Prediction of Heart Failure by Amino Terminal-pro–B-Type Natriuretic Peptide and C-Reactive Protein in Subjects With Cerebrovascular Disease

Duncan J. Campbell, Mark Woodward, John P. Chalmers, Samuel A. Colman, Alicia J. Jenkins, Bruce E. Kemp, Bruce C. Neal, Anushka Patel, Stephen W. MacMahon

Abstract—B-type natriuretic peptide (BNP) and C-reactive protein (CRP) are elevated in persons at risk for congestive heart failure (CHF). However, limited data are available directly comparing BNP-related peptides and CRP in persons at risk of CHF. To evaluate amino terminal–pro–BNP (NT-proBNP) and CRP, separately and together, for assessment of risk of CHF, we performed a nested case-control study of the 6105 participants of the Perindopril PROtection aGainst REcurrent Stroke Study (PROGRESS), a placebo-controlled study of a perindopril-based blood pressure–lowering regimen among individuals with previous stroke or transient ischemic attack (TIA). Each of 258 subjects who developed CHF resulting in death, hospitalization, or withdrawal of randomized therapy during a mean follow-up of 3.9 years was matched to 1 to 3 control subjects. NT-proBNP and CRP predicted CHF; the odds ratio for subjects in the highest compared with the lowest quarter was 4.5 (95% confidence interval, 2.7 to 7.5) for NT-proBNP and 2.9 (confidence interval, 1.9 to 4.7) for CRP, and each remained a predictor of CHF after adjustment for all other predictors. Screening for both markers provided better prognostic information than screening for either alone. Elevation of NT-proBNP above 50 pmol/L and CRP above 0.84 mg/L predicted CHF with sensitivity of 64% and specificity of 66%. NT-proBNP and CRP predicted CHF in subjects receiving perindopril-based therapy. We conclude that NT-proBNP and CRP are independent predictors of CHF risk after stroke or TIA. Moreover, NT-proBNP and CRP may be markers of mechanisms of CHF pathogenesis distinct from those responsive to angiotensin-converting enzyme inhibitor–based therapy. (Hypertension. 2005;45:69-74.)

Key Words: heart failure | natriuretic peptides | cerebrovascular disorders | stroke | renin

B-type natriuretic peptide (BNP) is synthesized as a high molecular weight precursor, proBNP, which is cleaved to release BNP and the amino-terminal fragment NT-proBNP, and both peptides are released from the cardiac ventricles in response to increased wall stress.1 C-reactive protein (CRP) is released from the liver in response to inflammation.2 BNP-related peptides and CRP are elevated in congestive heart failure (CHF), and the levels correlate with symptom severity and prognosis.3–8 Additionally, elevated CRP level predicts risk of CHF,9–11 and recently, Wang et al12 reported BNP level predicts risk of death and cardiovascular events, including CHF, in an asymptomatic population. However, limited data are available directly comparing CRP and BNP-related peptides in persons at risk of CHF.13

We evaluated the prognostic performance of NT-proBNP and CRP in a population with cerebrovascular disease and increased risk of CHF by conducting a nested case-control study of 258 subjects who developed CHF and 516 control subjects who did not develop CHF, who were participants in the Perindopril PROtection aGainst REcurrent Stroke Study (PROGRESS). PROGRESS was designed to determine the effects of active therapy with a perindopril-based blood pressure–lowering regimen on the risks of stroke and other major vascular events among individuals with a stroke or transient ischemic attack (TIA) within the previous 5 years.14–16 This regimen substantially reduced the risk of stroke by 28% and myocardial infarction by 38%,14,16 as well as decreasing CHF incidence by 26%.16 We therefore, in addition, investigated whether NT-proBNP and CRP predicted CHF in subjects receiving perindopril-based therapy.
pants assigned placebo was 4.9% over a mean of 3.9 years, or per year.16 The design of PROGRESS has been described in detail previously.14–16 Briefly, 6105 participants were recruited from 172 participating centers in 10 countries from Australasia, Europe, and Asia between 1995 and 1997. Participants were randomized to either placebo (n = 3054) or active therapy (n = 3051), comprising a flexible regimen based on the angiotensin-converting enzyme (ACE) inhibitor perindopril (4 mg daily), with the addition of the diuretic indapamide at the discretion of treating physicians. The institutional ethics committee of each collaborating center approved the trial, and all participants provided written informed consent. Individuals were potentially eligible if they had a history of cerebrovascular disease and were at high risk of coronary heart disease, or CHF, was routinely recorded. All out-comes were coded according to the ninth revision of the International Classification of Diseases (ICD-9). CHF, because of any underlying cause, was defined as that resulting in death, hospitalization, or requiring withdrawal of randomized therapy (ICD-9 codes 428.0, 428.1, 428.9, 402.01, 402.11, 402.91, and 398.91).16 All deaths and potential strokes and myocardial infarctions were independently adjudicated, and other end points were determined by local study investigators on the basis of clinical findings and investigations.16 Details of biochemical analyses and statistical analyses are given in the data supplement available online at http://www.hypertensionaha.org.

