctions, and may be relatively analogous to the unstable angina study in terms of the pathophysiology in the study population. The drug was given between 1 and 3 days after the infarction, and follow-up was 14 days. Recurrent myocardial infarctions and refractory angina were less frequent in the diltiazem-treated patients than in the placebo patients, but mortality was not significantly different in the two groups and, in fact, tended to be minimally higher on diltiazem than on placebo. This trial does not strongly support diltiazem therapy, but tends to be positive and was accepted as such clinically, though not by the FDA. A larger study was then undertaken, the MDPIT Study, in patients with myocardial infarction. Overall, the study revealed no drug effect on mortality or myocardial infarction. On post hoc analysis, there was a striking and statistically significant excess in mortality among patients who had congestive heart failure associated with infarction and a tendency toward fewer events in people who had hypertension. These findings were qualitatively similar to those seen with verapamil, although quantitatively different, but it is not reasonable to compare the two agents based on the fundamental similarity of the clinical trial designs because attention to the specific study protocols suggests potential differences in patient selection. Moreover, again, the diltiazem results in CHF and hypertension were analyzed post hoc, rendering them suboptimal as a basis for firm conclusions. Overall, these data suggest that, to define the utility of diltiazem for event reduction in populations with acute myocardial infarction or any subset thereof, another trial is needed to test the hypothesis that benefit will result. After review of all clinical trial data relating to verapamil, nifedipine and other dihydropyridines, and diltiazem, the strongest conclusion is that the data are inadequate for firm conclusions regarding most issues of interest. Certainly, no data suggest catastrophic results when these drugs are administered, although specific patient subgroups may have no likelihood of benefit, and some may suffer modest adverse event risk.

Fortunately, several trials now are ongoing, which may elucidate some of the issues requiring clarification. These trials largely are in patients with hypertension, which is, of course, the largest population at risk. However, most of the trials are not placebo-controlled, but are

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controlled with approved effective drugs, minimizing the potential for defining the magnitude of calcium channel blocker effect.

One additional safety consideration, the risk of cancer, requires discussion. As argued by one FDA consultant at the Advisory Meeting on labeling in 1996, calcium channel blockers block entry of calcium into cells; intracellular calcium appears to be necessary for apoptosis to occur; failure of apoptosis may facilitate cancer development by permitting unregulated cell division and proliferation; therefore blocking calcium entry into cells with calcium channel blockers may cause cancer. While this theory is attractive, it is, at best, tenuously if at all supported by experimental evidence. When available data bases were interrogated to seek clarifying evidence from clinical trials and observational studies, voluminous information was collected. It is beyond the scope of this discussion to present a detailed review of these data. However, a few observations may be helpful. Pahore and colleagues published two retrospective observational studies purporting to show that calcium channel blockers dramatically increase the risk of cancer. Further perusal of the literature reveals other, similar studies that reached opposite conclusions. The largest retrospective study, from Israel, involved more than 11,500 patients, half of whom received calcium channel blockers. This analysis revealed no difference between cancer incidence in patients treated with calcium channel blockers versus those patients treated with control agents and, similarly, revealed no difference in incidence of cardiovascular events. When the STONE Heart Study was evaluated retrospectively for cancer frequency, there were two events in the nifedipine group and eight events in the placebo group. That study involved a relatively long follow-up. These data suggest a risk ratio of 0.24 or 0.25 in favor of long-acting nifedipine. Perhaps long-acting nifedipine prevents cancer. As noted previously, the MIDAS trial showed more cardiovascular events in the isradapine-treated group, but less cancer was found in the isradipine group than in the thiazide group. Of course, there were far too few subjects for meaningful conclusions to be drawn. Do calcium channel blockers affect cancer incidence to a greater extent than other cardioactive drugs? In some studies, beta-blockers have been associated with a 1.5 to 2:1 risk of cancer compared with control agent. In the SOLVD trial, enala-

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pril was associated with a clear excess of cancers, 38 compared with 22 in the placebo group. Nonetheless, post hoc retrospective analyses of studies designed for other purposes are fraught with problems. In summary, calcium channel blockers may or may not be associated with an excess risk of cancer. Large clinical trials may not help very much in clarifying this issue because the number of events is relatively small; event rate is unlikely to be definitive, quantified in trials of the sizes now sought.

What conclusions can we draw?

1. When used as monotherapy, short-acting nifedipine, and perhaps other short-acting dihydropyridines, confer no event-reducing benefits in the setting of acute coronary syndromes. There may be a mortality risk exceeding that of placebo for these agents when used in this setting, although it appears that the risk, if it exists, probably is relatively small. Nonetheless, *there is no indication for the use of these drugs as monotherapy in this setting*. The drugs *never* have been approved in the U.S. for this purpose.
2. When used as monotherapy, some and perhaps all short-acting dihydropyridines may increase major ischemic event risk in patients treated for relief of chronic stable angina pectoris. The clinical trial data on this point are inconclusive. If excess risk exists, the magnitude of this effect really is not known. If such a detrimental effect exists, it would need to be balanced against any improvement in the quality of life attendant to angina relief. Therefore, it is necessary to know the extent of benefit to enable construction of the risk-to-benefit ratio. We do not have such data.
3. Finally, the effect of long-acting nifedipine is not yet known. However, at least from the STONE Heart Study and from the meta-analysis mentioned earlier, there is reason to retain the hypothesis that this dosage form may provide benefit in some settings, including chronic systemic hypertension.
4. Short-acting verapamil provides an event-reducing benefit when it is begun several weeks after myocardial infarction. This effect appears to be most marked in patients without

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heart failure, but with hypertension. Verapamil may reduce major ischemic event risk in other settings, most particularly after coronary angioplasty, but the data here are inconclusive. It is not appropriate to suggest that verapamil was indicated for this purpose.

5. Short-acting diltiazem may provide benefits similar to verapamil in patients with acute coronary syndromes, although the clinical trial data cannot support positive conclusions except in very highly circumscribed subgroups. No other event-reducing benefits have been associated with diltiazem.
6. In the setting of heart failure, there are even fewer data. There is the PRAISE Study of amlodipine, which for the group as a whole showed no benefit and no detriment, but has generated an important hypothesis regarding subgroup benefit. Amlodipine, a dyhydropiridine that is structurally different from nifedipine, is long-acting and provides neither benefit nor detriment when compared with placebo in patients with heart failure. However, in a post hoc analysis, patients with nonischemic heart failure had significantly lower rate of death than did patients on placebo. This finding led to generation of the ongoing PRAISE II study to test the hypothesis that amlodipine improves survival among patients with nonischemic CHF. Of potential importance is that in patients with ischemic disease and heart failure, no excess events occurred with amlodipine. Although not yet replicated, these results suggest that amlodipine may not be associated with adverse cardiovascular event risk when it is used for the indications of angina and/or hypertension. However, that is a ''leap of faith'' that may not be justified. Finally, several lines of evidence suggest potential for reduction in mortality risk when certain long-acting dihydropyridines are used in patients with heart failure of nonischemic origin, but a definitive trial is lacking.

More data are needed before definitive conclusions can be drawn. Therefore, it is not appropriate to suggest sweeping changes in calcium channel blocking drug use patterns from the available data.

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9
Panel Discussion

Dr. Borer (*Moderator*): It is important to define the terms ''hypertensive emergency'' and ''hypertensive urgency.''

Dr. Fenichel: In the U.S., off-label use of immediate-release nifedipine for hypertensive urgencies and emergencies is not infrequent. By hypertensive emergencies we mean evidence of on-going organ damage from uncontrolled or inadequately controlled high blood pressure. Such evidence includes depression of the normal state of consciousness, negative alteration in renal function, chest pain, papilledema, or some other abnormality indicating that critical end organs are jeopardized. To meet this definition, no specific cut point in blood pressure need be achieved, so long as blood pressure is abnormal: hypertension-induced organ injury or imminent threat of organ injury would suffice.

Urgency is high blood pressure sufficient in magnitude to bother physicians, which makes the physician very uncomfortable but nevertheless is not accompanied by evidence of organ damage.

Hypertensive emergencies are really quite unusual. I don't think there are any reliable incidence figures, so I will resort to anecdote: in 12 years of full-time emergency practice, I saw about 3 or 4. This is really not a common problem. Therefore, it is difficult to talk about defining a development program because it is hard to see how a controlled series of any kind could be established. Very few institutions will see very many cases. That being said, we can look at the drugs that are approved for hypertensive

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emergency. I think the only ones that are approved in the U.S. are sodium nitroprusside and i.v. labetalol. Intravenous hydralizine is also used, but I do not think that it is approved for this indication. Sodium nitroprusside is an old drug and was approved on the basis of what we would now regard as extremely limited evidence, actually anecdotal information, comprising uncontrolled trials in a very small number of patients, perhaps less than 30 patients, and everyone smiles and thinks of how implausible that is. If one had a drug whose claim was the cure of acute myelogenous leukemia and one gave it to five or six patients with histologically proven disease and all of them were alive at the end of a year, that would be all that is necessary to convince people the drug is effective, even without contemporaneous controls. That would be an utterly unprecedented result for a disease with a life expectancy of 6 weeks, and there would be no quarrel at all with approval. I don't anticipate that drug to appear, but the idea of approving something on the basis of a very few patients due to simply outstanding results that could not plausibly have arisen from chance is possible, although we would feel uncomfortable in most settings if nothing else were known about the drug. Having said that, it must be emphasized that what we know about the natural history of hypertensive crisis is very little. I think that when we look at ''hypertensive urgency,'' where people have equally high blood pressure as often is associated with hypertensive emergency (200/140, or whatever), one becomes very nervous. One somehow restrains oneself thinking, ''Well, this patient is perfectly comfortable, this blood pressure was discovered incidentally when he came in because of a laceration, or a twisted ankle, or whatever, and so I will use some ordinary means to alter blood pressure. I will just give the patient an oral agent that might be expected to work in ''a day or two,'' and, sure enough, the pressure comes down. It comes down before the drug could have done it. So many of these ''urgencies'' go away by themselves, but we don't know if that is true for hypertensive crisis. Certainly many cases of extreme high blood pressure do simply pass and that means that impressive effects are not easily allocated to drug in the absence of some sort of control. At the same time, it is a little bit like

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malignant ventricular arrhythmias. I don't know how to do a study in which one restrains oneself and allocates some people in that setting to placebo. It seems impossible. So I think it is one of those situations where one would either have to demonstrate a dose-response relation, or give mixtures of drugs. For example, with a titratable drug like sodium nitroprusside, one might design some sort of titration or double titration where you could alter each component independently and then demonstrate that, indeed, the freedom to titrate the new drug was as effective as the freedom to titrate sodium nitroprusside. That would be reassuring, but, as I have said, I don't know how good sodium nitroprusside is because this is not a situation in which the putative placebo has a fixed and known best possible effect. So it is very difficult, and we have not seen any submissions for some time. The question arises, as you might have surmised, as to what would constitute an appropriate drug development program for hypertensive crisis and I am not sure. It is really an orphan disease.

Dr. Somberg: I agree with what you've said, Bob, but one's view depends on where you work. Hypertensive crisis is not really an orphan disease. At Cook County Hospital in Chicago, a hypertensive crisis is seen several times per week. At the American Heart Association Scientific Session there was a luncheon panel on this issue and I was surprised at the different incidences between the north and south in the United States. The differences are considerable. The prevalence is far higher in the south, far higher among blacks than whites, far higher in rural populations than cities. Also it is very common to have this problem in Texas; it seems to be a Texas phenomenon! Some believe this has something to do with the consumption of salt. So I don't disagree with you, Bob, but my experience in suburban hospitals, or when I was in New York, was totally different than an experience in some place like Cook County. Also, there is hypertensive emergency and then there is hypertensive urgency. One of the things you have to ask is how the patient develops the emergency. Does he have chronic hypertension? I certainly agree that some people do present acutely. Some stop their medications and there is this intermediate group

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that includes people who don't feel right, have shortness of breath, are dizzy, have headaches. I used to think nothing of this group of hypertensives, but you do see patients with very high pressures and once they get treated they say they feel better. Then there is this intermediate group that has the high blood pressure and there is also the population that truly has chest pain, neurological sequelae, the true hypertensive emergency. If you can see papilledema, hemorrhages, etc., in the eye grounds, then the diagnosis for hypertensive emergency is made. Once a diagnosis is made, the question arises, how should you get the blood pressure down? Should you lower the blood pressure just a little bit, just enough to attenuate the problem or can you do this better by a titratable drug? Often physicians use sublingual nifedipine, an off-label use. Some claim the drug is absorbed by the buccal route, but it is really swallowed and then absorbed. Is this therapy to be criticized because it brings down blood pressure with some rapidity? If I have someone lying on the table and they have crushing chest pain that goes to the back and they have unequal pulses and one hears an aortic insufficiency murmur, you may think of aortic dissection. Here, I would like to lower the blood pressure to 70 systolic and call the surgeons because I can't do anything more for that person at that moment. Rapid reduction in blood pressure is indicated. If you have somebody who is having a stroke, for instance, a thrombosis in the middle cerebral artery distribution, the question is what to do. I have seen arguments where neurologists want to leave the blood pressure alone, the cardiologists want to reduce it, and some specialists in stroke even talk of raising the pressure. These patients have all been lumped together, but in fact the group can be very different and no one approach is suited to a host of etiologies. Could one therapy be appropriate? What therapy should be used? These are important issues. I must say I tend to like to use i.v. nitroglycerin because its effects on blood pressure are mild. Most of my patients have ischemic heart disease so one can use nitroglycerin for this condition. Nitroglycerin i.v. does not have the toxicity that nitroprusside possesses, especially with prolonged use of nitroprusside.

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Dr. Fenichel: I would like to just say a couple of things about that. First of all, there is another drug which is approved for hypertensive crisis that I forgot to mention. That is diazoxide. It is not very popular anymore. Two other points are worth raising. One, the argument against, and the recommendation in current U.S. labeling against, the use of immediate-release nifedipine for hypertensive crisis is not that it lowers the blood pressure very abruptly. With luck, it may not be any more abrupt than the effect achieved with sodium nitroprusside or one of the other intravenous agents, or nitroglycerin for that matter. The argument against it is that on relatively infrequent occasions, surely fewer than 10% of situations in which it is used, in patients with extremely high blood pressure who have reflexly shut down all of their counter-regulatory mechanisms, nifedipine will drop the blood pressure not too fast, but too low, to levels from which, because of the shutdown of all the counter-regulatory mechanisms, viable blood pressure cannot be easily retrieved. It is essentially a total peripheral vascular collapse, possibly similar to endotoxemia, and some of those patients will die, have strokes, MIs, or other hypotensive sequelae. It is not really a matter of rate, it is a matter of extent and control. One is unable to retrieve what one has done in the very nice way that one can retrieve it with rapid-acting intravenous agents with short time-action curves.

The drugs to use for major hemodynamic meddling with the patient are optimally the shortest acting drugs you can find, whether you are trying to raise the blood pressure or lower it, because when you don't know the effect of your actions on hemodynamics, you don't know where you are going, and the way to proceed is to feel one's way and to be able to retreat. That's why nitroglycerin is attractive, sodium nitroprusside is attractive, in the other direction dopamine is attractive, and even epinephrine. The idea is, if you don't like it, turn it off. You can do that with these agents, but not diazoxide, hydralazine, nifedipine, etc.

Dr. Singh: I thought I understood most of the hypertensive states, but I am a little confused with two things. One is the terminology.

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If you are going to conduct a trial, are we saying the same thing when we use the terms hypertensive crisis, hypertensive emergency, hypertensive urgency, or malignant hypertension? Are they different entities or are they the same thing? That is the first point. The second point is that I have not seen any drug that has been licensed directly for hypertensive urgency. What I am talking about is the patient with blood pressure of 230/130, who is otherwise fine. These are patients for whom I would be worried if I was the attending clinician. A second category that requires urgent treatment is toxemia of pregnancy. How to conduct a trial in those groups, I do not know. I cannot answer that question straight away, but I would say a placebo-controlled study is almost impossible.

Dr. Fenichel: I think the asymptomatic 230/130 patient would be a good example of what most people would say is a hypertensive urgency. That is a misleading term because it is not known that it is urgent to reduce that blood pressure. It is known on epidemiological grounds that this blood pressure, untreated, carries with it a 1-year mortality which probably is 50% or something on that order, but I'm not sure 24-h mortality has been defined, or is a quantitatively important concern. The fact that the patient is asymptomatic means that, in general, the patient who suddenly shows up with that blood pressure may very well have had that blood pressure for days or weeks or months. The pace of disease may well define the optimal or necessary rate of treatment. It is plausible that, in many patients, the pace of disease is quite slow. So yes, I think the urgency is much more common than emergency and it is a situation in which placebo-controlled trials are quite plausible.

Dr. Shah: I agree with most of the sentiments that have been expressed. It is quite correct that we see hypertensive emergency very rarely now because patients are encouraged to go to practitioners and have their blood pressures checked, so most people would receive treatment when they are in the mild-to-moderate state. Situations in which we would expect to see hypertensive emergencies would be pregnancy, pheochromocytoma, and a few

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related problems, and I know that diazoxide has been approved for use in hypertensive emergency.

We have not formulated requirements for such drugs. Nonetheless, our Advisory Committee would consider data generated following compassionate use, the numbers of patients studied would not be so critical for us, so determination of labeling requirements could be made if efficacy demonstrated by manufacturers. For now, it would be easier for me to give you my perspective of what are the ideal requirements of a drug for such purposes. My colleagues referred to nitroprusside, but I personally have had a nasty experience in a single patient who died of cyanide toxicity simply because of the lack of enzymes that are responsible for metabolizing the thiocynate. Also, nitroprusside is subject to tolerance and the tolerance develops quite easily if you give it too often. The drug that I would choose would lack tolerance, and would have a fairly low e_{max} in the dose-response curve, a fairly shallow dose-response curve, so if you give too much there is no risk of excessive hypotension, as we see with the short-acting nifedipine.

Dr. Lipicky: The opinions I've heard thus far sound like they've come from doctors, not regulators. I think the rules are the same in severe hypertension as in any other form. The basis for approval is a decrease in blood pressure. I don't think it is necessary to prove that decreasing blood pressure in people with very high blood pressure has a clinical benefit, but merely that one can reduce blood pressure. The problem of safety versus efficacy is based on all the issues raised today. In people with severe hypertension, the most important feature of a drug is its capacity for rapid titration up and down; also it must have a reproducible effect and its action must not be highly variable. A study would need to be placebo-controlled. The protocol would involve entry and continuance in the trial for as long as doctors are willing to randomize their patients and to be blinded to therapy, even if it is being titrated. The titration might be for a couple of hours only, but for those two hours, one would clearly be able to show that something happened as a function of drug that was different from placebo.

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After that couple of hours, one wouldn't have that control. Then one would *assume* that the effect is still a function of drug. If one were in the hypertensive emergency setting, the patients enrolled would have the characteristics not only of high blood pressure, but of organ damage that was acute and/or changing at the time of enrollment, because everyone can understand that medical condition. The thing that no one can understand is what high blood pressure means. No one can define that. So, the hypertensive urgency population would not receive a special indication because people would say, ''Why do you want to treat these people fast''? However, there is another problem implicit with the latter concept. If you review the trials of people who have used parenteral therapy (usually people who have severe hypertension), serious complications have been identified, including retinal artery thrombosis, myocardial ischemia and stroke. One obviously doesn't know whether this comes from lowering the blood pressure or from the disease. One doesn't know that the blood pressure needs to be treated quickly. However, as a regulator, one wants a trial that assesses whether a specific drug enables patients with high blood pressure to be lowered as a function of treatment and whether the change can be made to occur rapidly or slowly and whether it is possible to define precisely the regimen that will cause these changes to occur predictably. If the drug is approved, its application is up to the physician, and clearly involves a value judgment regarding whether, if a patient gets into trouble on therapy, you get out of trouble sufficiently rapidly by turning the infusion off. This is a principal problem. The pharmacokinetic and pharmacodynamic properties of the drug when administered parenterally need to be defined very carefully. Similarly, the problems associated with tolerance need to be defined. It would be perfectly acceptable for a drug, I think, to claim that it can control blood pressure for a specified period, and that toward the end of, say, 24 h, tolerance develops so something else must be done after that. That issue needs to be clearly defined in the data base. The value judgment, obviously, would be made in terms of whether or not to use the drug, and would be based on whether or not it

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looked like the drug acted fast enough or slowly enough or whether these characteristics were sufficiently well described to support clinical use.

