Review

B-type natriuretic peptide in cardiovascular disease

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Natriuretic peptide hormones, a family of vasoactive peptides with many favourable physiological properties, have emerged as important candidates for development of diagnostic tools and therapeutic agents in cardiovascular disease. The rapid incorporation into clinical practice of bioassays to measure natriuretic peptide concentrations, and drugs that augment the biological actions of this system, show the potential for translational research to improve patient care. Here, we focus on the physiology of the natriuretic peptide system, measurement of circulating concentrations of B-type natriuretic peptide (BNP) and the N-terminal fragment of its prohormone (N-terminal BNP) to diagnose heart failure and left ventricular dysfunction, measurement of BNP and N-terminal BNP to assess prognosis in patients with cardiac abnormalities, and use of recombinant human BNP (nesiritide) and vasopeptidase inhibitors to treat heart failure.

Historical perspective

A series of experiments done in the mid 1950s established the heart as an endocrine organ. First, Kisch and colleagues[1] detected secretory granules in guineapig atria. Henry and Pearce[2] subsequently described increased urinary flow after balloon stretch of the canine left atrium. In an experiment done 25 years later, de Bold[3] injected homogenised atrial tissue into rats and noted increased sodium excretion and urinary volume. In 1984, the structure of atrial natriuretic peptide (ANP) was identified,[4] and in 1988 a compound was isolated from pig brain that caused natriuretic and diuretic responses similar to ANP.[5] Although this peptide was called brain (B-type) natriuretic peptide (BNP), the primary site of BNP synthesis is ventricular myocardium.[6,7] In 1990 a third member of the natriuretic peptide family was identified, also from pig brain, and called C-type natriuretic peptide (CNP).[8] CNP is structurally distinct from ANP and BNP and is expressed to a much greater extent in CNS and vascular tissues than in the heart.[9]

Synthesis and release of ANP and BNP

The stimulus for ANP and BNP release is myocyte stretch, rather than transmural pressure load.[10–13] Both hormones are synthesised as aminoacid precursor proteins, and undergo intracellular modification to prohormones. Pro-ANP is sequestered in atrial storage granules, and cleaved into a 98 aminoacid N-terminal fragment (N-terminal ANP) and the 28 aminoacid active hormone (ANP) on release into the circulation. Regulation of ANP secretion seems to occur at the level of release from storage granules, whereas BNP regulation takes place during gene expression.[14] BNP is synthesised in bursts and constitutively released from ventricular myocytes as a 76 aminoacid N-terminal fragment (N-terminal BNP) and a 32 aminoacid active hormone (BNP). By contrast with ANP, BNP gene expression can increase very rapidly in response to an appropriate stimulus.[15]

Lancet 2003; **362:** 316–22. Published online April 23, 2003
http://image.thelancet.com/extras/02art2325web.pdf

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Although ANP concentrations are more closely related to left-atrial pressure, and BNP to left-ventricular pressure and volume indices,[16,17] some overlap between sites of release exists. For example, BNP is released in small amounts from atrial tissue,[18,19] and is stored together with ANP in atrial storage granules.[20,21] In patients with myocardial infarction or left-ventricular dysfunction, ANP can be released from both atrial and ventricular tissues in large quantities.[7,22] In addition to primary regulation via myocyte stretch, natriuretic peptide synthesis can be augmented by tachycardia,[23] glucocorticoids,[24] thyroid hormones,[25] and vasoactive peptides such as endothelin-1 and angiotensin II,[11,12] independent of the haemodynamic effects of these factors.

