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Developing Drugs to Prevent and Treat Arterial Thrombosis

By ROBERT A. HARRINGTON, M.D.

Cardiovascular specialists and general internists spend the majority of their professional lives assessing the value of medical products (drugs/biologics/devices) and applying this knowledge to make treatment recommendations for their patients. Yet, few clinicians have a detailed understanding of the process of drug development, including the complexities of the regulatory system in the United States. For the clinician caring for patients with vascular disease, therapies designed to prevent and treat arterial thrombosis are among the most commonly prescribed. This issue of *Cardiology Rounds* addresses general issues in new drug development and examines the pathobiology of arterial thrombosis to better understand and categorize thrombotic diseases of interest. Finally, by using the lessons learned from examining the clinical development and trials of several arterial antithrombotic compounds, we will be able to draw some inferences about key recurring themes that may help in understanding the potential limitations of the process and how they relate to a drug's clinical usefulness or failing.

Drug development

Genome

The last 10-15 years of basic science investigation have ushered in an unprecedented era in our basic understanding of the biology of human diseases. This focus on the fundamental understanding of biological processes has created tremendous opportunities to offer new and innovative treatments for a variety of diseases. More specifically, recent reports on the sequencing of the human genome offer a unique opportunity to consider more specialized therapies for individual patients based on an understanding of genes and their proteins.¹ Prior to the genome era, the estimated number of known drug targets was approximately 500; today, the estimate is 3000-5000 potential drug targets based on the knowledge provided by the genome.^{2,3} Although it is enticing to believe that all this individual-specific genetic and protein-based knowledge can provide unequivocal insight into the health of an individual, multiple examples over the years have demonstrated that an understanding of basic disease mechanisms may not translate into useful human therapeutics. The bottleneck in putting new therapies into clinical practice will clearly be our ability to test these therapies in clinical trials.

Drug development

The process of drug development involves multiple constituencies, consumes an enormous amount of financial resources, and takes considerable time. Preclinical evaluation of a potential drug typically takes several years, while the clinical evaluation (Phase 1-3 clinical trials) may take upwards of 10 years. Recent estimates from the Tufts Center for Drug Development suggest that the cost of developing a successful drug exceeds \$800 million dollars; this includes not only the actual development costs,



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Table 1: History of key regulatory (FDA) milestones in new drug development

1906 Pure Food and Drug Act
Outrage over food manufacturing processes Drug labels complete and accurate (no testing)
1938 Food, Drug and Cosmetic Act (FDCA)
SE Massengill: "Elixir Sulfanilamide" (diethylene glycol) Banned interstate commerce unapproved drugs New Drug Application (NDA) Scientific proof of safety
1962 FDCA Amendment (Kefauver-Harris)
Thalidomide disaster Now requires extensive preclinical testing Investigational New Drug (IND) "Substantial evidence" of efficacy and safety
1992 Prescription Drug Users Fee Act (PDUFA)
Response to length of approval process User fees for NDAs Goals: 12 month standard; 6 month priority

FDA = U.S. Food and Drug Administration

but also the capitalization of the entire development portfolio.⁴ Thus, it is not surprising that the pharmaceutical industry "outspends" the National Institutes of Health (NIH) for research and development in human health. Recognizing this reality, clinicians interested in the process of developing new therapeutics should know the basic elements that govern the regulated process of drug and device development.

Regulation of drug development

Table 1 lists the major milestones associated with the establishment and growth of the Food and Drug Administration (FDA). Investigators involved with the process at any level, whether as a local investigator or as a university researcher proposing novel studies, must acquire a working knowledge of the regulatory issues in order to appropriately participate in drug evaluation work. Given the funding mechanisms in the US, this is critical for anyone attempting to be involved in studies of human therapeutics.⁵

New product evaluation – the importance to clinicians/academics

Clinicians should keep in mind several questions that will guide their understanding of the process. These questions will not only influence and guide the development process, but can also be the framework for considering new therapeutics for their own patients. Is the new therapy effective in improving clinical outcomes relative to current therapies (ie, does the new therapy cause people to live longer, feel better, or avoid unpleasant experiences?). Is it safer than alternative choices? What does the new therapy cost and is it cost-effective?