In summary, for approvability of a drug for hypertension, a sponsor should study a patient population that has a disease defined according to characteristics everyone can agree upon. Urgent hypertension is a nonentity because one can argue about its definition forever. When one gets into the Ob-Gyn arena, it is another problem. But, the parameter of interest there is clear, and can be summarized by the question, ''What happens to the baby''? That can't be ignored, if hypertension is in pregnancy, so what happens to the pregnancy and to the child is a very important part of the descriptor that would be a part of the trial. It wouldn't just be, ''was the baby delivered?'' It would be, ''Did the baby get delivered and was it normal?'' That determination would require some follow-up. If all of these things were together in a package and reasonably enough described, then any regulator should be able to evaluate it, though not necessarily approve it.

Ultimately, in addition to defining the capacity to lower blood pressure in hypertensive emergencies, it is necessary to define safety, which may be harder to guarantee than in the chronic stable hypertensive patient, and has been the subject of much of the concern in the earlier discussion. For assessment of these issues in parenteral drugs for hypertensive emergencies, it might also be reasonable to think in terms of a positive control.

Dr. Borer: Let me suggest a proposition. As you said, there has never been a precise definition given for what is called ''hypertensive urgency.'' Let's say a sponsor wanted to develop a drug for patients who have no neurological or obvious cardiac effects of hypertension, but have a blood pressure greater than 130 diastolic, for example. The endpoint in the trial I am proposing would not *just* be lowering blood pressure, but would be the incidence of neurological or cardiac events, myocardial infarction or stroke, during the 3 weeks after onset of therapy. I would think that if one wanted to undertake such a study, though I'm not sure that

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anybody would, then after having defined the population clearly, so that an instructive label could be written, and if there was a clear clinical benefit associated with drug use versus placebo or versus active comparator, then I would propose that this would constitute an approvable package.

Dr. Lipicky: I don't think so because there wouldn't be an active comparator that could be used.

Dr. Borer: O.K., then placebo.

Dr. Lipicky: If you could do it with placebo, but I don't think you could do the trial.

Dr. Borer: Why could you not use an active comparator? We are talking about asymptomatic patients.

D. Lipicky: You compare it against placebo in a population like that.

Dr. Borer: All I've described is people with severe hypertension. Don't we have drugs approved for severe hypertension?

Dr. Lipicky: You have drugs approved for severe hypertension, yes, but you don't have placebo-controlled trial data for that patient population. Therefore, you can't tell from your active control that, had placebo been there, the new drug would have beaten it. All you can say is you have approved the active control.

Dr. Fenichel: The hypothesis could be that you are beating the active control.

Dr. Borer: Yes.

Dr. Lipicky: Then that's possible.

Dr. Borer: Beating an approved antihypertensive drug.

Dr. Lipicky: O.K., but this wouldn't be compared to placebo. It would be beating an approved drug. Then what would you get? What indication you would get is that this is a drug to treat hypertension.

Dr. Borer: To treat people who have a diastolic pressure of 130 or greater to prevent the likelihood of the event.

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Dr. Lipicky: Well, drug labeling doesn't distinguish severity. All drugs are for the hypertension, some to be used in an emergent or ''urgent'' hypertension.

Dr. Borer: But all I studied were people who had a diastolic pressure over 130. Can't I define the syndrome, particularly since I prespecified the need to show event reduction?

Dr. Lipicky: No, it is just another hypertensive population.

Dr. Fenichel: No, I don't agree. The claim is not simply that the drug beats the comparator in bringing the blood pressure of this population down. The claim is that in the next 3 weeks there would be discernibly fewer events in the experimental group than in the comparator group.

Dr. Lipicky: You are not going to convince me with a positive control trial. I would still argue that the indication you would get is for an antihypertensive drug.

Dr. Borer: I don't understand that.

Dr. Lipicky: Well, what would you like? That I am for people with diastolics of 130 and do not use it for people whose diastolic is 95?

Dr. Borer: No. I think you misunderstand my proposal.

Dr. Lipicky: Ah. So you don't really want to get it used for everything, right?

Dr. Borer: What I am suggesting is that you have clearly defined a group of patients whom you have tested and you have shown the clinical benefit of the use of a drug in that population.

Dr. Lipicky: But, again, my argument would be that if you beat positive control used in some reasonable dose (not necessarily the approved dose), you don't know what the best dose is, and you ''won'' on morbid/mortal assessment, that would get you approved as an antihypertensive. Labeling would say I am another antihypertensive. Or, would you suggest that on the basis of that trial that all other labeling must be rewritten to say now there is

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a drug for this kind of hypertension that affects morbid and mortal events? No other drug has that.

Dr. Borer: I would suggest that you put the results in the label so that the sponsor could advertise it: ''If I give this drug in this way, I can be reasonably certain that such and such is going to be a benefit of the treatment.''

Dr. Lipicky: The study result should be put in the labeling. The indication would be for hypertension.

Dr. Shah: I absolutely agree with Dr. Lipicky, having just gone through a relevant experience only last week. A sponsor applied for severe hypertension as one of the indications for a new drug, and it had a very well-conducted, very well-designed study. There was an active comparator, 80 patients were studied, and the new drug was quite convincingly better than the comparator. I was perfectly happy to allow the phrase ''severe hypertension'' in the indication section. Our advisory committee also agreed that this could be done. But, when the drug went elsewhere, there were lots of negative comments on this indication. As a compromise, we agreed to remove the word ''severe'' from the hypertension indication section, and would be restricted to mild-to-moderate hypertension, as Ray is saying. But, I felt that the company had done such a good study that it would be silly to deprive them completely of the benefit so I gave them one whole paragraph to describe the study in the pharmacodynamic section of the SPC.

Dr. Lipicky: To complete the picture, I have one additional comment. We are contemplating, and will sometime soon, rewrite all antihypertensive labeling. All antihypertensive drugs will have a section in their labeling that says ''some drug regimens have been tested against placebo in (specific) patient populations and have been shown to affect morbidity and/or mortality. This drug has not been tested in that fashion, but it lowers blood pressure.'' Therefore, the indications would be written saying, ''This is for the treatment of hypertension.'' Occasionally, labeling would discriminate in the sense that this is for severe or this is for emergency hypertension.

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Dr. Singh: Would you consider extrapolating data from one kind of hypertension to another? What I'm thinking of specifically is if an applicant has shown in a very substantial population that the drug is effective in mild-to-moderate diastolic hypertension and then has done one additional study in less than 100 patients in isolated systolic hypertension. Would you then allow isolated systolic hypertension as an indication or not?

Dr. Lipicky: I guess the answer to that is yes, provided that the study was like SHEP in that it started out with chlorthalidone and then added the drug under study.

Dr. Borer: Can I ask a methodological question? Ray, you said that if a sponsor intends to develop an antihypertensive drug with some hope of indicating in labeling that the putative benefits of an antihypertensive drug can be inferred, the measurements in pivotal trials need to be made by casual cuff blood pressure in the office. Therefore, if you used 24-h ambulatory monitoring and checked the blood pressure at 9:00 AM (trough) on the ambulatory monitor in the placebo-control group and in the drug-treated group and found 15 mm of mercury lower blood pressure in the treated group, this would not be a basis for approval. Could not that study serve as a pivotal study for an antihypertensive drug application?

Dr. Lipicky: Yes. I said that. I think that is a correct statement.

Dr. Borer: So you can't use 24-h blood pressure monitoring to do a pivotal trial.

Dr. Lipicky: For the basis of approval, that is correct.

Dr. Borer: Will there be anything in the new labeling that reflects information about mortality and morbidity data?

Dr. Lipicky: The label will say there is outcome data for these drugs and list them and it will clearly say for this particular drug, there is no such outcome data.

To return for a moment to our earlier discussion, I do not know of any data that say that if someone is in hypertensive crisis

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with evolving end organ damage, that you alter the patient's outcome if in fact you don't get their blood pressure controlled within 4 h, or 12 h, or some other specific temporal window. What we know is that you have got to get it controlled, but no one has ever defined the time window. You also know that in people with severe hypertension who don't have evolving end organ damage, when you drop the pressure suddenly, bad things happen. So the definition of how you should treat is totally unknown. Some doctors obviously believe they know and you would never get them to delay or wait a couple of hours and watch. Other doctors believe they can delay and then their participation in trials to clarify these issues would depend on how much they feared malpractice suits and related problems.

Dr. Borer: We never discussed one very interesting area that Dr. Shah brought up this morning. You suggested categorizing drugs according to their metabolism, including the metabolism of the parent compound and the enantiomers. These enantiomers may have dramatically different actions. This characterization would be very useful. I infer that you are suggesting that it should be done. It will not be done if it is not required.

Dr. Shah: In the European Union there are guidelines for the pharmacokinetic package which include the need to define activity of metabolites. We actively look at this problem for every application.

Dr. Borer: But defining metabolism may involve a study of a relatively homogeneous group of patients. My inference from your talk is that you really don't want to look at a relatively homogeneous group of patients. You want to look at a relatively heterogeneous group of patients so that you can see the differences that may exist, the different metabolic patterns that may define groups that will or will not respond well with this drug. Is that required by the new guidelines?

Dr. Shah: It is required and if it is not done in a specifically targeted study we would ask for it.

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Dr. Borer: Ray, do we do anything like this requirement in the U.S. and, if not, what are our future plans?

Dr. Lipicky: At a recent meeting of the Cardio-Renal Advisory Committee (which was then constituted of a large number of clinical pharmacologists) this issue came up; we asked the Cardio-Renal Advisory Committee to recommend that such determinations should be incorporated into the guidelines. They demurred, indicating that the implications of such information are not well enough established to define significance clinically. Nonetheless, it might make sense to gather samples of lymphocytes, for example, so retrospective assessments can be done if difficulties occur during development. We have for a long time recommended what Jeff said, and that is to enroll people who are heterogeneous and to do frequent blood samples, a pharmacokinetic screen, if you will, and then, to identify outliers to identify the possibility of kinetic problems that need specific studies. Some sponsors have done something like this, but not very well and it was not useful to them. That doesn't mean that, if they had done it well, it might not have been useful. This problem has been discussed. It is not a formal guideline, it is not a recommendation, but, our thinking is evolving on this topic.

Dr. Singh: For this kind of assessment, the drugs have to be selected carefully. There are 20 beta-blockers with active centers, but I would not consider the metabolic issue to be a ''big deal'' with these agents. The dose response curve by and large is sufficiently shallow. When you have a steep dose response curve, I think this issue should be important. So sometimes we do these things too late. I mean encainide, flecainide, etc., have been studied too late to assess these problems and then the drug is finished due to adversity that could have been avoided.

Dr. Somberg: Ray, the duration of antihypertensive drug studies has not been established. How long should you treat? Two months, 6 months, a year, or more? Does the FDA suggest treating for 3 or 4 months? Is this enough time?

Dr. Lipicky: There are three ACE inhibitors, captopril, enalapril, and

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lisinopril that have been studied, all against placebo. The lisinopril data in fact looked at treatment for about 6 weeks and then stopped. It was an intent-to-treat study and the effect was very small, but better than placebo. I don't know that there is a good way of approaching that.

Dr. Fenichel: What John is proposing is something that might be viewed as a dose response trial without placebo. One can have two arms, one of which goes for 6 weeks and then turns into placebo and the other goes for 12 weeks, and, for example, assuming that 12 weeks beats 6, that would be like a ''placeboless'' trial. If higher and higher doses seem to get better and better, you don't need a placebo that shows you have an active drug. So one could fasten on that aspect of what we remain ignorant about and do a trial that would not include a placebo and would not include failing to treat patients who are now known to require treatment. I think that would work out well.

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III

DEVELOPMENT OF ANTIARRHYTHMIC DRUG THERAPY

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Antiarrhythmics: Indications, Claims, and Trial Design

Raymond John Lipicky

The following comments should be taken neither as formal Agency policy nor as guidance. They are offered here only for the purpose of eliciting questions during the following discussion period, since assertions are incompletely developed and problems related to drug development programs are only partially identified.

Antiarrhythmic drugs can achieve four therapeutic goals: (1) Prevent the first occurrence of an arrhythmia, supraventricular or ventricular; (2) convert the arrhythmia to normal sinus, supraventricular or ventricular; (3) allow a supraventricular arrhythmia to persist, but simply control ventricular rate; and (4) given normal sinus at the moment, lengthen the time to arrhythmia recurrence, supraventricular or ventricular. It would seem appropriate, regardless of the goal, to determine the clinical relevance of achieving any of these goals (e.g., do patients feel better or live longer or both). To date, one can only marginally identify the clinical benefit associated with having achieved any of these goals (except in the case of supraventricular arrhythmias), though a large number of antiarrhythmic drugs have, in fact, achieved each of these goals and are approved.

In a companion paper, Dr. Fenichel presents some details applicable to supraventricular arrhythmia suppression, study designs, claims and problems, but for the sake of contrasting supraventricular with ven-

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tricular arrhythmias, I will also discuss them briefly. The supraventricular area has been inadequately explored until recent years; nonetheless, all development programs for drugs for supraventricular tachycardias (to lengthen the time between recurrence) have been successful, in large part because the goal of most supraventricular tachycardia programs is symptom relief and the method of documenting treatment effect (difference from placebo) is based upon transtelephonic EKG telemetry, which is essentially a symptom measurement. Patients randomized are asked to transmit an EKG any time they are having symptoms that they think are due to their arrhythmia. What counts is a transmission that contains the index arrhythmia. Therefore, the data collected are a direct measure of symptoms. An analysis that shows a difference from placebo favoring the drug can be directly interpreted as a symptom benefit.

We have come to the conclusion that in the case of chronic paroxysmal supraventricular tachycardias, it is not possible to evaluate morbidity/mortality, because the incidence of morbid/mortal events is so low. If one wanted to conduct a randomized, placebo-controlled, morbidity/mortality trial in patients with supraventricular tachycardias, one would need to enroll essentially all patients in the U.S. with the arrhythmia into a trial that would last about 1 year. For the entire duration of the trial patients in the placebo arm would need to be continued on placebo regardless of whether they had a recurrence of their supraventricular tachycardia or not. Thus, a definitive evaluation of morbidity/mortality is practically impossible to obtain, and we do not require such evaluation. The approved indication, however, limits use to patients who are very symptomatic and who have no evidence of structural heart disease. This limitation exists because of the known proarrhythmic effects of all antiarrhythmic agents and because of the known increased propensity of proarrhythmic effects in patients with structural heart disease. This limitation might be avoided, if most patients enrolled in trials had structural heart disease, and morbid/mortal events were frequent enough to rule out a 50% increase due to drug.

Paroxysmal atrial tachycardia (PAT) and paroxysmal atrial fibrillation (PAF) have been the most fully studied supraventricular arrhythmias, although chronic atrial fibrillation (AF) has had some attention. Approvals for supraventricular tachycardias have been for three therapeutic goals: (1) convert and only show that one can convert (mainly

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in AF); (2) slow ventricular rate (mainly in AF); (3) lengthen the time to recurrence (mainly PAT and PAF but also AF).

One area in which a relatively complete evaluation may be possible but has not been studied is the new occurrence of supraventricular tachycardia in the early period after open-heart surgery. This is a frequent early complication of bypass and valve surgery, and represents a management problem. One could elect to develop a program that either treated the occurrence or prevented it (prophylaxis). Because these arrhythmias are transient, short-lived, and self-limiting, this area would be entirely devoid of long-term studies. The only concern is in-hospital. The aim of a trial, in addition to determining the effect on the arrhythmia, would be to detect some alteration in hospital course. At minimum, the duration of the trials would need to include the entire time in hospital (from hospital admission to discharge), but more appropriately would continue (drug-free, but with intent-to-treat analysis) for 30 days following discharge.

For ventricular arrhythmias, drug development involves greater challenges. One needs to remember that ventricular premature contractions do not require therapy, even if they are symptomatic. In high risk patients with VPCs, weight of randomized clinical trial results favors an *adverse* effect of drugs on mortality without any hint of symptom benefit. The focus of treatment, then, is restricted to life-threatening ventricular arrhythmias. Consequently, the only reasonable endpoint is mortality. Trials need to be randomized and placebo-controlled. The patient population needed for study comprises patients who have life-threatening ventricular arrhythmias but will not die while receiving placebo. The best, and perhaps only, population to meet this criterion includes those patients with an implanted ventricular defibrillator. The implanted defibrillator should be of the variety that records an electrogram documenting the reason for discharge. The major endpoint should be time-to-recurrence of the index life-threatening arrhythmia. A treatment benefit, documented as a decreased incidence of appropriate shocks in the drug group when compared to that of the placebo group, would be taken as a mortality benefit. A number of studies are ongoing in that population. What they will demonstrate is not yet known.

The number of shocks (regardless of the reason for the shock) delivered during a finite period of time is another reasonable endpoint

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worthy of consideration. It is unpleasant to have an implanted defibrillator actually discharge and it is worth preventing shocks if one can (a symptomatic benefit). Therefore, even if mortality is not affected, a decrease in number of shocks may be a basis of approval.

In today's clinical care climate it may be possible to enroll people with nonsustained ventricular tachycardia in placebo-controlled trials. A reasonable number of physicians and IRBs would find this both morally and ethically acceptable. Symptom relief almost certainly could be documented and, more importantly, morbidity and mortality could be definitively evaluated in such a population.

While antiarrhythmic therapy may be intrinsically effective, appropriate patient selection has been the biggest impediment to demonstrating efficacy. To solve this problem, a potentially useful approach to trial design would be to review past trials and attempt to identify the patient characteristics that, when associated with specific arrhythmias, predict mortality. For example, the simple presence of ventricular premature contractions, although definitely correlated with adverse survival, does not predict arrhythmic death. Perhaps, as some think, the presence or absence of heart rate variability does predict arrhythmic death. So, patients with the identified characteristic would need to be the population randomized for study.

Since randomized, controlled trials to date have not documented a treatment benefit of antiarrhythmic therapy compared to placebo among patients with ventricular arrhythmias, a study designed without a placebo control has virtually no hope of defining a treatment benefit. No surrogate has been shown to have predictive value for treatment benefit.

Finally, the problem of doses requires special consideration. Methods for determining doses to study have not been developed. Any trial design, in addition to the need for placebo control, should involve evaluation of more than one dose in order to appropriately evaluate both clinical benefit and safety.

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Supraventricular Tachycardia Drugs and Trial Design Issues

Robert Fenichel

Among supraventricular arrhythmias atrial fibrillation presents relatively unique regulatory concerns and will be the focus of this discussion. Some features of atrial fibrillation are not shared by some of the more organized supraventricular types of arrhythmias. In addition, atrial fibrillation is manifest in a very heterogeneous population. A problem in drug development is finding a specific population that truly may benefit from the therapy under study. Some subgroups of patients with atrial fibrillation feel well and are going to do well, and so, by giving a drug or by other intervention, all one can do is harm. However, there are other patients who feel ill and who are fated to do poorly, to have strokes, or to die; there is at least a possibility of doing good in these patients, but they must be identified first.

Why would one want to treat atrial fibrillation at all? What is bad about atrial fibrillation? First, atrial fibrillation causes the physicians taking care of the fibrillator to have symptoms. They don't like looking at it, they don't like the numbers or the appearance of the electrocardiogram. Then, patients can have symptoms. They have congestive failure symptoms, with shortness of breath, exercise intolerance, palpitations. Finally, patients are at risk of irreversible harms, mainly stroke, but also MIs and other embolic phenomena. For drug development, in theory, one might attempt to alleviate any of these problems. However,

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in practice, you get no points for treating the esthetic properties of the electrocardiogram. (This is analogous to the situation with left ventricular hypertrophy or the hemodynamic measures in chronic congestive failure.) If the physician has symptoms, let the physician take some medication for them. However, if patients have symptoms, this might be an appropriate therapeutic target. There are subgroups of patients with asymptomatic supraventricular tachyarrhythmias, including atrial fibrillation, and so this doesn't apply to them. Moreover, it is not clear what symptom characteristic is best to measure and is likely to improve with therapy. For example, a trial was reported at the 1996 AHA meeting called the PACE Trial, involving 161 patients with quite severe supraventricular arrhythmias, whose mean ejection fraction was not too low, and who were refractory to all conventional therapy. The patients were very uncomfortable. The AV node was ablated and then a pacemaker was implanted. This is not pharmacotherapy, but provides some insight into the potential of therapy to alter symptoms. Of interest even in those patients whose ventricular response to the atrial fibrillation had been modest, without tachycardia at rest, whose AV nodal function had been relatively poor, LV ejection fraction improved after the intervention. One might be tempted to make the claim that one is intervening in atrial fibrillation in order to improve ejection fraction. However, again, we do not accept this as an approvable claim. Some measures of symptomatic function also were greatly improved in the trial: New York Heart Association Functional Class improved and the investigators also defined other symptom-based measures of ability to engage in the activities of daily life which were immensely and successfully improved. On the other hand, the treadmill time was *not* improved and the VO_2 did *not* improve. If one had undertaken a drug trial and had picked on treadmill time as the measure of efficacy, a very attractive measure of symptom improvement, one would have failed. The point here is that improvement may be difficult to demonstrate with treatment of atrial fibrillation because the wrong endpoint was selected for study; unfortunately, it is by no means obvious what is the correct endpoint. Indeed, this parameter may be population-specific. Nonetheless, despite this problem, it is worthy of emphasis that a symptomatic claim stands on its own. Symptomatic claims need not be accompanied by any improvement in mortality rate or in the incidence of stroke or any other

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measure of natural history. The best illustration of this principle is surely the effects of quinidine, which improves symptoms in certain respects but which, in fact, increases mortality. That is acceptable for approval as long as it is known (i.e., if it is plausible that the irreversible harms are in fact being increased in frequency, this does not necessarily condemn the drug). Quinidine is approvable, but the patient who chooses that option must do so with some idea about the effects of his or her choice.

