Despite increased awareness and advances in resuscitation methodology, the average national survival from sudden cardiac arrest in North America remains 4.5%, ranging from 1.1% in the state of Alabama to 8.1% in Seattle, Wash.\(^1\) Given this 95% probability of instantaneous death once cardiac arrest occurs, the pursuit to identify effective preventive interventions must be unrelenting. The implantable cardioverter-defibrillator has been an effective modality that treats the crisis, but methodologies for effective risk stratification of the actual condition continue to elude us.\(^2\) The left ventricular ejection fraction can be a reasonable means of risk stratification in a subgroup of sudden cardiac death (SCD) patients but is clearly an inadequate predictor of overall risk.\(^3\)

Some mechanisms of SCD risk are likely to overlap between men and women,\(^4\) but there is growing evidence to suggest that there may also be sex-specific pathways leading to ventricular arrhythmogenesis.\(^5,6\) A recent study in a Medicare population sample (1991 to 2005) found that men were significantly more likely to undergo cardioverter-defibrillator implantation for both primary and secondary prevention of SCD (hazard ratio 3.15, 95% confidence interval 2.86 to 3.47, respectively),\(^7\) and this disparity between the sexes has also been reported in 2 other studies.\(^8,9\) Therefore, the identification of sex-specific SCD mechanisms is a crucial element in the quest for enhancing risk stratification.

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B-type natriuretic peptide (BNP) is preferentially synthesized and secreted from the ventricles (as opposed to the atria) but can be secreted from either chamber in the setting of cardiac disease.\(^10\) BNP is released as a response to pressure and volume overload, cleaved first to proBNP1–108, then to the biologically active BNP1–32 and the inactive amino-terminal fragment (NT-proBNP).\(^11\) Overall, the regulatory effect of BNP causes myocardial relaxation by counteracting the acute increases in ventricular volume brought about by the vasoconstriction and sodium retention effects of the activated renin-angiotensin-aldosterone system.\(^12\) Existing studies have been performed using either BNP and NT-proBNP measurements. Levels of both appear to be reasonably correlated, although absolute values are not interchangeable.\(^11\) Several published studies have reported the utility of BNP and NT-proBNP in predicting SCD, but all of these studies were performed in high-risk patients with heart failure or recipients of implantable defibrillators.\(^13,14\) Serum levels of C-reactive protein (CRP), a marker of systemic inflammation, have also been reported to predict risk of SCD in a study of apparently healthy men and in the implantable defibrillator population.\(^14,15\)

The article by Korngold and colleagues in the current issue of *Circulation* has refocused attention on NT-proBNP as a predictor of sudden death in the context of the overall population.\(^16\) They performed a prospective nested case-control analysis within the Nurses Health Study (121 700 participants, all women). A total of 99 participants met criteria for either definite or probable SCD and were matched to 294 control subjects from the same study. When subjects were divided into quartiles based on control serum levels of NT-proBNP measured in the study at time of enrollment, rates of SCD were 2-fold higher in the highest versus lowest quartiles (RR 2.37, *P*=0.05) when adjusted for coronary disease risk factors and biomarkers. However, there were no differences identified for high-sensitivity CRP (hsCRP) levels. Findings were similar when these 2 markers were analyzed as continuous variables. NT-proBNP levels above a prespecified cut point of 389 pg/mL were predictive of a 5-fold increased risk of SCD after adjustment for coronary disease risk factors and biomarkers (RR=5.68; 95% CI, 1.78 to 18.2; *P*=0.003). The prespecified clinical cut point for hsCRP levels (>3.0 mg/L) did not predict increased risk of SCD. Another finding of interest was that women who suffered SCD were more likely to be taking aspirin.

The authors have acknowledged the limitations of their analysis, including the selective nature of the cohort as well as the availability of a single baseline measurement of NT-proBNP levels. Another limiting factor is that, because the mean time to SCD was 10 years, the event may have occurred as long as 16 years after measuring baseline levels. BNP is secreted in response to increased ventricular wall stress as well as ventricular dilatation and dysfunction. Given that BNP is an established marker of worsening heart failure, it is conceivable that at least some in the high BNP group may have had asymptomatic or symptomatic LV dysfunction at baseline or in the interim. Evaluations of cardiac structure and function as well as heart failure diagnosis were not available, so these data do not provide us information on the relative distribution of LV size, LV hypertrophy, and systolic/diastolic dysfunction among those with NT-proBNP over 389 mg/L. Since NT-proBNP is secreted to counteract increased LV
wall stress, it may possibly reflect a propensity for myocardial stretch–related arrhythmogenesis even in the absence of overt LV dysfunction or heart failure. The higher use of aspirin among women who suffered SCD could be related to an imbalance in the specific kind of cardiovascular disease (myocardial infarction/angina/coronary artery bypass grafting versus stroke) or may indicate a primary myocardial arrhythmogenic mechanism for sudden death as opposed to coronary plaque rupture and thrombosis.

What are the implications of these interesting findings? NT-proBNP levels, even in asymptomatic individuals in the general population, appear to be predictive of future SCD. Because the Nurses Health Study only enrolled white women, a similar analysis is required in men before we can know whether this is a sex-specific marker for SCD risk in the general population, along with evaluation of relevance in nonwhite populations. Also, given that these findings may have been driven by a relatively small number of women with NT-proBNP levels over the cutoff value of 389 mg/L, they need to be confirmed in a larger population. A study population providing data on LV function and size, and other conditions associated with increased BNP levels such as renal failure, could help elucidate the usefulness of BNP as a predictor of SCD risk in conjunction with these clinical conditions. On the other hand, the negative findings with regard to hsCRP levels do suggest that this marker may have importance for men but not women. Overall, these findings contribute to a growing body of literature that will allow us to extend beyond the ejection fraction and enhance risk stratification for SCD.

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References

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