Methods
Patients and Study Protocol
We conducted a prospective nested case-control analysis among PROGRESS participants who were predominantly elderly population with cerebrovascular disease and were at high risk of coronary events and CHF.16 The incidence of CHF in PROGRESS participants assigned placebo was 4.9% over a mean of 3.9 years, or 1.3% per year.16 The design of PROGRESS has been described in detail previously.14–16 Briefly, 6105 participants were recruited from 172 collaborating centers in 10 countries from Australasia, Europe, and Asia between 1995 and 1997. Participants were randomized to either placebo (n = 3054) or active therapy (n = 3051), comprising a flexible regimen based on the angiotensin-converting enzyme (ACE) inhibitor perindopril (4 mg daily), with the addition of the diuretic indapamide at the discretion of treating physicians. The institutional ethics committee of each collaborating center approved the trial, and all participants provided written informed consent. Individuals were potentially eligible if they had a history of cerebrovascular disease (ischemic stroke, hemorrhagic stroke, or TIA, but not subarachnoid hemorrhage) within the previous 5 years, and no clear indication for, or contraindication to, ACE inhibitor treatment. CHF was a study exclusion criterion.

Before randomization, information was collected about history of vascular disease, other vascular risk factors, and current medications.14–16 Blood samples were collected (nonfasting, 10 mL into heparin and 10 mL into EDTA vacuum tubes) from 5918 of the 6105 subjects at enrollment before the run-in phase of the study, at which time none of the subjects were receiving ACE inhibitor or angiotensin receptor blocker therapy. After randomization, participants were scheduled to be seen on 5 occasions in the first year and every 6 months thereafter until the end of the scheduled follow-up period or death. The mean follow-up was 3.9 years. Information on all serious adverse events, including those resulting from stroke, coronary heart disease, or CHF, was routinely recorded. All out-

<table>
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<tr>
<th>Variable</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
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<tbody>
<tr>
<td>NT-proBNP (pmol/L)</td>
<td>Mean</td>
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<td>14.1</td>
<td>33.6</td>
<td>144.4</td>
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<tr>
<td>Range</td>
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<td>20.6–52.9</td>
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<td>Model 1</td>
<td>Odds ratio</td>
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<td>3.06</td>
<td>4.48</td>
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<td>95% Confidence interval</td>
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<td>1.89–4.96</td>
<td>2.69–7.46</td>
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<tr>
<td>CRP (mg/L)</td>
<td>Mean</td>
<td>0.73</td>
<td>1.8</td>
<td>3.9</td>
<td>14.2</td>
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<tr>
<td>Range</td>
<td>0.1–1.25</td>
<td>1.26–2.48</td>
<td>2.5–5.81</td>
<td>5.83–92.3</td>
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<td>95% confidence interval</td>
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Model 1 is not adjusted, except through matching.
Model 2 is adjusted through matching and also for baseline systolic blood pressure, body mass index, HDL cholesterol, creatinine, a history of coronary heart disease, atrial fibrillation, valvular heart disease, peripheral arterial disease, left ventricular hypertrophy on ECG, and diabetes, therapy with oral anticoagulants and antiplatelet agents, and CRP or NT-proBNP.

Results
The baseline clinical and biochemical characteristics of the 258 CHF cases and 516 controls without CHF are given in the table in the online data supplement. Subjects who developed CHF had higher baseline systolic blood pressure and body mass index, were more likely to have a history of coronary heart disease, atrial fibrillation, valvular heart disease, left ventricular hypertrophy on ECG, peripheral arterial disease, and diabetes, and to be taking oral anticoagulants and antiplatelet agents. In addition, CHF cases had lower baseline HDL cholesterol and higher creatinine, NT-proBNP, and CRP level.

