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THE AUTHORS REPLY: Kühn alludes to myocyte division as a potential effect of NRG–ERBB signaling in the heart, and we agree that this possibility deserves investigation. Our summary of downstream effects of neuregulin in the heart was biased by the classic view of cardiac myocytes as terminally differentiated cells with limited proliferative capacity. As Kühn points out, there is evidence that subsets of cardiac myocytes may be able to reenter the cell cycle, and thus the heart may be capable of very slow cell turnover. Preclinical work from Kühn's laboratory has shown that rNRG1 can induce subsets of cardiomyocytes to undergo cell division through the ERBB4 receptor (see supplemental movie S1 in the article by Bersell et al.[1]). However, we know that these intrinsic systems are clinically inadequate for many patients with cardiac injury and chronic heart failure. Perhaps this relates to the progressive decline with age in proliferative capacity that has been reported recently.[2] It remains to be seen whether myocyte proliferation is at all related to the adverse effects of ERBB2-targeted cancer therapies or to the potential therapeutic effects of NRG in patients with heart failure.

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

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Antiplatelet and Anticoagulant Agents in Hereditary Hemorrhagic Telangiectasia

TO THE EDITOR: Hereditary hemorrhagic telangiectasia (HHT) leads to hemorrhage, particularly nosebleeds (epistaxis), because of vascular telangiectasia and arteriovenous malformations.[1] Thrombotic conditions, including venous thromboemboli and ischemic stroke, are relatively common in patients with HHT.[2,3] These emergencies are managed by clinicians who may not be very familiar with HHT. Current guidance on the use of antiplatelet and anticoagulant agents in HHT is based on anecdotal evidence and expert opinion.[4]

To evaluate the effects of antiplatelet and anticoagulant agents on hemorrhage in HHT, relevant questions were included as a subsection of a broad international survey (www.imperial.ac.uk/medicine/HHTsurvey2012) that was approved by the National Research Ethics Service East Midlands–Derby 1 Committee, United Kingdom.

The unbiased survey methods are reported elsewhere[5] and described in the Supplementary Appendix, available with the full text of this letter at NEJM.org. A total of 1302 persons responded to the online survey, including 973 with a diagnosis of HHT that was supported by sufficient diagnostic features in the survey. The ages of the respondents ranged from 14 to 89 years (median, 53.1), and 655 of 973 were female (67.3%).

Of the 973 respondents with HHT, 700 (71.9%) stated they had never used antiplatelet or anticoagulant agents. Of these 700 respondents, 381 (54.4%) reported that they were advised by a doctor not to use these agents because they had HHT (in 334 patients [87.7%]), they already had bleeding (in 191 patients [50.1%]), or they had an arteriovenous malformation (in 75 patients [19.7%]). Five respondents stated that treatment for myocardial infarction had been withheld from a rela-

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Table 1. Reported Effects of Antiplatelet and Anticoagulant Agents in 273 Patients with Hereditary Hemorrhagic Telangiectasia.*

