SYSTEMATIC REVIEW

Prognosis associated with geometric patterns of left ventricular remodeling: systematic review and network meta-analysis [version 1; peer review: 1 approved with reservations, 1 not approved]

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Abstract

**Background:** There are four geometric patterns (normal geometry, concentric remodeling, concentric and eccentric hypertrophy) used to describe cardiac remodeling. Although left ventricular hypertrophy (LVH) is associated with adverse prognosis, the incremental prognostic value of geometric patterns is less certain. We examined characteristics and prognosis associated with the four conventional patterns of left ventricle (LV) remodeling.

**Methods:** A comprehensive literature search was performed on MEDLINE/PubMed, Embase and the Cochrane Library until January 2019. Network meta-analysis was used to pool data from direct and indirect prognostic comparisons of the four geometric patterns. All-cause mortality was defined as the study outcome.

**Results:** A total of 22 echocardiographic studies (76,142 individuals; 50.1% males; 64.4±7.9 years) of diverse cardiovascular diseases were included. Concentric LVH was associated with the highest prevalence of cardiovascular risk factors and diseases; and eccentric hypertrophy was associated with a high prevalence of atrial fibrillation and low LV ejection fraction. Compared to normal geometry, the risk of all-cause mortality was increased in concentric hypertrophy (risk ratio 1.97 [95% confidence interval 1.63-2.39]) but similar to eccentric hypertrophy (risk ratio 1.15 [95% confidence interval 0.97-1.36]).

**Conclusions:** The study populations examined in the meta-analysis...
were heterogeneous. Concentric LVH conferred the highest risk of all-cause mortality that overlapped with eccentric hypertrophy. Strategies to improve LVH risk stratification should be examined in future research.

**Keywords**
Left ventricular hypertrophy, geometric patterns of left ventricular remodeling, concentric remodeling, concentric hypertrophy, eccentric hypertrophy

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Introduction
The left ventricle (LV) remodels as a response to cardiovascular disease and myocardial injury. Characterized by an increase in LV myocardial mass, left ventricular hypertrophy (LVH) is an established predictor of poorer cardiovascular outcomes. Four classical geometric patterns of LV remodeling have been defined based on LV mass and relative wall thickness: normal, concentric remodeling, concentric and eccentric hypertrophy. This convenient approach of characterizing LV remodeling has been studied across various patient populations, including patients with coronary artery disease, aortic stenosis, hypertensive heart disease and community-based general populations. Whilst some studies demonstrated prognostic associations with these patterns of LV remodeling, others have not. Knowledge of remodeling patterns (concentric and eccentric hypertrophy) provided particularly limited incremental prognostic information beyond LVH.

In this study, we aim to conduct a comprehensive systematic review and network meta-analysis to examine the characteristics and prognosis associated with the four conventional geometric patterns of LV remodeling.

Methods
Literature search and eligibility criteria
A comprehensive literature search was performed on MEDLINE/PubMed (1946 onwards), Embase (1974 onwards) and the Cochrane Library (1996 onwards) until January 2019. Full text publications evaluating the four conventional LV geometry patterns (normal geometry, concentric remodeling, concentric and eccentric hypertrophy) and prognosis were included. The basic search protocol and specific terms used in the search strategy are available as Extended data. We conducted the literature search using Medical Subject Headings or Emtree, and free text terms. There were no restrictions on language.

Two investigators (Q.Z. and G.L.) independently searched for eligible studies based on the pre-defined eligibility criteria. Full-text studies that compared the prognosis of the four conventional LV geometry patterns (i.e. normal geometry, concentric remodeling, concentric and eccentric hypertrophy) and prognosis were included. We excluded publications in non-adult populations, case reports, commentaries, abstracts, letters-to-editors and review articles. The bibliography in the identified publications and review articles were also reviewed.

