Title : New anticoagulants spread, while some concerns linger

The 2010 FDA approval of dabigatran (Pradaxa), an oral thrombin inhibitor for stroke prevention in patients with non-valvular atrial fibrillation, was heralded as opening a new era in anticoagulant therapy. The product, developed by Boehringer-Ingelheim, represented the first authorization of a new blood thinner since the introduction of warfarin (Coumarin) more than a half-century earlier.

Dabigatran's early lead did not last long, however, as
it was soon joined on the market by a trio of direct Factor Xa inhibitors: rivaroxaban (Xarelto; Bayer), apixaban (Eliquis; jointly developed by Pfizer and Bristol-Meyers Squibb), and Daiiichi Sankyo's edoxaban, sold as Lixiana in Japan and Europe and Savaysa in the United States.

Like warfarin, these four new oral anticoagulants (NOACs) are used for reducing the risk of stroke and pulmonary embolism in patients with atrial fibrillation, a heart arrhythmia that primarily affects people above the age of 75. While their ability to reduce thrombus formation is broadly similar, the NOACs offer key advantages over warfarin, which requires frequent blood testing, regular dosage adjustments, and dietary restrictions. By 2014, the NOACs collectively accounted for 15.5% of the global sales for oral anticoagulants, a market that had been dominated by warfarin for over 50 years.

But there have been stumbling blocks for the NOACs as well. Soon after its approval in the United States, the maker of dabigatran, Boehringer-Ingelheim, was hit with thousands of lawsuits alleging that the drug was linked to cases of severe bleeding that could not be controlled by standard methods. The company settled 4,000 lawsuits against it in 2014 with a total payout of $650 million. In 2014, a *British Medical Journal* raised concerns that Boehringer-Ingelheim had withheld important data highlighting the clinical importance of monitoring plasma levels of the drug. The following year, a study by Pro Publica, which monitors pharmaceutical industry payments to physicians to promote drugs, found that the NOACs Eliquis, Xarelto and Pradaxa, were second, sixth and thirteenth on their list of most heavily promoted drugs.

A major limiting factor in the use of NOACs has been the lack of an antagonist drug capable of rapidly inhibiting their anticoagulant effects, which can be critical in emergency care situations. Warfarin, for example, can be quickly counteracted by a bolus of vitamin K, which has helped maintain its popularity as a blood thinner and stroke prophylactic. In October 2015, the FDA approved idarucizumab, a humanized antibody fragment that rapidly counteracts the effects of dabigatran, which may help boost sales of Pradaxa. "The effect of availability of such an antidote is mainly psychological for prescribers and patients," says Dr. Simon Manthas, a hematologist at Memorial Sloan Kettering Cancer Center in New York, who has studied the NOACs. "Both will feel more at ease using dabigatran knowing that there is an effective option for reversal."

Name	**Brand name**	**Distributor**	**Type**	**Antagonist available**
warfarin	Coumadin, various (generic available)	Bristol-Meyers Squibb, others	vitamin K_1 recycling inhibitor	yes
dabigatran	Pradaxa (US/EU) Prazaxa (JP)	Boehringer-Ingelheim	direct thrombin inhibitor	yes
rivaroxaban	Xarelto	Bayer	direct Factor Xa inhibitor (oral)	no
apixaban	Eliquis	Pfizer/Bristol-Meyers Squibb	direct Factor Xa inhibitor (oral)	no
edoxaban	Lixiana (JP/EU) Savaysa (US)	Daiichi Sankyo	direct Factor Xa inhibitor (oral)	no

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