In this context, a discussion of irreversible harms may be instructive. Most symptoms of atrial fibrillation are similar to those of other supraventricular tachyarrhythmias, and are all related primarily to that of the inappropriately rapid ventricular rate. *Irreversible* harm associated with the *regular* supraventricular tachyarrhythmias is extremely difficult to measure. That there are such irreversible harms is probably true, but they are of very low frequency. Irreversible harm is mainly associated with atrial fibrillation (and its close relative, atrial flutter), and include stroke, MI, death, and other peripheral emboli. However, if therapy is given to reduce the incidence of irreversible harms, then one also must consider and quantify those irreversible harms caused by the therapy. These can include bleeding, if one is attacking these risks by anticoagulation or proarrhythmia, if one is attacking them with an antiarrhythmic drug. The proper comparator may vary a lot with the patient population. Let me give you a couple of examples, once again chosen from presentations from the American Heart Association meetings. There was a report from the SPAF Trial (Stroke Prevention and Atrial Fibrillation). It was a moderately large trial, but the subpopulation of interest was not the whole 1044 patients, admitted as a group because of relatively high event risk as presaged by high blood pressure or LV dysfunction or age, or sex, or a prior event. If you consider only the subpopulation with a prior event, some of whom also had several or all of the other risk factors, despite adequate anticoagulation by current standards, that group had a 3½% per year stroke rate. This is a population in whom a reduction of that risk might be a good target because this population might benefit from risk-reducing therapy. At the same AHA meeting, another population was discussed, also well anticoagulated, much younger, without prior events; they had 0.2% strokes per year. It may be that treating those patients with some intervention, ei-

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ther getting them out of atrial fibrillation or, when out, keeping them from reverting, or rate control, or some other approach, will reduce their incidence of stroke. But it is almost impossible to imagine successfully demonstrating this in a trial because the baseline risk is so very low that a trial to demonstrate risk reduction would need to be unfeasibly large, whereas such a trial might be feasible in the population with the baseline risk of 3.5%.

Where does this leave us? Possible claims related to atrial fibrillation really are few, but there are many different ways to approach approvability. Success in this effort is based primarily on choosing an appropriate subpopulation. What is the claim? In the case of symptom relief, three possible claims include reducing symptoms in patients who are in AF, for which you must study a population that feels bad. This is not an option for the asymptomatic atrial fibrillation patients. You may have several different ways to make patients feel better. You can leave them in AF and reduce their rate, you can get them out of AF and demonstrate that that makes them feel better. In either case you must demonstrate that they feel better. It is not sufficient to say they must feel better because they are out of AF. Another possibility is to convert patients from AF. In this case, the symptom argument needs not be made and you simply say that they may feel just as bad as they used to, but are having fewer strokes. That is a good basis for development and obtaining an indication. Finally, one can look at the population that moves in and out of AF. If they are studied when they are not in AF, and demonstrate fewer symptoms in this state than when they are in AF, and then demonstrate reduction in the frequency of AF recurrence, it is reasonable to infer that they will have fewer symptoms than if they were in AF. Also, there may be the possibility of reducing irreversible harms in this group, even if this is achieved without affecting AF recurrence frequency. Even though, yes, they are back in AF, they hate it, and they need to be cardioverted. If, after all of that, you have somehow reduced their risk of stroke, that would be a meaningful endpoint. Those are some of the possibilities that one can outline.

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Antiarrhythmic Trials: Update

John C. Somberg

An overview of ventricular arrhythmia drug trials is very instructive in terms of the types of trials a sponsor might perform and the types of results that might occur.

First, it is important to divide trials into those for acute problems and those for chronic conditions. They are very different. As Ray said, for chronic antiarrhythmic drug development, we should have a placebo as a comparator. In acute trials, when patients are in marked distress, it is very hard to use placebo, but I think that lidocaine, an active drug commonly used for acute arrhythmias, has little more than placebo effect. An article in the *American Journal of Cardiology* by Pacifico and colleagues from Baylor shows that, in acute ventricular tachycardia, lidocaine works in 8% of cases. Another population with ventricular tachycardia was studied in the Netherlands in Heinz Wellens laboratory to compare procainamide with lidocaine, and found procainamide to be considerably more effective than lidocaine. Nonetheless, at least in the U.S., lidocaine is still the first-line drug. It is given in emergencies before anything else. However, lidocaine has such a low efficacy and relatively high toxicity that it might be a good comparator in an acute drug trial.

Among trials for chronic therapy in postmyocardial infarction patients, most studies that have shown significant results were those performed with the beta-blockers. In addition, the BASIS Trial and the

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Polish Trial with amiodarone showed significant results with drug treatment. The CAMIAT study with amiodarone is significant in terms of reduction in sudden death, but not in total mortality.

Let's consider the BASIS Swiss Trial more closely. This was a study of a very complex system of individualized therapy versus amiodarone versus a ''control'' population that also received therapy. There really was no placebo arm. The study demonstrates that some therapies can do better than others in reducing the probability of sudden death and increasing the arrhythmia-free interval.

In the Polish Study, the investigators studied postmyocardial infarction patients with treatment of either amiodarone or placebo. There was a dramatic difference between survival on amiodarone versus placebo, although both groups showed a very high mortality. This type of high-risk population is very useful to determine drug effect, although the results may not be extrapolable to the general population.

The amiodarone trial CHF-STAT had a very disappointing overall result, but in the group that had congestive cardiomyopathy there was a benefit. In terms of overall mortality and sudden death mortality, there was no difference. Some researchers believe that any antiarrhythmic benefit may have been overshadowed by the toxicity of amiodarone, but even when one looks only at sudden death mortality there is no difference between the placebo and amiodarone-treated groups. The CHF-STAT Trial is a larger study than the BASIS and some of the other studies discussed. The results are controversial given the unexpected negative results of the study. The portion of patients that stopped assigned therapy is considerable, about 40% for amiodarone, and relatively high even in the placebo group. There is a problem with a drug that is not well tolerated to this extent. The high discontinuation poses a significant problem in any study that is analyzed according to the intention-to-treat principle. When you have one-third to one-half of the population that is not taking the study medication, then it is very hard to ascribe negative results to lack of drug efficacy.

The CASCADE study evaluated amiodarone versus conventional therapy in cardiac arrest survivors. In this study there was a significant difference. With amiodarone, cardiac survival was improved: a larger number was free of death or sustained arrhythmia, a combined endpoint. Amiodarone showed an improvement over conventional therapy.

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In the last part of the CASCADE study, the use of defibrillators increased and amiodarone versus conventional therapy was compared in terms of shock frequency, an endpoint mentioned by Dr. Lipicky. Counting of shocks is a complex problem for analysis. Different generations of devices now exist. In the first generation, the basis for shocks was unclear. The second generation affords improvement with a memory system allowing one to diagnose the arrhythmia and to determine why the device fired. It is important to remember that the device fires because of heart rate, so you can have an appropriate shock for ventricular tachycardia at a rate of 200 beats per minute when the device is programmed to shock at 180 per minute or greater rate. If the person does not take prescribed beta-blocker and develops a sinus tachycardia or a supraventricular arrhythmia, such as PAT, then a shock could occur and it would be inappropriate. In this way an inappropriate shock would be counted as a drug failure with earlier generation devices. Also, an effective rate-reducing agent could lower shock rate without affecting arrhythmia risk. Thus, a drug could be approved based on fewer shocks, without reduction in arrhythmia risk. In the CASCADE study, we don't know if shocks were appropriate or inappropriate.

The CAMIAT Study is a post-MI study (secondary prevention study) with amiodarone. It was performed in Canada. Drs. Kerin and Conally are the principal investigators. The investigators evaluated several prespecified groups. Amiodarone reduced sudden death. However, in terms of total mortality, there was no improvement with amiodarone. Thus, you may decrease arrhythmia frequency, but you may not affect mortality. Is this because the drug is toxic in other ways and those people saved were balanced by those killed by the therapy due to other toxicities? A complementary study, EMIAT, reported recently by Dr. Camm and colleagues, looked at patients with acute myocardial infarctions and categorized them. EMIAT randomized patients to amiodarone or an alternative therapy. Once again, not much difference was seen, though a modest trend favoring amiodarone was reported for sudden death reduction.

A number of other type III agents block the repolarization current of potassium and have been studied or are being studied currently. The Diamond trial evaluates difetalide versus an active agent in patients with low EF post-MI, and measures a mortality endpoint. Since the

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Data and Safety Monitoring Committee did not stop the study, one might conclude that the drug is at least not doing harm and may be causing benefit. Study reported to show no mortality difference on or off the antiarrhythmic agent.

One of the greatest concerns for sponsors developing antiarrhythmic agents is that a mortality trial, costing $10–15 million, might provide negative results. A problem is that no good predictors are available to let a sponsor know which agent may be successful. For example, sotolol looked very promising in small, anecdotal studies. Sotalol was studied by programmed electrical stimulation and found to be very effective. However, there was no mortality trial. The studies available suggested benefit with sotalol as a racimate, which has both the beta-blocking and class III properties. When d-sotalol with predominately class III action and little beta-blocking effects was evaluated in the SWORD study, there was an adverse outcome—d-sotalol increased overall mortality—a replay of the CAST results suggesting proarrhythmia. The problem seemed to occur during the entire duration of the study. Some investigators suggest this contradicts the ESVAM study, but ESVAM was performed with dl-sotalol and ESVAM did not have a placebo group. ESVAM essentially combined a type II agent (dl-sotalol), with d-sotalol, a type III agent. SWORD evaluated patients with a remote MI and ejection fraction less than 30%, known high-risk groups for proarrhythmia.

An animal study done in my laboratory may explain the results of SWORD. In recent years, the predictive value of QT dispersion for lethal arrhythmia has become apparent. QT dispersion is determined from the 12-lead ECG as the longest QT interval minus the shortest. The greater the dispersion, the greater the heterogeneity, the greater the frequency of arrhythmias. In an animal study, we administered amiodarone, sotalol, and a saline placebo and measured drug effects on QT dispersion. Extra-arrhythmic stress was created with an epinephrine infusion. Amiodarone modulated (decreased) this dispersion. Sotalol (not the d-isomer) did not block the epinephrine-induced increase in QT dispersion nearly as effectively as amiodarone, even though sotalol is a beta-blocker. These findings may explain why sotalol, and particularly d-sotalol, is not as effective as amiodarone; in the SWORD study.

I agree with Ray Lipicky that studies in patients at risk for sudden

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death with implantable defibrillators will be undertaken more frequently. Such drug trials need to be randomized and may even involve drugs versus defibrillators. We know that for the first 3 years after defibrillator implantation, there is a very dramatic improvement in survival, after which the total mortality curves seem to converge again. That may be attributable to the underlying disease; the defibrillator certainly is not a cure for atherosclerotic disease or congestive heart failure. The impact of defibrillators early on, though, is very dramatic. A defibrillator is a very hard standard for antiarrhythmic drugs to beat. In America, drugs already have largely fallen to second-line, as a backup to try to reduce the number of shocks and to treat people who are not appropriate candidates for the defibrillator. However, the defibrillator is costly: third-generation devices cost about $40,000, and it costs ≥$20,000 to implant them and about $20,000 a year for maintenance follow-up, medications, and ancillary care. It is a very costly affair, but certainly very effective. The third-generation devices can tell you exactly why the defibrillator fired and can be inserted transveinously. Even though it is very appealing to do studies with defibrillators, it is very hard to avoid interference from other drugs given for rate control and for other concerns. The recent report of the results of the AVID study comparing amiodarone to the AICD shows that the device successfully reduces the risk for sudden arrhythmic death by 38% on average, a very significant reduction. The AVID results further support the use of a defibrillator as first-line therapy for sustained VT and these findings are similar to the use of the device for prophylaxis for nonsustained VT as advocated by the results of the MADIT study. Further drug development will need to superimpose pharmaceuticals on device therapy in well-defined populations.

In summary, people who treat arrhythmias often believe that amiodarone works, but a demonstration of this is very difficult. The results of EMIAT and CAMIAT suggest that amiodarone does not improve survival, which is really the primary goal of treatment. Finally, devices appear more effective than drugs and could be used as a comparator or as background enabling ethical placebo-controlled trials. If an antiarrhythmic agent could work in 80 to 90% of cases and the mortalities were very similar to those seen with the implantable defibrillator over a 3-year period, then that antiarrhythmic agent would be a useful addi-

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tion to therapy and would probably be approvable. Given an effective agent, I personally believe that most patients would prefer to take pharmaceutical therapy than have an implanted device. Now that we have devices that are proven effective, we need studies that prove that there are drugs that can be as effective and safe. An amiodaronelike agent without amiodarone's toxicity would be a good candidate. There are some pharmacological agents on the horizon that may act like this and our challenge is to test them adequately in well-designed, well-controlled clinical trials. Drugs are currently not the favored therapy, but their comeback is both possible and desirable.

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Inter-Ethnic Differences in the Susceptibility to Drug-Induced QT Interval Prolongation and Torsade de Pointes

Satish Singh

The title of my subject is *Inter-Ethnic Differences in The Susceptibility to Drug-Induced QT Interval Prolongation and Torsade de Pointes*. What I am going to speak about is a drug called teradaline, which was licensed in the United Kingdom in July 1986 and subsequently withdrawn worldwide in September 1991 because of 69 cases of torsade de pointes that were reported very quickly over a period of just 18 months. I make no apology for selecting this subject because the number of cardiac drugs that have gone by the wayside because of their arrhythmic effect and the number of noncardiac drugs that have similarly gone by the wayside makes this an important subject.

I think there is now a greater appreciation that safety is related not only to the usual traditional factors such as age, concurrent diseases, and concurrent drugs. It is now also realized that safety can be related to gender. We have seen many examples of this and also to the inter-ethnic differences in drug metabolism. I also believe myself that during the clinical trials a number of patients withdraw for a variety of reasons. This could be due either to failure of efficacy or because of some safety-related problems. I think that some of the most valuable information about the drug is to be gained from a much deeper examination of

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individuals like this. Therefore, the protocols, whether for cardiac failure, for antiarrhythmic drugs, or for some noncardiac indication, must address the issue of safety in the context not only of gender, age, concurrent drugs, and other risk factors, but also in terms of metabolism and inter-ethnic differences. This risk of proarrhythmia and/or increased mortality has a significant effect on the development and the market life of a number of cardiac drugs. Yesterday we talked about some of these like milrinone, enoximon, zemoterol, and possibly vasnaranone. Encainide was another drug which at one time looked very promising. But, following the results of the CAST study, and also because of the way it was metabolized, this drug was very difficult to handle and was withdrawn in 1991. As recently as 1993, another inotropic agent, flosequinon, was withdrawn because it was suspected that the metabolite may have a proarrhythmic effect. So much for cardiac drugs. What about noncardiac drugs? Between June 1990 and February 1996 the prescribing information of a number of compounds has been significantly amended to address this issue of proarrhythmic effects associated with their use. These drugs come from a variety of therapeutic areas. Consider, for example, the antihistamines terfenadine and estimazole, or the antipsychotic agent pimozide. Consider the gastric prokinetic drug, cisipride and recently the antimalarial drug, helafantrin. I can tell you that from the list of drugs that I am looking at there are another six in the pipeline with problems of QT interval associated with their use. I think this problem is now becoming very important. QT interval prolongation leads to an arrhythmia called torsade de pointes, which was first described in 1966 by de Seten and it has been reported with almost all the arrhythmic drugs. What is of concern is the fact that we are now seeing a very high incidence of QT interval prolongation and torsade de pointes with noncardiac drugs. This unexpected association of torsade de pointes, which is possibly fatal in many cases, prompts one to ask what pharmacokinetic factors may have led to the risk of QT interval prolongation and torsade de pointes and whether or not there are any structural pharmacokinetic or pharmacodynamic aspects of the drug that would allow us to gain some idea before the drug is licensed that the drug may have proarrhythmic activity.

I propose to discuss some of these aspects in the context of teradolyn as we have experienced in the U.K. and also in the context of its

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metabolism. Differences in metabolism have been known for a long time. As long ago as 1952, the first reports appeared from West Africa about Caucasians who were given chlorpromazine and had nasty reactions, while the Africans given the same drug from the same batch had no reactions at all. Subsequently, there have been some anecdotal reports, but the field of polymorphism took off in about 1962 when Mortofsky and Price Evans described esterification polymorphism. The problem with esterification polymorphism, although it explains some of the idiosyncratic reactions like isoniazide with hepatitis or isoniazide in neuropathy, was that very few drugs are metabolized by esterification. Approximately 70% of the drugs are metabolized by oxidation.

Thorasoprin was licensed in the United Kingdom in about 1970. It is an antihypertensive drug and it is still available. Because it is an old drug, the metabolism was not well defined, so we decided to study the metabolism of the drug in our laboratory. What happens when this drug is metabolized by 4-hydroxylation? There is great variability in the amount of drug metabolized. What we did was to do a ratio of the urinary excretion of visocrine or 4-hydroxy visocrine. The higher the ratio the less metabolism of the drug. When a frequency distribution is performed among the population studied there are two patterns of metabolites. Some people are poor metabolizers and others are extensive metabolizers. Through family studies, we have established that metabolism of vasoprine oxidation by the P-450 is controlled by two areas at least operating from a single gene locus. There is an area for fast metabolism and an area for slow metabolism. The area for fast metabolism is dominant, so if you inherit those two genes you are an extensive metabolizer. If you inherit the other two genes, you are a poor metabolizer. If you inherit both types, you are a heterozygote extensive metabolizer with an intermediate capacity to metabolize the drug. In one of the family studies, the father, mother, and offspring are all extensive metabolizers. One family consists of hetrozygote parents, with all three children poor metabolizers. This can be contrasted to another family, where both parents are poor metabolizers and both the children are poor metabolizers as well. A father can be a poor metabolizer, a mother a heterozygote, and two children (twins) poor metabolizers, and the third child a heterozygote extensive metabolizer. Now what is the pharmacokinetic effect of this metabolism? The difference is considerable.

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Your plasma pharmacokinetics, for example, the oral bioavailability of a drug that is metabolized by this route can vary two- to five-fold between the extensive and the poor metabolizer. The C_{max} can vary from two- to sixfold, AUC two- to fivefold, plasma half-life from two- to sixfold, and the clearance can be 10 to 50% between the two. This type of polymorphism has captured the attention of the people and the number of drugs that are known to be metabolized by this isozide 2D6 is increasing with the development of antiarrhythmics, antihypertensives, analgesics, psychoactives, as well as drugs. What is curious about this list of drugs is they are all drugs geared for long-term administration: Cardiovascular drugs and CNS drugs. How does it translate into what we are discussing here today? In a study of metoprolol during its critical development it was found that most of the volunteers in the study had mean plasma levels. But, there was one subject whose plasma level kept going up and up and up and he was discarded from consideration, because he distorted the standard deviation too much. He was found to be a poor metabolizer, who would spoil your safety record, your statistics, and everything if included. The next thing was to see whether or not this pharmacokinetic profile translates into some kind of pharmacodynamic effect. What we did was to view just 25 mg metoprolol. The normal dose is from 50 to 150 mg. We gave 25 mg to an extensive metabolizer and 25 mg to a poor metabolizer and we did their exercise test every 2 h. After 8 h, the poor metabolizer still has a substantial beta blockade, whereas the extensive metabolizer has exhausted the beta-blocking effect within 6 h.

Prehexalin is another drug that ran into problems and was withdrawn from the market. This was a very effective antianginal drug. It worked in patients who were resistant to other drugs, it was partially a calcium antagonist, but nobody really knows the mechanism. This drug ran into problems because it produced severe disability and I think irreversible neuropathy. On this drug some people were controlled on 150 mg and some people required 600 mg. You can almost see that by model distribution in the dose requirements a metabolic difference between patients was at work. Investigators measured the serum prehexalin level and the serum active metabolites in patients who had neuropathy and patients who did not have neuropathy. You can see that the ratio is about nine times higher in those who develop neuropathy.

