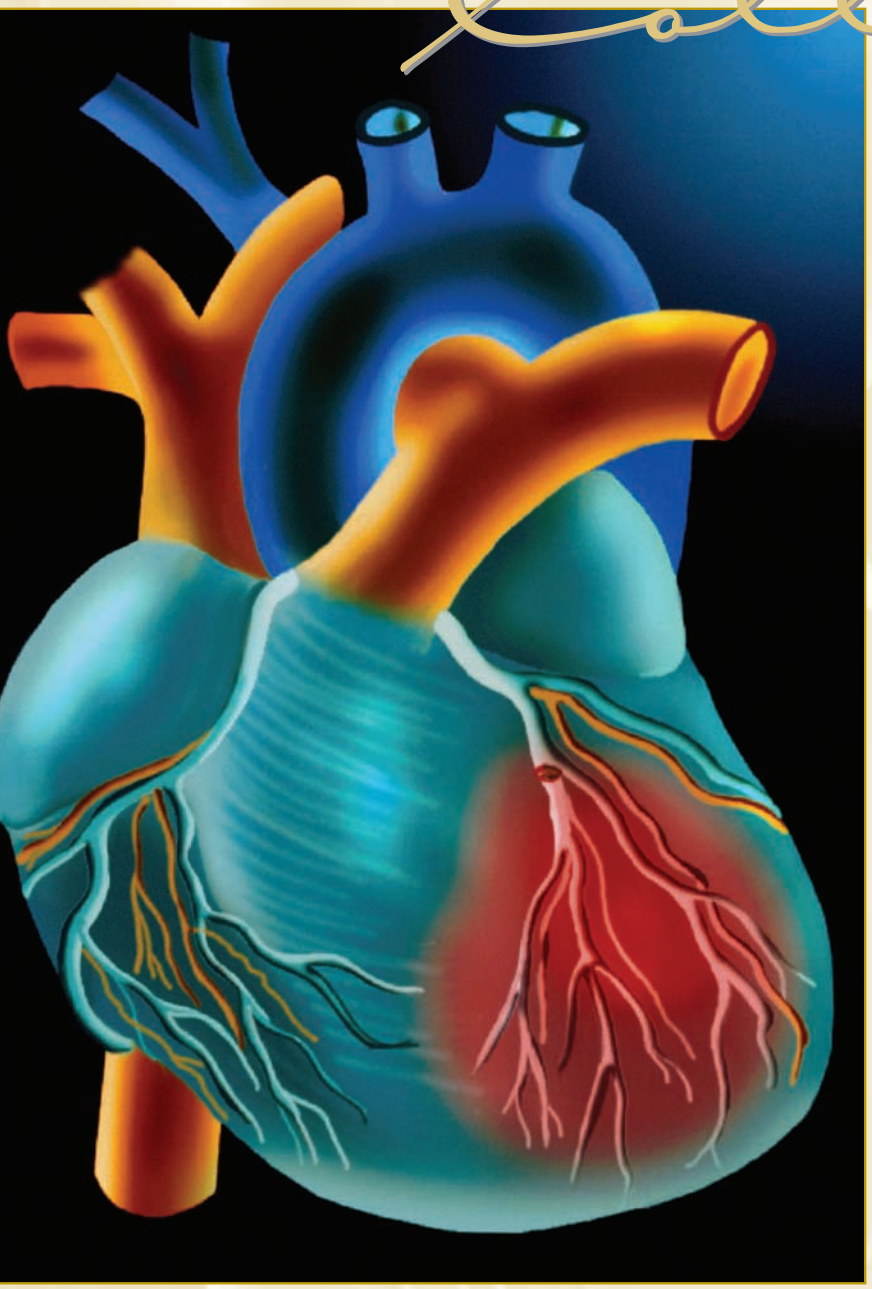
2004 Medical Director Colloquy



Exploring the Spectrum of Cardiovascular Care

Based on presentations at the 2004 Medical Director Colloquy, Dallas, March 25–27

Continuing education credit for physicians and pharmacists sponsored by

The Chatham Institute

SUPPLEMENT TO
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INTRODUCTION

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Cardiovascular disease is the leading cause of death in the United States, with direct and indirect costs of cardiovascular disease and stroke estimated at $368 billion (AHA 2003). Fortunately, great strides have been made in the development of new treatments for the various conditions encompassed by cardiovascular disease. Yet, a performance gap persists in translating advances into common practice in ambulatory settings. This occurs despite the regular publication of comprehensive guidelines that are designed to help clinicians decide which treatments are best for a given patient (ATP III 2001, JNC-7 2003, Grundy 2004).*

To assist clinicians in staying abreast of changes in a rapidly evolving field, AstraZeneca has provided an educational grant for a Medical Director Colloquy for three consecutive years. The first and second meetings focused on dyslipidemia, but this year's steering committee invited nationally prominent experts to draw from the entire cardiovascular disease spectrum. Edited proceedings of that meeting are being published as supplements to the September and October issues of MANAGED CARE.

In this supplement, offered to physicians and pharmacists for continuing education credit, John E. Wennberg, MD, MPH, presents an overview of unwarranted practice variation. Jack E. Ansell, MD, discusses emerging therapies in anticoagulation, notably, oral agents that target factor Xa. Ileana L. Piña, MD, explores advances in treatment of systolic heart failure, aimed at disrupting the neurohormonal cascade. Alan S. Go, MD, shows how, until such time as these new anticoagulants are approved, MCOs may find it advantageous to establish anticoagulation clinics to manage patients receiving warfarin, which many clinicians find worrisome.

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* As this publication goes to press, the National Cholesterol Education Program has issued a report that, in light of recently published clinical trials, refines the recommendations set forth in 2001 by its Adult Treatment Panel III. See: Grundy SM, Cleeman JI, Merz NB, et al, for the Coordinating Committee of the National Cholesterol Education Program. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation.* 2004;110:227–239.

PHOTOGRAPHS BY DENNY COLLINS

SUPPLEMENT TO
MANAGED Care
September 2004

Exploring the Spectrum Of Cardiovascular Care

A CONTINUING EDUCATION ACTIVITY

Based on the proceedings of the 2004 Medical Director Colloquy in Dallas

PRESENTATIONS

CONTINUING EDUCATION

This supplement is supported by an educational grant from AstraZeneca Pharmaceuticals LP. The material in this supplement has been independently peer reviewed. The grantor played no role in reviewer selection.

SELF-STUDY CONTINUING EDUCATION ACTIVITY

Exploring the Spectrum of Cardiovascular Care

Continuing education credit is offered to physicians and pharmacists who read pages 3 through 25 of this publication, complete the post-test on pages 26 and 27, and fill out the evaluation form on page 28. Estimated time to complete this activity is 2 hours.

PURPOSE AND OVERVIEW

These articles are derived from the 2004 Medical Director Colloquy, "Exploring the Spectrum of Cardiovascular Care," which took place in Dallas, March 25–27.

Cardiovascular disease — which includes high blood pressure, coronary heart disease (heart attack and angina), congestive heart failure, and stroke — is America's leading killer, claiming more lives than all other major causes of mortality. This activity focuses on best practices, from theory to implementation, for specific health outcomes for patients with diseases of the heart and blood vessels. From varying perspectives, the faculty explores current approaches to patient care and the utilization of therapies to optimize management of cardiovascular disease.

New data from the American Heart Association's *Heart Disease and Stroke Statistics — 2004 Update* reveal the extent of the burden associated with these often chronic diseases, and they underscore the need to establish standards of care to improve health care quality relative to these conditions. Novel drugs and other recent treatment advances also have generated a heightened need to educate physicians and health care executives on the most current approaches to care and ways to meet the challenges posed by the spectrum of cardiovascular disease.

EDUCATIONAL NEEDS ASSESSMENT

Educational objectives

After reading this publication, the participant should be able to:

- Understand the reasons underlying geographic variations in rates of health care utilization and the quality of health care
- Explain the differences among effective care, preference-sensitive care, and supply-sensitive care
- Describe the advantages and limitations of currently available anticoagulants
- Discuss the differences between oral factor Xa anticoagulants and currently available anticoagulants
- Understand the reasons for establishing clinics to manage patients on warfarin
- Compare the evidence supporting anticoagulation management services with usual medical care
- Know common signs and symptoms of heart failure, and cite several ways in which heart failure is misdiagnosed
- Gain insight into the rationale supporting pharmacotherapy aimed at interrupting the neurohormonal cascade in patients with systolic heart failure

Target audiences

Managed health care professionals, including physicians, pharmacists, medical directors, chief medical officers, pharmacy directors, and other senior managers in managed care organizations.

This activity is sponsored by The Chatham Institute.

CONTINUING EDUCATION

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This activity provides 2.0 contact hours (0.2 CEU) of continuing education for pharmacists. Credit will be awarded upon successful completion of the post-test and the activity evaluation.

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Faculty disclosures

Jack E. Ansell, MD, has reported that he has received grant and/or research support from and has served on speakers' bureaus for AstraZeneca, Aventis, and Sanofi. Ileana L. Piña, MD, has reported that she has served on speakers' bureaus for AstraZeneca, Novartis, and GlaxoSmithKline.

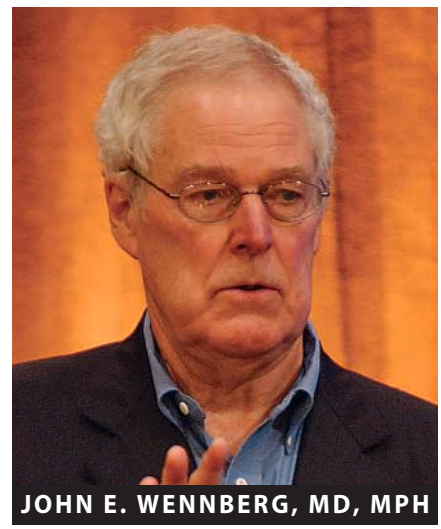
John E. Wennberg, MD, MPH, and Alan S. Go, MD, have reported that they have no financial interest, arrangement, or affiliation that would constitute a conflict of interest concerning this continuing education activity.

Practice Variation: Implications For Our Health Care System

JOHN E. WENNBERG, MD, MPH

Director of the Center for the Evaluative Clinical Sciences, Peggy Y. Thomson Professor for the Evaluative Clinical Sciences, Professor of Epidemiology and Community and Family Medicine, Dartmouth Medical School; Principal Investigator, Series Editor, Dartmouth Atlas Project

The United States leads the world in health care expenditures per capita, but there are wide variations in the intensity and quality of care provided to different populations within the nation. These variations in health care utilization and quality are widely recognized but not well understood by most of the medical community. The dramatic geographic differences in quality of care are unrelated to the level of spending; in fact, the level of spending and quality of care appear to be inversely related.



JOHN E. WENNBERG, MD, MPH

Small area variations

Cross-sectional variation in utilization rates could be attributable to one of four factors: illness rate, the patient's decision to contact a physician, the physician's diagnostic decisions, and the physician's treatment decisions.

Small area analysis (SAA), because it relates specific providers to the populations they serve, is useful for evaluating the effect of physician practice style and the supply of resources on utilization rates. Much of the variation observed through the lens of SAA is unwarranted, because it cannot be explained on the basis of illness, access, or patient preferences. SAA uses large administrative databases to determine population-based rates of resource utilization and allocation. The Dartmouth Atlas Project allows researchers from various disciplines to evaluate several extremely large health care claims databases (e.g., Medicare and several Blue Cross organizations) and serves as the foundation for most of our research on health care variation by geographic areas. The Atlas Project has determined the rates of resource and utilization in 3,436 hospital service areas, which have been aggregated into 306 hospital referral regions.

