asymmetric and progressive and commonly involves the intraventricular septum, is detected in up to 80% of patients with a cardiac defect and may associate with significant left ventricular outflow tract obstruction in up to 40% of cases. Although treatment algorithms are similar between LS patients with ventricular hypertrophy and patients with familial HCM, without an evidence-based diagnosis, despite their analogous character it is clear that the pathophysiology and dynamics of HCM in LS differ from ventricular hypertrophy of other causes. On the contrary, the most common cardiac manifestation in NS is pulmonic stenosis resulting from dysplastic valve leaflets, followed (less frequently) by HCM, mitral stenosis, and atrial, ventricular and atrioventricular septal defects, or (rarely) by double outlet right ventricle.

To date, it is unclear whether the genotype may influence the clinical course in LS patients with HCM, especially because many of the affected individuals described in the literature are children and no clear risk figures based on a follow-up patient cohort study of a sufficient size is available. However, anecdotal reports provide enough evidence to state that long-term prognosis seems benign in LS patients with only mild cardiac abnormalities, whereas HCM in LS is indeed associated with a risk of fatal cardiac events as seen in primary HCM.

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

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

To the Editor,

With respect to the article “Findings and Implications of the ROCKET Study,” we are in agreement with López-Sendón et al. that the findings support the decision of the health authorities to grant authorization of rivaroxaban, and that these results could help change stroke and systemic embolism prevention strategies in patients with atrial fibrillation, given that the new oral anticoagulants represent a major therapeutic advance. However, several aspects are of particular importance when assessing the clinical implications of the ROCKET study, and these deserve special attention.

The first is related to the efficacy of rivaroxaban vs warfarin. On this point, we have detected a contradiction in the text. In the section “Findings of the ROCKET Study,” the authors state that there were no significant differences in the efficacy endpoint in the intent-to-treat analysis, whereas in the section “Clinical Implications of the ROCKET Study,” they state that, cost permitting, the new anticoagulants should displace warfarin in the prevention of stroke in patients with atrial fibrillation in most cases, given their greater efficacy and ease of administration. In our opinion, regardless of the associated costs, this latter statement is incongruent given that rivaroxaban was not shown to be superior to warfarin.

Regarding the bleeding complications, we agree with the authors that rivaroxaban does not increase the risk of serious or clinically relevant bleeding compared to warfarin and significantly decreases intracranial and fatal bleeding. However, we find no allusion to the increase in severe gastrointestinal bleeding in the group treated with rivaroxaban compared to warfarin (odds ratio=1.60; 95% confidence interval, 1.29–1.98).

Moreover, although it is true that the new oral anticoagulants represent major progress in medical treatment, we should nevertheless be aware of their limitations. In fact, although the lack of need for monitoring is considered an advantage, lack of follow-up could negatively affect adherence to treatment. In view of the short half-lives of these drugs, this aspect is of particular importance, as missed doses may quickly have an effect on the efficacy of treatment. Poor adherence could cancel out the potential clinical benefit of new oral anticoagulants compared to vitamin K antagonists and even increase the risk of stroke or systemic embolism. As observed in the ROCKET study, patients who discontinue treatment with rivaroxaban had a higher incidence of stroke or systemic embolism compared to those who discontinued warfarin. Likewise, other limitations, in no way insignificant, for the use of new oral anticoagulants are the lack of a specific antidote to reverse their effect and the limited experience in the management of bleeding complications in patients treated with these drugs. Finally, as with any other new drug, the available safety information is currently limited.

Thus, we do not agree with the authors when they state that the new oral anticoagulants should replace warfarin in most cases if costs allow. It is clear that the direct cost of treatment with new anticoagulants is markedly greater than treatment with vitamin K antagonists. However, economic motives are not the only reasons for caution in the use of these drugs, as there are also important aspects related to efficacy that are worthy of consideration.

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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. 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 [9.0-1.20]) 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, the Spanish Ministry of Health, and the Spanish Agency for Medicines and Healthcare Products, 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 foracenocoumarol? 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.

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