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This suggests that the drug is not metabolized by some individuals, leading to toxicity. The results also tell you that the toxicity is probably related to the parent compound and not to the metabolite. In terms of neuropathy, there were no poor metabolizers in the non-neuropathic group, whereas in the neuropathic group at least half of the patients or more than half were poor metabolizers. Confirming that the metabolism of prehexalin is also mediated by this pathway, you can predict beforehand which patients are likely to develop neuropathy.

Sotalol also manifests interesting properties. In the SWORD study, the d-isomer was thought to be more effective but it did not turn out to be that way at all. The 2D6 pathway is also very stereoselective. Prehexalin has a racimic carbon center and it has two enantiomers. You can see dramatic differences between the isomer ratios. This tells which isomer might be responsible. This basic pharmacokinetic study had been done earlier on. It gave indications about the dose and the problems likely to be encountered with one or the other isomer of the drug. You can see that prehexalin accumulation is stereoisomer-specific in poor metabolizers.

What are the traumatic differences arising from this genetic polymorphism? The pathways that are mediated by these isozides are numerous. This is not just hydroxylation, but aromatic hydroxylation of drugs such as guenexen, alprinolol, propathanon, benzylic hydroxylation, devrizoquine, aliphatic hydroxylation, and oxidative denaturation of drugs such as codeine, encainide, and flecainide. Are there any safety consequences we have demonstrated with other drugs? Is it just with prehexalin? It has already been shown that the visoquine-induced hypotension can be quite marked, profound, and long lasting in poor metabolizers. Spartaine was an oxitoxic agent and these effects are more marked in poor metabolizers. Flecainide has proarrhythmic effects and some are wondering whether or not what we saw in the past may have been related in part to the oxidation phenotype of those patients.

Terodolyn is a drug that has an interesting history. It was licensed in the U.K. in 1986 for urinary incontinence. But, for some reason because of its structure I went back into the history of this drug and it transpired that it was licensed in early 1970s in Sweden for angina pectoris. One of the side effects that was encountered in the patients was that they developed urinary retention. So the company decided to

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abandon the ischemic heart disease claim and developed the drug for urinary incontinence. The drug was remarketed in 1986 under a different name for urinary incontinence. In the United Kingdom they received isolated reports of torsade de pointes from the drug years after it was licensed. By July 1991, there were 21 reports of life-threatening tachyarrhythmias and heart blocks, and the chairman of the committee wrote a letter warning physicians of these possible risks. Obviously the physicians had seen this effect, but had not associated the drug with the effect. After this letter, we suddenly received 10 more reports of torsade de pointes every day—a very frightening situation. By September, we had 53 reports, 8 of them fatal. In September 1991, the company voluntarily withdrew the drug worldwide. Now I can tell you that this drug was marketed in a number of countries, but the three major markets in the context of what I want to say were Sweden, the United Kingdom, and Japan. When we look at the risk factors in terms of dose or age there are patients scattered everywhere. There is no risk factor related to dose or the age of the patient. We look at the other risk factors such as whether the patients were very old or had ischemic heart disease, or hypokalemia. Some of them did, but there were a substantial number of patients (about 9–28%) in whom no risk factors would be identified at all. Toradolyn's structure reminded me of a drug called phrenilamin, which was marketed in the late 60s or early 70s. It was a very effective drug, but it ran into the same kinds of problems, torsade de pointes. By 1988, worldwide there were 153 reports of torsade de pointes and the company ultimately withdrew the drug. Its pharmacology, again, was thought to be very similar to toradalyn. Toradalyn is interesting because we test the chiral center and there were two enantiomers. The R toradalyn is predominantly a dopaminergic, whereas S toradalyn is predominantly a calcium antagonist. We wondered whether or not the toxicity resided in this stereospecificity of the enantiomers. It was confirmed that when the compound was orally administered it would be metabolized by hydroxylation and a cytochrome P450 might be involved with the metabolism being stereoselective. So one isomer will accumulate. We looked at the data which is all retrospective now, after the event. The metabolism is aromatic hydroxylation, just like prehexalin and phrenilamin. The half-life of 65 h varies from 11 to 83 h in healthy individuals, but in the elderly, who are the ones who

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will be using the drug for urinary incontinence, the half-life was 131 h, and varied from 63 to 237 h. This is a drug you do not need twice a day; this is a drug you need every Saturday. Why were there individual variations in C_{max}, C steady-state, AUC, and half-life? Now at that time we did not know what isoenzyme might be involved in the metabolism of the drug, but we can work it out actually because there are three isozymes. Hydrochrome P450 metabolizes about 70% of the drug. 2C9 metabolizes acidic drugs; 3F4 metabolizes essentially neutral drugs; and 2D6 metabolizes very nitrogenous compounds, of which teradalyn is an example. We looked at information on whether or not somebody has done studies on teradalyn. You find that in this study there are eight subjects. Looking at the C_{max}, half-life, and resident time you can see that the poor metabolism causes increased accumulation.

How does all this fit into the QT interval story? We know now following a recent publication that it is the L isomer of teradalyn that prolongs the QT interval, and it is the L isomer that accumulates in poor metabolizers. Similarly, a recent study has shown that the QT interval produced by tericulan parallels the visoprine oxidation phenotype. Poor metabolizers have a much longer QT interval prolongation, probably reaching into the proarrhythmic area. In fast metabolizers, the QT prolongation is not that marked, but there is a risk that the drug does not reach high enough levels to produce efficacy. Both problems need to be considered.

How does this relate to my topic of inter-ethnic differences? As I said to you this drug teradalyn was marketed in the three big markets, the U.K., Sweden, and Japan. Of the 69 reports of adverse arrhythmias, 64 came from the U.K., two from Germany, three from Sweden, and none from Japan. The volume of the drug used in Japan was just as great as in the U.K., so perhaps this difference can be explained by drug metabolism. In the U.K., 9% of the population are poor metabolizers, in Sweden, 3%, in the Middle East, 1.5%, in Africa 10%, and in Japan, about 0–1.4%. It is possible that in Japan the drug was selected at a dose patients were metabolizing without the isomer accumulating and therefore one did not see reports of toxicity from Japan.

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Panel Discussion

Dr. Somberg (*Moderator*): What I wanted to cover in the panel discussion are practical aspects of development of drugs for supraventricular arrhythmias, acute versus chronic, and then ventricular arrhythmias, acute versus chronic.

Let us first discuss supraventricular arrhythmias and discuss for a moment acute and then chronic. My understanding of the field is that it does break down well into this dichotomy for development. Often you have a drug that affects both supraventricular arrhythmias and ventricular arrhythmias. Let's face it, the ventricular development may often require a large trial where mortality must be evaluated for completion of the program. There is a lot of work involved, a lot of trying to figure out a dose based on a surrogate. VPCs are not a good surrogate. Often it is proposed to do a very nice parallel study in VPC suppression and you have a dose and those doses usually work out to be too high and wrong for the general population both for VT and SVT therapy. At least that is my impression. So this is a very hard area. Supraventricular arrhythmias are more demonstrable phenomena to show efficacy perhaps because the endpoints are more immediate. The arrhythmias are short-lived, especially for acute therapy, and therefore you often turn your drug into a therapy for supraventricular arrhythmias hoping not to even think about ventricular. In the case of one company that did get approved in the U.S. recently, the drug is only available for use in the i.v. formulation, but still approval was possible for the treatment of supraventricular arrhythmias. The question then becomes ''what sort of program would

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be recommended for development of a drug for supraventricular arrhythmia and can you do that in isolation, saying, well it is just not going to be used for ventricular so we don't need to know anything about the ventricular arrhythmia effects, efficacy or toxicity (proarrhythmia)?''

Dr. Borer: I would like to ask a question relevant to the issue you just raised, John. In terms of creating a development program, one population of patients with atrial fibrillation that is relatively easy to study and in which the safety considerations are more easy to deal with than certain other populations is the group of patients recovering in the early hospital phase of cardiac surgery. Thirty percent of those people will develop atrial fibrillation. Some transiently, some for longer periods, and there is great concern for those patients because of the kinds of procedures that have been done, about the development of thrombolic events in-hospital, and in that instability in the hemodynamic situation that exists during the early period after operation. The correction of as many hemodynamic problems as possible is a laudable and strongly sought goal and ridding the patient of the risks associated with supraventricular arrhythmias is most laudable. The question then is, can one obtain two things from studying these patients? Number one, demonstration of pharmacological effect, which might justify studies in other populations at other times. Second, is it possible to obtain an indication for prevention or relief of perioperative atrial fibrillation?

Dr. Fenichel: I am not really sure, Jeff, what you mean by ''is it possible to get an indication?''

Dr. Borer: Let me clarify. You pointed out that you have to make people feel better or you have to prevent irreversible harm. It is difficult in a week's time in a hospital to demonstrate that you have prevented irreversible harm. You might demonstrate some benefit endpoint if a large enough population was studied and if you followed the patients for 3 to 6 months afterward. You certainly could reduce in-hospital stay, which economically is good and may be considered a good thing and you certainly can make

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people feel better in the acute situation because people often don't feel well and because of all the surrounding problems that they have when they are in atrial fibrillation during the week after a cardiac operation. So, given those benefits that I have just suggested, is that enough to say that you provided a clinical benefit by preventing atrial fibrillation or curing it or reversing it with the drug so that you can get an indication for approval of the drug for those purposes for the perioperative situation?

Dr. Fenichel: Well, sure. I mean the thing is, suppose this is a little like treatment of angina where one wants a measurable effect that seems to relate to symptomatic improvement and one wants some evidence analogous to anti-ischemia in the angina world of a plausible mechanism that makes it hang together. So, if one gives something to postoperative patients and magically they seem to feel better and get out of the hospital earlier and do various other good things, surely some claim would come of that. That is fine. Now, would it be a claim for reduction in the frequency of or duration of something else or atrial fibrillation? Maybe and maybe not. Is that what you think is happening that keeps people from staying in the hospital that makes them happier? It is plausible that if you gave people after bypass surgery more opiates that they would get out of the hospital sooner because they would complain of their sternotomy pain less and so forth. That is all very well and that is perhaps a claim, but it is not a claim for the treatment of atrial fibrillation surely. It is just a claim for how to deal with postoperative patients and getting them out of the hospital. So there is surely a potential claim for that population. It is certainly not too limited a population. In a way it is ideal. It is a more or less homogeneous population. There are hundreds of thousands of those patients every year. This is not an orphan disease. It should not be hard to accumulate them and you don't have to follow them for a long time either. If it is plausible that such benefit is going to be achieved within a few days or a few weeks, then this is a good target population to study.

Dr. Somberg: One problem with a post-op population is that the findings may not be generalizable to the whole population with

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SVT. It is a large market so that might be redeeming. It may not be a generalizable population because of the high sympathetic tone and the arrhythmias tend to dwindle off very rapidly within a week's period. So you have to have a very well-controlled study. The dose obtained in this population may not be the correct one for other SVT situations not as driven by sympathetic tone. There may be some drugs that are antisympathetic and thus may work best in this situation, or there are drugs like amiodarone, which are antiarrhythmic and more antisympathetic than others. And since the sympathetic nervous system has a lot to do to promote those arrhythmias the drug could be superior post-op than in other situations for SVT. Does it worry you that this may be unique or that this may be one in which you could develop your drug and then not be able to generalize it to the whole supraventricular area?

Dr. Fenichel: I don't think it is generalizable. I think the post-op population is a very strange population. They have properties, which as you pointed out, are in an abnormal metabolic state for multiple reasons. Their activity level is different from their activity level when they are free ranging. They are different in any number of ways, so studies in that population could not be the basis for a general ''anti-atrial fib'' claim. But, they are a claim that is perfectly well encapsulated, distant, and obtainable.

Dr. Lipicky: I just wanted to press Bob a little bit on what you would get. Let's say that the measurements were whether or not the supraventricular arrhythmia was present. That the dosing and administration included starting drug before surgery so that it in essence was prophylactic and one measured hospital stay and ICU stay and the need for other medicines and clearly the arrhythmia did not occur, compared to placebo. ICU stay was the same, total hospital stay was the same, medications were all the same, except for antiarrhythmics and/or having to be defibrillated. Do you think that that would win an approval of some sort?

Dr. Fenichel: No, that is treating the physician's symptoms. What you described is something where the patient and the patient's

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family can make no claim that they had a good time compared to a parallel universe in which they didn't receive the drug.

Dr. Somberg: What is the endpoint that you want?

Dr. Fenichel: Out of the unit. Patients hate being in the intensive care postoperative unit. That is a perfectly good claim. Getting out of the hospital. Patients hate being in the hospital. That is a good claim. Having a comfortable physician is not a good claim.

Dr. Somberg: I understand where you are coming from. Bob, you have had a lot of emergency room experience and you know people get treated with many things. If someone comes in with rapid atrial fibrillation, do you convert him or rate control him? It is a big question. People with atrial fibrillation, atrial tachycardias will be treated. They will be treated with digoxin, they will be treated with beta-blockers. Is that the best treatment? Does that put them at some risk even though they don't know about it? Or, are you better off getting therapy ''Y''? Therapy ''Y'' may control the arrhythmia, may do it at a lower dose. It may have no proarrhythmia and no negative inotropy. To prove all that, at the risk or benefit to the patient, may be difficult.

Dr. Fenichel: That may be. I am not arguing with that. We treat people who come to the emergency department with atrial fib mainly in the situation where they have come to the emergency department because of atrial fib. So we know they are symptomatic and we know they would at least at some cost, perhaps not at any cost, rather not be in atrial fib or rather not be in whatever state they are in. Maybe they would be perfectly happy being in a slightly different state of atrial fib. Such as one with a different ventricular response, but that is different from, at least presumably, a symptomatic population who have anomalous EKGs but have no other problem. So the two cases are different.

Dr. Hoppe: Assuming a perioperative scenario and assuming you have a drug that makes the patients feel better because it reduces the atrial fib, I think I would have problems to approve it. I think I would at least want to know the acute outcome of these patients.

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The acute prognosis in terms of acute deaths, ICU stay, medication, MI, emboli, cardiac shock, hypotension, and maybe you could make a composite endpoint of these outcomes, measure it, and do statistical analysis on the results.

Dr. Lipicky: Let me come back to it again just so I understand what both of you are saying. So now I have incorporated one other measure. This measurement is one of patient comfort or discomfort on a visual analog scale. The findings are still the same. That is, in this prophylactic regimen the arrhythmia is absent and it is present in the placebo arm. ICU stay and everything else is all exactly the same, but in fact, because doctors and nurses did not hover about the bed and watch the monitor and frown patients felt better. Now what would you say?

Dr. Hoppe: It depends on the kind of nurse and doctor that hovers over the bed. All joking aside, the urgency of the hospital area, the number of interventions the patients undergo contribute to the well-being of the patient.

Dr. Lipicky: Do you definitively have patient benefit?

Dr. Fenichel: Well, I think this is a little bit like the business of giving medication to suppress PVCs where one might make the same claim that if you suppress PVCs there is less hovering and that is probably true, but does not justify a symptomatic or endpoint benefit for the treatment of PVCs. It seems to me your approach mainly is that there is a dominant strategy there that is wrong, while for SVT it may prove beneficial. There is a different treatment for ''irritating hovering'' and that is physician education. It seems to me that that option so dominates most drug therapies that this ''physician hovering'' argument is not very strong.

Dr. Borer: I have a hovering point here. I think that in the setting of the postoperative care area first of all there are seldom hovering physicians because they are all in the operating room and the nurses aren't hovering because they are there all the time anyway. My observation is that the benefits can be achieved by preventing or treating somebody with atrial fibrillation and getting them back

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into sinus rhythm as opposed to slower atrial fibrillation. In the perioperative care situation, it is that their exercise tolerance tends to be better. How can you measure that? You can't get them up on a treadmill at that point. I am sure a measurement device could be devised and there would need to be for a study of this sort. But, I think it would be possible to demonstrate reasonably and in a way that would be convincing to most people in a large enough study that patients in sinus rhythm feel better than patients in atrial fibrillation in the immediate perioperative period. If that were true, forget about the hovering, and even if length of stay actually was the same in the unit in the hospital, which I don't think it would be, but even if it was, feeling better would potentially be a benefit that you could serve as the basis for approval.

Dr. Lipicky: We have certainly approved drugs recently that just convert atrial fibrillation to normal sinus, absent of obvious clinical benefit.

Dr. Fenichel: We did that with ibutilide, but were not satisfied with the criteria for approval. We felt very stressed by that. It seemed plain to everyone that patients who came in to be converted came in to be converted because they were symptomatic. This was not the first experience for many of them. They probably came in anticipating that they were going to be cardioverted, which is not fun and were told ''oh, you have the chance instead to get this intravenous medication which sometimes avoids the risk for cardioversion'' and I think our thought was surely these patients must have come in expecting cardioversion. The avoidance of cardioversion was the benefit. This was not quite so obvious, though, and this is where the argument involves a certain amount of faith. Surely they must have received a symptomatic benefit because they left the hospital for the most part not in atrial fib anymore. I think our belief was that if this had been thought of a little better by the firm and by us that an instrument evaluating that could have easily enough been added to the file and would probably have shown that there was a symptomatic benefit. It was a miscalculation by the sponsor that this was lacking. I don't think that it is a model for future approval in the area of AF.

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Dr. Somberg: It is a problem that the field is very murky, but it is not clear cut that people in sinus rhythm feel better than people in atrial fibrillation. Some people with intermittent fibrillation feel the worse. Some people with chronic atrial fibrillation don't even know it. It is very subjective, varying from population treated, region of the country, and investigator training, patient evaluation, and criteria used.

Dr. Fenichel: That is absolutely true and that is why I alluded to this when I was talking about this before. You have to pick your population. If you have a population who are now perfectly comfortable, then there may be reason to convert them from atrial fibrillation if one can thereby reduce their incidence of stroke, or whatever, just as it is worthwhile treating asymptomatic hypertension, which is the most common kind of hypertension. However, the way to make this argument for approval is to say that the drug is indicated for people who we have demonstrated such and such an effect. We have demonstrated in this case that it converts people to sinus with such and such ill effects at the time and there are ill effects with most conversion techniques, including the recently approved one of ibutilide. Ibutilide causes an incidence of ventricular fibrillation, which occurs in an oxygenated person who is in front of you with an i.v. in place and so the ill effects of that VF are probably not very severe, but they must be near zero. Every once in a while you will find that, gee, your capacitor in the defibrillator has decayed since the last time you used it and so sooner or later someone is going to die from the adverse effect, torsade de pointes or VT degenerating to VF. Nevertheless, you put all of that together and there are patients who might reasonably choose that therapy or for whom that therapy might reasonably be chosen. There are others for whom it is a stupid thing to do. They are perfectly happy, their risk for stroke for whatever reason is very low, and it is not indicated. Physicians need to make these judgments when treating patients appropriately.

Dr. Lipicky: I think the moral of this discussion is that indeed if one thinks that, say, in the post-op period the presence of atrial fibrillation has some detriment, one should measure that detriment

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and I think that it would be unfortunate if the arrhythmia was absent and the detriment that was not supposed to be present was still there in spite of the arrhythmia being absent. That would be a problem and one could perhaps be a totally good antiarrhythmic and not win approval because of that.

Dr. Somberg: The detriment could be symptoms and it could also be a slower recovery or . . .

Dr. Lipicky: It could be whatever you think. I have no idea what will be defined, but one needs to measure the situation and have a hypothesis to test.

Dr. Somberg: There are symptoms and just for those who are not familiar, there is also concern about tachycardias causing a cardiomyopathy. In animals you can make a myopathy by repeated tachycardias or a sustained tachycardia for a few days. In the Netherlands, there is an investigator Alisie who employs intermittent AF caused by pacing in the atrium to produce chronic atrial fibrillation and a cardiomyopathy in goats. There is the concept that just intermittent tachycardias can produce myopathies as well as intermittent atrial fibrillation with a rapid ventricular response. However, nobody has correlated nicely that a drug prevents this from occurring in those people who develop a myopathy. Returning to the concept of what constitutes a benefit, could a benefit be the reduction in the need for anticoagulation and therefore the risk of bleeding be reduced?

Dr. Fenichel: That is certainly an excellent point because that again is another basis for splitting populations. There are populations in whom the risk of chronic anticoagulation is really fairly modest. Other populations in whom that risk seems to be just unavoidably high (elderly women). There are some obvious cases like alcoholics and people who are not likely to comply with their medication and have other risks of bleeding, but then even in larger, basically healthy populations there exists a risk. Once again, elderly women whose risk of stroke is highest for age and gender groups also appear to have the highest incidence of adversity with increased bleeding. There is a real difficulty in control-

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ling anticoagulation. Of course that is true. The net benefit in terms of reducing the incidence of irreversible harm has to include the harm avoided by avoiding alternative therapies.

