Research Article

Journal of Medical - Clinical Research & Reviews

# Echocardiographic Left Ventricular Hypertrophy (LVH) and Prognosis – A Meta-Analysis

**Deborah J Hilton MPH**[1,2]

[1]*Previously at the Baker Medical Research Institute, St Kilda Road Central, Melbourne, VIC 3004, Australia.*

[2]*Deborah Hilton Statistics Online, Australia (http://sites.google.com/site/deborahhilton/).*

***Correspondence:**
Deborah J Hilton, Deborah Hilton Statistics Online, Australia, E-mail: deborah.hilton@gmail.com.

**Received**: 14 December 2017; **Accepted**: 02 January 2018

**Citation:** Deborah J Hilton. Echocardiographic Left Ventricular Hypertrophy (LVH) and Prognosis – A Meta-Analysis. J Med - Clin Res & Rev. 2018; 2(1): 1-5.

## ABSTRACT

***Background:*** *Different formulae and partition values define left ventricular hypertrophy (LVH) using echocardiography. This diagnostic systematic review investigates further various formulae and cut-points and their predictive potential.*

***Methods:*** *Searches of Medline, EMbase, the Cochrane Library, reference lists and conference proceedings were conducted. Statistical analysis was performed using Meta-test version 0.6 and Epi-info statistical programs. Studies included cohort studies or randomised controlled trials (RCTs) of hypertensive persons where baseline LVH was measured and clinical outcome ascertained.*

***Results:*** *24 studies were identified that included subjects with outcomes such as all-cause mortality, cardiac death, non-fatal cardiovascular (CV) events and/or stroke. Of 10 studies assessing all-cause mortality, 6 were analyzed with the combined relative risk (RR), sensitivity and specificity values being 2.10 (95% CI 1.79-3.24), 57% and 68% respectively.*

***Conclusion:*** *LVH is associated with an approximate two fold increased risk for all-cause mortality.*

## Keywords

Hypertrophy, Left Ventricular; Myocardial Infarction; Meta-Analysis.

## Background

Left ventricular hypertrophy (LVH) confers a potent risk for subsequent cardiovascular (CV) morbidity and / or mortality [1-6], in particular increasing the risk of sudden death [7,8]. The risk is magnified in those with previous coronary artery disease (CAD) or ischaemic heart disease [9,10], CAD [11,12], or a history of prior thromboembolic stroke [13,14]. In addition, studies have shown that the persistence of LVH holds a greater risk than does the regression of LVH [15], and that the risk of sudden death increases progressively and is in direct relation to wall thickness [16], while many studies show that a reversal of LVH decreases the occurrence of adverse CV events in patients with hypertension [17]. Left ventricular mass index [LVMI] is also an independent predictor of cardiac events [18,19], as is a higher left ventricular mass [LVM] [20,21].

A meta-analysis showed that the adjusted risk of future CV morbidity associated with electrocardiographic and echocardiographic LVH combined was 2.3 [22], with the latter test having a greater sensitivity for detecting LVH and hence any adverse prognostic implications. It is also reported that echocardiographic LVH was more sensitive than electrocardiographic LVH in predicting new cardiac events [23]. More recent literature that includes two recently published LIFE sub-studies prospectively trialing anti-hypertensive treatment showed that the greater the reduction of LVH (assessed by electrocardiography or echocardiography) the greater the reduction in CV event rates, independent of treatment modality and of decreases in blood pressure [24]. In fact there are numerous examples in the literature of studies that have demonstrated that the reversal of LVH results in a decrease in the

occurrence of adverse CV events in patients with hypertension [17,25].

Thus, the prognostic importance of LVH therefore cannot be underestimated, for it has been found to be a stronger predictor of outcome when compared to many other conventional risk factors such as cholesterol, smoking or blood pressure [2,26]. This fact has been reflected by recent hypertension guidelines that specify LVH as target organ damage and therefore recommend pharmacological management at lower blood pressure levels due to increased absolute risk. The assumption here is that there is a consistent definition of LVH, however, there are a variety of LVM formulae, indexing methods and cut-points used to define echocardiographic LVH [22]. The primary aim therefore was to analyse the relationship between baseline LVH and subsequent adverse clinical events, assessing which formulae and cut-points are more predictive.