Small area analyses are constructed in three steps (Wennberg 1990):

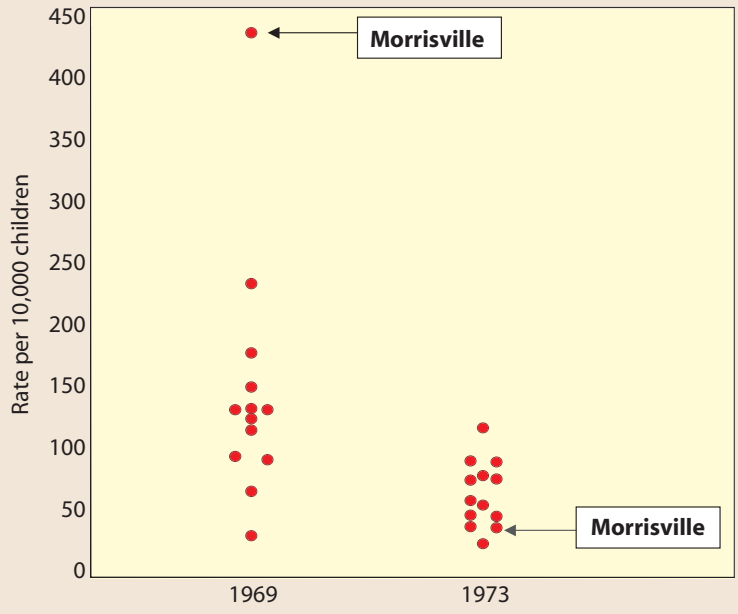
Defining geographic boundaries. It is possible to measure the delivery of care not only within specific administrative areas such as cities and states, but also by defining regions — or naturally occurring markets — by doing patient origin studies to assign ZIP codes to health care providers. The medical market boundaries used in the Atlas small area analyses are defined by groupings of ZIP codes according to where the plurality of residents within those ZIP codes receive medical care.

Resource allocation. Resources in geographic regions are calculated as the number of hospital beds, employees, admissions, or expenditures per resident of the defined region (e.g., hospital beds per 1,000 residents, medical admissions per 1,000 Medicare enrollees living in the ZIP code cluster).

Utilization rates. These are calculated for specific areas on a crude and age-adjusted basis, usually using the indirect method of standardization. Utilization rates represent events, not persons, as patients receiving the same service more than once are counted each time.

To illustrate cases of small area variations, consider the following: In an analysis of 13 Vermont hospital service areas in 1969 (Wennberg 1973), it was found that the rate of tonsillectomies was 75 percent higher in the Morrisville Hospital service area than in the hospital service area with the next-highest rate (Figure 1, page 4). Three years after these data were presented to the state medical society, the rate of tonsillectomies in the Morrisville service area was one of the lowest of the 13 areas evaluated. The question raised by the change in the rate of tonsillectomy in Morrisville was, which was the "correct" rate — and how could a correct rate be determined? The change in the rate from high to low did not, in and of itself, indicate

FIGURE 1 **Tonsillectomy rates among Vermont hospital service areas**



SOURCE: WENNBERG 1973, 1977

that a more ideal rate had been established. There were no clinical trials of the end results. Without the means to evaluate the health status outcomes, it is impossible to know which rate is the "right" one (Wennberg 1977).

Improved decision quality

In an ideal world, patients and their physicians would have information about the outcomes of different treatment options, and their decisions about what to do could be guided by a comprehensive understanding of the likely outcomes and side effects of each choice. The "right" rate of a given treatment would be established by incorporating informed patients' preferences into the decision about choice of treatment.

One barrier to this ideal is the lack of good information; another is the difficulty in communicating accurately with patients so that they can make treatment choices that reflect their preferences about the tradeoffs involved. We began to explore how to incorporate good information into the decision-making process for patients with benign prostatic hypertrophy (BPH) in the early 1980s, in Maine.

At that time it was generally believed that with BPH, a common condition in men over the age of 50, the prostate should be removed early in the course of the disease to prevent bladder decompensation and kidney failure later in life. Yet, after we had conducted a series of outcomes studies, it was evident that, for the vast majority of men, the risks of morbidity and mortality associated with the procedure outweighed any benefits from surgery that could be expected later in life (Wennberg 1988). The benefit of surgery for most men was a dramatic improvement in urinary tract symptoms; that benefit, however, was accompanied by a risk of sexual changes that an informed patient might not deem worth the relief of urinary symptoms. This understanding led to the conclusion that the "right" decision about surgery could not be made without involving the patient in the decision-making process — shared decision making.

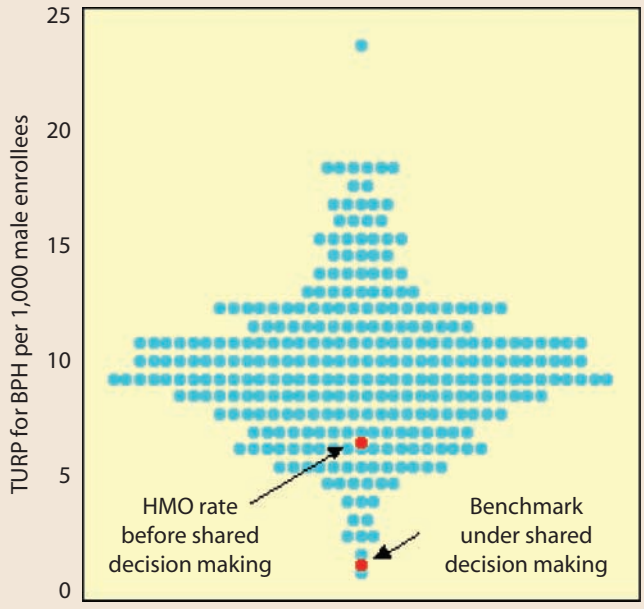
To evaluate the hypothesis that better decisions — those with which patients were more satisfied and that led to the clarification of patients' preferences — could be made through shared decision making, my colleagues evaluated the rate of surgery for BPH before and after the implementation of a decision aid that was introduced with two staff-model HMOs (Wagner 1995). They found that patients' attitudes about their sexual function and urinary function were better predictors of their decisions about surgery than the severity of their symptoms. Patients concerned about sexual function were much less likely to elect surgery for BPH than patients concerned with urinary function, independent of their symptoms' severity.

The overall effect of shared decision making was to depress the demand for BPH surgery among men who used the decision aid, even though the population already was having the surgery at a rate lower than the national average.

Figure 2 shows that the rate of BPH surgery among men enrolled in the HMO was in the bottom third of the national distribution of rates, prior to the implementation of the shared–decision-making program. After implementing shared decision making, the rate fell to almost the lowest of the national distribution. The conclusion was that informed men preferred surgery for BPH much less frequently than it was being performed in most regions of the United States. While attitudes and preferences certainly vary among different men and different populations, the goal of this study was to gain a better understanding of how variations in rates of surgery were influenced by patient preferences. This suggests the possibility of widespread overuse of this procedure during the early 1990s.

Decision aids, such as the shared–decision-making videos for BPH can help improve decision quality in diverse situations. They can be developed and integrated

FIGURE 2 **Effect of improved decision quality on surgery rates for benign prostate hyperplasia**



TURP=transurethral resection of the prostate.
SOURCE: DARTMOUTH ATLAS 1996

into practice based on the best available medical evidence and balanced representations of choices of care.

Patients with many common conditions can then become familiar with the safety, efficacy, and sequelae associated with different therapeutic options before making any decisions about their care. Such tools have been shown to be effective in terms of knowledge transfer and decision preferences. That is, better decisions are made when decision aids are in place (O'Connor 1999). In addition, decision aids lead to substantial improvements in the accuracy of patients' perceptions about probable outcomes with and without treatment (O'Connor 1999).

Categories of care

In looking at small area variations, we have found it useful to distinguish between three types of care: effective care, preference-sensitive care, and supply-sensitive care. They are defined by the relative importance of four factors: clinical theory, medical evidence, per capita supply of medical resources, and patient preferences. Table 1 outlines the categories of medical services and factors that influence their utilization (Fisher 2003a).

Effective care

Effective care refers to services of proven effectiveness that do not involve any significant tradeoffs (i.e., all persons with significant need should receive service), such as the Health Plan Employer Data and Information Set (HEDIS) measures. In the effective-care model, conflict between patients and providers over the value of care is minimal (Fisher 2003a). Failure to provide effective care can be viewed as a medical error — an error of omission (Wennberg 2002).

An annual eye examination for a diabetic patient is an example of effective care. The Dartmouth Atlas Project, however, shows a wide variation with respect to rates of eye examinations for diabetics in 306 hospital regions studied. In the region with the best overall record in 2001 — Mason City, Iowa — 77 percent of diabetic Medicare enrollees received eye exams. In the region with the lowest rate, Panama City, Fla., only 35 percent of patients had their eyes examined.

Preference-sensitive care

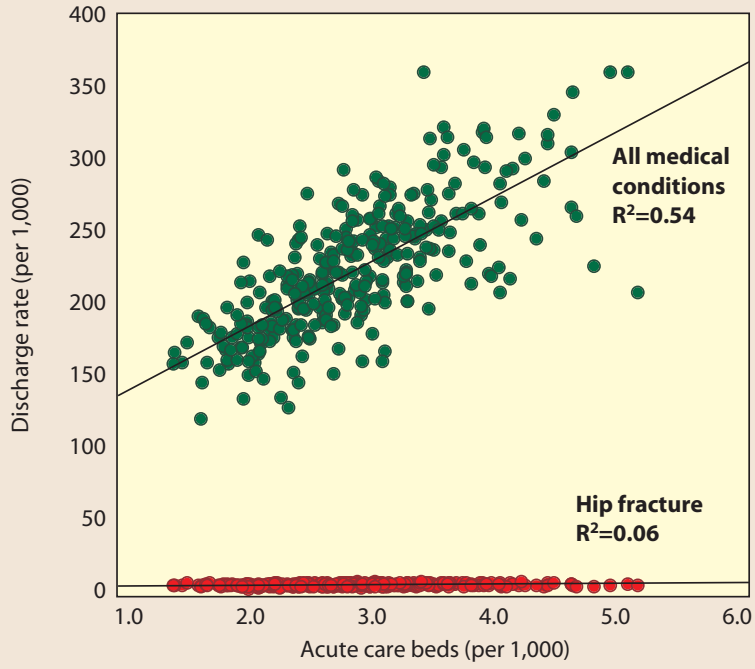
Preference-sensitive care involves tradeoffs. The patient has more than one treatment option to choose from, and the anticipated outcomes of each choice are different. The tradeoffs often involve competing aspects related to the quality of life. The tradeoffs between sexual and urinary tract function for BPH treatment is an example. Another example is the choice of treatment for early stage breast cancer between lumpectomy (breast-sparing surgery) and

TABLE 1 **Categories of medical services and factors influencing utilization**

	Factors influencing utilization			
	Clinical theory	*Medical evidence*	*Per capita supply of resources*	*Importance of patient preferences*
Effective care	Strong	Strong	Weak	Weak
Preference-sensitive care	Strong	Variable	Variable	Strong
Supply-sensitive care	Weak	Weak	Strong	Variable

SOURCE: ADAPTED FROM FISHER 2003a

FIGURE 3 Association between hospital beds and discharge rates



SOURCE: DARTMOUTH ATLAS 1998

mastectomy (complete removal of the breast). The patterns of practice and the changes that occur when shared decision making is introduced suggest that physician opinion now dominates in the clinical setting.

Supply-sensitive care

Supply-sensitive care includes physician visits for patients with chronic illnesses, diagnostic monitoring and testing, and admissions to intensive care. The relative frequency of use of these services is closely associated with the relative capacity of the local system to provide such services. More hospital beds per capita, for example, drives up the local rate of hospitalizations for medical conditions. More medical specialists drive up the frequency of visits to specialists. Supply-sensitive services are provided largely in the absence of evidence about the "right" rate — the frequency of use that results in optimal outcomes. The association between frequency of use of supply-sensitive care and outcomes is rarely a topic of clinical research. In contrast to effective care and preference-sensitive care, specific medical theories and medical evidence play a minimal role. In the absence of medical evidence and under the assumption that more is better, available supply drives the frequency of use.

Figure 3 illustrates the association between hospital beds per 1,000 residents and hospitalizations for medical conditions. The R^2 value of 54 percent indicates that more than half the variation in the overall discharge rate for Medicare enrollees is explained simply by counting the number of beds allocated to a region, independent of all other factors (e.g., occupancy rate) (Wennberg 1998). On the other hand, there is no association between hospitalizations for hip fractures and acute care bed capacity, because hospitalization for a hip fracture is determined primarily by the incidence rates; virtually all patients with hip fractures are hospitalized.