Natriuretic peptide binding and clearance

Three natriuretic peptide receptors have been identified (NPR-A, NPR-B, and NPR-C) (figure 1). Binding of natriuretic peptides to the A and B receptors on the surface of target cells leads to generation of the second messenger cyclic guanosine monophosphate, which mediates most of the biological effects of the natriuretic peptides. ANP and BNP bind preferentially to NPR-A and CNP to NPR-B.[26] NPR-C is a clearance receptor for ANP and BNP. Lower affinity of NPR-C for BNP contributes to a longer plasma half-life of BNP compared with ANP in human beings.[27] Natriuretic peptides are also inactivated by neutral endopeptidase, a zinc metallopeptidase that is present on the surface of endothelial cells, smooth-muscle cells, cardiac myocytes, renal epithelium, and fibroblasts.[28]

Actions of natriuretic peptides

ANP and BNP seem to have identical actions (table 1). In the kidney, they increase glomerular filtration and inhibit sodium reabsorption, causing natriuresis and diuresis.[29]

Search strategy and selection criteria

We searched the National Library of Medicine's electronic database using the keywords natriuretic peptide, atrial natriuretic peptide, brain natriuretic peptide, B-type natriuretic peptide, ANP, BNP, CNP, nesiritide, omapatrilat, vasopeptidase inhibitors, and neutral endopeptidase. Articles about basic physiology and with applications to people with cardiac disease were reviewed. We also searched the references of selected articles.

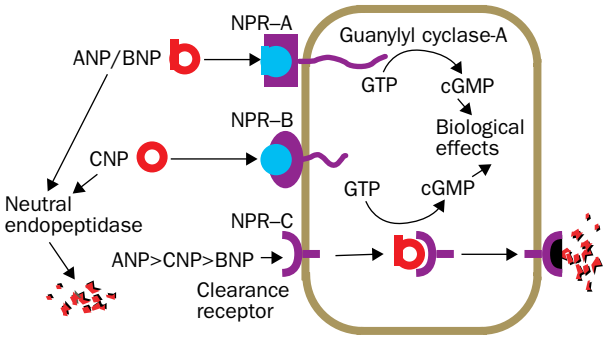

Figure 1: **Natriuretic peptide hormone binding and clearance**
GTP=guanosine triphosphate. GMP=guanosine monophosphate. Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) bind to natriuretic peptide receptor (NPR) A, a guanylyl cyclase receptor that mediates the biological effects of these peptides. The peptide is cleared via two mechanisms: binding to NPR-C and degradation by neutral endopeptidase.

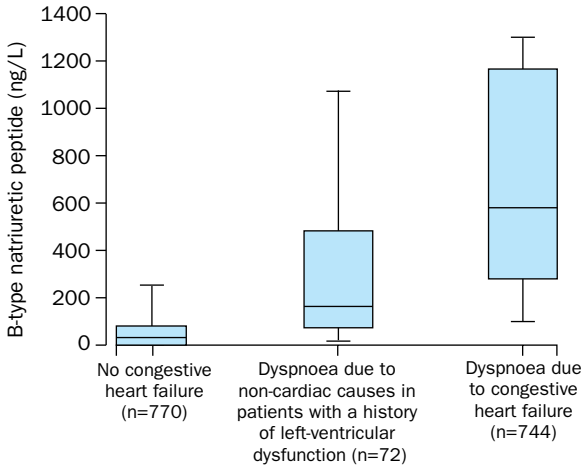

Figure 2: **BNP concentrations in patients presenting with dyspnoea and enrolled in the BNP multinational study**
Data are median (IQR). Bars are highest and lowest values. Reproduced with permission from Mosby Inc.[49]

Natriuretic peptides relax vascular smooth muscle, causing arterial and venous dilation and leading to reduced blood pressure and ventricular preload.[30,31] ANP and BNP also have important central and peripheral sympathoinhibitory effects. Both hormones block cardiac sympathetic nervous system activity, even when cardiac filling pressures fall.[32,33] These hormones also inhibit the renin-angiotensin-aldosterone axis: ANP infusion directly blocks secretion of renin and aldosterone and further inhibits the stimulatory effect of angiotensin II on release of aldosterone.[30,34,35] BNP has direct lusitropic (relaxing) properties in the myocardium,[36] and might have antiproliferative and antifibrotic effects in vascular tissues.[37,38] By contrast with ANP and BNP, CNP does not function as a circulating hormone,[39] but acts locally in the vasculature as a vasodilator and inhibitor of vascular cell proliferation,[40] and in the central nervous system, where it has several functions.[41]