Data extraction and quality assessment
The following data were extracted in duplicates by the two investigators (Q.Z. and G.L.) from the included studies: (1) study characteristics (publication year and patient population); (2) baseline characteristics (mean age, sex distribution, and proportion of patients with hypertension, coronary artery disease, diabetes and other significant risk factors); (3) the four LV remodeling patterns; and (4) adverse prognosis defined as all-cause mortality. Eligible studies that did not report all-cause mortality as an end-point were still included to examine clinical characteristics associated with geometric patterns of LV remodeling. Any disagreements were resolved by discussion with a third investigator (C.W.L.C.). In publications with survival curves, the cumulative survival rates were estimated by digitizing the plots (WebPlotDigitizer version 3.9, Austin, Texas, USA).

Two investigators (C.W.L.C. and Z.Q.) independently appraised the quality of each study using the Quality In Prognosis Studies tool. Six domains (study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding; and statistical analysis and reporting) were evaluated to assess the risk of bias in the prognostic studies. In each of the six domains, the risk of bias was classified as “low”, “moderate” or “high”.

Statistical analysis
A network geometry of the four LV remodeling patterns was constructed. Each node represented a remodeling pattern and its size was weighted by the number of individuals in that group. The connecting line between two nodes denoted direct comparison and its thickness reflected the number of studies included. The random-effects meta-regression models were used to measure the impact of baseline characteristics on the effect size of the outcome. The risk ratio (RR) of each LV remodeling group was estimated and reported in the study. To rank the prognosis of all the geometric patterns, we used surface under the cumulative ranking (SUCRA) values. Rank probabilities of all the groups were first estimated, then followed by a step function to summarize the cumulative ranking for estimating the SUCRA values of each group, ranging from 0 to 100%. Larger SUCRA values indicated better prognosis.

Both node-splitting and inconsistency modeling were used to test the consistency assumption. The former method involved fitting a series of node-splitting models, one model for each group pair in which there was direct and indirect comparisons. In the latter method, an inconsistency model was fitted and the global Wald test would determine if significant inconsistency was present. Statistical analyses were performed using Stata/MP Version 13 (StataCorp., College Station, Texas, USA), with the network and network graphs package.

Results
Studies and participants
From an initial 257 publications, 22 echocardiographic studies of diverse cardiovascular diseases satisfied inclusion/exclusion criteria and were included in this study (Figure 1). The thresholds used to define LVH and increased concentricity were heterogeneous across the studies (Table 1).

Of the 76,142 individuals pooled from the 22 studies (50.1% males; 64.4±7.9 years), 49.7% had normal geometry; and 31.1%, 10.5% and 8.7% had concentric remodeling, concentric and eccentric hypertrophy, respectively. The proportion of females with concentric and eccentric hypertrophy was high (40–45%). Compared to the other geometric patterns, concentric...
hypertrophy was associated with the highest prevalence of cardio-metabolic risk factors and cardiovascular diseases. Eccentric hypertrophy was associated with a high prevalence of atrial fibrillation and low LV ejection fraction (Table 2).

**Adverse prognosis associated with geometric patterns of left ventricular remodeling**

Most of the studies demonstrated low risk of bias in the six domains examined (Table 3). The network geometry of LV remodeling patterns was constructed in Figure 2. Concentric remodeling was associated with higher all-cause mortality compared to normal geometry (RR 1.56 [95% confidence interval (CI): 1.31 to 1.85]), and a lower mortality risk compared to concentric hypertrophy (RR 0.79 [95% CI 0.67 to 0.93]). The mortality risk of concentric remodeling was similar compared to eccentric hypertrophy (RR 0.91 [95% CI 0.76 to 1.09]) (Table 4).

