

ORIGINAL ARTICLES

Predicting Outcome in Patients with Acute Coronary Syndrome: Evaluation of B-Type Natriuretic Peptide and the Global Registry of Acute Coronary Events (GRACE) Risk Score

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Abstract

Background

Accurate risk stratification soon after admission for patients with acute coronary syndromes (ACS) is vital in guiding management. Clinical risk scores and B-type natriuretic peptide (BNP) can predict mortality and re-infarction in ACS, but it is unknown whether BNP provides prognostic information over and above that of the clinical risk scores.

Methods

142 unselected patients with ACS were prospectively studied. BNP was measured and patients were stratified according to BNP and Global Registry of Acute Coronary Events (GRACE) score. In-hospital and 30-day events were characterised.

Results

20.4% of ACS subjects had ST-elevation myocardial infarction (MI), 14.1%, non-ST elevation MI and 65.5% unstable angina. Elevated BNP predicted in-hospital and 30-day heart failure ($p < 0.01$), and the risk of in-hospital recurrent ACS ($p < 0.05$). Increasing GRACE score predicted in-hospital recurrent ACS ($p < 0.05$), heart failure ($p < 0.001$), arrhythmias ($p < 0.05$) and angioplasty ($p < 0.05$). GRACE score also predicted 30-day heart failure ($p < 0.05$). In contrast, the predictive accuracy of troponin elevation was less robust.

Conclusion

BNP and the GRACE score predict complementary outcomes from ACS, but both predicted heart failure. BNP is a powerful indicator of heart failure in patients with ACS and provides prognostic information above and beyond conventional biomarkers and risk scores.

Introduction

Acute coronary syndrome (ACS) encompasses a clinical spectrum from unstable angina (UA), through non-ST segment elevation myocardial infarction (NSTEMI) to ST-segment elevation myocardial infarction (STEMI).¹ Although these components of ACS share certain pathophysiological mechanisms, outcomes differ, and accurate risk stratification is critical in guiding the choice of therapy. Trial evidence and guidelines suggest that certain therapies should be restricted to higher risk patients (eg GP IIb/IIIa inhibitors, revascularisation).

Despite current treatment, 3-8% of patients with ACS die in hospital.² In the month following discharge, 10-20% of patients die or are readmitted with recurrent myocardial infarction (MI),³ and 5% go on to develop congestive heart failure (CHF).⁴ Current risk prediction based simply on clinical, electrocardiogram (ECG) and biochemical markers is relatively inaccurate.⁵ Recently, it has been hypothesised that B-type natriuretic peptide (BNP) may provide additional prognostic information in ACS, but analyses have been restricted to trial populations, rather than unselected patients.

BNP is synthesised in the ventricular myocardium.⁶ Its secretion is stimulated by ventricular wall tension, stretch⁷ or hypoxia⁸ and the peptide acts as a potent natriuretic, diuretic and vasorelaxant.⁹ After acute MI, BNP is released in a biphasic pattern, with peaks at 16 hours and 5 days.¹⁰ In retrospective trial populations, BNP predicts mortality at 30 days¹¹ and 1 year¹² after STEMI.

In addition to biomarkers of myocardial necrosis, multivariable prognostic models are increasingly used in the diagnosis and management of patients with ACS. The Global Registry of Acute Coronary Events (GRACE) is a large, multinational, observational study of patients with ACS. A risk stratification model has been developed and this predicts the risk of death or re-infarction after ACS (with a C index for death of 0.80 for STEMI and 0.78 for NSTEMI).^{13,14} It has a better predictive accuracy for these outcomes than either the Thrombolysis in Myocardial Infarction (TIMI) or Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrelin Therapy (PURSUIT) risk scores.¹⁴

However, the majority of current research into risk scores and biomarkers of cardiac necrosis is performed in carefully selected patients with confirmed diagnoses, or retrospective datasets. This may not reflect clinical practice in patients with suspected ACS. The added prognostic value of BNP, over and above the GRACE score, has not been assessed, nor has it been investigated for outcomes beyond congestive heart failure (CHF) and mortality. The hypothesis in this study is that BNP and the GRACE risk score predict in-hospital and 30-day outcomes in a "real world" population with ACS. The practical aim is to improve prognostic information and allow clinicians to tailor treatment to match the individual patient's risk. This may not only benefit patients at high risk but may avoid potential hazards in those with a good prognosis.

Methods

Study Population

Patients admitted to the emergency department, combined assessment area, coronary care unit and cardiology ward at the New Royal Infirmary of Edinburgh between October 2004 and May 2005 were eligible for participation. Eligible patients (n=149) were >18 years of age with a history of chest pain or other symptoms suggestive of ACS, and at least one of: ECG changes consistent with ACS, elevated biomarkers of cardiac necrosis, or documented coronary artery disease.