The odds ratio for CHF increased progressively with increasing baseline levels of NT-proBNP and CRP; for subjects in the highest compared with the lowest quarter, the odds ratio was 4.5 (95% confidence interval, 2.7 to 7.5) for NT-proBNP and 2.9 (95% confidence interval, 1.9 to 4.7) for CRP (Table). The cumulative incidence of CHF over time was approximately linear for each quarter of NT-proBNP and CRP (Figure 1). NT-proBNP and CRP remained independent
predictors of CHF in multiple-variable analysis (Table, model 2), and their combination had a multiplicative effect on the odds ratio for CHF such that individuals with NT-proBNP and CRP in the highest quarter had a 9-fold higher risk of CHF than subjects with both biologic markers in the lowest quarter (Figure 2). Other variables that were predictors after multiple-variable analysis were body mass index \((P<0.0003)\) and history of coronary heart disease \((P=0.0048)\), atrial fibrillation \((P=0.0273)\), peripheral arterial disease \((P=0.0497)\), and diabetes \((P=0.0226)\).

Interim cardiovascular events between randomization and onset of CHF in the index case occurred in 38% of cases and in 21% of control subjects \((P<0.0001)\). Cases were 3.5-fold more likely to experience an interim cardiac event (28% versus 7.9%; \(P<0.0001)\), comprising predominantly myocardial infarction (17% versus 2.9%; \(P<0.0001)\) and hospitalization because of unstable angina (13% versus 4.3%; \(P<0.0001)\). Similar proportions of cases and controls had interim coronary artery bypass grafts (3.1% versus 2.1%; \(P=0.41)\) and percutaneous coronary intervention (3.1% versus 2.25% \(P=0.06)\). Stroke occurred in a similar proportion of cases and controls (17% versus 16%; \(P=0.13)\).

Calculation of receiver operating characteristic (ROC) curves showed the combination of NT-proBNP and CRP provided better prognostic information than either biologic marker alone. Whereas there was borderline statistically significant difference between the areas under the curve for NT-proBNP \((0.668; 95\% \text{ confidence interval, 0.628 to 0.709)}\) and CRP \((0.617; 95\% \text{ confidence interval, 0.576 to 0.658}; P=0.06)\), the mean area for the combination of NT-proBNP and CRP \((0.692; \text{ confidence interval, 0.653 to 0.732})\) was higher than that for NT-proBNP \((P=0.01)\) and CRP alone \((P<0.0001)\). For CRP alone, the optimal threshold was 2.8 mg/L, achieving a sensitivity of 59% and specificity of 60% for CHF prediction. For NT-proBNP alone, the optimal threshold was 22 pmol/L, achieving a sensitivity of 64% and specificity of 63% for CHF prediction. For combined NT-proBNP and CRP, the global optima were 50 pmol/L for NT-proBNP and 0.84 mg/L for CRP, achieving a sensitivity of 64% and specificity of 66%.

The 26% reduction in CHF incidence by active treatment was similar across all quarters of NT-proBNP and CRP (data not shown). NT-proBNP level, measured in plasma samples obtained at the study baseline, before commencement of randomized therapy, was associated with similarly increased CHF risk in subjects assigned to placebo and active therapy (Figure 3). Plasma CRP level was also associated with increased CHF risk.
in subjects assigned to active therapy but not in subjects assigned to placebo, although the wide confidence intervals do not exclude such an association (Figure 3).

Discussion

NT-proBNP and CRP were independent predictors of CHF risk, and each marker provided information incremental to that obtained from established risk factors. In addition, baseline plasma levels of these 2 markers predicted CHF risk in subjects assigned to perindopril-based therapy who had 26% lower CHF incidence during a mean 3.9 years of follow-up.16

The optimal threshold NT-proBNP levels for prediction of CHF from ROC curve analysis of NT-proBNP alone (22 pmol/L) and from NT-proBNP and CRP in combination (50 pmol/L) were within the range currently regarded as normal.5,17,18 Median NT-proBNP levels from population studies approximate 33 pmol/L,5,17 although a lower median of 16 to 19 pmol/L is reported for healthy subjects without a history or symptoms of heart disease or other chronic disease.17,18 Wang et al12 similarly found BNP levels within a range currently regarded as normal were associated with an increased risk of CHF. The optimal threshold CRP levels for prediction of CHF from ROC curve analysis of CRP alone (2.8 mg/L) and from NT-proBNP and CRP in combination (0.84 mg/L) were also within the range currently regarded as normal. CRP values are categorized as low (<1 mg/L), average (1 to 3 mg/L), and high (>3 mg/L), with respect to risk of cardiovascular disease.2 Whereas previous studies found high CRP levels (>3 mg/L) predicted CHF,9–11 we found low and average CRP levels predict CHF, similar to the levels shown to predict ischemic heart disease.19,20 When measured after an acute coronary event, BNP-related peptides and CRP, separately and together, predict mortality and heart failure.13,21

