Commentary

Should we add screening for and treating left ventricular hypertrophy to the management of all patients needing secondary prevention of cardiovascular disease?

A.D. STRUTHERS J. DAVIES

From the Department of Clinical Pharmacology and Therapeutics, Ninewells Hospital, Dundee, UK

Introduction

Patients with overt vascular disease (TIA, CVA, peripheral vascular disease, etc.) and patients with diabetes are both well known to be at exceptionally high risk of cardiac death, and are generally thought to need more intensive risk factor control, i.e. secondary prevention. Their high risk of cardiac death is generally attributed to coincidental coronary artery disease, leading to cardiac death due to fresh ischaemic events. While coronary disease is undoubtedly important, left ventricular abnormalities could also be a major contributor to cardiac death in these patients, causing 'arrhythmic' as opposed to 'ischaemic' deaths. These left ventricular abnormalities consist of both left ventricular hypertrophy (LVH) and LV systolic dysfunction (LVSD). In this article, we focus only on LVH, as LVSD has often been discussed elsewhere.

That LVH is a risk factor is well established. In Framingham, the relative risk of cardiovascular mortality for every 50 g increment in echo LV mass was 1.73 in men and 2.12 in women, even after correction for risk factors such as blood pressure.\(^1\) Even in patients with established coronary artery disease, the extra risk for cardiac death due to LVH is 2.8, when adjusted for age, gender and hypertension.\(^2\) In patients with coronary disease, this extra risk due to echo LVH appears to be greater than that for multivessel coronary disease or to LV dysfunction: in one head-to-head comparison, the relative risks were 2.4, 1.6 and 2.0, respectively.\(^3\) Unfortunately, the simple ECG is a very insensitive way of assessing LVH.

The new problem of 'normotensive' LVH patients

LVH is now recognized as a risk factor even in patients who are traditionally regarded as 'normotensive'. In the Framingham population, LVH was present in 28% of women aged >60 years with systolic blood pressure between 125 and 139 mmHg (i.e. normotensive, and not requiring antihypertensive therapy by present guidelines).\(^4\) This is especially relevant in light of a recent analysis from the Framingham study, which shows worsened cardiovascular prognosis in such patients with blood pressures in the upper part of the normal range.\(^5\) The above studies add weight to the thesis that risk increases across the whole spectrum of blood pressure. Normotensive LVH patients are common, especially amongst high-risk groups. In one of our studies, LVH was present in 31% of diabetics, and systolic blood pressure was of no value in identifying those diabetics who had LVH.\(^6\)

In this dataset, 26% of normotensive (SBP <140)
LVH as a new therapeutic target

Why should we now want to start focusing on LVH per se as an added risk factor in the secondary prevention of cardiovascular disease? Firstly, LVH is common in patients needing secondary prevention (see above) but it is not routinely screened for (unlike other risk factors like smoking, cholesterol, etc.). In the only real survey of angina patients, LVH was present in 51% of patients, although this was a Black inner-city population. Secondly, LVH occurs commonly when the patient’s blood pressure gives little clue to its presence (see above). Indeed, the lack of correlation between BP and LVH is probably greater in those with previous vascular events, because (sub-clinical) myocardial infarctions (MIs) will reduce cardiac output, leading to a prevailing BP that is lower than the BP when the LVH arose. In addition, ventricular remodelling post silent MI may increase the LV mass while the BP falls. Overall, the lack of connection between LVH and BP is probably greater in those with previous vascular events. The third reason for wanting to direct more attention to LVH in secondary prevention patients is because LVH is such a large and independent risk factor (see above).

The fifth and crucial reason is that the treatment of LVH is known to be an effective way of reducing cardiologic risk. The best indication of this comes from Verdecchia et al. (1998), who showed that the cardiovascular event rate was 1.58 per 100 patient-years in those whose LVH regressed, but 6.27 in those whose LVH did not regress. Importantly, measuring BP changes were of little help in assessing prognosis in this study. Although this was not a randomized trial, the finding has been corroborated by several similar studies, and little doubt now remains that LVH regression reduces risk, to the extent that a formal randomized trial of LVH regression vs. no LVH regression would now be considered unethical.

Since the LIFE and HOPE trials, a cynic might conclude that withdrawing angiotensin II is all that is required to treat LVH. However, the risk of LVH is still great even after angiotensin II withdrawal (losartan or ramipril). For example, the risk ratio for LVH is around 2–4 and yet losartan and ramipril only reduced events by 14–25% in LIFE and HOPE, which leaves a lot of room for further improvement in treating LVH. In any case, since HOPE, many patients needing secondary prevention receive ramipril anyway and the challenge now is how much to add to the ramipril rather than whether to block angiotensin II in the first place.