Natriuretic peptides as cardiac biomarkers

For a biomarker to be valuable in clinical practice, it should be able to be measured rapidly and accurately at a reasonable cost; add diagnostic or prognostic information to available methods; and help to guide patient management. BNP and N-terminal BNP fulfil most of these criteria in patients with suspected heart failure. BNP predicts disease state and prognosis better than ANP or N-terminal ANP.[42–45] Although adequately powered head-to-head comparisons have not been done, N-terminal BNP seems to provide much the same information as BNP,[46] and assays for N-terminal BNP are also now available commercially.

Diagnostic use

Heart failure

Heart failure can be difficult to diagnose accurately, because the signs and symptoms of this disorder are neither sensitive nor specific.[47] These limitations are especially relevant when symptoms are mild or when patients are elderly or have comorbid disorders that mimic heart failure, such as pulmonary disease or obesity. In early pilot studies, raised concentrations of BNP distinguished heart failure from other causes of dyspnoea more accurately than did left-ventricular ejection fraction, ANP, and N-terminal ANP, with a sensitivity of greater than 90% and a specificity of 80–90%.[42,43] These findings were supported by the results of a series of small studies[47,48] from a single centre using a commercially available point-of-care BNP assay, and have recently been validated in a multicentre study of 1586 patients presenting to the emergency room with dyspnoea.[49] In this study, concentrations of BNP were highest in patients with decompensated heart failure, intermediate in those with known left-ventricular dysfunction but no acute heart failure exacerbation, and lowest in those without heart failure or left-ventricular dysfunction (figure 2). Using a threshold of greater than 100 ng/L to diagnose heart failure, BNP did better than all other clinical variables[49] and the clinical judgment of the emergency room physician,[50] and contributed explanatory power to a multivariable model that incorporated diagnostic variables from the patient history, examination, and chest radiograph.[49] BNP was especially useful for ruling out heart failure; at a BNP threshold of 50 ng/L, the negative predictive value was 96%[49] (table 2).

Asymptomatic left-ventricular systolic dysfunction

Asymptomatic left-ventricular dysfunction is at least as common as symptomatic heart failure. A simple screening test to identify this disorder might help to identify patients at risk of developing heart failure who would benefit from treatments that prevent progression to heart failure, including angiotensin converting enzyme inhibitors and β blockers. Such screening could be targeted to patients at high risk for left-ventricular dysfunction, such as those with

Renal	Vascular	Cardiac	SNS/RAAS
↑ GFR	↓ Arterial tone	Lusitropic	↑ Vagal tone
↓ Na^+ resorbtion	↓ Venous tone	Antifibrotic	↓ SNS activity
	Antiproliferative	Antiproliferative	↓ Renin release
			↓ Aldosterone release

GFR=glomerular filtration rate. SNS=sympathetic nervous system. RAAS=renin-angiotensin-aldosterone system

Table 1: **Actions of natriuretic peptides**

Threshold	Sensitivity	Specificity	PPV	NPV	Accuracy
50 ng/L	97%	62%	71	96	79%
80 ng/L	93%	74%	77	92	83%
100 ng/L	90%	76%	79	89	83%
125 ng/L	87%	79%	80	87	83%
150 ng/L	85%	83%	83	85	84%

Adapted from reference 49. PPV=positive predictive value. NPV=negative predictive value

Table 2: **Operating characteristics of BNP thresholds in the multinational study**

