A Closer Look at the Cardiology PRN

Overview of the PRN

The Cardiology Practice and Research Network (PRN) is composed of students, residents, fellows, clinical pharmacists, and other practitioners with an interest in cardiovascular disorders. As the fourth largest PRN within ACCP, its total membership of 1419 includes 341 students, 75 residents, and 8 fellows. The Cardiology PRN's mission is to advance the pharmacotherapy of cardiovascular disorders through the promotion of excellence in education, research, and clinical practice by enhancing the knowledge, skills, and productivity of its members. The PRN's objectives are to provide a means for communication and networking among members; provide quality educational programming at national meetings; use the Internet to facilitate access to information, expertise, and professional opportunities available through the PRN; and provide opportunities for collaborative research.

The PRN is very active, with many opportunities for professional growth through service on its eight committees: Membership, Budget/Finance, Research/Scholarship, Resident/Student, Programming, Nominations, Communications/Social Media, and Executive. Each of the committees has defined responsibilities to advance the field of cardiology pharmacy practice, with new charges developed each year.

The Cardiology PRN is constantly looking for ways to reach members through various platforms. The e-mail list is quite active with frequent questions that generate discussion regarding patient scenarios and clinical controversies. A new development this year is the Communications/Social Media Committee, which provides communication through more contemporary outlets. The newly developed Cardiology PRN website (cardprn.accp.com) has a calendar of upcoming events and announcements. In addition, there is a Twitter account (@accpcardprn) and a Facebook page (www.facebook.com/accpcardprn) to help keep all of our members informed.

Opportunities and Resources

The Cardiology PRN has a strong presence of resident, fellow, and student members and supports the active involvement of those members in the PRN. As a new initiative this year, a special task force has been developed to establish various ways for residents and students to be involved with the PRN. Student, resident, and fellow members are also encouraged to serve on any of the PRN committees with the exception of the Executive Committee. In fact, every student, resident, and fellow who volunteered was successfully placed on a committee for service this year.

To facilitate professional growth and networking, the Cardiology PRN sponsors two $500 travel awards for residents, students, or fellows to attend the ACCP Annual Meeting. Often, these awards allow students and residents to present their scholarship in the form of a poster at the general meeting and during the Cardiology PRN business meeting. At the Annual Meeting, the PRN strives to engage all student, resident, and fellow members with networking opportunities and recognition during the PRN business meeting.

The Cardiology PRN also has unique opportunities for resident and student members to promote professional growth. Through the mentoring program, learners are matched with seasoned practitioners who have similar professional interests and meet with their mentors regularly throughout the year. The mentors provide a plethora of resources and advise the students in many areas such as professional development, scholarship, and career opportunities as students matriculate through their training programs. In addition, the online journal club program allows residents to engage the entire PRN

through a once-monthly journal club webinar of recent articles pertaining to cardiovascular pharmacotherapy. Planning is under way to provide a professional development series to all Cardiology PRN members.

Current Clinical Issue – Idarucizumab and Andexanet Alfa

The direct thrombin inhibitor dabigatran and direct factor Xa inhibitors apixaban, edoxaban, and rivaroxaban are FDA approved for stroke prevention in nonvalvular atrial fibrillation and prevention/treatment of venous thromboembolism, including DVT (deep venous thrombosis) and PE (pulmonary embolism).[1-4] Compared with the vitamin K antagonist warfarin, these direct oral anticoagulants (DOACs) have consistently shown less life-threatening bleeding in clinical trials.[5-10] Although this is clinically significant, bleeding events still occur and are associated with an increased risk of death and thrombotic events, regardless of drug class.[11,12] In addition, patients may require emergency surgery in which antithrombotic reversal is desired. Until recently, the absence of a DOAC antidote was a major limitation to use of these agents.

Direct Thrombin Inhibitor Antidote

In October 2015, idarucizumab (Praxbind) was FDA approved for the urgent reversal of dabigatran in emergencies. This first-in-class monoclonal antibody gained approval because of the preliminary results of the first 90 patients enrolled in the phase III clinical trial RE-VERSE AD (Reversal Effects of Idarucizumab on Active Dabigatran).[13] In this ongoing study, investigators plan to enroll more than 500 patients across 400 centers worldwide. Patients are placed in one of two groups: patients presenting with uncontrolled or life-threatening bleeding (group A) and patients not bleeding but requiring emergency surgery or other invasive procedures that cannot be delayed for at least 8 hours (group B).[13] All patients receive a total of 5 g of idarucizumab by two 2.5-g rapid intravenous boluses no more than 15 minutes apart.[9] This mirrors current package insert instructions. Clinical efficacy has been based on the maximum ability of idarucizumab to normalize diluted thrombin time (dTT) and ecarin clotting time (ECT) within 4 hours of drug administration. These assays were chosen because of their excellent correlation with dabigatran concentrations; however, most institutions lack the ability to perform either analysis in a timely fashion. Of note, patients were enrolled according to clinical presentation, not according to clotting assay results because these results were not made available to practitioners in real time to guide therapy. Almost 90% of the first 90 enrollees were using dabigatran for a means of stroke prevention secondary to a diagnosis of atrial fibrillation.[13] The median maximum percentage reversal for patients in groups A and B was 100% (95% CI, 100–100). Furthermore, within 4 hours of the initial infusion, the concentration of unbound dabigatran was around 1 ng/mL, and at 24 hours post-dose, almost 80% of patients' plasma concentrations were less than 20 ng/mL, which produces minimal anticoagulant activity.