Table 2: Thrombosis-dependent acute and chronic cardiovascular diseases

Acute coronary syndromes (ACS)
<ul style="list-style-type: none">• STE AMI (ST elevation acute myocardial infarction)• NSTEMI AMI (non-ST elevation acute myocardial infarction)• UA (unstable angina)
Coronary revascularization
<ul style="list-style-type: none">• PCI (percutaneous coronary intervention)• CABG (coronary artery bypass graft surgery)
Acute CVA/TIA (cerebrovascular accident/transient ischemic attack)
Acute peripheral occlusion
Secondary prevention
<ul style="list-style-type: none">• CAD/ACS (coronary artery disease/acute coronary syndrome)• CVA/TIA (cerebrovascular accident/transient ischemic attack)• PAD (peripheral arterial disease)
Congestive heart failure
Atrial fibrillation
Mechanical heart valves

Arterial thrombosis

Pathophysiology and clinical syndromes

Table 2 lists a number of acute and chronic thrombosis-dependent cardiovascular diseases. Current thinking links the inflammatory system, lipid metabolism, and thrombosis into a pathophysiological triad that underpins these cardiovascular diseases.⁶ Additionally, it has become increasingly clear that thrombosis involves complex interactions and relationships between platelet hemostasis and coagulation. These interactions are relevant when considering the development of antithrombotic therapies since it is likely that the most effective treatments are actually combination strategies that target various components of these complex systems.

Acute coronary disease

Focusing on acute arterial disease, there are pathophysiological similarities between the acute coronary syndrome (ACS) and the thrombotic complications of percutaneous coronary intervention (PCI). Both involve atherosclerotic plaque disruption as the inciting event that triggers the thrombotic process. In fact, PCI may be an important model for understanding arterial thrombosis and antithrombotic therapies. Unlike ACS, the exact timing of plaque disruption with PCI is known to be at the time of device activation. This has important ramifications for antithrombotic drug development since these therapies can be utilized during PCI as the initial assessment of their biological effectiveness. Additionally, when considering the development of a proposed antithrombotic agent for patients with ACS, it is crucial to remember

Table 3: Considerations and challenges in antithrombotic drug development for PCI and ACS

Acute coronary syndromes <ul style="list-style-type: none">• Older population; increased co-morbidities• US-based practice<ul style="list-style-type: none">– Early catheterization/PCI/CABG– Pressures on hospital length of stay• Multiple effective drugs already in use• Monitoring effects (assays and interpretation)
Percutaneous coronary intervention <ul style="list-style-type: none">• “Upstream” ACS treatment• Multiple effective drugs in lab• Device-drug interactions• Monitoring effects

that, in the United States, about half of these patients will undergo PCI. Therefore, knowledge of how the therapy behaves in the catheterization laboratory setting is crucial to a successful development strategy.

Paradigm – how to balance bleeding with efficacy

The accepted longstanding paradigm for the development of an antithrombotic therapy is to balance the reduction in thrombosis (and in the case of arterial thrombosis, a reduction in organ ischemia) and the risk of bleeding. When important and irreversible damage to an organ like the heart or the brain can be reduced or prevented, some amount of bleeding, especially when limited in size and scope, is acceptable. In fact, an “optimal” antithrombotic effect may not be achieved unless some bleeding occurs. This trade-off between potential benefit and potential risk depends on an appreciation of the severity of the clinical events. Reducing the overall risk of death at the expense of serious bleeding events requiring blood transfusions is usually acceptable, while reducing the risk of recurrent ischemia without a concomitant reduction in death, and causing an increased risk of intracranial hemorrhage, is less acceptable. So, understanding this issue of balance is critical.