Dr. Borer: I think that is a very important point. But, just to clarify for development programs, if I understood correctly, Bob, you were suggesting that if you wanted to say that it is a good thing to be on this drug because it precludes the need for anticoagulation with all its hazards you should have a measurement that shows that there were fewer of these hazards occurring in the people who were on the drug in the study that you are using for approval than people who aren't on the drug. Not that the principle is wrong, but you should have to measure it to show that is correct.

Dr. Fenichel: I am not absolutely sure that that is so. I mean it might be possible to show that as far as anyone can tell the drug prevents relapse into atrial fibrillation in a risk-prone person. Regardless of other factors that it just has that property or that action upon the heart. One might then say, well it comes with various proarrhythmic risks or whatever of its own and we can evaluate those and that gives us some sort of net benefit. Then it might be possible without actually doing the associated studies to say O.K. we know what it does in the setting of atrial fib. We know that its inherent risks are unassociated with bleeding or anything else and now we can say O.K. that package will be weighed against anticoagulation. We can say the drug will be of benefit in populations whose risk of anticoagulation is worse than ''such and such'' and it will be of no benefit and even a detriment in populations of low anticoagulation risk and it might be reasonable to leave it at that. If the figure of how much anticoagulation risk was enough to justify using this therapy could be said to be in the range of known anticoagulation risks. You will never identify exactly the amount anticoagulation puts a particular patient at risk by looking at the trials. What one would come up with, I imagine, is something like the risk of using the drug (a proarrhythmic risk, mortality from using the drug, or stroke risk); we could estimate the risk to be at the 1% level. Well, we know that there are anticoagulated

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patients who have major bleeding episodes more frequently than that and other anticoagulated patients in populations who have major bleeding episodes much less than that. It is a combination of age and gender and phenotypes, I am sure, and concomitant medication and the amount of variability in the diet and a million other things, and one will, I think, leave that to the physician. I am not sure that one would have to identify a population in a single trial in which one would go head to head with anticoagulation against the therapy.

Question: Dr. Lipicky just said this morning that we can achieve some clinical benefits like conversion to sinus rhythm that decrease the rate of AF. But, you said you cannot say anything about people who can benefit by achieving this. If you have a drug that claims both prevention and conversion to sinus rhythm, does that mean that you need benefit in all these areas?

Dr. Somberg: The question can be rephrased that to obtain a claim for a supraventricular arrhythmia specifically, atrial fibrillation conversion, do you need a mortality trial to essentially look at the safety because many of these drugs will be looked at in terms of treatment of ventricular as well as supraventricular therapy? Do you need a mortality trial for the efficacy of the drug as well as its safety for long-term therapy in different arrhythmia populations?

Dr. Lipicky: Let me give you the short answer first. Probably.

Dr. Somberg: Probably, for which reason?

Dr. Lipicky: Well, that is the long answer. If what you are talking about is chronic AF, there is a very real question in my mind at least from existing trial data of whether you ought to convert those people at all or you ought not to choose putting them on anticoagulants because the clinical event rate of interest is stroke, probably. You do very well with just anticoagulation and forgetting about the arrhythmia.

Dr. Somberg: There is a trial addressing that particular issue. A very major one called the AFFIRM trial that is sponsored by the NIH.

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It is in over 100 centers and will look at the issue of rate control versus prophylaxis of recurrent AF.

Dr. Lipicky: So that is what was bothering Dr. Fenichel in part when he was responding to these other questions of whether you would have to take anticoagulation on head to head. So the long-term therapies in chronic atrial fibrillation are problematic. Why should you convert them at all? Why should there be some risk of mortality really if you are using an antiarrhythmic to slow the rate of recurrence when you have good clinical benefit leaving an arrhythmia alone and just treating it with an anticoagulant. You probably would need a mortality trial in that setting to say that I should convert and then continue using drug to slow the rate of regression. With ibutilide recently we didn't have to face that problem because all they wanted to do was convert. That is smart and then no one had to address the issue of why do you want to convert. They said all we want to do is convert and we kept our eyes blind to the fact that maybe you shouldn't. Maybe next time we will address these issues of the need for conversion and chronic maintenance therapy.

Dr. Fenichel: I assume that when you say one would need a mortality trial you mean to say one would simply need to know what the mortality effect was in a trial, the net mortality effect. That you are saying that one would need to show a mortality or irreducible harm benefit and that has not been our recent policy as demonstrated by what we did with quinidine. Quinidine comes with an awful lot of historical baggage, but nevertheless we at least stated that we were willing to rise above that baggage and consider the issue as if afresh, and should the drug remain on the market given that its mortality effect when used long-term for the prevention of return or reduction of relapse into atrial fibrillation. Its mortality effect in that setting is adverse; nevertheless, it does provide reduction in recurrence of AF. It does in some patients provide symptomatic benefit. They would rather be in sinus rhythm than not and we thought at least some patients would take the quinidine route as a means of being in sinus rather than going and taking flecainide or propafenone or something else. Now it may be we

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are kidding ourselves that we really were unable to bring ourselves face to face with the idea of taking from the market a drug that has been there for hundreds of years, but I don't think so. I think we actually made a correct decision so I think that is a little bit inconsistent with what you just said.

Dr. Lipicky: That is correct.

Dr. Somberg: There indeed are a number of overview analyses that support the thesis that in both a population with SVT as well as VT, quinidine has a net adverse proarrhythmic effect.

Dr. Lipicky: So there is a problem and I don't know what you have to do. To talk about chronic atrial fibrillation and the problem of what should you do there. It is not quite clear what the desired goal is. What a development program for a brand new chemical entity would need to be. I think we need some very careful consideration. I think Dr. Fenichel is right. I was probably wrong in how I answered you. But, that would really loom as should you or should you not? Because there is a big problem there from that vantage point and I think we would probably end up saying you don't have to do a mortality trial, but for sure you would have to do something big enough to have a point estimate of adversity.

Dr. Somberg: My recollection is that in May in Washington you said something to the effect, and tell me if I am recollecting incorrectly, that the treatment of supraventricular arrhythmias with a drug (to prevent recurrent PATs or recurrent atrial fibrillation) would be sufficient if you expose the drug to a defined population and show that it was safe.

Dr. Lipicky: One would need to show efficacy as well as a point estimate for safety and this would need to be judged acceptable.

Dr. Somberg: I am talking about people who go into atrial fibrillation. The majority of atrial fibrillators go in and out of atrial fibrillation for a period during their life history before the arrhythmia becomes chronic because there are developing progressive structural changes. But there are people who go in and out for days and weeks, and those are the most at risk, as opposed to the person

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who has long-standing chronic large atrium. Even if the patient has a clot, the patients are thought to be less at risk because the time of risk is when the patient converts from AF to NSR. So what they are talking about is not a population that has 10 beat run and you can do a valsalvor, but we are talking about somebody who usually presents to the emergency room in AF and then is converted to NSR or a patient who is spontaneously converting and physicians want to maintain sinus rhythm. In this context, then, one would want to show a reduction in AF episodes, reduced adversity (emboli), as well as a measure of the proarrhythmia of the agent being employed. Am I recollecting incorrectly?

Dr. Lipicky: That sounds like something I could have said. Yes.

Dr. Somberg: Because the concern is that many a sponsor is developing their drug, their new IKr blocker or their new 1C for a supraventricular indication because the ventricular indication is so mercurial that approval seems doubtful.

Dr. Lipicky: That is consistent with what Dr. Fenichel corrected me about. That is for chronic atrial fib, not paroxysmal atrial tachycardia. Demonstrating that the rate of recurrence is decreased in a placebo-controlled trial—in a trial that was large enough to have some kind of an estimate of mortality—would probably be sufficient, and having a trial large enough to be able to definitively win on the basis of mortality alone would probably not be necessary. Which is essentially what John just said and what Dr. Fenichel suggested.

Dr. Somberg: We have a shorter time to cover the important area of ventricular arrhythmia drug development. That may be an even more vexing question. Let's say a company comes in with a very well-studied, well-defined pharmacologically active agent that has a mortality benefit in a given population, maybe a post-MI or recurrent cardiac arrest population that beats the comparator and I'm not sure what the comparator might be—possibly physician-directed conventional therapy, PES, guided alternative therapy, amiodarone, or a device. The new therapy beats the comparator but shows a sizable proarrhythmia. Let's say the proarrhythmia

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is in the 5 to 15% range. So the drug has a sizable proarrhythmia, probably of the torsade de pointes variety, if it is a type III agent. How would regulators look at that and what can a sponsor do to try to reassure and mitigate some of these major concerns to obtain approval?

Dr. Lipicky: Regulators should not even look at that trial.

Dr. Somberg: Why is that?

Dr. Lipicky: You said ''some kind of comparator.'' The only comparator that is of any regard is placebo. Otherwise you have no comparator at all. All you can tell, perhaps, is that the drug that is the comparator killed in excess and you won. Therefore, you are as good as placebo. That is a total unknown at the present, so there is no comparator that can be viewed as winning or being as good as or anything else that is of any value nor that should have some regulatory import for decision making. So the trial as you described it is something that no one should bring to us and ask us to make a decision on the basis of.

Dr. Shah: I don't think that was quite your question the way I understood it. Since he is sitting next to me I can rephrase it much better. I think what he means is that you have this drug, which can be compared to placebo or another comparator. Yes, it does decrease the incidence of potentially malignant ventricular arrhythmias and maybe it decreases mortality. But, I think what your question was, because you were alluding to the Diamond study, is suppose the incidence of other potentially lethal arrhythmias like torsade de pointes emerge at a greater rate, then what do you do?

Dr. Somberg: It's a two-part question. Ray answered one very strongly. To my knowledge most of the antiarrhythmic trials, if not all of them, have ''some sort of comparator'' whether it be standard therapy, amiodarone, a device, or a conventional PES guided therapy. These are the usual trials undertaken. Giving placebo can be done in the context of a defibrillator. There are some people trying to put together those trials, but that has proven most

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difficult. But, I am saying in one of the comparator trials you beat the comparator, not a placebo. You have a historic, point estimate out there and you know what worsening does, etc. You have some historic data, but probably not a historic placebo in a good trial either. The first thing Ray says is that that trial isn't worth showing. He won't look at it. The second part is that if it looked good, but still had a high toxicity, what would you do further. That was the second part of the question that I asked.

Dr. Fenichel: This gets back to what we mentioned yesterday. I used the example of a situation where you cannot rely on a positive control of tricyclics because they don't beat placebo all the time. Well, I shouldn't have used this example. I should have said ventricular antiarrhythmics. What is the positive control, which in a ventricular arrhythmia situation would be known without the presence of concomitant placebo, a parallel placebo to be better than placebo.

Dr. Lipicky: I think the way to view it is if you have an ICD that is background therapy and it is placebo versus drug. The comparator is placebo.

Dr. Fenichel: Right, they both have ICDs.

Dr. Lipicky: They both have ICDs.

Dr. Somberg: Oh, but you have to be careful. Fifty percent of people on ICDs are on an antiarrhythmic to slow the sinus rates or to prevent SVT.

Dr. Lipicky: Yeah, well not the people in this trial.

Dr. Fenichel: Leaving 50% out is a large exclusion.

Dr. Borer: To carry the question further. If you had a drug versus placebo trial, but the placebo-treated patients had and ICD, which of course could record the number of events, wouldn't that be adequate as a comparator.

Dr. Lipicky: Absolutely. But, it is important then to pick up on the three words that were said about third generation ICDs. Counting

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shocks is not adequate if one is looking for an antiarrhythmic claim. An antiarrhythmic claim that says I am using ICD shocks as a surrogate for death and therefore I am preventing death as a consequence of the measurement that I am making. The shock must be a shock that occurred as a consequence of a fatal ventricular arrhythmia. Not a shock that occurs that is due to some other kind of arrhythmia. So the ICD that is employed must be able to record, must be able to be interrogated, and must be able to indicate that the number of fatal ventricular arrhythmias was altered.

Dr. Somberg: Would a dose finding study be necessary to choose the dose to test or should several doses be used?

Dr. Lipicky: I think there is no such thing as a dose-finding study in an ICD population. It comes back to the same philosophy that if one is going to jump into an ICD population to look for major efficacy, one would be crazy to study a single dose. So one should basically be studying a number of doses in this population and would be doing dose ranging and primary clinical efficacy in the same trial and I think you throw away the concepts of phase I, phase II, phase III.

Dr. Somberg: But you could if you knew the specific mechanism of the drug and there was a strong hypothesis that it was an IKr, an IKs, or an IKur blocker and then what you do is do an action potential duration. You do a dose response with that and then you come up with probably two doses that look like they do what you think the drug should do. Electrophysiologically you might want to explore that dose instead of having to do three/four arms and choose doses at random.

Dr. Lipicky: You can be crazy if you wish. We would not prevent that.

Dr. Fenichel: There are two separate claims that one might seek in an ICD population and indeed they might end up with different doses. There is a potential claim for reducing the incidence of shock because the shocks are unpleasant and they have an immediate unpleasantness and they have a delayed unpleasantness in

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that if there is a sufficient number of them, they increase the frequency of battery replacement surgery. So there is plenty of reason to reduce the incidence of shocks. In many jurisdictions, shocks can render one unable to drive legally. There are plenty of reasons to keep the shocks down. So that is a separate claim. It might be that a drug had the property of filling a gap in the design of the arrhythmia detection algorithms in the devices. If you want to put it that way, there are plenty of nonlethal arrhythmias that are detected by the devices and thought to be sufficiently close to lethal that the device doesn't know any safe way of not discharging when these arrhythmias are seen and an electrically active drug might suppress these arrhythmias even though when truly lethal arrhythmias came along the drug didn't do any good. Well that's O.K. Such a drug would reduce the incidence of spurious shocks as they happen and would be approvable for the fairly limited claim of usefulness in ICD patients to reduce the incidence of shock. It is certainly possible in what we have considered with much more interest in using the ICD population as a means of getting an antiarrhythmic therapy that would reduce the incidence of lethal arrhythmias. Arrhythmias that would not in fact be lethal because they have the device as a ''back up.'' The benefit shown in the ICD population would, in fact, be interpreted as prevention of death in similar patients—similar, except for the fact that they don't have ICDs. What is of greater interest is using the ICD population as a protected population in whom to predict what will happen in the larger population at risk for life-threatening arrhythmias.

Dr. Somberg: I might also interject that you might want to look at it making sure the drug doesn't raise the threshold for defibrillation. That is a concern that has been raised that has probably been dispelled with the current group of drugs, but that is a concern out there regarding this issue.

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IV

DEVELOPMENT OF ANTILIPID AND ANTI-ISCHEMIC THERAPY

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15
Antilipid Trial Endpoints

David Orloff

The issue of class efficacy for the HMG Co-A reductase inhibitors, or statins as they are called, is one which is under increasing scrutiny by the FDA. These agents have come of age over the past decade and have proved to be relatively safe, very well tolerated, and highly effective cholesterol-lowering agents (Table 1). Indeed, in recent years, the completion of several large clinical endpoint interventional trials has allowed us to answer a number of questions that have dogged this field for a considerable time about the event-reducing efficacy of cholesterol lowering. Moreover, these drugs, either alone or in combination with older therapies, have revolutionized the treatment of hypercholesterolemia. However, not surprisingly, with these developments new medical, scientific, and regulatory issues have evolved. The 4-S study (Scandinavian Symptomatic Survival Study) was a milestone in this area, demonstrating significant clinical benefits associated with pharmacological cholesterol lowering in hypercholesterolemic populations, not only in terms of coronary and cardiovascular morbidity and mortality, but also in terms of total mortality. The ultimate test of the safety and efficacy of a therapeutic intervention in chronic disease is mortality. In the past year, the similarly favorable results of two other studies have been published. The West of Scotland Coronary Prevention Study was published late last year and the CARE (Cholesterol And Current Events) trial was published earlier this fall. The accumulating body of evidence from these large trials speaks to the safety and efficacy of the

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Table 1 Statins: Class Efficacy

Similar trends in morbidity and mortality across at-risk populations
Other large trials ongoing promise similar results

individual statins and are supported by a host of smaller studies with different statins. These studies are primarily designed to assess the effect of cholesterol lowering on atherosclerosis progression and have raised important, although complex and somewhat difficult issues not only in the development of new pharmacological agents in this area, but in the regulation of this competitive field. I will discuss the salient features of these three large studies and compare the results across drugs and across trials to point out similarities to make some general conclusions about the effects of the statins in patients at risk for coronary artery disease. This should lead us into the discussion of class clinical efficacy for the statins.

The 4-S study was a secondary intervention trial in which >4000 men and women were randomized to receive either provastatin or a placebo with a primary endpoint of total mortality. The patients were aged 35 to 70 years. These were patients with coronary artery disease as manifest by a previous MI or angina, and the entry criterion for cholesterol was total cholesterol of 212–309. Patients were treated to achieve total cholesterol of 116–202 mg/dL by titration of their simvastatin dose. The follow-up averaged 5.4 years. Over the course of that period, the mean reduction in LDL cholesterol was about 35%. The trial met its hoped-for objectives. Over the course of follow-up there was an 8.2% mortality rate in the simvastatin group, as compared to 1.5% in the placebo group. There was a significant 30% risk reduction with drug that was clearly driven by reduction in the rate of coronary events and death. Importantly, in light of past trials with other lipid-altering agents, there was no increase in the rate of noncardiovascular death associated with simvastatin therapy. In particular, no increase in the rate of cancer deaths was observed.

By contrast, the West of Scotland Trial was a primary prevention study conducted in a high-risk population of men. This group was larger because of the anticipated lower rate of coronary disease and clinical events than in a secondary prevention population. In this study,

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some 6500 men aged 45 to 64 without a previous MI but with hypercholesterolemia evidenced by LDL cholesterol of 155–254 mg/dL were randomized to receive either placebo or a fixed dose of 40 mg per day of pravastatin. Over a 5-year follow-up, the mean LDL reduction was 25% and the primary endpoint was the first coronary event, either cardiac death or nonfatal MI, not death alone. The results of this study also were favorable, 5.3% of the pravastatin-treated patients had a first coronary event during the course of follow-up, while 7.5% of the placebo patients had a first coronary event, indicating a 31% risk reduction. When the components of the primary endpoint were divided, for nonfatal MI there was a statistically significant reduction of similar magnitude; for the coronary death component, when you included suspected coronary heart disease deaths, again drug treatment achieved statistically significant. There was no difference in the rate of noncardiovascular deaths between the two treatment groups, so total mortality benefit was of only borderline statistical significance but really was of clinical importance.

With these two studies, mortality and morbidity benefits from cholesterol lowering have been demonstrated in hypercholesterolemic populations both with and without established coronary disease. Furthermore, from these two trials we saw that for neither drug and for neither population did any adverse effect of treatment on noncardiovascular mortality reveal itself. Finally, with respect to these first two studies, while the clinical event rates were obviously different between the two trials, the observation of similar trends in clinical efficacy between the two populations using drugs acting via the same biochemical mechanism speaks to a common pathogenesis of coronary artery disease in both the primary and secondary populations. This is not a major scientific issue, but it is important in considering existence of class effect.

The most recent trial, CARE, like 4-S, was a secondary prevention study, although this time in a population with mean cholesterol that was not markedly elevated. The objective of this study was to assess the impact of cholesterol lowering, again with pravastatin, on the risk of recurrent coronary events in men and women with a recent MI, but without marked hypercholesterolemia. Approximately 4000 men and women, aged 21 to 75 years, with mean LDL cholesterol in the range of 115–174 mg/dL and an MI in the preceding 3 to 20 months, were

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randomized to receive either placebo or pravastatin, again at a fixed dose of 40 mg/day. The mean LDL cholesterol in this trial at baseline was 130 mg/dL. It is important to note that a large portion of the population randomized into the study would not otherwise have been candidates for lipid-lowering therapy based upon European and American treatment guidelines. The follow-up was 5 years. Over the course of the study, the mean LDL cholesterol reduction was 32%, yielding a mean LDL on treatment of 97 mg/dL. The primary endpoint was recurrent coronary events, either CHD death or nonfatal MI. The results were similar to those of the earlier studies noted above, with nonfatal MI or coronary death significantly reduced on the order of 24%, paralleled by a nonsignificant trend toward reduction in the rate of coronary death alone and a significant reduction in the rate of nonfatal MI. Total mortality was reduced by 9% in the pravastatin group. This was not statistically significant. Likewise, there was no difference in the rate of noncardiovascular deaths between the two groups. There was a highly significant excess of new breast cancer cases observed among women treated with pravastatin in this study. Despite this finding and the fact that it appears not to be explainable by an imbalance in breast cancer risk factors between the two treatment groups, this adverse result has not been confirmed in the data safety monitoring of an ongoing trial using pravastatin in a larger number of women and with a similar duration of exposure. Therefore, the importance of this unexpected finding is unclear, but is not yet considered dispositive. In this study, cholesterol lowering significantly reduced coronary heart disease morbidity and mortality in a high-risk population though the mean cholesterol had not been markedly elevated. Nonetheless, the degree of risk reduction for the primary endpoint as well as for all major coronary events was a function of baseline LDL cholesterol; that is, the higher the baseline LDL, the greater the reduction in risk as compared to placebo. Interestingly, for the patients whose baseline LDL cholesterol was less than 125 mg/dL, there was no benefit observed in this study. This may represent a lower boundary for a clinically important impact of LDL cholesterol on coronary risk or, alternatively, in order to achieve a benefit in this population you might need greater degrees of LDL lowering than were achieved in this trial.