The protocol was approved by the University of Edinburgh Research Project Ethics Committee before initiation of the study. Informed consent was obtained from all subjects, and the clinical history, including risk factors for ACS, was obtained from subjects, rather than from case records.

Assay of BNP

Following direct venous puncture, blood was collected into K-EDTA tubes within 24 hours of the onset of symptoms (mean time 14.4 ± 1.13 hrs). The samples were centrifuged within 3 hours of collection, and the plasma fraction was stored at -20°C. BNP was measured using the ADVIA Centaur assay (Bayer PLC Diagnostics, Newbury, UK). The assay has a range of <2.0-5000 pg/ml, with a specificity of 97% at 100 pg/ml.¹⁵ The between-assay coefficient of variation was <10% over the range of concentrations.

GRACE Risk Score Stratification

The rationale and design of the Global Registry of Acute Coronary Events has already been described.¹⁶ The GRACE Risk Score is derived from eight independent predictors of death and recurrent MI following ACS (heart rate, systolic blood pressure, creatinine, Killip class, resuscitated cardiac arrest, ST-segment deviation on ECG, and elevated cardiac biomarkers).¹⁷ The estimated risk of death or recurrent MI at 6 months is then calculated.¹³

Cardiac Biomarkers

Troponin I (TnI) was measured using the VITROS ECi automated immunoassay system (ORTHO Clinical Diagnostics, Amersham, UK). The cut-off was 0.2 ng/L (CV of 10%). Creatinine kinase was measured on an OLYMPUS AU2700 analyser (OLYMPUS, Lismeehan, Co. Clare, Ireland).

Patient Diagnosis and Follow-Up

STEMI was diagnosed based on ST-segment elevation >1mm (in 2 or more standard or chest leads), or new left bundle branch block, and at least one positive cardiac biomarker (either TnI or creatine kinase). NSTEMI was diagnosed in patients with a positive biomarker without new ST-segment

elevation. UA was diagnosed when biochemical markers were within the normal reference range for myocardial necrosis.¹ Seven screened patients had a non-cardiac cause for their symptoms and, by design, were not included in the study.

In-hospital follow-up was performed on all patients and outcomes were defined as all-cause mortality, recurrent ACS (defined as further ischaemic rest pain symptoms and/or ECG changes), cardiac arrest, new onset of an arrhythmia, heart failure (diagnosed by moderate to severe impairment on echocardiography and/or clinical and radiological signs), coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI).

Subjects were followed up by telephone interview after 30 days from admission. Outcomes were defined as all-cause mortality, re-hospitalisation, recurrent MI or angina, and heart failure (diagnosed by clinical symptoms).

Statistical Analysis

Patients were stratified into high and low risk groups for each biomarker. The concentrations of BNP were dichotomised at 100pg/ml based on previous studies and the recommended decision threshold.¹⁵ GRACE scores were categorised into low (<15%), intermediate (15-30%) or high risk (>30%) tertiles for risk of death/recurrent MI.

Continuous data were expressed as mean +/- standard error of the mean (SEM) and analysed using the Mann-Whitney U test. The Kruskal-Wallis one-way analysis of variance (with post-hoc Least Significant Difference tests) was used to test the equality of distributions in the three GRACE score groups. Categorical data were expressed as frequencies and percentages, and groups were compared using the chi-square test. Graphs are presented as percentages of patients in each group experiencing each event. P values of <0.05 were considered significant. Statistical analysis was performed using SPSS version 11.5 for Windows (SPSS Inc., Chicago, IL) and Excel version 9.0 for Windows (Microsoft, CA).

Results

The study cohort consisted of 142 patients, and their baseline characteristics and clinical diagnoses are summarised in Table I.

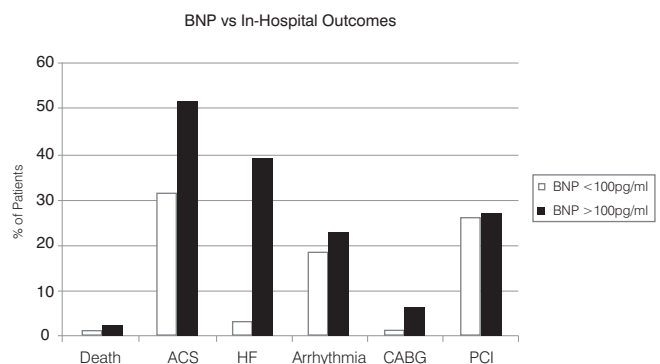
Characteristic	Percentage (n) or Mean ± SEM
Age (years)	66.2 ± 1.10
Male gender	60.6% (86)
<i>Previous medical history:</i>	
- Myocardial infarction	44.4% (63)
- Angina	57.7% (82)
- CABG	7.7% (11)
- PCI	23.9% (34)
- CHF	13.4% (19)
<i>Risk factors:</i>	
- Hypertension	53.5% (76)
- Hypercholesterolaemia	59.9% (85)
- Type II diabetes mellitus	11.3% (16)
- Current smoker	33.1% (47)
<i>Diagnosis:</i>	
- STEMI	20.4% (29)
- Non-STEMI	14.1% (20)
- UA	65.5% (93)