The relationship between antithrombotic effects and clinical outcomes may not be continuously linear. It is often impossible to ascertain the relationship between effects and outcomes until many thousands of patients have been studied in clinical trials. In the GUSTO-I study, Granger and colleagues showed that among patients with fibrinolytic-treated ST elevation acute myocardial infarction (AMI), there was a “U-shaped” relationship between the level of anticoagulation achieved with heparin (as measured by the aPTT) and 30-day mortality.⁷ Some newer antithrombotic therapies may challenge the traditional paradigm by targeting a particular mechanism of the thrombotic system that attenuates thrombosis, while preserving local hemostasis.

Examples/lessons learned in trials of antithrombotics for arterial thrombosis

Table 3 lists the considerations and challenges in developing antithrombotic treatments for patients presenting with ACS or for preventing the ischemic complications of PCI. In the following sections, examples from the development of antithrombotic agents are used to elaborate information about dosing, safety, use of surrogate endpoints, the importance of collaborations, combination therapies, chronic versus acute effects, clinical practice settings, and laboratory assays for monitoring.

Hirudin (GUSTO II)

Thrombin plays a central role in the process of thrombosis. Once formed from prothrombin, thrombin (Factor IIa) catalyzes the conversion of fibrinogen to fibrin. Thrombin aids in the cross-linking of fibrin through its action on Factor XIII, plays an important feedback role in its effect on protein C and S, amplifies its own production, and activates platelets. Given its central position in regulating thrombosis, thrombin has been an obvious target in the development of therapeutics that aim to modulate coagulation.

The hirudins are direct thrombin inhibitors based on proteins found in the salivary glands of the medicinal leech. By irreversibly binding to the catalytic and anion-binding exosites of the thrombin molecule, the hirudins are among the most potent inhibitors of thrombin. The development of the hirudins as arterial anticoagulants in the early 1990s held great promise. Dose-ranging studies suggested that when used in combination with fibrinolysis for the treatment of AMI, hirudin led to more rapid coronary blood flow during immediate coronary angiography and less visible coronary thrombus during non ST-elevation (NSTEMI) ACS.⁸ In studies of up to a few hundred patients, no major adverse bleeding events were observed with hirudin compared with heparin.

GUSTO II was a large-scale, international, clinical trial (planned for 12,000 patients) designed to test the hypothesis that hirudin was a more effective anticoagulant than heparin for the treatment of patients presenting with ACS, with and without persistent ST elevation. After approximately 2500 patients had been enrolled, the study’s independent data and safety monitoring committee observed that there was an unexpected excess of intracranial hemorrhage (ICH) among the hirudin-treated patients compared with those treated with heparin. Of equal interest was the fact that in the fibrinolytic-treated cohort (those randomized with STE AMI), the ICH rate in both the heparin and hirudin arms was higher than had been observed in the t-PA/heparin patients from the GUSTO-I study. Consultations among the safety monitoring committees for this trial and 2 similar, large, ongoing studies revealed that this observation was consistent across the 3 trials. On more

detailed analyses, investigators discovered that patients suffering ICH had markedly higher levels of anticoagulation, as measured by the aPTT, than those without ICH. It was then decided to recommend stopping enrollment into all 3 trials and resume amended studies after substantially reducing the doses of both the hirudin and the heparin.^{9,10}

The amended studies were resumed and completed with none showing a significant advantage for hirudin compared with heparin.^{11,12} Further development of these compounds for ACS was halted. Subsequently, an overview of all the randomized clinical trial data suggested a modest benefit of the direct thrombin inhibitors compared with heparin for patients presenting with ACS.¹³

GP IIb/IIIa inhibitors for ACS and PCI

The development of the platelet glycoprotein (GP) IIb/IIIa inhibitors provides insight into several drug development issues. First, targeting this particular platelet receptor for human therapy was based on an extensive understanding of its role in platelet aggregation.¹⁴ Second, the clinical development plan took advantage of the notion that the device-induced plaque rupture associated with PCI might mimic the spontaneous plaque rupture of acute coronary disease. Thus, PCI might serve as an ideal clinical testing ground for novel arterial antithrombotic drugs. Table 4 lists the major placebo-controlled clinical trials with GP IIb/IIIa inhibitors in PCI and ACS.