A similar relation of benefit to baseline LDL cholesterol was ob-

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served in the 4-S study. In that trial, as noted, patients were treated to a uniform goal regardless of their baseline LDL cholesterol so that those who had the highest baseline values on average had the greatest percent reduction in LDL cholesterol, and also had the greatest reduction in risk for primary and secondary endpoints.

Returning to the CARE results, the effect of pravastatin on the primary endpoint was seen in males and females and across ages greater than 60 and less than 60 and across other coronary heart disease risk factor strata, including hypertension, diabetes, smoking history and left ventricular dysfunction. It is interesting to note that for the primary endpoint of recurrent coronary events, as well as for all major cardiovascular events, the females in this study had a greater risk reduction than the males. This is perhaps explained by the finding that the women had a higher incidence of multiple coronary risk factors than did the men. In 4-S, the women and men benefited similarly and the findings held across age strata. When the CARE study was reanalyzed to include the subgroup of the CARE population who would have been eligible for entry into 4-S, the effects of pravastatin were of equal or greater magnitude than that which was seen for simvastatin in the 4-S study, hence replicating the 4-S results.

Thus, across three large trials for both primary and secondary prevention, using two different statins, there was consistently observed clinical benefit across the range of LDL cholesterol as well as across age, sex, and risk factor strata. Furthermore, as comparison of the 4-S and CARE results demonstrates, replication of results for patient populations met entry criteria for 4-S despite use of different drugs. What emerges is a pattern of risk reduction in hypercholesterolemic populations as a function of baseline risk. In addition to CARE, 4-S, and WOSCOP data from smaller statin trials, using other statins, show similar trends in morbidity and mortality and in some cases in overall mortality. This characteristic of the statin class is in contrast to previous findings from trials using the fibrates, resins, and hormones. We anticipate similar results from ongoing statin trials. As evidence mounts in favor of the statins, I think it is safe to say that the absence of a net reduction in all-cause mortality in the prestatin era trials was due to inadequate cholesterol lowering, as well as to the adverse effects of some of the drugs studied in those trials. These earlier problems appar-

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Table 2 Statins: Differences

Lipid-lowering potencies
Maximum LDL-C lowering at approved doses
Differential effectiveness in rx to goal

ently are not problems with the statins as a group. Now we're faced with the issue of interchangeability of these drugs. I believe it is becoming increasingly difficult to justify distinguishing them on the basis of presumed drug-specific clinical efficacies.

What are the differences between the statin drugs (Table 2)? Certainly they have different potencies and lipid lowering per milligram of drug. As such, at the highest approved doses of one statin will have a greater potential for lipid lowering than will another. Therefore, it can be expected that in head-to-head comparative trials, one statin will bring more patients to cholesterol goals than another as a function of the doses of each agent emphasized in the trials. Beyond these differences, there really are no data to refute the notion that, for equal degrees of LDL cholesterol lowering, clinical outcomes will be the same regardless of the drugs used. This latter hypothesis really has remained untested in a formal study. In addition to similarities in clinical efficacy, the statins share the same general safety profiles though perhaps differing in the degree to which they induce certain adverse effects. The adverse effects of the drugs include fairly common, but virtually uniformly benign hepatic effects presumably related to the mechanism of action of the drug, sometimes dose related, but certainly ameliorated by dose reduction or discontinuation of the drug and also sometimes correlated with the potency of the drug and lipid altering.

Myopathic effects are extremely rare and really can be considered idiosyncratic in nature; they also may be related to the mechanism of action of the drug, but also to systemic drug levels and probably to individual susceptibility factors. Nonetheless, clearly the myopathic risk is increased with concomitant use of certain drugs that inhibit the P450 enzymes responsible for metabolizing the statins in the liver and can acutely raise systemic levels of drug. Although no directly comparative safety data are available, the spectrum of adverse effects of the statins seems to be similar. The results of clinical trials must be strictly

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interpreted and attribution of effects of a drug, either positive or negative, must be based on adequate trial data using that particular agent. This argument certainly has theoretical as well as regulatory merit, and is the justification for differential labeling and advertising claims among statins. However, I think it is increasingly incumbent upon individual sponsors to bolster this argument with data speaking to mechanistic uniqueness because of accumulating evidence discussed and prevailing thought as to similarities of the statin class. As an example, the recent presentation of a clinical investigation using atorvastatin, a new HMG-Co A reductase inhibitor that demonstrated its efficacy in LDL receptor-negative homozygous familial hypercholesterolemic patients, suggests a mechanistic uniqueness for this agent. Given the known basis of hypercholesterolemia in this population, and the mechanism of action of statins as a group, these patients should not respond to statins, but did respond to atorvastatin. In the future, such evidence may be needed for differential labeling claims.

Finally, there is always the possibility of differences in safety and the question is whether that possibility should mandate against inferences in similar benefits without clinical trials to study all effects. Indeed, at present we have little information on risk vs. benefit in extreme long-term use and I doubt we ever will have clinical trial evidence. With the standards set in the trials that have been completed to date, and in trials that will be completed in the coming years, the ultimate benchmark of safety for these drugs or, for that matter, for any other lipid-altering agent, relates to the impact of therapy on noncardiovascular mortality, knowledge of which requires long-term, large-scale studies and may well differ across the class.

Assuming a declaration of class efficacy was adopted by regulatory authorities, let's examine some of the positive and negative consequences of such an action (Table 3). On the positive side, this would certainly be good for the have nots, those sponsors whose drugs have yet to be shown in clinical endpoint trials to have significant benefits. Promotion for these drugs, as well as other members of the class, would be based upon what were deemed class effects from studies using the other drugs. This might actually generate an effort to establish uniqueness. Sponsors might now be willing to conduct head-to-head trials that would yield comparative safety and efficacy data. It is conceivable that

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Table 3 Declaration of Class Efficacy

Positive consequences	Negative consequences
Good for the ''have nots''	Bad for the ''haves''
Comparative safety studies	End of an era
Head-to-head: uniqueness	
Easier to regulate	
Cost of treatment	

this would make it easier to regulate these drugs, although one could certainly take the opposite viewpoint. Whether this would impact favorably on the cost of treatment is not known. As far as the negative consequences, this would certainly be bad for the ''haves,'' those sponsors who have spent tens of millions of dollars on clinical trials assuming exclusivity for the efficacy claims based on trial results.

Will this spell the end of what has really been a remarkable era of medical progress by removing incentive to conduct large clinical trials in the field? Indeed, already it is difficult to conduct such studies because of presumed class effects of the statins and presumed effects of cholesterol lowering in general. I think this is a particularly complicated issue. Will it be possible to back-track, if unique efficacies are demonstrated? Personally, I assume that there will be a fine line between what have been deemed to be class effects and what a sponsor may present as presumably novel drug-specific effects.

In conclusion, the accumulating data from statin trials serve as robust confirmation of the cholesterol hypothesis that was formulated nearly half a century ago. In addition, they speak to apparent shared efficacy and safety across this class of lipid-lowering agents. As such, it is increasingly difficult to study new statins and perhaps other lipid-altering agents in controlled clinical trials. The issue of class efficacy is complex both scientifically and in terms of regulation. It is now appropriate for open discussion of this issue with industry.

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16
Natural History Endpoints and Angina Trials

Raymond John Lipicky

The following comments should be taken neither as formal Agency policy nor as guidance. They are offered here only for the purpose of eliciting questions during the following discussion period, since assertions are incompletely developed and problems related to drug development programs are only partially identified.

The Division of Cardio-Renal Drug Products considers antianginal therapy as symptomatic therapy; consequently, therapeutic benefit is judged simply upon demonstration of symptom relief. Improvement of a symptomatic endpoint requires comparison to placebo. Thus, for a drug to be approved for the treatment of angina, symptom benefit must be demonstrated in randomized, placebo-controlled, dose-ranging clinical trials. Measurement of the duration of symptom-limited exercise tolerance, whether by bicycle or treadmill, provides a convenient and suitable endpoint for such trials. An increase in exercise duration is taken as a direct measure of symptom relief. It is not a surrogate. The magnitude of the increase ordinarily is not considered important enough to require definition (except in terms of power calculations when designing the trial), nor is it important in the approval consideration.

Another suitable endpoint would be documentation of the frequency of anginal attacks during ordinary daily life. Other measures

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of symptoms might also be appropriate, but are uncommon enough not to be worthy of mention. There are insufficient numbers of patients who have chronic, stable angina and angina rates that are frequent enough to seriously entertain trials where frequency of angina is a major endpoint. This is probably true because of the current frequency of use of interventional procedures such as percutaneous transluminal angioplasty.

Symptom relief alone is inadequate. An antianginal therapy must also be shown to have an anti-ischemic effect, by comparison to placebo. The anti-ischemic effect can be evaluated as part of the exercise tolerance test, but need not be exclusively restricted to exercise tolerance testing. Wall motion abnormalities during imaging, or other common means of evaluation of myocardial ischemia (e.g., ambulatory ECG monitoring) are also appropriate methods that can be used.

Morbidity and/or mortality are not the principal focus. Of course, a claim for improving morbidity or mortality would be totally impossible simply on the basis of exercise tolerance data alone. Although not the principal focus, morbid and/or mortal events should be measured in any development program. More importantly, the results of exercise tolerance trials are scoured for potential adverse effects on morbidity/mortality. Our expectation is that all potential adverse effects will be thoroughly explored in dose-ranging studies.

An example of past action on a drug with possible disparate effects on symptoms and mortality is the case of the approved antianginal drug bepridil. Bepridil is a calcium channel blocker that was shown to be antianginal and also to be clearly anti-ischemic in randomized, placebo-controlled clinical trials using symptom-limited exercise tolerance testing. However, upon initial FDA evaluation, bepridil was not approved because it lengthened the QTC interval and induced torsade de pointes.

The ultimate path leading to approval of bepridil was based upon a randomized trial involving a patient population with angina that was refractory to a widely used approved drug. A patient was defined as being refractory if the patient had an unacceptable rate of angina at the maximum approved drug dose, or if dose-related side effects precluded an increase of the dose of the approved drug. Such refractory patients were then randomized (in a three-arm parallel group trial) to either placebo, the drug to which they were refractory or to bepridil. The

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rationale was that the drug with demonstrated risk must distinguish itself from an approved drug by either producing greater symptomatic benefit or equal symptomatic benefit but fewer side effects. Such a trial needed to be performed in a population easily identified as refractory to treatment; being known to be superior to placebo in some other population was not sufficient. In the case of bepridil, the sponsor did such a trial. Bepridil was superior to diltiazem with respect to symptom-limited exercise tolerance, and was consequently approved as second-line therapy.

Another point worthy of consideration is the performance of exercise tolerance testing for drug approval purposes. In an antianginal program, symptom-limited exercise is the endpoint of interest. Therefore, in all randomized patients, angina must be the symptom that limits exercise testing at the time of randomization. Patients who, prior to randomization, cannot exercise to moderate angina because of other symptoms should not be randomized. Once a patient is randomized, termination of exercise should be ''any''-symptom-limited; the test remains a symptom-limited exercise test, even if angina is not the symptom that is limiting. Any symptom (e.g., shortness of breath, fatigue, intermittent claudication) is acceptable after randomization and is the endpoint of the test.

For vasospastic angina the number of anginal episodes is counted and the number of anginal episodes is the principal endpoint; it remains symptomatic evaluation. The rarity of the vasospastic angina syndrome and the unpredictability of its occurrence have influenced our thinking with respect to a trial that would be reasonable. For an agent that already has been shown to be effective through symptom-limited exercise tolerance testing in chronic stable angina patients, a single, randomized, placebo-controlled, withdrawal study in patients with vasospastic angina would be sufficient. This single trial must be persuasive through being adequately powered and by showing consistent drug effect, with a p value in the range of 0.01 or smaller, using a two-tailed test.

Unstable angina will not be discussed, since that entity is, in essence, an acute coronary syndrome for which the prime considerations for approval are drug effects on irreversible damage (e.g., myocardial infarction) or morbid and/or mortal events.

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17
Development of Antiplatelet Drugs

Stephen Fredd

Cardiovascular diseases, including peripheral vascular disease, cerebral vascular disease, coronary disease, disease of the renal artery, etc., are highly prevalent throughout the world. Nonetheless, there are differences among the various nations in mortality rates, application of therapeutic procedures, and risk–benefit statistics. It is important to consider these in designing clinical trials that now commonly are multinational. For example, U.S. clinicians tend to be very aggressive in applying arterial stents by catheter. This fact may introduce a treatment-by-country interaction in clinical trials; this factor would require consideration in the plan for analysis and interpretation of data from such studies, and may affect the plan for inclusion of specific countries as a group in specific trials.

Regardless of such design considerations, however, the development of trials for antiplatelet drugs must begin with an understanding of the pathophysiology of thrombosis and the pharmacology of drugs that can affect this process. Atherosclerotic disease is characterized by instability at the endothelium. The causes of the instability are several, and can vary with the underlying disease processes: unstable angina, the effects of PTCA in traumatizing endothelium, etc., all involve pathophysiological particularities, but all have certain processes in common, including the release of vasoactive and thrombogenic materials. Indeed, teleologically, it has been suggested that our hemostatic systems have evolved in response to our evolution from a jungle envi-

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ronment. The clotting system protects us against bleeding by being cut by leaves and branches, etc., and therefore is highly responsive to any injury (and may be excessively responsive in the context of modern life).

An injury to the endothelium results in a series of reactions in which the platelets are ''prime movers,'' in a sense laying down a platelet bandage. Then there is propagation of the initial platelet layer into a plug. This would be both highly effective and safe as a response to an injury on the skin, but is relatively less safe in the coronary artery where the plug can obstruct the arterial lumen. Moreover, the lytic components of the hemostatic system, meant to lyse such clots and restore normal architecture, are not so well developed as the thrombotic components, so that the net effect of the hemostatic response can be pathological thrombogenesis.

Potential therapeutic approaches to this problem can aim at several targets. However, while demonstration of pharmacological effects against such targets may be relatively simple, the drug developer must consider the end to demonstrate clinical benefit against a standard of proof that can be relatively rigorous. The challenge, then, is to prove clinical efficacy; in an era in which other therapies exist and placebo control often is not possible in practice, an important question may be to define the appropriate comparator drug against which to demonstrate superiority.

The problems involved for the developer are best elucidated by example. One potential comparator in antiplatelet trials is aspirin, an inexpensive drug. Aspirin acetylates cyclo-oxygenase, preventing the homeostatic plug from propagating by preventing release of ADP from inside the platelet. It does not directly modify the receptors on the surface of the platelet. When endothelium is injured, many biologically active factors are released, and some of these interact with platelet surface receptors, enabling or promoting continued clot propagation. Therefore, though the pharmacological effect of aspirin is very effective in preventing clinical events in patients with coronary and cerebrovascular diseases, it is not clear that this must be the only or most effective basis for clinical efficacy of antiplatelet drugs. Aspirin has pharmacological effects in addition to prevention of cyclo-oxygenase

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acetylation, and some of these also may be important in the genesis of clinical benefit.

Because of these interesting pharmacological possibilities, sponsors have begun development of a series of platelet receptor blockers, including thromboxane receptor blockers, IIBIIIA receptor blockers, and ADP receptor blockers. For example, ticlopidine and clopidogrel are meant to block ADP receptors, although we have not yet identified the active moiety. (Thus, neither ticlopidine nor clopidogrel are active against platelets by themselves, but rather need to be transformed first into the active agent.) Moreover, if the ADP receptor is blocked, the activity of the IIBIIIA receptors also is affected, so that they do not respond normally to thrombin, collagen, etc.

The vitronecter receptor also is potentially involved in the pharmacological prevention of pathological thrombosis. Among IIBIIIA receptor antagonists, the prototype, ReoPro (abciximab) also blocks the vitronecter receptor, while integrelin, also a IIBIIIA receptor antagonist, does not. The importance of this difference remains to be demonstrated in clinical trials.

In considering clinical trials, particularly those that include previously approved drugs as background therapy, factorial design is important. Unless factorial design is incorporated in the clinical trial and demonstrates the independent efficacy of the new drug, then even if the drug is approved, labeling can only describe how the clinical trial was performed, and not recommended for or against other drugs such as aspirin and heparin. An example of this occurred in association with the approval of the J&J Palmaz-Schatz coronary stent. This stent expands in the coronary artery. Obviously, if one of these metal scaffolds is placed in a coronary artery, it is necessary to preclude clot formation on the stent. As I pointed out earlier, we are ''over-built'' for clotting. Therefore, the regimen empirically used in the trials involving the Palmaz-Schatz Stent included prophylaxis with a combination of aspirin and dipyridamole and low-molecular-weight destran and heparin and warfarin. The primary comparison did not take cognizance of the antithrombotic prophylaxis, but rather only of the use or nonuse of the stent. However, because the various potential combinations were not studied in a comparative design, as with factorial design, all of these

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needed to be mentioned in the stent labeling. After approval, this unwieldy regimen was totally unacceptable to clinicians, as it appeared to be associated with excessive incidence of bleeding at the femoral access area and increased hospitalizations for bleeding. The problem, which developed here, is very instructive. It is important to remember that there is an antithrombotic dose of these drugs and there is an anticoagulant dose of these drugs; depending on the specific clinical situation, one may not need to severely impair the coagulation cascade or platelet function to achieve acceptable antithrombotic efficacy. Dr. Columbo in Italy assessed the utility of less aggressive antithrombotic regimens. In fact, he used aspirin alone and employed intravascular ultrasound to show that the stent had been optimally placed. His data suggested that, when the stent was optimally deployed, patients could be protected against thrombosis by aspirin alone. However, another group, in France, suggested that optimal protection could be provided only by a combination of ticlopidine and aspirin. This led to the suggestion that a comparative clinical trial was appropriate.

Skeptics of the need for ticlopidine in addition to aspirin, myself included, preferred the simplest regimen possible, so a clinical trial, the STARS study, was done. In this trial, patients stented optimally by ultrasound criteria were randomized to aspirin alone, aspirin plus ticlopidine, or aspirin plus warfarin. This is an incomplete design, not entirely satisfactory; I'll explain why, but it gives you some information. Patients who were suboptimally stented were treated according to the biases and beliefs of the individual physicians.

The primary prespecified endpoints was a composite including death, Q-wave MI, emergent CABG at 30 days and angiographically demonstrated subacute closure. The results indicated that the best of the three regimens was aspirin plus ticlopidine, which was significantly more effective than the other regimens. This statistical superiority was based predominantly on the reduction in Q-wave MI associated with this regimen; neither death nor emergent CABG were importantly affected individually.

From these results it was concluded that aspirin plus ticlopidine is the regimen of choice for preventing complications of stenting. However, if you consider the design of the trial, the only legitimate conclusion is that ticlopidine is effective. It is not clear whether or not ad-

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junctive aspirin is necessary to achieve this effect. Thus, labeling could say that ticlopidine was studied in the presence of aspirin, but not that aspirin was required.

The hemostatic system depends on the synergy of several factors, including thrombin, platelets, other endothelial factors, leukocyte-derived factors, etc. Pharmacological therapy might involve antithrombin drugs, antiplatelet drugs, and drugs aimed at other targets. Therefore, let us consider now the development of drugs that may affect other than platelets, but which may be adjunctive to antiplatelet therapy. In an early thrombolytic study by SCATI Group, a mortality trial, there was a suggestion that if you added heparin to streptokinase, mortality was reduced in comparison with streptokinase therapy alone. However, these results were obtained in the absence of aspirin. ISIS-3, with 41,000 patients, showed no difference in mortality after MI with or without heparin. A trend toward reduction in reinfarction was seen with heparin, but this did not reach statistical significance in this very large trial. Indeed, several different regimens were studied in GISSI-2 and ISIS-3 in an effort to define the efficacy of heparin. These included subcutaneous regimens, given at various different times of onset of thrombolytic therapy, and, as a result, there were many potential reasons to explain the fact that heparin never seemed to demonstrate therapeutic efficacy. In fact, these studies indicate that, once aspirin is present in both arms of a trial assessing heparin, then even with 62,000 patients, one cannot detect an effect of heparin on mortality, though increased bleeding can be demonstrated. Thus, all these data indicate that, when added to thrombolytics, aspirin may improve efficacy, but the addition of heparin to the aspirin provides no additional benefit, while increasing risk of hemorrhage.