Compared to normal geometry, concentric hypertrophy was associated with highest risk of all-cause mortality (RR 1.97 [95% CI 1.63 to 2.39]; Table 4). The confidence limits overlapped with eccentric hypertrophy (RR 1.71 [95% CI 1.43 to 2.04]). Moreover, the mortality risk of concentric hypertrophy was not significantly increased compared to eccentric LVH (RR 1.15 [95% CI 0.97 to 1.36]). Based on the SUCRA values, the geometric patterns ranked from best to worst prognosis were: normal geometry, concentric remodeling, eccentric hypertrophy and concentric hypertrophy (Figure 3).

Results from both node-splitting method and inconsistency model showed no evidence on the violation of consistency assumption between direct and indirect comparisons. Specifically, the pooled estimates between models of consistency (red diamonds) and inconsistency (green diamonds) were identical because all the studies included the four remodeling patterns (Figure 4).

**Discussion**

In this systematic review and network meta-analysis of 22 echocardiographic publications (n=76,133 individuals), we report the characteristics and prognosis associated with the
### Table 1. Baseline characteristics of included studies.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Population</th>
<th>Patients (n)</th>
<th>Females (n)</th>
<th>Age (years)</th>
<th>Definition of left ventricular hypertrophy</th>
<th>Definition of increased concentricity</th>
<th>Follow-up duration (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beger 2011</td>
<td>Coronary artery disease</td>
<td>973</td>
<td>251</td>
<td>66.8</td>
<td>Males: 102; Females: 88</td>
<td>Posterior Wall thickness; 11mm</td>
<td>4.9</td>
</tr>
<tr>
<td>Verma 2008</td>
<td>Coronary artery disease</td>
<td>603</td>
<td>192</td>
<td>65.6</td>
<td>Males: 115; Females: 95</td>
<td>RWT; 0.42</td>
<td>2.1</td>
</tr>
<tr>
<td>Ghali 1998*</td>
<td>Coronary artery disease</td>
<td>446</td>
<td>201</td>
<td>56.9</td>
<td>Males: 131; Females: 100</td>
<td>RWT; 0.45</td>
<td>9.0</td>
</tr>
<tr>
<td>Shigematsu 1998</td>
<td>Hypertension</td>
<td>77</td>
<td>25</td>
<td>57.0</td>
<td>Males: 125; Females: 125</td>
<td>RWT; 0.44</td>
<td>Not stated</td>
</tr>
<tr>
<td>Gerdi 2008</td>
<td>Hypertension</td>
<td>937</td>
<td>388</td>
<td>65.5</td>
<td>Males: 116; Females: 104</td>
<td>RWT; 0.43</td>
<td>4.8</td>
</tr>
<tr>
<td>Fabiani 2017</td>
<td>Hypertension</td>
<td>749</td>
<td>325</td>
<td>62.0</td>
<td>Males: 115; Females: 95</td>
<td>RWT; 0.42</td>
<td>3.7</td>
</tr>
<tr>
<td>Verdecchia 1996</td>
<td>Hypertension</td>
<td>274</td>
<td>78</td>
<td>58.3</td>
<td>Males: 125; Females: 125</td>
<td>RWT; 0.45</td>
<td>3.2</td>
</tr>
<tr>
<td>Kohara 1999</td>
<td>Hypertension</td>
<td>201</td>
<td>100</td>
<td>48.0</td>
<td>Males: 143; Females: 102</td>
<td>RWT; 0.45</td>
<td>Not stated</td>
</tr>
<tr>
<td>Gerdts 2008</td>
<td>Hypertension</td>
<td>192</td>
<td>104</td>
