Hypothetical economic analysis of screening for left ventricular hypertrophy in high-risk normotensive populations

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Summary

Background: Left ventricular hypertrophy (LVH) measured by echocardiography is a powerful independent marker of increased cardiovascular risk. The prevalence of echocardiographic LVH in patients with high cardiovascular risk appears to be high, even in patients currently considered normotensive.

Aim: To ascertain the likely costs of screening for and treating echocardiographic LVH in normotensive patients at high risk of cardiovascular events.

Design: Hypothetical economic analysis.

Methods: Cost analyses were based on known costs of echocardiography, costs of selected cardiovascular medications and prevalence of normotensive LVH in at-risk populations, combined with treatment effect data from studies of hypertensive patients with echocardiographic LVH.

Results: Screening costs per case for echocardiographic LVH are likely to be low, because of the high prevalence of the condition and the low unit cost of echocardiography. Treatment costs are likely to be comparable to those currently deemed acceptable in treating high-risk cardiovascular populations, e.g. the HOPE study population.

Discussion: The costs of screening for and treating LVH in normotensive patients at risk of cardiovascular events do not appear to be prohibitively high. Trials of screening and treatment for normotensive LVH seem therefore to be warranted.

Introduction

Increased left ventricular mass index (LVMI) has been unequivocally demonstrated to be a powerful predictor of cardiovascular events, including myocardial infarction, heart failure, peripheral vascular disease, stroke and sudden cardiac death.¹ There is a continuous distribution of LV mass in the general population,² and the risk of cardiovascular events rises in line with LV mass index.³ It has been estimated⁴,⁵ that a 1 g/m² increase in LVMI increases the chance of a cardiovascular event by 1–2%.

LV mass index carries prognostic value that is independent of traditional risk factors such as diabetes, smoking, hypertension and hypercholesterolaemia.¹ The clinical significance of an elevated LV mass index is further illustrated by the improved cardiovascular prognosis following its reduction in hypertensive individuals.⁶,⁷ LV mass index could thus potentially be used as an integrative measure of cardiovascular health or rather the lack of it, thus allowing us to target more aggressive therapy at subgroups with the worst prognosis.

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Traditionally, left ventricular hypertrophy (LVH) has been regarded as a common sequel of systemic hypertension. Recent evidence, however, suggests that LVH also occurs commonly in patients who would usually be classed as normotensive, and that LV mass index is a marker of adverse prognosis in these populations. In studies in our department, 26% of normotensive diabetics had an elevated LVMI on echocardiography, as did 10% of normotensive stroke survivors. In the Framingham study, 28% of women over the age of 60 with a systolic blood pressure of 120–139 mmHg had an elevated LVMI. Thus elevated LV mass index is now known to be prevalent in populations at increased cardiovascular risk who would not be automatic candidates for antihypertensive therapy, as they are currently regarded as normotensive. In fact, the 1999 WHO-ISH hypertension guidelines emphasized the ‘rationale for expecting high risk subjects without hypertension to benefit from blood pressure lowering and the need for clinical trials to investigate this possibility’. Clearly this applies especially to patients with normotensive LVH, but no assessment of the likely cost-effectiveness of such an approach has been done.

If patients with elevated LVMI could be detected by screening, interventions such as weight reduction and antihypertensive therapy (aiming for a lower blood pressure target than has previously been the case) could potentially be applied to these subpopulations with the aim of regressing their elevated LVMI and hopefully reducing cardiovascular events, as we have argued recently in this journal. Such trials have not, as yet, been undertaken. The purpose of this paper is firstly, to estimate the costs that would be incurred if we undertook screening for LVH and treated it when found; and secondly, to derive an indication of the likely cost-effectiveness of doing so, in terms of preventing future cardiovascular events. This would help to ascertain whether detection and vigorous treatment of LVH might be a cost-effective strategy worth exploring in future intervention trials.

Methods

Costs of screening

Left ventricular hypertrophy has previously been diagnosed by electrocardiography, however recent work shows that ECG diagnosis grossly underestimates the prevalence of elevated LVMI. LVMI can be accurately measured via echocardiography; this technique is widely available, has been anatomically validated, and is easy to interpret. Also, unlike other measurement techniques such as magnetic resonance imaging, echocardiography is well tolerated by almost all patients. The drawbacks of echocardiography include problems obtaining good quality images, especially in obese patients and patients with hyperexpanded lungs, and the need for trained personnel to perform the examination.

In this paper we estimate the costs of preventing cardiovascular events by echocardiographic screening for elevated LVMI. The cost-effectiveness depends on the costs of performing screening examinations, the prevalence of the condition in the population under study, and the efficacy of treatment in preventing cardiovascular events. Although data for some of these variables are imprecise, a range of costs can be calculated which allows us to define the boundaries at which a screening and treatment programme would become affordable.