The bottom-line question, of course, is once again, "Which rate is right?" Two trials of elderly patients from the U.S. Veterans Affairs system found that increased office visits and more intensive primary care were correlated with increased rates of hospital stays but not with improvements in patient health. Furthermore, both studies found a slight nonsignificant association between higher frequency of physician office visits and increased mortality (Wasson 1992, Weinberger 1996).

When Fisher and colleagues evaluated the practice patterns and health outcomes among regions with similar baseline health status but widely varied utilization of services, they found that a greater frequency of use of supply-sensitive services was associated with slightly higher mortality. The quality of health care services and access to these services were also poorer among the higher spending regions (Fisher 2003b, 2003c). On the basis of this evidence, we believe that low-rate regions provide benchmarks of efficient practice; evidence that greater use of physician visits, hospitalizations, and intensive care does not result in better outcomes opens up the opportunity for improving efficiency by promoting patterns of practice seen in low-rate regions.

Conclusions

There is substantial underuse of effective care in all regions of the United States; underuse can only be remedied and quality improved through fundamental redesign of care processes. There are substantial variations in discretionary surgery and other preference-sensitive treatments. These variations are unwarranted, because provider rather than patient preferences seem to play the dominant role in determining which treatments are prescribed. Misuses of preference-sensitive care can be remedied only through improvement in decision quality through shared decision making. Patient decision aids

can help. There are substantial variations in physician visits, hospitalizations, and use of intensive care units — particularly among chronically ill Americans. Higher rates of use do not appear to result in better health outcomes. For these reasons, benchmarks for system capacity and utilization rates provided by low-cost, low-rate regions should be adopted in high-cost regions.

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Emerging Therapies in Anticoagulation

JACK E. ANSELL, MD

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Orally and parentally administered anticoagulants have a lengthy history and a well-deserved reputation as agents that save or prolong lives. Despite years of refinement, the ideal anticoagulant does not yet exist. If it did, it would offer a simple dosing formulation and route of administration, being given once or twice daily orally or perhaps subcutaneously (but not intravenously). It would be predictable in its response, and no monitoring would be required. Its adverse effects would be minimal; it would not interact with food or drugs; and its therapeutic effects could be reversed easily and rapidly. Finally, it would be available at a reasonable cost. This article will briefly review the existing anticoagulants and then discuss investigational products, with the intention of identifying the extent to which some emerging therapies capture the characteristics of the ideal anticoagulant.

JACK E. ANSELL, MD

History of anticoagulants

The history of oral anticoagulation therapy is rooted in agriculture, specifically in the growing of sweet clover in regions where the corn borer made it difficult to cultivate field corn as silage. In the 1920s, it was observed that some cattle that had eaten spoiled sweet clover died from internal hemorrhage. A researcher at the University of Wisconsin, Karl Paul Link, succeeded in isolating the substance in the spoiled sweet clover that acted as the anticoagulant — bishydroxycoumarin, or dicoumarol. A synthetic form of dicoumarol became famous as warfarin, named after the Wisconsin Alumni Research Foundation, to which Link (an alumnus of the university) transferred the patent. For many years, warfarin was used worldwide as a rodenticide, in d-Con; the modern version of that product contains a warfarin variant, however, because the pests eventually developed resistance to the poison.

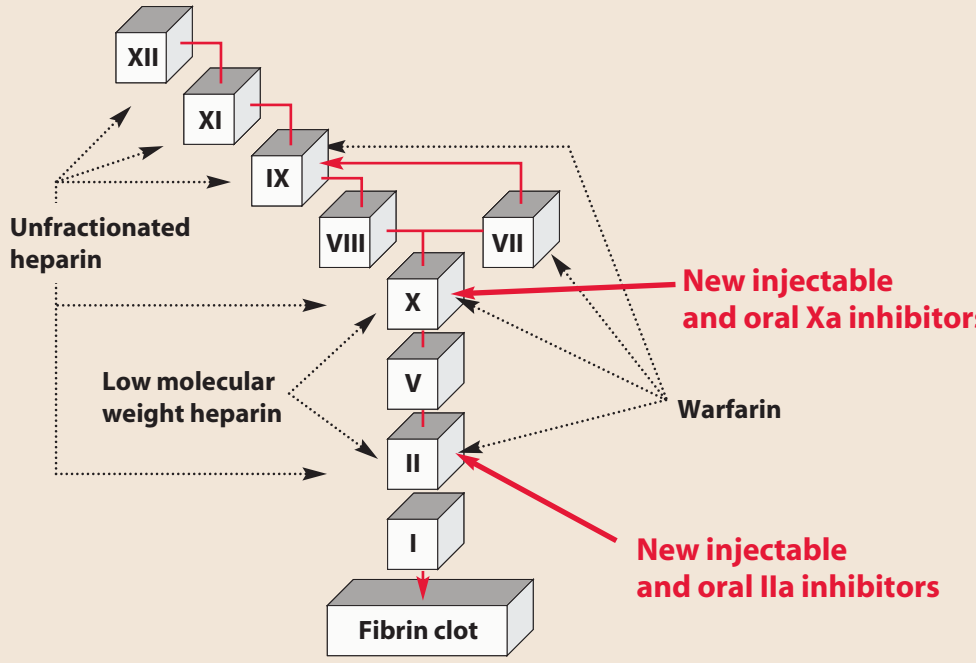
Even as warfarin led to the demise of countless rats and mice, it gained fame as a lifesaving treatment for humans — most notably, when given to President Eisenhower after a heart attack. Available generically and under the trade name Coumadin, warfarin acts by interfering with vitamin K, which is essential for the normal synthesis of coagulation factors II, VII, IX, and X (Figure 1).

Since Eisenhower's era, the utilization of warfarin has been refined through clinical trials, but warfarin remains difficult to use — such that this single drug has spawned an entire industry of anticoagulant clinics to manage its use. The problems associated with warfarin are multiple. Its onset and offset of action are slow; it takes several days for a patient to experience the effects of the drug, and several days for the effect to wear off when the agent is discontinued. Also, it is not easy to reverse the effects of warfarin; vitamin K can be administered, but it takes 12 to 24 hours to act. Fresh frozen plasma and other concentrates can be given, although with difficulty. In addition, warfarin is associated with numerous adverse effects, notably bleeding, which often stems from poor management.

Patients receiving warfarin must be monitored for several reasons. First, patients' response to warfarin is unpredictable. Second, many factors influence the response, such as drugs, diet, and liver disease. Third, warfarin has a narrow therapeutic index, meaning patients can bleed if they are over anticoagulated or develop a thrombosis if under anticoagulated. Unfortunately, the assay for monitoring warfarin, the prothrombin time (PT), is wanting. Even with employment of the international normalized ratio, a means of equilibrating results from laboratory to laboratory, the assay remains problematic.

Due to physicians' fears of the increased risk of bleeding associated with warfarin as well as the labor-intensive nature of warfarin management, many patients in need of anticoagulant therapy go undertreated or untreated. In some cases, physicians may decide electively that a pa-

FIGURE 1 **Old and new anticoagulants**



tient is not a good candidate for warfarin, or perhaps, the patient may refuse therapy. In the United States, approximately 50 to 60 percent of patients who should receive an oral anticoagulant for atrial fibrillation (AF) receive no treatment. Underutilization of warfarin seems greatest among those AF patients who would benefit the most — the oldest patients, with 19 percent of patients aged 80 years or older receiving warfarin, compared with 36 percent of younger patients (Stafford 1996). Warfarin utilization also varies according to geographic region, being received by only 16 percent of AF patients in the South, compared with 30, 35, and 46 percent of patients in the West, Northeast, and Midwest, respectively.

From a historical standpoint, heparin is a virtual contemporary of warfarin. Heparin was discovered in the early 1900s by the renowned Johns Hopkins physiologist, William Henry Howell, who was following up on a serendipitous observation made by a student, Jay McLean, who worked in his laboratory. Heparin is a heterogeneous mixture of polysaccharides of different molecular weights, some of which act by greatly accelerating — by a thousandfold — the activity of antithrombin, which inhibits thrombin (factor IIa) and other activated coagulation factors. Heparin molecules capable of inhibiting thrombin must consist of at least 18 monosaccharide units; shorter chains are less capable of binding to thrombin — which is required in addition to antithrombin binding.

Heparin presents its own set of problems, some shared with warfarin and some unique to heparin. Like warfarin, heparin elicits an unpredictable response, which requires monitoring with an assay that is inadequate. Heparin also is associated with adverse effects, notably bleeding, along with heparin-induced thrombocytopenia (HIT) and thrombosis.

Unlike warfarin, heparin must be administered parenterally, usually via continuous infusion, which necessitates hospitalization that is labor-intensive and costly. Because of protein binding, the bioavailability of unfractionated heparin is low, and some patients develop resistance to heparin.

Use of unfractionated heparin has diminished markedly during the last decade, owing to the introduction of low molecular weight heparin (LMWH), which offers an improved pharmacokinetic profile. The LMWH products available in the United States include dalteparin (Fragmin) and enoxaparin (Lovenox). LMWH is usually administered via subcutaneous injection, once or twice daily, given its longer half-life. Due to lack of protein binding, LMWH has good bioavailability and a predictable dose response. Monitoring, therefore, is not required and resistance is not encountered.

Fondaparinux (Arixtra) represents a further refinement of the heparin molecule. It is a pentasaccharide — five saccharide units (the minimum length that binds to and activates antithrombin), which then can neutralize

factor Xa and prevent the activation of prothrombin (factor II). Because of their longer saccharide chains, standard heparin and LMWH inhibit thrombin; however, with its five-unit saccharide chain, fondaparinux is too short to affect thrombin.

Unlike standard heparin and LMWH, which are extracted from animal tissues, fondaparinux is produced through chemical synthesis. Fondaparinux lacks protein binding, being totally bound to antithrombin. Fondaparinux is 100 percent bioavailable through subcutaneous once-daily administration and has a plasma half-life of 15 to 17 hours.

Fondaparinux has been shown to be effective for the prevention of deep-vein thrombosis (DVT) or pulmonary embolism (PE) after orthopedic surgery (Turpie 2001, 2002) as well as for the acute treatment of DVT or PE. Because it is given parenterally once daily, fondaparinux likely will be limited to inpatient as well as short-term outpatient use, similar to LMWH.

Idraparinux is another pentasaccharide that is under investigation for use as an anticoagulant. Due to modifications of the side chains of the molecule, idraparinux has a much longer half-life than does fondaparinux, which may enable once-weekly dosing and allow idraparinux to be a more reasonable alternative to warfarin for outpatient use. Idraparinux has been shown to be effective in phase 2 trials and is undergoing phase 3 trials for DVT and PE.

Direct inhibitors of factor Xa or factor IIa

In contrast to the pentasaccharides, which inhibit factor Xa indirectly via antithrombin, the small molecule razaxaban, a twice-daily oral agent, inhibits factor Xa directly. Razaxaban is in the early stages of development. In a phase 2 dose-ranging study, a dose-related reduction in the risk of total venous thromboembolism (VTE) compared to enoxaparin was seen during the 10±2 days following total knee replacement (Table 1), along with a dose-related increase in rates of major bleeding (Lassen 2003). It is important to note that without anticoagulation therapy, the incidence of DVT in these patients would be about 50 to 60 percent. This agent (along with other oral direct Xa inhibitors) looks promising, but further studies are needed to confirm its efficacy and safety.

Agents that directly inhibit thrombin include hirudin (named for the medicinal leech, *Hirudo medicinalis*), which is produced through recombinant technology and available clinically as lepirudin (Refludan); a modified hirudin, bivalirudin (Angiomax); and argatroban. These agents have limited indications (treatment of HIT [hirudin, argatroban]; adjunctive antithrombotic therapy in patients undergoing percutaneous coronary intervention [bivalirudin]), and all necessitate parenteral administration, along with monitoring of therapeutic levels. They are, therefore, appropriate only for hospitalized patients.