<td>65.5</td>
<td>Males: 116; Females: 104</td>
<td>RWT; 0.45</td>
<td>7.7</td>
</tr>
<tr>
<td>Shigematsu 1998*</td>
<td>Coronary artery disease</td>
<td>446</td>
<td>201</td>
<td>56.9</td>
<td>Males: 131; Females: 100</td>
<td>RWT; 0.45</td>
<td>Not stated</td>
</tr>
<tr>
<td>Krumholz 1995</td>
<td>General Population</td>
<td>3209</td>
<td>1813</td>
<td>57.0</td>
<td>Males: 131; Females: 102</td>
<td>RWT; 0.45</td>
<td>Not stated</td>
</tr>
<tr>
<td>Lieb 2014</td>
<td>General Population</td>
<td>4492</td>
<td>216</td>
<td>53.3</td>
<td>Males: 207; Females: 170</td>
<td>RWT; Males: 0.419; Females: 0.435</td>
<td>4.0</td>
</tr>
<tr>
<td>Gardin 2001</td>
<td>General Population (&gt;65 years old)</td>
<td>2506</td>
<td>1622</td>
<td>-</td>
<td>&gt;95th percentile</td>
<td>RWT; 0.48</td>
<td>6.0</td>
</tr>
<tr>
<td>Milani 2006</td>
<td>Patients EF&gt;50%</td>
<td>35,602</td>
<td>18,869</td>
<td>60.0</td>
<td>Males: 116; Females: 104</td>
<td>RWT; 0.43</td>
<td>3.2</td>
</tr>
<tr>
<td>Lavie 2006</td>
<td>Patients EF&gt;50% (&gt;70 years old)</td>
<td>9771</td>
<td>5569</td>
<td>77.5</td>
<td>Males: 116; Females: 104</td>
<td>RWT; 0.43</td>
<td>3.1</td>
</tr>
<tr>
<td>Lavie 2009</td>
<td>Patients EF&gt;50% (&gt;70 years old)</td>
<td>8088</td>
<td>4564</td>
<td>77.0</td>
<td>Males: 116; Females: 104</td>
<td>RWT; 0.43</td>
<td>3.1</td>
</tr>
<tr>
<td>Ghali 1998*</td>
<td>Patients EF&gt;45%</td>
<td>542</td>
<td>347</td>
<td>54.0</td>
<td>Males: 131; Females: 100</td>
<td>RWT; 0.45</td>
<td>9.0</td>
</tr>
<tr>
<td>Katz 2013</td>
<td>HFpEF</td>
<td>402</td>
<td>251</td>
<td>62.8</td>
<td>Males: 48g/m²; Females: 44g/m²</td>
<td>RWT; 0.42</td>
<td>1.0</td>
</tr>
<tr>
<td>Apostolakis 2014</td>
<td>Atrial fibrillation</td>
<td>2433</td>
<td>1058</td>
<td>69.0</td>
<td>Males: 115; Females: 95</td>
<td>RWT; 0.42</td>
<td>3.5</td>
</tr>
<tr>
<td>Shah 2014</td>
<td>Atrial Fibrillation</td>
<td>1088</td>
<td>496</td>
<td>69.1</td>
<td>Males: 115; Females: 95</td>
<td>RWT; 0.42</td>
<td>6</td>
</tr>
<tr>
<td>Debry 2017</td>
<td>Aortic stenosis</td>
<td>331</td>
<td>150</td>
<td>73.0</td>
<td>Males: 115; Females: 95</td>
<td>RWT; 0.42</td>
<td>3.1</td>
</tr>
<tr>
<td>Capoulade 2017</td>
<td>Aortic stenosis</td>
<td>747</td>
<td>426</td>
<td>69.0</td>
<td>Males: 115; Females: 95</td>
<td>RWT; 0.42</td>
<td>6.4</td>
</tr>
<tr>
<td>Rynuza 2017</td>
<td>Aortic stenosis (TAVI)</td>
<td>208</td>
<td>107</td>
<td>79.4</td>
<td>Males: 115; Females: 95</td>
<td>RWT; 0.42</td>
<td>1.5</td>
</tr>
<tr>
<td>Paoletti 2016</td>
<td>Chronic kidney disease</td>
<td>445</td>
<td>222</td>
<td>64.0</td>
<td>Males: 131; Females: 100</td>
<td>RWT; 0.45</td>
<td>5.9</td>
</tr>
<tr>
<td>Park 2018</td>
<td>Ischemic strokes</td>
<td>2069</td>
<td>787</td>
<td>65.5</td>
<td>Males: 115; Females: 95</td>
<td>RWT; 0.42</td>
<td>3.1</td>
</tr>
</tbody>
</table>

* Two populations were studied in the same publication.