## Methodology

The medical literature was systematically reviewed (Medline, EMbase, Cochrane, reference lists and conference proceedings) to identify cohort studies or RCTs where LVH status at baseline was determined in subjects many of whom had hypertension, with or without CAD and subsequent outcomes ascertained. CV events were defined within each study and included events such as: ventricular fibrillation or sudden death, athero-thrombotic brain infarction, stroke, myocardial infarction (MI), new onset angina, congestive heart failure, coronary artery bypass graft angioplasty and endarterectomy. A number of studies also analysed death from any cause.

The following search terms and strategies were used to search various databases:

- MEDLINE: search terms matched to medical subject headings (MESH): echocardiography AND LVH and the search term: left ventricular mass (text word); human subject limits
- Excerpta Medica Database (EMBASE) using the following search strategy; (left ventricular hypertrophy OR left ventricular mass) AND echocardiography followed by a more specific search using the terms: left ventricular hypertrophy AND echocardiography AND (myocardial infarct OR stroke OR cardiovascular event)
- The Cochrane Database of Systematic Reviews (CDSRs) using the terms: echocardiography and LVH.

Inclusion criteria for studies were that subjects were primarily adult hypertensive subjects, including subjects with resistant hypertension and/or prior coronary heart disease (CHD). Studies were excluded if subjects were to undergo coronary artery bypass graft surgery, or if they were being followed up immediately after cardiac procedures such as aortic valve replacement or following renal transplantation. Studies were also excluded if other conditions were primarily being studied. These conditions included those such as Pompe's disease or type IIa glycogenosis, end stage renal failure, acromegaly, childhood-onset growth hormone deficiency, primary cardiac osteosarcoma in the ventricles, amyloidosis, Friedreich's ataxia, sickle cell disease, primary aldosteronism or acute viral or idiopathic myopericarditis. Studies of elite sportspeople and pediatric subjects were also excluded. The titles were initially reviewed and if deemed suitable abstracts were then reviewed upon which those meeting the above stated inclusion and exclusion criteria were then selected. In total 24 studies were found with outcomes such as all-cause mortality, cardiac death, non-fatal cardiac events and stroke. 6 studies evaluated all-cause mortality.

Subject numbers being those with and without LVH and those who did and who did not experience a subsequent outcome of interest were collated into four by four tables, after which these values were subsequently entered into the Meta-test program [27] and Epi-info 3.3 program [Centers for Disease Control and Prevention 2004] for analysis in order to create individual and combined study relative risk scores [28]. Double checking of data was performed using Medcalc easy to use statistical software online tools [29].

## Results

Table 1 shows the demographics and study characteristics of the trials identified that assessed all-cause mortality outcomes, while table 2 shows the study relative risks and 95% confidence intervals calculated from the raw data in each individual study. The relative risks ranged from 1.5-7.3, while the combined relative risk was 2.1. This is also shown graphically in figure 1. Table 3 displays the true positive, true negative, false positive and false negative rates, sensitivities and specificities with 95% confidence intervals. The pooled sensitivity with a random effects model (REM) was = 0.57 (95% CI 0.42-0.70), while the pooled specificity using a REM was = 0.68 (95% CI 0.54-0.80).

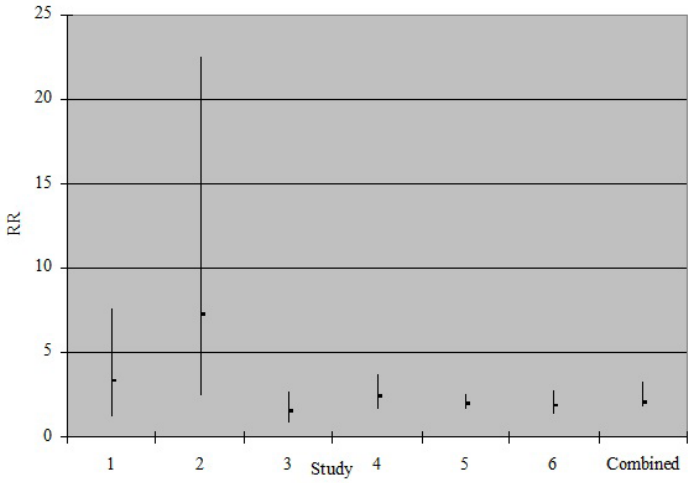


**Figure 1:** All-cause mortality (RR 95% CI)

## Discussion

Considerable controversy and wide variation exists over the most appropriate method of indexation of LVM and the most ideal cut-point for the diagnosis of LVH after indexation. Not only is LVM adjusted and indexed accordingly using various measures being height or size, but in addition different gender specific cut-points are subsequently utilised to diagnose LVH. Additionally risk ratios, hazard ratios and incident rates vary and are not always

