What is the most cost-effective strategy to screen for left ventricular systolic dysfunction: natriuretic peptides, the electrocardiogram, hand-held echocardiography, traditional echocardiography, or their combination?

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Received 7 November 2004; revised 18 June 2005; accepted 8 September 2005; online publish-ahead-of-print 2 November 2005

Aims
To assess the screening characteristics and cost-effectiveness of screening for left ventricular systolic dysfunction (LVSD) in community subjects.

Methods and results
A total of 1392 members of the general public and 928 higher risk subjects were randomly selected from seven community practices. Attending subjects underwent an ECG, N-terminal pro-brain natriuretic peptide (NTproBNP) serum levels, and traditional echocardiography (TE). A total of 533 consecutive subjects underwent hand-held echocardiography (HE). The screening characteristics and cost-effectiveness (cost per case of LVSD diagnosed) of eight strategies to predict LVSD (LVSD, 45% on TE) were compared. A total of 1205 subjects attended. Ninety six per cent of subjects with LVSD in the general population had identifiable risk factors. All screening strategies gave excellent negative predictive value. Screening high-risk subjects was most cost-effective, screening low-risk subjects least cost-effective. TE screening was the least cost-effective strategy. NTproBNP screening gave similar cost savings to ECG screening; HE screening greater cost-savings, and HE screening following NTproBNP or ECG pre-screening the greatest cost-savings, costing ~650 Euros per case of LVSD diagnosed in high-risk subjects (63% cost-savings vs. TE).

Conclusion
Thus several different modalities allow cost-effective community-based screening for LVSD, especially in high-risk subjects. Such programmes would be cost-effective and miss few cases of LVSD in the community.

Introduction
Heart failure is a common chronic disorder with high associated morbidity, mortality, and cost.1 Left ventricular systolic dysfunction (LVSD) often underlies heart failure but may be asymptomatic.2 Therapeutic intervention improves LVSD prognosis whether symptomatic or not.3,4 In addition, symptomatic LVSD is commonly misdiagnosed, especially in primary care where facilities may be limited.5 Accordingly, authors have proposed establishing programmes to screen for and treat LVSD,6 although who to screen, how to screen, and the cost-effectiveness of screening are unestablished.7 Although many subjects with heart failure have normal systolic function [diastolic heart failure (DHF)],8 this condition has no accepted diagnostic criteria, no simple diagnostic tests, and no proven therapeutic interventions,7,8 Accordingly, programmes to screen for DHF are not currently under consideration.

Hospital-based echocardiography is the traditional screening method of choice in detecting LVSD.9 Other potentially community-based screening modalities include natriuretic peptides, the electrocardiogram (ECG), and hand-held echocardiography (HE),6,10–13 all of which might improve screening cost-effectiveness.

Accordingly, this study aimed to assess the screening characteristics of the ECG, the natriuretic peptide N-terminal pro-brain natriuretic peptide (NTproBNP), HE, traditional echocardiography (TE), and combinations thereof in screening for LVSD and DHF in different at-risk community subjects, comparing their cost-effectiveness in screening for LVSD.
Methods

Subjects

A total of 1392 members of the general public ≥45 years old were randomly selected from the computer records of seven representative general practices in Harrow, North London and invited to attend. A further 928 high-risk subjects ≥45 years old were randomly selected from the same computer records from those with risk factors for LVSD (ischaemic heart disease (IHD), diabetes mellitus (DM), peripheral vascular disease (PVD), cerebrovascular disease (CVD), and heavy alcohol usage) and invited. Attendees were seen between January 2000 and December 2001.

Subject assessment

Attending subjects underwent a questionnaire, ECG, venesection for NTproBNP serum levels, and echocardiography.

Electrocardiography

ECG abnormalities were defined as: sinus tachycardia, atrial fibrillation or flutter, ventricular ectopics, intraventricular conduction defects, any ST or T-wave abnormalities, pathological Q-waves, paced rhythm, or left ventricular hypertrophy (Sokolow-Lyon criteria).

Echocardiography

All subjects underwent echocardiography by a traditional high specification machine using second harmonic imaging (SONOS 4500, Philips, Eindhoven, The Netherlands), depicted as TE. Furthermore, consecutive subjects attending between May 2000 and May 2001 also underwent additional echocardiography by a prototype HE machine (OptiGo, Philips, Eindhoven, The Netherlands), depicted as HE. The hand-held machine weighed 3 kg, the traditional machine 214 kg. All TE measurements were analysed from optical disc recordings at a later date without knowledge of the HE results.