Although a large proportion of CHF incidence can be attributed to known risk factors,22 many aspects of CHF pathogenesis are uncertain.23 We observed a 3.5-fold higher incidence of interim cardiac events in cases than controls, but most cases (72%) did not have an interim cardiac event before CHF onset. Active therapy reduced CHF incidence by 26%, indicating that a proportion of CHF incidence in PROGRESS participants assigned placebo was attributable to mechanisms responsive to this therapy; however, a larger proportion of CHF incidence was attributable to mechanisms unresponsive to this therapy. Our finding that NT-proBNP and CRP predicted CHF risk in subjects receiving perindopril-based therapy suggests NT-proBNP and CRP are markers of mechanisms of CHF pathogenesis distinct from those responsive to this therapy. Moreover, their independent prediction of CHF suggests they may be markers for separate mechanisms of CHF pathogenesis. Elevated NT-proBNP levels may indicate ventricular strain,1 whereas elevated CRP levels may indicate inflammatory processes,2 and these markers may contribute to identification of the pathogenic mechanisms they represent and thereby assist the development of novel therapies for the prevention and treatment of CHF.

Study Limitations

The potential limitations of these data merit consideration. First, our analyses are based on single baseline determinations that may not accurately reflect NT-proBNP and CRP levels over the mean of 3.9 years follow-up. Furthermore, whereas deaths attributable to CHF were adjudicated, hospitalization or withdrawal of randomized therapy because of CHF was determined by local study investigators on the basis of clinical findings and investigations, which may have caused lack of precision in diagnosis of CHF. However, it is important to note that neither of these sources of variability can account for the observed associations because any ran-
dom misclassification would bias results toward the null hypothesis. The PROGRESS protocol stipulated CHF to be a serious adverse event, and all participants were assessed for CHF at every visit, in accordance with the European Society of Cardiology guidelines that require symptoms to make the diagnosis.24

Our nested case-control design was matched for 5 baseline variables, but we were unable to match for all predictors of CHF, such as known cardiac disease, because of difficulties matching for >5 variables; however, we were able to adjust for these baseline predictors of CHF in our multiple variable analyses (Table, model 2). Another potential limitation was the lack of echocardiographic assessment of cardiac function at baseline to identify subjects with asymptomatic cardiac dysfunction. It is unlikely that subjects with elevated NT-proBNP had undiagnosed CHF at baseline because the cumulative incidences of CHF for different NT-proBNP quarters were approximately linear over time (Figure 1). There was no evidence of a plateau in CHF incidence in subjects with high NT-proBNP level or a lag in CHF incidence in subjects with a low NT-proBNP level.

Although echocardiographic evidence of cardiac dysfunction is an independent risk factor for CHF and cardiac death,25–27 a prospective study showed most incident cases of CHF have normal echocardiography at baseline.26 Studies of patients with symptomatic cardiac disease indicate that BNP and NT-proBNP levels are markers of increased ventricular strain, typically from pressure or volume overload.3,4,28,29 Elevated NT-proBNP in asymptomatic subjects probably reflects similar processes, but manifestations of this strain may be subtle and the underlying causes less apparent. In the study of Wang et al.,12 the association of BNP and risk of CHF in a community population persisted after adjustment for echocardiographic measurements of left ventricular mass and systolic function, suggesting that slight elevations of BNP may reflect either very early stages of pathologic processes that precede the development of CHF or diastolic dysfunction.30

Perspectives
The lifetime risk of developing CHF for those aged 40 years is 20% for men and women31 and exceeds the lifetime risk of many conditions commonly screened for in the community. Currently, >15 million patients have CHF in North America and Europe, with nearly 1.5 million new cases every year.24,25,32 Measurement of plasma levels of NT-proBNP and CRP may enable improved prediction of CHF risk and thereby assist earlier implementation of prevention strategies. Moreover, characterization of the mechanisms of CHF pathogenesis associated with elevated NT-proBNP and CRP levels may lead to development of therapies that provide additional benefits to those provided by current therapies for CHF and its prevention.

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