RWT regional wall thickness; HFpEF heart failure preserved ejection fraction; EF ejection fraction; TAVI transcatheter aortic valve implantation

### Table 2. Clinical characteristics associated with geometric patterns of left ventricular remodeling.

<table>
<thead>
<tr>
<th></th>
<th>Normal Geometry</th>
<th>Concentric Remodeling</th>
<th>Concentric Hypertrophy</th>
<th>Eccentric Hypertrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>61.7</td>
<td>65.3</td>
<td>65.4</td>
<td>64.1</td>
</tr>
<tr>
<td>Females, %</td>
<td>15.8</td>
<td>25.1</td>
<td>45.6</td>
<td>42.2</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>134.6</td>
<td>136.7</td>
<td>147.1</td>
<td>141.5</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>9.4</td>
<td>16.7</td>
<td>24.4</td>
<td>17.5</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>27.6</td>
<td>44.0</td>
<td>67.1</td>
<td>58.1</td>
</tr>
<tr>
<td>Coronary artery disease, %</td>
<td>6.9</td>
<td>12.8</td>
<td>22.1</td>
<td>9.7</td>
</tr>
<tr>
<td>strokes, %</td>
<td>3.5</td>
<td>5.5</td>
<td>7.1</td>
<td>4.4</td>
</tr>
<tr>
<td>Atrial fibrillation, %</td>
<td>11.2</td>
<td>21.3</td>
<td>23.9</td>
<td>22.3</td>
</tr>
<tr>
<td>Left ventricular mass index, g/m²</td>
<td>83.9</td>
<td>84.8</td>
<td>133.3</td>
<td>127.2</td>
</tr>
<tr>
<td>Regional wall thickness</td>
<td>0.95</td>
<td>1.13</td>
<td>1.29</td>
<td>1.08</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>59.2</td>
<td>60.9</td>
<td>58.9</td>
<td>53.3</td>
</tr>
</tbody>
</table>
Table 3. Assessing quality of prognostic studies in systematic reviews.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study participation</th>
<th>Study attrition</th>
<th>Prognostic factor measurement</th>
<th>Outcome measurement</th>
<th>Study confounding</th>
<th>Statistical analysis and reporting</th>
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</thead>
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<td>Krumholz 1995</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Verma 2008</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Lieb 2014</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Gardin 2001</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Milani 2006</td>
<td>Low</td>
<td>Low</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Lavie 2006</td>
<td>Low</td>
<td>Low</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Beger 2011</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
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<td>Katz 2013</td>
<td>Low</td>
<td>Moderate</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
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<td>Verdecchia 1996</td>
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<td>Low</td>
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<td>Kohara 1999</td>
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<td>Low</td>
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<td>Moderate</td>
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<td>Apostolaskis 2014</td>
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<td>Low</td>
<td>Low</td>
<td>Low</td>
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<td>Debry 2017</td>
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<td>Low</td>
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<td>Low</td>
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<tr>
<td>Paoletti 2016</td>
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<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
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<tr>
<td>Shigematsu 1998</td>
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<td>Low</td>
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<td>Low</td>
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<td>Gerdts 2008</td>
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<td>Low</td>
<td>Low</td>
<td>Low</td>
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<td>Fabiani 2017</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
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<tr>
<td>Park 2018</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
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<td>Lavie 2009</td>
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<td>Moderate</td>
<td>Moderate</td>
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<td>Capoulade 2017</td>
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<td>Rymuzza 2017</td>
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<td>Moderate</td>
<td>Low</td>
<td>Low</td>
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<td>Shah 2014</td>
<td>Low</td>
<td>Low</td>
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</tbody>
</table>

Figure 2. **Network constructed for the different left ventricular remodeling patterns.** The numbers on the connecting lines denote the studies included for direct comparison.
Table 4. Prognosis associated with geometric patterns of left ventricular remodeling. Results presented in risk ratio and corresponding 95% confidence interval.

