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Response to Letter Regarding Article, "N-terminal pro-B-type natriuretic peptide and stroke risk: the REasons for Geographic And Racial Differences in Stroke cohort"

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Galyfos provides valid points regarding utility of biomarkers for stroke in older versus younger people and men versus women. Indeed it is necessary to determine whether results differ by important subgroups in evaluation of the clinical utility of any risk prediction tool. Increasingly, public health organizations like the American Heart Association (AHA) are publishing science that addresses these issues, as the authors point out. AHA has published a guideline on cardiovascular disease prevention in women since 2004, and for the first time this year, a guideline specifically on prevention of stroke in women[1] pointed out gaps in the literature, including a need for research on sex-specific stroke risk factors and development of a risk score for stroke in women. Similarly, risk factors for cardiovascular disease may change with aging in terms of their prevalence and importance.

Our recently published study was a prospective study that showed that higher baseline N-terminal pro-B-type natriuretic peptide (NT-proBNP) was associated with a substantial increase in stroke risk over 5.4 years; adjusted hazard ratio for the top quintile 2.9 (95% CI 1.9-4.5) for overall stroke and 9.1 (95% Ci 2.9-29.2) for cardioembolic stroke[2]. Subjects were 546 subjects with ischemic stroke and 956 without stroke from the 30,239-person Reasons for Geographic and Racial Differences in Stroke (REGARDS) cohort. The age range was 45 and older (nearly ½ age 65 and older and >2000 were above 80). As we reported, there were no differences in the association of NT-proBNP by age or sex (interaction p values 0.14 and 0.31 respectively). Similarly, there were no differences in the association of NT-proBNP with stroke risk by sex in the Atherosclerosis Risk in Communities study, which reported hazard ratios similar to REGARDS and included 507 strokes (p interaction for sex and NT-proBNP >0.30)[3]. In Heinz Nixdorf Recall study, highlighted by Galyfos, indeed there was a weaker association of baseline BNP and stroke in women, but the hazard ratio was increased (1.85 per log 10 higher BNP; 95% CI 0.74-4.65)

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and analysis was based on only 36 stroke events. The hazard ratio in men was 3.07; (95% CI 1.52-6.21) with 53 events. An interaction p value was not reported so it is unclear whether the association truly differs by sex in that cohort. Given the data, in order to determine whether there are clinically important differences in the association of NT-proBNP with stroke by age or sex (or other factors), an individual level participant meta-analysis combining data from many prospective cohort studies would be very useful.

As research emerges on strong associations of NT-proBNP with risk of vascular diseases, we agree with Galyfos that further research is needed to determine if measurement of NT-proBNP is a useful adjunct to risk prediction scores for stroke and other vascular diseases, and this work should address diverse populations based on age and sex. We also point out that consideration of race-ethnicity is also crucial. The AHA and American College of Cardiology recently published a guideline on risk prediction of cardiovascular events, including stroke, that provided for the first time, sex- and race-specific estimates of cardiovascular disease risk for African-American and white men and women 40 to 79 years of age[4]. This is a great first step along the lines of what Galyfos calls for. Much more work is needed.

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