

Cervical cancer screening

(NOVEMBER 2011)

TO THE EDITOR: In their excellent review of cervical cancer screening,¹ Jin and colleagues discussed the current screening guidelines advocated by various medical organizations. The authors wisely advised clinicians to modify these guidelines when the lifestyle of an individual patient differs from the expected behavior of the patient's peer group. For example, they said "it is probably reasonable to continue screening in women age 70 and older who are sexually active with multiple partners and who have a history of abnormal Pap test results."

To this I would add that it seems reasonable to continue screening a woman over 70 who is sexually active with multiple partners, even if she still has no history of abnormal Pap test results. Similar reasoning might be applied to the statement, "women age 30 and older who had negative results on both Pap and HPV testing should be screened no more often than every 3 years." This makes sense on a population-wide basis, since women over 30 are more likely to be married and have fewer sexual partners. But why should women who continue to have multiple sex partners into their 30s be screened any less frequently than women in their 20s?

The high negative predictive value of HPV-plus-Pap testing is based on the risk characteristics of the population being screened, as well as on the technical characteristics of the tests. Rigid adherence to screening guidelines may be a disservice to individuals whose lifestyles place them at higher risk than the norm for their age cohort.

DAVID L. KELLER, MD
Providence Medical Group
Torrance, CA

■ REFERENCES

1. Jin XW, Sikon A, Yen-Lieberman B. Cervical cancer screening: less testing, smarter testing. *Cleve Clin J Med* 2011; 78:737-747.

doi:10.3949/ccjm.79c:03001

IN REPLY: We thank Dr. Keller for his excellent comment. The rationale for discontinuing screening in a woman over 70 who has multiple sexual partners without a history of an abnormal Pap test is that she is at lower risk of new-onset cervical intraepithelial neoplasia (CIN) than a younger woman because of her decreased rate of metaplasia and less accessible transformation zone. In addition, postmenopausal mucosal atrophy may predispose to false-positive cytology. False-positive results are likely to be followed by additional invasive procedures, anxiety, and cost to the patient. However, she is still at risk for acquiring human papillomavirus (HPV) and CIN. Given that cervical cancer develops slowly and risk factors decrease with age, it is reasonable to stop screening at this point. Also, the recommendation of the 3-year screening interval in women over 30 with multiple sexual partners who had negative Pap and HPV tests is based on the fact that they can acquire HPV the day after screening and subsequently develop CIN, but we can detect HPV and CIN in the next round of screening (3 years later) and so will not miss the opportunity to treat cervical dysplasia.

However, practice guidelines are never meant to replace a physician's sound clinical decision made on an individual basis.

XIAN WEN JIN, MD, PhD, FACP
Department of Internal Medicine
Cleveland Clinic

ANDREA SIKON, MD
Department of Internal Medicine
Cleveland Clinic

doi:10.3949/ccjm.79c:03002

Dabigatran

(OCTOBER 2011)

TO THE EDITOR: I read with interest the review of dabigatran (Pradaxa) by Drs. Wartak and Bartholomew, which provides an excellent overview of this new oral anticoagulant.¹

This article does not mention clearly two key points about the guidelines for using dabigatran, which are different in the United States than in the other 75 countries where it has been approved.¹ First, the RE-LY trial^{2,3} excluded patients with a creatinine clearance rate less than 30 mL/min/1.73 m², a common situation in the elderly. Second, in contrast to other countries, the US Food and Drug Administration (FDA) approved dabigatran for patients with a creatinine clearance rate of 15 to 30 mL/min/1.73 m², although at a lower dose.³ No dose adjustment is suggested in patients with less severe (mild or moderate) renal impairment.³ This may lead to potential misuse and problems. In fact, lethal side effects have been reported in France by Legrand et al.⁴ Furthermore, a report is in press on dabigatran-associated acute renal failure,⁵ and recently the German publication *Die Zeit* reported 50 deaths from bleeding in patients with atrial fibrillation treated with dabigatran.⁶

Therefore, despite suggestions that dabigatran does not require monitoring of its effects during treatment,^{1,3} renal, hematologic, and hepatic variables should be monitored before and after initiation of dabigatran⁵ until more experience is gained with this new drug, and especially in the elderly and those with chronic kidney disease that is stage 4 (estimated glomerular filtration rate 15–29 mL/min/1.73 m²) or stage 5 (< 15 mL/min/1.73 m²).

PATRICIO A. PAZMIÑO, PhD, MD, FACP, FASN
Nephrology, Internal Medicine & Hypertension (NIH) Center
El Paso, TX

REFERENCES

1. Wartak SA, Bartholomew JR. Dabigatran: will it change clinical practice? *Cleve Clin J Med* 2011; 78:657–664.
2. Connolly SJ, Ezekowitz MD, Yusuf S, et al; RE-LY Steering

Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009; 361:1139–1151.