The adverse effects of LVH are likely to often outweigh those of the conventional risk factors of hypertension, smoking, poor glycaemic control, and hypercholesterolaemia, especially since the latter...
are already treated to their target levels. These latter risk factors are longstanding risk factors, whereas LVH represents target organ damage, and therefore should lead more immediately to morbidity and mortality. Yet management of individuals needing secondary prevention generally focuses on these more easily measured, longstanding risk factors, while neglecting to ascertain whether LVH already exists. Hypertension, smoking, poor glycaemic control, and hypercholesterolaemia deserve the attention they are afforded, but to improve the outlook for the patient needing secondary prevention, attention should also be given to whether extra target organ damage (LVH) has already occurred.

The bottom line is that doctors have not previously appreciated that LVH could be a problem in their patients needing secondary prevention, because they are under the misapprehensions that blood pressure values tell them all they need to know to detect LVH, and that ACE inhibitors are an LVH cure-all. The upshot of all this is that addressing the problem of LVH in secondary prevention patients has the strong potential to eventually reduce their cardiac events and deaths, but we are only now at the first step in addressing this problem of LVH in secondary prevention patients.

**Ways to treat LVH**

The question naturally arises as to what is the best way to reduce LVH. It seems likely that the answer is to aim for a lower target BP than is traditional. It might seem odd that we are arguing that greater BP reduction might be a useful treatment in LVH patients, but epidemiologically we are arguing that BP is only one of many causes of LVH. The PROGRESS and HOPE studies help show that lowering BP, even when it starts in the normal range, can be of benefit in high-risk individuals. Furthermore, an analogy that also helps to explain this apparent anomaly is the recent Heart Protection study (HPS), where total risk was reduced by lowering cholesterol even when it started in the ‘normal’ range. In fact, the HPS illustrates that total cardiac risk can be reduced by lowering one risk factor from normal to low, without fully understanding the various risk factors at play, and without restricting treatment to those risk factors which are at high levels. In a similar way, BP is only a partial cause of LVH, yet reducing BP from normal to low/normal is still the most promising way of achieving extra LVH regression (along with angiotensin II withdrawal for all). Indeed, the TOMHS study has already proven that reducing BP within the normal range does reduce LV mass since, in the TOMHS study, LV mass regression occurred when BP was reduced further from a starting BP of only 140/91 (i.e. when BP was reduced from normal to lower/normal). Thus although BP is an imperfect screening test to identify LVH, the only way known to reduce LVH is to reduce BP further (and undertake angiotensin II withdrawal therapy), and it seems sensible to see how far we can push the idea of reducing BP (to reduce LVH) before moving on to tackling other risk factors for LVH, especially when other risk factors for LVH (e.g. genotypes) are ill understood. It is already appreciated that BP targets are lower for patients in the care of diabetologists (130/80) and nephrologists (120/80). Hence the idea of lower than traditional BP targets for those with LVH is not really a new leap of faith at all. Inevitably there will be many patients (true hypertensives) who cannot have their BP reduced any further, since reaching current BP targets is often difficult, but equally this is not an argument for not trying harder in those who have LVH and room for BP reduction.

A sceptic might say that there is no particular reason why secondary prevention patients should have more LVH than primary prevention patients with the same risk factor profile. This is not really true, since overt vascular disease implies even stiffer proximal arteries, which further increases afterload on the left ventricle. However, even if that were so, the key issue is that patients who have already developed established target organ damage (in their vasculature) are a secondary prevention group in whom we should redouble our efforts to reduce all risk factors. In other words, it is likely to be more cost-effective to detect and treat LVH in secondary prevention patients than it would be to do so in a primary prevention group of patients who happened to have exactly the same cardiovascular risk profile. In fact, viewed in this way, it appears almost scandalous that we currently ignore such a big independent risk factor (LVH) in a group of patients who need all the secondary prevention that they can get. Our inaction may well be because echo services are already stretched in the UK, but expansion of these echo services through additional resources could turn out to be money well spent.

**Summary**

In summary, since vascular patients (TIA, CVA, PAD, angina patients, and diabetic patients) represent a group needing intensive secondary prevention, it is unfortunate that such a large independent risk factor as LVH is generally neglected. Total cardiac risk might well be reduced if LVH were identified and treated to ensure its full regression in
every individual who is needing secondary prevention (including diabetics). The key question of whether it would be cost-effective to include the screening for, and treatment of, LVH in all secondary prevention patients will need to be addressed by a large megatrial, but the scientific case for such a trial appears strong. More generally, we need research into whether paying more attention to LVH will deliver on its potential benefits. Control of traditional risk factors (smoking, cholesterol, etc.) in secondary prevention has not eliminated the problem, and of the adjunctive culprits, LVH seems the most obvious one to address first.

Put most simply, we should be more aware of LVH as a generalized risk factor because it is common and adverse, we should not consider a BP of 140/90 necessarily appropriate for all patients, and we should try where possible for lower target BPs in LVH patients. Finally, we need more research on how we should best approach this common, adverse risk factor that is currently rather neglected.

References