Table I. Characteristics of the Study Population (n=142)

During their hospital stay, 2 patients (1.4%) died, 54 (38%) suffered recurrent ACS, 22 (15.5%) developed CHF, 28 (19.7%) suffered an arrhythmia, 4 (2.8%) underwent coronary artery bypass grafting (CABG), and 37 (26.1%) underwent percutaneous coronary intervention (PCI). By 30 days, 3 patients (2.1%) had suffered a subsequent MI, 29 (20.6%) developed CHF and 61 (43.3%) experienced episodes of angina.

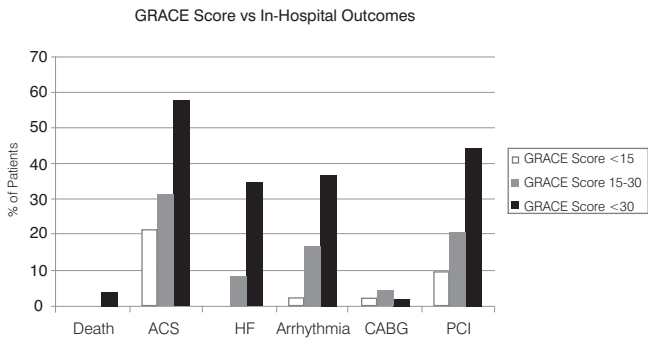
Elevated BNP was significantly associated with the development of CHF (p<0.001), and recurrent ACS (p<0.05) (Figure 1).

Figure 1



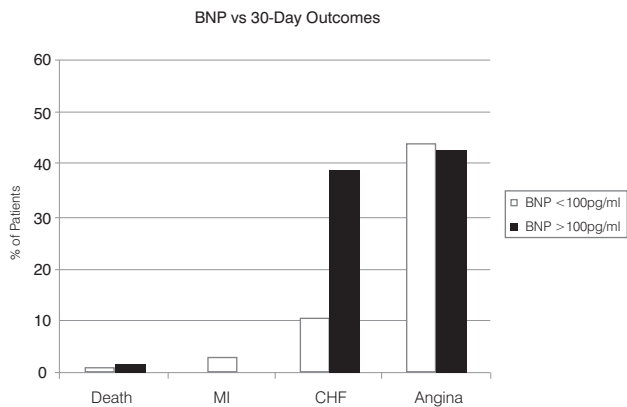
The GRACE score predicted in-hospital recurrent ACS ($p < 0.05$), arrhythmia ($p < 0.02$), CHF ($p < 0.02$) and PCI ($p < 0.05$) (Figure 2).

Figure 2



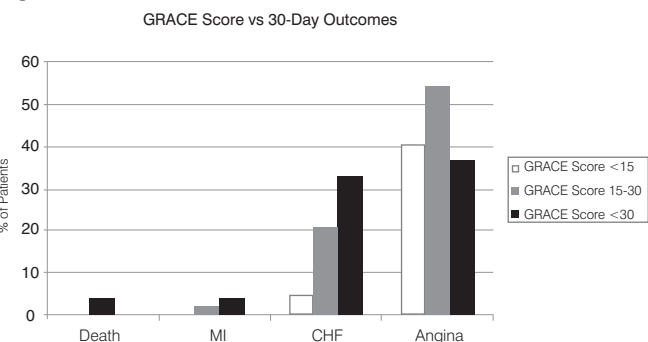
Elevated BNP was a strong predictor of CHF at 30 days ($p < 0.001$), but not other events (Figure 3).

Figure 3



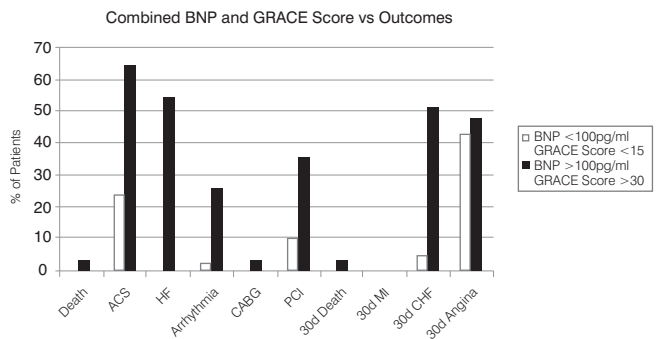
The GRACE score on admission also predicted the development of CHF (Figure 4), ($p < 0.05$). Interestingly, the incidence of stable angina at 30 days was not associated with either elevated BNP or the GRACE score.