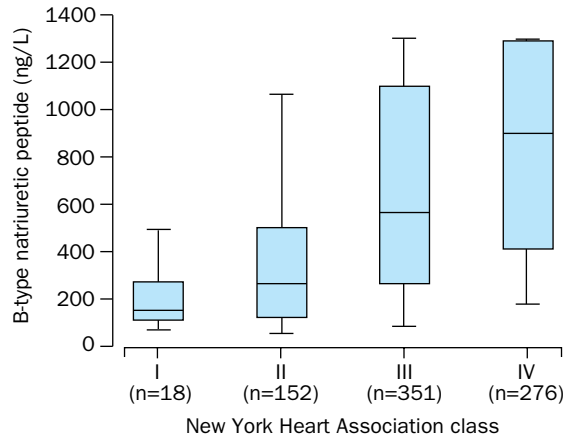

Figure 3: **BNP concentrations as a function of New York Heart Association functional class**
Data are median (IQR). Bars are highest and lowest values. Reproduced with permission from Mosby Inc.[49]

diabetes,[51] recent myocardial infarction,[52,53] end-stage renal failure,[54] or those receiving anthracycline chemotherapeutic drugs.[55]

BNP is less accurate in detection of asymptomatic left-ventricular dysfunction than for clinical diagnosis of heart failure, especially when left-ventricular dysfunction is mild; BNP concentrations in patients with mild left-ventricular dysfunction could overlap with normal concentrations.[56–58] This observation is not surprising in light of the close correlation between BNP and New York Heart Association (NYHA) functional class[16,49] (figure 3), and between BNP and haemodynamic indices, such as left-ventricular end-diastolic pressure and pulmonary capillary wedge pressure.[59,60]

Diastolic dysfunction

Concentrations of BNP are consistently raised in disorders associated with diastolic dysfunction, such as aortic stenosis, hypertrophic cardiomyopathy, and restrictive cardiomyopathy.[13,17,61] The concentrations are higher in patients with systolic dysfunction than in those with isolated diastolic dysfunction, and highest in those with both systolic and diastolic dysfunction (figure 4).[62] Among patients with preserved left-ventricular function, BNP correlates with doppler indices of diastolic dysfunction: concentrations are raised among patients with evidence of impaired relaxation and highest among those with a restrictive filling pattern.[63,64] Accuracy of BNP for diagnosis of isolated diastolic heart failure approaches that for diagnosis of heart failure due to systolic dysfunction.[64] BNP may play an important part in future clinical trials in diastolic dysfunction, which have previously been difficult to implement, due in large part to the absence of appropriate diagnostic criteria.

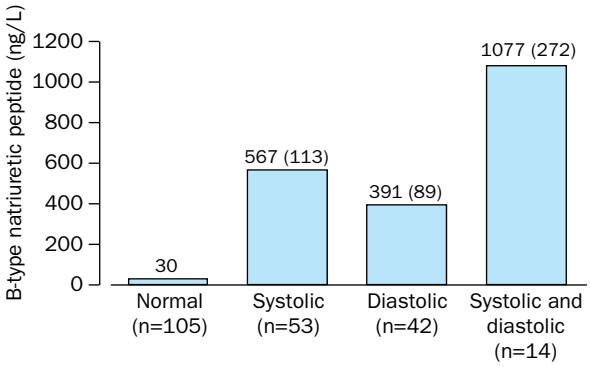

Figure 4: **BNP concentrations in patients with normal left-ventricular function, left-ventricular systolic dysfunction, left-ventricular diastolic dysfunction, and combined systolic and diastolic dysfunction**
Values are mean (SE). Adapted from reference 62 with permission from Mosby Inc.

Right-ventricular disorders

BNP concentrations increase in proportion to the degree of right ventricular dysfunction in several disorders associated with right-ventricular pressure overload or structural abnormalities in the right ventricle. For example, raised BNP concentrations have been described in patients with primary pulmonary hypertension,[65] cor pulmonale,[66] pulmonary embolism,[48] congenital heart disease,[67] and arrhythmogenic right-ventricular dysplasia.[68] However, the amount of BNP elevation seems to be less than that seen with processes leading to dysfunction of the left ventricle.[48]