3. Pradaxa (prescribing information). Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc, 2011.
4. Legrand M, Mateo J, Aribaud A, et al. The use of dabigatran in elderly patients. *Arch Intern Med* 2011; 171:1285–1286.
5. Pazmiño PA. Dabigatran-associated acute renal failure (DAARF). *El Paso Physician* 2011. In press.
6. Kaiser C. Pradaxa bleeding deaths raise concern. *MedPageToday*. www.medpagetoday.com/Cardiology/Strokes/29411. Accessed February 9, 2012.

doi:10.3949/ccjm.79c:03003

TO THE EDITOR: In their response to a letter to the editor (December 2011), Drs. Wartak and Bartholomew suggested the use of recombinant activated factor VIIa (NovoSeven) for bleeding in patients on dabigatran. They based this recommendation on a review by Stangier and Clemens,¹ which was based on phase II and III data on the efficacy and safety of dabigatran. There have been no controlled trials or prospective data on the use of this agent for this indication, nor are there data on its use in bleeding after intracranial hemorrhage, bleeding related to cardiac surgery, or trauma-related bleeding. In a systematic review, Yank et al² found that there is no lower mortality rate and an increased risk of thromboembolism when activated factor VIIa is used off-label. This agent is approved for use only in patients with hemophilia, and in fact Novo Nordisk paid a \$25 million settlement for off-label promotion of this drug for nonapproved indications.³ Recombinant factor VIIa costs up to \$10,000 per vial, and if it is used off-label, that cost is not reimbursed to the hospital.

Just because we can do something does not mean that we should do it. The use of recombinant factor VIIa for dabigatran-related bleeding needs to be studied in a controlled trial before it is routinely used. As seen in the cited review, indication drift can lead to adverse patient outcomes and will certainly lead to financial peril in hospitals across the country.

RONALD HIRSCH, MD
Elgin, IL

■ REFERENCES

1. **Stangier J, Clemens A.** Pharmacology, pharmacokinetics, and pharmacodynamics of dabigatran etexilate, an oral direct thrombin inhibitor. *Clin Appl Thromb Hemost* 2009; 15(suppl 1):95–165.
2. **Yank V, Tuohy CV, Logan AC, et al.** Systematic review: benefits and harms of in-hospital use of recombinant factor VIIa for off-label indications. *Ann Intern Med* 2011; 154:529–540.
3. **Silverman E.** Novo Nordisk pays \$25M for off-label marketing. *Pharmalot*. www.pharmalot.com/2011/06/novo-nordisk-pays-25m-for-off-label-marketing. Accessed February 9, 2012.

doi:10.3949/ccjm.79c.03004

IN REPLY: Dabigatran has gained significant popularity in the United States. From its approval in October 2010 and through August 2011, approximately 1.1 million prescriptions for it were dispensed, and 371,000 patients received it from US outpatient retail pharmacies.¹ We appreciate the letters from Drs. Pazmiño and Hirsch and believe there are reasons to be vigilant when using dabigatran.

In response to the letter from Dr. Pazmiño, we agree with his concerns and have covered them in our review. We would like to emphasize that our review was intended to help US clinicians understand this new drug and was not restricted to the RE-LY trial. The limitations of the trials of dabigatran to date (including the lack of patients with renal impairment in the RE-LY trial) have been mentioned in many articles, including ours. Please see the section **TOPICS OF FUTURE INTEREST**.²

The FDA did not recommend any dose adjustment for patients with moderate renal impairment (creatinine clearance 30–50 mL/min), as it was convinced that the 150-mg dose had a superior risk-benefit profile, even for patients with a higher risk of bleeding, compared with the 110-mg dose.³ It is hard for us to comment on the specific reasoning behind the FDA's approval for using 75 mg of dabigatran in patients with creatinine clearance between 15 and 30 mL/min. However, we know this was based on pharmacokinetic and pharmacodynamic modeling and not on efficacy and safety data.³ With respect to dosing and monitoring, we did stress this point in our article, stating that the use of dabigatran obviates the need for routine laboratory monitoring. However, one may measure the

drug's activity in certain situations (suspected overdose, bleeding, need for emergency surgery, impaired renal function, pregnancy, and obesity, and in children). Please see the section **DOES DABIGATRAN NEED MONITORING? CAN IT EVEN BE MONITORED?** in our review.²

Dr. Pazmiño suggests renal, hematologic and hepatic variables should be monitored before and after starting dabigatran. We agree that renal function should be monitored and have covered this point. Please see the section **WHO SHOULD NOT RECEIVE DABIGATRAN**.² Hematologic and hepatic variables can be monitored if a clinician decides to do so, but this is not limited specifically to dabigatran. Also, to clarify, dabigatran is not approved for those with stage 5 chronic kidney disease. And we share his concern about the lack of experience with this new drug, and we included a word of caution in the section **ADVANTAGES AND DISADVANTAGES OF DABIGATRAN**.²

We agree with Dr. Hirsch's concerns about recombinant factor VIIa. We are not recommending its use as a routine practice but as an available option. Our article was a global review on dabigatran, and our aim was to cover the best available evidence and treatment options in a comprehensive way. However, in response to Dr. Hirsch's comments, the systematic review by Yank et al⁴ drew its data from 16 randomized controlled trials but excluded patients on anticoagulants (except for those in a few observational studies), and factor VIIa was compared with placebo.⁴ So these findings are not applicable to patients with dabigatran-related bleeding, and to draw any definite conclusion would not be correct. If recombinant factor VIIa has failed to show a benefit in terms of a lower mortality rate, we could also point out that there was no mortality benefit seen in reversing warfarin anticoagulation in patients with acute intracranial hemorrhage with the use of vitamin K, fresh-frozen plasma, or prothrombin complex concentrate.⁵ This should not lead one to stop using these treatments.