Left ventricular ejection fraction (LVEF) was calculated quantitatively on TE using Simpson’s apical biplane rule, the average of three readings. LVSD was defined as LVEF <45%, as per European Society of Cardiology guidelines. This was the gold-standard definition of LVSD used in the study. Diastolic parameters assessed by TE included isovolumic relaxation time, mitral inflow peak E-wave velocity (E), peak A-wave velocity (A), E/A ratio, and E-wave deceleration time. DHF was defined according to European guidelines, namely as signs or symptoms of heart failure (exertional dyspnoea, orthopnoea, paroxysmal nocturnal dyspnoea, or crepitations) + normal or near normal LV systolic function + abnormal age-adjusted diastolic filling parameters. Further TE measurements included atrial and ventricular dimensions and an assessment of valvular structure and function.

LVSD was estimated qualitatively on the hand-held device by visual inspection. To ensure high sensitivity in detecting LVSD, subjects estimated to have LVEF ≤50% were depicted as having possible LVSD and scored as abnormal. Diastolic parameters were not assessed by HE.

<table>
<thead>
<tr>
<th>Table 1 NTproBNP upper reference values in the normal population</th>
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<tr>
<td>Males (45–59 years)</td>
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<tr>
<td>Median NTproBNP levels (SIQR) (pg/mL)</td>
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<tr>
<td>NTproBNP upper reference values (pg/mL)</td>
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<td>Number of subjects assessed</td>
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SIQR, semi-interquartile range.

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<th>Table 2 Screening strategies assessed</th>
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<tr>
<td>Strategy 1 All subjects to undergo TE (gold-standard strategy).</td>
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<tr>
<td>Strategy 2 All subjects to undergo an ECG. Those subjects with an abnormal ECG to undergo TE.</td>
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<tr>
<td>Strategy 3 All subjects to have NTproBNP serum levels measured. Those subjects with raised levels to undergo TE.</td>
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<tr>
<td>Strategy 4 All subjects to have an ECG and NTproBNP levels measured. Those subjects with either test abnormal to undergo TE.</td>
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<tr>
<td>Strategy 5 All subjects to have an ECG and NTproBNP levels measured. Those subjects with both tests abnormal to undergo TE.</td>
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<tr>
<td>Strategy 6 All subjects to undergo HE. Those subjects thought to have possible LVSD on visual inspection to undergo TE.</td>
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<tr>
<td>Strategy 7 All subjects to undergo an ECG. Those subjects with an abnormal ECG to undergo HE. Those subjects thought to have possible LVSD on visual inspection to undergo TE.</td>
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<tr>
<td>Strategy 8 All subjects to have NTproBNP serum levels measured. Those subjects with raised levels to undergo HE. Those subjects thought to have possible LVSD on visual inspection to undergo TE.</td>
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Natriuretic peptides

Blood was taken after 5 min supine rest into routine biochemistry gel serum separation tubes, allowed to clot, centrifuged, and serum separated and stored at −20°C for 24 h and then −70°C until analysis. Serum NTproBNP levels were analysed on the Elecsys® 2010 system (Roche Diagnostics, Switzerland) blinded to the echocardiography data. NTproBNP values were said to be abnormal if they exceeded age- and gender-specific upper reference values (97.5th centiles) in the local normal population (Table 1), subjects free from cardiovascular risk factors or disease, with normal ECGs and TE studies and no renal failure.

Statistical analysis

Sample size justification has previously been described. Screening characteristics and cost-effectiveness were calculated in three groups. The general population group consisted of all attending general population subjects. The high-risk group consisted of all attending subjects with risk factors for LVSD (hypertension, IHD, DM, PVD, CVD, heavy alcohol usage). The low-risk group consisted of all general population subjects free from such risk factors. Binomial confidence intervals (95%) were calculated for prevalence rates. Two-sided Yates corrected χ² tests were used to compare categorical groups. The screening characteristics and cost-effectiveness,
defined as the cost per case of LVSD found, of eight screening strategies (Table 2) were compared for each group. Strategy 1, or TE alone, was the gold-standard strategy. To account for multiple testing, \( p < 0.01 \) was taken as significant. Data were analysed using Analyse-it for Microsoft Excel version 1.48 (Analyse-It Software Ltd, Leeds, UK).