Figure 4



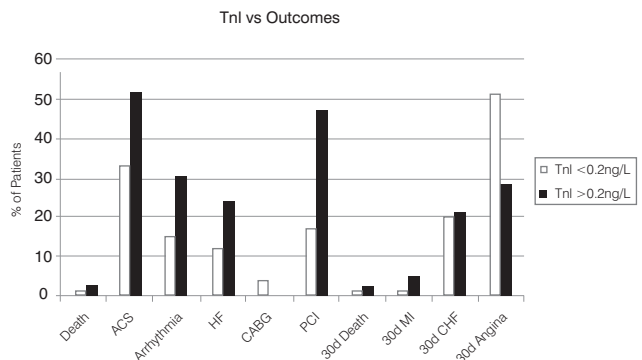
Furthermore, patients with low BNP and a GRACE score in the lowest tertile had a very low risk of cardiac complications in hospital and at 30 days. The group with elevation of both BNP and GRACE score were much more likely to suffer recurrent ACS ($p < 0.001$), in-hospital CHF ($p < 0.001$), arrhythmia ($p < 0.01$), undergo PCI ($p < 0.05$) and develop CHF at 30 days ($p < 0.001$) than those in the low risk group for both markers (Figure 5). Only 1/37 patients without elevated GRACE score and BNP experienced death, heart failure or arrhythmia, compared to 22/99 of those with troponins $< 0.2\text{ng/L}$.

Figure 5



High TnI ($> 0.2\text{ng/L}$) was less strongly associated with risk of recurrent ACS ($p < 0.05$), arrhythmia ($p < 0.05$). Stratification by TnI did not identify patients at risk of developing CHF in-hospital or at 30 days (Figure 6).

Figure 6



Discussion

This prospective study in an unselected cohort of patients with ACS demonstrates that simultaneously assessing BNP and the GRACE score provides complementary prognostic information over and above conventional biomarkers such as Tnl.

BNP was found to be a powerful indicator of the development of CHF both in-hospital and at 30 days. This concurs with previous findings,^{4,18,19} and establishes its validity in an unselected population. BNP differs from other biomarkers in ACS, in that it is an active neurohormone playing a role in the response to ischaemic injury.⁹ Elevated BNP after MI is associated with adverse LV remodeling,¹² predisposing high-risk patients to CHF. However, over 50% of those with an elevated BNP in this study did not develop CHF at 30 days, suggesting that it should not be used in isolation in this setting. Nevertheless, patients with low BNP and a GRACE score in the lowest tertile had a very low risk of cardiac complications in hospital and at 30 days and this finding may be useful in guiding further investigations and future management.

The GRACE score was developed to provide a simple decision tool for bedside risk estimation in patients surviving admission for ACS.¹³ The estimated risk of death or myocardial infarction at 6 months¹⁷ was used in this study. The GRACE score predicted patients at risk of in-hospital recurrent ACS, arrhythmias, PCI and development of CHF. It has already been demonstrated that patients with a high GRACE score are more likely to undergo angioplasty.¹⁴ However, for the first time, this study found that the GRACE score could predict the risk of other potentially life-threatening complications associated with ACS.

The limitations to this study include the modest size of the study population. A larger study with adjustment for potentially confounding factors (eg the natural increase in BNP with age) may increase the predictive accuracy of risk. The BNP level on admission was unknown and some patients may have had elevated levels prior to admission. Previous reports have suggested that sequential in-

hospital BNP measurements²⁰ may be required and peak BNP level occurs at about 16 hours after MI.¹⁰ The average time to measurement in this study was similar, at 14 hours. This study focused on 30-day follow-up and the findings should form the basis of a larger, longer term study. The major strength of this study is that it was performed in an unselected “real world” population of patients with ACS and not a defined clinical trial population, nor a retrospective dataset.

Conclusion

A good prognostic biomarker should augment the prognostic value of available tools, guide specific management decisions, and be available as a rapid, high quality and low cost assay.²¹ This study shows that BNP provides additional information on the prognosis of ACS and could guide future management with respect to CHF. However, the high cost may limit its application at present. Increased GRACE score was associated with heart failure, recurrent ACS, arrhythmia and PCI. Both BNP and the GRACE score provide unique information on prognosis, allowing clinicians to risk-stratify patients with ACS more effectively and potentially improving management decisions.

Acknowledgements

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