| Study | Population | LVH criterion | Follow-up (years) |
|---|---|---|---|
| Mensah et al 1993. [30] | Uncomplicated essential hypertension. n=193 | American Society of Echocardiography Recommendations. Penn convention in the anatomically validated formulae. LVMI = LVM/ body surface area [BSA]. LVH if LVMI >125g/m$^2$. | 11.6 |
| Koren et al 1991. [31] | Essential hypertension; no pre-existing cardiac disease. n=253 | American Society of Echocardiography and the Penn convention. LVMI = LVM/BSA. LVH if LVMI ≥125g/m$^2$. | 10.2 |
| Cooper et al 1990. [11] | High prevalence of hypertension. Normal size left ventricular chamber dimensions. n=744 | American Society of Echocardiography measurements. Modification of the Penn convention as proposed by Devereux and Reichek. LVMI = LVM/height. LVH if LVMI >128g/m; men & > 100 g/m; women. | 5 note; recruitment commenced 1982, follow up 1987. |
| Ghali et al 1992. [9] | Total n=785. Most had hypertension. Previous CAD n=381 No CAD n=404 | American Society of Echocardiography measurements. LVM was calculated using the formulae of Troy and colleagues. This was recalculated with the equation developed by Devereau and colleagues. LVMI = LVM/BSA. LVH if LVMI ≥131g/m$^2$; men & ≥100 g/m$^2$; women. | 4 |
| Ghali et al 1998. [32] | Total n = 988. Predominantly hypertensive. Presumed CAD No CAD; n=542 CAD; n=446 | American Society of Echocardiography measurements. This was recalculated with the formulae developed by Devereau and colleagues which were similar to that derived using the Penn convention measurement. LVMI = LVM/BSA. LVH if LVMI≥131g/m$^2$; men & ≥100 g/m$^2$; women. | 9 |
| Levy et al 1990. [2] | Framingham study; no cardiovascular disease [CVD]. 15.5-19.5% on treatment for hypertension. n=3220 | Echocardiography according to the American Society of Echocardiography convention. Measurements also according to the methods of Devereux and Reichek. LVMI = LVM/height. LVH if LVMI> 143g/m; men & >102 g/m; women. | 4 |

**Table 1:** All-cause mortality; population details and LVH criterion.

| Study | 1. | 2. | 3. | 4. | 5. | 6. | Combined |
|---|---|---|---|---|---|---|---|
| RR | 3.0 | 7.3 | 1.5 | 2.4 | 2.0 | 1.9 | 2.1 |
| 95%CI | 1.2-7.6 | 2.4-22.5 | 0.8-2.7 | 1.6-3.7 | 1.6-2.5 | 1.3-2.8 | 1.8-3.2 |

**Table 2:** Study relative risks [RR] (95%CI).

| Study | TP/FN | FP/TN | Sens % | 95%CI | Spec % | 95%CI |
|---|---|---|---|---|---|---|
| Mensah | 8/8 | 41/136 | 0.50 | 0.26-0.74 | 0.77 | 0.70-0.83 |
| Koren | 11/4 | 58/180 | 0.73 | 0.45-0.91 | 0.76 | 0.70-0.81 |
| Cooper | 27/17 | 357/343 | 0.61 | 0.46-0.75 | 0.49 | 0.45-0.53 |
| Ghali | 60/30 | 296/399 | 0.67 | 0.56-0.76 | 0.57 | 0.54-0.61 |
| Ghali | 167/100 | 280/441 | 0.63 | 0.56-0.68 | 0.61 | 0.57-0.65 |
| Levy | 35/81 | 565/2539 | 0.30 | 0.22-0.39 | 0.82 | 0.80-0.83 |

**Table 3:** All-cause mortality, individual study characteristics.

comparable due to the different populations studied or settings upon which the study sample was drawn.

While a resultant consensus or gold standard for determination of LVH would facilitate cross country epidemiological comparison and standardization, at the time when this original analysis was done no consensus appeared to be in existence.

