

Efforts Aim to Promote Safer Anticoagulant Prescribing

Bridget M. Kuehn

Despite the emergence of newer, easier to use formulations, anticoagulants continue to be the leading cause of emergency department visits for drug-related adverse events, accounting for 1 in 5 visits in 2013 to 2014, according to data from US Centers for Disease Control and Prevention (CDC). These ongoing safety concerns are sparking renewed calls from US agencies and advocacy groups for safer use of anticoagulants.

Balancing the risks of a life-threatening bleeding event with the benefits of preventing a stroke has always posed a challenge for clinicians. Many clinicians were hopeful that the emergence of non-vitamin K oral anticoagulants (NOACs), which have simpler dosing regimens and do not require frequent monitoring like warfarin, might help reduce adverse events. But CDC data published in *JAMA* in November along with an ongoing flow of reports to the US Food and Drug Administration (FDA) of serious harm or deaths linked to anticoagulants reveal the ongoing challenges facing prescribers. In fact, the CDC data suggest that anticoagulant-linked adverse events may actually be increasing.

“Five decades into use of anticoagulants and we still haven’t optimized their use and safety,” said Nadine Shehab, PharmD, MPH, a senior scientist with the CDC’s Medical Safety Program.



Ongoing safety concerns are sparking renewed calls from US agencies and advocacy groups for safer use of anticoagulants.

NEW CHALLENGES WITH NOACS

In the 7 years since the first NOAC was approved, the Institute for Safe Medication Practices (ISMP), an organization that monitors drug safety, has grown alarmed by the high numbers of serious and life-threatening adverse events reported in patients taking these drugs. In fact, the ISMP ranked oral anticoagulants as the highest-priority drug safety problem in 2016.

“Warfarin has always been viewed as a difficult to use, high-risk drug because it is hard to get the anticoagulant levels just right and not getting it right can lead to severe and life-threatening bleeds,” said Thomas Moore, a senior scientist in Drug Safety and Policy at ISMP.

Data from large, clinical trials demonstrated NOACs to be at least as safe and effective as warfarin. But as real-world evidence on NOAC

safety and efficacy grows, it has become clear that each drug also has its own safety profile.

“The major differences are differences in safety,” said Peter Noseworthy, MD, an associate professor of medicine and a cardiac electrophysiologist at the Mayo Clinic.

For example, an analysis by Noseworthy and his colleagues of a large US health insurer’s database published in the *Journal of the American Heart Association* in June 2016 showed that, in comparison with warfarin, apixaban was associated with a lower risk of stroke and major bleeding for patients with atrial fibrillation; dabigatran had a similar risk of stroke as warfarin and a lower risk of major bleeding; and rivaroxaban has comparable stroke and bleeding risks to warfarin.

Prescribing patterns also may have differed by drug. The study noted that patients receiving dabi-

gatan were younger and had lower bleeding risks than patients prescribed rivaroxaban or apixaban, and that doctors may have prescribed specific drugs for patients who better matched those enrolled in that drug's trials.

Although NOACs were designed to be easier to use than warfarin, they have proven to have dosing issues of their own. Xiaoxi Yao, PhD, assistant professor of health services research at the Mayo Clinic, explained that there have been documented problems with both overdosing and underdosing of patients with NOACs. For example, if a physician does not check a patient's kidney function or a patient's renal status changes during the course of treatment, the patient may end up receiving too high a dose.

"I don't think [anticoagulation] should be withheld, but we may have to screen patients for risk factors or regularly follow up to see if patients have had a change in medical history, especially renal function," Yao said.

Because NOACs are newer, physicians still need education on a slew of issues, including when to prescribe them, appropriate dosing, how to manage interactions with other drugs, how to transition a patient from warfarin, or how to discontinue NOACs for patients who need surgery, Shehab explained.

"For the NOACs, there is a need to strengthen the evidence base on how to prevent hemorrhages and to use them better," Shehab said.