An oral agent that directly inhibits clot-bound or free thrombin, ximelagatran, recently has completed phase 3 trials for the prevention of stroke in patients with AF and prevention and treatment of VTE. Ximelagatran is a prodrug that is converted rapidly in the blood to its active form, melagatran, which binds reversibly and transiently to the active site of thrombin. Similar to LMWH, melagatran achieves peak concentrations fairly quickly, reaching maximum levels at 1.5 to 2.5 hours after subcutaneous dosing. Melagatran has a half-life of 3 to 5 hours in patients, and thus, ximelagatran must be administered twice daily. It is not known to interact with other drugs or foods, and neither ximelagatran nor melagatran interacts with the cytochrome P450 isoenzymes. No monitoring via coagulation assays is necessary. This is because ximelagatran has a rapid onset of action, a predictable anticoagulant response, and no significant food or drug interactions.

Ximelagatran has been evaluated in the treatment of acute DVT. Patients typically present to the emergency room with a painfully swollen leg, and on ultrasound examination are found to have a clot in their leg. Conventional treatment is intravenous heparin during hospitalization of 5 to 7 days, or physicians might send these

TABLE 1 Efficacy and safety of razaxaban for the prevention of DVT in knee replacement surgery

	Razaxaban 25 mg bid (n=147)	Razaxaban 50 mg bid (n=123)	Razaxaban 75 mg bid (n=115)	Razaxaban 100 mg bid (n=121)	Enoxaparin 30 mg bid (n=150)
Patients (no.) achieving efficacy endpoint	93	84	83	71	107
Adverse effect					
VTE	8.6%	6.0%	3.6%	1.4%	15.9%
Proximal DVT or PE	2.2%	2.4%	2.4%	0.0%	6.5%
Major bleeding	0.7%	4.1%	3.5%	5.8%	0.0%

DVT=deep-vein thrombosis, PE=pulmonary embolism; VTE=venous thromboembolism
SOURCE: LASSEN 2003

TABLE 2 **Comparison of adverse effects of ximelagatran vs. warfarin in SPORTIF III and V studies**
Annual rates

	Stroke and systemic embolism			Intracranial hemorrhage			Major bleeding			Major and minor bleeding		
	Xim	Warf	*P*	Xim	Warf	*P*	Xim	Warf	*P*	Xim	Warf	*P*
SPORTIF III (N=3,407)	1.6%	2.3%	.10	0.2%	0.5%	NS	1.3%	1.8%	NS	25.5%	29.5%	.007
SPORTIF V (N=3,992)	1.6%	1.2%	.13	0.06%	0.06%	NS	2.4%	3.1%	.16	37%	47%	<.001

SPORTIF=Stroke Prevention Using an Oral Thrombin Inhibitor in Atrial Fibrillation, Warf=warfarin, Xim=ximelagatran.
SOURCE: HALPERIN 2003

patients home immediately or after an overnight stay on LMWH. Eventually, all these patients make the transition to 3 to 6 months of warfarin therapy.

In a study enrolling 2,491 patients with acute DVT, patients were randomized to standard treatment — subcutaneous enoxaparin followed by warfarin, or oral ximelagatran, 36 mg twice daily (Huisman 2003). After 6 months, there was no statistically significant difference in the cumulative incidence of recurrent DVT — 2.1 percent in the ximelagatran group vs. 2.0 percent in the enoxaparin/warfarin group. There was also no statistically significant difference in the rates of major bleeding — 2.2 percent in the enoxaparin/warfarin group vs. 1.3 percent in the ximelagatran group.

Once a patient has received 6 months of anticoagulation therapy following acute DVT, the next step usually is to discontinue the therapy. The belief is that by that point, the risk of warfarin-induced bleeding exceeds the risk of recurrent DVT. Therefore, the Thrombin Inhibitor for Venous Thromboembolism (THRIVE III) study, a double-blind, randomized, placebo-controlled trial, was designed to investigate the benefits of ximelagatran 24 mg bid vs. placebo, following 6 months of standard treatment in 1,233 patients (Schulman 2003). After 18 months, the estimated cumulative risk of recurrent VTE was 2.8 percent in the ximelagatran group vs. 12.6 percent in the placebo group ($P<.001$). The incidence of major bleeding events was similar (ximelagatran group, 6; placebo group, 5), as was the risk of major or minor bleeding or both (ximelagatran group, 134; placebo group, 111). The estimated cumulative risk of major or minor bleeding was 23.9 percent in the ximelagatran group and 21.0 percent in the placebo group ($P=.17$).

Ximelagatran also has been evaluated vs. warfarin in two studies for the prevention of stroke in AF populations — SPORTIF III (Stroke Prevention Using an Oral Thrombin Inhibitor in Atrial Fibrillation III), an open-label international trial conducted in 23 countries, and SPORTIF V, a double-blind trial conducted in the United States and Canada. The objective of each study was to establish the noninferiority of ximelagatran, relative to warfarin in terms of the primary outcome, which was stroke or systemic embolism. Both trials showed no statistically significant difference in the rates of stroke and system embolism, demonstrating that ximelagatran was equivalent to warfarin (Table 2). Similarly, there was no statistically significant difference in the rates of intracranial hemorrhage or major bleeding between the ximelagatran or placebo groups (Halperin 2003).

In all the ximelagatran trials, an elevation in liver enzymes was observed, with about 6 percent of patients in the ximelagatran groups experiencing serum alanine aminotransferase (ALT) levels exceeding 3 times the upper limits of normal, vs. less than 1 percent of patients in the warfarin groups. These ALT elevations usually occurred during months 2 through 6 of treatment, but the elevation was transient and returned to normal either spontaneously or on treatment cessation. If ximelagatran gains approval by the U.S. Food and Drug Administration for marketing, it is likely that regular liver function monitoring will be required during the first 6 to 12 months of therapy.

If ximelagatran becomes available in the near future, it will become another important alternative to warfarin, heparin, and LMWH. As an oral agent, ximelagatran may be more attractive than either of the subcutaneously administered pentasaccharides, even if idraparinux gains an indication for once-weekly administration. If ximelagatran or other oral factor Xa inhibitors in development are successful, the use of warfarin will slowly fade during the next 5 to 10 years. The new agents will enable many patients to be treated as outpatients, which will reduce the costs currently associated with hospitalization for anticoagulant therapy.

Perfectly managed, warfarin is an excellent drug, but its management often falls short. Due to their ease of use and presumed improvement in efficacy and safety compared with currently available anticoagulants, new agents

could extend the benefits of anticoagulation therapy to the AF patients who now are undertreated or untreated.

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Therapy for Systolic Heart Failure

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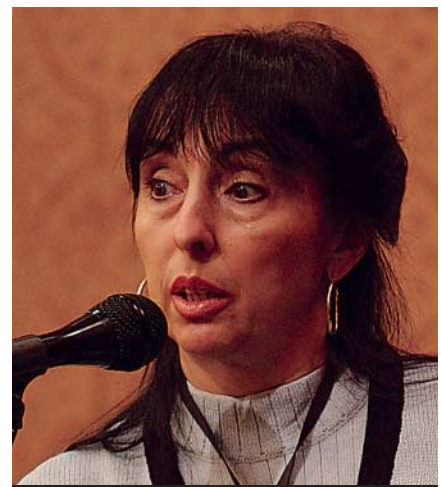
Heart failure affects approximately 5 million Americans, with an annual incidence of 550,000 cases (AHA 2003). The American Heart Association estimates that direct medical costs of heart failure will reach $23.7 billion this year, including $13.6 billion for hospitalizations. Hospitalizations have risen steadily; discharges increased 164 percent between 1979 and 2001, from 377,000 to 995,000. One hospitalization leads to another; in fact, it is common for a patient with heart failure to be hospitalized 2 or 3 times per year. Generally, this cycle ends in the patient's death, as 20 percent of patients die within 1 year of a diagnosis of heart failure, and 50 percent within 5 years (Levy 2002). In a cohort of patients hospitalized because of an exacerbation of severe heart failure, nearly 40 percent died within 1 year (Jaagosild 1998).



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To some extent, the increasing number of Americans with heart failure testifies to the strength of modern cardiology, in that many patients (especially men) who once would have died from a myocardial infarction (MI) now survive, only to develop heart failure (Levy 2002). From another perspective, however, the increasing prevalence of heart failure points to a nation of people whose poor diets and low level of physical activity cultivate the risk factors that lead to heart failure, such as hypertension, dyslipidemia, obesity, and diabetes. As a manifestation of poor diet and physical inactivity, overweight is conservatively estimated to have accounted for 385,000 deaths in the United States in 2000, rivaling smoking (435,000 deaths) as the leading actual cause of death (Mokdad 2004).

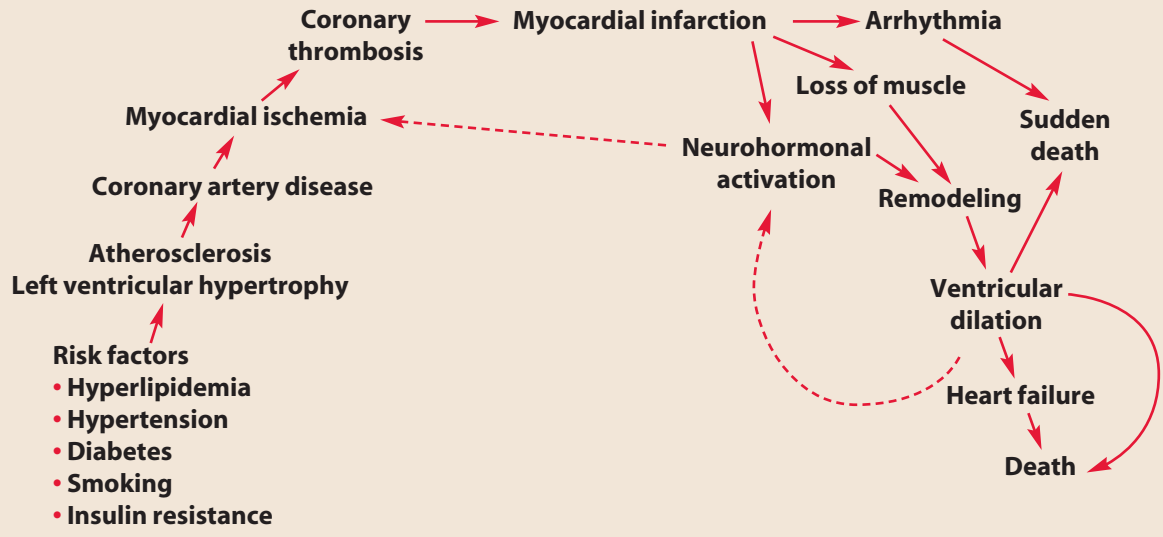
Heart failure patients have impaired diastolic or systolic function, or commonly both, and the difference between the forms tends to blur as the condition progresses. Diastolic dysfunction (heart failure with preserved systolic function) chiefly reflects impaired relaxation and filling of the ventricle, whereas systolic dysfunction, the focus of this paper, is the inability of heart myofibrils to shorten against increased load. Systolic dysfunction can be found in patients with and without overt symptoms of heart failure. In a community study in Minnesota that included 2,042 patients 45 years of age or older, the prevalence of confirmed heart failure was found to be 2.2 percent, and the prevalence of any systolic dysfunction (ejection fraction [EF] less than 50 percent) was 6.0 percent (Redfield 2003).

MI is one pathway that often leads to heart failure (Figure 1, page 14). When MI is the proximate cause of heart failure, ischemia/infarction results in loss of muscle that, in turn, causes structural changes — remodeling — of the left ventricle (LV). The neurohormonal activation resulting in ventricular dilatation can lead to worsening of myocardial ischemia in a vicious cycle of worsening heart failure.

Neurohormonal activation involves the renin-angiotensin-aldosterone system (RAAS). Renin is the enzyme that catalyzes the transformation of angiotensinogen into angiotensin I, a decapeptide. Through the action of angiotensin-converting enzyme (ACE), two amino acid residues are removed from angiotensin I, converting it into an octopeptide, angiotensin II (AT-II). AT-II has several receptors; of these, AT_1 and AT_2 are the best known.