While this analysis has compared the research and data to an extent using statistical methodology where different formulae and calculations are compared in the sensitivity, specificity and relative risk tables, the difficulty still remains with interpretation. No deduction or recommendation of a standard formulae and method of indexation as such from the results is possible.

It is well known that an increased LVM and a diagnosis of LVH are associated with an increased likelihood of CHD, stroke, sudden death and all-cause mortality even after adjusting for other risk factors [4,33]. In fact LVH is a potent marker and predictor of subsequent mortality and morbidity, including the risk of sudden death [7,8]. Associated hypertension, in particular severe or moderate hypertension, compounds the risk and it has been shown that systolic blood pressure is the principal determinant of LVH regression in hypertensive humans [34]. Evidence in the literature supports the theory that reversal of LVH is possible and this holds potential for the reduction of CV events with timely treatment. A published meta-analysis of studies on this topic showed that regression and/or reversal of LVM using antihypertensive therapy is related to the decrease in systolic blood pressure, duration of therapy, degree of pre-treatment LVH and antihypertensive drug class and that LVM decreased from 5% to 12% depending upon the medication taken with angiotensin-converting-enzyme [ACE] inhibitors followed by calcium channel blockers having the greatest impact while beta-blockers and diuretics had the least impact [35].

The recently published 2nd Australian National Blood Pressure Study (ANBP2) also found that ACE inhibitor antihypertensive treatment in older subjects, particularly men, appears to lead to better outcomes than treatment with diuretic agents, despite similar reductions of blood pressure [36]. Spirito and colleagues [16] quantified the degree of wall thickness in 480 persons and found that in persons with mild hypertrophy there is actually a low risk for subsequent sudden death.

More specifically with respect to LVH, in elderly people there is a high prevalence of this condition with reported estimates varying depending on the population studied and threshold values chosen for diagnosis. Chowdhury and colleagues [37] manuscript reported upon the LVH substudy of the ANBP2 estimating that the prevalence of LVH in elderly persons was 33%-70% depending upon the definition.

Therefore, given the high prevalence of this condition in our community along with the knowledge that correct diagnosis allows for timely pharmacological therapy, and hence the possibility for reversal of increased LVM and the diagnosis of LVH and the subsequent prevention of possible CV events such as sudden cardiac death or angina highlights the importance of a correct and timely diagnosis. This also holds potential for great cost savings to the community.

Alarmingly, but not surprisingly within the Australian community, the burden of CV disease is great with one report titled; "The shifting burden of CV disease in Australia" reporting that 1 in 6 Australians (over 3.2 million people) have some form of CVD. The direct health system costs of CVD are estimated at $7.6 billion in 2004 (11% of total health spending) [38].

The difficulty with meta-analytic methods as represented in this analysis that are used to understand diagnostic formulae and clarify risk is due to the heterogenous nature of the populations in the various studies, with the overall risk varying due to various concomitant conditions or factors such as ischaemic heart disease, valvular heart disease, diabetes and excessive alcohol consumption all of which increase the risk. While this analysis has sought to further consolidate and quantify the additional risk associated with LVH calculating an overall relative risk alternatively a risk stratification model accounting for factors specific to various populations and study groups could be used for the input and calculation of precise, individual risks applicable to different ethnic population groups.

This analysis reported that there is a 2.1 fold associated increased risk for all-cause mortality. Chowdhury et al. [37] analysis of patients with LVH at baseline, LVM indexed to BSA reported the hazard ratio for any fatal CV event as (2.11, [1.21-3.68], P = 0.01) over the longer term. While the tables 1-3 above in this analysis document all-cause mortality, the overall RR statistic calculated and the statistic calculated by Chowdhury and colleagues are equal. It should be noted that this analysis based upon six papers may be possibly updated as the research was conducted over a decade ago and the addition of subsequent manuscripts that have been published may enhance understanding. Other cohort studies that have been subsequently published reporting aggregate data could be incorporated mathematically into the equation and should funding become available this mathematical exercise maybe possible.