Clinicians are well accustomed to managing warfarin- or heparin-related bleeding using specific antidotes. It is very important to understand the mechanism of action of dabigatran, and to realize that there is no an-

tidote. Recombinant factor VIIa is a potent hemostatic agent, and there are many published case reports and case series highlighting its efficacy in preventing bleeding.⁶⁻¹² It is used when all other options are exhausted. It is never a routine practice: it is always a last resort a clinician takes to prevent catastrophic bleeding. We believe economic concerns are very important, but it will be difficult to extrapolate a specific benchmark while treating for an individual case. At present, it seems unlikely that a randomized trial of recombinant factor VIIa will be conducted, and guidance is to be based on available animal studies and clinical anecdotes. A recent review on reversing anticoagulation therapy¹³ proposes treating major bleeding complications of direct thrombin inhibitors with activated prothrombin complex and recombinant factor VIIa.¹³

We acknowledge that serious, even fatal bleeding events have been reported with dabigatran. The FDA is evaluating postmarketing reports and is also using an active surveillance system to compare new users of dabigatran and warfarin with respect to the likelihood of their being hospitalized for bleeding.¹ With time and experience, we will learn more.

Finally, as with any new drug, the absence of data on long-term safety and efficacy is an important issue and should be considered when prescribing this new medication.

SIDDHARTH A. WARTAK, MD
Cleveland Clinic

JOHN R. BARTHOLOMEW, MD
Cleveland Clinic

REFERENCES

1. **US Food and Drug Administration.** Pradaxa (dabigatran etexilate mesylate): drug safety communication—safety review of post-marketing reports of serious bleeding events. <http://www.fda.gov/Safety/MedWatch/Safety-Information/SafetyAlertsforHumanMedicalProducts/ucm282820.htm>. Accessed February 8, 2012.
2. **Wartak SA, Bartholomew JR.** Dabigatran: will it change clinical practice? *Cleve Clin J Med* 2011; 78:657–664.
3. **Beasley BN, Unger EF, Temple R.** Anticoagulant options—why the FDA approved a higher but not a lower dose of dabigatran. *N Engl J Med* 2011; 364:1788–1790.
4. **Yank V, Tuohy CV, Logan AC, et al.** Systematic review: benefits and harms of in-hospital use of recombinant factor VIIa for off-label indications. *Ann Intern Med* 2011; 154:529–540.
5. **Bechtel BF, Nunez TC, Lyon JA, Cotton BA, Barrett TW.** Treatments for reversing warfarin anticoagulation in patients with acute intracranial hemorrhage: a structured literature review. *Int J Emerg Med* 2011; 4:40.
6. **Warren O, Mandal K, Hadjianastassiou V, et al.** Recombinant activated factor VII in cardiac surgery: a systematic review. *Ann Thorac Surg* 2007; 83:707–714.
7. **Chapman AJ, Blount AL, Davis AT, Hooker RL.** Recombinant factor VIIa (NovoSeven RT) use in high risk cardiac surgery. *Eur J Cardiothorac Surg* 2011; 40:1314–1318; discussion 1318–1319.
8. **Vavra KA, Lutz MF, Smythe MA.** Recombinant factor VIIa to manage major bleeding from newer parenteral anticoagulants. *Ann Pharmacother* 2010; 44:718–726.
9. **Ilyas C, Beyer GM, Dutton RP, Scalea TM, Hess JR.** Recombinant factor VIIa for warfarin-associated intracranial bleeding. *J Clin Anesth* 2008; 20:276–279.
10. **Brody DL, Aiyagari V, Shackelford AM, Diringer MN.** Use of recombinant factor VIIa in patients with warfarin-associated intracranial hemorrhage. *Neurocrit Care* 2005; 2:263–267.
11. **Nagle EL, Tsu LV, Dager WE.** Bivalirudin for anticoagulation during hypothermic cardiopulmonary bypass and recombinant factor VIIa for iatrogenic coagulopathy. *Ann Pharmacother* 2011; 45:e47.
12. **Kobayashi T, Nakabayashi M, Yoshioka A, Maeda M, Ikenoue T.** Recombinant activated factor VII (rFVIIa/NovoSeven®) in the management of severe postpartum haemorrhage: initial report of a multicentre case series in Japan. *Int J Hematol* 2011; 95:57–63.
13. **Ghanny S, Warkentin TE, Crowther MA.** Reversing anticoagulant therapy. *Curr Drug Discov Technol* 2011; Oct 21 (epub ahead of print).

doi:10.3949/ccjm.79c:03005