Agent	Nosebleeds the Same		Nosebleeds Worse		Other Hemorrhage		No Other Hemorrhage	
	no. of patients/ total no.	*% (95% CI)*	*no. of patients/ total no.*	*% (95% CI)*	*no. of patients/ total no.*	*% (95% CI)*	*no. of patients/ total no.*	*% (95% CI)*
Antiplatelet agent								
Aspirin								
300 mg	28/80	35.0 (24.3 to 45.7)	52/80	65.0 (54.3 to 75.7)	4/78	5.1 (0.1 to 10.1)	74/78	94.9 (89.9 to 99.9)
75 mg	58/127	45.7 (36.9 to 54.5)	67/127	52.8 (44.0 to 61.6)	14/126	11.1 (5.6 to 16.7)	112/126	88.9 (83.3 to 94.5)
Other antiplatelet agents†	10/22	45.5 (22.9 to 68.1)	12/22	54.5 (32.0 to 77.1)	2/22	9.1 (–4.0 to 22.1)	20/22	90.9 (77.9 to 104.0)
Anticoagulant agent								
Heparin								
Subcutaneous	22/52	42.3 (28.4 to 56.2)	28/52	53.8 (39.8 to 67.9)	11/52	21.2 (9.7 to 32.6)	41/52	78.8 (67.4 to 90.3)
Intravenous	16/41	39.0 (23.4 to 54.6)	22/41	53.7 (37.7 to 69.6)	8/41	19.5 (6.9 to 32.2)	33/41	80.5 (67.8 to 93.2)
Warfarin	19/55	34.5 (21.6 to 47.5)	34/55	61.8 (48.6 to 75.1)	10/54	18.5 (7.8 to 29.2)	44/54	81.5 (70.8 to 92.2)
Dabigatran	0/2	0	2/2	1.0 (1.0 to 1.0)	0/2	0	2/2	1.0 (1.0 to 1.0)
All antiplatelet agents	96/229	41.9 (35.5 to 48.3)	131/229	57.2 (50.7 to 63.7)	20/226	8.8 (5.1 to 12.6)	206/226	91.2 (87.4 to 94.9)
All anticoagulant agents	57/150	38.0 (30.2 to 45.9)	86/150	57.3 (49.3 to 65.3)	29/149	19.5 (13.0 to 25.9)	120/149	80.5 (74.1 to 87.0)
All agents	153/379	40.4 (35.4 to 45.3)	217/379	57.3 (52.3 to 62.3)	49/375	13.1 (9.6 to 16.5)	326/375	86.9 (83.5 to 90.4)

* Some patients received more than one agent.

† Other antiplatelet agents were abciximab, clopidogrel, dipyridamole, prasugrel, ticlodipine, and tirofiban. Among patients who received both aspirin and clopidogrel, the number of patients who reported that nosebleeds were worse with aspirin than with clopidogrel was equal to the number of patients who reported that nosebleeds were worse with clopidogrel than with aspirin. Nine patients reported an improvement in nosebleeds associated with the following: aspirin at a dose of 75 mg (two patients), subcutaneous heparin (two patients), intravenous heparin (three patients), or warfarin (two patients).

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tive because of a diagnosis of HHT in the relative, and this had contributed to the relative's death.

A total of 273 participants with HHT (28.1%) reported the use of antiplatelet or anticoagulant therapy (Table 1). As expected, high proportions of participants reported worsening of nosebleeds (Table 1) that sometimes led to hospitalization, discontinuation of therapy, or both. Five respondents stated that treatment for myocardial infarction had led to hemorrhages that worsened the outcome in relatives with HHT who had later died.

It was surprising, however, that 153 of 379 patients with HHT who received antiplatelet or anticoagulant therapy (40.4%) reported no change in their nosebleeds. Nine of 379 patients (2.4%) reported an improvement in their nosebleeds (Table 1). Lower-dose aspirin (75 mg), heparin, and other anticoagulant agents appeared to aggravate nosebleeds less than higher-dose aspirin (300 mg) or warfarin (Table 1). In addition, more hemorrhagic events other than nosebleeds were reported by patients who received anticoagulant agents than by patients who received antiplatelet agents (19.5% vs. 8.8%) ($P=0.003$ by Fisher's exact test). Nevertheless, no change or an improvement in nosebleeds was reported by 43 of 93 patients who received heparin (46%) and by 21 of 55 patients who received warfarin (38%).

These data indicate unexplained and wide variation in the side effect profiles with respect to hemorrhage associated with the use of anticoagulant and antiplatelet therapies in patients with HHT. Lower-dose agents, particularly antiplatelet agents, did not appear to be associated with hemorrhage in high proportions of patients. These findings provide support for the use of antiplatelet or anticoagulant agents, with caution, in patients with HHT if there is a very strong indication for their use.

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