While the original analysis that also incorporated review of 13 studies reporting non-fatal and fatal CV events associated with LVH was done, these tables and data that were previously presented in poster format at conferences has not been documented in this manuscript. While one purpose was to investigate usage of the cut-points, formulae and indexation methodology with the aim to refine and choose an optimal cut-point for the clinical diagnosis of this potent condition, that analysis was unable to define an overall optimal cut-point for clinical use. The summary statistic that was calculated at the time was a 2.3 fold increased risk for non-fatal and fatal CV events associated with LVH, however unfortunately, due to the small number of studies using like criteria and the vast number of different cut-points in use, no conclusion was able to be made. Subsequent research however has answered this exact question, whereby Chowdhury and colleagues [37] report that LVH [LVM indexed to BSA] is a reliable predictor of future CV outcomes in the elderly. The hope is that further research will add to the growing body of knowledge and assist to consolidate consensus and refine the conglomeration and/or confusion that may exist with differences in methodology utilised.

## Acknowledgment

Prof CM. Reid (PhD) and Prof GLR. Jennings (MD, AO) [previously at the Baker Institute]; Ms E. Dewar [Alfred Hospital]; Prof M. Abramson [Monash Uni]; Ms S. Wind [Monash Health Medical Library]. Funding; Alfred Research Trusts Small Project Grant [2001].

## References

1. Aronow WS, Epstein S, Koenigsberg M, et al. Usefulness of echocardiographic left ventricular hypertrophy, ventricular tachycardia and complex ventricular arrhythmias in predicting ventricular fibrillation or sudden cardiac death in elderly patients. Am J Cardiol. 1988; 62: 1124-1125.
2. Levy D, Garrison RJ, Savage DD, et al. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. New Eng J Med. 1990; 322: 1561-1566.
3. Galinier M, Balanescu S, Fourcade J, et al. Prognostic value of ventricular arrhythmias in systemic hypertension. J Hypertens. 1997; 15: 1779-1783.
4. Schillaci G, Verdecchia P, Porcellati C, et al. Continuous relation between left ventricular mass and cardiovascular risk in essential hypertension. Hypertension. 2000; 35: 580-586.
5. Gosse P. Left ventricular hypertrophy as a predictor of cardiovascular risk. J Hypertens Suppl. 2005; 23: S27-33.
6. Alfakih K, Reid S, Hall A, et al. The assessment of left ventricular hypertrophy in hypertension. J Hypertens. 2006; 24:1223-1230.
7. Haider AW, Larson MG, Benjamin EJ, et al. Increased left