AT-II is a potent constrictor of vascular smooth muscle (40 times more potent than norepinephrine, mole for mole), which serves to increase both systolic and diastolic blood pressure. AT-II also acts directly on the adrenal cortex, stimulating the release of aldosterone, a mineralocorticoid that promotes sodium reabsorption. Among the other effects of AT-II are increased water intake through vasopressin, increased release of norepinephrine, and stimulation of myocyte growth as well as promotion of interstitial fibrosis.

FIGURE 1 Cardiovascular continuum



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In the Studies of Left Ventricular Dysfunction (SOLVD, both Treatment and Prevention), it was shown that the neurohormonal axis is activated in patients with LV dysfunction before symptoms of heart failure become evident (Francis 1990). In the asymptomatic patients with LV dysfunction, plasma levels of norepinephrine, atrial natriuretic peptide, vasopressin, and renin were higher than they were among patients in the control group but less than among those with overt heart failure. In the Vasodilator-Heart Failure Trial II (V-HeFT II), increasing mortality was associated with higher levels of plasma norepinephrine, with higher cumulative mortality found among patients with plasma norepinephrine levels >900 pg/mL, compared with levels in two other strata (601–900 pg/mL and <600 pg/mL) (Francis 1993). It is not necessary to assess plasma catecholamine levels to identify these patients, because they are readily identifiable based on their tachycardia, vasoconstriction, with cold and often clammy skin, sleep difficulties, and general jitteriness. These patients benefit from aggressive blockade of the neurohormonal cascade.

Classification systems for heart failure

The American College of Cardiology (ACC) and the AHA have jointly developed guidelines identifying four stages for the treatment of heart failure (Hunt 2001). These guidelines were developed based on an understanding of heart failure as (1) a preventable disease with established risk factors that can be modified, and (2) an evolving disease with asymptomatic and symptomatic phases that also can be modified by stage-specific treatments, thereby reducing morbidity and mortality.

A patient in ACC/AHA stage A is at high risk for development of heart failure but as yet has no structural heart disease or symptoms of heart failure. Risk factors in this patient population include hypertension, coronary artery disease, diabetes, use of cardiotoxins (e.g., doxorubicin), excessive intake of alcohol, or a family history of cardiomyopathy. Therapy that is aimed at modifying these risk factors includes the treatment of hypertension or dyslipidemia; smoking cessation; regular exercise; decreased use of alcohol and illicit drugs; and, for selected patients, ACE inhibition.

Left untreated, a patient in stage A, while remaining asymptomatic, develops structural heart disease and progresses to stage B. The stage-B patient population is characterized by a history of MI, LV dysfunction, and asymptomatic valvular disease. In addition to therapies that would be considered for stage-A patients, a beta blocker may be warranted for a stage-B patient.

Stage-C patients have symptoms of heart failure, such as shortness of breath, fatigue, and reduced tolerance for exercise. In addition to the previously mentioned therapies, drugs recommended for routine use in stage-C patients include diuretics, digitalis, ACE inhibitors, and beta blockers. These patients also require stringent sodium restriction.

Stage-D patients have marked symptoms at rest despite maximal medical therapy and, therefore, more advanced disease. In addition to all previously mentioned

treatments, mechanical assist devices, heart transplantation, palliative therapy (i.e., continuous intravenous inotropic infusions), and hospice care may be appropriate for these patients.

The New York Heart Association (NYHA) classification system is different from the ACC/AHA classification system. It is based on the physician's assessment of the patient's subjective symptoms. An NYHA class I patient has no limitations due to heart failure and no symptoms with ordinary activity. In class II, patients have slight limitations and notice symptoms with ordinary activity. In class III, patients have marked limitations and symptoms that emerge with less than ordinary activity. In class IV, patients have symptoms of heart failure even at rest.

Symptoms of heart failure

Shortness of breath is one of the most common symptoms seen in heart failure and often precipitates the office visit. Frequently, these patients have had shortness of breath upon exertion for a long time, but they have adjusted their lifestyle to compensate for the symptom. Instead of asking whether a patient feels fatigued, a more productive question would relate to an activity that the patient can no longer perform, or, for example, the length of time it takes to get dressed, compared with 5 years ago or the last time the patient remembers feeling really well.

Fullness and pain in the upper-right quadrant of the liver is another common symptom of heart failure, especially in younger patients, and is sometimes misdiagnosed as gall bladder disease — leading to unnecessary surgery. Misdiagnosis of heart failure seems to occur more often in women, who tend to have antecedent angina, not MI, and whose symptoms tend to be atypical and easily confused with other diseases and conditions. For example, congestive symptoms of heart failure sometimes are misdiagnosed as bronchitis, which fails to respond to treatment. Additionally, if a 60-year-old patient with no history of asthma suddenly appears to have developed asthma, it would be prudent to suspect heart failure until proven otherwise. Years ago, medical students were taught that this form of asthma is called cardiac asthma, and it still exists. Treating the heart failure resolves the condition.

Signs of heart failure may be minimal, but jugular venous distension is the most reliable sign, provided physicians remember to look for it. The S_3 heart sound, if it can be heard, is a powerful indicator of elevated ventricular pressure. On the other hand, even though pulmonary congestion is commonly thought to be a sign of heart failure, the vast majority of chronic heart failure patients have clear lungs. A clear lung field does not mean that heart failure can be ruled out, because the patient's pulmonary vascular tree may have adapted to the condition gradually.

Goals of therapy

Once a patient has been diagnosed with heart failure, the goal of therapy is to help the patient to feel better, avoid hospitalization, and enjoy an improved quality of life. To achieve these goals, patient education is essential, as patients need to know about the importance of following a proper, sodium-restricted diet; exercising appropriately; weighing themselves daily; and complying with drug therapy. The Heart Failure Society of America has patient education brochures available on eight different topics; a single copy may be downloaded free of charge from «www.hfsa.org», and multiple copies may be ordered inexpensively.

Conventional drug therapy for heart failure has employed positive inotropic agents (e.g., digoxin and other cardiac glycosides, and phosphodiesterase inhibitors), afterload reducers, and diuretics. Though promising on theoretical grounds, each of these modalities poses problems in practice.

Despite enhancing cardiac contractility, the most commonly used inotrope today, the phosphodiesterase inhibitor milrinone, has been shown to increase mortality and morbidity in a study enrolling 1,088 patients with severe heart failure (NYHA class III or IV) compared with placebo (Packer 1991). In this study, oral milrinone 40 mg or placebo was added to standard therapy with digoxin, diuretics, and ACE inhibitors. After a median follow-up period of 6.1 months, all-cause mortality was 28 percent higher in the milrinone group — and 53 percent higher in the class IV subset. Moreover, rates of serious adverse cardiovascular events (including hypotension) and hospitalizations were higher in the milrinone group than in the placebo group.

More recently, intravenous milrinone was found to be no better than saline placebo as an adjunct to standard therapy in a study enrolling 951 patients hospitalized because of worsening heart failure (Cuffe 2002). Ninety-two percent of this population had NYHA class III or IV heart failure. At 60 days after randomization, days of hospitalization and in-hospital mortality rates remained the same in each group. In addition, the rate of sustained hypotension necessitating treatment was higher (10.7 vs. 3.2 percent) in the milrinone group, as were new atrial arrhythmias (4.6 vs. 1.5 percent).

With respect to afterload reduction, it should have come as no surprise that the doxazosin arm of ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) was stopped prematurely because the risk of major cardiovascular disease, chiefly heart failure, was higher among patients randomized to doxazosin than among patients assigned to the diuretic chlorthalidone (ALLHAT 2000). Doxazosin is an α_1-adrenergic blocker, as is prazosin; both reduce blood pressure by dilating arteries and veins, and both stimulate the RAAS. In the first Vasodilator Heart Failure Trial (V-

HeFT), prazosin was no better than placebo in reducing mortality (Cohn 1986).

Commonly, when a patient is hospitalized with worsening heart failure, large doses of a diuretic are administered intravenously. Yet, a diuretic given alone also reactivates the neurohormonal system, because the resulting depletion of sodium leads to an increase in renin. The patient consequently retains more sodium and becomes even more edematous, often leading to readmission within 30 days if nothing is done to attack the neurohormonal cascade.

ACE inhibition is a means of disrupting the RAAS, and it has been shown to improve mortality in class IV patients (Effects of enalapril 1987) as well as class II and III patients (Effect of enalapril 1991, 1992). Despite the evidence base supporting the use of ACE inhibitors to treat patients with heart failure, they are still underused and underdosed in this population. Utilization is limited by clinicians' lack of knowledge of the benefits of ACE inhibitors, especially in class I and II patients. Underdosing is driven by concerns about hypotension, hyperkalemia, and renal function.

It is even more difficult to persuade physicians to prescribe beta blockers for their patients with heart failure. Used appropriately, beta blockers can revolutionize the care of heart failure patients, as these agents are antihypertensive, antiarrhythmic, anti-ischemic, and possibly antiatherogenic. Beta blockade has been shown to change the size and shape of the left ventricle. In this process of reverse remodeling, the ventricle loses mass and becomes more elliptical and less spherical. Although an improvement in ventricular function becomes evident after 1 month (coming after a mild initial reduction in function) and can be improved markedly after 3 months of beta blockade, the reverse remodeling unfolds more slowly, becoming apparent after 18 months (Hall 1995).

A mortality benefit has been demonstrated in large trials using three different beta blockers — bisoprolol (CIBIS-II 1999), carvedilol (Packer 2001), and extended-release metoprolol (Effect of metoprolol CR/XL 1999) (Table 1). Note that the mortality benefits did not vary with the selectivity of the agent for the adrenergic receptor subtypes: bisoprolol and extended-release metoprolol are both selective for the β_1 receptor, whereas carvedilol blocks the β_1, β_2, and α_1 receptors, but the results of all three studies were similar.

Unlike ACE inhibitors, beta blockers have been shown to reduce the risk of sudden death, a substantial source of mortality in patients with heart failure. In the Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF), there were 132 sudden deaths in the placebo group versus 79 in the treatment group (relative risk [RR], 0.59), and in the Cardiac Insufficiency Bisoprolol Study II (CIBIS-II), there were 83 sudden deaths in the placebo group versus 48 in the treatment group (RR, 0.56).

When initiating beta blockade, it is important to assess the patient's volume status. If the patient is volume-overloaded, diuretics should be used to achieve euvolemia. At that point, the patient can be started on a low dose, which can be uptitrated slowly.

When beta blockade is initiated, certain side effects may necessitate adjustments to the overall drug regimen. If the patient becomes hypotensive, diuretics should be decreased or stopped. Dizziness not related to hypotension usually is transient. Volume overload probably is the most common side effect, which is treated with a temporary increase in diuretics. Patients should be instructed to weigh themselves every day and follow, for example, the *Rule of 3* — a gain of 3 pounds in 3 days indicates the need to take an extra diuretic. Patients also should be reassured that feelings of fatigue will dissipate in a few weeks, and they should be encouraged to adhere to their beta-blocker therapy in the meantime because their cardiac function could improve dramatically in the next 3 or 4 months.

TABLE 1 Survival studies with beta blockers in heart failure

Trial	Study drug	N	NYHA class	EF, mean	Total mortality, placebo/β blocker	RR
CIBIS-II	Bisoprolol (β_1 antagonist)	2,647	III, IV	0.28	228/156	0.66
COPERNICUS	Carvedilol (β_1, β_2, α_1 antagonist)	2,289	III, IV (estimated from chronic advanced)	0.20	190/130	0.65
MERIT-HF	Metoprolol CR/XL (β_1 antagonist)	3,991	II, III, IV	0.28	217/145	0.65

CIBIS-II=Cardiac Insufficiency Bisoprolol Study II, COPERNICUS=Carvedilol Prospective Randomized Cumulative Survival Study, EF=ejection fraction, MERIT-HF=Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure, NYHA=New York Heart Association, RR=relative risk.