SAFER PRESCRIBING

In July, ISMP became the latest in a growing chorus of voices calling for renewed efforts to boost anticoagulant safety. The organization proposed several steps that prescribers, drug makers, health facilities, and regulators could take.

For physicians, ISMP recommended that caution be taken to avoid overuse of anticoagulants in patients

at low risk of stroke and that new guidelines be created for concurrent use of anticoagulants with antiplatelet agents to determine when the benefits outweigh the risk. Moore explained that concurrent use of such drugs has been linked with a 2 times higher risk of bleeding.

Currently, there are limited data to guide physicians on when it is appropriate to use multiple agents, noted Noseworthy, which may partly explain the lack of clear guidance. There are, however, trials ongoing.

"It's a rapidly evolving area," he said.

In addition, the ISMP recommends that drug makers and the FDA make available therapeutic ranges for dabigatran to help physicians identify patients who may be outside the therapeutic range and at risk of suboptimal or excess anticoagulation. Such therapeutic ranges and a test to assess them are available for warfarin, Moore noted.

Therapeutic ranges and tests could be helpful for these drugs, especially for patients who are likely to be outliers, Noseworthy said—for example, patients who are obese or have had gastric bypass surgery.

"The initial appeal of these drugs was no monitoring, but it is becoming their Achilles' heel," Noseworthy said. "I would love to have an assay that I could use to evaluate patients who are outside the norm." In addition, ISMP recommended wider availability of antidotes for anticoagulants. The FDA has approved an antidote for dabigatran, but antidotes for rivaroxaban and apixaban are not yet approved. Moore expects they will be soon. But he cautioned that even patients who receive an antidote may continue to bleed or die.

"It is helpful to have these agents, but they are by no means a panacea for the high rate of bleeds caused by these agents," Moore said.

They also recommend a reconsideration of rivaroxaban's once-daily dosing regimen to determine

whether twice-daily dosing might be safer. Yao noted, however, that once-daily dosing has been marketed as a way to boost adherence, and that there currently are not enough data to know whether twice a day would be better.

"There may be a trade-off with safety and adherence, but since no trials are available, we are not sure," Yao said.

The US Department of Health and Human Services released an [action plan](#) in 2015 that outlined steps that could be taken in both inpatient and outpatient settings to boost safe use of anticoagulants and other high-risk drugs. Among the recommendations was a call to boost patient education and education and greater use of anticoagulant management programs. Shehab explained that both anticoagulant management services and home testing of warfarin levels by patients are evidence-backed ways to reduce adverse events that are underused.

"We don't have nearly enough implementation," she said.

Although many of these recommendations require regulatory or systems-level efforts, individual physicians can also help boost anticoagulant safety. Noseworthy recommended that physicians be "meticulous about how they choose a starting dose," carefully reassess patients over time, avoid triple therapy (aspirin, plus an anticoagulant, plus an antiplatelet agent), consider whether the benefits outweigh the risks for patients at low risk of stroke, and be aware of the risk factors for bleeds.

"No matter how carefully they are used, anticoagulants will make serious bleeding events all the more serious and life-threatening," Noseworthy said. "We always have to make sure the use is justified." ■

Circulation is available at <http://circ.ahajournals.org>.

© 2017 American Heart Association, Inc.

Efforts Aim to Promote Safer Anticoagulant Prescribing Bridget M. Kuehn

Circulation. 2017;136:2508-2509

doi: 10.1161/CIRCULATIONAHA.117.032663

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Copyright © 2017 American Heart Association, Inc. All rights reserved.

Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:

<http://circ.ahajournals.org/content/136/25/2508>

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the [Permissions and Rights Question and Answer](#) document.

Reprints: Information about reprints can be found online at:
<http://www.lww.com/reprints>

Subscriptions: Information about subscribing to *Circulation* is online at:
<http://circ.ahajournals.org/subscriptions/>