<table>
<thead>
<tr>
<th>Reference group</th>
<th>Normal Geometry</th>
<th>Concentric Remodeling</th>
<th>Concentric Hypertrophy</th>
<th>Eccentric Hypertrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Geometry</td>
<td>1.00</td>
<td>0.64 [0.54, 0.76]</td>
<td>0.51 [0.43, 0.60]</td>
<td>0.59 [0.49, 0.70]</td>
</tr>
<tr>
<td>Concentric Remodeling</td>
<td>1.56 [1.31, 1.85]*</td>
<td>1.00</td>
<td>0.79 [0.67, 0.93]</td>
<td>0.91 [0.76, 1.09]</td>
</tr>
<tr>
<td>Concentric Hypertrophy</td>
<td>1.97 [1.63, 2.39]*</td>
<td>1.27 [1.08, 1.49]*</td>
<td>1.00</td>
<td>1.15 [0.97, 1.36]</td>
</tr>
<tr>
<td>Eccentric Hypertrophy</td>
<td>1.71 [1.43, 2.04]*</td>
<td>1.10 [0.92, 1.31]</td>
<td>0.87 [0.73, 1.03]</td>
<td>1.00</td>
</tr>
</tbody>
</table>

*p-value < 0.05

Figure 3. Forest plot of direct comparisons with pooled results from network meta-analysis. A, normal geometry; B, concentric remodeling; C, concentric hypertrophy; D, eccentric hypertrophy.

different patterns of LV remodeling. The study populations were heterogeneous and, importantly, the definitions used to classify the geometric patterns were not uniform. Concentric hypertrophy is associated with the highest prevalence of cardiometabolic risk factors and diseases. Eccentric hypertrophy is associated with a high prevalence of atrial fibrillation and the lowest LV ejection fraction. Although concentric hypertrophy is associated with the highest risk of all-cause mortality, the risks overlapped with eccentric hypertrophy. Eccentric hypertrophy has a similar mortality risk compared to concentric remodeling.

The pathophysiology of LVH has been well described and studied for the past 50 years. Cardiac hypertrophy is initially an adaptive response to the wall stress according to the Law...
Figure 4. (a) Rank probabilities of effectiveness and SUCRA scores; and (b) prognosis of the four geometric patterns of left ventricular hypertrophy.
of Laplace. Ultimately, cardiac decompensation occurs as a consequence of myocyte death and myocardial fibrosis\textsuperscript{34,35}. Whilst geometric patterns of LV remodeling are clinically meaningful to describe the hypertrophic response due to mechanical stress from either pressure (concentric hypertrophy) or volume overload (eccentric hypertrophy), it may not adequately identify the transition point where adaptive hypertrophy decompensates (Figure 5). This transition point before cardiac decompensation occurs is an important potential risk marker to target more intensive management and closer surveillance. In this study, we have demonstrated that both concentric and eccentric hypertrophy were associated with similar risks of increased all-cause mortality. These observations may suggest that the risk of adverse prognosis is increased once LVH develops, regardless of geometric patterns. It may also suggest that some patients with concentric or eccentric LVH may be in the compensated phase and begets the question of whether there are other strategies to identify high-risk LVH phenotypes.