Although these early phase III trial data are promising, many clinical practice questions remain. From a cost-effectiveness standpoint, will it make sense to provide every patient presenting with an acute bleed on dabigatran with idarucizumab? The current cost of a therapeutic dose is $4200 (2.5 g/50 mL vial = $2100).[9] It is difficult to assess the appropriateness of idarucizumab using coagulation tests such as PT (prothrombin time) or aPTT (activated partial prothrombin time), which have shown marginal correlation with the intensity of dabigatran anticoagulation. Even for institutions with dTT and ECT availability, like the investigators used, turnaround time is not rapid, and no true "therapeutic" range exists for dabigatran. This ultimately clouds the results and the reliability of using this information.[14] Current renal function and time since last dose must also be considered when determining whether idarucizumab is warranted, given a small margin of the study population's serum dabigatran concentration rebounding to an "anticoagulated" level 24 hours post-dose. Looking forward, we will

need to determine exactly when idarucizumab is appropriate for our patients in the landscape of current reversal strategies, whether re-dosing may be necessary, and what constitutes the appropriateness of use in patients with ischemic stroke who may otherwise be candidates for t-PA (tissue plasminogen activator).

Direct Factor Xa Inhibitor Antidote

Andexanet alfa is a recombinant modified human factor Xa decoy protein that is catalytically inactive, yet it can still sequester factor Xa inhibitors with high affinity and specificity, effectively restoring native factor Xa activity.[15] Andexanet alfa has previously been studied in phase II trials of various oral and injectable factor Xa inhibitors, where it has shown promising results.[16-19] Most recently, andexanet alfa was studied in two parallel, randomized, double-blind, placebo-controlled phase III trials, ANNEXA-A and ANNEXA-R, to establish its effect on reversing antifactor Xa (anti-Xa) activity and restoring thrombin generation.[20] A total of 101 healthy volunteers who received either apixaban or rivaroxaban were administered andexanet alfa as either a bolus infusion or a bolus followed by continuous infusion over 120 minutes. Of importance, because of pharmacokinetic and stoichiometric differences, the dose of andexanet alfa varied depending on which factor Xa inhibitor the patient was receiving. Within 2–5 minutes of completing the bolus infusion of andexanet alfa, patients had rapid reductions in anti-Xa activity, and thrombin generation was restored.[20] Andexanet alfa's duration of action was limited by its short pharmacologic half-life of around 1 hour; hence, the patients who received a bolus followed by continuous infusion had a more sustained pharmacologic response. No significant adverse effects were reported.[20]

The results of this study and of prior phase II studies support further development of andexanet alfa as a universal factor Xa inhibitor. There is an ongoing clinical trial investigating the clinical effects of andexanet alfa in patients with an acute, major bleed who are concurrently being anticoagulated with a factor Xa inhibitor.[21] According to the currently available data and the unavailability of a direct reversal agent for the fast-growing factor Xa inhibitor market share, andexanet alfa is anticipated to obtain FDA approval in 2016 through the accelerated approval pathway.

	Idarucizumab[9,22]	Andexanet Alfa[a,23]
Dosing and administration	• 5 g, given as two 2.5 g/50 mL vials, administered as consecutive IV infusions or boluses, no more than 15 min apart[b]	• Apixaban reversal: 400 mg IV bolus or 400 mg IV bolus followed by an IV infusion of 4 mg/min for 120 min • Rivaroxaban reversal: 800 mg IV bolus or 800 mg IV bolus followed by an IV infusion of 8 mg/min for 120 min
Pharmacokinetics	• V_{ss}, 8.9 L/kg • Metabolized by biodegradation • Initial $t_{1/2}$: 47 min • Terminal $t_{1/2}$: 10.3 hr • Urinary elimination: 32% within the first 6 hr and < 1% in the following 18 hr • Total CL is reduced in mild (CrCl ≥ 60 to < 90 mL/min/1.73 m^2) and moderate (CrCl ≥ 30 to < 60 mL/min/1.73 m^2) renal impairment, leading to an increase in AUC by 43.5% and 83.5%, respectively	• Effective $t_{1/2}$: 1 hr • Terminal $t_{1/2}$: 6 hr
Clinical trials	RE-VERSE AD[13] • Assessed the safety and efficacy of 5 g of idarucizumab in dabigatran-treated patients with serious bleeding (group A) or who required an urgent reversal procedure (group B) • The primary outcome was maximum percentage reversal of dabigatran within 4 hr, as measured by dTT or ECT • Among patients with an elevated dTT and ECT at baseline, the median maximum percentage reversal was 100% (95% CI, 100–100)	ANNEXA-A and ANNEXA-R[20] • Evaluated the safety and efficacy of andexanet alfa administered as a bolus or as a bolus plus a 2-hr infusion in the reversal of apixaban or rivaroxaban • The primary outcome was the mean percent change in anti-Xa activity • Compared with placebo, treatment with a bolus of andexanet alfa significantly reduced anti-Xa activity in apixaban-treated patients (94% vs. 21%; p<0.001) and rivaroxaban-treated patients (92% vs. 18%; p<0.001). Effects were sustained when given as a bolus plus an infusion
Adverse events	• Thromboembolic risk • Hypersensitivity reactions • Risk of serious adverse events in patients with hereditary fructose Intolerance because of sorbitol excipient	• Administration-site conditions • Gastrointestinal disorders • Immune system disorders

[a]Not FDA approved.

