Ann K. Wittkowsky, PharmD, CACP, FASHP, is Clinical Professor of Pharmacy at the University of Washington School of Pharmacy and Director of Anticoagulation Services at the University of Washington Medical Center. As a clinician and educator in the field of antithrombotic pharmacotherapy, she has contributed extensively to the care of patients and the education of healthcare providers about antithrombotic pharmacotherapy. She is the author of nearly 100 scientific papers, book chapters, and abstracts and coeditor of Managing Oral Anticoagulation Therapy: Clinical and Operational Guidelines. She has lectured widely throughout the United States and Canada, maintains an active clinical research program, and is board certified as an anticoagulation care provider. The Anticoagulation Services program at the University of Washington Medical Center, which Dr Wittkowsky directs, has served as a training site and model for pharmacist-managed anticoagulation clinics throughout the United States and Canada. Dr Wittkowsky serves as an editorial board member and reviewer for numerous medical and scientific journals, and serves on the board of directors for the Anticoagulation Forum, a multidisciplinary organization of anticoagulation care providers. She is the director of the Northwest Anticoagulation Consortium and a preceptor for the American Society for Health-System Pharmacists (ASHP) Research and Education Foundation’s Anticoagulation Service Traineeship. Dr Wittkowsky is the recipient of the 2003 ASHP Drug Therapy Research Award for her work in the pharmacogenomics of warfarin, and was recently honored by the University of Washington School of Pharmacy as its Distinguished Alumnus for 2003.

A senior clinical editor for Advanced Studies in Pharmacy (ASiP) interviewed Dr Wittkowsky to discuss the future of anticoagulant use.

ASiP: What are the goals of adjunctive pharmacologic therapy in patients undergoing percutaneous coronary intervention (PCI)?

Dr Wittkowsky: Anticoagulation and antiplatelet therapy both act to mediate the thrombus formation that occurs as a result of plaque rupture in acute coronary syndromes. During PCI, mechanical disruption of atherosclerotic plaque also occurs, and combined antiplatelet and anticoagulant therapy also has a role in this setting. The long-term goals of antithrombotic therapy in PCI are to reduce adverse events associated with PCI—post-procedural ischemia and myocardial infarction—and to enhance the effectiveness of PCI as a long-term prevention strategy for recurrent acute coronary syndromes.

ASiP: What are the standard therapies that are currently used in actual clinical practice?

Dr Wittkowsky: That is not only a moving target, but is also very different depending on where one is practicing. One component is anticoagulant therapy and that may be unfractionated heparin, low molecular weight heparin (LMWH), or bivalirudin, a direct thrombin inhibitor. In addition, an antiplatelet strategy is used, typically clopidogrel with or without an injectable glycoprotein (GP) IIb/IIIa inhibitor, usually eptifibatide or abciximab. The literature support for various combinations is something that changes frequently over time as new studies become available. At a particular site, specific treatment may depend on clinical experience with one combination or another, participation in clinical trials, and what drugs are on the formulary.

ASiP: Do the direct thrombin inhibitors possess advantages, in comparison with other anticoagulants, in terms of survival rates or morbidity, or other factors?
**Dr Wittkowsky:** Direct thrombin inhibitors do not activate platelets the way that unfractionated heparin and LMWHs do. From that perspective, there is a potential pharmacologic advantage. But the major clinical advantage of bivalirudin in PCI, in comparison with heparin, is a dramatic reduction in the rate of major bleeding complications.

**ASiP:** Can patients be identified who are especially good candidates for direct thrombin inhibitors?

**Dr Wittkowsky:** One of the purposes of the development of the direct thrombin inhibitors was to offer an alternative to heparin for patients with heparin-induced thrombocytopenia (HIT). Patients with a history of HIT or current HIT are very good candidates for direct thrombin inhibitors. But other good candidates for bivalirudin use in PCI are patients at highest risk for bleeding.

**ASiP:** Are there potential concerns regarding patients who come to the cath lab having recently received other anticoagulation therapy (eg, heparin or LMWH)?

