Cost-effectiveness and use of natriuretic peptides in clinical practice – do we have enough evidence yet?

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Clinicians find heart failure difficult to diagnose.[1] Confirmation of left ventricular dysfunction (systolic or diastolic) is only possible by cardiac imaging. Recent European Society of Cardiology guidelines and National Institute for Health and Clinical Excellence (NICE) guidance have suggested that B-type natriuretic peptide (BNP)/N-terminal prohormone BNP (NT proBNP) and electrocardiography be used as a diagnostic tool that supports general practitioners (GPs) in their assessment of patients with suspected heart failure.[2,3] Despite inclusion in guidelines[2,3] uptake of BNP or NT proBNP use has been slow in the National Health Service (NHS).

A recent survey of primary care trusts (PCTs) in England found that only 26% currently offered or had previously offered natriuretic peptides for use in primary care.[4] Clinicians and healthcare purchasers (PCTs in the UK) still harbour concerns about appropriate cut-offs, the extra cost of BNP/NT proBNP assays, which assay to use (BNP or NT proBNP/point-of-care or laboratory assay), lack of expedient referral pathways for patients with a raised BNP/NT proBNP level and absence of cost-benefit/effectiveness data from a prospective primary care study.

Landmark studies such as the Hillingdon heart failure study[5] confirmed the high negative predictive value (NPV) of BNP/NT proBNP for excluding heart failure but were not conducted *in* primary care, rather in patients referred *from* primary care. These studies do not address the role played by the GP's decision-making within the dynamics of the GP–patient consultation process; the real-life availability (or lack) of varied diagnostic facilities across the primary–secondary care divide; high co-morbidities and widespread use of cardio-active drugs (angiotensin-converting enzyme [ACE] inhibitors and diuretics for hypertension, beta blockers for angina) in elderly patients in the community, all of which will impact on the utility of natriuretic peptide use in primary care. Furthermore, the poor positive predictive value and low specificity of this test in real-life practice means that large numbers of patients with raised BNP/NT proBNP will not have heart failure due to left ventricular systolic dysfunction.

There have been arguments for the use of a single dichotomous cut-point versus several age and sex adjusted cut-points prior to referral. Some have suggested <125 pg/ml under 75 years of age and <450 pg/ml in those 75 years or older. Some clinicians have suggested higher decision cut-offs for those patients with renal impairment[6] or atrial fibrillation.[7] Further work is required in defining optimal decision cut-offs in prospective primary care studies before natriuretic peptides are made widely available to GPs in ruling out heart failure.

The cost issues

In an increasingly cost-conscious NHS environment cost-benefit/effectiveness data are required to show value for money to purchasers of healthcare. There have been several recent cost-effectiveness/benefit studies (or older) for NT proBNP. However, these have been either retrospective analyses,[8] decision-model estimates for screening,[9] small cohort studies of breathless patients using BNP and open access echocardiography referral[10] or analysis of use of BNP in evaluation and management of acute dyspnoea in a European secondary care setting.[11]

More recently, Goode *et al.* suggested that preliminary screening of high-risk primary-care patients using electrocardiogram (ECG) QRS width or NT proBNP alone was insufficiently precise to be clinically

useful.[12] However, including NT proBNP and QRS width in a logistic regression model, together with evidence of prior myocardial infarction and symptoms of breathlessness or peripheral oedema gave significant reductions in the number of false positive referrals and the cost per diagnosis of clinically significant left ventricular systolic dysfunction.[12] Furthermore, Lim and colleagues found that while initial NT proBNP estimation may be cost-effective in detecting any causes of heart failure, portable echocardiography remains the most cost-effective strategy to assess patients from the community with suspected heart failure.[13,14] Hence, there are still doubts concerning whether BNP or NT proBNP testing is cost-effective in primary care.

In this issue Scott and colleagues present a study using a deterministic cost-consequences analysis to compare alternative diagnostic strategies for symptomatic heart failure presenting to their GP (pages 199–204). The authors suggest that the model demonstrates that, for the base-case scenario, an initial diagnostic strategy of point-of-care BNP assay is superior to ECG in terms of diagnosis of symptomatic heart failure in patients presenting in primary care, despite slightly more initial false negatives and a marginally higher cost. However, they admit that there remains significant uncertainty about a number of key parameters.

This brings into question the practical applicability of this study in terms of the adoption of BNP in primary care. The factors that may contribute to uncertainty are the differences in performance (and ease of use by GPs) of a point-of-care BNP assay versus a laboratory-based BNP or NT proBNP assay; different decision cut-points between the three studies contributing to the alternative scenarios;[14-16] the widely differing costs of natriuretic peptide assays being levied by providers in the UK (personal experience confirms costs between £20 to £40 in different hospitals locally); and the fact that in all these studies the ECG was read by experienced secondary care clinicians rather than GPs. These factors may significantly alter the cost-consequence assumptions being made. Also, all these studies look at patients already triaged to secondary care and may not include all patients presenting to primary care. For these reasons before BNP/NT proBNP is recommended we need a prospective primary-care based study of the use of both point-of-care and laboratory assays that take all patients with suspected heart failure to a definitive diagnosis. This research need is mentioned in the discussion by Scott and colleagues.

Full assessment required

The prognostic power of BNP/NT proBNP extends beyond just left ventricular systolic dysfunction to most cardiac conditions. Ideally, all patients with raised natriuretic peptides deserve a full cardiac assessment and echocardiography followed by optimal use of evidence-based pharmacotherapy and health professional support. We need to find ways of providing expedient diagnostic and treatment services to these patients especially in healthcare rationed systems such as the NHS. Companies marketing these assays have rushed the test into clinical practice too quickly before conducting adequate studies in community-based patients. Until these issues are addressed, widespread natriuretic peptide use is unlikely within the UK

Conflict of interest

AF has received research and educational grants from Roche Diagnostics.

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