## Results

### Subject demography

In total, 1205 subjects (52%) attended, 734 (53%) general population invitees and 471 (51%) high-risk invitees. Age was the only significant demographic difference between attendees and non-attendees, with attendees 3 years younger on average \( (p < 0.0001) \). Sixty-four subjects had LVSD, 24 of whom (38%) had a general practice diagnosis of heart failure or LVSD or were taking loop diuretics. The prevalence of LVSD was 3.5% \((2.3–5.2\%)\) in the 734 attending general population invitees vs. 8.5% \((6.1–11.4\%)\) in the 471 attending high-risk invitees \( (p = 0.0004) \). Altogether, 290 general population attendees (40%) had risk factors for LVSD. Thus, 734 subjects made up the general population group, 444 the low-risk group, and 761 the high-risk group. Screenings characteristics

Table 4 shows the screening characteristics of the ECG, NTproBNP, HE, or their combination in detecting LVSD prior to definitive TE. Screening characteristics were not assessed in the low-risk group as only one case of LVSD was found. Table 5 shows the screening characteristics of the ECG and/or NTproBNP in detecting DHF. Fifty-three per cent of subjects with raised NTproBNP levels and 48% of subjects with abnormal ECGs had echocardiographic abnormalities (LVSD, DHF, left ventricular hypertrophy, valvular heart disease, or cor pulmonale).

### Cost-effectiveness of screening

The costs per case of LVSD found using the most likely current estimate of test costs are shown in Table 6.
For this analysis, general population screening characteristics were applied to the low-risk group; unit costs were estimated at 150 Euros (€) for TE (John Chambers, Guys and St Thomas’ Hospital data, personal communication); €37.50 for HE (Northwick Park Hospital data); €22.50 for NTproBNP, and €16.50 for the ECG (John Chambers, Guys and St Thomas’ Hospital data, personal communication). It was assumed that blood tests would be taken at the general practice and sent through post to a central laboratory; that ECGs would be performed at the general practice; that HE would be performed by a trained technician at a variety of large community practices, and that TE would be performed in hospitals.

In this analysis, screening low-risk subjects was always least cost-effective. Similarly, screening high-risk subjects was always more cost-effective than screening general population subjects. TE screening alone (Strategy 1) was always least cost-effective. HE pre-screening (Strategy 6) was always more cost-effective than both NTproBNP pre-screening (Strategy 3) and ECG pre-screening (Strategy 2), which in turn were always more cost-effective than performing both tests and combining the data (Strategies 4 and 5). HE screening after ECG (Strategy 7) or NTproBNP (Strategy 8) pre-screening provided the greatest cost savings, with Strategy 7 the most cost-effective of all. In high-risk subjects, Strategy 7 cost €650 per case of LVSD diagnosed, a cost saving of 63% compared with TE alone.

**Sensitivity analysis**

A sensitivity analysis was performed to assess the cost per case of LVSD diagnosed over a range of test costs in the general population group (Table 7), high-risk group (Table 8), and low-risk group (Table 9). In this analysis, screening high-risk subjects remained most cost-effective; TE screening alone (Strategy 1) remained least cost-effective, and no advantage was seen performing both an ECG and measuring NTproBNP levels. In general population subjects and low-risk subjects, NTproBNP pre-screening (Strategy 3) was more cost-effective than ECG pre-screening (Strategy 2), becoming more cost-effective than HE pre-screening (Strategy 6) once the NTproBNP unit cost fell sufficiently. In high-risk subjects, Strategy 6 remained more cost-effective than Strategies 2 and 3, with Strategy 3 becoming more cost-effective than Strategy 2, as the NTproBNP unit cost fell towards that of the ECG. Strategies 7 and 8 remained the most cost-effective strategies throughout, with Strategy 8 becoming most cost effective as the unit cost of NTproBNP fell.

**Discussion**

This is the first study to compare the ECG, the natriuretic peptide NTproBNP, and HE with TE in screening for LVSD in community subjects, evaluating screening cost-effectiveness in different at-risk groups.
The ECG in screening for LVSD

This study has found that the ECG gives high sensitivity in predicting LVSD in community subjects and significant cost-savings compared with TE alone. However, due to a relatively low specificity and thus high false-positive rate, it remained less cost-effective than NTproBNP or HE in the sensitivity analysis. Similar screening characteristics have been seen elsewhere, confirming this further. In a meta-analysis of four studies involving 1327 subjects, Khunti et al. found that the ECG gave a mean sensitivity of 86% (range 73–94%) and a mean specificity of 58% (range 20–61%) in detecting LVSD, similar values to the current study.