Limitations of diagnostic use of BNP

There are several important limitations to note when considering the diagnostic role of BNP. First, patients sometimes present with concomitant disorders, such as pneumonia and decompensated heart failure. Thus, a very high concentration of BNP, although specific for decompensated heart failure, does not exclude presence of other important diseases. Second, patients with chronic heart failure might have persistently high concentrations of BNP despite adequate treatment; here, accurate diagnosis might require comparison with the patient's baseline BNP concentration, rather than use of a predetermined diagnostic threshold, although the accuracy of this strategy has not yet been shown. Third, in patients who do not have symptoms, small increases in BNP are not specific for left-ventricular dysfunction, because several disorders are also associated with small or medium increases in BNP, such as right-ventricular dysfunction (see above) and left-ventricular hypertrophy.[57] Finally, when considering use of BNP to screen patients who are asymptomatic, doctors should recognise that the normal range of BNP is specific to age, sex, and assay.[69,70]

BNP for prognostic assessment

In patients with chronic heart failure, higher concentrations of BNP are associated with increased cardiovascular and all-cause mortality, independent of age, NYHA class, previous myocardial infarction, and left-ventricular ejection fraction.[71–73] In multivariate analyses,[71–73] BNP was more closely associated with mortality than was NYHA class or left-ventricular ejection fraction, and in one study of outpatients with chronic heart failure,[74] plasma concentrations of natriuretic peptides were more predictive of death or the need for cardiac transplantation than was peak oxygen uptake measured during cardiopulmonary exercise testing. Raised concentrations of BNP are also independently associated with sudden cardiac death in patients with chronic heart failure.[75] In addition to its association with death, BNP is associated with readmission for heart failure[76] and outcomes after presentation to the emergency department for heart failure,[77] a setting in which traditional risk factors do not have any prognostic value.[78] BNP also provides similar prognostic information for diastolic heart failure.[79] Serial testing might further enhance the prognostic value of BNP. Patients with persistently high concentrations of BNP despite aggressive treatment for heart failure are at especially high risk for adverse outcomes.[72,73,80]

BNP has prognostic value in disorders other than heart failure. After acute myocardial infarction, a raised concentration of BNP identifies patients at risk for adverse left-ventricular remodelling,[81] left-ventricular dysfunction,[81,82] heart failure,[82] and death, independent of age, history of heart failure, and left-ventricular ejection fraction.[45,82] Even in patients with unstable angina and no evidence of myocardial necrosis or heart failure, raised concentrations of BNP are associated with an increased risk of death.[83–85] In disorders leading to right-ventricular dysfunction, including cor pulmonale[86] and primary pulmonary hypertension,[87] BNP provides similar prognostic information. Indeed, several studies have extended the potential role of BNP measurement to risk stratification of the general population, in which long-term mortality increases in proportion to BNP concentrations, both in patients with and without evidence of cardiovascular disease.[88,89]

Effect of treatment on BNP concentrations

In patients with decompensated heart failure who are treated aggressively with diuretics and vasodilators, BNP concentrations fall rapidly together with intracardiac filling pressures.[59,90] ACE inhibitors,[52,91,92] angiotensin-II receptor antagonists (valsartan),[93] and an aldosterone antagonist (spironolactone)[94] also lead to modest reductions in BNP concentrations. The effects of β blockers on BNP concentrations are more complex. On the one hand, because adrenergic stimulation inhibits release of natriuretic peptides,[95] initiation of β blockade will slightly increase natriuretic peptide concentrations.[96,97] On the other hand, because long-term addition of β blockers to conventional treatment is associated with improvements in haemodynamic variables and left-ventricular function, the net effect is often a reduction in BNP concentrations.[73,98]