**Dr Wittkowsky:** In the Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) trial, patients who started on unfractionated heparin and then switched to LMWH or the reverse—they started on LMWH and switched to heparin—had a higher incidence of bleeding complications. Thus, there is a tendency in cath labs to try to avoid switching, and to continue whatever therapy the patient was initially started on. Whether that is true for direct thrombin inhibitors has not been investigated in a rigorous way. But one might assume that if a patient started unfractionated heparin or LMWH before PCI, the benefits of switching to bivalirudin may not be upheld because of exposure to an anticoagulant with a higher risk of bleeding.

**ASiP:** Several studies have shown that heparin plus a GP IIb/IIIa antagonist improves outcomes in PCI, but some cardiologists have written that this combination is currently underused. Do you think that this strategy is not used as often as it could be?

**Dr Wittkowsky:** I think this is a very common approach to PCI, particularly in higher-risk patients. I do not think it is underutilized, but I think it is a therapeutic combination that is changing. It is often common for low-risk patients to get clopidogrel alone followed by heparin. Higher-risk patients may get clopidogrel plus heparin plus a GP IIb/IIIa inhibitor. What appears to be changing is that more patients are being treated with bivalirudin rather than heparin, and that allows for a reduction in the need for the GP IIb/IIIa receptor antagonist. The advantage is not only the reduction in bleeding from using bivalirudin instead of heparin, but also some significant cost sav-
ings by being able to avoid the use of the concurrent GP IIb/IIIa antagonist.

AS/iP: What are the limitations of the direct thrombin inhibitors for use in PCI?

Dr Wittkowsky: The major limitation, in comparison with unfractionated heparin, is that there is a higher drug cost associated with bivalirudin use. The cost to the pharmacy for purchasing bivalirudin is greater. In the Randomized Evaluation of PCI Linking Angiomax in Reduced Clinical Events (REPLACE-2) economic analysis, the average cost of bivalirudin use was approximately $450, which seems very realistic. Comparatively, heparin costs pennies. That cost difference is erased by the lower cost of GP IIb/IIIa use, and by lower overall outcomes-associated costs to the healthcare system, in terms of lower complication rates. For example, there are some settings in which a hospital administration looks only at the pharmacy budget in isolation. They do not necessarily consider the whole cost savings to the healthcare system based on the reduction in adverse outcomes. Thus, the main disadvantage is higher drug cost, if drug cost is being evaluated in isolation.

AS/iP: But medically, are there limitations associated with direct thrombin inhibitors in PCI?

Dr Wittkowsky: Not specifically with bivalirudin; I think that bivalirudin actually offers significant advantages. However, the other direct thrombin inhibitors, argatroban and lepirudin, do not offer these advantages, and may in fact be detrimental from the perspective of bleeding complications.

AS/iP: Are there steps that can be taken to prevent hemorrhagic complications, or at least reduce the risk?

Dr Wittkowsky: The primary step is to make sure that a patient who is at highest risk for bleeding is treated with the most appropriate therapy to try to reduce that risk. In my estimation, that means using bivalirudin rather than heparin in PCI, if the patient has risk factors for bleeding, such as renal impairment, female gender, low body weight, or advanced age.

AS/iP: The REPLACE-2 trial compared a novel strategy of bivalirudin and provisional GP IIb/IIIa inhibition with a conventional strategy of heparin and routine GP IIb/IIIa inhibition. Have both of these strategies been used at your institution?

Dr Wittkowsky: Absolutely. Our cath lab does approximately 400 PCI procedures per year, and many more cardiac catheterization procedures. We have slowly seen a change from heparin plus abciximab to bivalirudin plus or minus abciximab. The REPLACE-2 study suggested that, in a population of patients with a variety of risks for recurrent ischemia, the use of the provisional GP IIb/IIIa inhibitor could be as low as 7%. We are not seeing a number anywhere near 7%—provisional abciximab use is in the neighborhood of 40%. The criteria for provisional GP IIb/IIIa antagonists in the REPLACE-2 study were perhaps as objective as they could be. However, in the real world, it may be more difficult to adhere to a protocol in quite the same way. There may be a bit more flexibility or leeway on the part of the interventional cardiologist to use a provisional GP IIb/IIIa inhibitor, which in our case is abciximab. Thus, in our case the number is more like 40% instead of 7%, as seen in the REPLACE-2 study. However, on an institutional basis, we have seen a reduction in our major bleeding complications with the use of bivalirudin as a replacement for heparin.