To address the complex interaction between LV dilatation and myocardial thickening in the pathophysiology of LVH, several studies have recently examined an expanded four-group LVH classification: dilated/non-dilated concentric hypertrophy and dilated/non-dilated eccentric hypertrophy\textsuperscript{36–40}. In this proposed four-group LVH classification, dilated concentric hypertrophy was associated with the worst prognosis and non-dilated eccentric hypertrophy had the most favourable profile\textsuperscript{36–39}. However, more guidance is needed before this complex classification can be integrated into routine clinical practice. Recently, we have developed the remodeling index (RI), based on a biophysical model of Laplace’s Law. The RI integrates LV volume and myocardial thickening into a single measurement\textsuperscript{41}. We further demonstrated that hypertensive LVH patients with abnormally low RI (suggestive of excessive myocardial thickening relative to LV dilatation) had increased myocardial fibrosis, elevated circulating markers of myocardial injury and wall stress; and in a small number of patients with dilated cardiomyopathy, an abnormally high RI (suggestive of excessive LV dilatation relative to myocardial thickening) was associated with adverse cardiovascular events\textsuperscript{41}. The prognostic value and clinical utility of this index are currently being examined in a large cohort of hypertensive patients (ClinicalTrials.gov identifier: NCT02670031).

These emerging data support the notion that cardiac remodeling in hypertrophy is heterogeneous and complex; and the conventional geometric patterns of LV remodeling is not adequate to risk-stratify patients with LVH.

**Study limitations**

The study populations included in the meta-analysis were heterogeneous. It is possible that the conventional remodeling patterns has incremental prognostic value in certain cardiac conditions. Unfortunately, the limited number of studies precluded stratified analyses to examine the prognostic value of LV geometric patterns in the different cardiovascular conditions. The definitions used for classifying geometric patterns were not consistent across the different studies. This is concerning and reinforces the necessity to apply consensus definitions in future studies\textsuperscript{2}.

**Conclusions**

Concentric and eccentric hypertrophy are associated with increased and similar all-cause mortality. Possible explanations for these observations include the heterogeneous populations, inconsistent definitions used in the classification and the inherent limitations of the conventional patterns of LV geometry to adequately risk stratify LVH. Well-validated novel approaches

![Figure 5. Relationship between geometric patterns of cardiac remodeling, mechanical stress and prognosis.](image-url) Geometric patterns of left ventricular remodeling are useful to identify the mechanisms of mechanical stress; but may not adequately identify the transition between myocardial adaptation and decompensation.
to improve risk stratification of LVH should be explored in future research.

**Data availability**

**Underlying data**

All data underlying the results are available as part of the article and no additional source data are required.

**Extended data**

Open Science Framework: Prognosis associated with geometric patterns of left ventricular remodeling: systematic review and network meta-analysis. [https://doi.org/10.17605/OSF.IO/3CJMW](https://doi.org/10.17605/OSF.IO/3CJMW). This project contains the following extended data:

- Data file.xlsx (Sheet 1 contains study questions, search date, search terms and eligibility criteria; Sheet 2 contains a list of the studies identified; Sheet 3 contains the six composites used in this study).

**Reporting guidelines**

Open Science Framework: PRISMA checklist for “Prognosis associated with geometric patterns of left ventricular remodeling: systematic review and network meta-analysis”. [https://doi.org/10.17605/OSF.IO/3CJMW](https://doi.org/10.17605/OSF.IO/3CJMW). Data are available under the terms of the Creative Commons Zero “No rights reserved” data waiver (CC0 1.0 Public domain dedication).

**Grant information**

The author(s) declared that no grants were involved in funding this work.

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**References**


Zheng et al performed a systematic review and meta-analysis of echocardiographic studies that included prognostic characteristics of 4 geometric patterns of cardiac remodeling. Through the combined total of 22 studies comprising diverse populations, including hypertension, aortic stenosis, heart failure with preserved ejection fraction, ischemic strokes, chronic kidney disease etc, the authors conclude that the presence of concentric LVH and eccentric hypertrophy was associated with a higher risk of all-cause mortality.

The overall aim of this study is commendable. Nonetheless, there are a few areas of note:

- The study includes populations both with and without pre-existing cardiovascular disease; in such a situation, the baseline risk profiles differ significantly (e.g. an apparently healthy individual with newly diagnosed hypertension has a substantially lower risk profile compared to an individual with pre-existing or longstanding aortic stenosis although both may develop LVH eventually).

