EDITORIALS

New Anticoagulants — The Path from Discovery to Clinical Practice

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For more than half a century, heparin and vitamin K antagonists have defined anticoagulant therapy for the short-term and long-term management, respectively, of thrombotic disorders of the venous system. The history of their development is instructive. In 1922, at the annual meeting of the American Physiological Society, William H. Howell of Johns Hopkins Medical School presented an extraction protocol for isolating heparin preparations. Dicoumarol, a bacterial antagonist of vitamin K in spoiled sweet clover, was recognized as the agent responsible for a fatal hemorrhagic disease in livestock by Karl Link and Wilhelm Schoeffel of the University of Wisconsin. In both cases, decades would pass before heparin and warfarin entered clinical practice, and even today the complex pharmacokinetics, pharmacodynamics, and optimal use of these anticoagulants are causes of uncertainty in the medical community.[1]

Two articles in this issue of the *Journal* describe the results of thromboprophylaxis with an orally active, highly selective, direct inhibitor of factor Xa, rivaroxaban, given at a fixed dose of 10 mg daily, as compared with the results with enoxaparin, a subcutaneously administered, indirect, nonselective factor Xa inhibitor, in patients undergoing major orthopedic surgery. Collectively, more than 7000 patients were included in the Regulation of Coagulation in Orthopedic Surgery to Prevent Deep Venous Thrombosis and Pulmonary Embolism (RECORD1) (ClinicalTrials.gov number, NCT00329628)[2] and RECORD3 (ClinicalTrials.gov number, NCT00361894)[3] studies, with similar results for total hip and total knee arthroplasty, respectively. As compared with enoxaparin, rivaroxaban was associated with significant reductions in symptomatic and asymptomatic venous thromboembolism and major venous thromboembolism, defined as a composite of proximal deep-vein thrombosis, nonfatal pulmonary embolus, or death related to venous thromboembolism. The frequency of major bleeding and other safety outcomes — including on-treatment bleeding, hemorrhagic wound complications, and hepatic enzyme elevations — was low and did not differ between the study groups.

The favorable observations regarding the use of rivaroxaban raise questions that reach far beyond individual drugs to the overall process of drug development. What are the guiding principles for developing safe, effective, and widely applicable anticoagulants? What properties, characteristics, and outcomes that are discerned through clinical trials will help clinicians to distinguish factor Xa inhibitors from one another should the future offer multiple options?

The environment in which the thrombus occurs is important. Biologic and physiological distinctions among the arterial, venous, and microvascular systems are well known, as are intrinsic patient-specific differences in thromboresistance. Indeed, the regulation of platelet–vessel wall interactions, coagulation proteases, and fibrinolytic systems occurs on the endothelial surface, suggesting that overall hemostatic regulation and the location, extent, and stability of thrombus formation are conditionally based on site-specific differences in endothelial-cell structure, function, and molecular responses to biologic and rheological conditions. The disease state (e.g., cancer) and clinical circumstance (e.g., surgery) exert profound effects on the site of predisposition to thrombo-

sis and the most effective target for intervention. After major orthopedic surgery, there is soft-tissue injury, bone injury with intravasation of bony fragments, and stasis of venous blood flow associated with surgical positioning of the limb. Surges of tissue-factor release occur, and endothelial injury that is caused by the intravasation of bone-cement constituents, such as methyl methacrylate monomer, contribute to the highly thrombotic environment.

Molecular signatures and biomarkers that are derived from genomics, pharmacogenomics, transcriptomics, proteomics, and metabolomics are likely to constitute the frontier for an improved understanding of pharmacotherapy as it applies to individual patients and disease.[4,5] These tools have the potential to inform patient care and make a strong case for conducting parallel mechanistic studies in phase 2 and 3 clinical trials. Understanding the disease, the drug,[6] and the patient offers a basis for the all-important selection of an appropriate dose and directs the physician toward monitoring disease response rather than drug response — the traditional end point of therapy with heparin and drugs of similar complexity and off-target potential.

Highly desirable properties of an anticoagulant are selectivity for the chosen hemostatic target and the thrombotic disorder, rapidity of onset, capacity for a patient-specific regimen, and rapid reversibility in the case of bleeding or a need for a procedure requiring complete hemostasis. An orally active drug with these characteristics offers flexibility for both acute and long-term administration. Gone are the days of nonselective anticoagulants with unfavorable pharmacokinetics and pharmacodynamics, archaic and highly vulnerable manufacturing processes,[7,8] and predictably unpredictable off-target effects.

