Predicting stroke mortality

BNP could it be?

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Physicians, patients, and families rely on clinical factors associated with stroke mortality to guide decisions of care and set goals of medical therapy. However, these factors, including age and baseline neurologic impairment, are at best imperfect predictors and additional prognostic tools are needed.[1] Biomarkers such as B-type natriuretic peptide (BNP) have potential. However, for a biomarker to be of clinical utility, it needs to add information beyond what clinical predictors can provide. BNP is produced by myocardial tissue in response to strain and acts to reduce systolic blood pressure through vasodilation and natriuresis. In stroke, BNP has been associated with increased mortality.[2]

In this issue of *Neurology*®, García-Berrocoso et al.[3] describe their meta-analysis of 16 studies (3,498 participants) to evaluate the association of BNP with stroke mortality and determine whether adding this blood biomarker improves clinical prediction of stroke mortality. Each study measured levels of BNP or the inactive N-terminal fragment of BNP (NT-proBNP) in patients with ischemic stroke, TIA, or hemorrhagic stroke. All-cause mortality was associated with an increase in both BNP and NT-proBNP, although analysis indicated a publication bias of positive data. Individual patient data were available from 10 of the 16 studies (n = 2,258). After adjustment for NIH Stroke Scale (NIHSS) score, age, and sex, both BNP (odds ratio 2.30, 95% confidence interval 1.32–4.01, $p = 0.003$) and NT-proBNP (odds ratio 2.63, 95% confidence interval 1.75–3.94, $p < 0.001$) levels were associated with stroke mortality. Stroke subtype and time from stroke onset to death did not affect the associations with mortality. However, only NT-proBNP added to clinical predictors of stroke mortality, reclassifying 8.1% of patients into more accurate mortality risk groups.

Why BNP should predict mortality in stroke remains unclear. Increases in BNP suggest left ventricular dysfunction, with increasing levels associated with severity of cardiac dysfunction on the New York Heart Association classification system. In practice, BNP levels are useful to rule out heart failure with reasonably high sensitivity (>90% at 100 pg/mL).[4] One might assume that increased levels of BNP observed in stroke reflect cardiac disease. Indeed, BNP is increased in patients with cardioembolic stroke and associated with worse stroke outcome.[5,6] In the current study, levels of BNP were increased in cardioembolic compared with noncardioembolic stroke among stroke survivors but not among those who died. This suggests that patients with ventricular strain, regardless of stroke cause, have increased mortality. Unfortunately, data regarding cardiac function were not available from all studies and cause of stroke was only available for half of the study subjects. Thus, additional evaluation will be required.

The ability of BNP to predict mortality after stroke may relate to disease other than stroke. Renal failure is associated with increased levels of BNP,[7] and NT-proBNP is an independent predictor of mortality in kidney disease. BNP also predicts mortality in diabetes,[8] cardiac surgery patients,[9] and nursing home residents.[10]

The current study demonstrates that NT-proBNP can reclassify 8.1% of stroke subjects into more accurate mortality risk groups. Whether this is clinically meaningful requires some consideration. The risk reclassification analysis compared the ability to predict stroke mortality using clinical factors alone (NIHSS score, age, sex) vs clinical factors combined with BNP or NT-proBNP. The 8.1% net reclassification reported for NT-proBNP was predominantly achieved by shifting stroke patients predicted to have high mortality risk by clinical factors into lower risk mortality categories (figure). Thus, there may be a subset of stroke patients in whom a low NT-proBNP may be useful to help determine mortality risk, particularly in those whose age, NIHSS score, and sex predict high mortality. However, additional studies must evaluate utility to predict not only survival but also poor functional outcome.

Strengths of the study include large sample size, evaluation of the relationship between clinical predictors and BNP to predict stroke mortality, and analysis of individual patient data that permitted consideration

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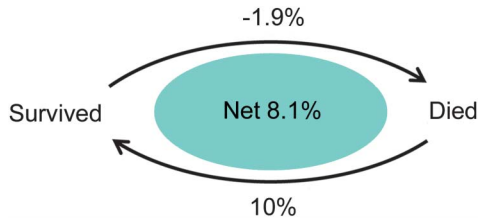
Figure **Net reclassification of stroke mortality achieved by the addition of NT-proBNP to clinical factors**



NT-proBNP shifted 10% of stroke patients from a predicted category of high risk of death to the correct category of survived. However, 1.9% of patients that survived were incorrectly predicted to belong to a high-risk mortality group. This resulted in a net reclassification of 8.1% of patients. NT-proBNP = N-terminal fragment of B-type natriuretic peptide.

of several covariates. However, there were a number of variables that were not available that may affect BNP, such as measures of cardiac and renal function. In addition, the cause of death could not be specifically analyzed because only all-cause mortality data were available. One might expect that BNP would be most predictive of cardiovascular death in patients with stroke, although this requires additional study. Finally, levels of NT-proBNP and BNP were variable among compared studies. Thus, standardized methods to measure BNP and NT-proBNP may improve the ability of these markers to predict stroke mortality in future studies.

This study provides support for the use of biomarkers to aid in the prediction of stroke mortality. However, NT-proBNP showed minor added value over clinical predictors. Thus, the need to better predict mortality after stroke remains. Potentially, NT-proBNP combined with other markers in a panel may be able to improve prediction. However, for the time being, clinical predictors should be the main factors relied on to estimate stroke mortality and provide prognostic information to patients and families.

AUTHOR CONTRIBUTIONS

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