Costs of echocardiography

We have assumed a cost per echocardiographic examination of £50 based on published costs of open-access echocardiographic services. This price includes the cost of leasing machines, echocardiography technician, cardiologist to report scans, plus disposables.

Prevalence of LVH

Prevalence is likely to vary significantly between populations, and also varies depending on the threshold used to define elevated LVMI. We have based much of our calculations on a cut-off point of 125 g/m² for both sexes, as more data are available for this cut-off figure than for other values. The populations quoted above have a relatively high prevalence; the prevalence in unselected populations is considerably lower. A range of prevalence figures is therefore used to calculate the costs presented in Table 1.

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<th>Prevalence</th>
<th>5-year NNT</th>
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<td>5</td>
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<td>1%</td>
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Table 1 Cost of echocardiographic screening for elevated LVMI per cardiovascular event prevented (costs in GBP)
Failed examinations

A proportion of patients screened will have a suboptimal examination, due to inability to obtain good quality M-mode tracings of the left ventricle. This may be due to obesity, abnormal cardiac geometry or hyperinflated lungs, e.g. chronic airways disease. The proportion of patients in whom technical failure occurs is therefore likely to vary markedly between patient populations. Advances in echocardiographic technology (e.g. the introduction of second-harmonic imaging) are likely to lead to fewer failed examinations. Published rates of imaging failure range from 2% to 40%,1,5,6,16–18 we have conservatively assumed a failure rate of 25% for this analysis.

Treatment efficacy

Data on the efficacy of various treatments for normalizing an elevated LVMI are incomplete, especially amongst patients currently classified as normotensive, hence a range of figures is presented. It is worth noting that mean blood pressure in the TOHMS study21 was only 140/91 mmHg; despite this relatively low level, antihypertensive therapy led to marked reductions in LVMI. Two studies suggest that successfully regressing LVH (diagnosed echocardiographically) leads to the cardiovascular event rate dropping to the same level as seen in subjects without echocardiographic LVH.6,7

The ‘number needed to treat’ (NNT) to prevent one cardiovascular event with 5 years of therapy is not known for treatment of normotensive patients with LVH. We have therefore based our cost calculations on a wide range of hypothetical NNTs from 5 to 100. To calculate the cost of screening to prevent one cardiovascular event, we multiply the ‘number needed to screen’ (NNS) to prevent one cardiovascular event by the cost of one echocardiographic examination.

\[
\text{NNS} = \frac{\text{NNT}}{\text{prevalence} \times \text{proportion of successful echo examinations}}
\]

Assuming that 25% of echo examinations will be technically inadequate, the proportion of successful tests is 0.75.

Thus the cost of screening per event prevented is equal to:

\[
\text{Cost} = 50 \times \frac{\text{NNT}}{\text{prevalence} \times 0.75}
\]

Using a range of possible prevalence figures and possible NNT figures, the following range of screening costs can be derived (Table 1).

Costs of treatment

We have approached the estimation of treatment cost in two different ways. In our first example, we have calculated the cost of a drug regimen using two antihypertensive medications: one cheap, the other less so. It is likely that combination drug therapy will be necessary to cause regression of elevated LVMI, as it so often is to effectively control hypertension. Prices are obtained from the British National Formulary (September 2002). We chose to examine losartan and chlortalidone, as both are drugs in common clinical use, both have been shown to reduce LV mass in clinical trials, and both have been shown to reduce cardiovascular event rates in hypertensive patients. There is little consensus as to which drugs are most efficacious at reducing LV mass index, although a meta-analysis predating the LIFE trial suggests that ACE inhibitors, calcium channel blockers and thiazide diuretics are all suitable agents.19

Five years supply of losartan 50 mg daily
\[= 61.5 \text{ p/day} = £1122.38\]

Five years supply of chlortalidone 50 mg daily
\[= 6.0 \text{ p/day} = £109.5\]

Combining these costs, as for a two-drug regimen gives a total of £1231.88 to treat one person for 5 years. In Table 2, we have combined the screening costs from Table 1 with the cost of drug treatment to prevent one cardiovascular event. The drug cost is calculated as the NNT × cost of treating one person for 5 years (i.e. £1231.88 × NNT). We have not included costs associated with other investigations or clinic/manpower costs, as we envisage this screening and treatment programme taking place within an existing disease management service.

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<td>1%</td>
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e.g. a diabetes service, whether in primary care or secondary care.

Table 2 gives the hypothetical costs of screening and treatment for a wide range of prevalence and efficacy indices. It is now possible to narrow down the likely cost range by using published data on the effectiveness of antihypertensives in regressing LVH and reducing cardiovascular events. Using these data, an estimate of the 5-year NNT can be made; if we then assume a similar 5 year NNT for therapy in a high-risk normotensive population, the NNT can be combined with an estimate of the prevalence of LVH in a hypothetical target population to derive an estimate of the cost to prevent one cardiovascular event, albeit only for single-drug therapy.

