Cost-effectiveness of screening with B-type natriuretic peptide to identify patients with reduced left ventricular ejection fraction


Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The use of screening with B-type natriuretic peptide (BNP) to identify patients with reduced left ventricular ejection fraction (LVEF).

Type of intervention
Screening.

Economic study type
Cost-effectiveness analysis and cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of 60-year-old men and women with no history of heart failure (HF).

Setting
The setting of the study was secondary care. The study was conducted in the USA.

Dates to which data relate
The effectiveness data were derived from literature published from 1992 to 2003. The costs were derived from sources published from 1994 to 2000. The price year was 2001.

Source of effectiveness data
The effectiveness data were derived from a review or synthesis of completed studies.

Modelling
A decision model was developed to estimate the economic and health outcomes for each of the screening strategies evaluated. A hypothetical cohort of 1,000 men and 1,000 women, aged 60 years and with no history of HF, was screened for reduced LVEF. The results for men and women were analysed separately. The ECHO results were deemed positive if the LVEF was found to be lower than 40%. Patients with true- and false-positive results were treated with angiotensin-converting enzyme (ACE) inhibitors to prevent the development of HF. Those with false-positive results received a decrement in quality-adjusted survival to account for the side effects of treatment. Patients with false-negative results were treated only when HF developed. Patients with true-negative results had a normal age-specific life expectancy.

A state-transition model was incorporated with four health states. Once patients developed HF they either remained stable, were hospitalised, or died. The model followed patients until all died (120 years). The Markov cycle length was
one year.

**Outcomes assessed in the review**
The outcomes assessed in the review included:

- the prevalence of reduced LVEF (LVEF=40%) in the general population of men and women;
- the test characteristics (sensitivity and specificity) of BNP and ECHO;
- the annual probability of transition from asymptomatic to symptomatic for untreated and treated patients;
- the annual probability of hospitalisation for symptomatic patients;
- the probability of hospitalisation during a first episode of HF;
- the proportion of patients adhering to therapy;
- the relative risk of death for asymptomatic untreated patients, asymptomatic patients treated with ACE inhibitors, symptomatic patients treated with ACE inhibitors, and symptomatic patients treated with ACE inhibitors and beta-blockers; and
- age- and gender-specific death rates in the general population.

**Study designs and other criteria for inclusion in the review**
It was reported that the BNP test characteristics and prevalence of reduced LVEF were derived from community cohort studies. The benefits of treatment were derived from randomised trials.

**Sources searched to identify primary studies**
Not stated.

**Criteria used to ensure the validity of primary studies**
Not stated.

**Methods used to judge relevance and validity, and for extracting data**
Not stated.

**Number of primary studies included**
Approximately 5 primary studies were included in the review.

**Methods of combining primary studies**
In the case of prevalence of low ejection fraction and age of cohort at the beginning of the model, the average of estimates derived from two studies was used.

**Investigation of differences between primary studies**
Differences between the primary studies included in the review were not discussed.

**Results of the review**

The prevalence of reduced LVEF in the general population was 3.5% for men and 0.45% for women.

The sensitivity of the BNP test was 0.65 for men and 0.80 for women.

The specificity of the BNP test was 0.86 for men and 0.90 for women.

The sensitivity of ECHO was 0.92 and the specificity was 0.96.

The annual probability of transition from asymptomatic to symptomatic was 9.8% for untreated patients and 6.5% for treated patients.

The annual probability of hospitalisation for symptomatic patients was 11%.

The probability of hospitalisation during a first episode of HF was 33%.

The proportion of patients adhering to therapy was 68%.

The relative risk of death was 3.3 for asymptomatic untreated patients, 2.9 for asymptomatic patients treated with ACE inhibitors, 6.5 for symptomatic patients treated with ACE inhibitors, and 4.9 for symptomatic patients treated with ACE inhibitors and beta-blockers.

The age- and gender-specific death rates in the general population that were used in the model were not reported.

Methods used to derive estimates of effectiveness
The authors made an assumption about the test characteristics of nuclear angiography in order to estimate the ECHO test characteristics.

Estimates of effectiveness and key assumptions
It was assumed that nuclear angiography was the 'gold' standard method for the measurement of LVEF (sensitivity and specificity 100%).

Measure of benefits used in the economic analysis
The measures of benefits used were the life-years (LYs) gained and the quality-adjusted life-years (QALYs). The benefits were discounted at an annual rate of 3%. The utility weights were derived from prior studies using the time trade-off technique.