Overall, the results of the GP IIb/IIIa inhibitor trials have been consistent across clinical settings and with multiple agents. The early randomized trials of GP IIb/IIIa inhibitors assumed, based on preclinical models, that the antithrombotic effect of these drugs would be maximized when given in doses that produced a $\geq 80\%$ inhibition of platelet aggregation, but there was little consistency among studies about how this should be determined (ie, collection medium, aggregation agonist, aggregation agonist concentration, method of assay),¹⁵ or even whether the assumption of a threshold dose was correct.

The first definitive trial of a GP IIb/IIIa inhibitor during PCI showed that a certain dose of abciximab, a monoclonal antibody, given during the procedure and for 12 hours afterwards, was associated with substantial clinical benefit.¹⁶ Many investigators assumed that these observations would be consistent across the entire class of drugs. When a large, randomized clinical trial of the small molecule inhibitor, eptifibatid, in the PCI setting failed to show a similarly robust effect,¹⁷ questions were raised as to the comparability of the monoclonal antibody and the small molecule inhibitors. However, further investigation revealed that measurement of the inhibition

Table 4: Major completed, placebo-controlled, randomized clinical trials of IV GP IIb/IIIa receptor antagonists

PCI Trials	NSTE ACS Trials	STE ACS Trials
EPIC	PRISM	GUSTO-V
EPILOG	PRISM-PLUS	ASSENT 3
CAPTURE	PURSUIT	RAPPORT
EPISTENT	PARAGON A	ISAR
IMPACT-II	PARAGON B	ADMIRAL
ESPRIT	GUSTO-IV	CADILLAC
RESTORE		

of platelet aggregation was highly dependent on the blood collection method. When samples were collected into citrate-containing tubes, the inhibitory effects of the GP IIb/IIIa inhibitor were being overestimated because of a calcium chelating effect of the citrate.

Rather than testing to determine if a level of $\geq 80\%$ platelet aggregation inhibition was beneficial, the earlier trial had actually evaluated a dose of eptifibatid that provided inhibition that was closer to 50%. Following further dose-finding studies, a second PCI study using much higher doses of the platelet inhibitor demonstrated much greater clinical benefit.¹⁸

When a head-to-head comparison of abciximab and tirofiban during PCI demonstrated superiority of the monoclonal antibody over the small molecule inhibitor,¹⁹ further investigation suggested that the doses of tirofiban utilized may not have provided levels of platelet aggregation inhibition comparable with abciximab.²⁰

Thus, the development of the platelet GP IIb/IIIa inhibitors provides insight into several useful lessons:

- properly and thoroughly understanding the dosing of a novel compound
- doing clinical outcome studies even for multiple drugs in the same drug class
- the limitations of surrogate measures of clinical effect.

Oral platelet inhibitors - GP IIb/IIIa inhibitors (chronic effects)

Because of the success of the intravenous GP IIb/IIIa inhibitors and the limitations of chronic aspirin therapy, there was tremendous interest in developing GP IIb/IIIa inhibitors that could be administered orally on a chronic basis. More than 40,000 patients with atherosclerotic vascular disease were randomized into large-scale randomized clinical trials in the late 1990s to determine whether chronic administration of an oral GP IIb/IIIa inhibitor would be beneficial (either with, or instead of, chronic aspirin therapy). Every one of these trials, studying 4 different drugs, revealed a consistent increase in

mortality. In overview analyses, this was determined to be an approximate 30% increased risk of death.²¹ It was clear that chronic administration of this therapy did not carry the same benefits as acute treatment. A variety of hypotheses were advanced to explain this unexpected and troubling observation.²²

Oral platelet inhibitors – clopidogrel (importance of practice settings)