Natriuretic peptides in screening for LVSD

B-type natriuretic peptide (BNP) and NTproBNP are co-released from cardiomyocytes in response to increased myocardial stretch as occurs in LVSD. In the current study, NTproBNP gave a sensitivity of 80% and specificity of 88% in detecting LVSD in general population subjects, similar to data published for BNP. Both peptides can be measured using fully-automated high throughput laboratory equipment, further supporting their screening use.

Nielsen et al. evaluated the cost-effectiveness of screening for LVSD using BNP prior to TE referral, finding similar results. Cost reductions of 45 and 26% were seen in general population subjects and high-risk subjects, respectively, assuming that BNP cost 1/20th of the price of TE. This was equivalent to Strategy 3 in the current study, which found equivalent cost reductions of 77 and 50%, respectively, at this price ratio. The current study found that these reductions could be reduced further to 87% in general population subjects and 73% in high-risk subjects when incorporating HE at a quarter of the cost of TE.

HE in screening for LVSD

Recent advances in ultrasound technology have led to the development of fully portable or ‘hand-held’ echocardiography machines. These machines are small, lightweight, and battery-powered, allowing full portability both within and for the first time outside the hospital setting. They are finding uses on coronary care and intensive care units, on ward rounds, and in outpatient clinics, where rapid answers to specific clinical questions may be required. Recently, it has been suggested that they could screen for LVSD in the community setting, giving close agreement to TE and being able to estimate LVEF in 97% of subjects.10 HE studies are generally focused, ruling in or out specific conditions, and only take a few minutes to perform. The current study found that a visual estimate of LVSD on HE could accurately screen for LVSD with high sensitivity and specificity, producing dramatic cost savings compared with TE, with even greater cost-savings seen when incorporating ECG or NTproBNP data.

Table 6  The cost-effectiveness of screening for LVSD using estimated current test costs

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<thead>
<tr>
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<th>Cost per case of LVSD found (£) (± 95% confidence intervals)</th>
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<tr>
<td>Low-risk population</td>
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<tr>
<td>64050</td>
<td>22846</td>
</tr>
<tr>
<td>General population</td>
<td>4236</td>
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<tr>
<td>High-risk population</td>
<td>1757</td>
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Table 7  The cost per case of LVSD found in general population subjects

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<th>Unit costs of each test (£)</th>
<th>Cost per case of LVSD found (£)</th>
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<tr>
<td>150</td>
<td>37.50</td>
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<td>150</td>
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What is the optimum screening strategy?

This study has found that ECG, NTproBNP, and HE pre-screening prior to TE all produce dramatic cost-savings compared with TE screening alone. NTproBNP pre-screening (Strategy 3) and ECG pre-screening (Strategy 2) give similar cost-savings at projected current costs, with NTproBNP pre-screening becoming more cost-effective as the unit cost of NTproBNP falls towards that of the ECG, a possibility in the future. Furthermore, as the ECG may be difficult to analyse in general practice, while venesection is routine, natriuretic-peptide-driven screening may be the preferred practical choice, also detecting more echocardiographic abnormalities than the ECG (53 vs. 48%), improving cost-effectiveness further. In such a programme, those with raised natriuretic peptide levels would be referred on for hospital-based TE. At projected current costs, such a programme would cost ~€1100 per case of LVSD diagnosed when screening high-risk subjects, a cost saving of 3% compared with hospital-based TE alone. Performing both an ECG and natriuretic peptide blood test and combining the data, a suggested screening strategy\(^{24}\) produces no additional cost-savings.

The use of HE may provide even greater cost savings, with Strategy 6 (HE pre-screening prior to TE) currently costing below €700 per case of LVSD diagnosed when screening high-risk subjects. Furthermore, performing HE after ECG (Strategy 7) or NTproBNP (Strategy 8) pre-screening provides the greatest cost-savings of all, potentially costing €500–600 per case of LVSD diagnosed.

Who should be invited for screening?

This study has shown that screening high-risk subjects is always more cost-effective than screening general population subjects and much more cost-effective than screening low-risk subjects. High-risk subjects were defined as those with any of: IHD, hypertension, DM, PVD, CVD, and heavy alcohol usage (≥40 units of alcohol per week). This study has confirmed these findings further, with 96% of general population subjects found to have LVSD having one or more of these risk factors. Thus limiting screening to these high-risk groups only would preclude few community-cases of LVSD while producing dramatic cost-savings. It should be stressed, however, that with such a screening programme to be widely established, as in any screening programme,
should a subject thought to not have LVSD from the screening programme then develop signs and symptoms necessitating echocardiography referral, this should be arranged.