BNP concentrations and decision-making in chronic heart failure

Beyond its diagnostic and prognostic value, BNP can also help physicians to make clinical decisions about patients with heart failure, although much work remains in this emerging field. The premise of this approach is that decisions to start or titrate pharmacological treatments, or to use a more invasive strategy such as cardiac transplantation,[99] might be based not only on symptoms and physical examination findings, but also on the concentrations of BNP.[71,76] Two provocative pilot studies[92,100] have prospectively assessed use of BNP to guide selection and intensity of pharmacotherapy. In one study,[100] 69 patients with heart failure were randomly allocated to receive either symptom-guided treatment or N-terminal BNP-guided therapy. The group assigned to N-terminal BNP-guided therapy received higher doses of ACE inhibitors and diuretics, and were also more likely to receive spironolactone. After about 10 months of follow-up, fewer events occurred in the group treated on the basis of N-terminal BNP concentrations than in the group treated according to traditional indices. In a second small randomised trial,[92] patients who had ACE inhibitor doses titrated to achieve the lowest BNP possible had significantly greater reductions in heart rate than did patients treated traditionally. Thus, BNP could ultimately prove useful in helping doctors to select the appropriate drugs and drug doses,[71,76,92,100] and of the need for more invasive, non-pharmacological strategies such as implantable defibrillators, ventricular assist devices, or cardiac transplantation.[75,99] Although these hypotheses are intriguing, large prospective trials are needed to define the role of BNP in therapeutic titration.

Therapeutic potential

The physiological properties of ANP and BNP, including natriuresis, arterial and venous dilation, inhibition of the sympathetic nervous system, and antagonism of the renin-angiotensin-aldosterone axis, fulfil many criteria for an ideal agent to treat heart failure. As a result, interest has focused on development of drugs that modulate the natriuretic peptide hormone system. Two approaches have reached late-stage clinical development: administration of exogenous natriuretic peptides and potentiation of the endogenous effects of natriuretic peptides by inhibiting neutral endopeptidase, an enzyme that degrades ANP and BNP.

Nesiritide

Recombinant human BNP (nesiritide) is now available for treatment of decompensated heart failure. In early phase 1 and 2 studies, BNP infusion decreased pulmonary capillary wedge pressure and improved cardiac index and urinary flow rate in a dose-dependent manner;[101–104] the reduction in cardiac filling pressures was independent of the diuretic effect of the agent.[105] In addition, favourable neurohormonal effects were recorded, including a reduction in norepinephrine and aldosterone concentrations.[101,102,105]

Phase 3 development of nesiritide focused on assessment of haemodynamic benefit and safety, rather than of clinical event reduction. In a 127-patient placebo-controlled trial,[106] a 6-h nesiritide infusion significantly improved haemodynamic variables and symptoms. In a companion open-label trial, nesiritide and standard therapy (most commonly dobutamine) were associated with similar improvements in symptoms. However, symptomatic hypotension was more frequent in patients given nesiritide than in those given standard treatment, especially at higher doses.

In the Vasodilation in the Management of Acute Congestive Heart Failure (VMAC) trial,[107] 489 patients with decompensated heart failure were randomly allocated to receive nesiritide, nitroglycerin, or placebo. The dose of nesiritide used in VMAC (2 μg/kg bolus, followed by 0·01 μg/kg/min infusion, with optional titration to 0·03 μg/kg/min) was significantly lower than that used in the previous phase 3 study. Background treatment could include standard heart failure therapies such as dobutamine. Nesiritide decreased pulmonary capillary wedge pressure significantly more than did nitroglycerin at 3 h and 24 h, and was associated with improved dyspnoea scores compared with placebo but not with nitroglycerin. With the lower dose of nesiritide used in VMAC, symptomatic hypotension occurred in only 5% of patients in both the nesiritide and nitroglycerin groups.

Despite the approval of nesiritide for clinical use by regulatory authorities, when this agent should be used instead of other parenteral agents such as dobutamine, milrinone, sodium nitroprusside, or nitroglycerin remains unclear. Although nesiritide can lower cardiac filling pressures without causing tachycardia or ventricular arrhythmias,[108] several uncertainties remain about the advantages of this drug over agents such as dobutamine. Up to now, insufficient data are available from large randomised trials about the effects of nesiritide on major adverse clinical outcomes. Furthermore, the cost implications of using this agent versus traditional (less expensive) agents such as dobutamine, nitroglycerin, and diuretics, remains to be determined.

