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Available online 16 July 2013

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<http://dx.doi.org/10.1016/j.rec.2013.05.004>

New Oral Anticoagulants in Nonvalvular Atrial Fibrillation: Findings and Implications of the ROCKET Study. Response

Nuevos anticoagulantes orales en fibrilación auricular no valvular: resultados e implicaciones del estudio ROCKET. Respuesta

To the Editor,

We appreciate the interest in our review article expressed in a recent letter.^{1,2} While we agree with some aspects of the letter, we disagree with others, probably because we seem to have very different opinions about the overall assessment of the new oral anticoagulants. Below, we present our point-by-point response to the letter.

1. *Bleeding.* Yes, there is an increase in digestive-tract bleeding in patients treated with rivaroxaban. The data referenced in the letter can be found in the appendix to the original article, along with an abundance of other data. However, the total number of severe bleeding events was the same in both groups (1.04 [0.90-1.20]) while the number of the most serious bleeding events—that is, intracranial events (0.67 [0.47-0.93]; $P<.02$) and fatal bleeding events (0.50 [0.31-0.79]; $P<.003$)—was lower in the rivaroxaban group. Thus, in our opinion, the practical conclusions of the study with regard to bleeding are the following: a) bleeding is a problem with any anticoagulant drug, and b) the overall analysis of the risk of bleeding favors rivaroxaban over warfarin, as rivaroxaban reduces the most serious bleeding events.
2. *Efficacy.* It is true that the overall intent-to-treat analysis did not demonstrate noninferiority for reducing embolic episodes, but there was a decrease in intracranial bleeding and also in embolism in patients who received treatment for both drugs as per protocol: 0.79 (0.66-0.96) ($P<.001$). Perhaps the results of this study are less noteworthy than those of others with new anticoagulants, but it can nevertheless be affirmed that there is a benefit associated with rivaroxaban compared to warfarin. This was probably the opinion of the European Medicines Agency,³ the Spanish Ministry of Health, and the Spanish Agency for Medicines and Healthcare Products,⁴ when they approved this drug as a replacement for warfarin for this type of patient. Therefore, we believe there is no inconsistency in the statements in our article.

3. *Treatment adherence.* Of course, we should be aware that anticoagulants, whether new or old, prevent appropriate coagulation and so there is always a risk of bleeding. They should only be used as prescribed by a doctor. The patient should be appropriately informed and candidates selected for their ability to understand what they are taking, why they are taking it, and how it should be taken. There are patients for whom anticoagulation is indicated but who should nevertheless not receive therapy because of a suspicion that they will not meet these conditions. However, to hypothesize that the lack of need for frequent follow-up will lead to worse adherence to therapy, which will then lead to a greater incidence of embolic events, is pure speculation that would have to be supported by clinical evidence.
4. *Short half-life.* We believe that this is an advantage, not the drawback suggested in the letter. If a patient treated with a new oral anticoagulant misses a dose, he or she spends a few hours without anticoagulation. If a patient who is taking warfarin/acenocoumarol (whether taken correctly or not) has an INR below the therapeutic range, he or she may spend not hours but rather months without appropriate anticoagulation and therefore unprotected. If a patient suffers from bleeding, anticoagulation will cease for a few hours with a new oral anticoagulant, compared to days in the case of warfarin. Therefore, anticoagulation with a long half-life is more worrying.
5. *Antidote.* What is the antidote for warfarin? And the antidote for acenocoumarol? There are strategies for reversing the anticoagulation process, not antidotes.
6. *Limitations of rivaroxaban.* Even if the cited limitations of rivaroxaban compared to warfarin were real, they do not appear to have had sufficient impact to counteract the benefits of rivaroxaban shown in the ROCKET study.
7. *Limited information available.* How many patients have been included in controlled studies with warfarin? Hundreds. And with acenocoumarol (the oral anticoagulant used in Spain)? None. We have had no scientific evidence of the benefit or harm of anticoagulation with the most widely-used anticoagulant in Spain! Incredible but true. With the new oral anticoagulants, there are 4 contemporary, well-designed, clinical trials that have included more than 50 000 patients. Never before has so much valuable and reliable evidence been accumulated.⁵

Thus, we repeat that the new oral anticoagulants should displace warfarin and acenocoumarol in most cases if the costs so

permit. We know that this is an opinion shared by many healthcare professionals, but obviously not all.

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Available online 9 July 2013

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