Screening for diastolic heart failure

This study found that NTproBNP and the ECG give very poor sensitivity in detecting DHF, making screening programmes to detect DHF less justifiable, despite it occurring in up to half of heart failure cases, with therapeutic intervention also unproven.7,8 Redfield et al.25 found similar results for BNP, with age- and gender-corrected BNP cut-offs giving a sensitivity of only 41% in detecting moderate or severe diastolic dysfunction. Similarly, Caruana et al.26 found that only 39 of 109 subjects with clinically suspected heart failure referred for echocardiography and found to have normal LVEF and no valvular heart disease or atrial fibrillation had significant ECG abnormalities (sensitivity 36%).

Study limitations

Although data for Strategies 1–5 came from all attending subjects, data for Strategies 6–8 came from those undergoing HE only. Important differences appear unlikely, however, as virtually identical costs were seen when applying Strategies 1–5 to this subgroup. Secondly, strategies involving symptoms or medications were not assessed nor the strategy of stopping at HE and not performing TE. Thirdly, LVEF was not calculable by TE in 3% of subjects. An alternative gold-standard such as contrast echocardiography may be required in such subjects. Fourthly, despite the fact that a statistically significant difference between attendees and non-attendees could only be found in age, selection bias cannot be fully excluded. Fifthly, this study did not assess the cost-effectiveness of treating subjects once LVSD has been detected. Such analyses have been performed elsewhere, however, suggesting that this would be cost-effective.27,28 Michel et al.,27 in an extrapolation of the SAVE study, calculated that the cost per life-year gained in treating subjects with asymptomatic LVFS following acute myocardial infarction with the ACE-inhibitor captopril was approximately DFI 15 729 (range DFI 0–50 000), equivalent to €7138 (range €0–22 689). Once symptoms have developed, the cost-effectiveness of treatment improves further, with Glick et al.28 in an analysis of the SOLVD Treatment Trial finding that the cost per quality adjusted life-year saved in treating subjects with symptomatic LVFS with the ACE-inhibitor enalapril was $115, equivalent to €97. The cost-effectiveness of beta-blocker therapy in such subjects is yet to be established. Finally, a proportion of subjects with LVSD would be missed by each of the screening strategies. Any extra costs accrued with such subjects to present with clinical heart failure have not been evaluated.

Conclusions

This study thus supports the development of community-based programmes to screen for and treat LVSD, a condition shown to occur commonly in the community and to often go undiagnosed. It supports screening high-risk subjects only (those with one or more risk factor for LVSD), as this would be most cost-effective while missing few community cases of LVSD. It has shown that the ECG, the natriuretic peptide NTproBNP, and HE can all be used cost-effectively for screening, with the most cost-effective strategy of all being natriuretic peptide or ECG pre-screening prior to HE prior to formal TE.

Conflict of interest: none declared.

References

Clinical vignette

Striking left atrial enlargement as a consequence of mitral valve disease

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A 76-year-old woman was referred to our imaging department for evaluation of known mitral valve stenosis (MVS). The patient had been diagnosed as having MVS for 16 years and underwent balloon dilatation 10 years ago. During follow-up at the outpatient clinic, she refused any further interventional treatment. Recently, she was admitted to our emergency department with an acute myocardial infarction, which was treated by primary percutaneous coronary intervention. Chest X-ray demonstrated a strikingly enlarged heart, mainly due to left atrial dilatation (Panel A). Transthoracic 2D-echocardiography revealed a moderately decreased left ventricular function, MVS with severe mitral valve regurgitation and a dilated left atrium (LA) (Panel B, movie 1). As she also had post-infarction angina pectoris with left main stem disease, CABG and mitral valve replacement were considered. Magnetic resonance imaging (MRI) was performed for pre-operative evaluation and demonstrated a LA of 9 × 11 × 15 cm³ (1.5 L), a moderate to severe MVS (area 1.4 cm²), and a severe mitral valve regurgitation with a central jet (Panels C and D, movie 2). Left and right ventricular function was preserved. The patient was referred for CABG, mitral valve replacement, and surgical reduction of the LA.

Panel A. Chest X-ray anterior-posterior showing cardiomegaly.
Panel B. Transthoracic 2D-echocardiography. Apical four-chamber view.
Panel C. Cine MRI in systole. Three-chamber view with aorta (Ao), left ventricle (LV), and LA.
Panel D. Cine MRI in diastole. Three-chamber view with Ao, LV, and LA.