[b]Administration of an additional 5-g dose may be considered on the reappearance of clinically relevant bleeding with elevated coagulation parameters.
anti-Xa = antifactor Xa; AUC = area under the curve; CL = clearance; dTT = diluted thrombin time; ECT = ecarin clotting time; IV = intravenous; $t_{1/2}$ = half-life; V_{ss} = steady-state volume of distribution.

References:

1. Pradaxa® (dabigatran) [package insert]. Ridgefield, CT: Boehringer-Ingelheim, 2016.
2. Xarelto® (rivaroxaban) [package insert]. Titusville, NJ: Jansen Pharmaceuticals, 2011.
3. Eliquis® (apixaban) [package insert]. Princeton, NJ: Bristol-Myers Squibb, 2015.
4. Savaysa® (edoxaban) [package insert]. Parsippany, NJ: Daiichi Sankyo, 2015.
5. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139-51.
6. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365:883-91.
7. Granger CB, Alexander JH, McMurray JJV, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365:981-92.
8. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2013;369:2093-104.
9. Eikelboom JW, Quinlan DJ, van Ryn J, et al. Idarucizumab: the antidote for reversal of dabigatran. Circulation 2015;132:2412-22.
10. van der Hulle T, Kooiman J, den Exter PL, et al. Effectiveness and safety of novel oral anticoagulants as compared with vitamin K antagonists in the treatment of acute symptomatic venous thromboembolism: a systematic review and meta-analysis. J Thromb Haemost 2014;12:320-8.
11. Bayer-Westendorf J. Rates, management and outcomes of bleeding complications during rivaroxaban therapy in daily care – results from the Dresden NOAC registry. Blood 2014;124:955-62.
12. Held C, Hylek EM, Alexander JH, et al. Clinical outcomes and management associated with major bleeding in patients with atrial fibrillation treated with apixaban or warfarin: insights from the ARISTOTLE trial. Eur Heart J 2015;36:1264-72.
13. Pollack CV, Reilly PA, Eikelboom J, et al. Idarucizumab for dabigatran reversal. N Engl J Med 2015;373:511-20.
14. van Ryn J, Stangier J, Haertter S, et al. Dabigatran etexilate – a novel reversible oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity. Thromb Haemost 2010;103:1116-27.
15. Andexanet alfa: FXa Inhibitor Antidote. Available at https://www.portola.com/clinical-development/andexanet-alfa-prt4445-fxa-inhibitor-antidote/. Accessed February 1, 2016.
16. Crowther M, Lu G, Conley PB, et al. Reversal of factor Xa inhibitors-induced anticoagulation in healthy subjects by andexanet alfa. Crit Care Med 2014;42:A1469.
17. Crowther MA, Levy G, Lu G, et al. A phase 2 randomized, double-blind, placebo-controlled trial demonstrating reversal of edoxaban-induced anticoagulation in healthy subjects by andexanet alfa (PRT064445), a universal antidote for factor Xa (fXa) inhibitors. Presented at: 56th Annual Meeting of the American Society of Hematology; December 6–9, 2014; San Francisco, CA.
18. Crowther MA, Mathur V, Kitt M, et al. A phase 2 randomized, double-blind, placebo-controlled trial demonstrating reversal of rivaroxaban-induced anticoagulation in healthy subjects by andexanet alfa (PRT064445), an antidote for Fxa inhibitors. Presented at: 55th Annual Meeting of the American Society of Hematology; December 7–10, 2013; New Orleans, LA.

19. Crowther MA, Kittl E, Lorenz T, et al. A phase 2 randomized, double-blind, placebo-controlled trial of PRT064445, a novel, universal antidote for direct and indirect factor Xa inhibitors. J Thromb Haemost 2013;11(suppl 2):OC 20.1.
20. Siegal DM, Curnutte JT, Connolly SJ, et al. Andexanet alfa for the reversal of factor Xa inhibitor activity. N Engl J Med 2015;373:2413-24.
21. A Study in Patients with Acute Major Bleeding to Evaluate the Ability of Andexanet Alfa to Reverse the Anticoagulation Effect of Direct and Indirect Oral Anticoagulants. Available at https://clinicaltrials.gov/ct2/show/NCT02329327?term=andexanet&rank=3. Accessed January 1, 2016.
22. Praxbind (idarucizumab) [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, 2015.
23. Lauw MN, Coppens M, Eikelboom JW. Recent advances in antidotes for direct oral anticoagulants: their arrival is imminent. Can J Cardiol 2014;30:381-4.

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