SOURCES: CIBIS-II 1999, PACKER 2001, EFFECT OF METOPROLOL CR/XL 1999

The Randomized Aldactone Evaluation Study (RALES) was conducted before the results of MERIT-HF and the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) study were published, which explains why only approximately 11 percent of RALES subjects received spironolactone (or placebo) in addition to beta blockers, while nearly all patients received loop diuretics and ACE inhibitors (Pitt 1999). This study enrolled 1,663 patients with severe heart failure (NYHA class III or IV; LV EF ≤35 percent). The trial was stopped early, after a mean follow-up of 24 months, because the RR of all-cause mortality was 30 percent less in the spironolactone group than in the placebo group. Because spironolactone binds to androgen and progesterone receptors as well as mineralocorticoid receptors, gynecomastia and breast pain were reported by 10 percent of men receiving spironolactone compared with 1 percent of men in the placebo group. Rates of serious hyperkalemia were not statistically different, however, between the placebo and spironolactone groups (1 vs. 2 percent).

Today, another aldosterone blocker is available, eplerenone. Unlike spironolactone, eplerenone selectively blocks mineralocorticoid but not glucocorticoid, progesterone, or androgen receptors. It was evaluated in the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), which, as its name indicates, enrolled a post-MI population with LV dysfunction (N=6,642) (Pitt 2003). Eplerenone or placebo was added to optimal therapy, which could include ACE inhibitors, angiotensin-receptor blockers (ARBs), diuretics, and beta blockers. During a mean follow-up of 16 months, all-cause mortality was reduced by 15 percent in the eplerenone group relative to the placebo group (554 vs. 478 deaths), much of which was due to a 21 percent reduction in the RR of sudden death from cardiac causes (201 vs. 162 deaths).

Due to its selectivity, eplerenone is associated with lower rates of gynecomastia than spironolactone. Spironolactone should be considered as the initial aldosterone blocker for most heart failure patients, however, because it is inexpensive and because patients with severe heart failure are unlikely to become hyperkalemic unless they also have severe renal disease (which may be the case with diabetics).

Furthermore, it should be noted that adding candesartan to an ACE inhibitor also blocks aldosterone. In the Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) pilot study, the lowest levels of aldosterone were seen among patients in the arm in which the ARB candesartan was added to the ACE inhibitor enalapril (McKelvie 1999). This trial provided the context in which the Candesartan in Heart Failure — Assessment of Reduction in Mortality and Morbidity (CHARM) trials were designed. In the CHARM Added trial, candesartan was added to an ACE inhibitor. This regimen was based on the theory that ACE inhibition blocks one pathway by which AT-II is produced, but does not block all AT-II pathways. Consequently, AT-II levels rebound even while ACE inhibition is being used, as do aldosterone levels.

In the Valsartan Heart Failure Trial (Val-HeFT), patients with heart failure (N=5,010) were randomized to treatment with valsartan or placebo (Cohn 2001). The majority of patients were NYHA class II (62 percent), and 32 percent of patients were class III. As background therapy, an ACE inhibitor was used by 93 percent of patients, diuretics by 85 percent, and beta blockers by 35 percent. Overall mortality rates were similar in the valsartan and

TABLE 2 CHARM baseline characteristics

	Alternative (n=2,028)	Added (n=2,548)	Preserved (n=3,023)	Overall (N=7,599)
Mean age (years)	67	64	67	66
Women (%)	32	21	40	32
NYHA class (%)				
II	48	24	60	45
III	49	73	38	52
IV	3	3	2	3
Mean LVEF	30	28	54	39
Medical history (%)				
Myocardial infarction	61	56	44	53
Diabetes	27	30	28	28
Hypertension	50	48	64	55
Atrial fibrillation	25	26	29	27

CHARM=Candesartan in Heart Failure — Assessment of Reduction in Mortality and Morbidity, LVEF=left ventricular ejection fraction, NYHA=New York Heart Association.
SOURCE: GRANGER 2003, MCMURRAY 2003, PFEFFER 2003, YUSUF 2003

placebo groups, but a combined endpoint comprising mortality and morbidity was reduced by 13 percent in the valsartan group, relative to the placebo group. Subgroup analysis showed, however, that patients in the valsartan group who received ACE inhibitors and beta blockers seemed to do worse, in terms of the combined endpoint, than the placebo-group patients receiving these agents. In addition, the major improvement in hospitalizations was driven by the small percentage of patients who were not on an ACE inhibitor.

The CHARM trials looked further at the question of using an ARB to reduce mortality and morbidity among patients with heart failure. CHARM addressed three distinct populations (Table 2, page 17): 2,548 patients with an LV EF ≤40 percent who were using an ACE inhibitor (CHARM-Added), 2,028 patients with an LV EF ≤40 percent who were not using an ACE inhibitor because of intolerance (CHARM-Alternative), and 3,023 patients with an LV EF >40 percent (CHARM-Preserved).

For the overall program, the primary outcome was all-cause mortality (Pfeffer 2003); for the component trials, the primary endpoint was cardiovascular death or hospitalization for heart failure. In CHARM-Added, the RR of the composite endpoint was reduced by 15 percent in the candesartan group after a median follow-up period of 41 months (McMurray 2003). In CHARM-Alternative, the RR of the composite endpoint was reduced by 23 percent (Granger 2003). In CHARM-Preserved, there was no difference in the cardiovascular death rate between the candesartan and placebo groups, but hospitalization for heart failure was reduced in the candesartan group (Yusuf 2003).

In summary, multiple insults — whether hypertension, diabetes, or coronary artery disease — all can lead to heart failure, which develops before symptoms emerge. Regardless of the underlying cause, activation of the neurohormonal cascade is nearly identical. To reduce mortality and morbidity, patients with heart failure need to be identified at an early stage and treated with agents proven to interrupt the neurohormonal cascade.

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The Importance of Anticoagulation Management Services

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Warfarin, the most commonly used anticoagulant, is a highly efficacious treatment choice for patients requiring chronic anticoagulation therapy but is associated with an increased risk for bleeding. In addition to this risk, patients must be monitored closely to achieve target anticoagulation intensity using frequent international normalized ratio (INR) measurements and for potential drug-drug and drug-diet interactions. This need for a high level of both monitoring and quality of care for patients taking warfarin places a significant demand on primary care providers and the health care community as a whole. Coordinated anticoagulation therapy through use of an anticoagulation management service (AMS) may reduce the primary care burden and provide a higher quality of service to these patients, with the potential to improve patient outcomes.

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Overview: warfarin therapy

Warfarin is an oral vitamin-K antagonist and is highly efficacious for preventing and treating medical conditions such as venous thromboembolism (i.e., deep vein thrombosis and pulmonary embolism), valvular and nonvalvular atrial fibrillation (AF), ischemic cardiomyopathy, and following an acute myocardial infarction (especially post myocardial infarction ventricular aneurysm), as well as after certain procedures such as insertion of prosthetic heart valves. Among the disadvantages of using warfarin, however, are the association with a higher risk of bleeding, need for frequent INR monitoring, dietary restrictions involving alcohol and foods containing vitamin K, and numerous drug-drug interactions (Coumadin PI 2002). In addition, warfarin has a narrow therapeutic window (i.e., maximizes efficacy and safety within a narrow range of INR values) that requires frequent monitoring on the part of the patient and routine follow-up and warfarin dose adjustment by the treating physician. An INR level below the target range (e.g., INR <2.0) substantially increases the risk of a thromboembolic event, while an INR level above the target range (e.g., INR >4.0) increases the risk of major bleeding — especially intracranial hemorrhage.

To date, many medical practitioners and health care systems rely primarily on a model that includes a combination of clinicians and ancillary staff to track and manage patients receiving warfarin. This can be a challenging endeavor due to the complexity of managing this drug by the patient and physician, especially given all the concurrent medical conditions that must be managed.

This challenge contributes to the lower than ideal level of prescriptions for warfarin in eligible patients, especially those with nonvalvular AF. Furthermore, several surveys have shown that physicians often have an exaggerated perception of the absolute risk of bleeding associated with warfarin, which also contributes to underprescribing and inadequate anticoagulation intensity (Gross 2003). Many patients often spend time chronically below rather than above the target INR range, partially due to this overestimated risk of bleeding and the wish to *Primum non nocere*, or "First, do no harm." For example, an extremely elderly (>80 years old) patient with AF is at much higher risk to suffer a stroke off warfarin as well as a higher risk of bleeding on warfarin, with the latter often driving the anticoagulation decision despite the absolute risk of stroke being significantly higher than the risk of bleeding.

Nevertheless, given the probable 30 to 70 percent of eligible patients with nonvalvular AF who are not prescribed

warfarin and the time that many patients spend in the suboptimal therapeutic INR range, there is much room for improvement in the medical care system. It is clear that improvements in the use and control of warfarin therapy can occur by increasing the efficiency and decreasing the burden on patients and their health care providers.

Managing anticoagulation in outpatients

Anticoagulated patients traditionally were managed by their individual treating physician in combination with an ancillary staff. In addition, these physicians may or may not have offered point-of-care testing for INR measurements using hand-held testing devices, which might avert the need to use outside laboratories. Some estimates suggest that up to 70 percent of anticoagulated patients in the United States are managed this way.

Given the many challenges of providing optimal anticoagulation and the obstacles to physicians, staff, and patients, other methods to systematically manage chronic anticoagulation have been developed. Nurse- or pharmacist-run anticoagulation clinics (ACs) initially were developed as primarily *ad hoc* in-person clinics using paper-based tracking, with the majority of clinics not using point-of-care testing for INR measurements. More recently, with the advent of improved and less-expensive information technology, ACs have shifted toward dedicated services, using computerized tracking systems, telemanagement, and/or point-of-care testing at the clinic or satellite locations. They operate in accordance with standardized dosing guidelines and recommendations of the treating physicians when adjusting warfarin dosing for individual patients.

An increasing amount of resources has been invested to examine whether the current clinic-based model can be transformed further into a patient self-supported care model, similar to the one used in patients with diabetes mellitus who monitor their blood glucose levels. In this model, patients are educated about testing and provided with testing materials. Subsequently, patients report back to the health care provider or anticoagulation service responsible for treating them to ensure proper drug dosing for achieving the target anticoagulation intensity.

This approach is being studied further in patients who are implementing self-testing and self-management of drug dosing according to levels established by printed or computer-driven algorithms that are provided by their treating physician. It remains unclear, however, to what degree these strategies can be generalized to the majority of patients who require chronic anticoagulation and whether they will lead ultimately to fewer adverse events and reduced medical costs.

Anticoagulation management services

The potential advantage of an AMS includes the opportunity (1) to evaluate patient eligibility and related risks for chronic anticoagulation when initially considering treatment and over time, and (2) to facilitate the initiation of systematic dosing changes by a dedicated trained staff. On an ongoing basis, an AMS also can help to educate patients and physicians about how to optimize anticoagulation therapy. Yet, it may not be feasible for physicians to achieve optimal therapy in the setting of a busy clinic. In addition, in managing anticoagulation patients (e.g., continuous monitoring of INR levels, concomitant drug therapy, changing medical conditions, and dietary patterns), many time-consuming steps can be executed by a dedicated staff more efficiently than by physicians.

On the other hand, establishing an AMS often necessitates a substantial initial investment in personnel, training, and technology for tracking patients and ensuring high levels of quality. In addition to the initial investment, a commitment must be made to establish an organized system that can track patients throughout their clinical course based on measurement of INR levels and can react rapidly to changes in these levels. As the AMS expands and the anticoagulated-patient pool grows, additional personnel often will need to be added to the program despite gains in efficiencies. Before the program can begin to be cost-neutral, there must be an adequate number of patients and supporting providers in combination with an efficiently run AMS. Further, the AMS must achieve high-quality anticoagulation benchmarks to avoid costly and preventable thromboembolic and bleeding events.

Better than usual medical care?

Although it makes sense conceptually that use of a dedicated AMS would lead to better outcomes and greater patient and physician satisfaction compared with usual medical care, it has not been easy to demonstrate this conclusively in previously published studies. Several studies have documented that AMS-treated patients generally tend to spend a greater amount of time in the therapeutic INR range compared with patients receiving usual medical care (Chiquette 1998, Matchar 2002, Wilson 2003). Nevertheless, it was not clear whether the primary reason clinical outcomes (i.e., thromboembolism and bleeding) were systematically lower with an AMS compared with usual medical care was that these studies have a relatively small number of monitored patients, leading to few adverse outcomes.