Direct costs
The cost categories included were those of the patient and health service. The costs included in the analysis were for BNP testing, two-dimensional ECHO, hospitalisation for HF, ACE inhibitor and beta-blocker treatment, outpatient HF care, additional tests for patients with depressed LVEF (stress testing and angiography), and age-specific medical costs incurred because of increased survival. The cost of BNP testing covered phlebotomy and technician time, reagent, calibration, controls, maintenance and equipment rental. The cost of two-dimensional echocardiography comprised technical and professional component. The cost of outpatient HF care included non-beta-blockers, ACE inhibitor medications, office visits and diagnostic tests.

The costs and the quantities were not reported separately. The costing was based on Medicare reimbursement rates and cost-to-charge ratios for hospitalisation, US national pharmacy prices, and other published sources (1994 - 2000). To estimate the cost of BNP testing, it was assumed that 5,000 tests per laboratory were carried out per year. Lower volume laboratories were estimated to have a higher cost of visit. The cost of additional testing for patients with depressed LVEF was estimated, on the assumption that 100% of patients would undergo stress ECHO and 50% would receive coronary angiography. The total costs associated with each strategy evaluated were derived using modelling. The costs were discounted at an annual rate of 3%, as they were incurred over the lifetime of the patients. The costs
were adjusted to 2001 prices using the medical component of the Consumer Price Index.

**Statistical analysis of costs**
The costs were treated deterministically. No statistical analysis of the costs was undertaken.

**Indirect Costs**
The indirect costs were not included in the base-case analysis. The hypothetical value of lifetime income loss that would substantially affect the cost-effectiveness of the health technologies examined was estimated in a threshold sensitivity analysis.

**Currency**
US dollars ($).

**Sensitivity analysis**
A sensitivity analysis was carried out to test the robustness of the results. All input parameters of the model were varied over a range of values, which were based on assumptions, in a one-way sensitivity analysis. In addition, a threshold analysis was conducted by defining the parameter values that would lead to a cost-effectiveness ratio equal to $50,000 per QALY gained (a threshold of cost-effectiveness commonly used in the USA). Finally, a multivariate Monte Carlo analysis was performed. In this case each parameter was assigned a distribution (beta-distribution for probabilities and log normal for other parameters including costs) based on standard deviations of the mean values. The range of values used in the sensitivity analysis was mainly based on assumptions.

**Estimated benefits used in the economic analysis**
In a cohort of 1,000 men aged 60 years, no screening resulted in 13,860.2 LYs and 11,973.5 QALYs, the combination strategy in 13,867.7 LYs and 11,981.4 QALYs, BNP alone in 13,867.1 LYs and 11,981.0 QALYs, and ECHO alone in 13,871.4 LYs and 11,985.4 QALYs.

The incremental benefits were 7.5 LYs and 7.9 QALYs for the combination strategy compared with no screening, -4.3 LYs and -4.4 QALYs for BNP alone compared with ECHO alone, and 3.7 LYs and 4.0 QALYs for ECHO alone compared with the combination strategy.

In a cohort of 1,000 women aged 60 years, no screening resulted in 15,962.0 LYs and 13,802.8 QALYs, the combination strategy in 15,963.1 LYs and 13,804.1 QALYs, BNP alone in 15,962.2 LYs and 13,803.3 QALYs, and ECHO alone in 15,963.0 LYs and 13,804.1 QALYs.

The incremental benefits were 1.1 LYs and 1.3 QALYs for the combination strategy versus no screening, -0.8 LYs and -0.8 QALYs for BNP alone versus ECHO alone, and -0.1 LYs and 0 QALYs for ECHO alone versus the combination strategy.

All the benefits were estimated over the lifetime of the patients and were discounted at an annual rate of 3%.

**Cost results**
The total costs (in millions) for a cohort of 1,000 men aged 60 years were $40.724 with no screening, $40.900 with the combination strategy, $41.400 with BNP alone, and $41.894 with ECHO alone. The incremental costs were $176,000 for the combination strategy compared with no screening, $500,000 for BNP alone compared with the combination strategy, and $494,000 for ECHO alone compared with BNP alone.

The total costs (in millions) for a cohort of 1,000 women aged 60 years were $46.860 with no screening, $46.961 with the combination strategy, $47.367 with BNP alone, and $47.476 with ECHO alone. The incremental costs were...
$101,000 for the combination strategy versus no screening, $406,000 for BNP alone versus the combination strategy, and $515,000 for ECHO alone versus BNP alone.

All the costs were estimated over the lifetime of the patients and were discounted at an annual rate of 3%.

Synthesis of costs and benefits
The costs and benefits were combined in the form of incremental cost-effectiveness ratios (ICERs). These expressed the additional costs per LY gained or per QALY gained. The ICER of combination strategy compared with no screening was $23,500/LY gained or $22,300/QALY gained for men, and $91,800/LY gained or $77,700/QALY gained for women. BNP alone was dominated (it was less effective and more costly) by combination strategy in both men and women. ECHO incurred an incremental cost of $133,500/LY gained or $123,500/QALY gained compared with the combination strategy in men, and was dominated (less effective, more costly) by the combination strategy in women.

