EDITORIAL AND COMMENT

Warfarin: Not Dead Yet

Adam J. Rose, MD, MSc, FACP^{1,2}

¹Center for Healthcare Organization and Implementation Research, Bedford VA Medical Center, Bedford, MA, USA; ²Department of Medicine, Section of General Internal Medicine, Boston University School of Medicine, Boston, MA, USA.

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Warfarin is a very old drug. From the first description of "hemorrhagic sweet clover disease" in 1941,¹ to the purification and first clinical use of warfarin a few years later, we have been using this drug for a very long time.² There are many popular quips about this venerable and well-known drug. Patients like to say that it is rat poison, which of course is essentially true. Doctors like to quip that the US Food and Drug Administration (FDA) would never have approved warfarin today, which may or may not be true. It is the drug that everyone knows, and the drug that everyone loves to hate. Truly, warfarin can be inconvenient, can be dangerous, and can confound even the most skillful attempts at managing it.³ From the first time I heard about warfarin as a medical student, its very mention was invariably accompanied by a hope, a prayer really, that something better would come along soon.

Of course, in parallel to our decades-long pattern of hating warfarin, we have also been on a collective journey of learning how to use it better. Milestones along this journey have included the eventual international adoption of the international normalized ratio (INR) value, which after more than 40 years of warfarin use finally allowed any laboratory in the world to measure its effect in the same way.² This was followed soon after by standardized INR ranges for different indications,³ which of course could not have been possible without the existence of the INR test. There was also a gradually accelerating research agenda that improved our idea of who was most at risk for the complications of warfarin therapy. This effort included randomized trials to establish target ranges and indications, real-world registry-based outcome studies, as well as studies that examined care modalities for warfarin such as anticoagulation clinics and patient self-testing.³ Most recently, my colleagues and I have begun to build an organized regime of quality measurement and quality improvement for warfarin, to truly optimize the structures, processes, and outcomes of warfarin management.⁴

In summary, there have been two evolving stories regarding warfarin. First, it is the drug that we all love to hate and wish to see replaced. But second, it is the drug that has been something of a puzzle, a puzzle that we may finally be starting to solve as we truly move toward optimizing its management. The question seemed to be: would we abandon warfarin, or would we finally figure out how to optimize its use? The introduction of novel anticoagulants (NoACs) four years ago brought this question into sharper focus.

The early randomized trials for NoACs certainly looked good, and by the present standards of the FDA, which is not empowered to ask questions beyond safety and efficacy, they were enough for approval. The more interesting studies, in my opinion, were the inevitable cost effectiveness analyses (CEAs), given the price tag for these eagerly awaited drugs. The first major study of this type reached the conclusion that dabigatran was cost-effective,⁵ although only barely so (at a cost of about \$50,000/quality-adjusted life year [QALY], it represented very expensive care). After this CEA, an additional analysis of the RELY study concluded that dabigatran only performs better than warfarin when the warfarin is poorly controlled.⁶ A later CEA, which incorporated this new information, reached a more nuanced conclusion than the earlier study. Shah and Gage found that whether warfarin or dabigatran was the preferred agent depended somewhat on patient risk profile, but more than anything on the level of control that was achieved with warfarin.⁷ However, while this was certainly an improvement on the earlier study, there was still important information missing. There have certainly been reports of populations that achieve excellent anticoagulation control,⁸ more than good enough to render warfarin the preferred agent. What we do not know yet is whether it would be possible to deliberately improve the control of a population to this level if it is not already there, and also what that effort would cost.

In the current issue of *JGIM*, Dr. You performed an analysis which advances this discussion far beyond where it has been.⁹ Specifically, she compared costs and outcomes with NOACs vs. warfarin at different levels of anticoagulation control (percent time in therapeutic range, or TTR) and at different incremental levels of cost for managing warfarin. Quite reasonably, Dr. You assumed that it is possible to improve TTR, but that it might require an investment of additional resources to accomplish. The main findings were that, at a customary willingness-to-pay

threshold of \$50,000/QALY, NOACs were more cost-effective than warfarin with a population TTR of 60 % (relatively poor control) at the present cost, more cost-effective with a TTR of 70 % (very good control) when the cost of achieving this TTR was a two-fold increase in the cost of warfarin care, and at a TTR of 75 % (superb control), the break-even point was a three-fold cost increase. Predictably, raising the willingness-to-pay threshold to \$100,000/QALY greatly altered these results, as did changes in the price of NoACs.

These findings are a major advance over the previous literature, and give decision-makers *almost* everything they would need to make an informed formulary decision. However, this puzzle is not complete until we know how much we can improve TTR in real life, and how much it will cost to do so. To this end, our group is embarked on an ambitious 4-year effort to transform the management of warfarin in the New England region of the Veterans Health Administration (VA). The final results of our effort are expected by late 2016, but our aspirational goal is to increase TTR in this region of VA to at least 70 % and possibly as high as 75 %. We will also document the cost of this improvement, but we anticipate that the incremental cost will be minimal, and certainly not the two-fold or three-fold cost increase that Dr. You forecasted. When fit into You's model, such results, if achieved, would mean that NoACs would not be the preferred agents in our system of care, at least not until the distant future when their patents expire and presumably, prices plummet.

The foregoing discussion leaves aside the issue of whether outcomes with NoACs in real-life populations will match what was seen in clinical trials. There are many reasons to think that this may not be the case, from the relatively unforgiving half life of most NoACs (which makes them very susceptible to nonadherence), to their high price (also encouraging nonadherence), to the fact that they were studied in a younger and healthier population than the one that will ultimately use them (therefore minimizing adverse events). Over the next few years, there will be a tremendous number of observational studies of real-world outcomes with NoACs. The information produced by these real-world comparative effectiveness studies will also need to be factored into our decision about the place of NoACs in modern practice.

Dr. You is to be congratulated on her well-performed study, which truly advances the discussion regarding the place of NoACs in therapy today. The question it raises, above all, is one of value. Will we do more to create high-value health care by working to improve the management of warfarin, by abandoning warfarin as we have long wished

to do, or perhaps some combination of the two? Dr. You has outlined the main questions that should drive our analysis, namely, how much can we improve our management of warfarin, and what will it cost to do so? While simply adopting NoACs would unquestionably be the easier choice, I suspect that we can create greater value for our beleaguered health care system by working to improve the management of warfarin. Despite the many reports of its demise, warfarin is not dead yet.

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Corresponding Author: Adam J. Rose, MD, MSc, FACP; Center for Healthcare Organization and Implementation Research, Bedford VA Medical Center, 200 Springs Road, Mail Stop 152, Bedford, MA 01730, USA (e-mail: adamrose@bu.edu).

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