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Long-term outcome of nonobstructive versus obstructive hypertrophic cardiomyopathy: A systematic review and meta-analysis

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ABSTRACT

Background: Prognosis of hypertrophic cardiomyopathy (HCM) is particularly heterogeneous. Patients with nonobstructive HCM (NOCM) are thought to be at relatively low-risk as compared with obstructive HCM (HOCM) with no need of major treatment options. However, available evidence of NOCM comes mainly from tertiary centers where a referral bias is likely to occur. Aim of this study was to perform a systematic review and meta-analysis of the published literature on hypertrophic cardiomyopathy (HCM) in order to outline differences in presenting features and long-term outcome between NOCM and HOCM.
Methods: MEDLINE/Pubmed, EMBASE and Cochrane databases up to December 31, 2016, and reviewed cited references to identify relevant studies were used. The primary endpoints were HCM-related overall mortality rate and yearly rate of cardiac death. Other endpoints were incidences of sudden and congestive heart failure deaths.
Results: A total of 20 studies entered the meta-analysis on the long-term outcome of NOCM vs HOCM. They included a total of 7731 patients, 5058 patients with NOCM (65%) and 2673 patients with HOCM (35%). During the follow-up, annual mortality related to HCM averaged 1.55% in NOCM and 1.77% in HOCM (Relative Risk: 0.89, 95% confidence intervals: 0.68 to 1.17, $p = 0.40$). Overall, 5 studies reported significantly higher mortality for HOCM, 3 higher mortality for NOCM, and 12 no significant differences.
Conclusion: This large study-level meta-analysis shows that long-term mortality of patients with NOCM is not negligible and not significantly different from HOCM.

1. Introduction

The natural history of hypertrophic cardiomyopathy (HCM) is particularly heterogeneous and is still matter of debate [1–12]. Indeed, five decades following the initial description of HCM, there is still a dismal paucity of data regarding clinical presentation and long-term outcome of nonobstructive HCM (NOCM) patients with respect to obstructive HCM (HOCM) [2]. NOCM patients are often believed to experience a relatively stable clinical course without significant symptoms, high-risk profile, or the necessity of major treatment options [2–4]. However, available evidence of NOCM comes mainly from tertiary centers where a referral bias is likely to occur [2]. The presence of a left ventricular outflow tract obstruction (LVOTO) is said to be a major determinant of symptoms and prognosis [5], and has become the most visible and consistent target of therapeutic efforts in HCM based on reduction strategies [6]. This can be regarded as a paradox, as most

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patients with HCM do not require surgery or ablation, but nonetheless have significant symptoms and are at increased risk of sudden cardiac death (SCD) or progression to heart failure [7].

The aim of the NOCM (loNg-term Outcome in non-obstructive hypertrophiC cardioMyopathy) study was to perform a systematic review and meta-analysis of the published literature on HCM in order to define differences in presenting features and long-term mortality between NOCM and HOCM.

2. Methods

2.1. Study design

This meta-analysis was conducted following current guidelines, including the Cochrane Collaboration and Meta-analysis Of Observational Studies in Epidemiology (MOOSE), and the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) amendment to the Quality of Reporting of Meta-analyses (QUOROM) statement. The NOCM study was registered at the PROSPERO International prospective register of systematic reviews of the University of York, UK (Registration No. CRD42013005603). All activities were carried out independently by two reviewers (FP and VP). Divergences were solved after consensus.

2.2. Data sources

We searched and reviewed cited references up to December 31, 2016 to identify relevant studies. MEDLINE/Pubmed was searched with the following key-words: 'hypertrophic cardiomyopathy', 'nonobstructive', 'obstructive', 'outcome', 'prognosis' and 'SCD'. Additional studies were searched in the Cochrane Library, Google Scholar, and Scopus. Editorials and reviews from major medical journals published within the last 5 years were also considered for further information on studies of interest. No language restriction was enforced in order to minimize the risk of publication bias.

2.3. Study selection

Retrieved citations were first screened independently by two unblinded investigators (FP and VP) at the title and/or abstract level, with divergences resolved after consensus. Studies were screened in order to identify potentially suitable articles that should be assessed for eligibility for analysis of full-text. Noteworthy, a detailed review of study authors, dates, and locations was used to exclude redundancy. Studies with overlapping data were identified, and in cases of apparent serial reporting of a particular patient cohort, the publication with the largest number of patients was included in the meta-analysis. Only observational studies published in original articles in peer-reviewed scientific journals were taken into consideration. Studies were then selected according to the following explicit inclusion criteria (all had to be met for inclusion): (i) patient population of patients diagnosed as having HCM according to standard clinical guidelines; [13,14]; (ii) a minimum duration of follow-up >12 months; (iii) a detailed description of outcome results. The subset of studies with a comprehensive reporting of demographics, clinical and echocardiographic characteristics of HCM study patients with or without a LV outflow tract gradient were used also for comparing also NOCM vs HOCM.