The impact on study design and interpretation of background therapy, which now is increasingly necessary in clinical trials because of concerns about withholding benefits of established therapy, require further consideration. Another aspect of this problem is illustrated by the SAPAT trial in patients with chronic stable angina who were randomized to either aspirin or placebo, with both groups receiving background therapy with sotalol. According to the investigators, the reason for the background therapy in this trial was the desire to control the heart rate (clearly a factor in the genesis of angina) so that this variable was rela-

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tively similar in value in both groups at baseline. While there may be merit to this approach, it is not immediately clear why such equilibration of heart rate at baseline is needed in a placebo-controlled study. Clearly, the presence of background therapy in this case must confound interpretation of the results.

The ESPS-2 study is not really an ''add-on'' study involving background therapy, but it is instructive in terms of the frequent debate regarding the presumed ethical problems involved in undertaking placebo-controlled trials. ESPS-1 was designed to determine whether aspirin and dipyridamole was effective and acceptably safe among patients with prior strokes or TIAs. ESPS-1 was done in patients who had major stroke; the goal was to see if a second stroke and death could be prevented with just two arms, placebo versus dipyridamole plus aspirin. Dipyridamole plus aspirin beat placebo. However, the study was criticized because the design precluded determination as to whether dipyridamole was a necessary part of the prophylactic regimen. Therefore, ESPS-2 was designed as a four-arm study of placebo versus aspirin versus dipyridamole versus aspirin plus dipyridamole. The results indicated that both aspirin and dipyridamole beat placebo and that the combination beat either of the active components, as well as placebo. If the result proves to be convincing under close scrutiny, this will be powerful evidence that the combination is superior to aspirin alone, and would refute the notion that one can simply consider aspirin plus dipyridamole combinations to be the same as aspirin in meta-analyses. In terms of our discussion of the ethics of placebo-controlled studies, it is noteworthy that ESPS-2 has been criticized in *Science* magazine as unethical because of the use of placebo. Despite the importance of the results, the combination of aspirin and dipyridamole already had been superior to placebo in ESPS-1. The issue of the desirability of replication of such results, with major implications for public health, was not considered to mitigate this ethical concern.

Since antithrombotic anticoagulant drugs may be adjunctive or alternative to antiplatelet drugs in some situations, any consideration of antiplatelet drug development would be incomplete without some mention of this other group. Recent developments in this area include the description of previously unexplored pathways of clot inhibition,

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such as tissue factor pathway inhibitors. Additional studies will be needed, concluding with appropriately designated clinical trials, to determine the role of antithrombotics in therapeutic areas now dominated by antiplatelet drugs.

Finally, the development of antiplatelet agents recently has been complicated by a new challenge related to the use of placebo, exemplified by the issues raised at the recent consideration of clopidogrel for approval, based on the CAPRIE trial. Prior to the completion of CAPRIE, the Aspirin Trialists' Group had petitioned the agency to approve aspirin for a variety of indications. One of the bases for this request was Peto's meta-analysis of the effects of antiplatelet drugs, which supported the clinical benefit of prophylactic use of these drugs in several different clinical settings. However, this analysis lumped all drugs with antiplatelet activity, including aspirin, IIBIIIA inhibitors, ticlopodine, dipyridamole, etc., despite differences in pharmacological effects and, for some drugs, activities in addition to those affecting platelets. The trials that show clinical benefits, and were included in Peto's analysis, did not all involve use of aspirin; however, the analysis suggested that no substantial differences existed between antiplatelet agents in terms of clinical efficacy. If you are developing an antiplatelet agent and we accept the premise that there are no substantial differences between any antiplatelet drug and aspirin, the basis for marketing the new drug is unclear. While it is possible to define new pharmacological effects and new pharmacological targets associated with a new agent, it's quite another thing to prove in clinical trials that the new agent is superior to existing therapy (and to justify the increased cost of the new agent which is likely to be needed to offset resources employed in its development). With this concern in mind, the CAPRIE trial was designed to assess the relative effects of clopidogrel versus aspirin. Based on the prespecified efficacy analysis, clopidogrel did, indeed, prove significantly better than aspirin in prophylaxis against vascular events. However, some analyses raise concerns that for specific subpopulations, the relative benefit of the new agent versus aspirin may not exist. Using a ''putative placebo,'' based on the consistent difference between aspirin and placebo among many trials in the aspirin trialists' meta-analysis, there is little question that clopidogrel is effective in

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many situations. However, it may be difficult to conclude that it outperforms aspirin in all groups and all clinical situations, while it may in others (e.g., peripheral vascular disease patients).

In conclusion, new antiplatelet and antithrombin agents are needed and may add importantly to our therapeutic armamentarium. However, as such promising agents are developed, they should be studied in clinical trials designed to determine not only absolute but relative effectiveness and safety. In this way it will be possible to craft information labels for these drugs so as to avoid unnecessary polypharmacy and to provide the public with effective and safe management options at the lowest possible cost.

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Panel Discussion

Dr. Borer (*Moderator*): Dr. Singh, it seems from your comments that it may not be necessary to measure silent ischemia in an anti-anginal drug development program in the U.K. This would be consistent with U.S. policy. Will you clarify the U.K. position on this point?

Dr. Singh: What I was suggesting is that silent ischemia recordings may be supporting evidence of efficacy. If you decide not to do Holter monitoring to get a license for an agent, it will not be held against the drug or the company in the U.K. Regulation moves with science. If there are developments in science, regulation will follow. What I said was, under consideration, it is a useful and interesting concept. If I can see that a particular patient had 80 episodes of ischemia over a week and if you can demonstrate during subsequent investigation on drug that the number of events fell to 20, I think that would be very useful information. I am not suggesting that this be a mandatory requirement; at this stage European guidelines suggest Holter is only supporting evidence of efficacy.

Dr. Borer: Dr. Singh, I'd like to emphasize what you said during your discussion, which I think is an important point to consider if one is going to think about making ambulatory ECG testing mandatory, which it isn't yet. You said that one of the limitations of total ischemic burden testing with Holter monitoring is that

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morbidity and mortality data also must be collected if clinical benefit is to be evaluated. Perhaps it is more cost effective to do the outcome study and get a second claim.

Dr. Lipicky: We do require that an anti-ischemic effect must be documented for certainty, for an antianginal drug to be approvable; ambulatory monitoring is a perfectly adequate way of doing that. However, there isn't any reason to do exercise tolerance testing in one study and then Holter monitoring in another study.

Dr. Hoppe: I agree with Dr. Lipicky. The European guidelines ask for ischemia results as well. But, I think the guidelines and the CPNP consider maximum exercise capacity as being the most important endpoint and, thus, should be used as a primary endpoint in clinical trials though you should, as well, evaluate measures you can derive from the exercise test, like ST segment depression, time of onset of angina, and time of moderate angina, but should strongly focus on maximum exercise capacity. The European guidelines will be released for consultation within the next few months.

Dr. Fenichel: Thinking about total ischemic burden is a radical move in this business. It is really unrelated to angina because it is not a symptom-directed claim. It is a claim along the orthogonal axis in the diagram that Ray Lipicky showed. It must be a claim for a different outcome (that's what silent means) and so packaged with it one can imagine a drug that was ineffective at reducing the symptoms of angina, but which improves outcome in people who have lots of silent ischemia, just as one can imagine a drug taken post-MI in people with asymptomatic PVCs for purposes of improving outcome. This also is a silent phenomenon with unfavorable prognostic import. However, currently, we know of no drug that provides these benefits and we surely know that merely improving appearance of the phenomenological marker is not good enough. Therefore, there is a long way before ischemic burden will turn out to be of value. One can do Holters and see a change in ischemia, but it is hardly a cost-effective way of knowing an anti-ischemic effect. It seems unlikely that one would find

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a drug that produced it and was ineffective as an antianginal, and it is even harder to imagine a drug that is antianginal and anti-ischemic, but for which the anti-ischemic effect could not be seen during the exercising testing that you are doing anyway and could only be seen during Holter studies. That is fairly far-fetched.

Dr. Borer: I think it is fair to suggest that the Holter data may provide prognostically useful evidence, but this information isn't dispositive here because people don't die of ischemia that is detected on exercising testing or Holter. They die of a sudden change in a coronary lesion. Therefore, there is no direct biological connection between the event we want to prevent and ''ischemia'' testing that we use as the basis for saying that a drug is not likely to be dangerous if it relieves angina. I think that is a key issue when thinking about the role of this kind of ischemia testing in the development of drugs.

Dr. Shah: A large number of patients often is needed to define an effective dose in angina. That is not so much a result of the guidelines, as it is where the industry has gone in its efforts to define the doses. I am sure there are more efficient ways of defining doses. The way I see the two approaches, exercise tests tell you something about the antianginal effect and the anti-ischemic effect and Holter monitoring tells you at least as much as the exercise test. Possibly it might even tell you something more. We don't know, but if that were so, one might get rid of the exercise test and do all the studies with Holter monitoring.

Dr. Borer: You're suggesting here an extrapolation from Dr. Singh's data, that there is a statistically verifiable relation between the results of exercise testing and the results of Holter. I would suggest there is a problem with this extrapolation and I would like you to comment on this. With exercise testing, we know the stimulus that causes angina. With Holter monitoring, we have no idea of the magnitude of the stress associated with the ischemia frequency and ischemia severity which are recorded. Therefore, it may be difficult to draw the same kind of conclusions from exercise tolerance testing and from Holter monitoring. How would you respond to that?

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Dr. Shah: The exercise test is artificial, there are limits. When I saw the list of limitations there seemed to be a longer list of limitations with the exercise test than with Holter monitoring and, at the end of the day, whatever the stimulus to ischemia or angina, the efficacy of the drug must surely reside in relieving it.

Dr. Somberg: There may be a longer list of limitations where exercise testing is useful because we know the test well and it has been around so much longer than Holter monitoring. I think exercise testing has a very well-defined place in drug development, as Dr. Borer was saying. If we know the stimulus for angina and have a very well-defined prior data base on drugs prolonging that time to angina, as we do, the results of testing are very useful. I am concerned about the large number of patients who don't have reproducible angina and do have reproducible ischemia. I am also concerned about the number of patients who, on exercise testing, may actually no longer have angina, but still have ischemia. As Dr. Lipicky said, you want to show that people have angina and that you can actually prolong the time to angina with the study drug. In a recent study by my group, we noted response to TNG in a large number of patients. I noticed that one patient took TNG and then repeated the test and did more work, but had more ST depressions, significantly more ST depression, but no longer had any pain. I went back and looked at our data and noticed that a lot of people no longer had angina, but still had ischemia as measured by ST depression and then looked at myocardial perfusion scintigraphy results and found these people had perfusion abnormalities, showing that our finding is not just some sort of EKG artifact. In other words, there is a population that has silent ischemia, overt ischemia, which on TNG therapy has converted angina into silent ischemia. I think the Holter monitor enables interrogation of a different type of population than exercise testing. Maybe they overlap considerably, but also, as pointed out in a number of studies, people do not just have tachycardia-induced ischemia, they have ischemia due to mental stress or other factors that can induce ischemia. While it may not, as you say, relate to mortality because mortality is due to a hemorrhage into the

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plaque, it relates to ischemia and ischemia might at different provocations result in either symptomatic or silent ischemia. The beta-blockers post-MI reduce mortality, perhaps by reducing ischemia and associated phenomena, particularly electrical instability. For drug developers, I think it is useful to correlate drug action with silent ischemia reduction and with something more meaningful than an ST change because, unfortunately, there are so many products for angina now, one really has to distinguish a product to make it an economically viable investment for development.

Dr. Borer: Can you clarify one thing for me, John, before the panel responds to these issues. It sounds to me as if you are beginning to make an argument for doing Holter monitoring to define the acceptable safety of a drug for relief of angina. If I understand you correctly, the drug you postulate is still being tested to make people feel better to relieve angina. If that is the case, we must show that the Holter data with the increased ST segment depression actually relates to a meaningful, quantifiable safety concern that we ought to do something about. If it does not and we are saying, instead, that making ST segments go away is a good thing in and of itself, I would think we would have to show that somehow with a natural history endpoint study.

Dr. Somberg: You are absolutely right. Just making ST segments go away should not be equated with benefit of the product. That a patient is having wall motion abnormalities is important. In studies, ST segments correlate with wall motion abnormalities. Nuclear vest studies have been used to correlate ST changes and wall motion abnormalities in some studies. We want to have a clinical benefit. It is difficult to show efficacy, less myocardial infarctions, less mortality, more people alive at the end of the day. It is also difficult to show safety for those same reasons. I am not claiming that it is a safety claim or an efficacy claim. I'm saying in addition to the use of the exercise test, the Holter has value. The Holter tells about the drug's effect on ischemia as well as angina, but you have to correlate the Holter with something to make it meaningful, especially to regulators. This is a field that I think is ripe for further investigation. As a side comment, you

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referred to a well-controlled study of 600 patients. I think that 600 patients are inadequate. Dr. Orloff did a beautiful review of the lipid-lowering therapies and only when you start dealing in thousands and tens of thousands can you start talking of class effect. I think that angina/ischemia studies are grossly underpowered. You might have a 3 to 4% mortality. If you go down to a 2% mortality, a 50% reduction, which would be a wonderful result of drug therapy, you would probably need 2000 to 3000 patients to power that study. So all of these Holter studies are so inadequately powered for endpoints that we really can't say that these problems have been evaluated properly.

Dr. Singh: In one study, if I remember correctly, about 28% of patients showed transient ischemia on a Holter, but they were exercising to get it. In addition, the correlation between Holter ischemia and the subsequent development of the unstable angina needs to be clarified.

Dr. Hoppe: I think you should very carefully prove and try to validate the surrogate endpoint of silent ischemia for a clinical outcome because patients won't have any other obvious benefit if they don't suffer symptoms, but they will be at risk from the drug's side effects. Peter Cohn has shown that there might be different risk groups, based on outcomes, defined by Holter-based ST segment analysis, but quantitative relation between changing the ''risk factor'' and changing outcome is not known. From the regulatory point of view, you should carefully prove that this surrogate is associated with morbidity and mortality in the majority of patients and that its alteration invariably alters outcome.

Dr. Borer: FDA has proposed using point estimate differences from historical placebo controls as a basis for approval of certain drugs, such as thrombolytic agents, when they are studied against active controls that previously have been studied against placebo. This strategy has been suggested because it is difficult and often considered unethical now to do placebo-controlled trials in this area. There may be some difference in opinion between the European regulatory community and the American regulatory community

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about this issue, so can we have some discussion of the basis for approval of new thrombolytic agents.

Dr. Fenichel: This is a very good question because this is a very interesting area. A disclaimer, first of all, is that the Division of Cardio-Renal Drug Products is not the portion of the FDA that regulates thrombolytics. By historical precedent and because thrombolytics are, by and large, complex, large molecular weight brewing products, they are regulated by an arm of the Division of Biologics. What I say represents only my opinion and not that of the FDA. With that disclaimer and if anyone is still interested in listening, I will say something about the history of this issue. The important feature we noticed when looking back over the multiple placebo-controlled trials, was a consistent success in beating placebo. In a variety of populations, which varied in terms of severity of disease and access to other therapies over the course of multiple years of doing these studies, when the placebo population had a mortality rate following MI of, say, 12%, the thrombolytic group always had a rate of less than 10%. When the placebo group result had improved, because of different population or because it was a few years later and other therapies had improved, or however it may be, when the placebo group had improved to, say, 7%, the thrombolytic group was down below 5%, and so forth. We found that, typically, the extent to which placebo mortality was worse than thrombolytic-treated group mortality was 2.6%, and the 95% confidence limit indicated that you were quite sure that the placebo group was 0.1% worse. We proposed that one could run a trial of a new thrombolytic comparing the new thrombolytic to an old one, say tPA or streptokinase, and that this would not be an equivalence trial. The important concept is that an equivalence trial has the property that one has to choose an arbitrary standard as to how close is close enough and so on. We are not doing that. This is a trial of the new drug against placebo. Placebo does not happen to be present in the trial, but we are trying to show that the new drug beats a placebo value constructed from historical data; the assumption is that, had placebo been in the trial, we know how good that placebo could possibly have

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been. If in this trial of new drug against tPA, the mortality in the tPA group was 5%, we know historically that placebo could not have been better than the mortality of a little more than 7%. The first criterion that we set was the 95% worst confidence level of the drug has to be better than 7%, so the new drug might have a mortality of, say, 4% plus or minus 2%. Such a value would lead to approval, and would suggest the new drug was better than tPA. For that matter, the new drug might have a mortality of 6%, which is a little worse than tPA, but perhaps it is a big enough trial so that it is 6%, plus or minus 0.5%, a value which is still better than the best placebo could have done. That was our first criterion in this area.

The second thought, brought out by that particular set of numbers, is that we needed to deal with the situation in which a very, very big trial showed the new drug to have a mortality of 6.9%, plus or minus 0.1%, so it was better than placebo, but much, much worse than tPA. How does one deal with that finding? What came out in the original discussion, about 3 or 4 years ago, was the suggestion that the new drug has to preserve something on the order of half the benefit of standard drug. What some people took away from that was that in this example, with tPA coming in at 5% and the putative placebo with less than 7%, the new drug would not only have to have its 95% confidence limit better than 7%, but the point estimate would have to be $\leq$6%. That is not the only possible interpretation, as we have recently learned when a drug was discussed by an Advisory Committee. The Advisory Committee, just a few months ago, thought that there should be at least 50% of the benefit of the proved agent retained and the way one knows that that benefit has been retained is that the 95% confidence limit is better than 6%. I am troubled by that because it means that, for example, tPA running against itself might lose. Thus, there are other mathematical difficulties that come out of that interpretation, but as it turns out in the case where this came up with the drug that was being discussed at the time, there wasn't an issue because the drug turned out to be pretty good and so it won on either standard. There will be hard cases to decide based on the point estimate concept. We are going to have to thrash this

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out. I can't say what the policy is because it has not been tested by something falling in between the two interpretations of this 50% rule. But, that is the situation now as I understand it.

Dr. Borer: Dr. Singh, how would the European community or the U.K. look at this issue?

Dr. Singh: This is done by the Biologic section so I don't have direct hands-on contact with this subject. If it is not possible to carry on a placebo-controlled study in Europe, if I understand correctly we would accept a comparative controlled trial.

Dr. Borer: How would the new agent win?

Dr. Singh: It has to show equal efficacy.

Dr. Borer: What is the basis for calling it equivalent? Is there a point estimate difference that is considered acceptable?

Dr. Singh: Yes. Point estimate difference is acceptable. Second thing is that there is as yet no guideline for the European agency, but I believe they are working on it.

Dr. Borer: It doesn't sound as if the comparison with the putative placebo is part of that equation yet, or am I wrong?

Dr. Singh: No. It is not, on the basis of what we have followed in other cases. Where there is a good comparator, the study would be acceptable to have a comparative controlled trial with a point estimate.

Dr. Lipicky: How do you decide that there is a good comparator?

Dr. Singh: In the case of thrombosis for instance, what I understand at the moment is that tPA is employed for clearly defined indications and is the standard of care. Now, if a new drug has a similar indication in a similar group of patients and in large studies with two parallel groups running, one with tPA, one with the new drug, an evaluation could be made. The results would be acceptable for efficacy purposes. I would, however, point out that no claim for any superior efficacy would be allowed. The basis of approval on

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a comparative study would be acceptable on the ground that a placebo-controlled study was not possible.

Dr. Fenichel: There is something very special about the thrombolytics, which is this extraordinary consistency in beating placebo. That is the only way we may allow ourselves to base approval on a comparator evaluation. In many other areas (the one that comes most easily to mind is not in the cardiovascular arena, but rather the area of antidepressant therapy) drugs that are known to be good, which are approved, which are available, which might, in suicidal patients, be unethical to withhold, might be evaluated through a comparator, but sometimes, these agents don't beat placebo in good trials and we don't know why. Therefore, currently there is no possibility of doing a head-to-head study without placebo in that area because mere similarity, no matter how tight, may not prove anything at all. The different subject areas have to be looked at one at a time. Thrombolytics are a very hard case because the benefit of thrombolytics, although important from a public health point of view, are really small. A hundred patients with MIs come in and 95 of them are going to do well no matter what you do, three of them are going to die no matter what you do, and the remainder to receive benefit from a thrombolytic. So you have got to evaluate a lot of patients in order to estimate some difference in outcome.

Dr. Hoppe: I recently saw an interesting approach involving two regimens of tPA, one a double bolus regimen and the other an infusion. A sequential design was used and an absolute difference between the two treatments that shouldn't be crossed was employed to determine drug effect.

