Pseudonormal mitral filling is associated with similarly poor prognosis as restrictive filling in patients with heart failure and coronary heart disease: a systematic review and meta-analysis of prospective studies

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CRD summary
This review reported a four-fold increase in death associated with pseudonormal mitral filling in comparison with other non-restrictive filling in patients with coronary artery disease and heart failure; there was no significant difference between pseudonormal and restrictive filling. Limitations in the analyses and the unclear methodology and quality of the included studies suggest that the conclusions may not be reliable.

Authors' objectives
To compare pseudonormal mitral filling with restrictive filling and with other non-restrictive filling in relation to death in patients with heart failure or coronary heart disease.

Searching
MEDLINE and MEDLINE In-Process and Other Non-Indexed Citations (both via PubMed), EMBASE, Biological Abstracts, Clinical Evidence and Current Contents were searched. Search terms and dates were not reported. Reference lists of retrieved studies and reviews were examined for further studies. Authors of included studies were contacted for additional studies, unpublished data and ongoing studies.

Study selection
Studies that prospectively enrolled patients with heart failure or coronary heart disease, either post-acute myocardial infarction (AMI) or post-coronary artery bypass graft surgery (CABG), were eligible for inclusion in the review. Eligible studies had to perform baseline echocardiographic examinations, report diastolic parameters and assess long-term mortality.

Most included studies were in patients with heart failure; one study included patients post-AMI and another post-CABG. Mean age of included participants was 65 years (means ranged from 57 to 73 years). The pooled average ejection fraction was 34.5%. Where reported, the proportion of patients with coronary heart disease ranged from 37% to 100%. The definition of pseudonormal filling pattern varied between studies (further details reported in the review). Studies had a mean follow-up period of 15 months. Two studies were carried out in Italy and single studies in France, Denmark, New Zealand, Japan and USA. All-cause mortality was recorded. Baseline mitral filling pattern determined by echocardiography.

The authors stated neither how papers were selected for review nor how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
The authors stated neither how data were extracted for the review nor how many reviewers performed data extraction. The odds ratio (OR) for all-cause mortality with 95% confidence intervals (CIs) was calculated for each study that compared pseudonormal and other non-restrictive filling and restrictive and pseudonormal filling. Authors were contacted for missing data.

Methods of synthesis
Pooled odds ratios with 95% CIs were calculated using a fixed-effect model and the Mantel-Haenszel method. Subgroup analysis according to primary morbidity (coronary heart disease or heart failure) was carried out. Statistical heterogeneity was assessed using the $I^2$ statistic; a value of over 50% was considered to indicate substantial heterogeneity. Studies thought to contribute substantial statistical heterogeneity were excluded from further analyses.
Publication bias was assessed by means of a funnel plot.

**Results of the review**

Eight studies (n=887; 74.4% with heart failure and 25.6% with coronary heart disease) were included in the review. Sample sizes ranged from 62 to 240.

The odds ratio for all-cause mortality in the pseudonormal filling pattern group in comparison with the non-restrictive pattern group was 4.46 (95% CI 2.87 to 6.92; seven studies); however, there was evidence of significant statistical heterogeneity ($I^2=53.3\%$). There was no statistically significant difference in all-cause mortality between pseudonormal filling and restrictive filling (seven studies), but this result was also associated with a significant level of statistical heterogeneity ($I^2=67.2\%$).

Subgroup analysis showed no statistical heterogeneity in the coronary heart disease subgroup, but significant heterogeneity in the heart failure group, the latter due mainly to one study with a substantially longer follow-up duration and event rate. When this study was excluded the data still showed no statistically significant difference in all-cause mortality between pseudonormal and restrictive filling, but there was no longer any evidence of substantial statistical heterogeneity ($I^2=42.3\%$). The odds ratios for all-cause mortality comparing patients with pseudonormal filling and other non-restrictive filling or restrictive fillings were similar regardless of the type of primary morbidity (coronary heart disease or heart failure). Assessment of publication bias using a funnel plot was limited by the small number of included studies.

**Authors’ conclusions**

A four-fold increase in death was associated with pseudonormal mitral filling in comparison with other non-restrictive filling in patients with coronary artery disease and heart failure; there was no significant difference between pseudonormal and restrictive filling.

**CRD commentary**

This review answered a clear research question. Searches were carried out in a number of electronic databases to identify relevant data, but search dates and terms were not reported. Some attempts were made to search for unpublished data. A planned assessment of publication bias was not possible due to the small number of included studies. The risk of language bias was unclear. It was not possible to determine the risk of reviewer error and bias as the authors failed to describe their methods in sufficient detail. There was no assessment of study quality, which made it difficult to determine the reliability of the data. It was unclear what types of study designs were included in the review. The authors identified a number of limitations with respect to when and how the assessment of mitral filling pattern was carried out and whether an echocardiogram was carried out. Studies were combined despite significant statistical heterogeneity. Subgroup and sensitivity analyses were carried out, but these were unlikely to be reliable given the small numbers of studies and participants. Overall, limitations in the analyses and the unclear methodology and quality of the included studies suggest that the conclusions may not be reliable.

**Funding**

One author was supported by a Douglas Goodfellow Medical Research Fellowship from the Auckland Medical Research Foundation and another was supported by a National Heart Foundation of New Zealand Senior Fellowship.

**Bibliographic details**


**PubMedID**

19307097

**DOI**

10.1016/j.echo.2009.02.003
Original Paper URL

Other publications of related interest
Practice: The authors stated that this study confirmed the prognostic value of a pseudonormal mitral filling pattern in patients with established cardiovascular disease (American College of Cardiology/American Heart Association (ACC/AHA) stages B and C heart failure). Pseudonormal and restrictive mitral filling patterns were both associated with an increased risk of death. Such patients should be managed closely.

Research: The authors stated that there was a need for further studies to investigate the relationship between pseudonormal mitral filling and outcome in patients with a high risk of developing heart failure, but with no underlying structural heart disease (ACC/AHA stage A heart failure). A direct head-to-head comparison to determine the most accurate and time-efficient method of determining the mitral filling pattern as part of the routine echocardiographic risk stratification in patients with coronary heart disease was required.

Indexing Status
Subject indexing assigned by NLM

MeSH
Clinical Trials as Topic /statistics & numerical data; Comorbidity; Coronary Artery Disease /mortality /ultrasonography; Female; Heart Failure /mortality /ultrasonography; Humans; Incidence; Male; Mitral Valve Insufficiency /mortality /ultrasonography; Risk Assessment /methods; Risk Factors; Survival Analysis; Survival Rate

AccessionNumber
12009105828

Date bibliographic record published
05/08/2009

Date abstract record published
03/02/2010

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.