The transition from research on new drugs to the care of patients requires an enriched pipeline of drug discoveries, an infrastructure to foster the development of such drugs through early-phase testing, and an experienced and cohesive network of clinician investigators who are committed to conducting high-quality clinical research in a timely fashion. The National Institutes of Health Roadmap for Research (http://nihroadmap.nih.gov) is an example of a national biomedical research enterprise that serves as a foundation for improving clinical trials. In the case of trials sponsored by the pharmaceutical industry, a robust phase 2 program that fosters drug-dose selection for phase 3 trials, an equally robust phase 3 program, and a commitment to postmarketing safety surveillance are absolute prerequisites for success. In turn, investigators must show great rigor and consistency in designing clinical studies and defining end points.

Even the safest and most effective anticoagulant may not be used or may be used improperly in clinical practice. For example, thromboprophylaxis after orthopedic surgery, despite its efficacy and wide recommendation, is offered to less than 60% of patients.[9] Electronic alerts for anticoagulation do increase the rate of prophylaxis,[10] but they are not 100% effective,[11] which suggests that an integrated approach, up to the level of "order entry" and strict performance metrics, will be required to achieve greater success and optimal patient care.

Only through continued investigation and understanding of thrombosis and hemostasis can progress in anticoagulant therapy be realized. Myths, such as "an effective anticoagulant will, by definition, carry with it a risk of bleeding" or "it is easier to give a transfusion than to treat a blood clot" or "monitoring of an anticoagulant will prevent its uptake in clinical practice," are obstacles that must be pushed aside to make way for change. The path to safer and more effective anticoagulants is paved by scientific knowledge, discovery, due diligence on the part of sponsors working collaboratively with experienced clinicians, and evidence-based translation to patient care and widespread clinical practice.

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A Small Molecule for a Large Disease

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Almost three decades ago, Victor McKusick and I reviewed Marfan's syndrome in the *Journal* and advised traditional medical and surgical approaches to management.[1] The holy grail at that time was the cause of this autosomal dominant condition, based on the common presumption that understanding the cause would lead directly to effective therapy. In fact, life expectancy improved dramatically in subsequent years for all but the most severely affected patients, despite a lack of understanding of the underlying connective-tissue defect.[2] Dissection of the aorta was and remains the most common cause of death. However, the evolution of ever more effective surgical techniques, applied prophylactically, substantially prolonged life.[3] Treatment with beta-adrenergic blockade retarded the rates of aortic dilatation and dissection.[4,5] Serious complications, including mitral regurgitation, cardiomyopathy, pneumothorax, deformity of the thoracic cage, myopathy, and diminished visual acuity, still afflict some patients, especially infants and children at the most severe end of the phenotypic continuum.[6] Ironically, as people live longer with Marfan's syndrome, features that previously were unlikely to cause problems, such as lumbosacral dural ectasia, become major issues.[7] In addition, new age-dependent features have been recognized, such as renal and hepatic cysts and biliary stones.[8]

In 1991, the basic defect in Marfan's syndrome was discovered to be mutation of *FBN1*, the gene that encodes the large extracellular glycoprotein fibrillin-1.[9] This discovery raised expectations of more effective therapies, or even cure. However, the initial interpretations arising from this discovery proved to be inaccurate. Given that the fibrillins are integral components of vascular elastic fibers, ocular zonules, and other extracellular supporting structures, the notion arose that the various features of Marfan's syndrome developed because of "weak" connective tissue. Neat as this concept was, it did not explain many aspects of the disease, including overgrowth of tubular bones, underdevelopment of muscle and adipose tissue, and decreased bone mineral density.

The creation of mouse models of Marfan's syndrome, by introducing mutations known to cause the human disease into the mouse fibrillin gene, permitted focused investigations of pathogenesis. The fibrillins contain several motifs, including multiple copies homologous to latent transforming growth factor β (TGF-β) binding protein (LTBP). The cytokine TGF-β is bound and kept inactive by the LTBP complex. Hence, a defect in fibrillin structure might be expected to reduce binding and increase the activity of TGF-β. A number of groups began exploring whether TGF-β had a role in Marfan's syndrome. Dietz and colleagues studied the mouse model and showed that affected tissues had clear evidence of overexpression of TGF-β. The development of cystic lungs (which in humans predipose to pneumothorax), myxomatous mitral-valve leaflets, and aortic dilatation are all associated with increased signaling by TGF-β. Moreover, these common features of Marfan's syndrome can be prevented in mice by administering an antibody that binds TGF-β.[10-12]

These results dramatically altered the understanding of the pathogenesis of this archetypal heritable disorder of connective tissue. Notions of therapy quickly switched from "strengthening" the extracellular matrix or replacing the defective fibrillin to modulating signaling through a reasonably well understood pathway. The idea of developing a small molecule that can be taken orally for treatment of the disease gained currency.