Vasopeptidase inhibitors

ANP and BNP clearance involves two mechanisms: binding to the clearance (NPR-C) receptor and degradation by neutral endopeptidase, an enzyme that is upregulated in heart failure.[109] In addition to natriuretic peptides, neutral

endopeptidase degrades the vasodilators bradykinin and adrenomedullin, and the vasoconstrictors endothelin-1 and angiotensin II.[110] Therefore, selective neutral endopeptidase inhibitors can cause either vasodilation or vasoconstriction, depending on whether vasodilator or vasoconstrictor substrates are preferentially affected. The unpredictable effects of neutral endopeptidase inhibition on vascular tone are largely overcome by combining ACE and neutral endopeptidase inhibition: greater haemodynamic and renal effects are recorded with combined inhibition of ACE and neutral endopeptidase than with selective inhibition of either of these enzymes.[110] Omapatrilat is the prototype agent in this new class of drugs, which have been termed vasopeptidase inhibitors.

Omapatrilat is more effective at lowering blood pressure than most available antihypertensive agents, especially with respect to systolic blood pressure, suggesting that it has favourable effects on large artery compliance.[110,111] In early studies in people with heart failure, omapatrilat caused dose-dependent lowering of blood pressure and pulmonary capillary wedge pressure, improvement in cardiac output, and reduction in norepinephrine concentrations.[112,113] Results from a phase 2 study[114] suggested that omapatrilat would be more effective than lisinopril in patients with heart failure. However, in the subsequent phase 3 Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE),[115] of 5770 patients with NYHA class II-IV heart failure treated for an average of 14·5 months, the primary endpoint of death or admission for heart failure requiring intravenous treatment did not differ between patients taking omapatrilat and those taking lisinopril (hazard ratio 0·94; 95% CI 0·86–1·03). In post-hoc analyses from that trial, randomisation to omapatrilat was associated with a significant reduction in the composite of cardiovascular death or readmission, with most benefit shown in patients with hypertension,[115] leaving some room for cautious optimism despite the disappointing overall results of the trial.

Enthusiasm for omapatrilat has been dampened further by concerns about angio-oedema, thought to be caused by increased circulating concentrations of bradykinin, which is inactivated by both ACE and neutral endopeptidase.[116] In the Omapatrilat Cardiovascular Treatment Assessment Versus Enalapril (OCTAVE) trial,[117] 25 000 patients with hypertension were randomly allocated to omapatrilat or enalapril. As expected, blood pressure reduction was greater with omapatrilat than enalapril; however, angio-oedema occurred in 2·2% of patients given omapatrilat (*vs* 0·7% taking enalapril), and angio-oedema was recorded in 5·5% of black patients.

The future

Measurement of BNP will probably become a routine component of care for patients with known or suspected heart failure. In patients presenting with dyspnoea, a low concentration of BNP can accurately rule out decompensated heart failure, whereas a very high concentration of this peptide clearly supports the diagnosis of heart failure but does not exclude presence of other processes contributing to dyspnoea. Small rises in BNP are not specific since many diseases have concentrations of BNP within this range, and patients with small rises in this peptide should therefore have further assessments. BNP is less accurate as a general screening test for detecting cardiac structural abnormalities in patients who are asymptomatic than in those with symptoms, but might be helpful in selected populations at high risk. Raised BNP is independently associated with an increased risk for death and heart failure progression in several disorders, including chronic heart failure, acute coronary syndromes, and processes involving the right ventricle. In patients with heart failure, repeating BNP measurement after treatment has started seems to increase its prognostic value, help assess response to treatment, and possibly guide therapeutic titration. The major limitation of using BNP to assess prognosis is that specific therapeutic strategies for patients with raised concentrations of BNP have not been defined.

Conflict of interest statement

J de Lemos has received honoraria from Biosite (manufactures an assay to measure BNP) for participation in advisory panel meetings, and has done research with the Biosite BNP assay. J de Lemos has also received speaking honoraria from Bristol-Myers-Squibb (manufactures omapatrilat) for lectures unrelated to omapatrilat.

Acknowledgments

This study had no specific funding source.

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