The results were sensitive to the prevalence of depressed LVEF and the accuracy of the screening tests.

If the prevalence of LVEF was at least 1%, then the ICER of the combination strategy was $50,000 or less per QALY gained for both men and women. In order for the ICER to be less than $20,000/QALY gained, the prevalence should be greater than 3% for women and greater than 4% for men.

Screening all patients with ECHO would cost less than $50,000/QALY gained if the prevalence of LVEF was at least 9% for men and 14% for women.

If the BNP test characteristics were improved (sensitivity 80% for men, 100% for women; specificity 86% for men, 92% for women) then the ICER of combination strategy versus no screening would become $19,500/QALY gained for men and $63,600/QALY gained for women.

If ECHO was characterised by a sensitivity and specificity of 100%, then the combination strategy would have an ICER of $18,100/QALY gained for men and $75,700/QALY gained for women in comparison with no screening. The ICER of ECHO alone versus the combination strategy was $75,700/QALY gained for men in this case.

The base-case results were not sensitive to the benefit of ACE inhibitor treatment, the costs of care and the cost of screening.

Screening became slightly more attractive for women and remained attractive for men at older ages.

The results were changed when the indirect costs were included in the estimation of the costs. Screening would be unattractive (>100,000/QALY gained) if a diagnosis led to a loss of lifetime income of $30,000 for men, or $7,000 for women, because of difficulty in obtaining employment.

Screening would also be unattractive if diagnosis led to significant decreases in quality of life.

From the probabilistic analysis, in men, the combination strategy compared with no screening had an ICER of less than $50,000/QALY gained in 88% of simulations and an ICER of less than $100,000/QALY gained in 98% of simulations. For women, these percentages were 27% (<$50,000/QALY) and 72% (<$100,000/QALY), respectively.

Authors' conclusions
B-type natriuretic peptide (BNP) testing followed by echocardiography (ECHO) was a cost-effective screening strategy for men and possibly for women at age 60 years. Screening populations with a prevalence of depressed left ventricular ejection fraction (LVEF) of 1% with this strategy should provide a health benefit at a cost comparable to, or less than, other accepted health interventions.

CRD COMMENTARY - Selection of comparators
The selection of the comparators was implicitly justified. ECHO was described as one of the 'gold' standard methods for the identification of patients with reduced LVEF. The no screening comparator allowed the active value of screening strategies to be evaluated. The combination of two screening tests resulted in a strategy with increased accuracy. You should consider whether the screening strategies serving as the comparators represent widely used technology in your own setting.

**Validity of estimate of measure of effectiveness**

The authors did not state that a systematic review of the literature had been undertaken. The effectiveness rates from primary studies were combined in only two cases, where it was reported that the average of the effectiveness estimates was calculated. Differences between the primary studies included in the review were not discussed.

**Validity of estimate of measure of benefit**

The estimation of benefits was modelled. The decision analytic model used to derive a measure of health benefit was appropriate for this purpose, as it included all possible main events following screening over the lifetime of the hypothetical cohort of men and women examined.

**Validity of estimate of costs**

It was stated that a societal perspective was adopted in the study. However, direct non-health care costs and indirect costs were not considered in the analysis. The costs and the quantities were not reported separately, which limits the generalisability of the results. A sensitivity analysis of the costs was conducted. Although not fully justified, the ranges used appear to have been appropriate. In the case of hospitalisation costs, cost-to-charge ratios were used. These reflect the resources used in a more accurate way than charges. Discounting was performed, which was appropriate since the costs were incurred over the lifetime of the patients. The year to which the prices referred was reported, and this contributes to the reproducibility of the results.

**Other issues**

The authors made appropriate comparisons of their results with those from other studies. The issue of the generalisability of the results to other countries, to populations with different prevalence of reduced LVEF, and to younger populations, was discussed. The authors acknowledged a number of limitations of their study. First, the absence of data on the effect of ACE inhibitors in patients with no cardiac disease. Second, the lack of consideration of implications after the diagnosis of depressed LVEF, in terms of quality of life and potential difficulties in obtaining insurance and employment. Third, the failure to include the potential screening benefits of identifying diastolic dysfunction or significant valvular disease in the model design. Finally, the omission of other screening tests for identifying reduced LVEF, such as chest radiography and electrocardiography, from the economic evaluation. The results of the study were reported in full and the authors' conclusions reflected the scope of the analysis.

**Implications of the study**

Screening with BNP followed by ECHO should be considered in populations with at least 1% prevalence of reduced LVEF, as it is economically attractive. The authors recommended additional research to determine the most cost-effective screening strategy for identifying depressed LVEF, and the impact of population screening on the costs and health benefits.

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