The successful development of the thienopyridine, clopidogrel, demonstrates the difference between a statistically positive clinical trial and one that changes clinical practice. Clopidogrel was initially approved for use among patients with vascular disease based on the results of the large Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial that demonstrated a modest benefit of clopidogrel over ASA in patients with coronary, cerebrovascular, or peripheral arterial disease.²³ Its benefit as acute care antiplatelet therapy was uncertain, however, so a trial was performed comparing clopidogrel plus ASA versus ASA alone among patients presenting with a NSTEMI ACS.²⁴

This large (>12,000 patients), randomized, clinical trial (the Clopidogrel in Unstable angina to prevent Recurrent Events [CURE] study) demonstrated that the combination of clopidogrel and aspirin was better than aspirin alone in reducing the composite risk of cardiovascular death, myocardial infarction, or stroke. Although CURE was a well-conducted trial that had a markedly positive result, some major questions were raised regarding the applicability of its results to clinical practice, especially in the United States. The CURE trial enrolled <600 patients (of the total of 12,000) in the United States, thus providing little information for making inferences regarding the benefits and risks of the therapy in an environment that favored early (≤ 24 -48 hours) cardiac catheterization and subsequent revascularization, including coronary artery bypass grafting. Overall, CURE revealed an increased risk of major bleeding that was especially pronounced among patients who had undergone bypass surgery within 5 days of receiving clopidogrel.

CURE lacked broad applicability because it was not performed in an environment where an aggressive use of intervention was common. Clinicians could not accurately assess the trade-off between bleeding risk and anti-ischemic benefit. Clinical trials that are intended to impact clinical practice should be performed in a practice setting where they will ultimately be used.²⁵

Factor Xa inhibitors

The ongoing development of the direct Factor Xa inhibitor, Dabigatran, reveals a common problem encountered in the attempts to assess the biological effect of a

novel anticoagulant. The common tests used to measure anticoagulant effect, (eg, aPTT, PT/INR, or ACT) were developed to assess the anticoagulant effect of specific agents, namely unfractionated heparin or warfarin. Because a direct Factor Xa inhibitor has a much different mechanism of action than heparin, it is unlikely that prolongation of these assays reflects a level of similar biological effect.²⁶

How can a decision be made from preclinical models and early clinical studies if the dose of a novel anticoagulant is at an optimal level, meaning at a level that is high enough to provide antithrombotic activity, but low enough not to cause excessive bleeding? There are no straightforward answers. The first step is to consider the totality of the preclinical data to determine whether a certain concentration of a new agent is capable of reducing or preventing induced-thrombosis in several animal models. The next step is to assess a variety of assays in humans to determine if one of them might be reliably correlated with drug concentration. The next steps, however, are more challenging and involve the exposure of high-risk human subjects to a drug that may or may not have adequate antithrombotic effects. The PCI model can be especially useful here as it provides a clinical setting where thrombosis is an obligatory part of the device-induced plaque disruption and where the exact timing of the thrombotic stimulus is known. Hence, careful dose-exploration studies can be quite valuable when performed in the PCI population, even if this clinical setting is not the ultimate target for the new agent.

Conclusion

Complex dynamics among multiple constituencies drive the process of drug development in the United States. Clinicians seeking to become clinical investigators with an interest in investigating novel therapies need to understand the process, the ethical principles guiding human experimentation, the regulations governing the drug development process, and the market forces that drive research in various directions. For cardiovascular clinicians, the development of therapies to prevent and treat arterial thrombosis can provide insight into this complicated process. These therapies form the cornerstone of treatment for ACS and include reducing the risk of the ischemic complications of PCI.

One must understand drug dosing, laboratory assays to assess antithrombotic effects, the unpredictability of drug combinations, the need to study therapies in the practice setting in which they will ultimately be used, the inadequacy of depending on biomarkers or surrogate endpoints to assess clinical benefits and risks and, finally, the absolute necessity of broad collaborations across the healthcare environment.

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