ventricular mass and hypertrophy are associated with increased risk for sudden death. J Am Coll Cardiol. 1998; 32: 1454-1459.
8. Tin LL, Beevers DG, Lip GY. Hypertension, left ventricular hypertrophy, and sudden death. Curr Cardiol Rep. 2002; 4: 449-457.
9. Ghali JK, Liao Y, Simmons B, et al. The prognostic role of left ventricular hypertrophy in patients with or without coronary artery disease. Ann Intern Med. 1992; 117: 831-836.
10. Liao Y, Cooper RS, Mensah GA, et al. Left ventricular hypertrophy has a greater impact on survival in women than in men. Circulation. 1995; 92: 805-810.
11. Cooper RS, Simmons BE, Castaner A, et al. Left ventricular hypertrophy is associated with worse survival independent of ventricular function and number of coronary arteries severely narrowed. Am J Cardiol. 1990; 65: 441-445.
12. Kakturskii LV. Sudden cardiac death state of the art. Arkh Patol. 2005; 67: 8-11.
13. Aronow WS, Ahn C, Kronzon I, et al. Association of plasma renin activity and echocardiographic left ventricular hypertrophy with frequency of new coronary events and new atherothrombotic brain infarction in older persons with systemic hypertension. Am J Cardiol. 1997; 79: 1543-1545.
14. Aronow WS, Ahn C, Kronzon I, et al. Association of left ventricular hypertrophy and chronic atrial fibrillation with the incidence of new thromboembolic stroke in 2,384 older persons. Am J Cardiol. 1999; 84: 468-469.
15. Muiesan ML, Salvetti M, Monteduro C, et al. Various ways of calculating echocardiographic left ventricular mass and their relative prognostic values. J Hypertens. 1998; 16: 1201-1206.
16. Spirito P, Bellone P, Harris KM, et al. Magnitude of left ventricular hypertrophy and risk of sudden death in hypertrophic cardiomyopathy. N Engl J Med. 2000; 342: 1778-1785.
17. Diez J, Gonzalez A, Lopez B, et al. Effects of antihypertensive agents on the left ventricle: clinical implications. Am J Cardiovasc Drugs. 2001; 1: 263-279.
18. Casale PN, Devereux RB, Milner M, et al. Value of echocardiographic measurement of left ventricular mass in predicting cardiovascular morbid events in hypertensive men. Ann Intern Med. 1986; 105: 173-178.
19. Bolognese L, Dellavesa P, Rossi L, et al. Prognostic value of left ventricular mass in uncomplicated acute myocardial infarction and one-vessel coronary artery disease. Am J Cardiol. 1994; 73: 1-5.
20. Levy D, Garrison RJ, Savage DD, et al. Left ventricular mass and incidence of coronary heart disease in an elderly cohort. The Framingham Heart Study. Ann Intern Med. 1989; 110: 101-107.
21. De Simone G, Devereux RB, Koren MJ, et al. Midwall left ventricular mechanics. An independent predictor of cardiovascular risk in arterial hypertension. Circulation. 1996; 93: 259-265.
22. Vakili BA, Okin PM, Devereux RB. Prognostic implications of left ventricular hypertrophy. Am Heart J. 2001; 141: 334-341.
23. Aronow WS, Koenigsberg M, Schwartz KS. Usefulness of echocardiographie and electrocardiographic left ventricular hypertrophy in predicting new cardiac events and atherothrombotic brain infarction in elderly patients with systemic hypertension or coronary artery disease. Am J Noninvasive Cardiol. 1989; 3: 367-370.
24. Braz Nogueira J. Regression of left ventricular hypertrophy in hypertension--does it reduce cardiovascular risk? Rev Port Cardiol. 2005; 24: 1007-1013.
25. Okin PM, Devereux RB, Jern S, et al. LIFE Study Investigators. Regression of electrocardiographic left ventricular hypertrophy during antihypertensive treatment and the prediction of major cardiovascular events. JAMA. 2004; 292: 2343-2349.
26. Jennings GL, Wong J. Reversibility of left ventricular hypertrophy and malfunction by antihypertensive treatment. In: Hansson L, Birkenhager WH, eds. Handbook of Hypertension. 1997: 18: 184-229.
27. Lau J. Meta-Test version 0.6. 1997, New England Medical Center, Boston.
28. Epi-info version 3.3. 2004 Centers for Disease Control and Prevention, Atlanta, Georgia, USA.
29. Medcalc Online statistical software tools; https://www.medcalc.org/calc/relative_risk.php https://www.medcalc.org/calc/diagnostic_test.php © 1993-2017 MedCalc Software bvba.
30. Mensah GA, Pappas TW, Koren MJ, et al. Comparison of classification of the severity of hypertension by blood pressure level and by World Health Organization criteria in the prediction of concurrent cardiac abnormalities and subsequent complications in essential hypertension. J Hypertens. 1993; 11: 1429-1440.
31. Koren MJ, Devereux RB, Casale PN, et al. Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. Ann Intern Med. 1991; 114: 345-352.
32. Ghali JK, Liao Y, Cooper RS. Influence of left ventricular geometric patterns on prognosis in patients with or without coronary artery disease. J Am Coll Cardiol. 1998; 31: 1635-1640.
33. Benjamin EJ, Levy D. Why is left ventricular hypertrophy so predictive of morbidity and mortality? Am J Med Sci. 1999; 317: 168-175.
34. Verdecchia P, Angeli F, Gattobigio R, et al. Does the reduction in systolic blood pressure alone explain the regression of left ventricular hypertrophy? J Hum Hypertens. 2004; 18 Suppl 2:S23-S28.
35. Schmieder RE, Schlaich MP, Klingbeil AU, et al. Update on reversal of left ventricular hypertrophy in essential hypertension (a meta-analysis of all randomized double-blind studies until December 1996). Nephrol Dial Transplant. 1998; 13: 564-569.
36. Wing LMH, Reid CM, Ryan P, et al. For the Second Australian National Blood Pressure Study Group. A Comparison of Outcomes with Angiotensin-Converting–Enzyme Inhibitors and Diuretics for Hypertension in the Elderly. New Engl J Med. 2003; 348: 583-592.
37. Chowdhury EK, Jennings GL, Dewar E, et al. ANBP2 Echo Study Committee. Predictive Performance of Echocardiographic Parameters for Cardiovascular Events Among Elderly Treated Hypertensive Patients. Am J Hypertens. 2016; 29: 821-831.
38. National Heart Foundation and Access Economics Pty Ltd. 2005. The shifting burden of cardiovascular disease in Australia. Report.