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Point-of-Care Warfarin Monitoring in the ROCKET AF Trial

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dysplasia or villous architecture, rather than tubulovillous architecture.

The inadvertent reversal of data on cancer detection by the stool DNA test and FIT in Table 3 of my article notwithstanding, the thrust of the message of Table 3 is that stool-based tests for advanced adenoma do not fare well as compared with colonoscopy; this has been adroitly shown to be valid in the studies by Imperiale et al. and Quintero et al. (cited as references 5 and 61 in my article, respectively). The assumption by Itzkowitz and Ahlquist that stool DNA testing might reach a sensitivity of 90% by a second round of screening at 3 years is an estimated outcome that has not been proved. Stool DNA testing is an appealing approach to screening, but it involves several obstacles,² including cost-ineffectiveness, since a positive test requires colonoscopy as a second procedure.^{3,4}

Castellsagué and colleagues note mutations that are associated with colon-cancer syndromes.

Although a discussion of genetic syndromes was not a goal of my article, these mutations were noted in a reference to an article by Stoffel and Boland (cited as reference 15 in my article).

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Since publication of his article, the author reports no further potential conflict of interest.

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Point-of-Care Warfarin Monitoring in the ROCKET AF Trial

TO THE EDITOR: On February 5, 2016, the European Medicines Agency (EMA) released an assessment report on rivaroxaban (Xarelto), in which it described Bayer's comparison of the international normalized ratio (INR) values obtained by the Alere INRatio Monitor System (formally known as the Hemosense INRatio device) and those obtained by a central laboratory on samples collected at weeks 12 and 24 during the ROCKET AF trial.¹ Although the point-of-care device reported lower INR values than those shown by the laboratory results, the error was not influenced by either anemia or conditions causing elevated fibrinogen levels. Since this finding negates the fundamental assumption in the post hoc analysis of the ROCKET AF data by Patel et al.,² how should their results be interpreted? Of the 767 central-laboratory samples with an INR of more than 4 at week 12, the point-of-care device reported values of less than 3 for 219 samples (29%).¹ Although the EMA found insufficient evidence to alter the benefit-risk conclusion of the original rivaroxaban study, the agency did not address several important questions. How many warfarin-treated patients had major bleeding as a result of this error in the point-of-care

device? Did this error result in a change in the percentage of time that patients receiving warfarin were in the therapeutic range? Answers to these questions could alter the relative benefit-risk relationship between rivaroxaban and warfarin. They could also diminish the validity of the ROCKET AF study.³

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No potential conflict of interest relevant to this letter was reported.

1. European Medicines Agency assessment report: Xarelto. February 5, 2016 (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000944/WC500201726.pdf).
2. Patel MR, Hellkamp AS, Fox KAA. Point-of-care warfarin monitoring in the ROCKET AF trial. *N Engl J Med* 2016;374:785-8.
3. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;365:883-91.

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THE AUTHORS REPLY: In response to the comments of Powell and to provide further insight, we now present the results of additional analyses using central-laboratory INR measurements on

stored blood samples that were drawn on the same day that point-of-care tests were performed at 12 weeks and 24 weeks (paired samples) in the ROCKET AF trial. Paired samples at either time point were obtained from 87% of the trial patients (Table S1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org). These paired samples represent 22,250 of 356,654 total point-of-care INR tests (6%) that were performed. At baseline, more patients with paired samples were male and had a history of greater use of vitamin K antagonists than did those without paired samples (Table S2 in the Supplementary Appendix).

We used the discrepancy criteria of the International Organization for Standardization¹ to define discrepancies in measurements of the prothrombin time and INR between point-of-care tests and central-laboratory values; the Food and Drug Administration (FDA) requires 90% agreement (i.e., $\leq 10\%$ discrepancy) for equivalence. We found that among samples obtained from patients receiving warfarin, discrepant INR values between the point-of-care and central-laboratory testing were present in 13% of the samples obtained at either 12 weeks or 24 weeks and in 4% of the samples obtained at both time points (Tables S3 and S4 in the Supplementary Appendix). These discrepancies were unrelated to the presence of conditions (e.g., inflammatory disorders, infections, and anemia) that are listed in the FDA recall notice. The point-of-care INR was in the same range with respect to treatment criteria (i.e., < 2 , 2 to 3 , or > 3) as the laboratory INR in approximately 60% of the paired values, in a lower range in slightly more than one third, and in a higher range in 4% (Table S5 in the Supplementary Appendix). The time that patients spent in the therapeutic range according to discrepancy is presented in Table S6 in the Supplementary Appendix.

Event rates among warfarin-treated patients with discrepant values were higher for both bleeding and stroke than among those with nondiscrepant values (Tables S7, S8, and S9 in the Supplementary Appendix). If INR values that were potentially underestimated by the point-of-care device had led to clinical events, then higher rates of bleeding but not of stroke would have been expected in the patients receiving warfarin. We also examined discrepancies between the point-of-care and central-laboratory results among

rivaroxaban-treated patients (Tables S10 and S11 in the Supplementary Appendix). Patients receiving rivaroxaban who had discrepant point-of-care results also had higher bleeding rates but lower stroke rates (Table S12 in the Supplementary Appendix).

We performed an analysis of the trial outcomes after the removal of all patients with discrepant point-of-care and central-laboratory values (Tables S13 through S18 in the Supplementary Appendix). For the primary efficacy end point of stroke or systemic embolism, among patients with nondiscrepant values at both time points, there were 1.46 events per 100 patient-years with rivaroxaban and 1.37 events per 100 patient-years with warfarin (unadjusted hazard ratio, 1.06; 95% confidence interval [CI], 0.78 to 1.45; $P=0.70$ for superiority; $P=0.03$ for noninferiority) (Table S15 in the Supplementary Appendix). For the principal safety end point of major and nonmajor clinically relevant bleeding, there were 11.36 events per 100 patient-years with rivaroxaban and 12.42 events per 100 patient-years with warfarin (unadjusted hazard ratio, 0.92; 95% CI, 0.82 to 1.03; $P=0.13$).

These results are consistent with the originally reported overall trial results. However, we acknowledge the limitations of these analyses. To be fully informative, we would need to provide paired central-laboratory and point-of-care INR values throughout the trial, and these values are not available.

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Since publication of their letter, the authors report no further potential conflict of interest.

This letter was published on July 6, 2016, at NEJM.org.

1. International Organization for Standardization. ISO 17593: 2007: clinical laboratory testing and in vitro medical devices — requirements for in vitro monitoring systems for self-testing of oral anticoagulant therapy. 2011 (http://www.iso.org/iso/iso_catalogue/catalogue_tc/catalogue_detail.htm?csnumber=36872).

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