Dr. Shah: Like Dr. Singh, I am not involved in the group that deals with thrombolytic products, but could give my personal views. The way I see it, there seem to be some differences in emphasis between the MCA and the FDA. Across the Atlantic the emphasis is on curing disease whereas in the European Union the emphasis seems to be on management of disease, and on the other side of

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the Indian Ocean, in Japan, the emphasis seems to be on making the patients comfortable (i.e., on efficacy or safety or something in between). Regarding the use of placebo, which has been considered here, in Europe we are increasingly questioning the use of placebos in a number of situations. Recently Dr. Hoppe and I were in Barcelona where we discussed the use of placebo in angina studies. I would tend to agree with Dr. Singh that we now discourage use of placebos in situations where active comparators are available. The next question is what is a good comparator? In the EU we take a very pragmatic view that the comparator that we like to see used is the product that is most widely used in the community because at the end of the day the new product, if it is better, will replace that product on the market. This is what we would encourage as an active comparator. The next question then becomes, what is a cure? How beneficial is the cure? I suppose the answer applies in any situation just as much as it applies here. Today, ''cure'' study would need to be sufficiently adequately powered to detect small differences, but with the statistical analysis of the total test that you can accept either possibility with confidence that your treatment is worse than the one to which you are comparing or it is statistically better than the one to which you are comparing.

Dr. Hoppe: I have to admit I disagree with the opinion of Dr. Shah regarding the best standard. I think there might be national differences within the EU, and at least in Germany, we consider those agents to be the standards which have the best data in terms of the survival rate within a certain amount of time. For example, within 6 h for front-loaded tPA.

Dr. Somberg: In a number of areas through the next few days we are going to be talking about how to compare therapies. We usually think about pharmacological comparisons. However, there may be nonpharmacological comparisons. For arrhythmias, we are looking at the internal defibrillator and for thrombolytics I think we can look at urgent angioplasty. Rescue angioplasty versus a thrombolytic might be another way to look at how one goes

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about evaluating a modality of therapy. The agent's place in therapy, the pharmacological efficacy versus alternative approaches, may be defined.

Dr. Hoppe: I certainly think that the data about urgent PTCA are very promising. The only thing that I think should be considered are the centers employed in the study. I think the success of PTCA and risk to patients is very dependent on the experience of the staff and I think it is very difficult to generalize these results to community practice.

Dr. Borer: Dr. Orloff discussed the potential for class labeling for the HMG Co-A reductase inhibitors. In some ways, that concept presents a problem that is a little bit different from the problem presented by the antianginals or perhaps even the thrombolytics or some of the other cardioactive or vasoactive agents. The HMG Co-A reductase inhibitors are active in the liver. There is no evidence that they do anything directly to the blood vessels; the beneficial effect presumably is due to cholesterol lowering or some alteration in metabolites made by another organ. However, that also means that the safety of the drug has to be scrutinized differently because it is working primarily at a site distant from where it has its beneficial effect. You discussed the safety issues, but I would like to question you a bit more about this. You pointed out that in two of the three largest studies done most recently there was no difference in the incidence of cancer, whereas in the third of the three studies there was a difference and, of course, in the earlier studies there was a suggestion of an increased risk of cancer with other cholesterol-lowering agents as compared with placebo. In earlier studies there was also the suggestion that once one dropped below a certain cholesterol level, other problems would begin to develop, specifically neurovascular problems at a total cholesterol below 160. If you extrapolate to the Tangier Island population, in which total cholesterol levels below 100 are seen, a vascular biologist might say this would be wonderful for atherosclerosis prevention, but major neurological abnormalities have been found in that population that had nothing to do with the vasculature. Cholesterol is a necessary component of cell

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membranes and since neurons have the most cell membrane, you could imagine any number of problems as cholesterol goes down further. What are your thoughts about these other potential problems of the HMG Co-A reductase inhibitors? How are we going to deal with monitoring or labeling of these drugs as we push cholesterol ever downward and add potential safety problems?

Dr. Orloff: First of all, reports of problems with the HMG Co-A reductase inhibitors really have been just anecdotal presentations of strange psychoneurological changes in association with cholesterol lowering. Really, thus far, in a broad experience (though, admittedly we have a problem in learning about these things only through a spontaneous reporting system), these are not particularly common events. I think that they have to be called idiosyncratic and for most people do not constitute a problem. Whether there is a lower limit of cholesterol that is going to induce such problems, we don't yet know. One of the theoretical adverse problems from cholesterol lowering is abnormal adrenal function and gonadal steroidogenesis. It turns out that, at least with reductase inhibitors, this also has not been a problem. Early on, slight decreases in adrenal reserve, as measured in long-term ACTH testing, were shown. Such changes never have been shown with the reductase inhibitors in short-term testing. One instance with one of the drugs revealed a decrease in the HCG response to testosterone, in boys, but it has never been shown in adults and has never been shown in ASD patients. There are alternative routes whereby these steriodogenic tissues get their cholesterol. For example, in the adrenal gland there are HDL receptors that seem to effect the delivery of cholesterol as transported by HDL to those tissues. So even when their indigenous synthesis is inhibited by a reductace inhibitor, there is still a source for critically important tissues. Those same kinds of backup systems might well exist in other tissues.

Dr. Borer: What about the loss of incentive to do trials if class labeling can be obtained. Has your division thought about any kind of equivalence or putative placebo-controlled trial that would allow drugs to continue to be developed?

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Dr. Orloff: This is a big problem. I think it is perhaps unique to this class of drugs because of what you mentioned about the important issue that was resolved, that is, the absence of adverse impact on noncardiovascular mortality in recent trials that had been suggested in other studies. In retrospect, it may have been bad luck in some of the earlier resin and fibrate drug studies, for example, the increase in violent and accident-related deaths that made people wonder about possible noncardiovascular adverse impacts of these agents. Nevertheless, the statins stand out, at least in the history of the field, as unique in not causing those problems. So that is the standard to which we must hold other drugs. What this means is that if you wanted to study a new agent, even an LDL-lowering agent, for the purposes of initial approval, the regulatory requirement would be the demonstration of efficacy in lipid lowering. Sufficient exposure to assess safety in a relatively short period would be difficult. In the view of some IRBs, to do even an active controlled study is impossible in an era where we have statins as options for treatment that we know are going to decrease morbidity and mortality. I think it is appropriate to promote drug development to approve an agent based on active control studies without a background of statin therapy in one arm. On the other hand, if you are trying to develop a drug that alters lipids other than by lowering LDL, then you've got a big problem because we have stated that we want to see clinical endpoint data and yet you have very wide use of statins already in patients with elevated LDL. The known beneficial effects of these drugs cause difficulty in stopping them. So, in many instances, I think it would be virtually impossible to do other than a trial with background therapy with the statins in both arms.

Dr. Somberg: Dr. Orloff, you seem to be suggesting, for drug approval, that you would still need the large safety database, but you wouldn't have to perform a mortality trial to say that lowering LDL cholesterol with a statin gives you a clinical benefit. However, if you came in with any other drug besides a statin, as you were just pointing out, you would have to do a mortality trial. So I really don't think it is going to limit acquisition of useful data

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from clinical studies because the frontiers in this area are beyond statins.

Therapy is fine if you have an elevated cholesterol and you want to reduce cholesterol an average amount (10–30%). But there are a lot of patients with hyperlipidemias in whom this degree of reduction doesn't really normalize lipids. There are an awful lot of people out there that have been on statins for 3 or 4 years and are still having progressive atherosclerosis and ischemia and events. There is a large frontier for needed adjuvant therapy, combination therapy. In fact, the combinations now available are really difficult to use. In patients with a high LDL on a statin, you would want to add a fibric acid drug, but you can't do that due to a heightened risk for rhabdomyolysis. New, more potent agents, as well as supplemental agents are needed. I really think there is a need to do additional large randomized controlled trials.

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V
CONCLUSION

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Future Directions of Cardiovascular Drug Development

Jeffrey S. Borer

Cardiovascular drug development has been altered considerably during the past 18 years, the period during which the symposium series has been in existence. Changes have affected drug discovery, trial design, endpoints requiring investigation, consideration of drug interactions and relative emphasis on economic concomitants of therapy. These changes, all still occurring, define and circumscribe the foreseeable future of cardiovascular drug development.

DRUG DISCOVERY

Nowhere has change been more obvious than in the area of drug discovery and in the therapeutic targets at which this process is aimed. Drug development mirrors the understanding of the pathophysiological processes to be therapeutically modified. Two centuries ago, when disease was understood primarily as a phenomenological construct of symptoms and signs, digitalis was employed for treatment of dropsy and was characterized as a drug that enhanced urine flow, with relief of edema. A little more than a century later, with increasing knowledge of myocardial physiology at the organ level, digitalis was recharacterized as a drug that enhanced urine flow in patients with heart failure by increasing cardiac contractile force to increase blood flow to the

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kidneys. Subsequently, as insight into cell biology progressed, digitalis again was recharacterized. This time, the agent was seen as enhancing urine flow in patients with heart failure from left ventricular systolic dysfunction by altering intracellular calcium via an impact on sodium-potassium ATPase, while, at the same time, changing sarcolemmal ion channel activity in a manner that can result in potentially lethal arrhythmias. Tomorrow, as the basis of heart failure is further refined to include such biological variations as subnormal expression of the gene coding for structural peptides and alteration in the expression of cytokine cell signaling molecules, digitalis may be recharacterized once again.

Thus, over the course of two centuries, the level at which we understand cardiovascular pathophysiology has progressed successively from phenomenology through whole organ physiology, cell biology, and molecular biology. The ferment that currently envelops cardiovascular drug development is at least in part attributable to the relatively recent application of molecular biological research techniques to unlock the secrets of cardiovascular physiology and pathophysiology, and the impact of this progression on drug discovery.

Molecular biology encompasses a set of powerful tools which hold promise of discovery at a level more fundamental than ever previously approached, that of the genetic control mechanisms underlying all biological function. As applied to pharmacological therapy, molecular biological research holds the keys to two different and complementary lines of inquiry, as well as to technology enabling production of some of the new products generated by research. First, molecular techniques permit identification and definition of the cellular metabolic abnormalities of cardiac diseases in a manner that is both more efficient and more precise than any that previously has been available. This information can be used to ''design'' or to modify conventional drugs which can beneficially modulate pathophysiological cell biology. Second, molecular research can identify gene products that can be enhanced or diminished *directly*, potentially mitigating pathophysiological processes by so-called ''gene therapy'' to direct production of metabolically active peptides and of cell surface receptor molecules.

Both lines of inquiry promise extraordinary benefits. However, the technical difficulties in effecting gene therapy suggest that, for most cardiovascular diseases, practical application of such therapy is several

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years away. While these developments progress, molecular techniques already have enabled the production of large quantities of pharmacologically active biopeptides by harnessing the genetic controls of a horde of captive bacterial ''laborers'' which work more efficiently than any currently available synthetic machinery to produce such drugs.

Examples of these new developments abound. Exogenously administered cytokine neutralizers have mediated experimentally induced heart failure; synthetic peptides have successfully blocked platelet receptors central to pathological hemocoagulation; transfected genes have produced cytokines to support angiogenesis after transmyocardial laser-based angioplasty; genetically engineered bacteria have mediated production of extraordinary quantities of rt-PA for thrombolysis early after myocardial infarction. These contributions merely hint at what soon will be possible.

TRIAL DESIGN

The past 18 years have witnessed development of numerous effective cardiovascular therapies. Treatments have mitigated symptomatic debility and, in some cases, have beneficially altered the natural course of disease. In achieving the latter, some therapies have come to be regarded as essential, to the extent that it is now considered unethical to perform research in patients who are not receiving them. Therefore, with increasing frequency, successful new drug development has precluded subsequent placebo-controlled trials of new monotherapies.

A therapeutic effect can be demonstrated only in three ways (i.e., by comparison with placebo treatment, by demonstration of a positive dose-response relation for the effect, or by proving statistically significantly more effective than an existing, well-established therapy). In fact, it can be argued that the quantitative impact of monotherapy with any drug cannot be defined accurately unless that drug is assessed in direct comparison with placebo, administered in blinded fashion and in the absence of confounding background therapy (or, at least, in the presence of a sufficient variety of background therapies to demonstrate

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that the new drug's effect is relatively constant regardless of background). If placebo treatment is unacceptable, some other basis must be defined to confirm a treatment effect. For U.S. regulatory purposes, drugs generally are considered effective if their performance significantly exceeds that of a previously approved drug (''active comparator'') employed at a previously approved dose. This criterion entails an important and possibly unsupportable burden on a new drug that may be effective and yet may not be superior to the active comparator. Currently, there is no statistical method to verify drug equivalence. Therefore, though possibly useful as an alternative therapy, the new drug may not be approvable.

To fill this void, the FDA has developed the concept of the ''putative placebo.'' A ''putative placebo'' is constructed from the historical data relating an active comparator to placebo. In order for this comparison to be useful for approval purposes, the active comparator must have been compared to placebo in a sufficient number of studies so that the variability of differences in drug effect and placebo can be determined with reasonable quantitative accuracy. Further, from assessment of this variability, it must be shown that the difference in effect between comparator and placebo is relatively constant across studies. This concept has been useful in assessing thrombolytic therapies for which the difference in effects between placebo and active drug has been relatively constant among multiple studies of single drugs and also among studies involving several different treatments. (The same might be said of the effects of HMGCoA reductase inhibitors on cholesterol lowering and, possibly, even on coronary event rates.) Currently, however, this concept would not be applicable for development of a new drug for heart failure or for angina. In these areas, the quantitative difference in effect between active drug and placebo has varied widely among studies of any single drug, and even more widely among different drugs.

If the putative placebo has only limited applicability, what other methods can provide evidence of effectiveness for drugs that cannot be compared with placebo directly? One might be the development of statistical methods, such as those called ''surface analysis'' procedures, which would enable determination of the likely effect of monotherapy by extrapolation from the effects of combinations of the new drug and

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existing ''mandatory'' therapy in multiple different dose combinations. In theory, these methods require that each combination need be given only to a relatively small number of patients. It is obvious that this approach would have important implications for the design characteristics of drug trials.

Another approach might be the development of ''surrogates'' which can be measured either in vivo, using previously validated assessment criteria, or ex vivo in some appropriate model system. Surrogates are drug effects different from those which define clinical benefit, but which might be the pharmacological basis of the benefit or, for some other reason, might be associated invariably with the beneficial effect. Blood pressure lowering is the most obvious example of a surrogate accepted as an index of clinical benefit for purposes of drug approval. In this area, considerable archival data already are available to define the behavior of blood pressure in hypertensive patients receiving placebo therapy, and to define the effects of drugs that beneficially alter natural history while lowering blood pressure. Interrogation of these archived data may enable definition of a measure of blood pressure, or its variation, which can be used to identify patients who will benefit from specific treatments. An attempt to define such a characteristic now is being directed by the Cardio-Renal Division of the F.D.A., employing data archived on 24-h ambulatory blood pressure recordings.

At a more fundamental level, with increasing understanding of the cellular and molecular biology of cardiovascular diseases, cell culture systems from diseased patients some day may serve as a basis for defining appropriate surrogates for clinically beneficial drug effects. Already, patents for therapies can be based on the effects of drugs on pathophysiological characteristics observed in culture, though the approvability of such treatments still must be proven in conventional clinical trials.

Of course, a simpler approach to the problem of approvability of alternative agents would be to define, by consensus, a magnitude of difference between effects of a new drug and an active comparator that is clinically unimportant, providing a basis for declaring similarity of drugs.

Considerable statistical research (and associated trial design cre-

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ativity), now is underway to define new approaches to validating therapeutic utility. Whatever the outcome, it is likely that, in the future, drug trials for regulatory purposes will differ considerably from those currently employed.

ENDPOINTS

One of the miracles of modern cardiovascular drug therapy is that, for several well-defined populations, benefits now include prolongation of life and/or prevention of major morbid events. However, modern clinical research also has demonstrated that, even with drugs that are lifesaving in some situations and some populations, application in situations and/or populations which are defined more broadly can lead to life shortening and important debility. The most notable example of this dichotomy is in the area of arrhythmia prevention, though similar concerns have been raised with drugs for angina, heart failure, and hypertension. Similarly, recent research has indicated that benefits that are apparent at 3 months of therapy may have disappeared, or even reversed, by 6 months or longer.

As a result, even when drugs are developed for relief of symptoms and not for effects on natural history endpoints, it has become necessary to obtain information about the effects on the natural course of disease in order to acceptably define the risks against which benefits must be measured if drugs are to be given. Similarly, as new instances of late alterations in drug effects are discovered, the duration of exposure required for adequate definition of drug effects has lengthened. These tendencies are likely to become progressively more apparent, driving up the cost of drug development and, concomitantly, the cost of developed drugs. Recognition of these trends will alter the planning of drug development strategies. An associated benefit will be development of increasing knowledge of pathophysiology and pharmacology. This knowledge, particularly if it extends to the cellular and molecular levels, may provide a basis for predicting future drug effects that may mitigate the need for ever-lengthened and broadened trials. If not, however, we can expect inhibition of new drug development due to the

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costs associated with longer follow-up and larger samples increasingly needed to define benefit-to-risk relations to support approvability.

DRUG INTERACTIONS

With the increasing range of drugs for various cardiovascular (and other) diseases, it is increasingly unusual for a patient to be treated with only one agent. This is particularly true in disease areas, like heart failure or myocardial infarction, for which certain drugs have been shown to prolong life and to diminish major morbidity. It follows, then, that, during the past 18 years, the potential for drug interaction has progressively increased. Some interactions may be beneficial or synergistic. Others are potentially harmful. The latter are a primary concern of drug regulators and are highlighted for identification in drug development programs. Indeed, prudence dictates, at the very least, the need to define interactions among the drug combinations most likely to be employed. Traditionally, such interactions have been sought from observational data bases of patients exposed to the new drug with varying background regimens either through planning or serendipity during the course of development. However, many drug interactions are uncommon, requiring specific host characteristics or specific dose combinations for their expression. As a result, specific drug interaction studies have become more common and sometimes have been requested by the FDA during development. This trend can be expected to continue. However, here, as well, important changes can be expected from application of cellular and molecular biological tools. Just as the effects of drugs can be better understood and predicted as the knowledge of host physiology reaches a very fundamental level, so, too, is it likely that drug interactions increasingly will be understood and predicted as fundamental biological knowledge accumulates. Before another 18 years have passed, it is conceivable that drug interactions will be studied, at least in part, in ex vivo or in vitro systems, reducing both patient risk and the escalating costs of development. In addition, the same statistical research aimed at facilitating the identification of drug benefits may be applicable to detect and quantitatively predict drug interactions with data bases smaller than those now required for the purpose.

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PHARMACOECONOMICS

The cost of medical care is a major and constant concern. Therefore, it was inevitable that Federal agencies, like the FDA, should take official notice of this issue. The FDA now requires some assessment of the economic impact of a new drug therapy as part of the NDA. This is laudable, but is unlikely to be the last word on the subject. In time, the US is likely to emulate several other countries that have required that a new drug, if not the first or ''breakthrough'' prototype of its class or group, must be superior to others of that class in order to be approvable. Such a restriction involves many potential difficulties: (1) currently, we have relatively little understanding of the most fundamental mechanisms underlying the therapeutic effects of most drugs; (2) we know by empirical observation that many drugs of the same putative class have different pharmacological and clinical effects; and (3) many otherwise similar drugs have differing side-effect profiles in any single individual. These facts argue against limitation of drugs to a single or small group of prototypes. However, the proliferation of ''me too'' drugs also absorbs considerable development capital, which might be employed in other and more useful investments, including research into new and novel treatments.

Here, once again, the growing capacity to understand drug actions at a very fundamental level may enable identification of agents which, despite membership in an existing class, offer new and additional benefits for some patients, or which may be applicable to specific patient populations not responsive to other class members.

SUMMARY

Since the inception of the Symposia on Cardiovascular Drug Development 18 years ago, methods employed in discovering and evaluating new therapies have evolved considerably, while the social milieu that circumscribes this activity has changed dramatically. For the future, changes of even greater magnitude can be expected. The single most important factor driving this progression is application of cellular and molecular biological tools for assessment of cardiovascular pathophysi-

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ology and its therapeutic alteration. The molecular era began with the development of recombinant gene technology and the capacity for ex vivo replication of genetic materials by polymerase chain reaction (PCR). Defined in this way, our current capacities have been available roughly only for a decade. However, the power of our new tools defines and circumscribes the future of drug development and promises extraordinary benefits in drug discovery, in efficient identification of benefits and of drug interactions, and even in cost-effective production methods. It is safe to say that the era to come will be even more exciting and productive than the era that has passed.

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