2.4. Data extraction and quality

Analysis was performed at the study level, as it was not possible to obtain individual patients data. Data from each study were extracted by two independent reviewers (FP and VP) and entered into a structured spreadsheet. Disagreements were resolved by consensus. Dichotomous variables were used in absolute numbers and were recalculated when percentages were reported. Continuous variables were extracted and weighted means for the total study population were calculated. The primary endpoint was HCM-related death. Other endpoints were the incidence of SCD and death due to congestive heart failure. SCD was defined as instantaneous and unexpected natural death, or an aborted cardiac arrest with documented ventricular fibrillation in patients previously in stable clinical condition. Appropriate implantable cardioverter defibrillator interventions were counted once as SCD equivalent [15]. Heart transplantations were counted once as death due to congestive heart failure equivalent. The longest available clinical follow-up was exploited to abstract data on mortality. Methodological quality of all studies was assessed using the Methodological Index for Non-Randomized Studies (MINORS). Studies were defined to be low-quality and high-quality studies based on their MINORS scores of <16 and ≥16 points [16].

2.5. Data analysis and synthesis

All analyses were performed using the Review Manager 5.2 freeware software (available from The Cochrane Collaboration at http://www.cochrane.org). Since heterogeneity of results was expected, the inverse variance method for random effects was used to estimate pooled risk ratios [17]. We tested the heterogeneity of the included studies with Q statistics and the extent of inconsistency between results with I2 statistics [18]. However, we did not exclude outliers based on heterogeneity since heterogeneity is expected in meta-analyses of epidemiological studies [19]. The possibility of publication bias was assessed by funnel plot analysis. Data are presented as risk ratio with 95% confidence intervals, with statistical significance set at $p < 0.05$ (two-tailed).

3. Results

3.1. Search results

From 1012 initial citations that were retrieved from multiple databases, a total of 90 articles were analyzed as full reports according to predefined selection criteria. After excluding 58 studies because of several reasons (Table 1 Supplemental), 32 investigations were finally deemed as eligible for inclusion in our systematic review. Of them, 20 studies entered the meta-analysis of the long-term outcome of NOCM vs HOCM [20–39], with 9 of them being used also for comparing presenting features between NOCM and HOCM [20,27,29,30,32,34,35,38,39]. These 20 studies included a total of 7731 patients, 5058 patients with NOCM (65%) and 2673 patients with HOCM (35%). In addition, 14 studies on a total of 1417 patients with apical HCM were entered into a separate analysis [34,37,40–50]. The progress through the different steps of the search results is illustrated in Fig. 1 Supplemental. Selected studies were published previously (between 1990 and 2016) and included series of patients from North America, Europe, and Asia (Table 2 Supplemental).

3.2. Presenting features

Comparison of clinical features at referral was carried out in a total of 4474 patients enrolled in 9 studies, 2849 patients with NOCM (64%) and 1625 patients with HOCM (36%) (Table 3 Supplemental). A New York Heart Association functional class III or IV was found in a lower proportion of NOCM than HOCM patients (8% vs 16%, $p = 0.0001$). Maximal LV wall thickness (20 vs 22 mm, $p = 0.005$) and left atrial dimension (41 vs 45 mm, $p = 0.0001$) were smaller in NOCM than HOCM patients. Mitral regurgitation was less common in NOCM than HOCM patients (9% vs 17%, $p = 0.002$). Comparison of risk factors (Table 4 Supplemental) disclosed that family history of SCD (26% vs 16%, $p = 0.0001$) and nonsustained ventricular tachycardia (19% vs 14%, $p = 0.0001$) were more frequent in NOCM than HOCM. As compared with NOCM, patients with HOCM were more commonly treated with beta-blockers (60% vs 39%, $p = 0.0001$), calcium antagonists (31% vs 23%, $p = 0.0001$), and disopyramide (10% vs 2%, $p = 0.0001$).

3.3. Long-term outcome

All 20 included studies reported data on HCM related death thus allowing computation of annual mortality (Table 1). Annual mortality related to HCM averaged 1.55% in NOCM and 1.77% in HOCM, thus resulting slightly lower in NOCM vs HOCM (Relative Risk: 0.87, 95% confidence intervals: 0.66 to 1.14 $p = 0.31$) (Fig. 1). Overall, 11 studies reported significantly higher mortality for HOCM, 8 higher mortality for NOCM, and 1 no significant difference.

3.4. Sudden and heart failure death

All studies reported data on the incidence of SCD, whereas death due to heart failure was assessed in 14 of the 20 studies. Annual incidence of SCD was 1.14% in NOCM and 1.43% in HOCM, thus resulting slightly lower in NOCM vs HOCM (Relative Risk: 0.79, 95% confidence intervals: 0.58 to 1.07, $p = 0.13$) (Fig. 2). Overall, 3 studies reported significantly higher incidence of SCD in HOCM [21,23,30], 2 higher incidence of SCD in NOCM [20,38], and 13 no significant differences [22,24–29,31–37,39]. Annual death due to heart failure was 0.38% in NOCM and 0.43% in HOCM, with no significant difference between the two groups (Relative Risk: 0.90, 95% confidence intervals: 0.49 to 1.64, $p = 0.72$) (Fig. 3). Overall, 1 study reported significantly higher incidence of death due to heart failure in HOCM [25], 2 studies higher