Rivaroxaban in Rheumatic Heart Disease–Associated Atrial Fibrillation

TO THE EDITOR: In the INVICTUS (Investigation of Rheumatic AF Treatment Using Vitamin K Antagonists, Rivaroxaban or Aspirin Studies) trial conducted by Connolly et al. (Sept. 15 issue),[1] a substanstial fraction of the trial population presented with nonvalvular atrial fibrillation (with moderate-to-severe mitral stenosis absent in 14.4% of patients). Moreover, 43.6% of the enrolled patients had a very low thromboembolic risk (as predicted by a CHA_2DS_2VASc score of <2; on a scale from 0 to 9, with higher scores indicating a higher risk of stroke), which prompts the question of whether oral anticoagulation was needed.[2] Thromboembolic events occurred much less frequently than anticipated, with an event rate of only 0.9% per year; however, of alarming importance, mortality within this young population (mean age, 50.5 years) was high (7.2% per year), with 65.0% of all deaths being caused by pump failure or sudden cardiac death. In addition, 38.5% of the enrolled patients presented with signs of heart failure at baseline. These findings give the impression that the preservation of ventricular function rather than stroke prevention is an important goal of therapy in this highly vulnerable, young patient population.

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

1. Connolly SJ, Karthikeyan G, Ntsekhe M, et al. Rivaroxaban in rheumatic heart disease–associated atrial fibrillation. N Engl J Med 2022;387:978-88.
2. Lip GYH, Collet JP, de Caterina R, et al. Antithrombotic therapy in atrial fibrillation associated with valvular heart disease: executive summary of a joint consensus document from the European Heart Rhythm Association (EHRA) and European Society of Cardiology Working Group on Thrombosis, endorsed by the ESC Working Group on Valvular Heart Disease, Cardiac Arrhythmia Society of Southern Africa (CASSA), Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), South African Heart (SA Heart) Association and Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología (SOLEACE). Thromb Haemost 2017;117:2215-36.

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TO THE EDITOR: The results of the INVICTUS trial are hard to understand on the basis of clinical and pathophysiological grounds. In this trial of anticoagulants, the incidence of bleeding was similar in the two treatment groups, with fewer fatal bleeding events in the rivaroxaban group than in the vitamin K antagonist group. Kaplan–Meier curves for death overlapped until month 20 after randomization and then diverged, with higher mortality in the rivaroxaban group than in the vitamin K antagonist group. Interestingly, curves for stroke or systemic embolism overlapped until much later (month 32), which suggests that stroke did not contribute to higher mortality. A sudden and steep change in the slope at that time resulted in increased risk of stroke with rivaroxaban (number needed to harm, 263 per year). Furthermore, the authors confirmed that the increase in mortality with rivaroxaban was not driven by a higher rate of embolism: "The difference in mortality was almost entirely due to lower rates of sudden cardiac death and of death due to mechanical or pump failure in the vitamin K antagonist group than in the rivaroxaban group." These are end points for which anticoagulants have an unproven effect. Reasons for the highly unusual change in slope for the stroke curve, requiring specific statistical handling,[1] and the effect of anticoagulants on sudden death and pump failure remain to be explained.

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

1. Andersen PK, Perme MP. Pseudo-observations in survival analysis. Stat Methods Med Res 2010;19:71-99.

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THE AUTHORS REPLY: Hammer and colleagues suggest that the almost 15% of patients in the INVICTUS trial with a mitral-valve area of more than 2 cm^2 had nonvalvular atrial fibrillation.

This is unlikely because rheumatic heart disease is typically a multivalvular heart disease,[1] and evidence of clinically significant echocardiographic rheumatic valve disease was required for trial entry. Furthermore, in this relatively young population, atrial fibrillation was probably due to the hemodynamic (elevated left atrial pressure) and structural (left atrial enlargement and fibrosis) consequences of valve disease and therefore is best not categorized as nonvalvular. Although the risk of stroke in this population of patients with well-controlled anticoagulation was low (approximately 1% per year), the estimated risk without anticoagulation therapy would probably be more than 2%,[2] which should be considered clinically relevant and would warrant the use of anticoagulation therapy. Nevertheless, we agree that given the high risk of death due to heart failure, the treatment of valve disease (with timely valve surgery or balloon interventions) is of primary importance in improving outcomes in these patients. The Kaplan–Meier curves crossed for the outcome of stroke or systemic embolism at approximately 12 months, plausibly because of the improvement in international normalized ratio in the vitamin K antagonist group. On the other hand, the favorable effect of vitamin K antagonist therapy on mortality, which began to emerge at about 18 months, is not easily explained. We agree with Providencia that the association of vitamin K antagonist therapy with mortality in rheumatic heart disease requires further study.

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

1. Zühlke L, Engel ME, Karthikeyan G, et al. Characteristics, complications, and gaps in evidence-based interventions in rheumatic heart disease: the Global Rheumatic Heart Disease Registry (the REMEDY study). Eur Heart J 2015;36:1115-1122a.
2. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med 2007;146:857-67.

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Chronic Urticaria

TO THE EDITOR: With respect to the review article on chronic urticaria by Lang (Sept. 1 issue),[1] angioedema may be of special interest. Bradykinin-mediated angioedema was not addressed in the review. This rare chronic hereditary urticaria mediated by bradykinin may be life-threatening, and treatments for this condition have been developed.[2] Clinicians may also see angiotensin-converting–enzyme (ACE) inhibitor–induced angioedema that does not respond to treatment with antihistamines and glucocorticoids.

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

1. Lang DM. Chronic urticaria. N Engl J Med 2022;387:824-31.
2. Cohn DM, Viney NJ, Fijen LM, et al. Antisense inhibition of prekallikrein to control hereditary angioedema. N Engl J Med 2020;383:1242-7.

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TO THE EDITOR: In the review article on chronic urticaria, Figure 3 describes stepped care. The author states that the information in this figure was synthesized from recommendations based on clinical guidelines. I respectfully disagree with the decision to include H_2-antihistamines and antileukotriene agents as adjunctive therapies in step 2 rather than using recent guidelines from a consensus group.[1] To my knowledge, the first publication regarding the use of H_2-antihistamines for the treatment of chronic urticaria was in 1978,[2] and that for the use of antileukotriene agents was in 1998.[3] A recent consensus