THE AUTHORS REPLY: Arellano-Rodrigo correctly points out that treatment for low-risk MGUS is not recommended by current evidence-based guidelines, except in clinical trials. However, our patient's paraprotein was associated with a disabling clinical syndrome of renal lymphangiectasis. Although we did not know whether the paraprotein played a role in the lymphangiectasis, MGUS-level paraproteins may be associated with a wide variety of symptoms, as for example in the syndrome of polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes (POEMS). Although clinical trials exist for treatment of patients with MGUS and symptoms such as polyneuropathy (e.g., Study of Lenalidomide as a Treatment for Neuropathy Associated with Monoclonal Gammopathy of Undetermined Significance; ClinicalTrials.gov number, NCT00665652), our case appeared to be unique, with no relevant protocols. Our rationale for suggesting lenalidomide was based on its effectiveness in both myeloma and anecdotally in POEMS syndrome,[1] as well as the knowledge that immunomodulatory agents such as thalidomide and lenalidomide inhibit angiogenesis, and therefore they might directly affect lymphatic vessels.[2,3]

Correspondence we have received since the publication of our article suggests that there are other examples of this syndrome. Thus, we may eventually be able to define a disease that will permit establishment of therapeutic trials in the future.

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

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Newly Identified Events in the RE-LY Trial

TO THE EDITOR: We wish to update our article about the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial (Sept. 17, 2009, issue).[1] After the database was locked on August 15, 2009, we identified several additional primary efficacy and safety outcome events during routine clinical site closure visits. These events included two systemic embolic events and nine major hemorrhages. Subsequently, after discussions with the Food and Drug Administration, the primary and secondary efficacy and safety data were checked for consistency, and the study database was reevaluated for possible underreporting of events. To achieve this, all free text, outcomes, and adverse events in the database were searched with the use of multiple algorithms to identify any symptom that might suggest the possibility of any primary or secondary event or bleeding. This included an examination of all decreases in the hemoglobin level by more than 2 g per deciliter between visits, other markers of potential bleeding, new pathologic Q waves on routine electrocardiography (ECG), and any report of weakness or other symptoms that might be potentially related to a stroke. This process resulted in the identification of 81 new events in 80 patients. These included 1 stroke, 1 systemic embolic event, 4 clinical myocardial infarctions, 1 pulmonary embolism, 5 transient ischemic attacks, and 69 major hemorrhages.

Although silent myocardial infarction, defined as the new appearance of pathologic Q waves on ECG, was part of the RE-LY definition of myocardial infarction, no cases of silent myocardial infarction were reported by investigators during the course of the study. However, review of the routine ECG reports revealed 28 cases fulfilling the criteria for silent myocardial infarction.

All these newly identified events were adjudicated in a blinded fashion and in accordance with the study protocol. Two rounds of data entry were performed for all data on the international normalized ratio (INR), for purposes of validation. This resulted in a change in the mean percentage

Table 1. Published and Revised Data for Primary Efficacy and Safety Outcomes and Myocardial Infarction, According to Treatment Group.*

Event	Dabigatran, 110 mg (N=6015)		Dabigatran, 150 mg (N=6076)		Warfarin (N=6022)		Dabigatran, 110 mg, vs. Warfarin		Dabigatran, 150 mg, vs. Warfarin	
							Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value
	no. of patients	*%/yr*	*no. of patients*	*%/yr*	*no. of patients*	*%/yr*				
Stroke or systemic embolism										
Published	182	1.53	134	1.11	199	1.69	0.91 (0.74–1.11)	0.34	0.66 (0.53–0.82)	<0.001
Revised	183	1.54	134	1.11	202	1.71	0.90 (0.74–1.10)	0.30	0.65 (0.52–0.81)	<0.001
Major bleeding										
Published	322	2.71	375	3.11	397	3.36	0.80 (0.69–0.93)	0.003	0.93 (0.81–1.07)	0.31
Revised	342	2.87	399	3.32	421	3.57	0.80 (0.70–0.93)	0.003	0.93 (0.81–1.07)	0.32
Myocardial infarction										
Published	86	0.72	89	0.74	63	0.53	1.35 (0.98–1.87)	0.07	1.38 (1.00–1.91)	0.048
Revised	98	0.82	97	0.81	75	0.64	1.29 (0.96–1.75)	0.09	1.27 (0.94–1.71)	0.12

* Data are shown for all patients who had at least one event. All analyses were based on the time to the first event. P values are for superiority. CI denotes confidence interval.

of the study period in which the warfarin INR was within the therapeutic range, from 64.2% to 64.4%.

Inclusion of the newly identified events did not materially change the study results, as shown in Table 1 (more detailed tables are provided in the Supplementary Appendix, available with the full text of this letter at NEJM.org). The study conclusions remain unchanged.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

1. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009; 361:1139-51.

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