- A suggested approach would be to stratify the risk of LVH based on aetiology (e.g. hypertension-related, aortic stenosis related, multifactorial etc.) which would make the meta-analysis more applicable to the above sub-groups of patients rather than providing a single risk ratio for an entire phenotypic category of cardiac remodeling.

- The authors may consider excluding the studies involving the general population to limit the study population to those with pre-existing disease, as the absolute number of Framingham subjects with LVH was actually small.

- Importantly, the classification of LVH and RWT differed in certain studies, so applicability is affected. Although the authors listed this as a limitation, studies with substantial differences in quantifying LVH might need to be excluded in order to keep the study population...
homogenous.

- In Table 2, regional (or relative, as stated by the American Society of Echocardiography and other international echocardiography societies) wall thickness for all 4 categories of cardiac remodeling ranged between 0.95 to 1.29. Do check if this is correct, as that would classify all subjects in the concentric geometry.

- For the conclusion, the authors are right to say that the study populations were heterogeneous. As such, it might be more appropriate to generate different risks for the larger subsets of patients (eg. LVH from hypertension vs LVH from aortic stenosis vs LVH from combined causes) rather than to generalise risk for all patients regardless of aetiology.

Are the rationale for, and objectives of, the Systematic Review clearly stated?
Yes

Are sufficient details of the methods and analysis provided to allow replication by others?
Yes

Is the statistical analysis and its interpretation appropriate?
I cannot comment. A qualified statistician is required.

Are the conclusions drawn adequately supported by the results presented in the review?
Partly

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Sports cardiology; Athlete's heart; physiological vs pathological cardiac remodeling in athletes.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 16 October 2019
https://doi.org/10.5256/f1000research.21845.r54455

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systematic review and network meta-analysis” by Zheng et al aims to identify different prognostic profile of different left ventricular remodeling patterns. Although the aim is of interest, the method to select data from the international literature is quite messy. In fact, populations are not homogenous (from population-based studies like the FHS, to patients with stable CAD, to patients with hypertension, aortic stenosis, HFpEF, etc). In addition, methods reported in studies to categorize left ventricular remodeling are still not homogeneous. Consequently, conclusions of the paper are erroneous.

Authors stated that the new classification of left ventricular remodeling proposed by Khouri is “complex” and “more guidance is needed before this complex classification can be integrated into routine clinical practice”, so that they propose a more simple index (the remodeling index) which at moment is tested by the authors in a trial of hypertensive patients.

We thank the Author for the suggestion, i.e. to use their index; of course, to demonstrate in the future that their index is superior to that used in the past, they will have to perform a correct statistical analysis, confronting their index with clear-cut values suggested by guidelines and more recently by Khouri, (which, I guess, is very easy to use into clinical practice) for the identification of left ventricular remodeling patterns.

Are the rationale for, and objectives of, the Systematic Review clearly stated?
Yes

Are sufficient details of the methods and analysis provided to allow replication by others?
No

Is the statistical analysis and its interpretation appropriate?
No

Are the conclusions drawn adequately supported by the results presented in the review?
No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Hypertension

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 16 Oct 2019

Calvin Chin, National Heart Center Singapore, Singapore, Singapore

We thank the Reviewer for the comments. We wish to highlight the issues raised by the Reviewer are inherent to the individual studies and not the methodology of the meta analysis. We agree with the Reviewer that the study populations included in the study are heterogeneous. Unfortunately, the limited number of studies precluded further analyses to examine prognostic value of LV geometric patterns in different cardiovascular conditions.
The definitions used for classifying geometric patterns were not consistent in the studies as highlighted by the Reviewer, a limitation that reinforces the necessity of applying consensus definitions in future studies. Both of these points have already been listed as study limitations.

**Competing Interests:** None