AS/iP: Patients with AMI were excluded from the study; would you expect to see a similar outcome in this group of patients?

Dr Wittkowsky: That is hard to say. What is interesting in REPLACE-2 is that there was actually a numerically higher rate of MI [myocardial infarction] in patients who received bivalirudin than in those who received heparin, although not statistically significant. I would imagine that the main advantage of bivalirudin, a reduction in bleeding complications, would indeed hold up in patients who are receiving PCI in the setting of AMI. However, whether the neutral outcome of the triple endpoint of death, MI, or urgent revascularization would hold up is unknown.

AS/iP: The success of PCI is often limited by complications from bleeding or ischemic events. What are the economic consequences of these complications?
Dr Wittkowsky: Adverse events increase the cost of care. They are not part of the expected costs of PCI. If adverse events increase hospital resource utilization, whether from increased length of stay, an emergency room visit, or from a repeat hospital admission, then the overall cost of care increases. This is a burden on the institution, third-party payers, and the patient.

ASiP: An economic analysis of data from this trial suggested that the bivalirudin and provisional GP IIb/IIIa inhibitor strategy was cost saving compared with the conventional strategy. Do you think the results of this analysis will have an impact on how these strategies are used?

Dr Wittkowsky: The question is whether the pharmacy budget is isolated from overall healthcare costs or is included in overall healthcare costs. It is entirely possible for one system or another to view the higher expense of bivalirudin alone compared with heparin as an impediment to use. However, other medical centers may be able to look at the overall cost of antithrombotic therapy, in addition to the overall cost of care, and realize that by spending a little bit more on bivalirudin there is an overall savings by reducing the use and thus the costs of GP IIb/IIIa inhibitors, and the cost of complications. It is likely that as the thinking about this process changes, this economic evaluation will have some role in improving the uptake of bivalirudin. However, I think the main driver of uptake is recognition of a significant reduction in bleeding complications that is associated with the use of bivalirudin over heparin.

ASiP: The REPLACE-2 economic analysis found that the bivalirudin and provisional GP IIb/IIIa strategy reduced costs by an average of approximately $400 per patient. Is this magnitude of cost savings meaningful, considering the high costs involved in performing a percutaneous procedure?

Dr Wittkowsky: Drug cost savings are always relevant, whether the accounting is being done by the pharmacy department or by the institution as a whole. The ability to reduce the overall costs of antithrombotic therapy in PCI while improving safety without compromising effectiveness is a significant advance.

ASiP: Do you think that direct thrombin inhibitors will come to replace heparin in acute cardiovascular care?

Dr Wittkowsky: I think that this is the direction in which PCI therapy is moving. It may be that there are low-risk patients in whom it is possible to use only an oral antiplatelet agent with heparin, and without GP IIb/IIIa inhibition. The Intracoronary Stenting and Antithrombotic Regimen-Rapid Early Action for Coronary Treatment trial suggested that the addition of abciximab to high-dose pre-PCI clopidogrel plus heparin in low-risk patients added no additional benefit to clopidogrel plus heparin alone. Bleeding rates may very well be lower in this setting if bivalirudin replaced heparin. However, for moderate- and perhaps even high-risk patients, it may be that the combination of a pre-PCI oral antiplatelet agent and intraprocedural bivalirudin with provisional GP IIb/IIIa inhibition will offer the best possible clinical outcomes. I think that over the next few years we are going to see an increase in the number of patients who are exposed to this combination, in practice and perhaps also in clinical trials, and that is going to have a dramatic impact on long-term outcomes.

REFERENCES