Based on cohort studies, Koren et al. calculated that a reduction of 1 g/m² in LVMI equated to a 1.3% relative risk reduction in cardiovascular events over a 10-year period. Casale et al. calculated that a reduction of 1 g/m² in LVMI equated to a 2.3% relative risk reduction in cardiovascular events over a 5 year period.

Event rates in hypertensive populations with an LVMI of > 125 g/m² are: (Verdecchia) 3.9% per patient per year, (Casale) 4.6% per patient per year, and (Koren) 2.6% per patient per year. The following examples are calculated based on the event rate of Verdecchia et al., given that their rate represents the middle of those available.

**Results**

**Chlortalidone**

In the TOMHS (Treatment Of Mild Hypertension Study), 4 years of treatment reduced LVMI by up to 17.7 g/m² (on chlortalidone); most of this improvement was seen at 1 year.

The data from Casale et al. suggest a 2.3% relative risk reduction at 5 years per 1 g/m² reduction in LV mass. Thus for a 17.7 g/m² reduction, 17.7 × 2.3 = 41% relative risk reduction at 5 years.

Similarly, data from Koren et al. suggest a 1.3% relative risk reduction at 10 years per 1 g/m² reduction in LV mass. Assuming that the event rates in each group stay constant from year to year, the relative risk reduction at 5 years would also be 1.3% per 1 g/m² reduction in LV mass. Thus for a 17.7 g/m² reduction, the risk reduction would be 17.7 × 1.3 = 23% at 5 years.

Thus, if chlortalidone was used as treatment, a relative reduction in events of between 41% and 23% at 5 years can be expected. If the absolute event rate is 3.9% per patient per year, this equates to a fall to between 2.3% (3.9 × 0.59) and 3.0% (3.9 × 0.77) per person per year. At 5 years, the absolute event rate after treatment would thus be between 11.5% (2.3 × 5) and 15% (3.0 × 5), compared to an absolute risk without treatment of 19.5% (3.9 × 5).

The absolute risk reduction at 5 years is thus 4.5% (19.5%–15%), or 8% (19.5%–11.5%). These figures correspond to NNTs of 100/8 = 12.5, or 100/4.5 = 22 to prevent one cardiovascular event with 5 years treatment.

We can plug the above NNTs back into our earlier calculation. Thus, for a population with a 30% prevalence of LVH and an event rate of 3.9% per patient per year, screening and treatment for 5 years of LVH with chlortalidone alone would cost £2778–£4889 to screen, plus £1368–£2409 to treat, which is £4146–£7298 per CV event prevented (assuming a NNT in the range 12.5–22).

If the prevalence of LVH was as low as 10%, the costs of screening would rise, giving a total of £9702–£17 076 per CV event prevented.

**Losartan**

In the LIFE (Losartan Intervention For Endpoint reduction study), 2 years reduced LVMI from 123 g/m² to 103 g/m², i.e. 20 g/m².

If losartan was used as treatment, a reduction in events of between 46% at 5 years and 26% at 10 years can be expected. For an event rate of 3.9% per patient per year, this equates to a fall to between 2.1% (5 year NNT=11) and 2.9% (5 year NNT = 20).

Treatment with losartan, rather than chlortalidone, thus costs £14 790–£26 892 per CV event prevented (assuming a NNT in the range 11–20).

Again, if the prevalence of LVH was 10% rather than 30%, screening costs rise to give a figure of £19 679–£35 781.

**Costs per event-free life year gained**

It is not possible to calculate actual life years gained from the published data, as a breakdown of cardiovascular events is not available. Without this data, it is not possible to estimate the effect of treatment on saving life years due to stroke, MI, peripheral vascular disease or sudden death. It is possible to express the above calculations as cost per event-free life year gained, however.

Using the example of chlortalidone treatment given above, the absolute event rate after 5 years was estimated at 19.5% without treatment, and between 11.5% and 15% with treatment. Assuming that the frequency of events was the same in each of the 5 years, we can calculate the event-free
life years saved as the area between the curves in Figure 1.

For chlortalidone, the event-free life years saved over a 5-year period are thus: 0.5/C2 (19.5–11.5)/C2 5 = 20, or 0.5/C2 (19.5–15)/C2 5 = 11.25. The above calculations assume that 100 patients are treated.

In order to find 100 patients to treat, assuming a prevalence of 30% in the population to be screened, a total of:

\[ \frac{100}{0.3 \times 0.75} = 444 \text{ patients} \]

need to be screened. The cost of screening is thus £50 \times 444 = £22 200. The cost of treating 100 patients with chlortalidone for 5 years is 100 \times £109.50 = £10 950.

