

# Letter to the Editor

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## Response by Di Tullio et al to Letter Regarding Article, “Left Ventricular Ejection Fraction and Risk of Stroke and Cardiac Events in Heart Failure: Data From the Warfarin Versus Aspirin in Reduced Ejection Fraction Trial”

### In Response:

In their interesting letter, Chen et al point out that there was no placebo arm in the WARCEF trial (Warfarin Versus Aspirin in Reduced Cardiac Ejection Fraction), preventing an estimation of stroke incidence without antithrombotic treatment and, therefore, of the benefit, if any, of such treatment for stroke prevention. Although this is true, it should be noted that some antithrombotic treatment is usually prescribed to patients with systolic heart failure, whether because of a previous myocardial infarction, and therefore the need of antiplatelet treatment for secondary prevention, or of past episodes of atrial fibrillation, which are frequent in heart failure and mandate systemic anticoagulation. Also, heart failure is associated with blood hypercoagulability,<sup>1,2</sup> and an ischemic, possibly embolic, mechanism is involved in the majority of strokes observed in patients with systolic heart failure,<sup>2</sup> both circumstances that make antithrombotic treatment a reasonable choice for stroke prevention in heart failure and that inspired the study design of WARCEF in the first place.<sup>3</sup> Although we agree that antithrombotic treatment should not be prescribed indiscriminately to all heart failure patients, we think that our article makes a significant contribution to the knowledge of the interaction between degree of left ventricular dysfunction, antithrombotic treatment, and stroke risk under real-world conditions, that is, in heart failure patients as they are encountered in clinical practice.

Chen et al advocate the creation of better stroke predictive tools in heart failure, to aid in the decision to initiate antithrombotic treatment. For this purpose, they suggest that the combination of CHA<sub>2</sub>DS<sub>2</sub>-VASC score and left ventricular ejection fraction (LVEF) <15% (cutoff of increased risk in the WARCEF trial) might produce an effective new prognostic model. The CHA<sub>2</sub>DS<sub>2</sub>-VASC score, initially developed to predict the stroke risk in patients with atrial fibrillation, has recently been used to predict outcomes in other conditions, including heart failure. Comprising powerful individual stroke risk factors (age, hypertension, diabetes mellitus, previous stroke or transient ischemic attack, presence of vascular disease), the CHA<sub>2</sub>DS<sub>2</sub>-VASC score is bound to be an effective stroke predictor in any patient population. However, as Chen et al point out, the CHA<sub>2</sub>DS<sub>2</sub>-VASC score was only modestly predictive of stroke in WARCEF.<sup>4</sup> The addition of extra points for especially low LVEF, perhaps by creating for LVEF a 2-tiered scoring system similar to that applied for age, might theoretically help refine the score's predictive power in heart failure patients. However, this hypothesis cannot be reliably tested in our study. In WARCEF, the LVEF cutoff of increased stroke risk (<15%) identified a subgroup of 219 patients, and only 14 of them experienced a stroke during the follow-up. This relatively small sample size and the low event rate preclude the possibility of obtaining reliable risk estimates when modeling LVEF as a 2-tiered variable in the predictive score.

Although we agree that more robust predictive models for stroke risk in heart failure may be desirable, we also think that one important contribution of the WARCEF trial was the demonstration that, in patients with systolic heart failure treated with currently recommended medical regimen, the stroke risk is remarkably low when any form of antithrombotic treatment is used, even though warfarin was superior to aspirin in this respect.<sup>3</sup> Our recent report further refines the information on stroke risk by narrowing it to patients with especially low LVEF<sup>5</sup>; this knowledge may be especially valuable in the present era, when an emphasis on individualized medicine and the wider use of newer antithrombotic agents may open the door to stroke-preventive strategies targeted to individual patients.

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### Disclosures

None.

#### Marco R. Di Tullio, MD

Department of Medicine  
Division of Cardiology  
Columbia University Medical Center  
New York

#### John L.P. Thompson, PhD

Department of Biostatistics  
Mailman School of Public Health  
Columbia University Medical Center  
New York

#### Shunichi Homma, MD

Department of Medicine  
Division of Cardiology  
Columbia University Medical Center  
New York

for the WARCEF Investigators

1. Lip GY, Gibbs CR. Does heart failure confer a hypercoagulable state? Virchow's triad revisited. *J Am Coll Cardiol*. 1999;33:1424–1426.
2. Haeusler KG, Laufs U, Endres M. Chronic heart failure and ischemic stroke. *Stroke*. 2011;42:2977–2982. doi: 10.1161/STROKEAHA.111.628479.
3. Homma S, Thompson JL, Pullicino PM, Levin B, Freudenberger RS, Teerlink JR, et al; WARCEF Investigators. Warfarin and aspirin in patients with heart failure and sinus rhythm. *N Engl J Med*. 2012;366:1859–1869. doi: 10.1056/NEJMoa1202299.
4. Ye S, Qian M, Zhao B, Buchsbaum R, Sacco RL, Levin B et al. CHA<sub>2</sub>DS<sub>2</sub>-VASC score and adverse outcomes in patients with heart failure with reduced ejection fraction and sinus rhythm. *Eur J Heart Fail*. 2016;18:1261–1266. doi: 10.1002/ehf.613.
5. Di Tullio MR, Qian M, Thompson JL, Labovitz AJ, Mann DL, Sacco RL, et al; WARCEF Investigators. Left ventricular ejection fraction and risk of stroke and cardiac events in heart failure: data from the warfarin versus aspirin in reduced ejection fraction trial. *Stroke*. 2016;47:2031–2037. doi: 10.1161/STROKEAHA.116.013679.

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Marco R. Di Tullio, John L.P. Thompson, Shunichi Homma and for the WARCEF Investigators for the WARCEF Investigators

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