Furthermore, it is often difficult to compare studies due to different patient populations receiving warfarin therapy, the use of different INR target ranges, and variation in the dose-adjustment algorithms. These issues are highlighted in the following brief review of selected studies that have attempted to compare outcomes of AMS versus usual medical care.

As part of a natural experiment in which a university AC was open or closed for different periods of time, Chiquette and colleagues examined the medical records of

145 newly anticoagulated patients receiving usual medical care and 183 newly anticoagulated patients. They received care at the AC to examine the level of anticoagulation control, rates of thromboembolic events and bleeding, and differences in costs for hospitalizations and emergency department visits (Chiquette 1998). Patients were included if they received warfarin treatment for at least 3 months and had at least one outpatient visit. Results showed that patients receiving treatment at the AC spent slightly more time in the therapeutic INR range and less time at an INR less than 2.0 or greater than 5.0 compared with those receiving warfarin and usual medical care. The AC group also had lower crude rates of major bleeding and thromboembolic events, though the number of events was small in each group and not statistically significant. Furthermore, the study suggested potential cost savings through reduced hospitalizations and emergency department visits.

Another group of researchers conducted a randomized trial to evaluate the role of an AMS versus usual medical care in managing patients age 65 or older with nonvalvular AF (Matchar 2002). Patients in six MCOs were randomly assigned to receive care at a "high-quality" AMS or at their usual medical care provider. During a 9-month follow-up period, approximately 56 percent of AMS patients were in the therapeutic INR range versus 52 percent of patients in the usual medical care group. These data suggested that starting an AMS offered minimal benefit for this quality measure. This study, however, had several important limitations, including the relatively small sample size, difficulties establishing an effective AMS in all health plans, incomplete and often varied implementation of the intervention, use of different INR target ranges by different physicians, relatively short clinical follow-up, as well as the lack of clinical outcomes. Also, the study was based on the assumption that if an AMS was started in a health plan, the majority of physicians would refer all their eligible patients for assessment and treatment would begin, but this did not routinely occur for reasons that are unclear.

Finally, another trial in Canada evaluated 221 patients who were currently stable on warfarin treatment (Wilson 2003). Patients were randomly assigned to receive anticoagulation care from an AMS or their primary care provider. Patients were followed for 3 months to observe time spent in an expanded therapeutic INR range (2.0 to 3.0 for standard-risk patients; 2.5 to 3.5 for high-risk patients). After 3 months, a modest increase in the time spent in the therapeutic INR range was observed among patients using the anticoagulation service versus usual medical care, 82 percent versus 76 percent (P=.034), respectively. No differences were observed in clinical outcomes and a low absolute event rate was reported in both groups. Interestingly, the majority of the 170 patients completing the patient satisfaction questionnaire were more satisfied when their anticoagulation treatment was managed through an AMS than when it was managed by their primary care provider (P=.001).

AMS in a large integrated health care delivery system

Kaiser Permanente of Northern California is a large integrated, capitated health care delivery system serving a racially and ethnically diverse population of more than 3 million persons — representing more than a third of insured adults in the San Francisco and greater Bay Area. The system comprises 17 medical centers and 31 outpatient clinics, with medical care provided through physicians of the Permanente Medical Group.

The Kaiser AMS is a series of geographically distributed, pharmacist-managed ACs that are linked to individual Kaiser medical centers. The first AC was started in 1993 in San Francisco and initially served as the only clinic for the entire Northern California Kaiser population. Most of the work was conducted through a combination of in-person clinic visits and telephone follow-up during a time when AC enrollment was much smaller.

At present, there are 21 ACs, including the newest clinic, which opened last March. These clinics serve approximately 26,000 to 28,000 Kaiser patients currently receiving chronic anticoagulation treatment (85 to 90 percent of all Kaiser anticoagulation patients). Clinic sizes range from 300 to 2,000 patients, depending on the location and the need. To support this population, Kaiser employs approximately one full-time pharmacist for each 700 to 750 patients in the AC and one full-time pharmacist assistant per 1,000 patients, with systematic tracking using computerized software systems linked to the comprehensive Kaiser regional laboratory for INR values.

Initially, the clinics offered in-person services exclusively — patients had to make regular visits to the clinic to receive dosage adjustments. Now, however, the system primarily utilizes telemanagement (with 90 to 95 percent of patients receiving care in this way). Patients can go to a local Kaiser laboratory for their INR measurement, and their AC pharmacist uses software programs to monitor INR levels and to make warfarin dosing adjustments by phone, based on standardized treatment recommendations and those of a dedicated staff physician. Dose adjustments are based primarily on the American College of Chest Physicians Consensus Guidelines for Antithrombotic Therapy (Ansell 2001) and are updated routinely as new evidence emerges.

To increase efficiency and increase the adherence to recommended INR testing frequency, a new automated system that phones patients and reminds them of the need for INR testing is being evaluated in Northern California. INR tests are preordered and the patient can go to the nearest Kaiser laboratory to have an INR test done, with follow-up care provided by AC staff.

With this model of care, a referral still is required from an outpatient primary care provider or attending physician, if the patient is being discharged from the hospital on warfarin therapy. On enrollment, new patients receive initial screening and education in the form of classes, videos, and printed literature on warfarin, the need for regular INR testing, dietary guidelines, and potential drug-drug interactions. AMS laboratory needs are met by multiple Kaiser laboratories, located on site at each Kaiser medical center, which retrieves INRs directly into the automated clinical data system. In addition, limited INR point-of-care testing is conducted to facilitate the management of patients in the nursing home or home care setting.

Not surprisingly, the results of several informal Kaiser surveys show that physicians and ancillary staff highly value an AMS. The Kaiser AMS offloads the day-to-day burden of tracking INRs and dosing changes in large numbers of patients, thereby freeing up physician and staff time for increased overall productivity. Furthermore, the AMS benefits patients directly, as it offers a much faster response time to out-of-range INR values and/or treatment-related complications, as well as ongoing education.

An AMS offers the additional advantage of a pharmacist evaluation of patients, which is of particular interest in the case of warfarin due to the increased potential for drug-drug interactions. Generally, the AMS provides this integrated service with the overall medical and legal responsibility remaining under the patient's primary or referring physician. This reinforces the need for clear and frequent communication between AMS staff and a patient's physician.

Case study

Stroke is the leading cause of disability and third leading cause of death in the United States (Higashida 2003). AF affects at least 1 in 25 Americans age 60 years or older and 1 in 10 adults age 80 years or older, with more than 2.3 million adults with nonvalvular AF currently. AF directly accounts for more than 75,000 strokes each year and independently increases the annual risk of stroke by approximately fivefold (Friedman 1968, Wolf 1991, AFI 1994). The primary mechanism of stroke in AF is through the development and dislodgement of blood clots in the heart. Nontransient AF results in venous stasis in the left atrium, especially in the left atrial appendage, which activates the clotting system and promotes development of a thrombus. Embolization of the predominantly fibrin clot results in systemic thromboembolism and, particularly, ischemic stroke.

Table 1 presents a summary of recent meta-analyses of pooled data from randomized clinical trials of antithrombotic agents and their ability to reduce the incidence of ischemic stroke. Adjusted-dose oral anticoagulation vs. no antithrombotic therapy showed a 68 percent reduction in the relative risk of stroke (AFI 1994). In the case of aspirin versus no antithrombotic therapy, only a mild reduction was observed (AFI 1997). Adjusted-dose warfarin offers a 52 percent relative advantage over aspirin with respect to relative reduction in the risk of stroke (van Walraven 2002).

The screening process for these trials was extremely rigorous, with enrollment of only 4 to 7 percent of patients who were screened (AFI 1994,1997; van Walraven 2002). The ability to generalize these findings is limited also because patients enrolled in these trials were generally younger, had fewer coexisting illnesses, and were closely monitored (i.e., received extra medical care due to enrollment in the trial), the latter being difficult to replicate outside the clinical trial setting. For these reasons, many physicians often have been extremely cautious about interpretations of these data, as bleeding risks may be higher in the real-world setting of typical clinical populations and practice.

TABLE 1 Meta-analyses of antithrombotic prescriptions from pooled randomized clinical trial data

Treatment comparisons	Relative risk reduction* (95% CI)
Adjusted-dose oral anticoagulation vs. no antithrombotic therapy	68% (50% to 79%)
Aspirin vs. no antithrombotic therapy	21% (0% to 38%)
Adjusted-dose oral anticoagulation vs. aspirin	52% (37% to 63%)

* Outcome is ischemic stroke. Note that trials involved in each analysis are not identical.
SOURCES: AFI 1994, 1997; VAN WALRAVEN 2002

The ATRIA study

To examine the question of whether the high quality of anticoagulation and associated favorable outcomes could be replicated outside the randomized trial setting, colleagues from the Kaiser Permanente of Northern California Division of Research and Massachusetts General Hospital initiated the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study, drawing on the Kaiser Permanente of Northern California patient pool (Go 2003). Between July 1996 and December 1997, 13,559 health plan members were enrolled based on the presence of nonvalvular AF, which was ascertained using serial outpatient diagnoses and electrocardiogram findings of AF. At study entry, 54 percent of eligible patients were taking warfarin. Of those, 80 percent were followed

TABLE 2 ATRIA study baseline patient characteristics

Characteristic	ATRIA cohort (N=13,559)
Women	42.7%
Mean age ± SD (yr)	71.6 ± 11.6
Prior ischemic stroke	9.2%
Diagnosed heart failure	30.6%
Diagnosed hypertension	50.9%
Diabetes mellitus	17.3%
Prior coronary heart disease	29.0%
Prior intracranial hemorrhage	0.7%
Prior gastrointestinal bleed	4.4%
Prior other bleed	1.0%
Prior mechanical fall	3.8%
Diagnosed dementia	3.0%
Seizure disorder	1.2%
Cirrhosis or hepatitis	1.4%

ATRIA=Anticoagulation and Risk Factors in Atrial Fibrillation study

in one of the existing ACs. Patients were followed to monitor clinical outcomes, including ischemic stroke and major bleeding. Table 2 details the patient demographic and clinical features; of particular interest is the large population of women included in this analysis.

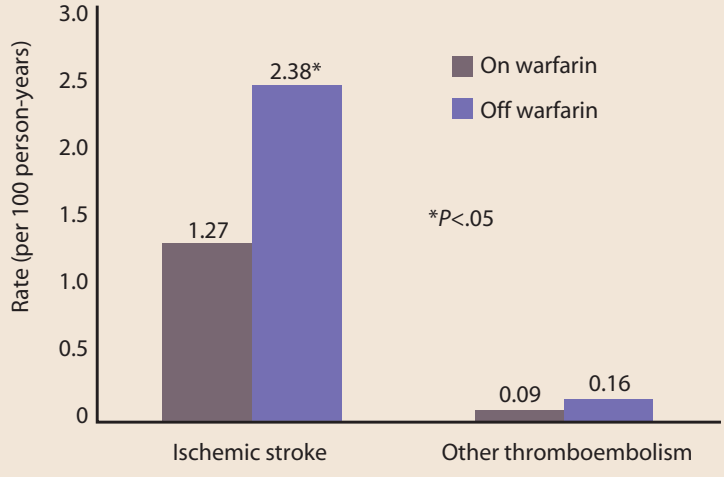
We found that the rate of ischemic stroke in patients taking warfarin was approximately 2.4 percent versus 1.3 percent ($P<.05$) in patients not currently taking warfarin (Go 2003). Not surprisingly, we observed an extremely low rate of other types of embolism, such as in the gastrointestinal or renal arterial system (Figure 1). The crude rate of intracranial hemorrhage was 0.51 per 100 person-years among patients taking warfarin versus 0.33 per 100 person-years among those not taking warfarin ($P<.05$). Interestingly, the rate of gastrointestinal bleeding was slightly higher for patients not currently taking warfarin (1.36 vs. 1.05 per 100 person-years), which may have occurred because patients at high risk for a gastrointestinal bleed are not routinely treated with warfarin.