Thus the cost to gain between 11 and 20 event-free life years by screening and treating with chlortalidone is £33 150, or between £16 58 and £30 14 per event-free life year gained.

A similar calculation can be performed for treatment with losartan to derive a cost of between £5916 and £10 756 per event-free life year gained.

**Discussion**

The results derived above are subject to a number of caveats, mostly regarding the effect of treatment on elevated LV mass index in our putative target populations. A number of assumptions are necessary because of the current lack of data regarding the effect of treatment in normotensive populations with elevated LVMI.

Firstly, we assume that antihypertensives or other medications can reduce LVMI by similar amounts in normotensive populations to those seen in trials of hypertensive subjects. Clearly, there is little need to screen hypertensive populations for LVMI in order to commence treatment, as these populations should be treated anyway. Normotensive patients, diabetic patients and patients with known vascular disease with elevated LVMI are more suitable targets, as finding elevated LVMI in these patients would lead to a change in management if antihypertensives were shown to reduce LVMI in these populations.

Secondly, we assume that similar reductions in LVMI are achievable in patients with LVMI >125 g/m²—patients in TOHMS and LIFE had lower mean LV mass indices. Furthermore, we assume that elevated LVMI confers similar (or greater) risk of cardiovascular events in non-hypertensive groups (as discussed above) as it does in hypertensives. This does appear to be the case.\(^8,22\)

Thirdly, we assume that reductions in risk following treatment in non-hypertensive groups with LVH are similar to those seen in hypertensives with LVH. We also assume that regression of LVH on therapy will produce reductions in LVMI and risk that are equivalent to that seen at a lower level of LVMI in the cohort studies discussed. Some evidence for this assumption is provided by the fact that regression of LVMI to normal in hypertensive patients with elevated LVMI reduced the event rate to that of patients who had normal LVMI at the start of the follow-up period.\(^6,7\) A meta-analysis of the effect of antihypertensives on LVMI suggested that the reduction in LVMI was in fact greater with a higher starting LVMI;\(^19\) thus patients with an LVMI of > 125 g/m² may in fact sustain larger falls in LVMI than patients in the LIFE and TOHMS trials who were used to produce our estimates.

We were only able to perform an economic analysis of screening and treatment in terms of cost per event prevented, and cost per event-free life year gained, but not cost per life year gained, due to the fact that studies examining regression of LVH have not subdivided the cardiovascular event rate further. We thus decided to present our findings as cost per event prevented. In order to place these findings in context, we have for comparison calculated the cost per event prevented for treatment of high-risk individuals with ramipril, as per the HOPE study criteria.

The HOPE trial\(^23\) compared the ACE inhibitor ramipril 10 mg/day with placebo in high risk patients (age > 55 years, with diabetes or vascular disease, plus at least one other cardiovascular risk factor). Ramipril produced a reduction in cardiovascular endpoints (CV death, MI, stroke) from 17.8% to 14.0% at 4.5 years, equivalent to a 4.2% absolute risk reduction at 5 years (i.e. 5-year NNT = 24).

Ramipril 10 mg/day for 5 years costs £847. The cost of preventing one CV event in the HOPE population is therefore £20 300. Comparing this figure with Table 2, we see that for populations with a prevalence of LVH of 5% or greater, a 5-year NNT of < 20 gives similar costs to the cost of preventing
one cardiovascular event in the HOPE population. Thus the costs of screening and treating elevated LVMi in high-risk normotensive populations may not be dissimilar from the cost of treating high-risk patients in the HOPE population—a cost which it appears that Western healthcare systems are prepared to bear. As a wider range of cardiovascular medications become available in generic versions, the cost of screening and treating LVH will fall dramatically; the cost of treatment constitutes the bulk of the expenditure, as the differences between Table 1 and Table 2 illustrate. One advantage of our method of presenting cost estimates is the wide range of prevalence and treatment efficacies that we can encompass; factors such as age, sex and comorbid disease are likely to affect the prevalence of disease and the number needed to treat, and data on these factors can be used in our tables as they become available.

**Conclusion**

Left ventricular hypertrophy is associated with an adverse cardiovascular prognosis, and the high prevalence of LVH even among normotensive patients at high risk of cardiovascular events makes it an attractive target for screening and therapy to try to reduce cardiovascular events in these high-risk groups. The costs associated with screening for elevated LV mass index, and the treatment costs thus incurred, appear to be within the range that is likely to make screening and treatment of elevated LV mass index economically viable. Randomized controlled trials of therapies to reduce elevated LV mass index in high-risk normotensive subjects now seem warranted, as our analysis suggests that the cost of such a strategy is far from prohibitive.

**References**

5. Koren MJ, Devereux RB, Casale PN, Savage DD, Laragh JH. Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. *Ann Intern Med* 1991; **114**:345–52.