In an attempt to account for such differences between patients taking warfarin versus those not taking warfarin, we adjusted for age, gender, known stroke risk factors, potential contraindications to anticoagulants, and time-varying probability of receiving warfarin. Nevertheless, it was found that use of warfarin therapy still was associated with a 51 percent relative reduction in the risk of stroke and other thromboembolic events. The adjusted relative risk of intracranial hemorrhage was almost 70 percent higher with warfarin versus without warfarin, but the absolute rate of intracranial hemorrhage was substantially lower than the rate of ischemic stroke. There also was no significant association of warfarin use with major bleeding after multivariable adjustment. In terms of the quality of anticoagulation, we were able to achieve 62 percent of the INR time in the therapeutic range, which was extremely similar to that seen in the published randomized trials of warfarin therapy for AF.

Based on these findings, we concluded that the use of coordinated anticoagulation among patients with AF facilitated time in the therapeutic INR range at a rate similar to that observed in recent clinical trials. The use of warfarin was associated with a 50 percent reduction in risk of stroke and only a modest increase in the risk of intracranial hemorrhage.

As noted above, a key element to facilitate achieving optimal outcomes is the close coordination of anticoagulation care between the AMS and patient's responsible physician within the context of the patient's entire medical condition. The AMS focuses primarily on monitoring anticoagulation intensity and dose adjustments, along with regular patient education. The patient's responsible physician can work effectively with the AMS in the ongoing assessment of eligibility for use of anticoagulants and

FIGURE 1 Rate of ischemic stroke and other thromboembolism associated with warfarin treatment



SOURCE: GO 2003

evaluation of the projected net benefit or harm for individual patients, notifying the AMS when initiating therapies that could have an impact on the effectiveness and safety of anticoagulation.

In addition, an important element that likely contributed to the successful implementation of the AMS within Kaiser Permanente of Northern California is the integrated health care delivery system structure, in which there are fewer competing financial or other goals between those who provide and fund coordinated anticoagulation services. This presents ongoing difficulty for other types of health systems with more distributed networks; AMS care is not easily reimbursable through current federal or private insurance sources and necessitates a longer-term perspective allowing a reduction of the rate of adverse events (e.g., clinical events, lost productivity, reduced quality of life, and functional status).

The Center for Medicare and Medicaid Services (CMS) also should strongly consider allowing appropriate billing of AMS services while requiring evidence of high-quality care, but this option is not available today. Nonetheless, given the potential net advantages from various perspectives (e.g., patient, provider, hospital, insurer, pharmacy, and laboratory), creative efforts are needed by these key stakeholders at the local and national level to collectively and collaboratively identify ways to implement coordinated anticoagulation such that financial risk is shared and continuity is ensured for patients and providers. With the fragmented nature of the majority of health care systems in the United States and continued shift of health care costs onto patients, this will be especially challenging.

Conclusions

The population of patients in the United States in need of long-term anticoagulation therapy is growing, and there is mounting evidence that coordinated AMSs are superior to usual medical care for achieving time in the therapeutic INR range. Data indicate that coordinated anticoagulation can facilitate improved outcomes among patients with nonvalvular AF. There are important financial and logistic implications for establishing and maintaining an anticoagulation management service, and the role of this service may change with the introduction of oral anticoagulants that do not necessitate long-term laboratory monitoring. Warfarin, however, will continue to be an important option for many patients, and improved strategies to optimize clinical and patient-centered outcomes are needed.

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CONTINUING EDUCATION POST-TEST

Exploring the Spectrum of Cardiovascular Care

On the combined answer sheet/evaluation form on page 28, please place an X through the box of the letter corresponding with the correct response for each question. There is only ONE correct answer to each question.

1. Many patients who might benefit from warfarin therapy go untreated or undertreated because of:
a. The high cost of warfarin.
b. Physicians' exaggerated perception of risk of bleeding for patients on warfarin.
c. Patients' exaggerated perception of risk of leukemia while on warfarin.
d. An inadequate supply of warfarin.

2. For elderly patients with atrial fibrillation, which of the following statements is true?
a. Being off warfarin therapy presents a higher risk of stroke, relative to being on warfarin.
b. Being on warfarin therapy presents a higher risk of bleeding, relative to being off warfarin.
c. The absolute risk of stroke for patients off warfarin therapy is much higher than the absolute risk of bleeding for patients on warfarin therapy.
d. All the above.

3. In a population of health plan members with atrial fibrillation, warfarin therapy was associated with:
a. A 51 percent relative reduction in the risk of stroke and other thromboembolic events.
b. A 70 percent relative reduction in the risk of intracranial hemorrhage.
c. Both of the above.
d. None of the above.

4. Among patients receiving warfarin, an international normalized ratio (INR) above the highest level increases the risk of:
a. Myocardial infarction.
b. Deep vein thrombosis.
c. Ischemic stroke.
d. Intracranial hemorrhage.

5. With respect to clinical outcomes, published studies comparing anticoagulation management services (AMS) with usual medical care show that:
a. Results are unequivocal.
b. AMS is superior to usual care.
c. Usual medical care is superior to AMS.
d. No studies have been published on this topic.

6. Razaxaban is a twice-daily oral agent that acts through:
a. Indirect inhibition of factor Xa, via antithrombin.
b. Direct inhibition of factor Xa.
c. Direct inhibition of thrombin.
d. Interfering with vitamin K.

7. Which agent does not necessitate monitoring via coagulation assays?
a. Argatroban.
b. Bivalirudin.
c. Heparin.
d. Warfarin.
e. Ximelagatran.

8. Heparin acts by:
a. Accelerating the activity of antithrombin.
b. Inhibiting the activity of antithrombin.
c. Preventing the activation of prothrombin.
d. Interfering with vitamin K.

9. Without anticoagulation therapy, the incidence of deep-vein thrombosis in patients who have undergone total knee replacement would be about:
a. 5 percent.
b. 25 percent.
c. 50 percent.
d. 75 percent.

10. In the ximelagatran trials, a transient elevation in liver enzymes has been observed.
a. True.
b. False.

11. A diagnosis of heart failure usually can be excluded on the basis of clear lungs.
a. True.
b. False.

12. Structural changes of the left ventricle stemming from heart failure have been shown to be:
a. Irreversible.
b. Reversible with angiotensin-converting enzyme inhibition.
c. Reversible with beta blockade.
d. Reversible with intravenous diuretics.

CONTINUING EDUCATION POST-TEST, continued

Exploring the Spectrum of Cardiovascular Care

13. Which statement is true about ACE inhibition in patients with heart failure?
a. ACE inhibition has been shown to reduce the risk of sudden death.
b. ACE inhibition blocks all ACE pathways.
c. ACE inhibition reduces mortality in patients with NYHA class II, III, or IV heart failure.
d. ACE inhibition is contraindicated in patients with heart failure.

14. Piña's "Rule of 3" points to the need to:
a. Always prescribe a trio of drugs for a patient with heart failure: an ACE inhibitor, an angiotensin-receptor blocker, and a beta blocker.
b. Follow up with patients every 3 weeks.
c. Follow up with patients every 3 months.
d. Instruct a patient to take an extra diuretic upon gaining 3 pounds in 3 days.

15. In patients with heart failure, the best mortality benefit is obtained with:
a. Nonselective blockade of the β_1, β_2, and α_1 adrenergic receptors with carvedilol.
b. Selective blockade of the β_1 receptor with bisoprolol.
c. Selective blockade of the β_1 receptor with extended-release metoprolol.
d. Any of the above.

16. In two studies involving Veterans Affairs patients, it was found that increased office visits and more intensive primary care were correlated with:
a. Increased rates of hospital stays and improvements in patient health.
b. Increased rates of hospital stays but not improvements in patient health.
c. Decreased rates of hospital stays and improvements in patient health.
d. Decreased rates of hospital stays but not improvements in patient health.

17. Which statement best describes supply-sensitive care?
a. The frequency of the use of care is driven by the available supply.
b. The frequency of the use of care is driven by medical necessity.
c. Health care providers are sensitive to the need to conserve health care resources in short supply.
d. Health care providers are sensitive to the need to ration all health care resources.

18. In the clinical setting, most treatment decisions appear to be based on:
a. Patients' preferences.
b. Informed consent.
c. Physician opinion.
d. Shared decision making.

19. Higher rates of health care utilization result in better health outcomes.
a. True.
b. False.

20. The "right" decision about a surgical procedure involving tradeoffs in outcomes is more likely to be made when the surgeon:
a. Relies on his/her professional judgment.
b. Consults with colleagues.
c. Follows national guidelines.
d. Involves the patient in the decision-making process.

CONTINUING EDUCATION ANSWER SHEET/CERTIFICATE REQUEST

Exploring the Spectrum of Cardiovascular Care

CME/CE Credit for Physicians/Pharmacists

I certify that I have completed this educational activity and post-test and claim *(please check one)*
___ Physician credits
___ Pharmacist contact hours

Signature: _____

First name, MI _____

Last name, degree _____

Title _____

Affiliation _____

Specialty _____

Address _____

City_____ State ___ ZIP_____

Daytime telephone (____) _____

Fax (_____) _____

E-mail _____

Physicians — This activity is designated for a maximum of 2.0 category 1 credits toward AMA Physician's Recognition Award.

Pharmacists — This activity is approved for 2.0 contact hours (0.2 CEU).

ACPE Universal Program Number (UPN): 812-000-04-012-H01
Release date: Sept. 15, 2004
Expiration date: Sept. 15, 2005

To receive credit, complete the answer sheet/evaluation form and mail or fax to:
The Chatham Institute
26 Main Street, 3rd Floor
Chatham, NJ 07928
Fax: (973) 701-2515

Credit will be awarded upon successful completion of assessment questions (70 percent or better) and completion of program evaluation. If a score of 70 percent or better is not achieved, no credit will be awarded and the registrant will be notified. Please allow up to 6 weeks for processing.

EXAMINATION: Place an X through the box of the letter that represents the best answer to each question on pages 26 and 27. There is only ONE correct answer per question. Place all answers on this form:

	A.	B.	C.	D.	E.
1.	☐	☐	☐	☐	
2.	☐	☐	☐	☐	
3.	☐	☐	☐	☐	
4.	☐	☐	☐	☐	
5.	☐	☐	☐	☐	
6.	☐	☐	☐	☐	
7.	☐	☐	☐	☐	☐
8.	☐	☐	☐	☐	
9.	☐	☐	☐	☐	
10.	☐	☐			
11.	☐	☐			
12.	☐	☐	☐	☐	
13.	☐	☐	☐	☐	
14.	☐	☐	☐	☐	
15.	☐	☐	☐	☐	
16.	☐	☐	☐	☐	
17.	☐	☐	☐	☐	
18.	☐	☐	☐	☐	
19.	☐	☐			
20.	☐	☐	☐	☐	

PROGRAM EVALUATION
So that we may assess the value of this self-study program, we ask that you please fill out this evaluation form.

Have the activity's objectives been met?

1. Understand the reasons underlying geographic variations in rates of health care utilization and the quality of health care ☐ Yes ☐ No

2. Explain the differences among effective care, preference-sensitive care, and supply-sensitive care ☐ Yes ☐ No

3. Describe the advantages and limitations of currently available anticoagulants ☐ Yes ☐ No

4. Discuss the differences between oral factor Xa anticoagulants and currently available anticoagulants ☐ Yes ☐ No

5. Comprehend the reasons for establishing clinics to manage patients on warfarin ☐ Yes ☐ No

6. Compare the evidence supporting anticoagulation management services with usual medical care ☐ Yes ☐ No

7. Know common signs and symptoms of heart failure, and cite several ways in which heart failure is misdiagnosed ☐ Yes ☐ No

8. Gain insight into the rationale supporting pharmacotherapy aimed at interrupting the neurohormonal cascade in patients with systolic heart failure ☐ Yes ☐ No

Was this publication fair, balanced, and free of commercial bias? ☐ Yes ☐ No

If no, please explain: _____

Did this educational activity meet my needs, contribute to my personal effectiveness, and improve my ability to:

Strongly agree — *Strongly disagree*

Treat/manage patients?
5 4 3 2 1 N/A

Communicate with patients?
5 4 3 2 1 N/A

Manage my medical practice?
5 4 3 2 1 N/A

Other _____
5 4 3 2 1 N/A

Effectiveness of this method of presentation:

Excellent	*Very good*	*Good*	*Fair*	*Poor*
5	4	3	2	1

What other topics would you like to see addressed? _____

Comments: _____